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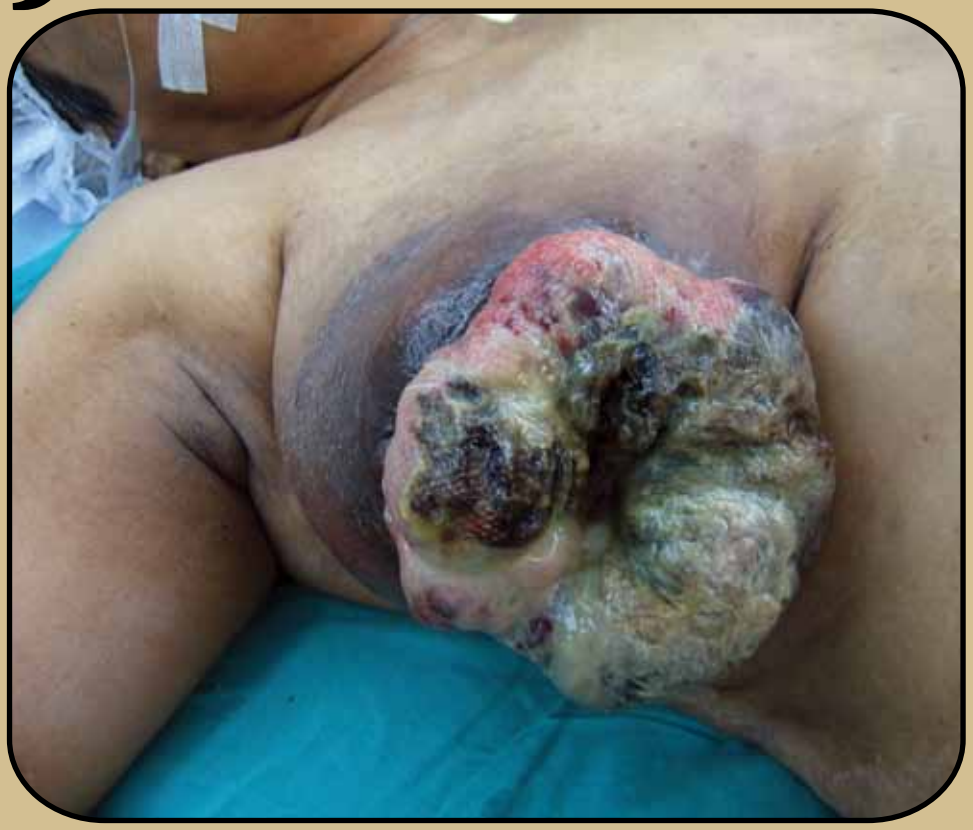

Volume 13 Number 1 2010

This journal is indexed/abstracted by Elsevier (Scopus) and MyAIS

Journal of the
University of Malaya
Medical Centre

jummec.um.edu.my

UNIVERSITI
MALAYA

June 2010
Volume 13 Number 1

JUMMEC

Journal of the University of Malaya Medical Centre

UNIVERSITI MALAYA

JUMMEC

Journal of the University of Malaya Medical Centre

Volume 13 Number 1 **2010**

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Volume 13 Number 1 **2010**

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Journal of University Malaya Medical Centre (JUMMEC),
The Dean's Office,
Faculty of Medicine,
University of Malaya,
50603 Kuala Lumpur, MALAYSIA.

Publisher
The Journal of University of Malaya Medical Centre (*JUMMEC)* is published two times a year by the University of Malaya Medical Centre.

An online archive of *JUMMEC* issues is available through the website: jummec.um.edu.my.

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Cover
"A mushroom within the breast."
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Printed by
Touch Graphic, No. 21-1, Jalan Wangsa Delima 10, D'Wangsa Maju, Kuala Lumpur, Malaysia.

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MIND, BODY AND CANCER

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New molecular and pharmacological tools have made it possible for us to identify the intricate network that exists between the immune system and the brain, a network that allows the two systems to signal each other continuously and rapidly. Chemicals produced by immune cells signal the brain, and the brain in turn sends chemical signals to restrain the immune system. These same chemical signals also affect behavior and the response to stress. Disruption of this communication network in any way, whether inherited or through drugs, toxic substances or surgery, exacerbates the diseases that these systems guard against: infectious, inflammatory, autoimmune, and associated mood disorders. Many researchers studies have shown that stressful life events, from the death of a loved one to the loss of a job, are linked to an increase in certain health problems, particularly heart disease, diabetes, and hypertension. Many people assume that stress leads to cancer as well. Evidence for this, however, is not clear. However, the significance of mind-body interactions in medicine is now increasingly being recognised (1).

Disruption of an individual's natural sleep-wake cycle has been determined to be a contributing factor in the development of organ disease. The effect of shift work on cancer, particularly breast cancer, has received increasing interest from the lay media since a panel of the International Agency for Research on Cancer declared in 2007 that "shift work that involves circadian disruption is probably carcinogenic to humans." The majority of studies have dealt with shift work and risk of cardiovascular disease,in particular coronary heart disease, have given conflicting results possible because methodological problems are present in most studies in relation to selection bias, exposure classification, and the appropriateness of comparison groups. The study by Moy FM in this issue does not provide any evidence for a relationship between shift work and cardiovascular risk factors (2).

Cancer is the second commonest cause of death in Malaysia. A total of 21,773 cancer cases were diagnosed among Malaysians in Peninsular Malaysia in the year 2006 and registered in the National Cancer Registry. It comprises of 9,974 males and 11,799 females. The Age standardised Incidence Rate (ASR) for all cancers in the year 2006 regardless of sex was 131.3 per 100,000. and the five most common cancer among the population of Peninsular Malaysia in 2006 were breast, colorectal, lung, cervix and nasopharynx. A national cancer control programme on modifying risk factors for developing cancer (prevention), early detection, treatment and rehabilitation of patients with cancer is important in reducing the morbidity and mortality from this disease.

Breast cancer is the commonest cancer in women in Malaysia. Lifestyle can reduce the risk of breast cancer. Breast feeding for a prolonged period can protect against breast cancer and should be encourages. However a study on the prevalence of breast feeding in Kedah showed that only 21% of mothers breast-feed exclusively for 4 months, and women of higher education are more likely to practise breast feeding as they understand the benefits of breast feeding (3).

Occupational hazard play a small role in the causation of cancer, especially in the rare cancers such as squamous cell carcinoma of the scrotum, which has been associated with paraffin and shale oil workers (4).

Cancer may sometimes present not as the primary tumour, but as a para-neoplastic syndrome such as the oncogenic osteomalacia, characterised by bone pain and muscle weakness, and these are caused by a tumour of mesenchymal origin that secrete phosphaturic substances (5).

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Cancer patients on chemotherapy experience psychological distress which is often under-diagnosed. This may be due to the side-effects of chemotherapy, and also the uncertainty of having a life-threatening disease. Hence it is important to recognize and treat distress early (6). Targeted therapy, which does not have the side-effects of chemotherapy, is being developed, and these drugs inhibit specific pathways involved in pathogenesis of cancer, and one such drug is temsirolimus, which is an mTOR inhibitor shown to have efficacy in renal cell carcinoma (7)

Cancer survivorship issues and quality of life are becoming increasingly important as with better and more effective treatment, women with breast cancer are living longer. Because breast cancer occurs in relatively young women, with more than 50% of women in the premenopausal age group, women with breast cancer face a multitude of problems related to sexuality. Surgery is often mutilating, chemotherapy brings on premature menopause, and there is a deterioration in sexual functioning which can post medical and psychological problems (8).

A fear of recurrence persists even after several years after a cancer is diagnosed and treated. Prognosis in breast cancer is generally good; however recurrences can occur even after many years. Clinicopathological features can be used to predict the likelihood of a relapse, and the study by Rozita AM *et al* in UMMC showed that disease stage, nodal status and estrogen receptor status were significantly correlated with risk of relapse (9).

Finally, we must not forget that while prescribing drugs such as chemotherapy and targeted therapy may carry side-effects, even simple drugs like antibiotics, is also not without adverse effects, and antibiotics can lead to Stevens- Johnson syndrome, and judicious use of medication with patients education is important (10).

References

1. Boey C. Reflections on the significance of relationship between mind and body in medicine. *JUMMEC* 2010; 13(1): 3-11.
2. Moy FM, Hoe VCW, Tan CPL, Rosmawati M. Cardiovascular risks among shift and non-shift workers in a public medical centre in Kuala Lumpur. *JUMMEC* 2010; 13(1): 45-49.
3. Yadav H. Breastfeeding practices in a rural community in Kedah. *JUMMEC* 2010; 13(1): 38-44.
4. Shanggar K, Ng CH, Razack HR, Dublin N. Squamous cell carcinoma of scrotum: a rare case of scrotal neoplasm. *JUMMEC* 2010; 13(1): 59-62.
5. Vijay P, Tan ATB, SuhaidaAM, Chan SP. Oncogenic osteomalacia, you say? Better start looking then—A Case Report. *JUMMEC* 2010; 13(1): 63-68.
6. Nor Zuraida Z, Ng CG. Pshychological distress among cancer patients on chemotheraphy. *JUMMEC* 2010; 13(1): 12-18.
7. Ng C. A retrospective analysis of patients with advanced renal cell carcinoma treated withh temsirolimus. *JUMMEC* 2010; 13(1): 19-23.
8. Loh SY. Counselling changes in sexual functioning women with breast cancer. *JUMMEC* 2010; 13(1): 33-37.
9. Rozita AM, Marniza S, Mastura MY, Wan Zamaniah WI, Yip CH. Patterns of breast cancer relapse at University of Malaya Medical Centre. *JUMMEC* 2010; 13(1): 24-32.
10. Rokiah CI, Shasha K, Rokiah I. Severe cutaneous adverse drug reactions: Stevens-Johnson Syndrome and toxiv epidermal necrolysis, a report of 4 cases seen at UMMC. *JUMMEC* 2010; 13(1): 50-58.

REFLECTIONS ON THE SIGNIFICANCE OF THE RELATIONSHIP BETWEEN MIND AND BODY IN MEDICINE

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ABSTRACT:

In the last three centuries, medicine has focused predominantly on the physical body as the source of disease, placing very little importance on the mind. However, the significance of mind-body interactions in medicine is now increasingly being recognised. True health must include both the physical body and the mind. This article traces our concepts of the relationship between mind and body since primitive times and explores its relevance to the maintenance of health. *(JUMMEC 2010; 13(1): 3-11)*

KEYWORDS: *mind-body interaction*

Introduction

For centuries, scientific thinking had been based on the concept of the separation of body and mind. 'Body' refers to all matter and physical phenomena, including the human body. 'Mind' refers to the unseen, spiritual, psychological aspects of life, including reason, intellect, memory, attention, will and emotion. It is the aspect of a person that enables the person to be aware of the world, to think and to feel.

Rene Descartes, the seventeenth-century French philosopher and mathematician, drew a strict distinction between mind and body. Descartes' mind-body dualism became the foundation of Western thought for many years and contributed to the separation of theology and science, of materialism and spiritualism, of body and mind. It supported the distinction in medical science between physical phenomena or diseases and those of a mental or emotional nature. To Descartes, the human body was a machine reducible to elementary parts and systems. While the idea of mind-body separation still remains strong to this day, the distinction has begun to fade as science and medicine make new discoveries.

A historical overview of our understanding of mind-body interaction

In primitive society (10000BC), disease was thought to be primarily caused by spiritual powers and, therefore, could be treated only by spiritual means. The evil spirit entering the human being had to be liberated through exorcism and similar means. The emphasis was almost exclusively on the spirit and there was very little consideration of the physical body. In some societies, even today, there is a dangerous lack of respect for medical science and an excessive reliance on superstition.

In the ancient civilizations such as the Babylonian-Assyrian Civilizations (2500-500BC), medicine was often dominated by religion. Many Egyptian beliefs were based on myths and legends. However, there is evidence that in ancient Egypt, interest in human anatomy started to increase and there existed people who were referred to as physicians.

With time, a more holistic approach was adopted. There was more interest in the scientific study of the physiology of the human body, in addition to the psychological and spiritual aspects of life. The ancient Greek physician, Hippocrates, thought to have lived around 460BC to 370BC and often referred to as the 'father of medicine', wrote in his treatise, entitled *Tradition in Medicine*, that "no one can understand the science of medicine unless he knows what man is" (1), emphasizing that in order to cure the human

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body, it is necessary to have a knowledge of the whole of things. Over the following hundreds of years (100BC-AD400), various theories of the causation of disease were put forth, such as Galen's humoral theory that disease was caused by disturbance in the body fluids. This continued until the Middle and Dark Ages (around AD500-1450) when mysticism again dominated medicine. Sinning was thought to be the cause of mental and somatic illnesses.

During the Renaissance period (1500-1700), there was revival of interest in the natural sciences and their application to medicine as well as advances in anatomy, autopsy, microscopy and others. Around the 17th century, Descartes' concept of the 'dualism' or separation of the mind and body started to exert a strong influence on Western thought. In the 19th century, modern laboratory-based medicine, such as that practiced by Pasteur and Virchow, opened up a new era in medicine. From that time onwards, doctors began to feel that disease had its origin in disorders of the cell. The development of better microscopes enabled more details to be examined. Medicial practitioners became convinced that all disease must be associated with some kind of structural or functional cell change. Our understanding of the workings of the human body as well as of pathological processes progressed by leaps and bounds.

As time went on, however, the inter-relationship of the mind and the body was rejected as unscientific and matters related to the mind were relegated only to the realm of religion and philosophy. In the last three centuries of human existence, medicine has focused predominantly on the physical body as the source of disease, placing little importance on the mind. We have swung completely in the opposite direction from the days of our forefathers in primitive society where illness was thought to be entirely caused by spiritual powers. Although it has brought about many benefits, progress in the scientific understanding and treatment of disease is, unfortunately, in many instances also accompanied by a situation where the disease is treated, but not the whole patient. With its analytical and specialising approach, western medical science, though possessing great knowledge about pathological conditions, often regards illness and the diseased organ as separate from the human beings who are inflicted by the illness. This is an unfortunate consequence of the concept that mind and body are separate entities.

Professor Felix Unger, head of Cardiac Surgery at Salzburg State Hospital and President of the European Academy of Sciences and Arts, comments on the state of medical science today as follows: "Its strong inclination towards the natural sciences has caused medicine unintentionally to regard patients as peculiar cases describable in natural-scientific terms" (2).

Psychological and physical illness — is there a real division?

A large proportion of the training of doctors today is centred on the scientific diagnosis and treatment of diseases of the body. In doing so, we often categorise and compartmentalise. While this is important to enable us to make sense of the large and ever-increasing body of medical knowledge, it has also led us, whether consciously or not, to separate the so-called 'mind' problems and the 'body' problems in our clinical practice, ignoring their inter-relationship.

It is now a common tendency to classify illnesses into those that we think have a physical or organic cause and those, which we consider to be psychological or psychosomatic or non-organic in origin. This is undoubtedly convenient for the busy clinician but there is increasing awareness that such clear-cut division of diseases into 'physical' (body) and 'psychological' (mind) categories is an oversimplification and often wrong. We are beginning to recognise that all diseases, even genetic diseases and congenital malformations, have both physical and psychological elements that we cannot ignore. The mind and the body may appear separate, but they are, in fact, unified.

When patients discover they have serious illnesses, the accompanying shock has major effects on their mental and emotional states. Illness affects how one feels in many ways, often causing one to plunge into the depths of depression. In the case of children, their self-image and development can also be affected. In many instances, the impact upon their young minds can have lasting consequences.

The mind can also affect the body. It is well recognised that symptoms of 'physical' diseases such as peptic ulcer disease can worsen in times of stress. Severe

emotional turmoil can precipitate a cardiac arrest. Great joy as well as deep sorrow lead one to shed tears. Expressions in the English language such as 'trembling with fear', 'the heart beating in excitement' and 'shaking with laughter' show that even long ago, people have recognised the influence of emotions on the body. One's emotional state is revealed in one's physical appearance and attributes of the mind such as confidence is reflected in the quality of one's voice.

Functional gastrointestinal symptoms in children

There are a large number of children with severe physical complaints - such as headache, abdominal pain and vomiting - without any detectable physical cause. The pain experienced by these patients is real, and often, very severe and yet, conventional tests could not reveal any pathology.

A survey of elementary school-children in Malaysia revealed that about ten percent of them suffered from the syndrome of recurrent abdominal pain, defined as at least three episodes of stomach-aches intense enough to interfere with their daily lives over a period of at least three months (3). Among Malaysian children with recurrent abdominal pain who were admitted to hospital, a significant proportion of over 95% were found not to have detectable abnormalities that could account for the symptom, whether on physical examination or investigation (4).

The presence of organic pathology does not necessarily imply that it is the cause of a patient's symptoms. For example, the organism *Helicobacter pylori* was once proposed to be an important cause of childhood recurrent abdominal pain. However, analyses of various paediatric studies suggest that there is insufficient evidence to support this proposal (5). In a study on *H. pylori* sero-positivity, a relatively high prevalence of *H. pylori* (16.7%) was noted in asymptomatic Malaysian teenagers, indicating that the organism could be present without causing symptoms (6). Furthermore, the prevalence of *H. pylori* sero-positivity among asymptomatic Malaysian children was lowest in Malays (6.6%), intermediate in Chinese (10.4%) and highest in Indians (17.9%) (6). Interestingly, this was the opposite of the prevalence pattern of recurrent abdominal pain found in the same population where recurrent abdominal pain was most common in the Malays (11.9%), intermediate in the Chinese (9.3%) and least common in the Indians (8.2%) (7).

Current research shows that childhood recurrent abdominal pain is multi-factorial in origin with a major psycho-social component. For instance, a strong correlation has been found between stressful life-events and the occurrence of recurrent abdominal pain in both rural and urban school-children aged between nine and fifteen years (8, 9, 10). The life-events included the loss of a family member through death, the change in occupation of a family member, hospitalisation of a family member, the child's own hospitalisation, recent change of address, change in occupation of an immediate family member, failure in a major school examination and bullying at school. Stressful life-events was not only associated with increased complaints of physical symptoms, but was also linked to poor academic performance (11). What is worrying is that children with recurrent abdominal pain often miss school on account of their symptoms, with studies showing that at least a third of these children missed more than two weeks of school over a six-month period (7).

Another condition frequently seen is the syndrome of cyclical vomiting, which is a condition characterised by recurrent stereotypical bouts of vomiting with intervening periods of normal health and the absence of an organic cause. Many of these patients have some kind of psychosocial precipitating factor.

The following case of a ten-year-old boy with recurrent vomiting illustrates the problem. He was the only child of well-educated parents. The child's episodes of vomiting occurred several times a year and were often severe, resulting in electrolyte disturbances. Hospital investigations did not reveal any organic cause for the symptoms. There were no obvious precipitating factors at first. However, a more detailed history revealed that there was a feeling of guilt in the family originating in the grandfather and transmitted also to his father. The grandfather was a soldier who had killed during war and unresolved feelings of profound guilt led him to commit suicide a number of years ago. The family did not discuss this matter openly. However, it was a severe shock to the sensitive young boy and suppressing it all was likely to be an important cause of his symptoms. Once this possibility was recognised and the whole family was

encouraged to talk about it, the episodes of vomiting started to reduce significantly.

The above studies and case report show that issues of the mind cannot be separated from those of the body. It is essential not to just look at the physical aspect alone, even though it may appear that the patient – whether adult or child - is only complaining of a physical symptom such as "abdominal pain" and "headache" or diagnosed with a so-called "physical disease" like "asthma" and "diabetes". It is important to know what the patient and, indeed, the family are thinking about and feeling – otherwise the management of the patient is incomplete. A doctor needs to pay attention to more than a diseased organ, more even than the whole man – it is crucial that he considers the man in his world.

An important obligation of adults today is to create the conditions in the family, the school and in society for children to grow up happily with healthy bodies and minds. Symptoms such as stomach-aches and vomiting can often be a child's subconscious cry for help. Giving adequate time to the child and listening with concern to whatever he or she has to say is essential if we wish to understand the world of our children and help them. Parents and teachers who do not realize this point exacerbate the problem and end up putting further pressure on the child. This can lead to chronic illness.

The body's reaction to psychosocial stress and depression

One of the areas where mind-body interactions has been studied is the effects of mental conditions such as depression and stress on the body. 'Stress' can be described as a condition that affects people when the demands made on them exceed their capacity to meet those demands (12). A number of papers have shown that there is association between depression and stress on the one hand and diseases traditionally thought to be 'physical' or organic diseases on the other.

Depression was found to coexist with Crohn disease more often than would be expected by chance (13, 14). It is unclear whether depression occurred as a result of the disease, or whether depression played a role in facilitating the expression of the inflammatory bowel disease. Depression has also been found to increase mortality and morbidity in patients with heart failure. Such adverse associations persist after adjustment for conventional prognostic risk factors (15).

It is not entirely clear what the mechanisms are that account for the observed association between various diseases and depression or stress. In recent years, there have been various studies that attempt to look at possible mechanisms, although, we still do not have a completely satisfactory explanation. For instance, depression has been found to be associated with inflammation as evidenced by the finding of increased levels of C-reactive protein (16). Increased TNF-alpha levels and coagulation factors have also been shown to be present in depression (17, 18). Animal studies show that mice subjected to maternal deprivation develop a behavioural pattern reminiscent of depression and are more susceptible to inflammation (19).

It has also been proposed that another possible mechanism linking depression with disorders such as cardiac pathology is autonomic imbalance. Some of the abnormalities that have been found include impaired parasympathomimetic functions and a dominant sympathetic drive (20, 21).

Whatever the mechanisms may be, mental or psychological stress has been linked to a variety of other conditions such as skin disorders, allergies, asthma and even malignancy. Depression and hopelessness seem to reduce the body's resistance, making one vulnerable to various illnesses. Further studies are needed to obtain more evidence but what is available, so far, seems to support the concept that mind and body are inseparable.

The effect of a positive mind-set on the body

While there have been some studies on the negative effects of stress and depression on the body, even less is known about the effect of a positive mind-set. It seems reasonable, however, to propose that a positive mind-set should also have positive effects on the body. What are the effects of positive psychological events on the body? We are still in the early stages of understanding and there are not many studies that test and document this possibility. There are, however, many anecdotal reports from reputable sources and it would be unwise to disregard them.

Using again the example of Crohn disease quoted earlier, my own unpublished experience suggests that there are some patients with a severe form of the disease who have better outcome than others with less severe physical disease but who are anxious, tense and withdrawn. These patients are usually positive individuals, who do not let their illness limit their functioning, participating in a wide range of academic and extracurricular activities.

The late Dr. Norman Cousins (1915–1990), formerly an adjunct professor at the School of Medicine, University of California, Los Angeles (UCLA), wrote in an article published in 1976 in the New England Journal of Medicine as follows:

"The will to live is not a theoretical abstraction but a physiologic reality with therapeutic characteristics…I have learned never to underestimate the capacity of the human mind and body to regenerate – even when the prospects seem most wretched. The life-force may be the least understood force on earth…. Human beings tend to live too far within self-imposed limits. It is possible that these limits will recede when we respect more fully the natural drive of the human mind and body toward perfectibility and regeneration. Protecting and cherishing that natural drive may well represent the finest exercise of human freedom" (22).

What was it that led Dr. Cousins to make such a comment? In the 1920s, when Dr Cousins himself was diagnosed with tuberculosis, he was sent away to a sanatorium where he noticed that although two patients might have similar medical conditions, the one who was hopeful and optimistic was far more likely to actually recover. Years later, he himself survived a life-threatening connective-tissue disease at the age of 50 and recovered from cardiac infarction at the age of 65. While cooperating fully with his physicians, Dr Cousins also realised that a crucial factor in his recovery was his own powerful determination to beat his illness. He, subsequently, became convinced that a positive determination to overcome illness could actually stimulate our organs and even individual cells towards health.

Exactly one hundred years ago, in 1910, Dr. William Osler, Regius Professor of Medicine at Oxford University made a similar observation in the British Medical Journal.

"Nothing in life is more wonderful than faith - the one great moving force which we can neither weigh in the balance nor test in the crucible. Intangible as the ether, ineluctable as gravitation, the radium of the moral and mental spheres, mysterious, indefinable, known only by its effects, faith pours out an unfailing stream of energy…" (23).

The importance of giving patients the courage not to be defeated by their illness

What is the practical clinical implication of knowing that there is close interaction between mind and body?

Based on his experience, Dr. Cousins stated, as follows: "One of the doctor's biggest jobs is to encourage to the fullest the patient's will to live and to mobilize all the natural resources of body and mind to combat disease" (22, 24, 25).

S is a patient who is now in her twenties. She had biliary atresia and had a Kasai operation. Although the operation managed to overcome biliary obstruction and re-establish bile flow, her liver had already been damaged before surgery and she needed constant follow-up and surveillance. About five years previously, her mother, who had been her pillar of support, died from breast cancer. Her bereavement, together with her own chronic illness, caused her to fall into the depths of depression and she lost the will to live. However, with constant encouragement from her father as well as the medical and nursing staff, she managed not only to live on but also developed the courage to pursue tertiary education.

When one of her doctors saw her, she told him with pride that she had completed her university thesis on the activities of young women during the Second World War. It was an academic thesis but at the same time, it was full of feelings of sympathy for the plight of war victims. Her sensitivity was, no doubt, sharpened by the fact that she had undergone illness and bereavement herself. She had managed to turn her own misfortune into something very positive.

This experience illustrates that illnesses can serve to nourish one's heart. A person who accepts his illness positively and perseveres through it will achieve greater depth and strength as a human being.

It also serves to remind health care professionals of the importance of providing constant warm encouragement to their patients in addition to dealing with the actual disease itself. Encouragement does not simply mean unreasonably telling the patient that an illness can be cured completely. It means not giving up on the patient as a human being even when the disease cannot be cured. This experience emphasises the importance of encouraging patients to develop the strength of mind that enables the patient to rise above an illness and achieve great satisfaction despite the disease still being present.

Lessons from the life of Helen Keller

The positive interaction between mind and body is well-illustrated in the lives of many people, some well-known while others, less so. They all demonstrate the fact that the severity of a physical handicap varies according to the person's emotional reaction to it. Blindness and deafness, for example, may seem to be completely physical problems. However, does the handicap result in loss of hope or does it become a challenge to be overcome? Helen Keller was a shining example of someone who had attained great heights despite being physically handicapped.

Helen Keller was born in Alabama in 1880. At the age of nineteen months, she was afflicted by an acute life-threatening illness that eventually left her blind and deaf. The years that followed were hellish for her family. There was no way to communicate with the young child. Imprisoned in her body, lonely in a silent world and unable to tell others her feelings and wishes, Helen would often rage about like a wild animal.

Helen's life was transformed when she met her teacher, Anne Sullivan, who was herself partially blind. There was a significant moment when Helen first realised that things around her had names. It was the moment when Ann Sullivan placed one of Helen's hands in a stream of water and then spelled the word water into her other palm.

Helen described her feelings at that moment in her autobiography, *The Story of My Life*:

"I stood still, my whole attention fixed upon the motions of her fingers. Suddenly, I felt a misty consciousness as of something forgotten – a thrill of returning thought; and somehow the mystery of language was revealed to me. I knew then that 'w-a-t-e-r' meant that wonderful cool something that was flowing over my hand. That living word awakened my soul, gave it light, hope, joy, set it free! There were barriers still, it is true, but barriers that could in time be swept away" (26).

From that moment onwards, Helen continued to make astounding progress. She eventually graduated from college and dedicated herself to helping the blind and handicapped.

Helen Keller's story is a testimony to the powerful interaction between mind and body, and shows that the remarkable potential latent within the life of a single determined individual need not be held back by physical disability. Conversely, even if someone has great physical strength, but lacks a resolute spirit, he cannot reach the full potential of full play to his abilities.

Helen's story also contains an important lesson for health-care professionals. Her moment of break-through, related above, is now well-known but it was actually only possible because of something less well-known but equally important - Ann Sullivan's patience and her belief in Helen's potential. Helen had initially rejected any contact with Ann Sullivan, but as a result of Sullivan's painstaking effort to reach out to Helen, a warm and solid relationship of trust was forged which enabled the break-through to occur. Doctors, nurses, teachers and indeed everyone who has the responsibility to care for a patient, have much to learn from the courageous example shown by Ann Sullivan.

Strength of the mind in the face of terminal illness

Terminal care is an area where careful consideration of the mind is of great importance but sadly, often forgotten.

T was an eleven-year old girl who died of leukaemia a few years ago in the University of Malaya Medical Centre. Coming from another part of Malaysia, it was not easy for her to adapt to life in Kuala Lumpur while having to come to terms with the reality of her diagnosis. In the beginning, she fell into depression and shut herself up from other people. Over the

subsequent months, however, she developed a great realisation. She realised that the quality and significance of one's life is not necessarily dependent only on its length, but increases in proportion to the depth in which one lives one's life and the value one creates. It was a remarkably profound and mature realisation for any person, let alone for a child of her age. Young children, especially sick ones, often have thoughts that are more profound than we can ever imagine.

During the last year of her short life, she was determined to do something useful with her life. She decided to challenge herself to do well in her primary school examinations. Although her illness resulted in her missing a lot of school, her determination was strong and she gave everything she had to her studies.

As Helen Keller once said, "When we do the best that we can, we never know what miracle is wrought in our life, or in the life of another". T's parents and many friends around her age were greatly moved and encouraged when she managed to obtain four distinctions in the examination, in spite of her illness. It was not the examination result itself that was most important but rather it was the tenacity of her spirit and the determination not to be defeated by her illness that really moved others.

Just before she died, she expressed a wish to attend university. Although some may call her unrealistic, one cannot help but marvel at the resilience and positivity of her spirit. T eventually grew weaker and, finally, passed away. Although weak and diseased, she had a peaceful countenance at death. One's appearance at death is a good indicator of one's state of mind.

At a time when a disease is incurable, it is easy for both patient and doctor to harbour feelings of futility and uselessness. There is also a temptation to carry out desperate, heroic acts. There is much for both doctors and nurses to learn from the courageous attitude of this young patient in facing death. This experience shows how important it is for care-givers to be sensitive and to carefully consider a patient's state of mind in the final moments of life. It is a grave mistake to separate the mind from the body and consider only the physical disease. This can lead to treatment being administered to terminally-ill patients excessively and unreasonably, thereby causing more pain and anguish. Such an attitude also leads to despair and loss of hope for both the terminally ill patient and care-giver when all medical treatment is futile.

There is an important difference between the courage to look the truth in the face, accepting the fact that all living things must die while creating value out of the remaining days of life, and the typically arrogant pathological view that life and death should be subject to our will, desire and control.

Conclusion — Looking towards the future

Evidence, both laboratory and clinical, is accumulating that the mind and the body interact very closely. Concepts concerning the relationship between mind and body are moving from dualism to inseparability. True health must include both the physical body and the mind.

With regard to children's health, this article emphasizes that an important obligation of adults today is to create the conditions in the family, the school and in society for children to grow up happily with healthy bodies and minds. Giving adequate time to the child and listening with concern to whatever he or she has to say, is essential if we wish to understand the world of our children and help them.

One of the most important implications of our understanding of the interaction between the mind and body is an appreciation of the tremendous potential that exists in the life of each individual. We have seen examples that the strength of the heart or mind is an important key to release this energy. Therefore, in addition to offering the best of medical and surgical therapy, it is essential to fully engage the patients' own ability to mobilize the forces of mind and body in their battle against illnesses. With regard to this, it is the bond of trust between care-giverand patient, between one human being and another, that most of all, can help the patient to strengthen the power of the mind.

To ensure that future generations of doctors, nurses and other health-care professionals realize the full significance of these points and appreciate the dignity of life is one of the most important tasks of a medical school. Dr. Norman Cousins once emphasised that one of the biggest needs in medical education today is to

attract students who are well-rounded human beings; who will be interested in people and not just in the diseases that affect them; who can comprehend the reality of suffering and not just its symptoms; whose prescription pad will not exclude the human touch. In essence, what is needed is a profound reverence for the dignity of life as expressed poetically in the following words by Dr. Daisaku Ikeda:

There is something vaster
than the wide open sky—
and that is, my life
There is something deeper
than the fathomless sea—
and that is, your life.
There is something more precious
than all the treasures of the universe—
and that is, our lives (27).

(This article is based on an inaugural lecture delivered on 26th May 2009 at the University of Malaya)

References

1. Hippocrates. Tradition in Medicine. In: *Hippocratic Writings*. Ed. GER Lloyd. Middlesex, England: Penguin; 1983.
2. Unger, F, Ikeda D. A Dialogue – Compassion and Tolerance. *J Orient Studi* 2005; 15: 8-9.
3. Boey CCM, Yap SB. The prevalence of recurrent abdominal pain in eleven to sixteen-year old Malaysian school-children. *J Paediatr Child Health* 2000; 36: 114-116.
4. Boey CCM , Goh KL, Hassal E, Magid M. Endoscopy in children with recurrent abdominal pain. *Gastrointest Endosc*. 2001; 53:142-143.
5. Sherman PM, Macarthur C. Current controversies with Helicobacter pylori infection in the pediatric population. *Front Biosci* 2001; 6: E187-192.
6. Boey CCM, Goh KL, Lee WS, Parasakthi N. Seroprevalence of Helicobacter pylori infection in Malaysian children: Evidence for ethnic differences in childhood. *J Paediatr Child Health* 1999; 35(2): 151-152.
7. Boey CCM. Recurrent Abdominal Pain in Malaysian Children. (MD Thesis). Kuala Lumpur: University of Malaya, 2000.
8. Boey CCM, Goh KL. Stressful life events and recurrent abdominal pain in children in a rural district in Malaysia. *Eur J of Gastroenterol Hepatol* 2001; 13: 401-404.
9. Boey CCM, Goh KL. The significance of life-events as contributing factors in childhood recurrent abdominal pain in an urban community in Malaysia. *J Psychosom Research* 2001; 51(4): 559-562.
10. Boey CCM. Somatization and recurrent abdominal pain. In: Pediatric Gastroenterology 2004. Reports from the 2nd World Congress of Pediatric Gastroenterology, Hepatology and Nutrition (Paris, France July 3-7, 2004). Medimond, Bologna, Italy; 319-325.
11. Boey CCM, Omar A, Phillips JA. Correlation among academic performance, recurrent abdominal pain and other factors in year 6 urban primary school children in Malaysia. *J Paediatr Child Health* 2003; 39(5): 352-357.
12. Kaplan, Sadock. *Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry*. 8th Edition. Lippincott: Williams & Wilkins; 1998.
13. Gerbert B. Psychological Aspects of Crohn's Disease. *J Behav Med* 1980 Mar; 3(1): 41-58.
14. North CS, Alpers DH. A review of studies of psychiatric factors in Crohn's disease: etiologic implications. *Ann Clin Psychiatry* 1994 Jun; 6(2): 117-124.
15. Jiang W, Krishnan, RR; O'Connor CM. Depression and heart disease: evidence of a link, and its therapeutic implications. *CNS Drugs* 2002;16: 111–127.
16. Ford, DE, Erlinger TP. Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2004;164:1010–1014.
17. Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E. Increased serum tumor necrosis factor-alpha levels and treatment response in major

depressive disorder. *Psychopharmacology* (Berl.) 2003; 170: 429–433.

18. Panagiotakos DB, *et al*. Inflammation, coagulation, and depressive symptomatology in cardiovascular disease-free people; the ATTICA study. *Eur Heart J* 2004; 25: 492–499.

19. Varghese AK, *et al*. Antidepressants attenuate increased susceptibility to colitis in a murine model of depression. *Gastroenterology* 2006; 130: 1743–1753.

20. Nahas Z, *et al*. Serial vagus nerve stimulation functional MRI in treatment-resistant depression. *Neuropsychopharmacology* 2007; 32: 1649–1660.

21. Gorman JM, Sloan RP. Heart rate variability in depressive and anxiety disorders. *Am Heart J* 2000; 140(4 Suppl): 77-83.

22. Cousins N. Anatomy of an Illness as Perceived by the Patient. *New Engl J Med* 1976; 295: 1458-1463 .

23. Osler W. The Faith that Heals. *Br Med J* 1910 June 18; 1(2581): 1470–1472.

24. Cousins N. *Anatomy of an Illness as Perceived by the Patient, Reflections on Healing and Regeneration*. NY: Bantam Books; 1981.

25. Cousins N. *Healing and Belief, Human Options*. NY: WW Norton; 1981.

26. Keller H. *The Story of My Life*. NY: Bantam Books; 1990.

27. Ikeda D. Peace—The Foundation for Lasting Human Happiness (a poem). *SGI Newsletter* (2007): 7234.

PSYCHOLOGICAL DISTRESS AMONG CANCER PATIENTS ON CHEMOTHERAPY

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ABSTRACT:

Distress has become a major issue in cancer population. Patients may suffer from either physical, psychological distress or both. Cancer patients who are undergoing chemotherapy are more likely to experience psychological distress. This could be due to the negative effects of chemotherapy agents, the uncertainty of post-treatment, and the occurrence of psychosocial problems. As a result, the patient may experience a normal reaction such as sadness or may develop common psychiatric disorders such as depression and anxiety. *(JUMMEC 2010; 13(1): 12-18)*

KEYWORDS: *psychological distress, anxiety, depression, cancer, chemotherapy*

Introduction

Psychological distress is the uncomfortable emotional response to a perceived harmful event such as upon receiving a diagnosis of cancer. "Distress" is the most commonly used term in oncology literature to describe the whole range of negative psychological responses experienced by the cancer patients (1,2). It has been defined as "a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment" (3,4).

A lot of research has been done in determining psychological distress in cancer patients (5-7). The prevalence of long-term psychological distress in cancer patients ranges from 20% to 60% (8,9). It is due to the inconsistencies of study methods such as the assessment tools used and study populations included. Among the various types of psychological responses, anxiety and depression received most attention in the studies of cancer patients (10). Anticipatory anxiety and post traumatic stress disorder are the two types of anxiety known to be related to the initiation and consequence of cancer treatment (10-13). Depression encompasses a spectrum that ranges from normal sadness to major depressive disorder. It is an understandable reaction to the fear of cancer and closely linked with the somatic complaints and its treatment (10).

Chemotherapy is the most frequently used treatment modality in cancer patients. It is well-known in causing a wide range of side effects such as nausea and vomiting, tiredness or fatigue, sore mouth, reduced fertility, peripheral neuropathy, and skin problems (14,15). It leads to high level of distress and impacts on the quality of life in cancer patients receiving chemotherapy. As people live longer after treatment for cancer, attention turned to the survivor's quality of life and the distress that they may experience (10). As a result, it is important to monitor the psychological well—being in this group of patients as part of the routine care (4). It can be achieved by increasing the awareness and proficiency of oncology health care provider in recognizing and instituting optimal treatment for psychological distress in cancer patients.

Psychological distress in cancer patients who are on treatment, particularly chemotherapy, need to be determined and understood (16). This is the primary focus of this article.

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Factors Related to Psychological Distress in Cancer Patients

Before we discuss the psychological issues that arise in patients receiving chemotherapy, we need to understand the factors related to psychological distress in these patients. It was described by Andrykowski *et al* that psychological distress is due to the imbalance between two variables (17). The first variable is the "stress and burden" perceived by the cancer patients. It disrupts the psychological health of a patient. The second variable is the "resources" available to cope with the stress and maintain the psychological equilibrium (17). Various patient and disease characteristics that were found to be potential risk factors for psychological distress increase the burden experienced by the cancer patients. For example, the number of stressful life events, previous history of depression and premorbid psychiatric status (18).

Similarly, those factors that reduce the resources to cope with stress will result in higher psychological distress in cancer patients. Marital status, social class and financial status were predictors of high psychological distress which reduce the coping resources of a cancer patient (19, 20). A study on patients who underwent chemotherapy in Malaysia suggested that the prevalence of psychological distress determined by a "distress thermometer" was 51%. Distress was significantly associated with psychosocial problems (16). Another interesting example is the effects of age on emotional distress after a mastectomy. The results revealed that younger women apparently have resources that protect them against depression, although they are more likely to fear the recurrence of the disease and they worry more about disfigurement resulting from surgery. It conflicted with other studies that suggest marriage is protective against distress during stressful life events (21).

Normal Response to the Stress of Cancer

Rasmussen and Elverdam described cancer as a "symbol of disruption of life and time, and the harmony of ordinary life disappears" (22). The psychological response toward a life threatening disease such as cancer varies between individuals. It begins with shock and disbelief, followed by a mix of negative psychological responses and somatic complaints. Most people will recover from the emotional turmoil and recollect the psychological equilibrium (2,17). The period of recovery relied on the support from family, friends, personal coping skill and physician for those who opt to have a treatment plan that offer hope (2,23).

Some individuals do not fully recover and continue to have a low level of psychological distress which persists for weeks or months. For some, the condition deteriorates and leads to marked physical, psychological and social impairment and subsequently requires psychiatric treatment (17). An early study found that 53% of these patients were adjusting normally to stress; the remaining 47% had apparently clinically psychiatric disorders. Of the 47% with psychiatric disorders, 68% had adjustment disorders with depressed or anxious mood, 13% had a major depression, and 4% had a preexisting anxiety disorder (21).

Anxiety

Anxiety is well documented in patients with the diagnosis of cancer and the initiation of treatment (10-13). Patients are confronted with the worry of death at the time of diagnosis. It leads to a substantial level of anxiety. Gradually, it is followed by the fear of recurrence, disrupted belief of life expectancy and loss of focus in living (22, 24-28). The initiation of treatment such as chemotherapy add further emotional burden to the patients, which attributed to the potential adverse effects. There are two specific anxiety disorders, namely anticipatory anxiety and post-traumatic stress disorder (PTSD), which are believed to be closely linked with the treatment of cancer that significantly affect the patient's functioning, compliance and quality of life (10-13, 22, 24, 29).

Nausea and vomiting are common side effects of chemotherapy. It leads to several physical complaints such as loss of appetite and weight. The subsequent development of psychological nausea and vomiting which is known as anticipatory nausea and vomiting (ANV) is widely studied (10-13, 30-37). The common explanation for ANV is conceptualized as a learning process (38). The stimulation during drug administration followed by the drug related side effects triggers a conditioning process. As a result,

nausea and vomit are experienced during the next cycle of treatment even before drug administration. Autonomic reactivity and conditionability of an individual play distinct roles in determining the risk of developing ANV during chemotherapy (36). Patients with trait anxiety and post-treatment nervousness have a higher risk of ANV (35). Other predicting factors for ANV found in previous studies are younger age, history of susceptibility to motion sickness and history of side effects from previous chemotherapy (37). Understanding of this concept is important for health care providers who provide screening and treatment of ANV in cancer patients who are receiving chemotherapy.

Another specific type of anxiety that received much attention in the study of cancer patients is PTSD. The reported prevalence ranges from 18-80% depending on the time period of study and severity of the disorder (39-41). A study that used stringent diagnosis criteria for cancer related PTSD in breast cancer patients after completion of treatment shown that the prevalence rate was as low as 3% (42). However, before considering the biological explanation for PTSD in cancer patients, we need to accept that the diagnosis of cancer or treatment resembles a typical type of event or trauma that gives rise to PTSD (24). An abrupt disclosure of the diagnosis of cancer and the administration of treatment closely represent a traumatic event comparable with the disease itself which is an ongoing stress for an individual.

Many studies, which look into the underlying neuroendocrinologic processes that lead to PTSD in cancer patients has been conducted (43-45). Previous studies found that there were corticotrophin releasing factor (CRF) hypersecretion with relatively low level of adrenocorticotropic hormone (ACTH) and cortisol in cancer related PTSD. Negative feedback inhibition was hypothesized by Yehuda to explain this hypothalamic-pituitary-adrenal (HPA) alteration in PTSD (43). Another interesting finding was the lower amygdala volume in PTSD patients (44-45). These biological changes were suggested to trigger the emotional response and persistent of anxiousness in patients with PTSD. The patients re-experience and have persistent intrusive thoughts or memories of the traumatic events. The knowledge regarding the causative process of PTSD is helpful in the development of treatment for this group of patients.

Depression

Cancer is recognized as a significant psychosocial stressor and predisposes to depression. Many researchers have assessed depression in cancer patients in the past decades and the reported prevalence varies significantly because of the varying diagnosis criteria, measurement or rating scales used and differences in the study populations (21, 46-49). Based on the study by Derogatis *et al*, 6.1% of the cancer patients met the criteria for major depressive disorder (21). According to the review article by Mc Daniel *et al*, the figure was higher for cancer inpatients which is 8% and 15 to 36% for all depressive disorders (46). The prevalence also determined by the site of cancer. It is highly prevalent in oropharyngeal and pancreatic cancer but less common in gynaecological and lymphoid cancer (50).

There was a long standing debate on the diagnosis of depression in cancer patients (21). It is due to the overlapping of somatic symptoms in depression with the physiological symptoms in cancer and its treatment such as fatigue, loss of appetite and weight, sleep difficulties, poor memories and concentration. This group of symptoms was referred to as "sickness syndrome" by the recent researchers and believed to be caused by the pathophysiological process of the cancer and its treatment (51, 52). It involved the activation of immune system and proinflammatory cytokine system and lead to depression in cancer patients (51-53).

Increased level of stress hormone, cortisol and hyperactivity of the stress system were another hypothesis suggested as the pathophysiological process of depression (24,54). It is associated with the progress of cancer and affects the treatment outcome by lowering the defense mechanisms (55). It is recognized that the treatment of depression is beneficial regardless of the etiology of the "sickness syndrome" (56).

In addition, arousal (alertness vs boredom) and valence (positive vs negative) are two dimension of emotion that could predict fatigue and depression in

patients undergoing chemotherapy (57-60). This was the pathophysiologic explanation that depression is associated with stress response system.

Depressed patients were more likely to develop anxiety, fatigue and insomnia. It leads to non compliance, refusal of treatment, poor quality of life and shortened life expectancy (61, 62). A study shown that only 51.3% of breast cancer patients with concomitant depression accepted and received the proposed chemotherapy as comparing to the 92.2% of the control group (63).

It is often reported that the recognition of psychiatric need in cancer patients is poor among health care providers. There were fewer than half of the patients with cancer related depression symptoms were offered treatment (64-67). Health care providers do not prioritize mental health issues and lack of effective communication with patients is the two main reasons of under-recognition and under-treatment of depression in cancer patients (64, 65). Depression is a progressive condition and it responses better to treatment at the earliest phase because of the nature of the alteration in the neurological process (68, 69). Oncology health care providers should be more proficient in psychosocial assessment and able to detect subtle signs, monitor risk factors and reduce depression in cancer patients. Adequate management of depression required the consistent and informed involvement of health care providers and caregivers (69). This will improve the quality of care and reduce the psychological distress in cancer patients.

Conclusions

The significant experience of psychological distress among cancer patients undergoing chemotherapy should not be left unrecognized and untreated. Factors that concern the patients should be addressed accordingly, and in doing so, there may be a need for a multidisciplinary approach. Therefore, the role of the mental health team in managing cancer patients is very important.

References

1. Ridner SH. Psychological distress: concept analysis. *J Adv Nurs* 2004; 45(5): 536-545.
2. Ann MB, John LS, Jamie HVR. Principles and Practice of Palliative Care and Supportive Oncology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2007: 445-466.
3. Wilkes G. Depression. Cancer Source RN. 2003. http://www.cancersourcern.com/search/getcontent.cfm?DiseaseID=1&Contentid=16193. Accessed 20 Sept 2009.
4. Distress management clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2003; 1(3): 344-374.
5. Grassi L, Travado L, Moncayo FL, Sabato S, Rossi E, SEPOS Group. Psychosocial morbidity and its correlates in cancer patients of the Mediterranean area: findings from the Southern European Psycho-Oncology Study. *J Affect Disord* 2004; 83: 243-248.
6. Jacobsen PB, Donovan KA, Trask PC, Fleishman SB, Zabora J, Baker F, Holland JC. Screening for psychological distress in ambulatory cancer patients. *Cancer* 2005; 103(7): 1494-1502.
7. Gil F, Grassi L, Travado L, Tomamichel M, Gonzalez JR, Southern European Psycho-Oncology Study Group. Use of distress thermometers to measure psychosocial morbidity among southern European cancer patients. *Support Care Cancer* 2005; 13: 600-606.
8. Breitbart WS. Identifying patients at risk for, and treatment of major psychiatric complications of cancer. *Support Care Cancer* 1995; 3: 45-60.
9. Rieker PP, Fitzgerald EM, Kalish LA, Richie JP, Lederman GS, Eabril SD, Garnick MB. Psychological factors, curative therapies and behavioral outcomes: a comparison of testis cancer survivors and a control group of healthy men. *Cancer* 1989; 64: 2399-2407.
10. Vachon M. Psychosocial distress and coping after cancer treatment. *AJN* 2006; 106 (3) supp; 26-31.
11. Desaive P, Ronson A. Stress spectrum disorders in oncology. *Curr Opin Oncol* 2008; 20: 378-385.
12. Olafsdottir, Sjödèn PO, Westling B. Prevalence and prediction of chemotherapy-related anxiety, nausea and vomiting in cancer patients. *Behav Res Ther* 1986; 24: 59-66.

13. Watson M, Mc Carron J, Lam M. Anticipatory nausea and emesis, and psychological morbidity: assessment of prevalence among out-patients on mild to moderate chemotherapy regimes. *Br J Cancer* 1992; 66: 862-866.

14. Del Mastro L, Costantini M, Morasso G, Bonci F, Bergaalio M, Banducci S, Viterbon P, Cente P, Rosso R, Venrarini M. Impact of two different dose-intensity chemotherapy regimes on psychological distress in early breast cancer patients. *Eur J Cancer* 2002; 38: 359-366.

15. Priestman T. Coping with Chemotherapy. London: Sheldon Press; 2005; 32-41.

16. Nor Z, Hui K, Hang T, Bustam A. Prevalence of distress in cancer patients undergoing chemotherapy. *Asia-Pacific J Clin Oncol* 2007;3: 219-223.

17. Andrykowski MA, Lykins E, Floyd A. Psychological health in cancer survivors. *Semin Oncol Nurs* 2008; 24(3): 193-201.

18. Followfield FJ, Baum M. Psychosocial problems associated with the diagnosis and initial treatment of breast cancer. In: Bland KI, Copeland EM III, editors. The breast: comprehensive management of benign and malignant diseases. Philadelphia: WB Saunders: 1991: 1081-1092.

19. Dean C. Psychiatric morbidity following mastectomy: preoperative predictors and types of illness. *J Psychosom Res* 1987; 31: 385-392.

20. Mishra S, Bhatnagar S, Philip FA, Singhal V, Rana SPS, Upadhyay SP, Chauhan G. Psychosocial concerns in patients with advanced cancer: anobservational study at regional cancer centre, India. *Am J Hosp Palliat Care* 2010; 18: 1-4.

21. Derogatis LR, Morrow GR Fetting J, Penman D, Piasetsky J, Schmale AM, Henrichs M, Carnicke CL Jr. The prevalence of psychiatric disorders among cancer patients. *JAMA* 1983; 249(6): 751-757.

22. Rasmussen DM, Elverdam B. Cancer survivors' experience of time-time disruption and time appropriation. *J Adv Nurs* 2007; 57(6): 614-622.

23. Burgess C, Morris T, Pettingale KW. Psychological response to cancer diagnosis II. Evidence for coping styles (coping styles and cancer diagnosis). *J Psychosom Res* 1988; 32(3): 263-272.

24. Ronson A. Psychiatric disorders in oncology: recent therapeutic advances and new conceptual frameworks. *Curr Opin Oncol* 2004; 16: 318-323.

25. Vachon MLS, Lancee WS, Ghadirian P, Adair W. Final report on the needs of persons living with cancer in Manitoba. Toronto: Canadian Cancer Society; 1990.

26. Vachon MLS, Conway B, Lancee WS. Final report on the needs of persons living with cancer in Prince Edward Island. Toronto: Canadian Cancer Society; 1989.

27. Vachon MLS, Lancee WS, Ghadirian P, Adair W. Final report on the needs of persons living with cancer in Quebec. Toronto: Canadian Cancer Society; 1991.

28. Sanson-Fisher R, Gigis A, Boyes A, Bonerski B, Burton L, Cook P. The unmet supportive care needs of patients with cancer. Supportive Care Review Group. *Cancer* 2000; 88(1): 226-237.

29. Wise MG, Rundell JR. Psychiatric in the medically ill. The American Psychiatric Publishing Textbook of Consultation-Liaison Psychiatry. 2nd ed. Washington: American Psychiatric Publishing, Inc; 2002: 657-678.

30. Andrykowski MA, Redd WH, Hatfield AK. Development of anticipatory nausea: a prospective analysis. *J Consult Clin Psychol* 1985; 53: 447-454.

31. Andryskowski MA. Defining anticipatory nausea and vomiting: differences among cancer chemotherapy patients who report pretreatment nausea. *J Behav Med* 1988; 11: 59-69.

32. Nerenz DR, Leventhal H, Love RR. Factors contributing to emotional distress during cancer chemotherapy. *Cancer* 1982; 50: 1020-1027.

33. Altmaier EM, Ross WE, Moore K. A pilot investigation of the psychological function of patients with anticipatory vomiting. *Cancer*1982; 49: 201-204.

34. Ingle RJ, Burish TG, Wallston KA. Conditionability of cancer chemotherapy patients. *Onco Nurs Forum* 1984; 11: 97-102.

35. Jocobsen PB, Bovbjerg DH, Redd WH. Anticipatory anxiety in women receiving chemotherapy for breast cancer. *Health Psychol* 1993; 12(6): 469-475.

36. Kvale G, Hugdahl K, Asbjornsen A, Rosengren B, Lote K, Nordby H. Anticipatory nausea and vomiting in cancer patients. *J Consult Clin Psychol* 1991; 59(6)894-898.

37. Morrow GR. Clinical characteristics associated with the development of anticipatory nausea and vomiting in cancer patients undergoing chemotherapy treatment. *J Clin Oncol* 1984; 2: 1170-1176.

38. Ellis HC, Bennett TC, Daniel TC, Rickett EJ: Psychology of learning and memory. Monterey, CA: Brooks Cole Publishing; 1979: 33-34.

39. Kwekkeboom KL, Seng JS. Recognizing and responding to post-traumatic stress disorder in people with cancer. *Oncol Nurs Forum* 2001; 29(4): 643-650.

40. Miovic M, Block S. Psychiatric disorders in advanced cacner. *Cancer*2007; 110: 1665-1676.

41. Smith MY, Redd WH, Peyser C, Vogl D. Post-traumatic stress disorder in cancer: a review. *Psychooncology* 1999; 8(6): 521-537.

42. Hakamata Y, Matsuoka Y, Inagaki M, Nagamine M, Hara E, Imoto S, Murakami K, Kim Y, Uchitomi Y. Structure of orbitofrontal cortex and its longitudinal course in cancer-related post-traumatic stress disorder. *Neurosci Res* 2007 ;59(4): 383-9

43. Yehuda R. Hypothalamic-pituitary-adrenal alterations in PTSD: are they relevant to understanding cortisol alterations in cancer? *Brain Behav Immun* 2003; 17 Suppl 1: S73-83.

44. Bremner JD. Neuroimaging studies in post-traumatic stress disorder. *Curr Psychiatry Rep* 2002; 4(4): 254-263.

45. Matsuoka Y, Yamawaki S, Inagaki M, Akechi T, Uchitomi Y. A volumetric study of amygdala in cancer survivors with intrusive recollections. *Biol Psychiatry* 2003; 54(7): 736-743.

46. McDaniel JS, Musselman DL. Depression in patients with cancer: diagnosis, biology, and treatment. *Arch Gen Psychiat* 1995; 52(2): 89-99.

47. Kathol RG, Mutgi A, Williams J, *et al*. Diagnosis of major depression in cancer patients according to four sets of criteria. *Am J Psychiat* 1990; 147: 1021-1024.

48. Massie MJ, Holland JC. Depression and the cancer patient. *J Clin Psychiat* 1990; 51: 12-19.

49. Sellick SM, Crooks DL. Depression and cancer: an appraisal of the literature for prevalence, detection, and practice guideline development for psychological intervention. *Psychooncology*; 8: 315-333.

50. Noyes SR, Holt CS, Massie MJ. Anxiety Disorders. In: JC Holland (ed). Psycho-Oncology. NY: Oxford University Press; 1998; 548-563.

51. Raison CL, Miller AH. Depression in cancer: new developments regarding diagnosis and treatment. *Biol Psychiatry* 2003; 54: 283-294.

52. Kent S, Bluthe Rm, Kelley KW, Dantzer R. Sickness behaviour as a new target for drug development. *Trends Pharmacol Sci* 1992; 13: 24-28.

53. Dentzer R. Cytokine-induced sickness behaviour: where do we stand? *Brain Behav Immun* 2001; 15: 7-24.

54. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. *Biol Psychiatry* 2003; 54: 269-282.

55. Miranda CR, de Resende CN, Melo CF, Costa Al Jr, Friedman H. Depression before and after uterine cervix and breast cancer neoadjuvant chemotherapy. *Int J Gynecol Cancer* 2002; 12:773-776.

56. Yirmiya R, Weidenfeld J, Pollak Y, Morag M, Morag A, Avitsur R, Barak O, Reichenberg A, Cohen E, Shavit Y and Ovadia H. Cytokines, "Depression Due to A General Medical Condition," and Antidepressant Drugs. *Adv Exp Med Biol* 1999; 461: 283-316.

57. Kim YM, Hickok JT, Morrow G. Fatigue and depression in cancer patients undergoing chemotherapy: an

emotion approach. *J Pain Symptom Manage* 2006; 32(4): 311-321.

58. Russell JA. A circumplex model of affect. *J Pers Soc Psychol* 1980; 39: 1161-1178.

59. Thayer RE. The biopsychology of mood and arousal. NY: Oxford University Press; 1989.

60. Watson D, Tellegen A. Toward a consensual structure of mood. *Psychol Bull* 1985; 98: 219-235.

61. Lenz ER, Pugh LC, Milligan R, Gift A, Suppe F. The middle-range theory of unpleasant symptoms. An update. *Adv Nur Sci* 1997; 19(3): 14-27.

62. Redeker NS, Leu EL, Ruggiero J. Insomnia, fatigue, anxiety, depression and quality of life of cancer patients undergoing chemotherapy. *Sch Inq Nurs Pract* 2000; 14: 275-290.

63. Marco C, Mario M, Giullia P, Chris R, Anne B, Aron G. Depression and degree of acceptance of adjuvant cytotoxic drugs. *Lancet* 2000; 356(9238): 1326-137l.

64. Kadan-Lottick NS, Vanderwerker LC, Block SD *et al*. Psychiatric Disorders and Mental Helath Service Use in Patients with Advanced Cancer. A Report from the Coping with Cancer Study. *Cancer*2005; 104: 2872-2881.

65. Maguire P, Tait A, Brooke M *et al*. effect of counseling on the psychiatric morbidity associated with mastectomy. *Br Med J* 1980; 281: 1454-1456.

66. Passik SD, Dugan W, McDonald MV *et al*. Oncologists' recognition of depression in their patients with cancer. *J Clin Oncol* 1998; 16(4): 1594-1600.

67. McDonald MV, Passik SD, Dugan W *et al*. Nurses' recognition of depression in their patients with cancer. *Oncol Nurs Forum* 1999; 26(3): 592-599.

68. Lovejoy NC, Tabor D, Matteis M, Lillis P. Cancer-related depression: Part I—neurologic alterations and cognitive-behavioral therapy. *Oncol Nurs Forum* 2000; 27(4): 667-678.

69. Lovejoy NC, Tabor D, Deloney P. Cancer-related depression: Part II—neurologic alterations and evolving approaches to psychopharmacology. *Oncol Nurs Forum* 2000;27(5):795-808.

A RETROSPECTIVE ANALYSIS OF PATIENTS WITH ADVANCED RENAL CELL CARCINOMA TREATED WITH TEMSIROLIMUS

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ABSTRACT:

The clinical experience of the novel drug temsirolimus on eight patients with metastatic renal cell carcinoma and who were refractory to other forms of treatment is reported. Although none of the patients showed complete or partial response, three patients had stable disease. One patient was prematurely withdrawn due to pneumonitis. Five patients died during the period of observation of twenty months and the median survival time from start of treatment was ten months. Three patients showed no evidence of adverse events (AE). Five patients showed dyslipidemia and two had pneumonitis for which, the drug had to be withdrawn in one of them. None had significant leucopenia. We conclude that temsirolimus has activity even in heavily pretreated patients in advanced renal cell carcinoma and in addition, has the benefits of ease of administration and good tolerability. *(JUMMEC 2010; 13 (1): 19-23)*

KEYWORDS: *temsirolimus, metastatic renal cell carcinoma, adverse events*

Introduction

Renal cell carcinoma (RCC) represents 2-3% of all cancers and there appears to be a gradual increase in its incidence (1). It is often diagnosed late and distant metastases are present in more than one-third of cases. It is usually asymptomatic and the classic triad of flank pain, gross haematuria and palpable abdominal mass is now a rarity (2). A very important prognostic indicator is its stage (3). Of the histological types the clear cell type is the commonest, occurring in about 80 to 90% of cases (4).

Nephrectomy is the primary treatment of choice. But in the presence of metastatic disease conventional chemotherapy, radiotherapy or even immunotherapy are ineffective. Molecular targeted therapy is recommended (5). The first line therapy for patients with good to intermediate prognosis has been sunitinib or sorafenib. Interleukin-2 and interferon alpha alone or in combination have also been used. In patients with poor prognosis temsirolimus is recommended (6). Its effective use in advanced renal cell carcinoma has been observed in Phase 2 trials and improved survival reported in phase 3 trials (7, 8).

The main objective of the study was to assess our experience of temsirolimus in patients with advanced renal cell carcinoma who were treated in a local setting as per standard of care. In particular the objectives were three.

Firstly, it was to assess the efficacy of temsirolimus in terms of the number of patients deriving clinical benefit in a group of patients with advanced disease and who were not responsive to other treatment modalities. Secondly, to assess the incidence, type and degree of adverse events seen and thirdly, to assess the survival rate following treatment with temsirolimus in this small group of patients

Methods

The case records of eight patients with advanced renal cell carcinoma and who were treated with temsirolimus were reviewed. All patients had nephrectomies and some form of prior treatment. Such treatment included either radiotherapy, alpha-inteferon, sunitinib, sorafenib or pazopanib.

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Patients were administered intravenous temsirolimus 25mg as an intravenous infusion over no less than 30 minutes but with completion of infusion within 60 minutes. Premedication with intravenous diphenhhydramine 25 to 50 mg was given about 30 minutes prior to treatment. The treatment was repeated weekly up and until either the drug had to be stopped due to toxicity or if there was disease progression.

Clinical benefit was defined as the patient having complete response, partial response or if they remained in stable disease. No benefit was when the patient went on to progressive disease after a minimum of eight doses of temsirolimus or when the drug had to withdrawn due to toxicity. Response to treatment was assessed based on clinical grounds and where indicated, radiologically either by x-rays or CT scans.

The adverse events were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE v3.0) (9). Survival was based on all-cause mortality.

Results

There were eight patients with advanced and metastatic renal cell carcinoma who were treated with temsirolimus. Their clinical characteristics are summarized in Table 1. All had lung metastases at the time of commencement of treatment. Most had prior treatment with either interferon, sunitinib, sorafenib or pazopanib.

Table 1: *The demographic and clinical characteristics of the patients in the study*

Patient	Age (years)	Gender	Histology	Stage at diagnosis	Prior treatment	Site of metastasis at start of temsirolimus
1	57	Male	Clear cell	1	Interferon	Lungs, bone adrenal
2	31	Male	Clear cell	3	Sunitinib	Lung, bone, lymph node, adrenal
3	44	Male	Clear cell	2	Sunitinib, Sorafenib Pazopanib	Lung, lymph nodes
4	55	Male	Clear cell	3	Sunitinib, Sorafenib	Lung
5	51	Male	Clear cell	3	Radiotherapy Sunitinib	Lung, bone, adrenal
6	50	Female	Clear cell	4	Chemotherapy Sunitinib	Lung
7	46	Male	Clear cell	2	Interferon Pazopanib	Lung
8	47	Female	Clear cell	4	Interferon Interleukin Sunitinib Dendritic cell vaccine Bevacizumab Sirolimus	Lung

There were seven patients who had completed a minimum of eight doses. One patient had died after three doses were given i.e. patient number 4. In terms of response, none of the patients showed complete or partial response. However, three patients had stable disease while on treatment i.e. patient number 5, 6, and 8. The remaining four patients showed either progressive disease or died soon after eight does of the drug were given.

Of the eight patients, three showed no evidence of adverse events (AE). In the remaining five patients the number of patients affected, type, grade and outcome of the adverse events seen is summarized in Table 2. Of interest was the relatively frequent incidence of some form of dyslipidemia. All these patients were non-dyslipidemic before treatment. Also seen were two cases of pneumonitis ; in one, the drug had to be withdrawn temporarily and in the other after 20 doses were given. The implications of these findings are discussed.

Five patients died during the period of observation and their survival pattern in this group of patients is shown in Figure 1. The median survival time from start of treatment was ten months.

Discussion

Metastatic renal cell carcinoma is a therapeutic challenge because of its poor response to conventional chemotherapy and radiotherapy. Over the last few years, three agents that target critical signaling components involved in tumor angiogenesis and tumor cell proliferation—sorafenib, sunitinib and temsirolimus have been approved for use in metastatic renal cell carcinoma. While the first two agents have been recommended as first or second line treatment for all patients, temsirolimus has been recommended as first line only for patients with poor prognosis (5,6).

The results of the present study show that although none of the eight patients showed complete or partial response to temsirolimus, three patients had stable disease. It must be remembered that these patients were patients with metastatic disease and who did not respond to other treatment. Notwithstanding,

Table 2: *Adverse events seen in the patients*

Number of patients	Adverse event (AE)	Grade*	Treatment	Action to study drug	Outcome
2	Leucopenia	1	None	Continued	Resolved
2	Pneumonitis	1 & 3	Symptomatic	Stopped	Resolved
3	Mouth ulcer	1	Symptomatic	Continued	Resolved
3	Rash over arm face and neck	1	Symptomatic	Continued	Resolved
4	Hypercholesterolemia	1 & 2	Fenofibrate	Continued	Resolved
1	Deranged liver function tests	3	None	Stopped temporarily	Resolved
2	Hyperlipdemia	1 & 2	Fenofibrate	Continued	Resolved
1	Dry mouth/stomatitis	1	Symptomatic	Continued	Resolved
1	Chest discomfort	1	Symptomatic	Continued	Resolved
1	Photosensitivity	2	Avoid light/creams	Continued	Resolved
1	Facial edema	2	None	Continued	Resolved
1	Dry tongue/stomatitis	1	Symptomatic	Continued	Resolved
1	Alteration to taste	1	None	Continued	Unresolved
1	Epistaxis	1	Symptomatic	Continued	Resolved
1	Hyperpigmentation over arms and buttocks	1	None	Continued	Resolved

** 1 = mild AE; 2 =moderate AE; 3 = severe AE; 4 = life threatening or disabling AE; 5 = death related to AE*

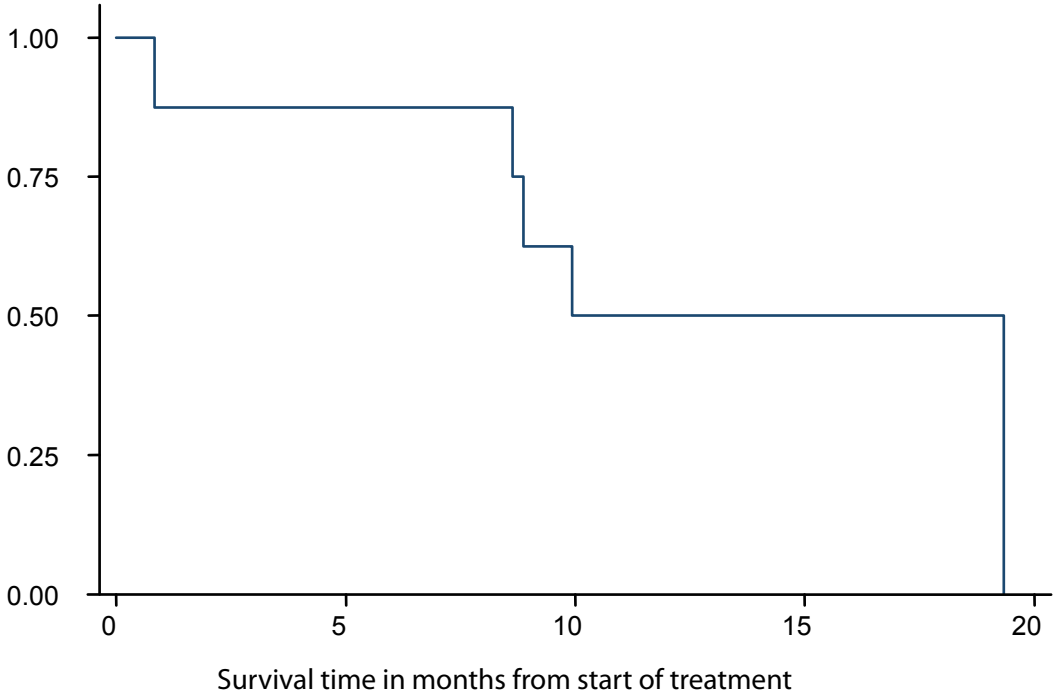

Figure 1: *Kaplan-Meier Survival pattern of eight patients*

the overall median survival rate was 10 months from commencement of treatment.

In a multicentre trial involving 626 patients with previously untreated poor-prognosis metastatic renal cell carcinoma receiving either alpha-inteferon alone, temsirolimus or a combination of the two showed that when compared to alpha interferon , temsirolimus improved the survival rate. The addition of interferon did not make any difference to the survival rate (8). Of interest was that the survival in the temsirolimus only treated group was similar to ours being close to 10.8 months .

The pharmacological action of temsirolimus is novel. It is an antineoplastic agent that acts as a selective inhibitor for mTOR(mammalian target of rapamycin) kinase (10), a signaling pathway involved in the growth and proliferation of cells. Temsilorimus, a rapamycin analogue, acts as a selective inhibitor of mTOR by binding to an intracellular protein (FKBP-12) and the protein-drug complex binds and inhibits the activity of mTOR that in turn controls cell division (11). High concentrations result in complete cell growth inhibition in vitro, whereas inhibition mediated by FKBP12/ temsirolimus complex alone results in approximately 50% decrease in cell proliferation. Inhibition of mTOR activity results in a G1 phase growth arrest in treated tumour cells resulting from selective disruption of translation of cell cycle regulatory proteins such as D-type cyclins , c-myc and ornithine decarboxylase. When mTOR activity is inhibited, its ability to phosphorylate and thereby control protein translation factors that control cell division is blocked. The anti-tumour effect of temsirolimus may also in part arise from its ability to depress levels of hypoxia-inducible factors (HIF) and vascular endothelial growth factor (VEGF) in the tumour microenvirionment and thereby impair vessel development (12).

Notwithstanding its novel pharmacological actions, like all anti-neoplastic agents, its adverse reaction may have been of concern. However, in our small sample of patients no adverse events were seen in three patients. None of the patients had significant leucopenia. The majority of the patients had only Grade 1 severity and was easily managed with supportive care. Of interest was the relative frequency of some form of dyslipdemia and interstitial lung disease. These adverse effects are known (13) and others have had similar experience (14,15)). The mechanism for hyperlipidemia remains unclear but presumably, being an mTOR inhibitor it is involved in lipid metabolism. The mechanism of development of pneumonitis is also unclear although

T-cell mediated delayed type hypersensitivity mechanism has been proposed (15). Treatment had to be discontinued in both our patients, one temporarily and the other after 20 doses were given. In the other patient with deranged liver function tests it was only temporarily withdrawn.

The recommendations are that temsirolimus be reserved as the first line only for patients with poor prognosis (6). Based on the results of our albeit small sample, we have shown that temsirolimus has activity even in heavily pretreated patients and it has the added benefits of ease of administration and good tolerability. The results of more randomized controlled trials are needed to confirm whether it has a role even in patients with good prognosis and more importantly to determine optimal sequencing of targeted agents and their role in adjuvant therapy (16).

Acknowledgements

The author has no potential conflicts of interest to disclose.

References

1. Lindbald P. Epidemiology of renal cell carcinoma. *Scand J Surg* 2004; 93: 88-96.

2. Lee CT, Katz J, Fearn PA, P R. Mode of presentation of renal cell carcinoma provides prognostic information. *Urol Oncol* 2002; 7: 135-140.

3. Patard JJ, Leray E, Rioux-Leclercq N, *et al*. Prognostic value of histological subtypes in renal cell carcinoma: a multicenter experience. *J Clin Oncol* 2005; 23: 2763-2771.

4. Eble JN, Sauter G, Epstein JI, IA S. In: Pathology and genetics of tumours of the urinary system and male genital organs. IARC Press. Lyons; 2007.

5. de Reijke TM, Bellmunt J, van Poppel H, Marreaud S, M A. EORTC-GU group expert opinion on metastatic renal cell cancer. *Eur J Can* 2009; 45: 765-773.

6. National Comprehensive Cancer Network. Practice guidelines in oncology: kidney cancer. 2009.

7. Atkins MB, Hidalgo M *et al*. Randomized Phase II Study of Multiple Dose Levels of CCI-779, A Novel Mammalian Target of Rapamycin Kinase Inhibitor, in Patients with Advanced Refractory Renal Cell Carcinoma. *J Clin Oncol* 2004; 22: 909-918.

8. Hudes G, Carducci M, Tomczak P, *et al*. Temsirolimus, interferon alpha, or both for advanced renal- cell acrcinoma. *N Engl J Med* 2007; 356: 2271-2281.

9. National Cancer Institute. Common terminology criteria for adverse events; 2006.

10. Bjornsti MA, Houghton PJ. The TOR pathway: A target for cancer therapy. *Nature Reviews/Cancer* 2004; 5: 335-348.

11. Leone M, Crowell KJ, Chen J, *et al*. The FRB domain of mTOR: NMR solution structure and inhibitor design. *Biochem* 2006; 45: 10294 -10302.

12. Abraham RT. mTOR as a positive regulator of tumour cell responses to hypoxia. *Current Topics in Microbiol Immunol* 2004; 279: 299-319.

13. Product Information (2008). Temsirolimus concentrate for injection. Wyeth

14. Duran I, Siu LL, AM O, *et.al.* Characterization of the lung toxicity of the cell cycle inhibitor temsirolimus. *Eur J Cancer* 2006; 42: 1875-80.

15. Pham PT, Pham PC, Danovitich GM, *et al*. Sirolimus associated pulmonary toxicity. Transplantation 2004; 77: 1215-20.

16. Motzer RJ, Molina AM. Targeting Renal Cell Carcinoma. *J Clin Oncol*. 2009; 27: 3274-3276.

PATTERNS OF BREAST CANCER RELAPSE AT UNIVERSITY OF MALAYA MEDICAL CENTRE

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ABSTRACT:

Despite being the major cause of cancer-related death in Malaysian women, local data on patterns of breast cancer relapse and their long term outcomes are still scarce. We conducted a retrospective study on all patients treated for non-metastatic invasive breast cancer in 1999-2000 at the University of Malaya Medical Centre (UMMC), who subsequently developed relapse. We sought to analyse the patterns of relapse, their associated clinicopathological features and the overall survival ratefollowing the relapses. Univariate and multivariate analyses were used to analyse demographics and clinicopathological factors. Survival was analysed using the Kaplan and Meier method and compared by the log rank test. A total of 268 patients with a mean age of 50, were identified for the study. At a median follow-up of 50 months, 73 patients (27.2%) had relapsed. Local, regional and distant relapse rates were 5.5%, 1.9% and 19.8% respectively, whereas, the 5-year survival rates were 61%, 40% and 21% respectively ($p < 0.01$). Most relapses occurred within the first five years of diagnosis. Patients with long disease-free interval had better survival. The most common distant relapse site was the lungs while bone was the distant relapse site with the best prognosis. Disease stage, nodal status and oestrogen receptor status were found to have correlation with the risk of relapse. We concluded that the survival of patients with relapsed breast cancer was associated with the site(s) of first relapse and the disease free interval and clinicopathological factors can be used to predict the risk of relapse. *(JUMMEC 2010; 13 (1): 24-32)*

KEYWORDS: *relapsed breast cancer, relapse site, survival*

Introduction

Breast cancer is the most common cancer affecting women in Malaysia. The third issue of the National Cancer Registry on cancer incidence in Peninsular Malaysia reported 11,952 new cases of breast cancer in 2003-2005, accounting for 31.3% of newly diagnosed cancers in women. Breast cancer was also the most common cancer in all ethnic and age groups of females above 15. The peak age-specific incidence rate was in the 50-60 years age-group (1).

Breast cancer is also the most frequent cancer in women worldwide. It accounts for 23% of all cancers. With an estimated number of 1.15 million new cases in 2002, it ranked second overall when both sexes were considered together (2). Despite the increasing trend in the incidence of breast cancer worldwide, survival has steadily improved over the recent decades. This may be explained by the development of improved treatment modalities and earlier detection as a result of effective screening programs and increased awareness among women. Nevertheless, breast cancer remains as the leading cause of death in women worldwide (3).

The aim of treating of non-metastatic invasive breast cancer is to cure. Management of breast cancer in UMMC was evidence-based and later guided by the

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Ministry of Health Clinical Practice Guidelines on 'Management of Breast Cancer' which was issued in December 2002 (4). The treatment involves a multidisciplinary team which includes breast surgeons, clinical oncologists, pathologists, radiologists and other allied health personnel.

Non-metastatic breast cancer has the tendency to relapse despite adequate curative therapy. The site(s) and the timing of relapse are important determinants of outcome in relapsed breast cancer. They also play a significant role in determining the appropriate management of the patients. Local and/or regional relapse may still be suitable for curative local treatment, whereas patients with distant relapse are usually offered systemic therapy, with palliative intent. The risk of relapse may be estimated based on the clinical and pathological risk factors. Due to this risk, patients are given long term follow-up after completing all curative treatment.

In 2006, Elder *et al*. reported the results of a study on the patterns of breast cancer relapse of 2509 patients treated at Strathfield Breast Centre (TSBC) in Australia (3). They found that most relapses occurred within the first five years of diagnosis, with the greatest risk between one to two years from primary surgery. The relapse rate was 18% and bone was the most common site of relapse. The prognosis was dependent on the timing and site(s) of relapse. Late relapses resulted in better survival compared to early relapses. They reported a 5-year survival rate of 41%, 20% and 13% for local, regional and distant relapse respectively. In patients with distant relapse, the survival rate after relapse in the bones was higher than in the viscera. Two other studies by Imkampe *et al*. and Giordano *et al*. also showed similar outcomes based on the sites of relapse (5, 6).

Furthermore, these studies also showed the important role of clinicopathological factors in determining breast cancer outcome. Higher stage, large tumour size, positive node and high tumour grade are poor prognostic factors associated with a higher risk of relapse (3, 5, 6).

In 2008, Taib *et al*. reported the survival outcome of 413 Malaysian women with breast cancer diagnosed between 1993 and 1997 at the UMMC. The objectives were to analyse the overall survival and the prognostic factors that affect survival. They suggested that ethnicity may be one of the significant prognostic factors in addition to stage, size of tumour, nodal status and tumour grade in influencing survival (7). Oestrogen receptor (ER) status was not found to be a significant prognostic factor in this study.

A study conducted at the University of Texas involving 647 patients showed that ER status had a significant effect on the rate and likely sites of relapse (8). ER negative had a significantly higher rate of relapse compared to ER positive. There was a significantly higher rate of relapse in the viscera and soft tissues in ER negative patients whereas ER positive status was associated with a higher rate of relapse in the bones.

Currently, there is no available published data on the patterns of breast cancer relapse in Malaysia. Therefore, this study was performed to analyse the patterns of breast cancer relapse and the prognosis following relapse.

Methodology

This was a retrospective study conducted on all women diagnosed with non-metastatic invasive breast cancer in UMMC between 1st January 1999 and 31st December 2000. Patients who defaulted on surgery or adjuvant treatment were excluded from the study. Those who developed relapse were selected for further analysis.

Data on patients' demography, clinicopathological factors, treatment and relapses were obtained from available records. Survival data was obtained from the National Registry of Birth and Death. Patients who did not come for follow-up were contacted to determine their current status. Uncontactable patients were deemed as 'unknown'. Staging of cancer was based on the 2002 Tumour Node Metastasis (TNM) classification of Malignant-Tumours by the American Joint Committee on Cancer (AJCC).

Site of relapse was categorized into local, regional or distant. Local relapse is occurrence of relapse either in the conserved breast or the chest wall of patients who had undergone mastectomy.

Regional relapse is disease recurring in the regional lymph nodes either in the ipsilateral axillary, supraclavicular or infraclavicular fossa. Distant or systemic relapse refers to distant metastases. Relapses were recorded according to the first or most significant site of relapse. Simultaneous local and regional disease is categorized as regional relapse while any simultaneous occurrence of distant relapse with local or regional disease was categorized as distant relapse.

Disease free interval (DFI) was defined as the time from the date of primary breast cancer surgery to the date of relapse. Overall survival was defined as the time from the date of relapse to death of any cause. Analysis of the overall survival according to site of distant relapse was carried out on patients with only one site of distant relapse. Univariate and multivariate analyses were used to analyse demographics and clinicopathological factors. Overall survival was analysed using the Kaplan and Meier method and compared by the log rank test.

Table 1: *Patient Demographics*

Variable	n=268	%
Age		
< 40	27	10.1
40-49	127	58.6
50-59	62	23.1
≥ 60	22	8.2
Ethnic group		
Malay	53	19.8
Chinese	174	64.9
Indian	37	13.8
Others	4	1.5
Tumour size		
≤ 2 cm	95	35.4
> 2 and ≤ 5 cm	139	51.9
> 5 cm	33	12.3
Unknown	1	0.4
Axillary nodes status		
Positive 1-3	82	30.6
Positive 4-9	36	13.4
Positive > 10	16	6.0
Negative	134	50.0
Histologic grade		
G1	25	9.3
G2	107	39.9
G3	80	29.9
Unknown	56	20.9
Oestrogen receptor status (ER)		
Postive	147	54.9
Negative	104	38.8
Unknown	17	6.3
Types of surgery		
BCS	72	26.9
Mastectomy	196	73.1

Results

Patient Demographics

A total of 268 patients diagnosed with non-metastatic invasive breast cancer were identified. The mean age was 50 (range 26-81). Chinese ethnic group scored the highest incidence rate followed by Malay and Indian. The most common tumour size was between 2 and 5cm. Half of the population had positive axillary lymph node involvement at diagnosis. The most prevalent tumour grade was grade 2 followed by grade 3 and grade 1. More than 50% of the patients were ER positive. Majority of patients underwent mastectomy (73.1%) while the remainders had breast conservation surgery (BCS) (Table 1).

Following BCS, only 81.9% had adjuvant radiotherapy (RT) to the conserved breast whereas half of the patients who underwent mastectomy received adjuvant RT. Most patients received adjuvant systemic therapy which included either chemotherapy or Tamoxifen or both (Table 2).

Table 2: *Types of adjuvant therapy*

Adjuvant treatment	Types of surgery	
	BCS n = 72(%)	Mastectomy n = 196 (%)
Radiotherapy	59 (81.9)	132 (67.3)
Systemic therapy #	65 (90.3)	186 (94.9)

Note: Some patients received both radiotherapy and systemic therapy for adjuvant treatment, hence the total percentages are greater than 100%.

Includes chemotherapy and tamoxifen

Patterns of relapse

At a median follow up of 50 months (range 5 -107 months), 73 patients (27.2%) developed

relapse. A total of 15 patients (5.5%) had local relapse, 5 patients (1.9%) had regional relapse and 53 patients (19.8%) had distant relapse. Within the distant relapse category, 22 patients (41.5%) had more than one site of relapse and lung was the most common site of distant relapse (47.2%) (Table 3 and 4).

The median DFI was 29 months (range 1-92 months). The relapse rate was 3.7% at 12 months after surgery, peaked to 9.7% at 24 months and later declined to 2.4% at 36 months. The risk of relapse declined steadily after five years to less than 5.0%, as shown in Figure 1.

Clinicopathological factors associated with relapse

Logistic regression analyses showed that stage, axillary node and oestrogen receptor status had statistically significant correlation with relapse, with p=0.001, p=0.001 and p=0.042, respectively. The data are illustrated in Table 5 below (Table 5).

Table 3: *Relapse rate*

Sites of relapse	n = 268	%
Not relapse	195	72.8
Relapsed	73	27.2
Local relapse	15	5.5
Regional relapse	5	1.9
Distant relapse	53	19.8

Table 4: *Number of relapse according to sites of distant relapse*

Sites of distant relapse	Number of patients	%
Bone	24	45.3
Lung	25	47.2
Liver	8	15.1
Brain	9	16.9
Others	9	16.9

Note: Patients may have more than one site of distant relapse, hence the total percentage is greater than 100%.

*Other sites involved were ovary, peritoneum and adrenal gland

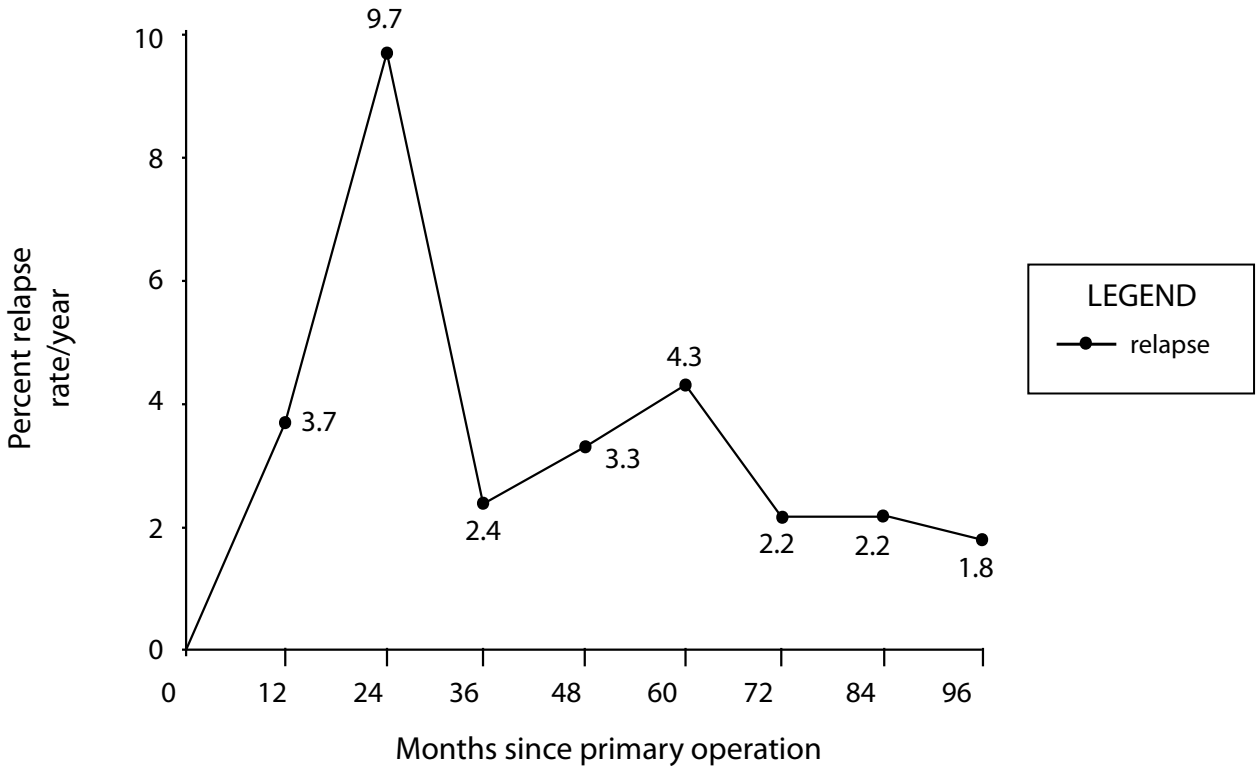

Figure 1: *Yearly risk of relapse after primary surgery for breast cancer*

Overall Survival

Overall survival according to disease free interval

More than half of the relapses (56.2%) occurred within the first 36 months after primary surgery. This duration was subsequently chosen to differentiate between short (less than 36 months) or long (more than 36 months) DFI in this study population. Short DFI resulted in lower overall survival rate than long DFI ($p < 0.001$) (Figure 2).

Overall survival according to sites of relapse

Patients with only local relapse had the best prognosis with a 5-year overall survival of 61% compared to patients who developed regional or distant relapse with 40% and 21% 5-year overall survival rate respectively ($p < 0.01$) (Figure3).

Overall survival according to sites of distant relapse

Two-year overall survival rate for patients with bone metastasis only was 61% compared to 20% in those with lung metastasis. None of the patients with liver or brain metastasis were alive at 2 years while patients with relapse at other sites had 2-year overall survival of 50% (Figure 4).

Discussion

This study involved 268 patients with the mean age of 50 years (range 26-81 years). The highest incidence was in the Chinese ethnic group and this is consistent with the Malaysian NCR 2003-2005 report (1).

Approximately 18.1% of patients who had BCS in this study population did not receive adjuvant RT, either due to patients' refusal or reasons unknown. RT to the residual breast is a standard indication after a BCS to reduce the risk of relapse in the conserved breast. Two thirds of the patients who had mastectomy received RT. Of particular note was the high proportion of systemic treatment given following the BCS (90.3%) or mastectomy (94.9%). These figures are higher than as compared to the study done by Elder *et al*. which reported 62.7% of BCS and 70.7% of mastectomy patients receiving systemic treatment (3). This may be explained by the larger proportion of

Table 5: *Number of relapse according to clinicopathological factors of primary tumour*

Characteristics	Total no. of patients (X) n = 268	No. of patients with relapse (Y) n = 73	Percentage Y/X x 100%
Stage			
1	69	12	17.4
2	121	27	22.3
3	78	34	43.6
Tumour size			
≤ 2 cm	95	20	21.1
> 2 and ≤ 5 cm	139	39	28.1
> 5 cm	33	14	42.4
Unknown	1	0	0.0
Axillary node status			
Node positive	134	48	35.8
Node negative	134	25	18.7
Tumour grade			
Grade 1	25	5	20.0
Grade 2	107	30	28.0
Grade 3	80	30	37.5
Unknown	56	8	14.3
Oestrogen receptor status			
Positive	147	34	23.1
Negative	104	37	35.6
Unknown	17	2	11.8

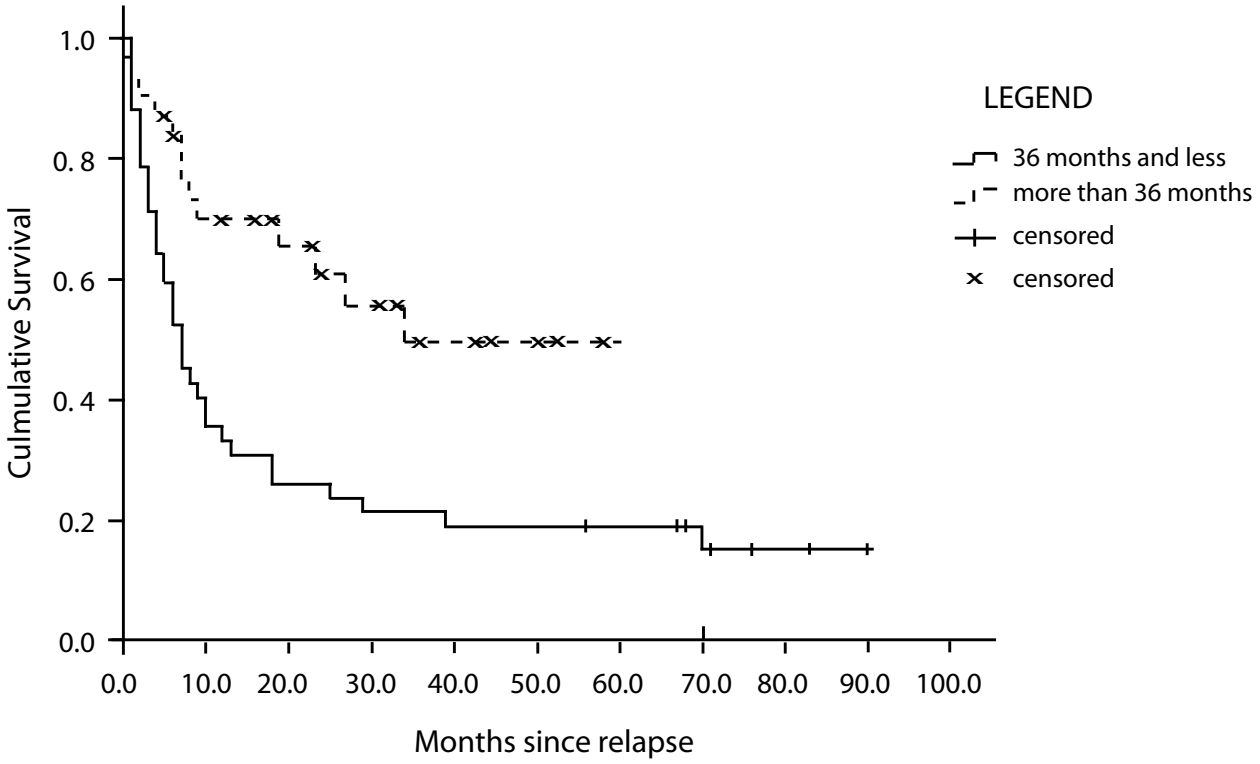

Figure 2: *Overall survival according to disease free interval*

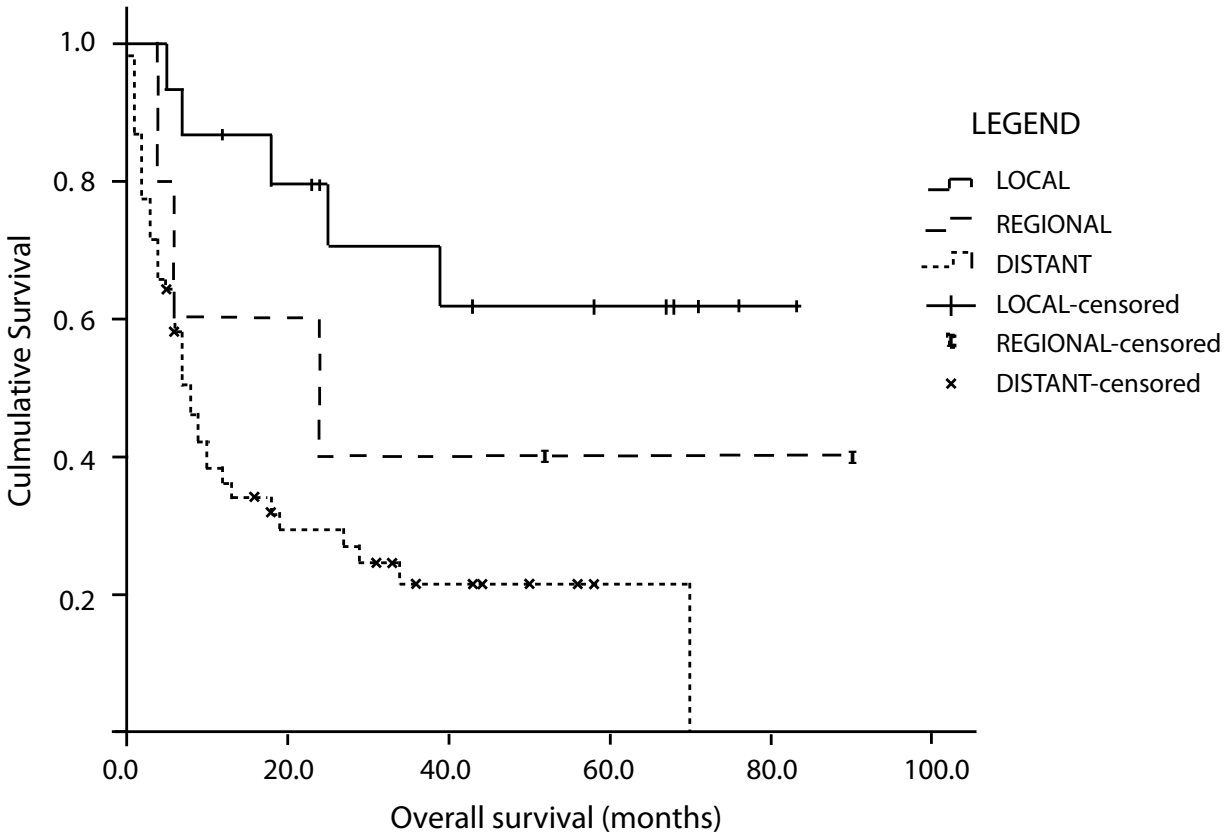

Figure 3: *Overall survival according to sites of relapse*

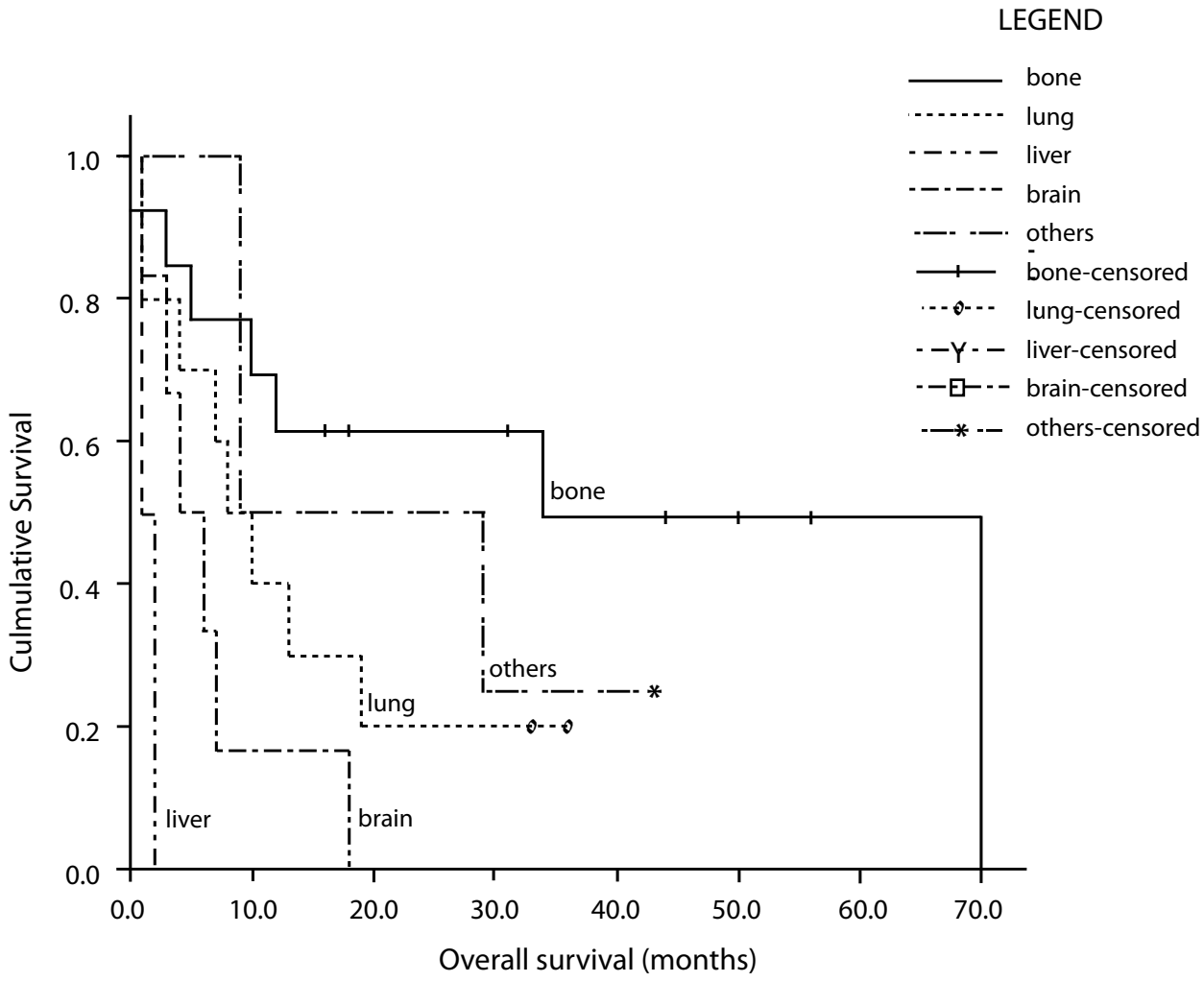

Figure 4: *Overall survival according to sites distant relapse.*

Note: Analysis was done on patients with only one site of distant relapse.

patients with higher stage disease in this study who require adjuvant systemic treatment. Furthermore, more than half of the study population had ER positive disease and therefore received tamoxifen as part of the systemic treatment.

The relapse rate in this study was 27.2% with local, regional and distant relapse rates of 5.5%, 1.9% and 19.8% respectively. Elder *et al*. reported a lower relapse rate of 18% with local, regional and distant relapse rates of 4.9%, 1.0% and 11.4% respectively (3). The higher relapse rate seen in our patients may be explained by more patients with higher stage disease who were at a higher risk of developing relapse. Stage 3 disease in this study was 29.0% compared to 3.9% from the study by Elder *et al* (3). The most common site of distant relapse was the lung which accounted for 47.2% of cases followed by bone, liver, brain and other sites.

Majority of relapse occurred within the first five years from primary surgery, in agreement with published data (3). The highest risk of relapse was between one to two years from surgery (9.7%) and beyond five years, the risk of relapse decreased steadily. The median DFI in this study was 29 months. If patients have not relapsed within the first five years of surgery, the likelihood of relapsing thereafter is very small. However, patients with a history of breast cancer suffer excess mortality for more than 30 years after surgical therapy (9).

Similar to the findings by Elder *et al*. and Imkampe *et al* (3, 5), tumour stage, axillary node involvement and oestrogen receptor status were found to have statistically significant correlation with relapse in this study. Patients with higher tumour stage, positive nodes and oestrogen receptor positive status were more likely to relapse. However, the correlation between tumour grade and relapse was not significant, (p=0.07). This could be due to high proportion of unknown grade (14.3%) in the relapsed cases in this study population and the reasons for this was unclear.

DFI was an important prognostic factor for breast cancer relapse. Patients who had relapse after 36 months had better survival rate than those who relapsed earlier. The difference in survival was statistically significant ($p < 0.001$) and consistent with other studies (3).

Patients with local relapse had better prognosis compared to regional and distant relapse. The five-year overall survival for patients with local, regional and distant relapse were 61%, 40% and 21%, respectively. The overall survival was higher compared to the study by Elder *et al*. which quoted 41% for local relapse, 20% for regional and 13% for distant relapse (3). There were 11 patients (15.1%) who did not come for follow-up and were not contactable. Therefore, they were deemed as 'unknown'. This could be one of the reasons for the overall higher survival rate seen in this study. Another reason could be due to effective treatment delivered to patients with relapse but this needs further studies to confirm. For those with local relapse, about 66% had salvage surgery and they were still alive until the end of the study. This may explain the relatively good overall survival for local relapse.

Bone metastases had better prognosis than visceral metastases (3, 5). In this study, two-year overall survival for bone metastases was 61%, lung metastases was 20% and 0% for those with liver and brain metastases. The reasons for the relatively better prognosis of bone metastases are still unclear. A randomized study looking at the clinical course of bone metastases for breast cancer reported that bone metastases were more common in receptor positive or well differentiated tumours which are associated with better prognosis (10).

Limitations and Recommendations

This was a retrospective study, therefore, the documentation in the case notes were not standardised and some data were missing or incomplete. The study sample was relatively small compared to other studies.

To ensure more reliable and accurate data, a prospective study with larger sample size, longer duration and a longer follow-up is recommended. A mechanism which allows a continuous data collection through a prospective database, either at an international or a national level, would be beneficial.

Conclusions

Most relapses occur within the first five years of diagnosis and patients with late relapse have better survival than early relapse. Survival of patients with relapsed breast cancer is associated with the site of first relapse. The prognosis is better for local and regional relapse compared to distant relapse. Clinicopathological factors are useful to predict risk of relapse in patients with breast cancer after completing treatment.

Disease relapse is one of the worries faced by patients with breast cancer after completing their curative therapy. Data on patterns of relapse and its prognosis is both important and useful to clinicians when discussing long term outcome with the patients. This is the first study to provide data on breast cancer relapse in Malaysia. The results will be an invaluable information for our clinicians in the management and counselling of patients with breast cancer.

Acknowledgements

I would like to thank Professor Yip Cheng Har and Associate Professor Nur Aishah Mohd Taib from the Department of Surgery, Faculty of Medicine, University Malaya Medical Centre (UMMC), for their help in providing the UMMC Breast Cancer Prospective Database for this study.

References

1. Lim GCC, Halimah Y, Rampal S. *Cancer Incidence in Peninsular Malaysia, 2003-2005. The Third Report of the National Cancer Registry, Malaysia.*

2. Parkin MD, Bray F, Ferlay J, Pisani P. 2005, 'Global Cancer Statistics, 2002', *CA Cancer J Clin*; 55: 74-108.

3. Elder EE, *et al*. Patterns of breast cancer relapse. *EJSO* 2006; 32: 922-927.

4. MOH Clinical Practice Guidelines of *'Management of Breast Cancer'*, Dec 2002.

5. Imkampe A, *et al*. The significant of the site of recurrence to subsequent breast cancer survival. EJSO 2007; 33: 420-423.

6. Giordano SH, *et al*. Is breast cancer surviving improving? *Cancer* 2004; 100: 44-52.

7. Taib NA, Yip CH, Ibrahim M. Survival Analyses of 413 Malaysian Women with Breast Cancer: Results from the University Malaya Medical Centre. *Asian Pac J Cancer Prev* 2008; 9(2): 197-202.

8. Hess KR, *et al*. Estrogen receptors and distinct patterns of breast cancer relapse. *Breast Cancer Res Treat* 2003 Mar; 78(1):105-118.

9. Hibberd AD, Horwood LJ, Wells JE. Long term prognosis of women with breast cancer in New Zealand: study of survival to 30 years. *Br Med J (Clin Res Ed)* 1983; 286: 1777-1779.

10. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. *Br J Cancer* 1987; 55: 61-66.

COUNSELLING CHANGES IN SEXUAL FUNCTIONING FOR WOMEN WITH BREAST CANCER

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ABSTRACT:

As women with breast cancer are living longer, issues beyond survivorship like the much neglected sexual functioning and issue of quality of life have become increasingly important. Experiences of significant alterations in sexual functioning need to be addressed. However, these sexual issues are often not acknowledged in our traditional medical model of health care delivery. This paper briefly reviews the changes in sexual functioning after a diagnosis of breast cancer, with implication for clinical practice and medical curicula. *(JUMMEC 2010; 13 (1): 33-37)*

KEYWORDS: *sexuality, oncology, counseling*

Introduction

With over 100 years of research, it is now well known that breast cancer is a disease driven by hormones, genetics (sex, body compositions, genes), and lifestyle (1). Studies showed that there is a rapid increase in incidence rates of breast cancer before menopause (ages 40–50) and then a decline in rates (2). Women are now living longer with breast cancer, and may be dealing with numerous intimacy-, relationship-, and sexuality-related issues, including those related to reproduction (3), especially so for younger women (4, 5). The prevalence age of breast cancer onset amongst Malaysian women are generally younger at 40-50 years compared to developed countries.

Sex plays an important role, beside its basic function for procreation, in enhancing interpersonal relationships, and building a more intimate, meaningful bond. Managing the medical tasks, and the modifiable factors (like diet, weight, physical activity) are important (2, 6, 7-10), but these should be complemented with patient self management of emotional tasks as well as role and relationships. American Cancer Society found that cancer survivors were not pursuing healthy lifestyles (11), and equally important, they need to pursue happy lifestyle behaviors. In fact, evidence shows that having a general feeling of happiness and optimism has a "protective effect" on the etiology of breast cancer (OR-0.75, 95% CI:0.64-0.86) (12). In short, issues of sex and sexuality are integral components of human behavior, adding romance, enjoyment and enhancing the quality of life of women. However, in the traditional Asian clinics, sexuality is still neglected, and/or takes a back seat to cancer treatment and survival issues in people with cancer. Even in the more developed Asian countries, like Japan, a study on breast cancer patients (n=102) found that discussing body image and sexuality were disregarded in therapeutic decision-making situations (13).

Cancer treatment and altered sexual functioning

Normal aging, by itself can greatly impair the sexual functioning of humans. Sexuality amongst men have gained a bit more attention where hypothetical surveys even suggest that men express a willingness to trade away survival time just so they can preserve or improve their sexual function (Singer PA, Tasch ES, Stocking C, *et al* 1991). Studies show an increase incidence of erectile dysfunction in men without cancer, up to threefold between the fifth and eighth decades of life (Feldman HA, Goldstein I, Hatzichristou DG, *et al* , 1994), whilst one-third of older men report experiencing a significant impairment in sexual function (Litwin, 1999). Do women have the same significant concerns and issues of sexual functioning? Studies have

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documented that approximately 50% of women who have experienced breast or gynecologic malignancy have serious concerns regarding sexual functioning (14), whereby sexual complaints can occur in up to 90% of women with a history of a cancer diagnosis (15). It appears that a diagnosis of breast cancer have further compounded whatever negative impact of normal aging on sexual functioning of women. One study found that sexual functioning of women (n=558) who received chemotherapy compared to those who did not, regardless of the type of surgery ($p<0.001$) was significantly affected (16). Many women are distressed by treatment-related sexual function or fertility-related adverse effects of treatment, but they are reticent to bring up the topic of sexuality given their lack of experience and low self-confidence, especially among the younger women (17).

Specifically, breast reconstruction has been shown to be associated with loss of breast sensation (18), whilst both mastectomy (with or without reconstruction) and lumpectomy were associated with altered body image; potentially affecting sexuality (18, 19), a decrease in perceived sexual attractiveness and reduced sexual interest (20). Radiation therapy causes changes in breast sensation, fatigue or arm mobility. (21), whilst Tamoxifen therapy is linked to pain, discomfort and vaginal tightness during intercourse (22). Women undergoing chemotherapy have experienced ovarian failure, hormonal changes, menstrual cycle disruption, amenorrhea, vaginal dryness and atrophy, and decreased sexual arousal and desire (23).

The issues of sexual dysfunction amongst women

In four focus groups conducted with Malaysian women living with breast cancer (n=39), a rising theme was on the neglect of sexuality issues (24). In one of the groups, the women were quite open about their intimate relationships with their husband. This dispels the notion that Malaysian women in general are reluctant to talk about their private lives. However, as this was not typical in all groups, the use of focus groups may have led to their openness regarding the topic. These women's expressions negate the current belief that patients do not want to discuss about sexual issues. Sexuality and intimacy were two main role-related themes that emerged consistent as an unmet need across the groups. In general, the women felt that their intimate relationships were affected to some extent, but they felt the main reason was 'within themselves' rather than with their spouse whom they reported as being 'encouragingly supportive'. Some women seek clarifications and asked, 'Can we still have sex?' - as if sex after breast cancer will bring about detrimental consequences either on themselves or their spouse. In fact, one spouse of the informant came forth with his query on the toxicity of chemotherapy during sexual act of intimacy. While some utterances from the women may seem to be exaggerated, this issue of sexual concerns does seem to weigh heavily on both the survivors and their spouse's minds. Myths surrounding the issues of intimacy, chemotherapy and sexuality were not uncommon across the groups. Factors like age and side effects of hormonal treatment causing dryness; (including myths that too much excitement can trigger the cancer cells, and toxicity of chemotherapy can 'travel' to their spouse during sexual intercourse) were revealed (24). Acute or chronic sexual function problems resulting from treatments such as mastectomy, lumpectomy, radiation, and chemotherapy are not uncommon. The excerpt below highlights some examples of common myths related to chemotherapy and cancer.

"My husband believed that with chemotherapy, I have the toxins all over my body, so it's better not to have it (sexual intercourse)".

"I heard that cancer patient cannot have too much sex because I heard that sexual excitement can lead to recurrence, and I want to know if it's true or not?"

Cancer is a debilitating illness. It robs years from life and life from years because it traumatizes and detracts confidence, self-image, feelings of worth and pride, and the sense of normalcy from the survivors' daily functioning. One study examining the sexual problems of women below 50 years (n=209), revealed specific problems in four areas (lack of interest in sexual activity, difficulty in becoming aroused, difficulty relaxing and enjoying sex, and difficulty achieving orgasm), with a lack of interest being the main challenge (25). These needs are critical but have been ignored in our traditional medical model care delivery system. Sexual functioning, like other functioning, needs to be viewed as fundamental to health and quality of life. Thus, management of cancer care must be emphasized as incomplete without full attention to

the women's personal responses and experiences to illness, including sexual function. However, literature shows that hormonal and pharmacological therapies have been marketed to treat sexual desire and arousal disorders, and many if not none have been approved by the FDA nor have any been proven effective by clinical trials (26)

Counseling Sexual Issues With women

Psycho-behavioral intervention is a key part of the comprehensive sexual dysfunction treatment schema. In order for it to be comprehensive, an educational program that fosters open discussions regarding concern is a start. Healthcare professionals are often too embarrassed or feel ill-equipped to discuss sexual issues and patients are too embarrassed to ask (27). These issues of sexual functioning are often viewed as a difficult issue to handle when caring for patients. The topic is often absent from the curricula of most medical and health schools, as well as residency programs and fellowships program. This may explain why many healthcare professionals feel ill-equipped to address issues of sexuality during the course of routine health care and in the management of women with cancer. Any changes, for it to take effect, must target at the policy levels and to ensure health intervention are sufficiently broad based to address the vast needs (including addressing issues related to cultural myths) of the service users. It is especially pertinent to discuss sexuality issues with women – at before, during, and after cancer treatment. Therapists and health professionals in the oncology community need to sharpen their diagnostic and therapeutic skills in this area of sexuality counseling.

Counseling with survivors of breast cancer may start with the broad range of sexual function concerns that survivors as a group may experience, including fear and myths, genital pain, lack of lubrication, satisfaction, arousal, and desire, and then ask if the survivor has questions about any of these or would like information or referrals for additional information. Strategies like local non-medicated, non-hormonal vaginal moisturizers including vitamin E suppositories agents, used two to three times weekly, can provide alternative relief for the symptoms of vaginal atrophy by maintaining the elasticity and pliability of the vaginal mucosal lining (28). Sexual function, body image, and relationship problems experienced by women due to breast cancer and cancer treatments may be addressed via individual and interpersonal counseling (29). A sensitive, open-minded, and forthright attitude about issues of sexual functioning is timely when caring for women with breast cancer. Sexual counseling helps normalize the experience of sexual problems after cancer treatment, and can be effectively conducted in group work and/or further one-to-one intervention if needed. Conscious effort must be made to allow patients a safe environment to vent their fears, and provide the reassurance needed. A sexual psycho educational program in an oncology setting is necessary to provide comprehensive care to the patient. There is much to learn from the field of counseling which is deeply rooted in social-humanistic sciences. Overall, a bio-psychosocial model of care, in place of the stifle, traditional-hierarchical medical model of care can provide the foundation for addressing the much neglected aspect of sexual functioning amongst patients.

Conclusion

Breast cancer affects quantity and quality of life and every aspect of functioning, including sexual influences, the ultimate goal being to facilitate the readjustment of women towards independent functioning and meaningful living despite a diagnosis of breast cancer. In addressing the unmet sexual needs of women and providing counseling about changes in sexual functions, as well as therapeutic tips to enhance sexuality, healthcare professionals must be aware that they are treating the patient as a whole and not just the cancer.

Acknowledgements

The paper draws from the phase 1- qualitative study on the SAMA project funded by MAKNA and University Malaya Fundamental grant. The authors expressed deep gratitude to women who came forward to participate in the focus groups

References

1. Washbrook, E. Risk factors and epidemiology of breast cancer. *Women's Health Medicine* 2006; 3(1): 8-14.

2. Bray F, McCarron P, Parkin D. The changing global patterns of female breast cancer incidence and mortality. *Breast Cancer Research* 2004; 6(6): 229-239.

3. Walsh S, Manuel J, Avis N. The impact of breast cancer on younger women's relationships with their partner and children. *Fam Syst Health* 2005; 23: 80-93.

4. Avis N, Crawford S, Manuel J. Psychosocial problems among younger women with breast cancer. *Psycho-Oncology* 2004; 13(5): 295-308.

5. Bakewell RT, V DL. Sexual dysfunction related to the treatment of young women with breast cancer. *Clin J Oncol Nurs* 2005; 9: 697-702.

6. Stuart K, *et al*. Life after breast cancer. *Australian Family Physician* 2006; 35(April 2006): 177-258.

7. Rock C, Demark-Wahnefried W. Can lifestyle modification increase survival in women diagnosed with breast cancer? *J Nutrition* 2002; 132(11): 3504S.

8. Goodwin P, Boyd N. Body size and BC prognosis: A critical review of the evidence. *Breast cancer Res Treat* 1990; 16: 205-215.

9. Ziegler R, HooverR. Migration patterns and Breast cancer risk in Asian American woman. *J Nat Cancer Institute* 1993; 85: 1819-1827.

10. Deapen D, *et al*. Rapidly Rising Breast Cancer Incidence Rates Among Asian-American Women. *Intl J Cancer* 2002; 99 (3): 747-750.

11. Blanchard C, Courneya K, Stein K. American Cancer Society's SCS-II. Cancer survivors'adherence to lifestyle behavior recommendations and associations with health-related quality of life. *J Clin Oncol* 2008; 26(13): 2198-2204.

12. Peled R, *et al*. Breast cancer, psychological distress and life events among young women. *BMC Cancer* 2008; 8(1): 245.

13. Adachi K, *et al*. Psychosocial factors affecting the therapeutic decision-making and postoperative mood states in Japanese breast cancer patients who underwent various types of surgery: body image and sexuality. *Jpn J Clin Oncol* 2007: hym041.

14. Andersen B. How cancer affects sexual functioning. *Oncology (Huntingt*.) 1990; 4: 81-94.

15. Anderson B, Woods X, Copeland L. Sexual self-schema and sexual morbidity among gynecologic cancer survivors. *J Consult Clin Psychol* 1997; 65: 221-229.

16. Ganz P, *et al*. Quality of life at the end of primary treatment of breast cancer: first results from the moving beyond cancer randomized trial. *J Natl Cancer Inst* 2004; 96(5):376-387.

17. Wenzel L, *et al*. Age-related differences in the quality of life of breast carcinoma patients after treatment. *Cancer* 1999; 86: 1768-1774.

18. Wilmoth M, Ross J. Women's perception: breast cancer treatment and sexuality. *Cancer Pract* 1997; 5: 353-359.

19. Schover L, Yetman R, Tuason L. Partial mastectomy and breast reconstruction: A comparison of their effects on psychosocial adjustment, body image, and sexuality. *Cancer* 1995; 75: 54-64.

20. Al-Ghazal S, Fallowfield L, Blamey R. Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. *Eur J Cancer* 2000; 36: 1938-1943.

21. Bakewell R, Volker D. Sexual dysfunction related to the treatment of young women with breast cancer. *Clin J Oncol Nurs* 2005; 9: 697-702.

22. Mortimer J, *et al*. Effect of tamoxifen on sexual functioning in patients with breast cancer. *J Clin Oncol* 1999; 17: 1488-1492.

23. Knobf M. The menopausal symptom experience in young mid-life women with breast cancer. *Cancer Nurs* 2001, 24: 201-210.

24. Loh SY, *et al*. Perceived barriers to self management in Malaysian women. *AP J Pub Health* 2007; 19(3): 53-57.

25. Burwell S, *et al*. Sexual Problems in Younger Women after Breast Cancer Surgery. *J Clin Oncol* 2006; 24: 2815-1821.

26. Manson J, *et al*. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2002; 239 (6): 523-543.

27. Turns D. Psychosocial issues: pelvic exenterative surgery. *J Surg Oncol* 2001; 76:224-236.

28. Amsterdam A, Krychman M. Sexual function in gynecologic cancer survivors. *Expert Rev Obstet Gynecol* 2008; 3(3): 331-337.

29. Lev E. Counseling women with breast cancer using principles developed by Albert Bandura. *Persp Psych Care* 2000; 36(4): 131-138.

BREASTFEEDING PRACTICES IN A RURAL COMMUNITY IN KEDAH

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ABSTRACT:

Breast feeding has been actively encouraged in Malaysia in the last few years in all public hospitals. This study proposes to find out the prevalence of breast feeding in three villages in a rural community in Kedah, Malaysia. This was a cross sectional study on breastfeeding practices in Kubang Pasu, a district of Kedah. Majority of the mothers initiated breast feeding but exclusive breastfeeding was only 21% for four months and predominant breastfeeding was about 12.6%. The breastfeeding practice was more prevalent among women from the higher educational strata and higher income than those from the lower strata and lower income ($p<0.05$). Mothers with a positive attitude on breastfeeding and those who possess a higher knowledge were associated with a longer mean total duration of breastfeeding ($p<0.05$). Spouse and family members played an important role in building up a mother's confidence to breast feed her child. Majority of the mothers received breast feeding information before birth from mainly the doctors and nurses. Older mothers, house wives and mothers with formal education practiced a longer duration of breast feeding ($p<0.05$). The study also showed that there is an increase in the knowledge of breast feeding among the mothers and that they have a positive attitude to breastfeeding. Most of the mothers initiated breast feeding early and they received support on breastfeeding from the nurses and doctors. *(JUMMEC 2010; 13 (1): 38-44)*

KEYWORDS: *exclusive breastfeeding, predominant breastfeeding, rural Malaysia*

Introduction

Feeding practice during infancy is an important determinants of future physical and mental well-being because of rapid growth spurt and developmental of organ and tissue occurring during the first year of life (1, 2). They vary with socio-economic stratification and are regulated by a variety of factors such as education, custom beliefs and taboos (1, 3). Breastfeeding is the optimal feeding practice for infants in view of its benefits to both children and mothers. The advantages of breastfeeding include fulfilling the nutritional needs of infants, immunological protection, bacteriologic ally safe, minimal allergic reaction, economical, mother to child bonding, increased birth spacing and many others (4, 5). UNICEF estimated that, if every baby was exclusively breastfed from birth up to 6 months, 1.5 million lives would be saved each year (6, 7). Thus in 1981 the World Health Organization (WHO) introduced the code of ethics to safeguard the marketing practices which are detrimental to breastfeeding.

The WHO Global Data Bank on Breastfeeding presently covers 94 countries and 65% of the world's infant population (<12 months). Based on the latest data, it is estimated that 35% of these infants are exclusively breastfed between 0-4 months of age. In South-East Asia, the ever-breastfed rate has increased somewhat in recent years, for example in Thailand it increased from 90% in 1987 to 99% in 1993. The increase in exclusive breastfeeding rates is due mainly to breastfeeding campaigns, and additional Baby-friendly Hospitals and trained breastfeeding counselors (8)

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In Malaysia, active national promotion on breastfeeding began since 1976. Early local studies documented that breastfeeding is widely practiced in rural areas, particularly among Malay mothers (9, 10, 11, 12). Recent findings from Sarawak reported that more children are being breastfed than in earlier decades. However, the median duration of breastfeeding is similar to that of earlier researches in Peninsular Malaysia i.e. 3 months (13).

This purpose of this study is to assess the prevalence of breastfeeding practices among women of reproductive age (15–49 years old) in three selected rural villages in Kubang Pasu District, Kedah and also to investigate the relationship between the attitude of the mother towards breast feeding and the duration of breast feeding.

Materials and Methods

This was a cross sectional descriptive study on practices of breastfeeding and it was conducted in three rural areas, namely Kampung Keda Wang Tepus, Kampung Changkat Setol and Felda Bukit Tangga in Kubang Pasu, Kedah. The kampungs were selected due to the cloosness to the health centres. The selection criteria may have introduced a bias in the study. The study was conducted from 8-15 June 2005. The inclusion criteria for our sample was women in their reproductive age (15 – 49 years old) with at least one living child aged two years old, regardless of their marital status. Every woman was randomly selected from a household who fulfilled the criterion was included in the study. A household may report one or more respondents. However, women who were unable to breastfeed due to serious illnesses (heart disease, cancer, nephritis, and active or untreated TB, HIV or AIDS, active herpes lesions on the breast and severe malnutrition) were excluded from this study. The interview was a face-to-face using a structured questionnaire. The questionnaire was pre-tested at the Obstetric & Gynaecology and Paediatrics Wards in Hospital Tengku Ampuan Rahimah, Klang to minimise errors. Errors related to the understanding of ever breast fed, exclusive breast fed were modified so that the mother understood their meaning. Despite this there were problems for the mothers to understand as some of them were uneducated. The collected data was then coded, computed and analysed using the SPSS version 10. The knowledge on breastfeeding among the respondents was assessed based on a list of 12 true-or-false statements. These statements were further categorized into 3 categories namely benefits of breastfeeding (5 statements), techniques of breastfeeding (4 statements) and contraindications of breastfeeding (3 statements). The Chi-square test was used to determine the associations and the level of significance was set at $p<0.05$.

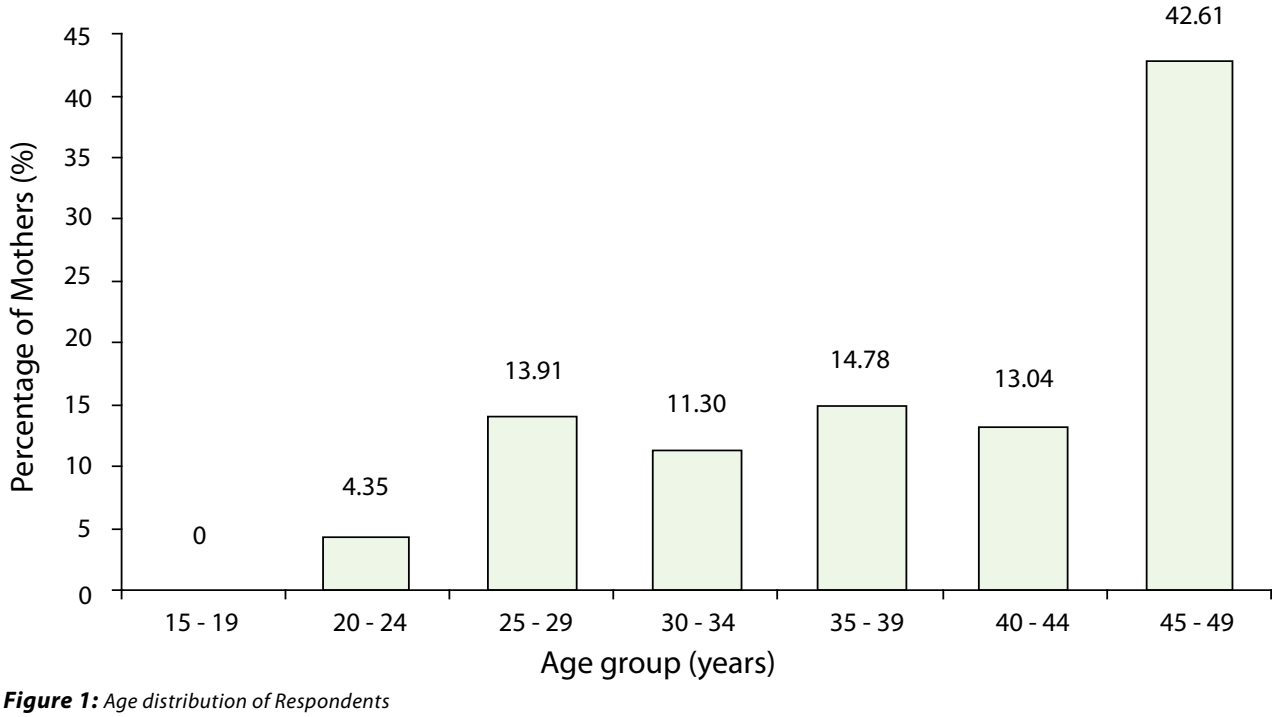

Figure 1: *Age distribution of Respondents*

Results

There were 115 mothers who fitted the inclusion criteria and they were interviewed face to face. Majority of the mothers 111 (96%) respondents were married. Only 3% of them were widowed and one respondent was a single mother. Figure 1 shows that the age distribution of female respondents who fall within the reproductive age group of 15 to 49 years old. The majority of mothers 49 (42.6%) were aged between 45 to 49 years age group. Mothers aged between 35 to 39 years comprised 17 (14.8%) of the study population, followed by the age group of 25 to 29 years 16 (13.9%), 40 to 44 years 15 (13.0%), 30 to 34 years 13 (11.3%) and 20 to 24 years 5 (4.4%).There were no young respondents aged between 15 to 19 years. All respondents interviewed were Malays since they were from a rural area in Kedah.

Most of the respondents 43 (37%) had primary level of education. This was followed by lower secondary 28 (24%) and upper secondary level education 23 (20%). Meanwhile, a total of 16 (14%) respondents were not educated formally or only had informal education. Only 6 (5%) received tertiary education. More than half of the respondents 69 (60%) were unemployed. This group included a majority of homemakers, which is not uncommon in a kampung setting. A total of 24 (21)% of the total study population were employed. Self-employed respondents were those that involved in home businesses e.g. seamstress. They made up of about 22 (19 %) of the study population.

The mean income per capita for the study population was RM206. In Figure 2 about 75 (54.8%) of the study population was found to have an income per capita of below RM 200. In contrast, there was only 2 (1.74%) who earned between RM600 and RM800.

Knowledge on Breastfeeding

The 12 point questionnaire to find out the knowledge level of the mothers was used and the results are shown in Figure 3. Three respondents or 2.6 % of mothers managed to obtain a perfect score of 12. There were no mothers who scored below 3. Those who scored 7 and above were considered to have high knowledge on breast feeding and those who had 6 or lower were considered to have low knowledge.

Half of the total respondents 55 (47.8%) correctly answered all 5 statements regarding the benefits of breastfeeding. Out of 4 statements regarding the techniques of breastfeeding, most respondents 46 (40.0%) scored 50% i.e. 2 statements were correctly answered. A high knowledge was considered to be more than 7 correct answers and the low level of knowledge was considred to be 6 and below.

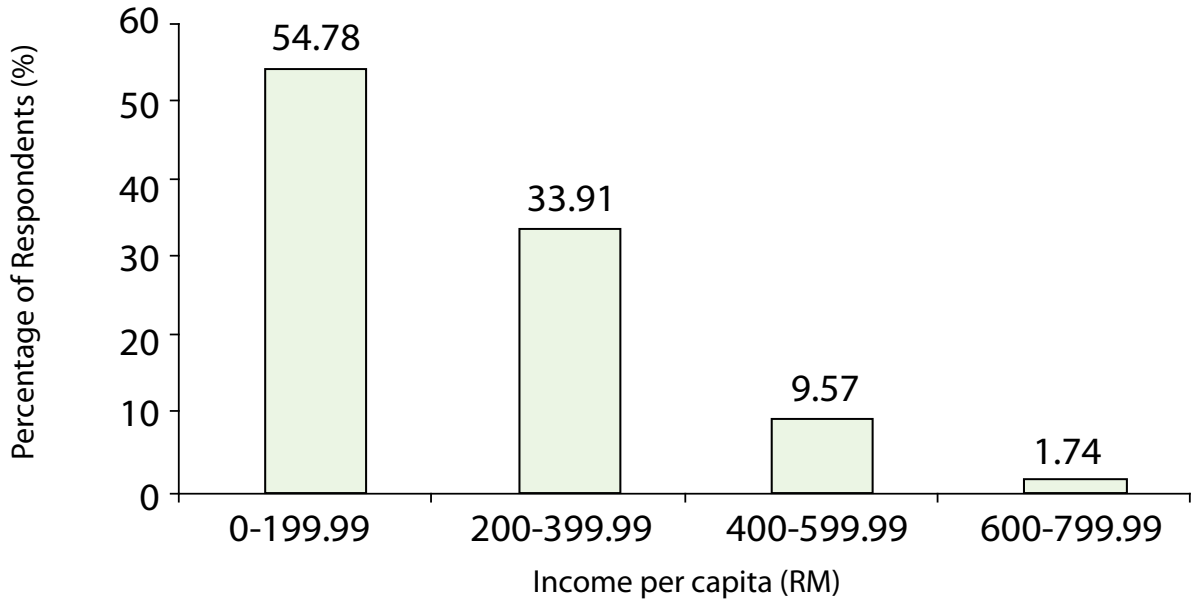

Figure 2: *Financial status of Respondents*

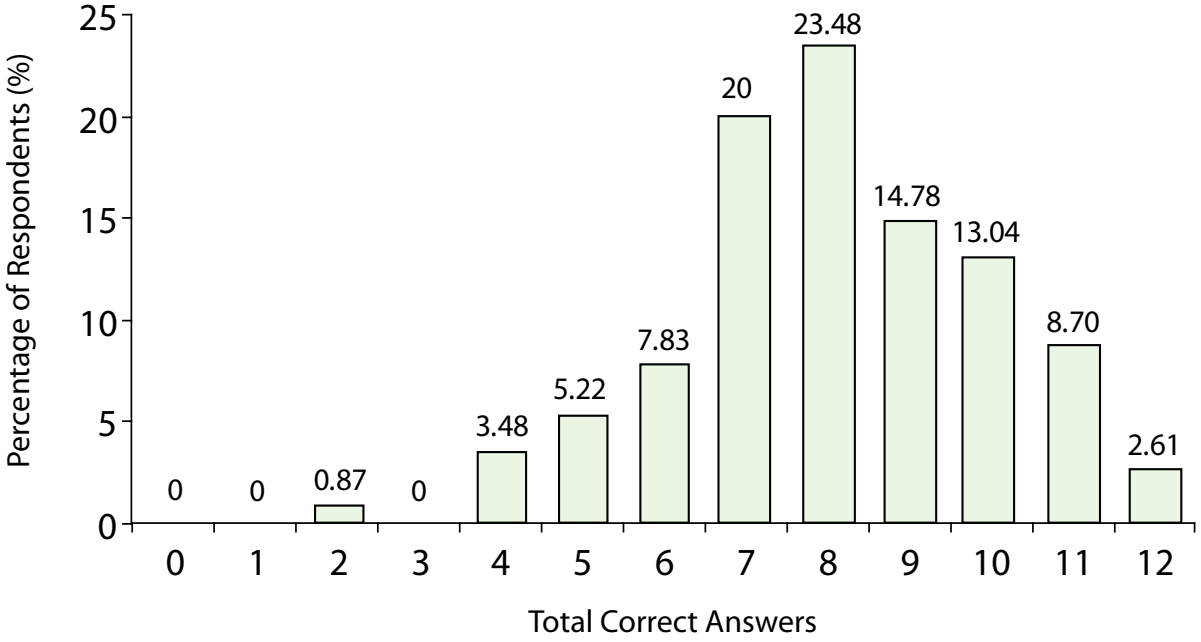

Figure 3: *Knowledge on Breastfeeding among Respondents*

Attitudes towards Breastfeeding

Of the 115 respondents who were interviewed, a total of 113 (98%) mothers had positive attitude regarding the practice of breastfeeding. Only 2% of them were not sure. None felt that breastfeeding was not beneficial.

Reasons for Breastfeeding

Most mothers 75 (65.2 %) cited child's health as the main reason for breast feeding. The next most popular reason was that 'breastfeeding is more economical' which was cited by about 17 (14.7 %) of the mothers. This was followed closely by 15 (13.3 %) who said that 'breastfeeding strengthens the bond between my child and me,' and about 10 (9.3 %), cited 'convenience' and only 8 (7.3 %), cited that 'breast milk is nutritious' and 4 (3.3%) cited mother's health' and others e.g. prevention of cervical cancer, religious reasons 3 (2.6%).

Breastfeeding Practice

Almost all the mothers 114 (99%) initiated breastfeeding but exclusive breast feeding for a period of 4 months was only by 24 (21.0%) of the mothers and predominant breastfeeding practice (breast feeding with addition of water) was about 14 (12.2 %) and complementary breast feeding (breast feeding with addition of food or fluid) was 75 (65.2%). Majority of the mothers 53 (46.0%) breast fed between 20 to 30 months whereas 25 (21.7 %) breast fed between 10-20 months and about 28 (24.3 %) breast fed between 0- 10 months. There were only 8 (7.5%) who breast fed after 30 months. A large proportion of mothers 104 (90%) received support to breastfeed their child while only 11 (10%) of them did not. The main source of support was from their spouses 42 (36.5 %), followed by family members 40 (35.4%), health personnel 27 (23.4 %) and others like. friends and neighbours constituted only 6 (5.2%).

Information on Breastfeeding

About 110 mothers (96.0%) received information on breastfeeding and only a minority of them 5 (4%) had never been informed. From the informed group 83 (79%) of them obtained information before the birth of their child whereas about 18 (16.6%) received it after birth of their child only and 5% received both before and after delivery. In this section, respondents were required to rank the following three sources of information i.e. mass media, family members and health personnel with 1 being the least helpful and 3 being the most helpful. Approximately 92 (80%) of mothers felt that health personnel (e.g. maternity ward nurses and doctors) were the most helpful source of information and about 90 (78%) of mothers listed mass media as the least helpful source ($p>0.05$).

Relationship between age and duration of breastfeeding

Most of the mothers in the older age group i.e. > 32 years to 49 years old practiced breastfeeding for a longer duration when compared to the younger mothers (< 32 years) breastfed for a shorter time ($p<0.05$). Therefore the duration of breastfeeding, whether exclusively or otherwise, increases with the mother's age.

Relationship between educational level and duration of breast feeding

Mothers who received formal education tend to breastfeed longer compared to uneducated mothers or those who were educated informally. Education plays an important part in increasing the awareness among mothers on the benefits of breast milk to both mother and child ($p<0.05$).

Relationship between occupational status and duration of breastfeeding

Unemployed mothers including homemakers practiced breastfeeding for a longer duration with 12 (17 %) of them breastfeeding for about a year while 36 (52 %) mothers breastfeeding for more than a year. In contrast, a shorter duration was noticed among employed and self-employed mothers. This result is not surprising as many mothers claimed that lack of time at home prevented them to breastfeed their child ($p>0.05$).

Relationship between financial status and duration of breastfeeding

Figure 4 shows that mothers with a higher financial status (RM600–RM799) have a lower mean duration of breastfeeding (19.83 months) when compared with mothers with lower income. As breast milk is more economical compared to infant formula milk, therefore mothers who earn a lower income in this area have a tendency to breastfeed longer period of time although this findings is not significant ($p>0.05$).

Relationship between attitudes of mothers and duration of breastfeeding

The relationship between attitude of the mothers and duration of breastfeeding.was assessed . There were no mothers with a negative attitude, all agreed that breastfeeding is good for the baby and the mother. Among mothers who felt that breastfeeding was good, a majority of them 80 (69.5%) respondents tend to breastfeed longer. Only 2 mothers were unsure and both of them still breastfed for more than a year ($p>0.05$).

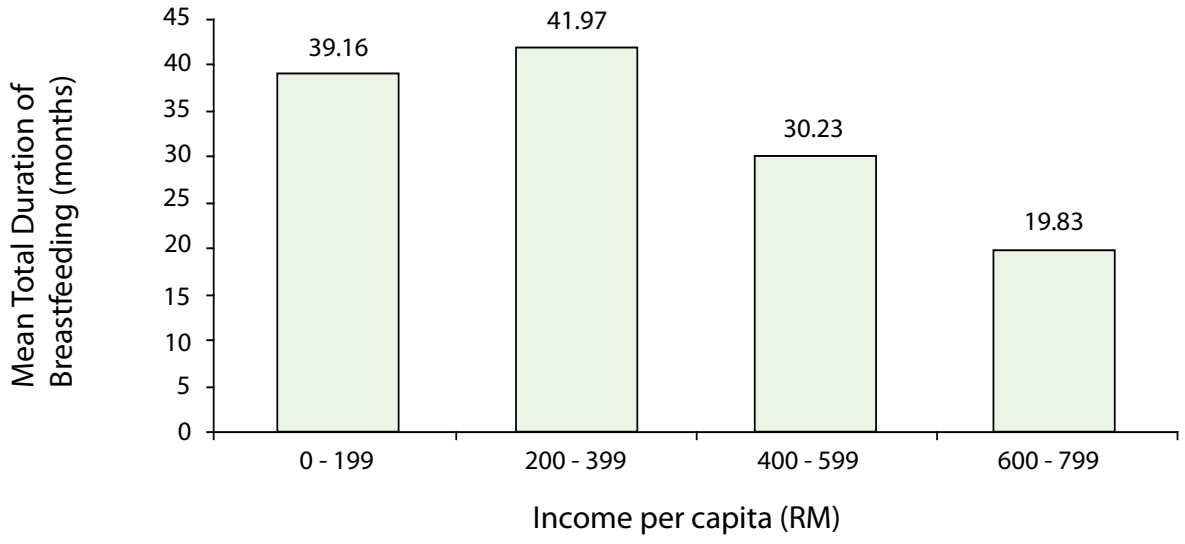

Figure 4: *Relationship between Financial Status and Duration of Breastfeeding*

The relationship between knowledge on breastfeeding and duration of breastfeeding

As shown above, mothers who scored more than 50% in more than seven correct answers in the knowledge questions demonstrated a longer duration of breastfeeding. This could be due to the fact that mothers who are aware of the benefits, techniques and contraindications of breastfeeding would naturally breastfeed longer ($p>0.05$).

Discussion

Majority of the mothers 114 (99%) in the rural villages of Kedah ever breastfed their children and this finding is consistent with findings from earlier studies (1, 10, 12) on the practice of breastfeeding in rural areas which reported a prevalence of more than 90%. A more recent study (6) of an urban community in 2002 revealed a high prevalence of 99.3%.

However, the incidence of exclusive breast feeding in this study was only 21% while predominant breast feeding and complementary feeding was higher. A similar survey in Kubang Pasu Maternal and Child Health Centre in 2004 mothers in the district found similar results.However the national health and morbidity study (NHMS) in 2006 found the exclusive breast feeding to be 14.9%. A high proportion or 46% of the mothers breastfed their children for an average of 20 to 30 months in this study. Most of them who initiated breastfeeding were homemakers or unemployed and they had low monthly income and received some formal education up to primary school level ($p<0.05$). The educational level, working status and income level of the families were not found to be significantly associated with the duration of breastfeeding in this study ($p<0.05$). In another survey, breastfeeding duration was significantly higher among mothers with primary education compared to those with tertiary education (3, 14). However, a study by Siah & Yadav (6) proved otherwise. Low educational level, lack of social exposure and mobility in many ways restrict the career choices and capability of these women. As a result they are tied down to perform traditional women's role as housewives and breastfeeding practice is commonly expected of them. However, it cannot be overlooked that breastfeeding is a rational and natural choice by the mothers, and apart from being a traditional practice, breastfeeding is also encouraged by Islam, the religion of the community.

This study also showed that mothers with a reasonably high knowledge (more than 7 correct answers) on breastfeeding do so for a longer duration of time i.e. more than a year and those who reflected a positive attitude towards breastfeeding tended to breastfeed longer. This shows that knowledge and attitude play an important role in one's decision to breast feed and also the duration of breastfeeding. A high percentage of mothers felt that the most helpful source of information on breastfeeding comes from health personnel e.g. doctor, nurses and staff in the maternity ward. This proves that the government's efforts in promoting and educating the public on breastfeeding are showing signs of success.

However, while most mothers were aware of the benefits of breastfeeding, many were still unsure about the correct technique and conditions or practices that contraindicated breastfeeding. Incorrect breastfeeding methods can affect the initiation, pattern and duration of breastfeeding besides reducing the mothers' confidence and breastfeeding skills when faced with repeated failure to express milk. Furthermore, multiple unproductive trials leave the babies unsatisfied, frustrated and in return irritate or discourage the mothers. In contrary, successful breastfeeding eventually raises the confidence and evokes interest in mothers who feed their children with milk from their breasts.

Clearly, the knowledge and attitude of breastfeeding among the mothers is interrelated and it provides a positive feedback to each other. However, ignorance of breastfeeding can lead to undesirable medical conditions such as infant infection.

Acknowledgements

I would like to thank all the members of the Community Residency Programme CRP) and special thanks to Adeline Khaw Mae Li, Cindy Niap Pei Sze, Ang Tick Suan, Tan Tiam Siong who helped prepare the initial report and without their help this paper would never have been completed. Special thanks to Dr. Azilah bt. Abdullah, the Medical Officer of Health Daerah Kubang Pasu and all the Ketua Kampung of the various kampongs. Thanks also to Mr. Hazreen Abdul Majid who helped the CRP group during the posting.

References

1. Zulkifli A, Daw WK, A Rahman Isa. Breastfeeding and weaning Practice in Rural communities of Kelantan. *Mal J Nutr* 1996; 2:148-154.

2. Waterlow JC, editor. Protein energy malnutrition. London:Edward Arnold, 1992

3. Nagra SA, Gilani AH. Variation in infant feeding practices in Pakistan with socio-economic stratification. *J Trop Paed* 1987; 33: 103-106.

4. Jelliffe DB, Jelliffe EFP. Human Milk in the Modern World. New York: Oxford University Press, 1978.

5. Jelliffe EFP. Breastfeeding and the prevention of malnutrition. *Med J Mal* 1986; 41: 88-92.

6. Siah C K, Yadav H. Breastfeeding Practices among Mothers in and Urban Polyclinic. *Med J Mal* 2002; 57:188-193.

7. Breastfeeding: Foundation for a Healthy Future. New York, USA. Division of Communication, UNICEP 1999. (Internet Communication, 29 October 2000 at http://www.unicef.org). Accessed 15 Dec 2009.

8. World Health Organization. The prevalence and duration of breastfeeding; a critical review of available information. World Health Statistics Quarterly 1982; 35:92-116.

9. Wan A Manan. Breastfeeding and infant feeding practice in Selected Rural and Semi-urban Communities in Kemaman, Terengganu. *Mal J Nutr* 1995; 1:51-61.

10. Teoh SK. Breastfeeding in Rural Area in Malaysia. *Med J Mal* 1975; 30:175-179.

11. Pathmanathan I. Breastfeeding—A Study of 8,750 Malaysian Infants. *Med J Mal* 1978; 33: 113-139.

12. Balakrishnan S, Hasbullah H Breastfeeding in Kelantan. *Med J Mal* 1977. 32: 22-24.

13. Kwa SK Breastfeeding and the use of maternal health services in Sarawak. *Mal J Reprod Health* 1993; 11(1): 8-19.

14. Public Health Institute, Ministry of Health. Conference on National Health and Morbidity Survey II 1996, 20-22 Nov 1997. Hospital Kuala Lumpur 1997; 18 (appendix): 1-17.

CARDIOVASCULAR RISKS AMONG SHIFT AND NON-SHIFT WORKERS IN A PUBLIC MEDICAL CENTRE IN KUALA LUMPUR

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ABSTRACT:

Night work and rotating shift work are found to be detrimental to the health of workers. A cross sectional analytical study was conducted among the employees of a public medical centre in Kuala Lumpur. A total of 380 employees participated in the health screening and questionnaire survey. The majority of the respondents were Malays, females, and with mean age of 49 years old. The shift workers persistently had higher but non-significant proportions of being overweight/ obesity and unhealthy clinical indicators such as systolic and diastolic blood pressure, fasting blood glucose and lipid profile except waist circumferences and HDL-cholesterol. There were also slightly more shift workers diagnosed with diabetes mellitus, hypertension or coronary heart disease (p>0.05). Although the present study could not provide established evidence for a relationship between shift work and cardiovascular risks, this could serve as a pilot study for future studies in this area. *(JUMMEC 2010; 13 (1): 45-49)*

KEYWORDS: *shift work, cardiovascular risks*

Introduction

Shift work is an employment practice designed to make use of the 24 hours of the clock, rather than a standard working day. The term shift work includes both long-term night shifts and work schedules in which employees change or rotate shifts (1). Night work and rotating shift work disrupt the circadian timing system. This disruption may produce significant deleterious symptoms in some workers. Certain medical conditions may be aggravated by shift-work scheduling, and shift workers are at increased risk of experiencing cardiovascular, gastrointestinal, and reproductive dysfunction (2-4). However, shift work is a requirement of nursing and essential health workers to provide patients with optimum levels of continuous care in health care settings.

Shift work has been associated with an increased risk of cardiovascular disease (CVD). Findings showed that non-day workers had a relative risk (RR) for all circulatory diseases of 1.31 (95% CI 1.06-1.63) compared to day workers (5). The increased risk of CVD associated with shift work is related to the greater incidence of Metabolic Syndrome (MetS) among these workers. The metabolic syndrome incidence was found to be significantly higher in shift workers than in other workers (OR: 4.10, 95% CI 1.34-12.55) who were healthy at baseline (6). The MetS incidence rate among shift workers (60.6 per 1000 person-years) was increased in comparison with day workers (37.2 per 1000 person-years) with an odds ratio (95% CI) of 1.77 (1.34-2.32) (7). A study by Copertaro *et al* (8) showed a high prevalence of metabolic syndrome detected among shift workers. The above could be explained by evidence that a significant relation was found between years of working nights (more than 10 years) and high cholesterol values (RR=2.58; CI=1.07-6.27) (9). Positive relationship was also observed between BMI and waist to hip ratio (WHR) and duration of shift work experience, with an adjustment for age (10).

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Therefore, a study should be conducted among all employees of hospitals or medical centres to investigate the relationship of shift work with health particularly cardiovascular risks. This paper attempts to explore the association of shift work with the cardiovascular risks among employees of a public medical centre in Kuala Lumpur.

Materials and methods

This was a cross-sectional study conducted in 2005 to 2006. Universal sampling was conducted where all employees aged 40 years and above of the university's medical centre were invited to participate in the health screening and questionnaire survey. Ethics clearance was obtained from the Ethics Committee of the medical centre that governed all studies involving humans. Informed consent was obtained from all respondents.

All respondents were required to fast overnight for the screening of biochemical indicators including lipid profile (total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol) and fasting blood glucose. Venous blood was obtained following standard procedures by medical officers of the staff health clinic from the medical centre. All analyses of blood samples were conducted by the Clinical Diagnostic Laboratory of the same medical centre.

Anthropometric measurements (weight, height and waist circumference) and a self-administered questionnaire survey were also conducted. The questionnaire was pre-tested and enquired on socio-demographic characteristics, medical history, occupational history (work in shifts, overtime, job satisfaction etc).

All data was entered and analysed by SPSS for windows version 15.0. Appropriate statistical analysis was conducted and the significant level was preset at 0.05.

Results

Out of a total of 1,007 workers who had undergone the health screening, only 380 responded to the questionnaire survey (response rate of about 38%). Although the response rate was less than satisfactory, there was no significant difference observed between respondents and non-respondents (Table 1).

Out of the 380 respondents, only 112 (29.5%) of them worked on shifts. Shift work in this medical centre was on rotation basis with three shifts throughout the 24 hours. The three shifts were morning, afternoon and night shifts. The mean number of night shifts for the respondents was 3.56 ± 2.18 per month. There was no significant difference in race, gender, marital status, education level and age among the shift and non-shift workers (Table 2). Both groups were predominantly Malay, female and married with secondary education. The mean age of both groups was about 49 years old. Respondents working as nurses and security staff comprise the majority of the shift workers.

There was no significant difference in the mean BMI, systolic and diastolic blood pressure, fasting blood

Table 1: *Comparison of respondents and non-respondents*

		Respondents (n=380) n (%)	Non-respondents (n=627) n (%)	p-value
Race	Malay	313 (82.3)	496 (79.1)	0.652
	Chinese	27 (7.1)	52 (8.3)	
	Indian	39 (10.3)	78 (12.4)	
	Others	1 (0.3)	1 (0.2)	
Gender	Male	122 (32.2)	232 (36.9)	0.126
	Female	258 (67.8)	395 (63.1)	
Age (years)	mean + s.d.	49.40 ± 4.80	49.96 ± 5.22	0.09
BMI (kg/m^2)	mean + s.d.	27.06 ±5.00	27.00 ± 4.91	0.85

Table 2: *Socio-demographic characteristics of shift and non-shift workers*

		Shift workers (n=112) n (%)	Non-shift workers (n= 268) n (%)	p-value
Race	Malay	92 (82.1)	221(82.5)	0.193
	Chinese	5 (4.5)	22 (8.2)	
	Indian	14 (12.5)	25 (9.3)	
	Others	1 (0.9)	0 (0.0)	
Gender	Male	40 (35.7)	82 (30.6)	0.393
	Female	72 (64.3)	186 (69.4)	
Marital Status	Married	104 (92.9)	233 (87.5)	0.105
	Single/divorced	8 (7.1)	33 (12.5)	
Education Level	Primary	9 (8.0)	17 (6.4)	0.586
	Secondary	75 (67.0)	172 (64.7)	
	Diploma	21 (18.8)	49 (18.4)	
	Tertiary	7 (6.3)	28 (10.5)	
Occupation	Nurses	52 (46.4)	88 (32.8)	<0.001
	Medical assistants	7 (6.3)	24 (9.0)	
	Technician	5 (4.5)	37 (13.8)	
	Administrative	0 (0)	59 (22.0)	
	Security	34 (30.4)	0 (0)	
	Attendants	14 (12.5)	60 (22.4)	
Age (years)	**mean ± s.d**	49.78 ± 4.71	49.21 ± 4.85	0.287

sugar, lipid profile except waist circumference and HDL-cholesterol between shift and non-shift workers (Table 3). However, the shift workers had persistently higher but non-significant proportions of overweight/obesity and abnormal clinical indicators as shown in Figure 1. There were also slightly more shift workers diagnosed with diabetes mellitus, hypertension or coronary heart disease but the associations were not significantly different ($p>0.05$).

Discussion

Although the response rate was unsatisfactory, the baseline socio-demographic characteristics of the respondents and non-respondents were comparable. There was also no significant difference in the socio-demographic characteristics of the shift and non-shift workers in this medical centre except the occupation status due to the nature of their work. There were more nurses and security guards who worked shift while most of the non-shift workers were in the administrative and non-critical fields.

The shift workers persistently had higher proportions of diagnosis with chronic diseases such as diabetes mellitus, hypertension and coronary heart disease although not statistically significant different ($p>0.05$).

There was no significant difference found in their mean body mass index (BMI), systolic and diastolic blood pressure, and lipid profile among the shift and non-shift workers except waist circumferences and HDL-cholesterol ($p<0.05$). When these workers were divided into normal and abnormal groups based on all the above, the shift workers persistently had higher proportions of abnormal health indicators. These insignificant results might be due to the small sample size. Further study should be conducted on a larger sample to establish significant associations.

Although some evidences had shown that working shifts affected the health of workers (8, 11, 12), the current findings did not show significant difference between workers who worked shift and non-shift. Similar results were shown by Dochi *et al* (13) in their 14-year cohort study of 5510 male workers in a steel company. No consistent association was found between shift work and hypercholesterolemia. A study by Morikawa *et al* (14) too did not find

Table 3: *Clinical indicators of shift and non-shift workers*

	Shift workers Mean ± s.d	Non-shift workers Mean ± s.d	T-test p-value
BMI	27.48 ± 4.75	27.04 ± 4.90	0.424
Waist (cm)	91.38 ± 8.63	85.91 ± 12.00	0.036
Systolic blood pressure (mmHg)	119.42 ±16.08	116.73 ± 14.07	0.108
Diastolic blood pressure (mm Hg)	72.81 ± 6.37	71.70 ± 6.37	0.124
Fasting blood sugar (mmol/l)	5.55 ± 1.73	5.58 ± 1.89	0.883
Total cholesterol (mmol/l)	5.68 ± 1.02	5.69 ± 0.89	0.900
HDL-cholesterol (mmol/l)	1.19 ± 0.31	1.29 ± 0.32	0.005
LDL-cholesterol (mmol/l)	3.79 ± 1.00	3.75 ± 0.86	0.697
Triglyceride (mmol/l)	1.65 ± 1.73	1.47 ± 1.04	0.210

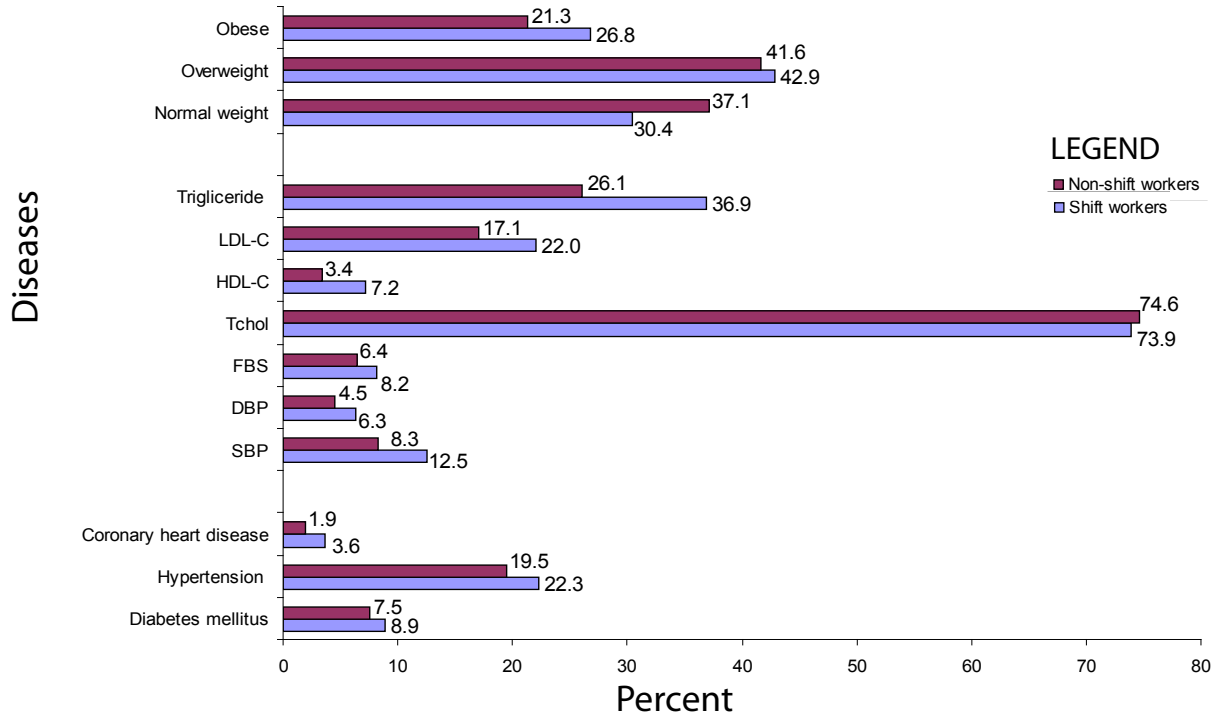

Figure1: *Proportions of abnormal BMI groups, clinical indicators and diagnosis of chronic diseases among shift and non-shift workers*

significant difference in total cholesterol between daytime workers and shift workers. However, they found that shift work was considered to be a risk factorfor excess weight. Another study conducted in Malaysia among factory workers showed that BMI was increased among shift workers but no significant difference found on health indicators (15). According to Sharifian *et al* (16), shift work acted as an oxidative stressor in inducing medical disorders, while aging and obesity made them more sensitive to this hazardous effect.

Therefore, shift workers' health should be safeguarded through preventive check-ups and regular controls by occupational health physicians. This might involve occupational health physicians to inform shift workers on coping strategies, and to assess health disorders (17). This "higher-risk" subgroup may benefit from targeted interventions to reduce potential adverse effects from shift work (18).

Poor response rate giving rise to a small sample size is the limitation faced by this study. Efforts such as mail

reminders and telephone calls were taken to increase response rate. However, due to the demanding nature of these health care workers, most of them declined to participate. Both the respondents and non-respondents had similar socio-demographic background, which showed that the results are still generalizable to the employees of this medical centre.

Conclusion

Although the shift workers seemed to be at higher risk for cardiovascular diseases, the present study could not provide established evidence for a relationship between shift work and cardiovascular risks. However, this could serve as a pilot study for a better designed study to be conducted in the future.

Acknowledgement

The authors would like to acknowledge the funding from the Ministry of Higher Education. Data collection by Ms Woon SC and Miss Joey Eng was also acknowledged. Last but not least, our sincere gratitude to all respondents of the study.

References

1. Monk TM, Folkard S. Making shift work tolerable 1992: CRC Press; 1992.
2. Scott AJ. Shift work and health. *Prim Care* 2000; 27(4): 1057-1079.
3. Knutsson A. Health disorders of shift workers. Occup Med (Lond) 2003; 53(2): 103-108.
4. Brown DL, Feskanich D, Sanchez BN, *et al*. Rotating Night Shift Work and the Risk of Ischemic Stroke. *American Journal of Epidemiology* 2009; 169(11): 1370-1377.
5. Tuchsen F, Hannerz H, and Burr H. A 12 year prospective study of circulatory disease among Danish shift workers. *Occup Environ Med* 2006; 63(7): 451-455.
6. La Sala M, Pietroiusti A, Magrini A, *et al*. (Metabolic syndrome and work: identification of populations at risk). *G Ital Med Lav Ergon* 2007; 29(3 Suppl): 445-447.
7. De Bacquer D, Van Risseghem M, Clays E, *et al*. Rotating shift work and the metabolic syndrome: a prospective study. *Int J of Epidemiol* 2009; 38(3): 848-854.
8. Copertaro A, Bracci M, Barbaresi M, *et al*. Assessment of cardiovascular risk in shift healthcare workers. *Eur J Cardiovasc Prev Rehabil* 2008; 15(2): 224-229.
9. Portela LF, Rotenberg L, and Waissmann W. Self-reported health and sleep complaints among nursing personnel working under 12 h night and day shifts. *Chronobiol Int* 2004; 21(6): 859-870.
10. van Amelsvoort LG, Schouten EG, and Kok FJ. Duration of shiftwork related to body mass index and waist to hip ratio. *Int J Obes Relat Metab Disord* 1999; 23(9): 973-978.
11. Härmä M. Shift work among women—a century-old health issue in occupational health. *J Work Environ Health* 2008; 34(1): 1-3.
12. Kroenke CH, Spiegelman D, Manson J, *et al*. Work characteristics and incidence of type 2 diabetes in women. *Am J Epidemiol* 2007; 165(2): 175-183.
13. Dochi M, Sakata K, Oishi M, *et al*. Relationship between shift work and hypercholesterolemia in Japan. *Scand J Work Environ Health* 2008; 34(1): 33-39.
14. Morikawa Y, Nakagawa H, Miura K, *et al*. Effect of shift work on body mass index and metabolic parameters. *Scand J Work Environ Health* 2007; 33(1): 45-50.
15. Chee HL, Mirnalini K, Maimunah K, *et al*. Body mass index and factors related to overweight among women workers in electronic factories in Penisular Malaysia. *Asia Pac J Clin Nutr* 2004; 13(3): 248-254.
16. Sharifian A, Farahani S, Pasalar P, *et al*. Shift work as an oxidative stressor. *J Circadian Rhythms* 2005; 3: 15.
17. Garbarino S. (Shiftwork. Impact on health and safety in the working environment). *G Ital Med Lav Ergon* 2006; 28(1): 89-105.
18. DeMoss C, McGrail M, Jr., Haus E, *et al*. Health and performance factors in health care shift workers. *J Occup Environ Med* 2004; 46(12): 1278-1281.

SEVERE CUTANEOUS ADVERSE DRUG REACTIONS: STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSISA, A REPORT OF 4 CASES SEEN AT UMMC

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ABSTRACT:

Prescribing medication is not without its adverse effects. Complications due to drug therapy are on the rise in Malaysia, especially when antibiotics are used indiscriminately. We reviewed cases admitted to the Acute Medical Ward of University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia, over a two-month period from March to April 2009. The authors found that Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) were the most common severe adverse cutaneous reactions due to ingestion or parenteral use of drugs. In this report, is a brief description of the two conditions and ways to manage them. The authors have come to a conclusion that judicious use of medications with adequate patient education is important in order to avoid these adverse effects. *(JUMMEC 2010; 13 (1): 50-58)*

KEYWORDS: *Adverse cutaneous drug reactions, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis*

Introduction

Complications due to drug therapy are the most common types of adverse reactions in hospitalized patients (1). Studies have shown that between 2% and 6% of patients are hospitalized due to adverse drug reactions (2). These cutaneous reactions range from macular rash to extensive blistering lesions. Although a majority of cutaneous drug reactions are not severe, immediate recognition can prevent the progression to severe reactions that may result in prolonged hospital stay, increased morbidity and mortality and increasing costs due to usage of medications and laboratory charges (3). In a recent report, based on the findings from a large population of hospitalized Medicare patients in the United States, it was shown that those with adverse drug reaction, which affects only 1.73% of those hospitalised, incurred 9.15% more charges on drugs, 2.82% more on laboratory costs and had an 8.25% increase in length of hospitalisation (3). This would also inevitably lead to an increase in indirect costs due to prolonged time off from work.

In 2008 alone, the National Centre for Adverse Drug Monitoring of Malaysia has received 4826 local reports of spontaneous adverse drug reactions, an increase of 57.3% in comparison to the previous year. The most number of adverse drug reactions were attributed to cardiovascular drugs, followed by use of antimicrobials (4). With increasing awareness of the health care professionals and improved reporting, it is predicted that the frequency and number of adverse drug reactions may be on the increase; more so when antibiotics are used indiscriminately.

Case Reports

In this report, we focus on two types of severe cutaneous adverse drug reactions, i.e Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

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We reviewed the cases admitted to the Acute Medical Ward of the University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia, over a two-month period from March to April 2009. We noted that these two types were the most common severe adverse cutaneous reactions due to ingestion or parenteral use of drugs.

Case Report 1

A 48-year-old Bangladeshi man presented to his General Practitioner (GP) with low-grade fever and generalized body aches. He was prescribed amoxicillin, paracetamol and multivitamins. Two days later he saw another GP after developing painful ulcerations in the mouth and lesions on his limbs and trunk. He was sent home with cefadroxil (a cephalosporin) and paracetamol. Despite taking the medications, his condition did not improve. He revisited the same GP the next day and was given oral prednisolone and cetirizine. Because his skin lesions were worsening, he sought treatment at the Accident and Emergency Unit (A & E) of UMMC on the third day after the first ulcerations appeared. At the A&E, the medical officer noted that he had large areas of hyperpigmented lesions with blisters and superficial erosions in some, involving the limbs and trunk along with erythematous superficial ulcerations on the hard palate. He had no previous allergies and noted that he had taken cefalexin (a cephalosporin) and amoxicillin in the past with no adverse reactions. He was then admitted to the Acute Medical Unit under the care of the Dermatologist. The case was reviewed and detailed history including previous drug history was taken. A diagnosis of Toxic Epidermal Necrolysis (TEN) secondary to amoxicillin and cefadroxil was made.

Because of the severity of the drug reaction involving almost 40% of the skin, he was given intravenous hydrocortisone followed by high dose oral prednisolone. Over the next seven days, the skin lesions improved and he was able to eat. For blisters on the body, he was given wet wraps with dilute solution of potassium permanganate solution ($KMnO_4$). Subsequently when the lesions were drying up, topical steroid creams were applied. He was discharged on the tenth day with 40mg of prednisolone daily and advised on a tapering dose of the steroid within the next two weeks. From the history of his previous exposure to amoxicillin and cephalosporin, it could have been that he had his sensitising dose then.

Case Report 2

A 48-year-old Indian lady with type 2 diabetes mellitus, below-knee amputation of the left leg and a right diabetic foot ulcer, was admitted with abdominal pain and distension, associated with nausea and breathlessness. She also had fever with poor urine output. An initial diagnosis of nephrotic syndrome and sepsis secondary to the right diabetic foot ulcer was made. Intravenous Unasyn (ampicillin and sulbactam) was given after blood cultures were taken. She was also given intravenous frusemide for the fluid retention.

On the fifth day of admission, she developed erythematous, target-like, blistering lesions on the dorsum of her right hand and on the antecubital fossa of her left arm (Figures 1a and 1b). These lesions appeared around the area of the branula site. The initial impression was that these lesions could have been caused by the extravasation of the antibiotics into the tissue around the branula. She gave no past history of adverse reactions to any medication. She was prescribed dilute potassium permanganate soaks to the areas of the blisters. One percent hydrocortisone cream was prescribed topically on the non blistered target lesions.

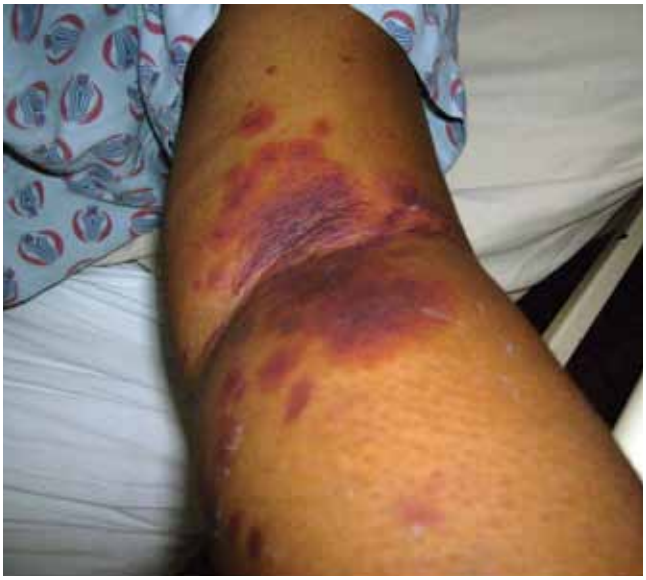

Figure 1a: *48-year- old female with Bullous Erythema Multiforme*

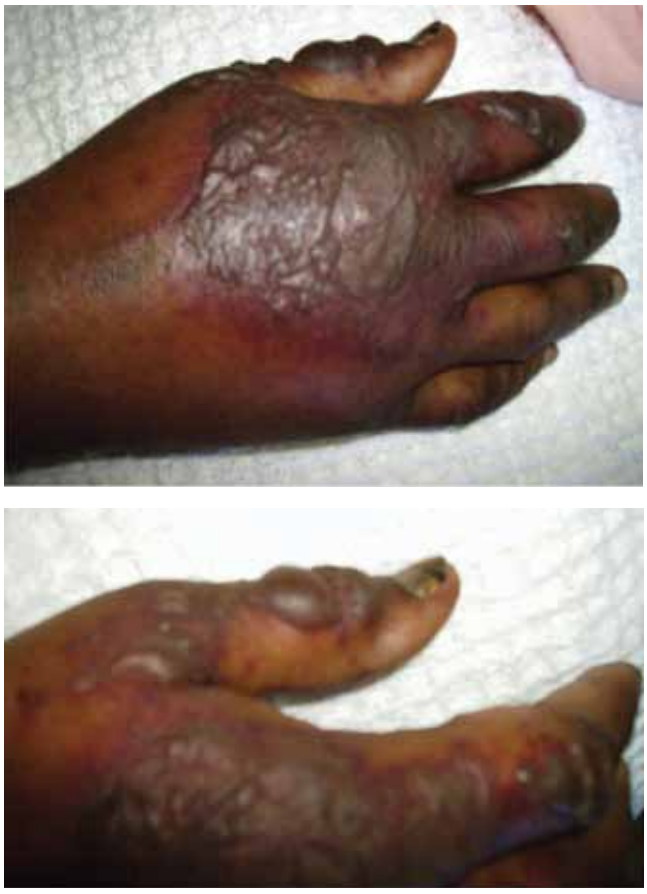

Figure 1b: *Same patient showing bullous eruptions on the dorsum of the hand*

Over the next two days, the lesions progressed, involving both limbs and the upper part of her trunk. She was then started on intravenous hydrocortisone. A diagnosis of bullous erythema multiforme secondary to ampicillin and sulbactam (Unasyn) was made.

Case Report 3

A 44-year-old Malay man, with a background history of nephritic syndrome secondary to focal segmental glomerulosclerosis, chronic renal disease and hypertension, was seen by a General Practitioner (GP) for fever, sore throat and itchiness of his eye. He was initially prescribed cefixime (a cephalosporin) and then a week later, was given amoxicillin clavulanate (Augmentin) and paracetamol. One day after taking amoxicillin clavulanate, he developed rashes around his neck. He however continued taking the medication. Three days later, the rashes became worse and the fever persisted.

He presented to the A&E of UMMC on the third day after the rash appeared and was admitted with red eyes, mucosal erosions and multiple target lesions, some of which were confluent, over the trunk and limbs. He also developed difficulty and pain on swallowing. He suffers from seafood allergy but has no known previous allergies to drugs.

He was admitted to the Acute Medical ward under the Dermatology unit. The next day, we requested a list of medications from his GP whom he had visited four times in the past one month, for various complaints. He was on a number of drugs namely colchicine, allopurinol, ibuprofen, meloxicam, simvastatin, cefuroxime and amoxicillin clavulanate.

As his renal profile was deranged and he had worsening of the renal functions, (urea=24.4mmol/l, creatinine=809µmol/l) an ultrasound scan of his kidneys was done which showed bilateral renal parenchymal disease. A diagnosis of toxic epidermal necrolysis possibly due to cefuroxime, allopurinol and or amoxicillin clavulanate was made. He was put on intravenous hydrocortisone and subsequently a tapering-down course of oral prednisolone. For the skin lesions, wet wraps with dilute potassium permanganate were done. The patient recovered fully and was discharged ten days later. He was advised on the medications that he should not take and was given a medic alert badge with allergies to cefuroxime, allopurinol and amoxicillin clavulanate.

Case Report 4

A 28-year-old man who sustained head injuries during a road traffic accident, was admitted to the UMMC Intensive Care Unit (ICU). During his one-month stay in ICU, he was started on several intravenous antibiotics at different intervals, amoxicillin clavulanate, piperacillin tazobactam (tazocin), polymyxin and ampicillin sulbactam (unasyn). He was later transferred to the Neurosurgical ward. There he developed a nosocomial infection. He was given intravenous amoxicillin clavulanate for three days. On the sixth day of hospital stay in the neurosurgical ward, he noticed an erythematous rash associated with pruritus starting at the neck and left antecubital fossa. He was also started on cetirizine and ponstan. His rash improved.

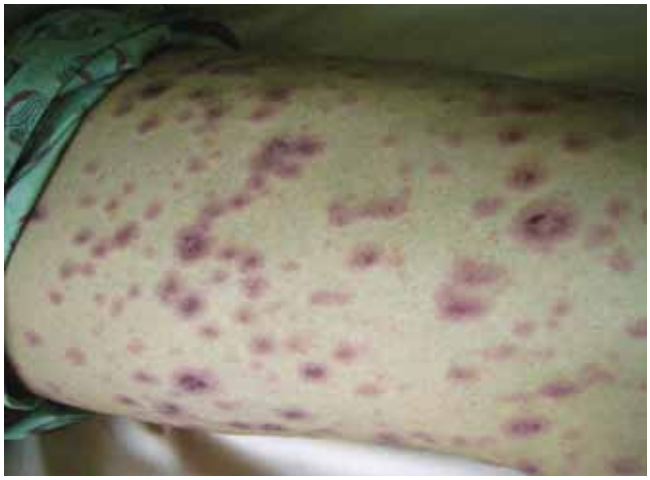

Figure 2a: *A 28 –year-old male with SJS showing target lesions.*

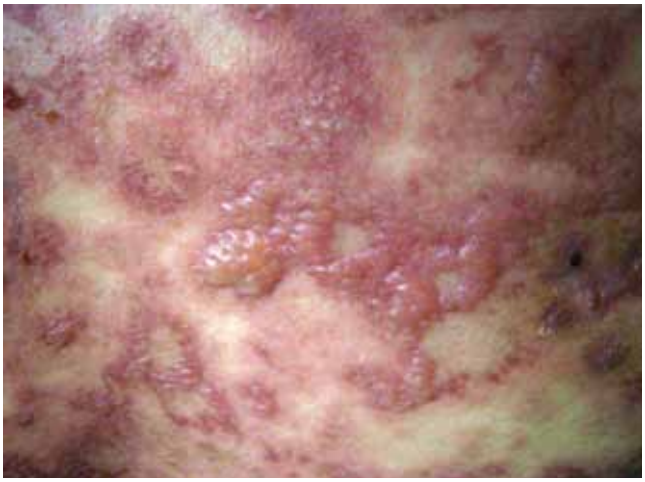

Figure 2b: *Same patient showing superficial blisters appearing on the trunk*

Table 1: *Summary of similarities between the four cases.*

	Case 1	Case 2	Case 3	Case 4
Known drug allergies	Nil	Nil	Nil	Nil
Common Drug Denominators seen:	Amoxicillin, Cefadroxil	Ampicillin Sulbactam (Unasyn)	Cefuroxime, Amoxicillin clavulanate (Augmentin), Allopurinol	Amoxicillin clavulanate (Augmentin)
Previous exposure to drugs:	Treated with cefalexin and amoxicillin in the past.	No previous use of ampicillin sulbactam recorded.	Treated with cefuroxime, amoxicillin clavulanate and allopurinol in the past.	Treated with intravenous amoxicillin clavulanate on two occasions.
Re-challenged with current drugs. Shortened onset of symptoms.	2nd day of antibiotic use	5th day of antibiotic use	2nd day of antibiotic use	6th day of antibiotic use
Diagnosis:	Toxic Epidermal Necrolysis (TEN)	Bullous Erythema Multiforme (BEM)	Toxic Epidermal Necrolysis (TEN)	Steven Johnson Syndrome (SJS)
Response to corticosteroids.	Discharged after 10 days of admission.	Rashes improved after 12 days. Was not discharged as she had other comorbidities	Discharged after 10 days of admission.	Discharged after 7 days of admission.

Table 1 summarises the similarities between the 4 cases seen. In 3 of the cases seen, sensitisation to the drug had occurred previously when the patients were exposed to the initial dose. The last case (case # 4) was sensitised during the admission to the UMMC for his head injury where he was given amoxicillin clavulanate.

After a week, he was discharged with amoxicillin clavulanate, and cetirizine. The rashes worsened after one day and started to spread to the upper and lower limbs, chest and abdomen. He was readmitted the next day with widespread painful maculopapular rash and joint pain. Blisters were present, especially on the trunk, palmar aspects of his hands, dorsum and sole of his feet (Figure 2a and 2b). He also had oral ulcers and areas of superficial erosions on his penis.

He was referred to the Dermatology team, who saw the patient and a diagnosis of SJS secondary

to amoxicillin clavulanate was made. He was started on oral prednisolone, dilute potassium permanganate topically to the areas of blisters and additional topical creams to the erythematous, non blister areas.

The patient recovered and was discharged one week later.

In relation to the four cases above, the similarities are highlighted in Table 1.

Discussion

Epidemiological Data And Clinical

SJS and TEN are two related mucocutaneous reactions characterised by blistering lesions involving the epidermal region of the skin and erosions of the mucous membrane. The incidence are 1 to 6 and 0.4 to 1.2 per million person-years respectively (1, 5).

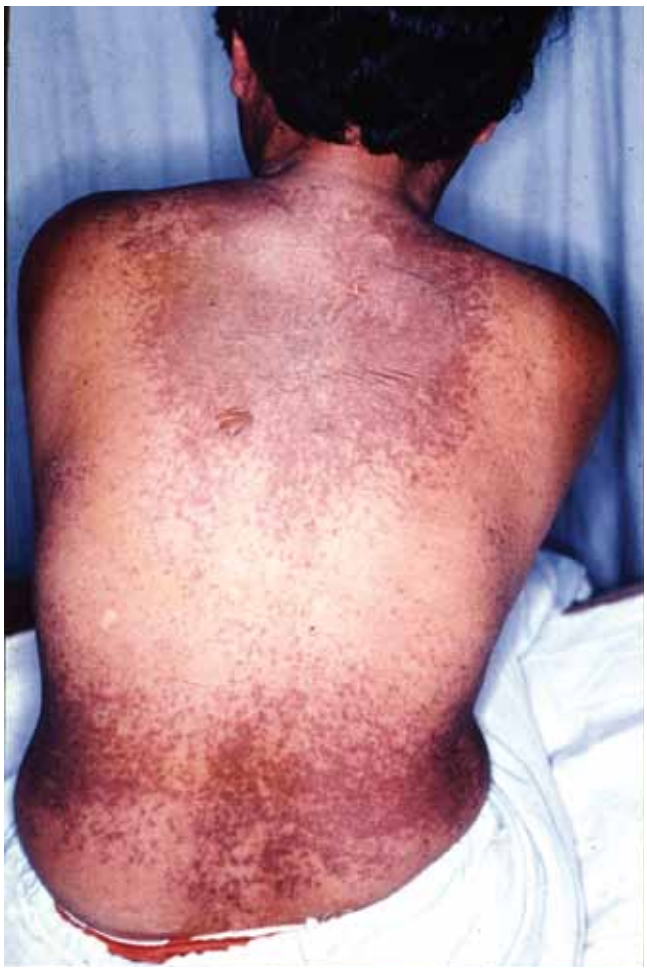

Figure 3: *TEN- Slide of another patient with a similar condition*

The spectrum of cutaneous drug reactions range from the mild macular-papular erythematous rashes to fixed drug eruptions, erythema multiforme (EM), bullous erythema multiforme (BEM), Steven Johnson Syndrome (SJS) and the most severe which can lead to significant mortality, toxic epidermal necrolysis (TEN). (Table 2).

Table 2: *The spectrum of Adverse Cutaneous Drug Reactions*

Maculopapular rash	MILD
Erythema Multiforme	↓
Bullous Erythema Multiforme	↓
Erythema Multiforme Major	↓
Stevens-Johnson Syndrome	↓
Toxic Epidermal Necrolysis	SEVERE

Table 2 summarises the spectrum of cutaneous drug reactions ranging from mild maculopapular rash to life-threatening TEN

The usual mild forms of cutaneous drug reactions include dusky erythema without blisters as in erythema multiforme, target lesions, where there is some degree of ischaemia to the superficial layer of the skin, to the most severe form involving separation of the epidermis from the dermis as in toxic epidermal necrolysis (TEN), whereby sheets of the epidermis separate out from the dermis. (Figure 3) This is the most severe, and in some cases, can be fatal if prompt treatment is not instituted (6).

SJS and TEN have a strong association with specific medication. In most studies, it has been shown that the rates of exposure to certain types of drugs are similar in SJS, SJS-TEN overlap and TEN (1, 5, 7, 8). Around 50% of SJS and more than 80% of TEN is caused by drugs (1, 9, 10). The list of drugs with the most significant association are shown in Table 3. The risk was found to be highest within a period of 4 to 28 days between the first initiation of the drug and onset of adverse reaction (10). Adverse drug reactions occur more frequently in recent times partly due to improper use of antibiotics, as can be seen in the cases highlighted above. Antibiotics are most commonly prescribed for

Table 3: *Medications associated with high risk of SJS or TEN[10]*

Antibiotics:
· Cotrimoxazole
· Anti-infective sulfonamides
Sulfasalazine
Allopurinol
Anti-inflammatory drugs:
· Sulfasalazine
· Oxicam-NSAIDs
Antiepileptic drugs:
· Lamotrigine
· Carbamezapine
· Phenytoin
· Phenobarbital
Antiretroviral:
· Nevirapine

Table 3 summarises the list of drugs that are regularly associated with causing SJS or TEN.

upper respiratory tract infections, as is the case of three of the cases above (11). Other risk factors include HIV infection, cancer and collagen vascular disease (7). The high risk reflects frequent drug use in comparison to the general public.

The immune system is thought to play a role in most adverse drug reactions including those which involve the skin (12). There have been many papers that postulate an immunological reaction to drugs as the cause of SJS and TEN (1, 12). This is further strengthened by the fact that SJS and TEN can recur within 48 hours of a rechallenge, in comparison to an average of 14 days after initial reaction (1). This is because it takes around two weeks of continuous treatment for sufficient antibodies to develop and cause a reaction. Some drugs, like antibiotics, are used for five to seven days and therefore the antibodies produced are not adequate to cause a reaction. However, when the offending drug is unknowingly re-introduced to the patient, this would cause a sensitisation effect as can be seen in the cases above, mounting a severe reaction within a short period of time.

The hapten hypothesis has been used to explain the immunological mechanism of SJS and TEN (12). Not only is the skin equipped with an active immunological defence system, it is also able to metabolise drugs. The hypothesis proposes that drugs or the reactive metabolites of the drugs, act as haptens which bind covalently to endogenous proteins (which in this case would be the epidermal proteins) forming a compound that would trigger the immune system (12). The epidermis is then infiltrated with activated lymphocytes, mostly CD8 cells and macrophages (1, 12)

With the two disorders, sepsis is the major cause of death. Visceral involvement, increased urea and creatinine and extensive epidermal detachment indicate poor prognosis (1). However, prognosis is not affected by HIV infection or the type and dosage of drug used.

Histopathology

SJS and TEN are shown to be similar in terms of histopathological findings. Very severe cases of SJS may include large areas of patchy epidermal necrolysis with bullae and target lesions; while in TEN there would be large areas of the body with sheets of epidermis separating from the dermis. The difference noted between the two are the extent of epidermal detachment, which is more pronounced (>30%) in TEN causing a higher mortality rate (7). Cases that involve epidermal detachment between 10 to 30% are considered an overlap of the two syndromes (1, 6, 7).

In most cases, a skin biopsy is not necessary as it does not help in determining the cause, whether it is drug-induced or not. A diagnosis of adverse cutaneous drug reaction, either SJS or TEN, can be made with a careful and detailed history as well as an accurate account and confirmation of the previous medications taken and the time sequence of the occurrence of the typical lesions, usually gives an accurate clinical impression. This is further enhanced by finding the typical lesions on the skin (target lesions, with or without intraepidermal blisters, and a positive Nikolsky sign, and or superficial erosions on the mucous membranes). A re-challenge with the likely causative drug, although NOT usually done because of the possible severe reaction which can be life-threatening, may confirm the definite drug causing the reaction. However, this is not advisable because

it is unethical to subject a patient to a possibly life-threatening test.

Management

Adverse cutaneous drug reactions, if severe, like SJS and TEN, should be recognized as an acute dermatologic emergency and therefore, should be managed on the wards. Depending on the severity and the extent of the skin involvement, it may be necessary to have the patient monitored in the intensive care unit or the burns unit.

The management is similar to that of a patient with thermal burns which includes aggressive fluid replacement, nutritional support special attention given to ensure that the patient gets a high protein diet; if there is sepsis, careful choice of antibiotics is absolutely essential, to prevent more reactions; aseptic handling and avoidance of adhesive material and proper skin care with open dressings and the use of dilute potassium permanganate wet wraps will assist in the prevention of superficial infection and allows the healing process to occur. Hence, optimal nursing care is vital to ensure a smooth and rapid recovery. Also all potentially responsible medication should be withdrawn immediately. All drugs, especially those introduced within a month of the reaction should be considered suspect (1).

Most therapies by administering corticosteroids or other disease-modifying therapies have yet to be proven for their effectiveness by controlled studies. There has been much debate on whether corticosteroids should be used in the treatment of SJS and TEN (1, 6, 13). Therapeutic use of systemic corticosteroids have been advocated in some studies (6) and have been found inconclusive in others (13). Although toxic epidermal necrolysis can develop in patients receiving high-dose corticosteroid therapy (10), recent studies have not found a direct causal effect (14). Others like plasmapheresis and immunoglobulin therapy have been attempted but their effectiveness remain doubtful. Most papers suggest aggressive supportive treatment should be the main priority instead. From our experience, as can be seen in all four cases above, the use of corticosteroids is beneficial in improving and reducing further advancement of skin lesions.

Conclusion

The diagnosis and management of SJS and TEN are complex and controversial. As these conditions are associated with devastating sequelae, more effort should be made to clarify the classification of clinical features of this disorder. It is important for physicians to promptly recognize the signs and symptoms as only early intervention is best at this point in time. Drug-induced reactions should always be part of the differential diagnosis for any adverse reaction. Even if a certain drug borders on 'probable' that drug should be withdrawn. At UMMC, any allergic or adverse reaction to a drug is notified to the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) via a written form. After recovery, patients should be advised to subscribe to MedicAlert, to obtain some form of identification in order to prevent future occurences; and avoid the drug and all its chemically-related compounds.

A multidisciplinary approach is required to manage these two conditions. Regular and consistent input is needed from the dermatologists and the plastic surgeons to reduce progression of the skin lesions. The nursing staff plays a vital role in ensuring that the proper skin care and dressings are carried out. Nutritionists are also involved as a high-protein diet is known to speed up the healing process.

In Malaysia, where the practice of "doctor shopping" is common, it is essential that patient education be emphasised as an important part of patient management. This should be taken up by medical schools to ensure that this component is part of their undergraduate curriculum.

With the increasing awareness of health care professionals and improved reporting, it is predicted that the frequency and number of patients with adverse drug reactions may be on the increase; more so when antibiotics are used indiscriminately. Over-prescribing antibiotics can also lead to antibiotic resistance, resulting in ineffective treatment of infections. In fact, the World Health Organization identified this issue as one of the threats to global public health security and suggested the urgent need to promote judicious and rational antibiotic prescribing practices (15). The cases above could have been avoided had there been careful

use of medication, especially antibiotics. Clinicians should not succumb to the pressure of prescribing antibiotics just to please their patients. Antibiotics should be prescribed only if they are proven to be beneficial to the patient.

Although the likelihood of a severe reaction is very slim, less than 1 reaction per 5000 exposed patients, they are mostly undetected in premarketing clinical trials (1). Therefore it is the clinician's responsibility to detect and report these reactions to the regulatory bodies, when they do occur. In Malaysia, all drug-induced reactions should be reported to the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC). The report can be made by filling up blue cards which are available at the hospital or submitted via the Internet at their website (16).

The current practice of prescribing and dispensing of medicines done at private clinics and dispensaries should be reviewed. With the increasing numbers of adverse cutaneous drug reactions seen recently , the authors suggest that prescribing of drugs should be done judiciously and with adequate patient education. Patient should also be given information of the effects and possible side effects of the drugs prescribed. This should be re-emphasised when the drugs are dispensed by the pharmacists. The authors believe that the prevalence of adverse drug reactions, may, to some extent be reduced if there is a separation between prescribing and dispensing of the drugs as is practiced in hospitals in this country.

Acknowledgements

We would like to thank our colleagues for their support. We are also grateful to the nursing staff of Ward 12U (UMMC) for their dedication in caring for these patients.

References

1. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs, *N Eng J Med* 1994; 331: 1272-1285.

2. Fiszenson-albala F, *et al*. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Bri J Dermatol* 2003; 149: 1018-1022.

3. Bond CA, *et al*. Adverse Drug Reactions in United States Hospitals. *Pharmacotherapy* 2006; 26(5): 601-608.

4. Adverse Drug Reactions (ADR) Reports for 2008- and overview. Malaysian Adverse Drug Reactions Newsletter. http://www.bpfk.gov.my. Accessed 5 Aug 2009.

5. Roujeau JC, *et al*. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Eng J Med* 1995; 333: 1600-1607.

6. Patterson R, *et al*. Erythema multiforme and Stevens-Johnson syndrome: Descriptive and therapeutic controversy. *Chest* 1990; 98: 331-336.

7. Auquier-Dunant A, *et al*. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome and toxic epidermal necrolysis. Results of an international prospective study. *Arch Dermatol* 2002; 138: 1019-1024.

8. Bastuji-Garin S, *et al*. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme. *Arch Dermatol* 1993; 129:92-96.

9. Schopf E, *et al*. Toxic Epidermal Necrolysis and Stevens-Johnson syndrome: An epidemiologic study from West Germany. *Arch Dermatol* 1991; 127: 839-842.

10. Roujeau JC, *et al*. Toxic Epidermal Necrolysis (Lyell syndrome): Incidence and drug etiology in France, 1981-1985. *Arch Dermatol* 1990; 126: 37-42.

11. Yasmin AM. Judicious use of amoxicillin-clavulanate in acute upper respiratory infections: Part 1, Malaysian Medical Association Newsletter CME, 2009; 1.

12. BK Park, *et al*. Metabolic activation in drug allergies. *Toxicol* 2001; 158: 11-23.

13. Schneck J, *et al* l. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR study. *J Am Acad Dermatol* 2008; 59(5): 898-899.

14. Mockenhaupt M, *et al*. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR study. *J Invest Dermatol* 2008; 128: 35-44.

15. The World Health Report 2007, World Health Organization (WHO). http://www.who.int/entity/whr/2007/whr07_en.pdf. Accessed 10 Aug 2009.

16. Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) website. http://www.bpfk.gov.my. Accessed 5th Aug 2009.

SQUAMOUS CELL CARCINOMA OF SCROTUM: A RARE CASE OF SCROTAL NEOPLASM

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ABSTRACT:

Malignant tumours of the scrotum are very rare. Several type of occupations have been identified as high risk for the development of SCC of scrotum e.g paraffin and shale oil workers (1), textile workers (2) etc. We report a rare case of SCC of scrotum. Search of our records in the Urology and Pathology departments of our Centre showed that this is the only case of SCC of the scrotum in the last 10 years. *(JUMMEC 2010; 13 (1): 59-62)*

KEYWORDS: *squamous cell carcinoma, scrotum, inguinal lymph node*

Introduction

A 76-year-old gentleman was referred with a history of progressively worsening ulcer on the left side of his scrotum of 6 months duration. He denied any history of trauma to the scrotum and there was no exposure to industrial irritants noted.

Examination revealed a fungating ulcer with everted edges mainly at the left side of scrotum encroaching slightly the base of the penis and to the right side of the median raphe. There was also bilateral fixed and matted inguinal lymphadenopathy.

His laboratory tests were within normal limits. Wedge biopsy of the lesion showed a moderately differentiated SCC. A computed tomography (CT) imaging scan and a Magnetic Resonance Imaging (MRI) for staging revealed a well localized lesion in the scrotum with bilateral inguinal lymphadenopathy and with no evidence of other distant metastasis (Figure 1).

The patient was subjected to a wide local excision of the tumour with scrotal skin flap reconstruction. Histopathology revealed a well-differentiated SCC with no lymphovascular permeation and surgical margins were noted to be free of tumour. He then underwent and completed three cycles of chemotherapy with carboplatin and 5-Fluorouracil (5-FU) regime in view of the matted bilateral inguinal lymphadenopathy. Post Chemotherapy, he underwent bilateral radical inguinal lymphadenectomy for the persistent lymphadenopathy and the histopathology confirmed no spread to the lymph nodes (10 and 28 lymph nodes on the right and left respectively) except for the skin nodule overlying the left nodes.

This gentleman has not presented with any evidence of recurrence or metastasis in the last two years of follow-up, both clinically and on imaging.

Discussion

Malignant tumour of the scrotum is a very rare condition worldwide. The SCC of the scrotum is the commonest of the various neoplasm of the scrotum like Basal Cell Carcinoma, Malignant Melanoma and Paget's disease (3). The incidence of this disease is only about 0.2 to 0.3 cases per 100,000 men above the age of 35 years (4). Age of patients presenting with SCC of scrotum usually ranges from 50 to 60 years old (5).

As in most cutaneous lesions, they usually seek medical advice about 12 months after the onset of the ulcer because of extensive usage of topical treatment (6). This delay could lead to a more advanced stage at the time of diagnosis.

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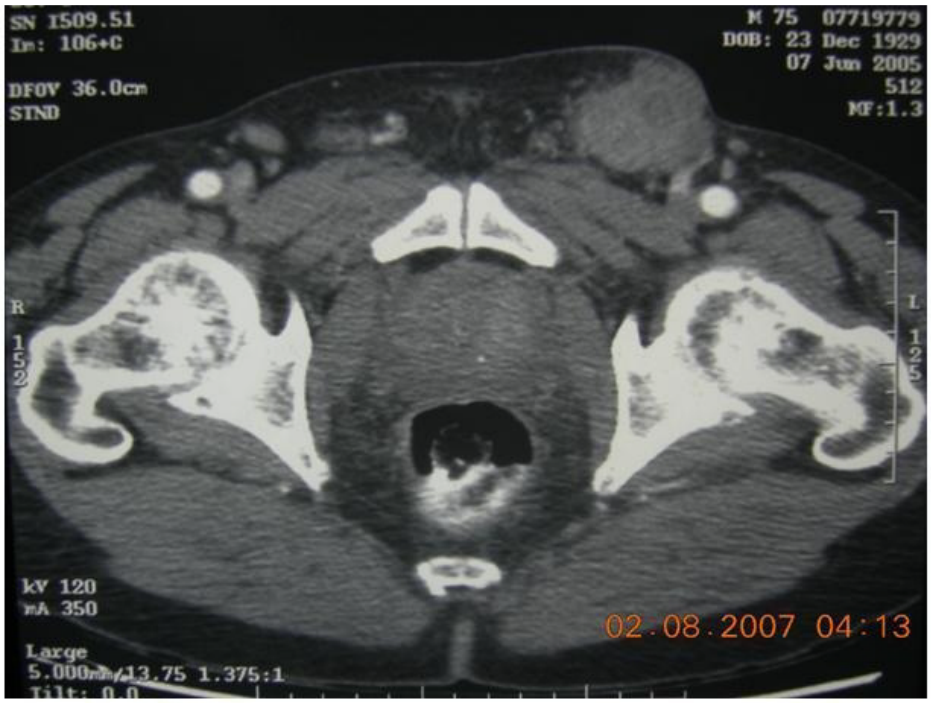

Figure 1: *CT scan showing enlarged Bilateral Inguinal lymph nodes*

Ipsilateral inguinal lymphadenopathy is usually noted in about 40% to 50% of patients and only half of them i.e 25% have proven metastasis to the lymph nodes (6).

Staging of the disease can be done with CT scan, although it is not a reliable modality to differentiate between inflammatory and metastatic lymph nodes (3). MRI is rapidly emerging as a reliable tool for this purpose (7). Currently used staging system for SCC of the scrotum is shown in Table 1.

Figure 1: *Staging system for Scrotal Carcinoma (6)*

Stage	Description
A1	Localised to scrotal wall
A2	Locally extensive tumour invading adjacent structures (testis, spermatic cord, penis, pubis, perineum)
B	Metastaticdisease involving inguinal luph nodes only
C	Metastatic disease involving pelvic lymph nodes without evidence of distant spread
D	Metastatic disease beyond the pelvic lymph nodes involving distant organs

Upon confirmation of the diagnosis by biopsy of the scrotal lesion, the treatment of choice is a wide local excision with a margin of 2 cm and the defect is closed primarily or with split-thickness skin grafting if necessary (3). Lymph node management is controversial—unilateral versus bilateral lymphadenectomy and the timing of lymphadenectomy (prophylactic versus delayed). The need for radical inguinal lymph node dissection is debatable as only 25% of cases show evidence of metastasis as compared to the morbidity of the procedure. Therefore, it is recommended that lymph node dissection be undertaken in cases with proven metastasis i.e Sentinel node biopsy positive (3). Sentinel biopsy as described by Cabanas in 1977 (8) for penile cancer is no more recommended due to high false negative rates (25%, range 9-50%) (9). Similarly, we feel that sentinel biopsy for scrotal squamous cell carcinoma should not be done and a better alternative would be a modified radical inguinal lymphadenectomy. Our patient was noted to present with bilateral fixed and matted inguinal lymphadenopathy which would have complicated any attempt of an inguinal lymph node dissection. Therefore, a course of chemotherapy was given. Clinical improvement of the lymph node status was noted but in view of the persistence, it was then decided that the patient should undergo a left radical

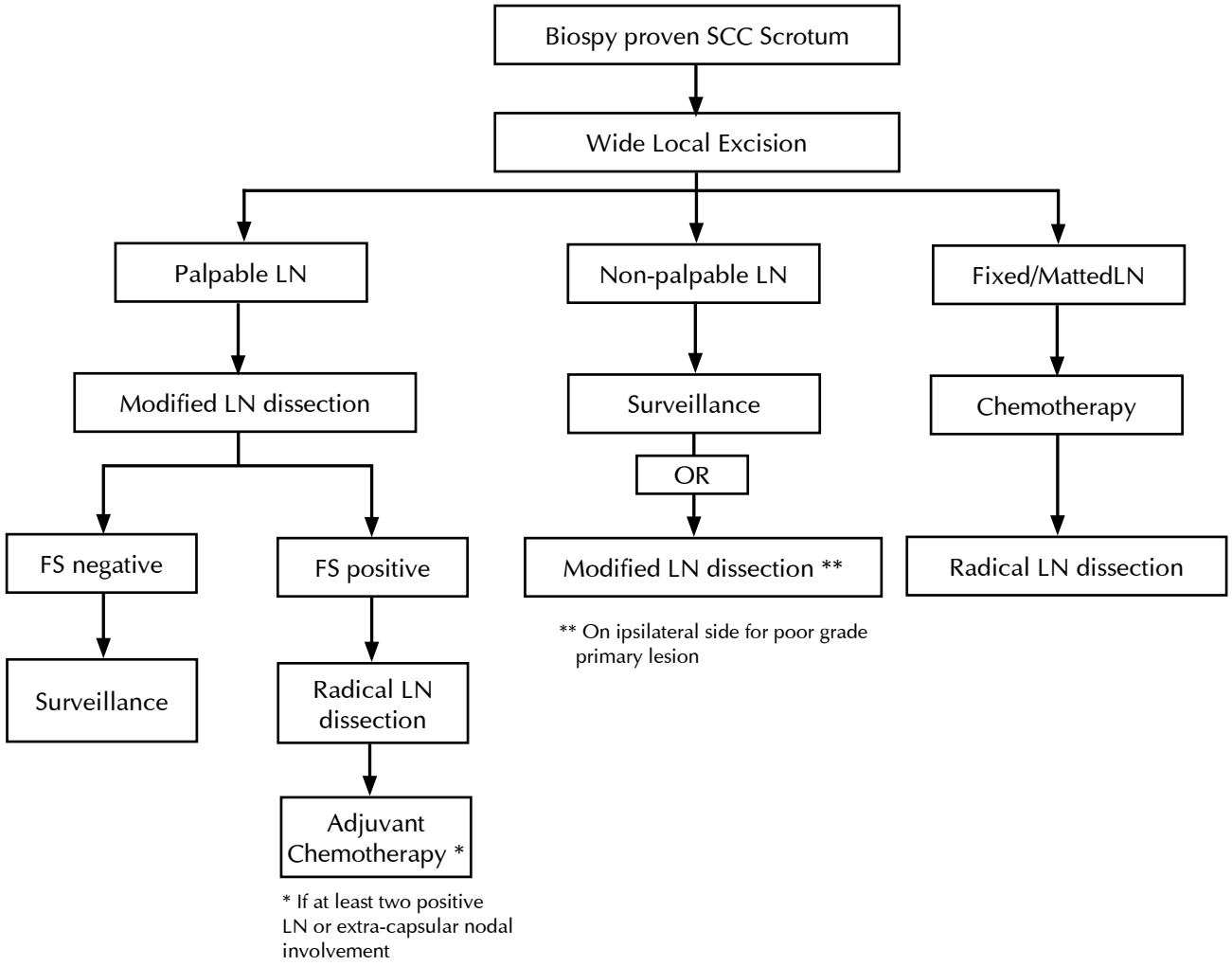

Figure 2: *Algorithm for management for biospy proven SCC*

FS – Frozen section; LN – Lymph node

lymphadenectomy plus a right modified inguinal lymphadenectomy. To the patient's advantage, it was found in the histopathology that the lymph nodes had no evidence of metastasis and the operation itself was less morbid. Therefore, we propose the following algorithm (Figure 2) be used in the management of biopsy proven SCC of scrotum.

Radiation therapy is not effective in this condition and is reserved only for those with incomplete surgical resection and in patients who are unfit to undergo surgery (10). Chemotherapy has been reported to be quite successful in preventing the spread and recurrence of the disease. Reports showed good success in a couple of patients using bleomycin. However, these patients had low grade disease (11). Combination therapy of methotrexate, bleomycin and cisplatin achieved a 72% response rate in patients who had inoperable or metastatic squamous cell carcinoma of the male genital tract (12). Successful treatment was also reported by Hussein *et al* and Fisher *et al* by using a combination of Cisplatin and 5 Fluorouracil (13 & 14). Although, the number of patients was small i.e 29, those treated with neo-adjuvant Cisplatin and 5-Fluorouracil for fixed or recurrent nodal disease for penile cancer showed good response (66%) and in 38% of them, resection could be performed (14). Carboplatin was used in our patient because of the possible toxicity of Cisplatin in geriatric patients. Randomized multicenter trials are needed to determine the role of chemotherapy in the management of scrotal SCC.

Prognosis of this condition is poor with many series reporting death within 2 years of diagnosis; however, the prognosis is related to the stage of the disease as reported by Ray and Whitmore (6). Stage A1 has a survival rate of more than 75%, Stage B only 44%, whereas, Stage C & D has very minimal chance of survival (3 & 15).

Conclusion

SCC of the scrotum is a rare but aggressive condition. The best prognosis for this disease is achievable if diagnosed in early stage where a wide local excision with or without radical inguinal lymph node dissection and adjuvant chemotherapy could be administered.

References

1. Graves RC, Flo S. Carcinoma of the scrotum. *J Urol* 1940 43: 309.
2. Castiglione FM Jr, Selikowitz SM, Dimond RL. Mule spinner's disease. *Arch Dermatol* 1985; 121: 370.
3. Lowe FC. Squamous-Cell Carcinoma of the Scrotum. Urologic Clinics of North America 1992; 19: 2 63-65.
4. Lowe FC. Squamous-Cell Carcinoma of the Scrotum. *J Urol* 1983; 130: 423.
5. Kickham, CJE, Dufresne, M. An assessment of carcinoma of the scrotum. *J Urol* 1967; 98: 108.
6. Ray B, Whitmore Jr WF. Experience with carcinoma of the scrotum. *J Urol* 1977; 177: 741-745.
7. Muglia V, Tucci S, *et al*. Magnetic resonance imaging of scrotal diseases: when it makes the difference, *Adult Urology* 2002; 59; 419-423.
8. Cabanas RM. An approach for the treatment of penile carcinoma. *Cancer* 1977; 39:456-466.
9. Pettaway CA, *et al*. Sentinel lymph node dissection for penile carcinoma: the M.D. Anderson Cancer Center Experience. *J Urol* 1995; 154: 1999-2003.
10. McDonald MW. Carcinoma of scrotum. *Urology* 1982; 19: 269.
11. Ichikawa T, Nakano I, Hirokawa I. Bleomycin treatment of the tumours of penis and scrotum. *J Urol* 1969; 102: 699.
12. Dexeus FH, Logothetis CJ, Sella A., *et al*. Combination Chemotherapy with Methotrexate, Bleomycin and Cisplatin for Advanced Squamous Cell Carcinoma of the Male Genital Tract. *J Urol* 1991; 146: 1284-1287.
13. Hussein, AM, Benedetto, P. and Sridhar, K.S.: Chemotherapy with Cisplatin and 5-fluorouracil for penile and urethral squamous cell carcinomas. *Cancer* 1990; 65: 433.
14. Fisher, HAG, Barada JH, Horton, J, Von Roemeling,R. Neoadjuvant therapy with Cisplatin and 5-fluorouracil for stage III squamous cell carcinoma of the penis. *J Urol*, part 2, 143: 352A, abstract 653,1990.
15. Andrews PE, Farrow GM, Oesterling JE: Squamous cell carcinoma of the scrotum: Long-term follow-up of 14 patients. *J Urol* 1991; 146: 1299.

ONCOGENIC OSTEOMALACIA, YOU SAY? BETTER START LOOKING THEN—A CASE REPORT

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ABSTRACT:

Tumour-induced or oncogenic osteomalacia (OOM) is a rare paraneoplastic syndrome characterized by bone pain and muscle weakness. A biochemical profile consisting of normocalcaemia, hypophosphataemia, phosphaturia, increased serum alkaline phosphatase and inappropriately low serum levels of 1, 25-dihydroxyvitamin-D is diagnostic. OOM is usually caused by an osseous or soft-tissue tumour of mesenchymal origin that secretes phosphaturic substances leading to increased urinary phosphate wasting. These tumours are small and slow growing. The diagnosis continues to be easily missed and when eventually made, localization of the tumour can be difficult. We describe the case of a young man who presented with severe generalized pain associated with muscle weakness. He was extensively investigated and eventually diagnosed to have OOM 3 years after initial presentation. Specialized investigations were necessary to localize the offending tumour. *(JUMMEC 2010; 13 (1): 63-68)*

KEYWORDS: *oncogenic osteomalacia, tumour-induced osteomalacia, hypophosphataemic osteomalacia.*

Case Report

An ethnic Chinese male welder aged 32 initially presented to an orthopaedic surgeon complaining of gradually worsening low back pain associated with weakness of his lower limbs after a fall at home eight months earlier. Magnetic Resonance Imaging (MRI) of the lumbar spine showed a prolapsed intervertebral disc at the L5/S1 level. He, subsequently, underwent a discectomy. Post-operatively, MRI of the spine was reported as normal, however, his symptoms persisted and in fact worsened with pain involving his upper limbs especially the right elbow. The generalized musculoskeletal pain and weakness limited his movement. He complained of difficulty rising from his chair. He required a walking aid, became housebound and was unable to work.

He lived with his parents and there was no family history of malignancy, bone disease or fractures. He had no dietary restrictions. He smoked about five cigarettes and consumed alcohol, three cans of beer daily.

He consulted a neurologist a year after his spine operation. Lumbar puncture and cerebrospinal fluid examination, nerve conduction studies, electromyogram and somatosensory evoked potentials were normal. MRI imaging of the brain, cervical and lumbar spine showed no significant abnormality. He was then referred to a rheumatologist and given a trial of corticosteroids empirically, dexamethasone 4mg TDS for 1 week for suspected connective tissue disease but did not improve.

Skeletal survey radiographs showed multiple lytic bony lesions proximally and distally in the long bones of all four limbs with some pathological fractures more marked over the right proximal radius (Figure 1). ^{99m} Technitium-methylene diphosphonate bone scintigraphy showed multiple symmetrical foci of increased uptake in the articular surfaces of his shoulders, hips, knees, several ribs bilaterally and the right elbow joint, consistent in hindsight with Looser's zones/fractures (Figure 2). (26) Computerized tomogram (CT) of the neck, thorax, abdomen and pelvis was normal.

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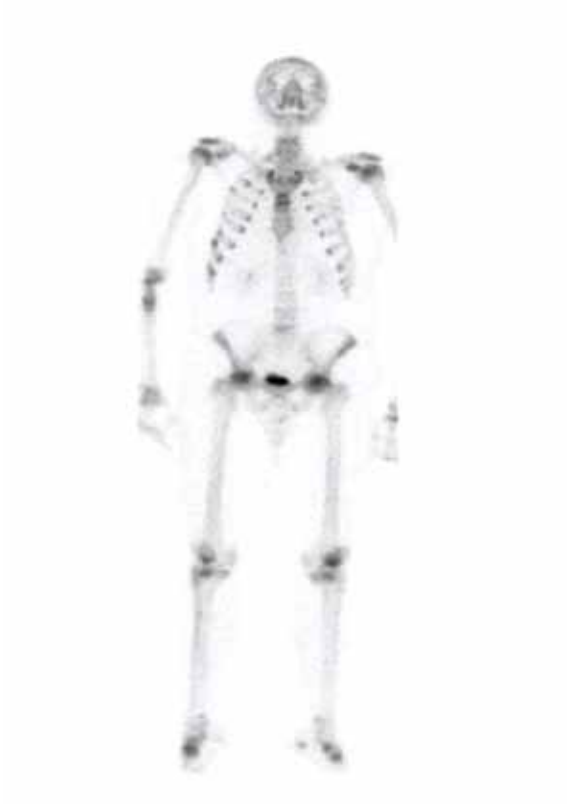

Figure 1: *^{99m} Technitium-methylene diphosphonate bone scintigraphy (anterior view) shows multiple abnormal foci of increased uptake. (Dark areas)*

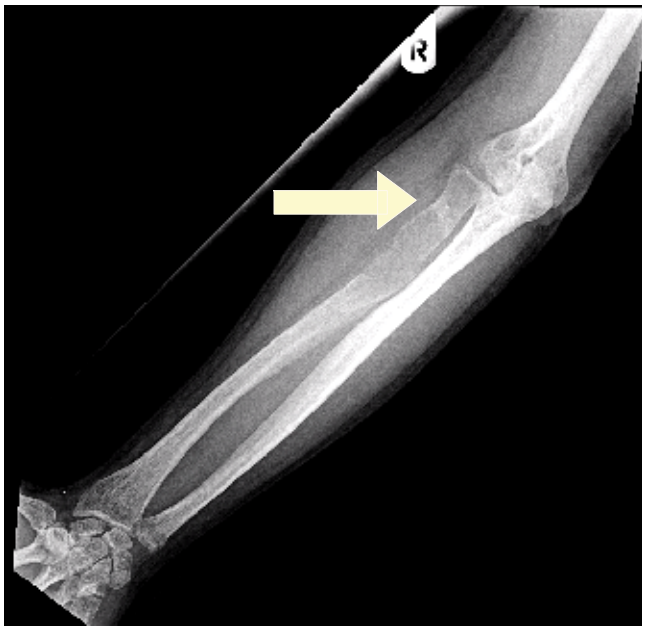

Figure 2: *Radiograph of the right radius and ulna shows a lytic lesion at the proximal radius with a healing pathological fracture. (Arrow)*

Subsequently, he was referred to an orthopaedic oncologist with the presumptive diagnosis of primary or metastatic bone malignancy. Core needle bone biopsy of the right radius showed features suggestive of osteofibrous dysplasia or reactive bone formation. Diagnosis of myeloma or other haematological malignancy was excluded after appropriate investigations. Review of his biochemistry at this stage prompted an endocrinology consult to exclude metabolic bone disease.

Physical examination revealed an alert, well-nourished man who was unable to walk unaided. His weight was 94kg and height was 160cm with no obvious skeletal deformity. He had gained 10kg due to immobility attributed to his illness. There was no muscle wasting. Grading of power was difficult as movement was limited by musculoskeletal pain in all four limbs. Proximal myopathy was evident; power was 4/5 at the hips and shoulders and 5/5 distally. Passive movement of his limbs and palpation of his ribs also caused pain. He had no sensory deficit and was not incontinent. Knee, ankle, biceps, triceps and supinator reflexes were brisk bilaterally. Central nervous, cardiovascular, respiratory and abdominal systems examination was normal.

Full blood count, erythrocyte sedimentation rate, renal, liver and thyroid hormone profile as well as plasma protein electrophoresis urinanalysis and urine for Bence-Jones protein were normal. Serum alkaline phosphatase (ALP) was elevated 302 IU/l (25-100 IU/L), calcium 2.31 µmol/l (2.2-2.6 µmol/L), albumin 36 g/L (35-50 g/L), phosphate was low 0.5 mmol/L (0.8-1.5 mmol/L), intact parathyroid hormone (iPTH) 7.4 pmol/L (1.1-7.3 pmol/L), 24 hour urinary phosphate was inappropriately normal 16.7 mmol/24H (15-50 mmol/24H)- indicating urinary phosphate wasting in the presence of hypophosphataemia, 24 hour urinary calcium excretion 3 mmol/24H (2.2-7.5 mmol/24H) and 25-hydroxyvitamin-D low 35 mmol/L (60-160 mmol/L). Serum 1, 25-dihydroxyvitamin D was not assayed.

He was diagnosed to have hypophosphataemic osteomalacia, most likely due to oncogenic osteomalacia (OOM). He was commenced on oral neutral phosphate solution 45 mls TID, calcitriol (1,25-dihydroxycholecalciferol) 0.25 µg BID and calcium carbonate 1 g BID. Despite treatment, his serum phosphate remained low and symptoms unchanged. His compliance to this regime was questionable.

A search for the primary tumour was initiated. First, he was referred to an otorhinolaryngologist and endoscopic examination revealed a small (0.5 x 0.5 cm) soft tissue nasopharyngeal mass which was surgically

removed but this did not lead to biochemical or clinical improvement. Histopathology showed fragments of seromucinous glands and lymphoid tissue partially covered by respiratory-type epithelium and stratified squamous epithelium.

Positron Emission/Computerized Tomogram using 17.3 mCi (640 MBq) fluorodeoxy-D-glucose (PET/CT-F-18-FDG) was performed which revealed an area of increased uptake and a corresponding lesion at the superior posterior aspect of the right arm. (Figures 3 and 4) Clinical examination revealed a small firm mass. It was surgically removed resulting in prompt normalization of his biochemical parameters. Macroscopically a 3 cm x 1.5 cm x 1.5 cm mass of fibrofatty tissue was excised. Microscopy revealed a lesion consisting of plump proliferating fibroblasts showing mild cellular pleomorphism and mitosis with scattered multinucleated giant cells. An area of osteoid formation continuing into an area of lamellar bone was also noted.

Discussion

McCance described a patient in 1947 whose vitamin D-resistant osteomalacia was cured by resection of a benign osteoid tumour of the femur (1). OOM is characterized by the biochemical profile of low serum phosphate, normal calcium, elevated ALP, low plasma 1, 25-dihydroxyvitamin-D, increased or inappropriate 24 hour urinary excretion of phosphate

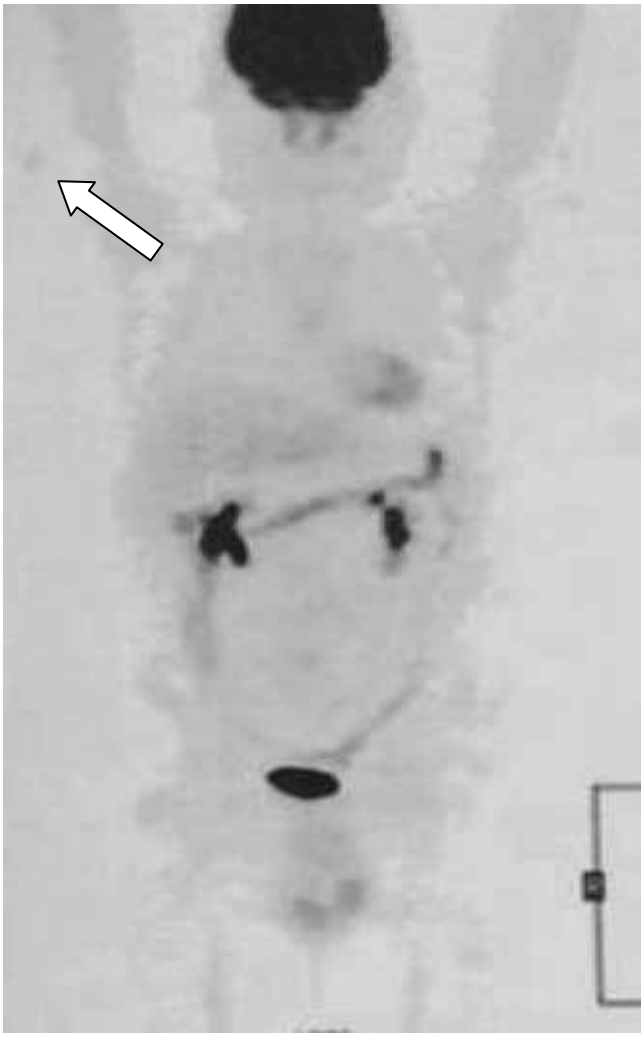

Figure 3: *PET F-18-FDG coronal image shows abnormal increased uptake at the superior posterior aspect of the right arm. (Arrow)*

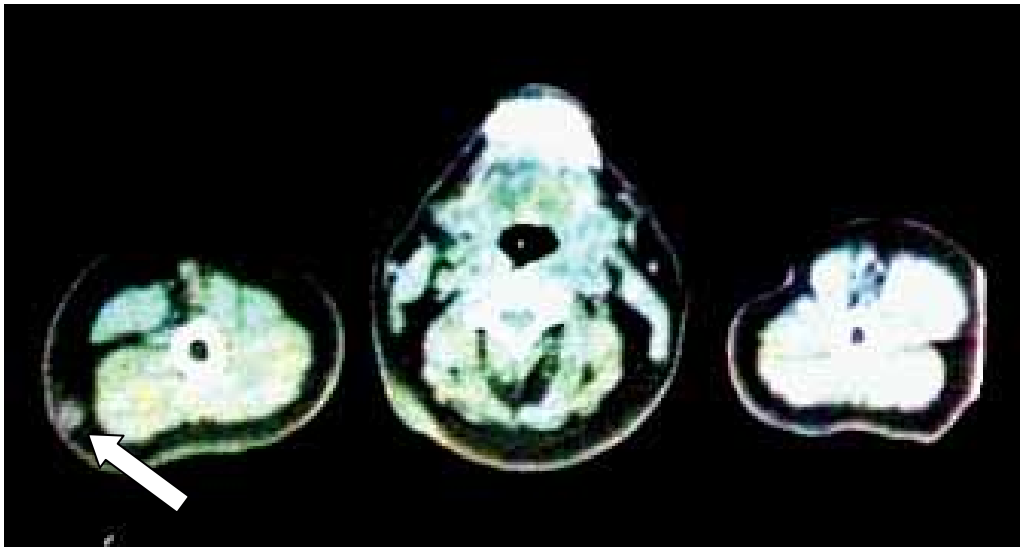

Figure 4: *Corresponding CT image shows a lesion at the superior posterior aspect of the right arm. (Arrow)*

Table 1: *Causes of hypophosphataemic osteomalacia*

Inherited causes	Acquired causes
X-linked hypophosphataemic rickets (associated with loss of function of PHEX)	Oncogenic osteomalacia
Autosomal dominant hypophosphataemic rickets (mutation of FGF-23 gene)	Vitamin D deficiency
Autosomal recessive hypophosphataemic rickets (mutation of dentin matrix protein)	Fanconi's syndrome
	Aluminum ingestion (reduces gastrointestinal absorption of phosphate)

and osteomalacia (2). Serum iPTH is usually normal or mildly elevated (3). Our patient had biochemical features consistent with the diagnosis. Differential diagnoses of hypophosphataemic osteomalacia are shown (Table 1).

Common causes of osteomalacia include phosphate depletion and disorders of vitamin D metabolism. Elevated ALP is a nonspecific finding consistent with bone fracture from any cause. It does rule out hypophosphatasia, a rare heritable cause of osteomalacia, which presents in adulthood with recurrent metatarsal stress fractures or symptomatic chondrocalcinosis. Hypophosphataemia, caused by renal phosphate wasting is normally a potent stimulator of 1, 25-dihydroxyvitamin D production. Low levels of 1, 25-dihydroxyvitamin D however is not diagnostic of oncogenic osteomalacia. Low 1, 25-dihydroxyvitamin D levels combined with severe hypophosphataemia suggest rare disorders that cause both renal phosphate wasting and down regulation of 25-hydroxyvitamin D-1-α-hydroxylase resulting in osteomalacia. An inherited cause is unlikely in our patient given no family history of metabolic bone disease and advanced age at presentation, suggesting an acquired disorder is more likely (4, 5). Fanconi's syndrome, or renal phosphate wasting associated with glycosuria, aminoaciduria, hyperuricosuria and type-2 renal tubular acidosis is usually inherited but may be acquired. Causes include myeloma, Sjogren's syndrome or heavy metal exposure. Uric acid and bicarbonate were normal. Urinalysis did not show glycosuria. Low 25-hydroxyvitamin D is not a feature of OOM. We hypothesize that the low levels seen in this patient may have been the result of long term lack of sun exposure due to immobility.

Patients with OOM as in this case typically have muscular weakness and bone pain that progresses gradually over months to years and can resemble a systemic disease or neuromuscular disorder resulting in diagnostic delay. OOM should be considered if radiographs demonstrate Looser's zones and malnutrition as a cause of osteomalacia has been excluded. There should be no gastrointestinal or genitourinary problem to account for the abnormal biochemical profile (6-8).

The primary tumour is usually of mesenchymal origin with prominent fibrous and vascular characteristics. Hemangiopericytoma, benign angiofibroma, giant cell tumours of bone and soft tissue, tumours associated with multiple myeloma, chronic lymphocytic leukemia, fibrous dysplasia of bone and neurofibromatosis have been described to cause OOM (2, 7-10). The tumor is often small, benign and slow growing; usually located over the extremities, head and neck. 50% of the tumours are located in the skeleton and not easily detectable on physical examination or routine radiography accounting for delay in diagnosis (3, 11-13).

Dual-energy x-ray absorptiometry may show low bone density, consequence of decreased mineralization of bone due to osteomalacia, not osteoporosis (4). T2-weighted short-tau inversion-recovery (STIR) MRI,^{201} thallium and whole body ^{99m} technetium sestamibi scintigraphy have been recommended for tumour search, as well as ^{111} indium pentetreotide or octreotide scintigraphy (7, 8, 11, 14, 15). Tumours frequently express somatostatin receptor subtype-2 and bind ^{111} indium labelled octreotide. Not all mesenchymal tumours causing OOM are positively identified by this

method (17). We did not have this facility. Successful tumour localization using PET/CT-F-18-FDG when multiple other imaging tests have failed has been described with increasing frequency (16).

The tumour produces fibroblast growth factor 23 (FGF-23), phosphatonin or phosphaturic hormone which underlies all the metabolic abnormality associated with hypophosphataemic syndrome. FGF-23 inhibits renal phosphate transport and 1, 25-dihydroxyvitamin D production (17-21). The injection of FGF-23 transfected cells into mice results in the characteristic features of OOM (3). However FGF-23 level is also increased in patients with X-linked hypophosphataemic rickets by the loss of function of the phosphate regulating gene with homologies to endopeptidase on the X chromosome (PHEX). It is speculated that PHEX protein functions as a protease to cleave FGF-23 and inactivate its function (3, 22, 23). Some other factors such as matrix extracellular phosphoglycoprotein and secreted frizzled-related protein 4 have also been implicated in the pathogenesis of OOM. Successful selective venous sampling for FGF-23 with MRI to localize tumours has been described (13, 16).

The clinical course of OOM is dramatically affected by removal of the causative tumour, resulting in rapid resolution of biochemical abnormalities. There is gradual improvement of bone mineralization and symptoms (2, 8, 10). Phosphate 1-4 grams/ day in divided doses and 1, 25-dihydroxyvitamin D replacement is recommended but with limited success (3, 8). Long term complications of treatment include secondary hyperparathyroidism and ectopic calcification, including nephrocalcinosis (24). As short term treatment, octreotide has been shown to rapidly correct serum phosphate levels and ALP activity in patients with tumours that were detected by octreotide scintigraphy (25). Others report failure to normalize serum phosphate but successful suppression of serum FGF-23 with octreotide therapy (26). CT guided radio frequency tumour ablation has been described; it may offer an effective, less invasive alternative to classical surgery especially for inaccessible tumours (27).

Conclusion

Diagnosis of OOM requires recognition of the typical clinical, biochemical and radiological features. Other conditions associated with hypophosphataemia must be excluded. Follow up with surveillance for tumour recurrence and biochemical monitoring is warranted. Our patient presented with the typical features of OOM and followed the classical route; with delay in obtaining the final diagnosis and difficulty locating the primary causative tumour. Fortunately, he responded promptly with normalization of phosphate and alkaline phosphatase accompanied by resolution of pain after tumour resection.

References

1. McCance RA. Osteomalacia with Looser's nodes (Milkman's syndrome) due to a raised resistance to vitamin D acquired about the age 15 years. *Q J Med* 1947; 16: 33-46.

2. Cai Q, Hodgson SF, Kao PC, *et al*. Brief report: inhibition of renal phosphate transport by a tumor product in a patient with oncogenic osteomalacia. *N Engl J Med* 1994; 330: 1645-1649.

3. Carpenter TO. Oncogenic osteomalacia – A complex dance of factors. *N Engl J Med* 2003; 348:1705-1708.

4. Reilly BM, Hart PD, Mascarell S, Chatrath H. A question well put. *N Eng J Med* 2009; 360: 1446-1451.

5. Jan de Beur SM, Levine MA. Molecular pathogenesis of hypophosphatemic rickets. *J Clin Endocrinol Metab* 2002; 87: 2467-2473.

6. Edminster KA, Sundaram A. Oncogenic Osteomalacia. *Semin Musculoskelet Radiol* 2002; 6: 191-196.

7. Sundaram A, McCarthy EF. Oncogenic osteomalacia. *Skeletal Radiol* 2000; 29: 117-124.

8. Jan de Beur SM. Tumor induced osteomalacia. *JAMA* 2005; 294:1260-1267.

9. Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets. *Cancer* 1987; 59: 1442-1454.

10. Folpe AL, Fanburg-Smith JC, Billings SD, *et al.* Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *Am J Surg Pathol* 2004; 28(1): 1-30.

11. Fukumoto S, Takeuchi Y, Nagano A, Fujita T. Diagnostic utility of magnetic resonance imaging skeletal survey in a patient with oncogenic osteomalacia. *Bone* 1999; 25: 375-377.

12. Drezner MK. Tumour associated rickets and osteomalacia. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 3rd ed. Philadelphia: Lippincott-Raven, 1996: 319-325.

13. Takeuchi Y, Suzuki H, Ogura S, *et al*. Venous sampling for fibroblast growth factor-23 confirms preoperative diagnosis of tumor-induced osteomalacia. *J Clin Endocrinol Metab* 2004; 89: 3979-3982.

14. Gershinsky M, Croitoru S, Dickstein G, *et al*. Imaging of oncogenic osteomalacia. *IMAJ* 2007; 9: 566-567.

15. Rhee Y, Lee JD, Shin KH, *et al*. Oncogenic osteomalacia associated with mesenchymal tumour detected by indium-111 octreotide scintigraphy. *Clin Endocrinol (Oxf)* 2001; 54: 551-554.

16. Khadgawat R, Singh Y, Kansara S, Tandon N, Bal C, Seith A, Kotwal P. PET/CT localisation of a scapular haemangiopericytoma with tumour-induced osteomalacia. *Singapore Med J* 2009; 50(2): 55-57.

17. Brame LA, White KE, Econs MJ. Renal phosphate wasting disorders: clinical features and pathogenesis. *Semin Nephrol* 2004; 24:39-47.

18. Kumar R. Tumor-induced osteomalacia and the regulation of phosphate homeostasis. *Bone* 2000; 27: 333-338.

19. Schiavi SC, Moe OW. Phosphatonins: a new class of phosphate-regulating proteins. *Curr Opin Nephrol Hypertens* 2002; 11: 423-430.

20. Nelson AE, Bligh RC, Mirams M, *et al*. Fibroblast growth factor-23: A clinical marker for oncogenic osteomalacia. *J Clin Endocrinol Metab* 2003; 88: 408-494.

21. Sommer S, Berndt T, Craig T, Kumar R. The phosphatonins and the regulation of phosphate transport and vitamin D metabolism. *J Steroid Biochem Mol Biol* 2007; 103: 497-503.

22. Jonsson KB, Zahradnik R, Larsson T, *et al*. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphataemia. *N Engl J Med* 2003; 348: 1656-1663.

23. Shimada T, Muto T, Urakawa I, *et al*. Mutant FGF-23 responsible for autosomal dominant hypophosphataemic rickets is resistant to proteolytic cleavage and causes hypophosphataemia in vivo. *Endocrinology* 2002; 143: 3179-3182.

24. Huang QL, Feiq DS, Blackstein ME. Development of tertiary hyperparathyroidism after phosphate supplementation in oncogenic osteomalacia. *J Endocrinol Invest* 2000; 23: 263-267.

25. Seijas R, Ares O, Sierra J, Pérez-Dominguez M. Oncogenic osteomalacia: two case reports with surprisingly different outcomes. *Arch Orthop Trauma Surg* 2009; 129: 533-539.

26. Elston MS, Stewart IJ, Clifton-Bligh R, Conaglen JV. A case of oncogenic osteomalacia with preoperative secondary hyperparathyroidism: description of the biochemical response of FGF23 to octreotide therapy and surgery. *Bone* 2007 Jan; 40: 236-241.

27. Hesse E, Rosenthal H, Bastian L. Radiofrequency ablation of a tumor causing oncogenic osteomalacia. *N Engl J Med* 2007; 357: 422-424.

ERRATA IN VOL 12(2), 2009

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Challenge and Support for Breastfeeding Mothers in Highly Motivated Malaysian Mothers
Nazatul SB, Ruby H *(JUMMEC 12(2): 70-73)*

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Parameswaran M, Sivaprakasam S, Dublin N, Rampal S, Razack AH, Thun TH, Chua CB *(JUMMEC 12(2): ????)*

We regret this mistake.