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EDITORIAL

Zika on Board

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The Olympics and Paralympic games bring joy to millions of people worldwide. This year it was held in Rio de Janeiro, Brazil amidst the Zika virus epidemic. On 1 February 2016, six months leading to the Olympics, the excitement was dampened by the World Health Organization declaration of the unprecedented vector-borne Zika virus (ZIKV) infection as a public health emergency of international concern [1]. At that point in time, people in Malaysia also felt the heat but had the consolation that the epidemic occurred across the Atlantic on the other side of the world. On 27 August 2016, Singapore reported the first local confirmed case of ZIKV infection in the city-state [2]. It was only a matter of time that Malaysia reported its first confirmed case of ZIKV infection on 2 September 2016 [3]. A 58-year old woman from Klang, Selangor was diagnosed as the first ZIKV case, who had earlier visited her daughter in Singapore who was infected by the ZIKV. As of 22 September 2016, the number of confirmed ZIKV cases in Malaysia has mounted to six with both Polynesia and Micronesia strains [4]. The occurrence of the disease in our continent brings to light how rapidly globalization and free movement of population across geographical borders can accelerate the arbovirus threat across the globe.

The ZIKV is spread through the bite of infected female *Aedes* mosquitoes and evidence has shown it can also spread via sexual and blood transmission [5]. Most of the cases are asymptomatic or subclinical while the symptomatic cases are self-limiting. Other manifestations include neurological (Guillain-Barré syndrome and meningoencephalitis) and autoimmune (thrombocytopenic purpura and leukopenia) complications. More alarming is the association of the virus with infants born with microcephaly as a result of pregnant mothers infected with ZIKV with the risk of microcephaly ranges between 1-13% [6, 7], though the direct causal relationship is still under investigation.

In line with the international response, Malaysia has intensified the surveillance and management activities to control its ZIKV epidemic. These include clinical surveillance, laboratory surveillance, microcephaly and Guillain-Barre Syndrome case detection as well as preparedness and response at all ports of entry [8]. The public health delivery system in Malaysia has improved tremendously over the years following lessons learned from the emerging and re-emerging infectious diseases that affected the country over the recent years. Apart from those commendable measures; in light of this ZIKV outbreak, there are looming questions even though may appear elementary are nevertheless pertinent which the healthcare fraternity should address. Where do we go from here? What more do we need to know and do to help us manage and control this outbreak more efficiently and effectively? These questions would certainly pose a challenge to our public health especially when this arbovirus shares the same transmission vector with dengue and chikungunya i.e., *Aedes* mosquito where the authorities in Malaysia are still struggling to achieve a satisfactory control level in the country.

What shall we do? We need a paradigm shift. We need to look at the re-emergence of ZIKV in a bigger perspective and manage it accordingly. Thus, instead of reacting merely to the notified ZIKV cases, we need to start strategizing how the transmission dynamics of the arbovirus family can be altered; this possibly means to look out of the box for the solutions. The conventional measures for prevention and control should also be complemented with two other elements

which are often neglected and underestimated in most outbreak response i.e., effective communication and social mobilization [9]. We must actively engage in communication with the public to hasten the containment by using all available forms of social medium. With tons of information about the virus in the media, the message should emphasize more on health education; empowering community on the case reports, transmission routes and infection complications rather than general statements on impact and world reaction towards ZIKV [10]. Only then social mobilization, which is commonly underutilized, may help mitigate the social and economic impact during an outbreak. An informed public understands the limitation and the need for the community. Only then we will appreciate the ripple effects - they will bring the community on board, educate the community to actively participate in the outbreak management, and share the responsibility as well as the outcome. Even when the community is faced with great anxiety, an informed public would be able to understand and support any move or decision made by the authorities concerned.

Of late, the controversy which surrounded ZIKV in Malaysia involved the ethical issue in dealing with termination of pregnancy in women with possible ZIKV-related fetal brain abnormalities. This was following a statement made by the Mufti of the Federal Territory, saying that Muslim women could abort their pregnancies if they were infected by the Zika virus to avoid the adverse effect on the lives of their families or the baby itself [11]. In Malaysia, the current law does not provide for abortion for pregnant mothers infected with Zika unless the pregnancy poses a threat to the mother's life [12]. The recent Centres for Disease Control guideline does not include pregnancy termination as an option in managing suspected or confirmed Zika infection. It advocates monitoring the pregnancy with serial fetal ultrasounds in suspected or inconclusive cases and retest for ZIKV when ultrasound suggests abnormalities consistent with Zika infection and fall short in mentioning the alternative path of termination of pregnancy [13]. On the other hand, World Health Organization guideline mentions subtly on the discontinuation of pregnancy as a possible next step in the management of pregnancies with the likelihood of foetal brain abnormalities and states that women who wish to discontinue their pregnancy should receive accurate information about their options to the full extent of the law [14]. The failure to include guidelines on the option of safe, legal termination of pregnancy in Zika-response strategies is not only an issue of reproductive rights but also an issue of reproductive justice [15]. At the time of writing, it is learned that the Ministry of Health of Malaysia will hold a discussion on the matter with the National Fatwa Council regarding termination of pregnancy for women infected by the Zika virus in order to reach a consensus. Irrespective of the outcome of the *fatwa*, we are in the opinion that whether a woman who wishes to carry her pregnancy to term or discontinue the pregnancy should be offered appropriate counselling so that she, together with her partner, will be able to make a fully informed choice on the next step of action.

Despite being a re-emerging disease, there is still much evidence required to effectively manage and control the ZIKV outbreak. The disease behaviour remains dynamic, and a concerted effort by the health authorities and policy makers in implementing the appropriate dynamic alignment to meet the challenges is imperative. It also requires heightened public awareness of personal responsibility which is of paramount importance. The public health preventive strategies remain the cornerstone in the control of this mosquito-borne disease.

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EDITORIAL

Herd Immunity or Heard Not of Immunity?

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INTRODUCTION

The Lancet published this early report by Andrew Wakefield et al on February 28th, 1998; "*12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain….Onset of behavioural symptoms was associated, by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children*" [1].

This article flipped the concrete evidence-based success story of vaccination into an emotionally charged and debatable topic of the century. It was only after a decade of much larger studies which failed to replicate their findings that it became evident that there was no association between Measles, Mumps and Rubella (MMR) vaccination and autism. While it is well known that scientific investigations can be wrong but what is unacceptable here is the fraudulent research practice, in this case, the presentation of wrong data, and the lead author's overwhelming undeclared conflict of interest. The aftermath could not be more devastating, Lancet withdrew the paper fully and the loss of his license to practice medicine in the UK in 2010.

THE WIDER IMPLICATION

The MMR-Autism link saga to the medical world meant that more research, time and money were poured to refute the study and also to expose the fraud but the repercussions however were not only confined to the medical profession. The greatest damage was the appalling tangential increase in vaccine refusal among parents worldwide which fuelled the measles outbreak across the United Kingdom (UK), United States and Canada in the year 2008 and 2009. UK for example, saw a drop in vaccination rates from 87.4 percent to 79.9 percent in the year 2000-01 and 2003-04 respectively and not surprisingly, a dramatic increase in measles cases in the UK in the year 2007-08, which was equal to the combined total measles notifications for the past decade [2].

As the news coverage on the controversy intensified, and coupled with advancement of technology in the social media network, the public perception on vaccination has suddenly changed, the most successful health revolution in the 20th century is now at stake. Seemingly increasing public distrust and confusion over the safety of vaccination were echoed and mischievously elaborated geographically, reaching out to most of the third world countries including Malaysia causing the dreaded domino effect of declining immunisation rates in many countries including our own.

THE BLIGHT ON OUR SUCCESS

We began our free national immunisation programme for Diphteria, Pertussis and Tetanus in 1958, the vaccination for Tuberculosis, Polio and Measles were gradually added into the immunization schedule between the years 1960 to 1980s. Malaysia has done very well since, based on the latest Millenium Development Goal (MDG) report in 2015, we have reached almost full coverage for one-year-old intake of the Measles, Mumps and Rubella (MMR) vaccine. The rate of intake of this vaccine was initially 70.1% in 1990, with massive improvement to 94.3% (2008) and 95.2% in 2013 [19], validated by a recent study in 2016 from a rural clinic in Sabah at 98.5% [29].

Lurking behind this success however is the rising trend of parents refusing to vaccinate their children. We now notice an increase in the number of vaccine refusal from 470 cases in 2013 to 648 in the following year and 1292 in 2015. Among the states in Malaysia, Kedah state recorded the highest number of vaccine rejection cases with steady rise from 239 cases in 2014 to 318 cases a year later.

Why is this happening? Data from the state of Kedah health statistics suggested that the major cause for the refusal was the concern regarding the vaccine contents and their religious permissibility (*halal*). This is supported by a cross-sectional study in 2013 done in Perak that showed the main reasons for parental immunisation refusal were preference to alternative treatment (75%), assumption that vaccines have no effect (37.5%) and apprehension on the vaccine contents (25%), other reasons included not being informed regarding vaccination from health practitioners, information from family members and media, religious influence, personal belief and long waiting time in the clinic [18]. In this study the refusal rate was 8 per 10,000 children per year and immunisation defaulter rate was 30 in 10,000 children per year. Vaccine refusal could also be caused by deferral which could be due to either ill infants or parents missing the schedule or appointments [17].

The number of vaccine preventable diseases has also showed steady increment for the past few years, in tandem with the decrement of immunisation rates. Measles cases in Malaysia has quadrupled from 195 cases in 2013 (6.6 cases per million population) to 794 cases up till September 2016 (34.7 per million population). This is certainly a blight on our success and it pushes us off track from the MDG target of global measles elimination by 2015.

APPREHENSION OF VACCINE CONTENT

Certain chemicals are present as ingredients in the vaccines to ensure safety and effectiveness of the final products. These substances naturally exist in the environment and only become toxic if they reach or exceed a certain threshold.

Among chemicals used in vaccine preparation include thimerosal (mercury), which is an organic compound containing ethylmercury. Its primary role is to prevent bacterial and fungal contamination and has been used as vaccine preservative since 1930's [30].

Virtually all vaccines are now mercury-free; and even if present its potential harmful effect is almost negligible as the chemical content in the vaccine is extremely low.

Aluminium is another compound used in vaccine preparation. It acts as an adjuvant to enhance the immune response to the vaccine antigen [30]. Exposure to aluminium from vaccines is well below the current minimum risk level of 2.0 mg/kg per day [30]. Interestingly, the content of aluminium is higher in breast milk compared to vaccines [31] as well in certain medications such as antacids [31].

However, another reason of apprehension that is being used as bone of contention by anti-vaccination campaigners is the permissibility (*halal*) of the vaccine contents.

THE ISLAMIC VIEWPOINT

The objectives of Islamic law (*maqasid shariah*) are the preservation of five fundamental elements in a person; religion, life, lineage, intellect and property. Correspondingly, the maxim of Islamic law (*Qawaid al Fiqh*) adheres to the principle of avoiding harm, thus taking steps towards maintenance of health and this includes vaccine administrations to prevent serious and life-threatening illnesses among children are in accordance to these principles.

As stated earlier, the main religious consternation regarding vaccination among Muslims parents revolves around the issue of permissibility (*halal*) of the vaccine contents. In this regard, many scholars in Islamic Jurisprudence have in fact issued clear ruling (fatwa) regarding the permissibility of most vaccines used as part of national immunisation programmes worldwide, including Bacillus Calmette-Guerin (BCG), Hepatitis B, Diphtheria, Tetanus, Pertussis and Rubella vaccines [20-24].

Differences of opinion however does exist among the scholars regarding vaccines that have substances derived from pork, which are forbidden (*haram*) in Islam, being used during their manufacturing process. As an example, for the production of oral polio and rotavirus vaccines, trypsin enzyme of porcine origin is used during production to

dissociate the virus from cultured cells, but it is later removed through the process of microfiltration. The use of this substance however has led the Malaysian Fatwa Committee National Council of Islamic Religious Affairs in 2008 to issue a ruling that the use of Rotavirus vaccine is forbidden, other religious considerations by the council include the availability of an alternative trypsin source and the absence of an urgent state (*darurah*) for its use. But other opinion does exist which can be considered to be more in tune with the spirit of Islam that discourages complexity in performance of religious duties, the ruling from the European Council of Fatwa & Research in 2003 led by Yusuf al-Qardhawi. He concluded that the use of oral polio vaccine was permissible based on the following reasons; the negligible amount of trypsin used in the vaccine preparation, the fact that trypsin is filtered and thus not detectable in the final vaccine, and finally what is forbidden (*haram*) is made permissible in the state of necessity. As a result of this ruling, many Muslim countries such as Saudi Arabia, Bahrain, Yemen, Qatar, Iraq, Morocco, Sudan and Pakistan [20] have incorporated Rotavirus vaccine that uses porcine trypsin in their national immunisation programmes.

THE WAY FORWARD

This requires efforts by all relevant stakeholders, government and non-government, to reverse the trend we see locally as well as worldwide. One great stride forward was the WHO approved Global Vaccine Action Plan, a framework to prevent millions of deaths by 2020 through more equitable access to existing vaccines for all peoples in all communities [30]. The aims here are to strengthen routine immunisation to meet vaccination coverage target, accelerate control of vaccine-preventable diseases as well spur research for development of new and improved vaccines [30].

Healthcare providers are undoubtedly the front liners in educating the parents and clarifying any doubts which may prohibit vaccine adherence among them. We know that counseling parents with clear information about the risks and benefits of vaccines, and taking advantage of clinical consultation visits for explanation of immunisation are among the most effective strategies suggested to achieve this [31]. In Malaysia, forums and educational talks to the general public are actively organised by the Malaysian Ministry of Health and other non-governmental organisations to reach for these parents at all levels and localities. Besides that, social media is also very effective and is a borderless educational platform to reach the community.

Finally, the history of vaccination had been a great success story of the last century, Measles vaccination alone has been estimated to have helped save 17.1 million lives in the year 2000 [27]. Lack of knowledge on the issue compounded with contradictory information in social media have led to the disruption of herd immunity that previously had been the gate keeper in protecting our children from vaccine-preventable disease. We must do all we can to ensure it remains a success.

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REFLECTIONS

Medical Education in Malaysia: The Evolving Curriculum (Part 1)

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THE TRADITIONAL CURRICULUM

Medical education in Malaysia has evolved in the past 50 years since independence. This paper highlights the various stages of curriculum development that were made to meet the needs of the developing country.

Malaya was under British rule between the 18th and the 20th Centuries. British Malaya as it was then known comprised of the Peninsular States and the Straits Settlements of Penang, Malacca and Singapore. Western medicine was introduced to the then Malaya in Singapore, with the setting up of the first medical school in 1907. It was called the Government Medical School and later became known as the King George VII College of Medicine in Singapore. In 1910 the first batch of seven male Medical graduates received their Licentiate in Medicine and Surgery (LMS) [1].

In 1949, the University of Malaya was established, based in Singapore, with a branch set up in Kuala Lumpur in 1959. In 1961, both governments of Singapore and Malaya agreed and passed legislation in Parliament to make the Kuala Lumpur Campus an autonomous body known as the University of Malaya; with its own medical school and teaching hospital. Thus in 1962, the government approved the setting up of the University of Malaya Medical Faculty, together with its teaching hospital, in the Klang Valley. The Faculty became fully functional in 1964 with the first intake of 64 medical students. After the hospital was built, the whole complex was named the "University of Malaya Medical Centre (UMMC)", with facilities for undergraduate medical teaching, hospital services, the nursing school and other ancillary services put in place [2].

Professor Thumboo John Danaraj who was then Professor of Medicine in the Medical Faculty at the University of Singapore, was appointed as Founding Dean of the Medical Faculty, University of Malaya in Kuala Lumpur [3]. With his appointment, the process of "head hunting" and appointment of academic staff began together with the selection of potential students for the first academic session.

It was mandatory that the Faculty get relevant and competent professionals to start the ball rolling. These medical academicians came from different parts of the globe, including Sri Lanka, Canada, Singapore and the UK (Figure 1).

Front Row: Professor Winifred Danaraj, SPM (2nd from left), Professor TJ Danaraj, Dean (5th from left), Professor Loke, Biochemistry (6th from left)
Back Row: Professor Chan Kok Ewe, Pharmacology & other Professors (from left to right)

Figure 1 The founding teachers: Faculty of Medicine, University of Malaya, 1965 (Courtesy of the late Prof. TJ Danaraj).

With these academicians on board, the toiling of planning and designing of the medical curriculum started since the first batch of medical students was scheduled to enter the medical school in 1964.

Globally, the medical curriculum followed the traditional didactic teaching of basic sciences comprising of anatomy, physiology and biochemistry

in the first year of undergraduate medical course. In the second year, the subjects of pathology, pharmacology, medical microbiology and parasitology were introduced. This was interspersed with topics on communicable diseases and principles of social and preventive medicine (SPM). The thrust of the undergraduate curriculum then was in the various aspects of issues related to social and preventive medicine. This was deemed to be important because the newly formed Malaysia, for the most part, was still mostly rural.

Professor Danaraj, having had experience as an academician in Singapore, felt that the didactic teaching of "dry" basic science subjects may not be perceived as interesting and relevant by the medical students. Thus, early on in the undergraduate medical curriculum, he introduced the clinical correlation classes (CCC) with clinical cases brought to the auditorium to demonstrate the physical signs and correlate them with basic science topics that were learnt during the previous week (Figure 2). This made the preclinical students understand the importance of basic medical science subjects in order to be able to explain the symptoms and the development of physical signs when disease occurs.

Figure 2 Clinical Auditorium, University of Malaya Medical Faculty. Clinical integration with patients starts in year 1 (CCC) (1967) [Courtesy of the late Prof. TJ Danaraj].

This was perhaps the earliest change in the curriculum to facilitate the teachers to think about possibilities of making basic science "dry topics" more interesting to the students. This gradual introduction of clinical medicine into basic science "preclinical years" and *vice versa* in the clinical years was perhaps the beginning of integrated teaching and the evolution of the undergraduate medical curriculum in Malaysia in the late 1980's.

The clinical years begin from years 3 to 5 with rotations in general medicine, surgery, paediatrics orthopedics and obstetrics and gynaecology. In the clinical years, the integration of basic sciences in the form of clinico-pathological case (CPCs) discussions in the final year, sets the stage for future developments in the undergraduate curriculum. The clinical postings and the CPCs were meant to expose the students to develop their critical and analytical thinking skills during their clinical clerkships. Thus, learning to make reasonable diagnoses based on patho-physiological processes that had occurred, with minimal investigative procedures. This was meant to prepare them for their general medical service as medical officers in the rural areas, and also providing them with the basics for future career development.

NATIONAL STRATEGIES TO IMPROVE HEALTH CARE FOR THE POPULATION

Let us now look at the needs of the country then, and how the medical schools were tasked by the Government to contribute towards improving the health services in the then rural Malaysian society.

During the British Administration of the then Malaya, the legacy left behind by the British was a network of health services that extended to the really remote parts of Peninsular Malaya [4], as depicted in Figure 3.

When Malaya had her independence in 1957, the health programs were somewhat coordinated although there was a gross deficiency of doctors to run the district hospitals and the general hospitals. Healthcare then was provided at best by the hospital assistants (now known as medical assistants, MA).

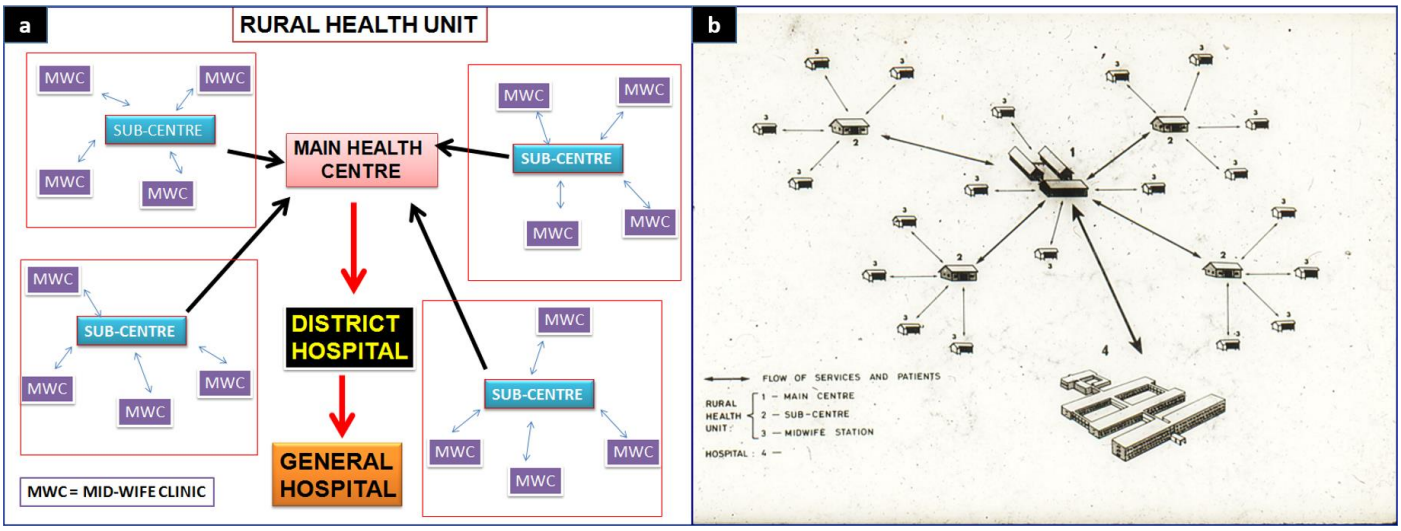

Figure 3 Network of Government run Health Care Services (Legacy from the British Rule of Malaya). a) Rural health unit. b) Replica of the original photo (Courtesy of the late Prof. TJ Danaraj).

During this period the teaching of medicine closely followed the British medical education system that was practiced in the UK. In those early days, the teaching of medicine was by apprenticeship with some knowledge of basic sciences to explain the symptoms.

Then came the didactic (traditional); and scientific discipline model. This preceptor-ship had advantages especially when there was as yet no formal structured curriculum mapping. To this day, clinical mentoring and preceptor-ship is practiced to some extent in the clinical ward rounds with bedside teaching. The concept of mentoring and development of clinical acumen was very apt in clinical practice; both during the undergraduate days and continues in the world of medical academia to this day. This is an art that is slowly dying with the advent of investigative medical practices.

While doctors have to know how to use modern investigative tools, clinical acumen is still required, to be able to make reasonable diagnosis and institute treatment; to be able to determine what investigations are appropriate and when referrals are necessary. This is so because government-sponsored medical graduates face compulsory service that may be in rural areas where there is scarce advanced investigative tools to aid them in making the diagnosis.

In the 1990's with the inevitable trend of producing more specialists, it was deemed necessary for the Ministry of Health to ensure that there will be enough primary care providers and general physicians who would approach patients in a holistic manner. This was tasked to the universities to take the lead to develop programs to train medical officers as generalists and family and primary care physicians.

Medical schools in Malaysia, in developing their medical curriculum, need to address these issues and tailor-make the curriculum to suit the healthcare needs of the country.

To be continued in Part 2: The Blended Curriculum

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CASE REPORT

A Case Report of Intramuscular Abscess Secondary to *Epicoccum nigrum* infection

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ABSTRACT

A 36-year-old man with underlying chronic lymphocytic leukemia had left arm swelling for a duration of 3 months. Clinically, the affected arm was swollen, erythematous and tender. *Epicoccum nigrum* was isolated from the culture of the tissue that was obtained intra-operatively. He was treated and responded to voriconazole therapy. To the best of our knowledge, this is the first case of intramuscular abscess as a result of *E. nigrum* infection in an immunocompromised patient.

KEYWORDS: Epicoccum, *Epicoccum nigrum*, intramuscular abscess, pyomyositis

INTRODUCTION

Intramuscular abscess, also known as pyomyositis, is a disease that is characterized by suppurative lesion within skeletal muscles. *Staphylococcus aureus* has been described as the most common causative agent [1]. However, fungi such as dematiaceous moulds have rarely been described as one of its causative agents.

The term 'dematiaceous moulds' (also known as black moulds) are a fascinating and complex group of fungi characterized by the formation of a dark pigment due to the production of melanin in the cell walls of hyphae or conidia or both [2]. These fungi have a worldwide distribution and are commonly isolated from soil and plants. It has been considered as an opportunistic fungi and a rare causative agent in humans. Saprophytes were historically considered as a rare cause of diseases in humans; however, they are now considered as emerging fungal pathogens [3].

Generally, the clinical spectrum of diseases caused by these fungi include eumycotic mycetoma and chromoblastomycosis, predominantly in hosts with normal immune systems, and phaeohyphomycosis, which is most common among immunocompromised patients [4, 5]. These diseases are frequently diagnosed on the basis of a unique histologic picture of the fungus in tissue, followed by isolation of the fungus in culture and morphologic evaluation.

Epicoccum sp. is one of the dematiaceous moulds and has been described as an opportunistic fungal pathogen. It has also been described as one of the pathogens responsible for the acute skin infection in an elderly patient [6].

Here, we report a case of a 36-year-old immunocompromised man with underlying chronic lymphocytic leukemia who presented with *Epicoccum* intramuscular abscess in his left arm.

CASE PRESENTATION

A 36-year-old Malay male, who is a known case of having chronic lymphocytic leukemia (CLL), had been previously admitted for prolonged intermittent fever 1 week prior to current admission. He was initially treated as having pneumonia and empirically was started on intravenous Tienam 1 g three times daily.

In the ward, the clinician-in-charge had noticed that his left arm was swollen. On further history taking, it was found that he had experienced the swollen arm for the past 3 months prior to admission, and that it was associated with pain and redness. The swelling was actually precipitated by lifting heavy objects. The swelling became worst for a few days while in the ward. There was no pus discharge or complaint of swelling on other body sites.

On examination, he was afebrile, conscious, alert, not toxic looking and vital signs were stable. The swelling on his left arm was measured about 5 x 5 cm, and was erythematous, warm, soft and fluctuated. No discharge of pus was noted from the swollen area. On systemic review, there were crepitations that was heard on his right lower zone. Thus, he was treated as having pneumonia. There was also hepatosplenomegaly, which most probably was due to his underlying CLL. Other systemic review was unremarkable.

In the beginning, in view of the left arm swelling, he was treated as having left arm cellulitis and referred to the orthopaedic team. A left arm ultrasound was done and it showed an hypoechoeic lesion extending from the left mid arm to forearm (anterior part within intramuscular measuring about 9.24cm) which was highly suggestive of a left arm intramuscular abscess. Upon X-ray of the left arm and forearm, it only showed a soft tissue swelling with no evidence of bony lytic lesion. He was then treated with intravenous Cloxacillin 1 g four times daily.

Incision and drainage procedure was done on the swelling. Pus aspirate and tissue were collected for microbiology investigations. Tissue biopsy also was sent for further histopathological examination. However, there was no growth obtained from the pus aspirate culture.

In view of the patient's fever still prolonging despite having been given antibiotics, disseminated fungal infection of soft tissue, lung and spleen was suspected. Thus, he was started with oral Voriconazole 400 mg twice daily and intravenous Amphotericin B 20.8 mg per day empirically.

After a 9-day-incubation of tissue culture, dematiaceous mould was noted on culture media. However, histopathology examination only showed acute non-specific inflammation with no organism seen. The patient was still febrile with spiking temperature after 1 week of combination anti-fungal therapy (Amphotericin B and Voriconazole). Thus, intravenous Amphotericin B was increased up to 38 mg per day and Voriconazole was reduced to 100 mg twice daily. Intravenous Caspofungin 70 mg stat followed by 50mg/day was added to the list of combination medications.

After 2 weeks, the fungal culture was identified as *Epicoccum nigrum.* Amphotericin and Caspofungin were discontinued. Tablet Voriconazole was changed to 200 mg twice daily for 8 weeks. The patient responded well and was afebrile after 4 weeks of Voriconazole therapy. The post-operative wound was clean with no pus discharge or slough.

Laboratory investigation

Other relevant laboratory investigations were as follows: Full blood count on admission showed leucocytosis (total white cell count: 16.3 $X10^3$/uL), severe anaemia (haemoglobin: 7.6g/dL) and thrombocytosis (platelet: $616X10^3$/uL).

Full blood picture showed a left shift which is suggestive of being due to an underlying infection and is consistent with chronic lymphocytic leukemia. Septic workup such as blood culture from peripheral and central blood, urine culture, sputum for acid fast bacilli, and melioidosis serology were unremarkable.

DISCUSSION

Dematiaceous fungi cause a wide range of diseases, ranging from localized to disseminated infection and allergic diseases [7]. *Epicoccum nigrum* is one of dematiaceous fungi that is commonly found in soil, decayed plants, air, and water. It has mainly been described as the cause of hay fever and allergic manifestations such as skin allergy and allergic fungal sinusitis [8]. Besides that, a few reports have reported that *Epicoccum sp*. has been isolated from air sampling [9, 10].

Its role as an opportunistic pathogen has been described earlier in immunocompromised patients with skin allergy [9]. *Epicoccum sp*. is also known as one of the toxigenic moulds due to its capability of producing toxins, which include flavipin, epicorazine

A and B and indole-3-acetonitrile, which has antibiotic-like-substance properties [11]. Furthermore, *E. nigrum* are capable of synthesizing extracellular fungal polysaccharides known as epiglucan [12].

This pathogen has also been reported to be as one of the causative agents in a case of an elderly patient who presented with acute skin infection in the lower part of the leg with co-infection with *Aspergillus flavus, Emericella nidulans,* and *Pestalotiopsis sp.* In another case report, *E. nigrum* had been isolated in renal bezoars of a young male patient with history of percutaneous nephrolithotomy to remove his renal stones as the treatment of his renal calculi and severe hydronephrosis [11].

With regards to our case, the underlying immunocompromised state of chronic lymphocytic leukemia has played a role as a predisposing factor in the disease process. The possible explanation on disease acquisition would be that the underlying immunocompromised state has changed the nature of the saprophytic fungi to pathogenic fungi in humans. According to the literature, *E. nigrum* has been found to colonize the nasal sinus [8]. This could possibly explain its route of entry into the lungs and body systems. Other possible explanations pertaining to this case would be primary localized infection which probably has disseminated to the lungs. However, there was no strong evidence to conclude fungal pneumonia in this patient. Besides that, there was no history of skin trauma that provides an entry of this saprophytic pathogen to correlate with the possibility of it being the source of infection.

Choice of treatment and appropriate management will depend on the clinical presentation, whether as a localized or disseminated disease. Localized infection can be treated with just excision alone. Systemic or disseminated illness may be difficult to treat with anti-fungal therapy and is associated with a high mortality rate. Generally, triazoles such as Voriconazole, Posaconazole, and Itraconazole have the most consistent *in vitro* activity against dematiaceous moulds [7].

Combination therapy has been reported to have synergistic effects in some species. However, there is lack of data specifically against *E. nigrum* [7]. Combination therapy was also reported to be effective in combating the Epicoccum infection. A previous case of *E.nigrum* pyelonephritis was successfully treated with combination therapy of Amphotericin B and Voriconazole for 2 weeks duration [11]. Based on the current findings and previous published cases, Voriconazole should be considered as it has been found to be helpful in the treatment of *Epicoccum* infections.

CONCLUSIONS

In conclusion, the present case showed that *E. nigrum* should be considered as one of the causative agents in an opportunistic infection. Proper and adequate therapy is crucial in the management of the patient.

Conflict of Interest

Authors declare none.

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