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Educational Corner – Case Report

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Talaromyces marneffei Fungemia in a Patient with AIDS: The First Reported Observation in the Middle East

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Abstract
We report the case of a patient who presented with septic shock and multiorgan failure. Methicillin-resistant *Staphylococcus aureus* and *Talaromyces marneffei* were cultured from his blood. He was treated with a course of vancomycin along with amphotericin. Further work-up revealed him to be HIV positive with an absolute CD4 count of 14 cells/μL. Despite aggressive medical support, he eventually succumbed to his illness with *Klebsiella pneumonia* sepsis. To the best of our knowledge, this is the first reported *T. marneffei* infection in the Middle East and the first observation of concomitant community-acquired methicillin-resistant *S. aureus* bacteraemia and talaromycosis from the Middle East region.

Introduction

Talaromyces marneffei infection is an emerging public health problem, especially among the HIV patients in South East Asia. Talaromycosis carries a very high mortality rate if untreated, and early initiation of amphotericin is recommended to improve the outcome. It is therefore becoming more important for those who are involved in the care of patients with HIV infection to be familiar with this pathogen. Laboratory confirmation of the infection is crucial since the diagnosis is often difficult due to the overlap between the clinical presentations of various opportunistic infections in HIV patients.

Case Presentation

A middle-aged patient was brought in by ambulance with fever and status epilepticus. The patient had history of fever, weight loss, abdominal pain, and vomiting for the past 2 months, which were

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Table 1. Initial laboratory test results upon arrival to the emergency department

Laboratory parameter	Patient's result
WBC	2×10^3/μL (absolute lymphocyte count: 1.6×10^3/μL)
Hb	6 g/dL (normocytic normochromic)
Platelet	62×10^3/μL
INR	2
APTT	72 s (28–41)
D-dimer	15 mg/L (<0.5)
Fibrinogen	350 mg/dL
Pro-BNP	9,500 pg/mL
ESR	140 mm/1 h
CRP	120 mg/dL
PCT	65 pg/mL
Lactate	4.2 mg/dL
Blood culture	Negative
Liver function test	ALT: 121 IU/L, AST: 597 IU/L, LDH: 2,400 IU/L ALP: 771 IU/L, GGT: 400 IU/L Albumin: 2.4 g/dL Globulin: 5.9 g/dL Total bilirubin: 0.5 mg/dL, ammonia: 17 μmol/L
CPK	2100
Renal function	Cr: 6.8 mg/dL Urea: 217 mg/dL Na: 139 mmol/L, K: 5.9 mmol/L HCO3: 8.8 mmol/L
Random glucose	90 mg/dL

treated by different general practitioners with various courses of oral antibiotics. The patient was of Bangladeshi background. There was no other significant past medical history. We were unable to gather any further collateral history from friends or the paramedical staff who accompanied the patient.

On arrival, the patient had a temperature of 37.8°C, heart rate of 140 bpm, blood pressure of 90/60 mm Hg, respiratory rate of 30 and pulse oximetry reading of 90% in room air. The Glasgow Coma Scale (GCS) was 3/15. Pupils were 4 mm with sluggish response bilaterally. There were no clinical signs of meningeal irritation. Chest auscultation revealed reduced breath sounds in both lung bases. Cardiovascular and abdomen examinations were unremarkable. There was no obvious skin rash or lymphadenopathy.

Initial lab workup revealed signs of multiorgan involvement with pancytopenia, uraemia, deranged liver enzymes, and coagulopathy. Table 1 shows the results of the initial laboratory tests at arrival.

Patient was intubated immediately at arrival due to low level of consciousness, and then resuscitated aggressively with fluids, inotropes, and steroids. A non-contrast brain CT scan showed diffuse brain oedema. Chest CT scan showed bilateral lower lobe consolidations with pleural effusions. Abdomen CT scan showed mild hepatomegaly with moderate ascites.

Lumbar puncture was deferred as the brain CT showed signs of cerebral oedema, and the patient also had a deranged coagulation profile. The initial impression was community-acquired pneumonia resulting in septic shock and multi-organ failure. He was hence started on IV meropenem and vancomycin.

Two sets of blood cultures (Bact Alert blood culture system, BioMerieux, France) were collected on admission. On day 2 of admission, the blood culture was positive for methicillin-resistant *Staphylococcus aureus* (MRSA). Renal-adjusted dose of IV vancomycin was continued with monitoring of blood vancomycin levels. On day 6 of admission, the other bottle of the same set showed growth of fungal elements (elongated yeast-like cells) which were later identified as *T. marneffei*. The isolate showed the typical yeast whitish growth on glucose dextrose agar at 37°C and the greenish fungus with white centre with the typical maroon colour pigment on the back of the plate at 28°C (Fig. 1). Microscopy of the fungus was also characteristic of the organism. The third set of blood culture collected on the second day of admission also grew methicillin-resistant *S. aureus* and *T. marneffei*. Renal-adjusted dose of Amphotericin B was started immediately after the report of fungal filaments. Meanwhile, the patient remained on mechanical ventilatory support and required a few sessions of haemodialysis.

Once we ascertained the presence of *T. marneffei* fungemia, a suspicion for immune-compromised state was raised and we proceeded to check the HIV status of our patient. HIV ELISA test was positive with absolute CD4+ cell count of 14 cells/μL and viral load of 120,000 copies/mL. HIV workup revealed the following results: HIV genotype group M, subtype G, with a pan-sensitive virus. Sputum cultures of the patient grew mycobacteria other than tuberculosis. The patient had no clinical or lab evidence of other AIDS –associated opportunistic infections or malignancies.

The patient's general condition was initially improving after receiving vancomycin and amphotericin. Repeated blood cultures collected until the third day of antifungal treatment remained positive for *T. marneffei* while cultures collected on day five were negative. His fever subsided, and his level of consciousness improved. There were no further seizures once his metabolic profile was corrected.

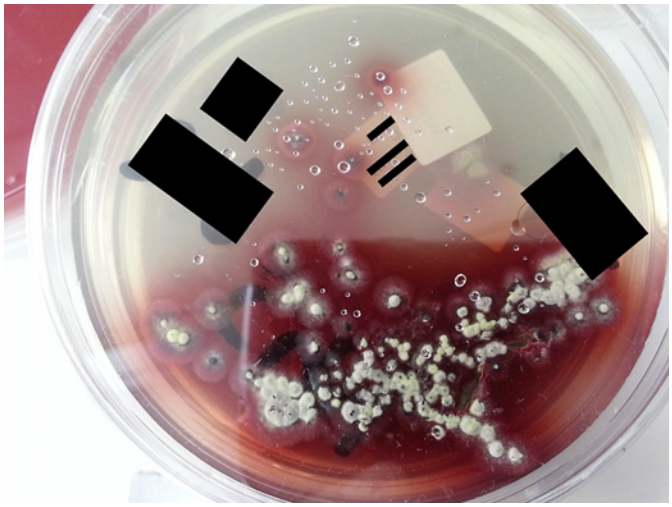

Fig. 1. The isolate showed the typical yeast whitish growth on glucose dextrose agar at 37°C and the greenish fungus with white centre with the typical maroon colour pigment on the back of the plate at 28°C.

Despite multiple attempts to wean him off mechanical ventilator, the trials were deemed unsuccessful due to clinical evidence of critical illness neuropathy. He was subsequently tracheotomised for further ventilatory support.

A transthoracic echocardiogram did not show any evidence of infective endocarditis. A transoesophageal echocardiogram could not be arranged as patient remained on ventilator support throughout his stay. He was also given induction therapy with amphotericin for 2 weeks and then kept on maintenance therapy with itraconazole.

Due to the risk of precipitating immune reconstitution inflammatory syndrome, it was decided to withhold the initiation of anti-retroviral treatment temporarily until his general condition stabilized. After a 4-week turbulent stay in ICU, he eventually acquired a bloodstream infection with carbapenem-resistant *Klebsiella* pneumonia. He was commenced on IV colistin but failed to show a favourable clinical response. He eventually succumbed to overwhelming sepsis and multi-organ failure.

Discussion

New HIV infections have been on the rise from the Middle East and North Africa (MENA) region. In 2016 alone, there were an estimated 18,000 new cases of HIV infection and a staggering 11,000 AIDS-related deaths from the MENA region that is reported by the UN [1]. These figures may not be a true depiction of the emerging HIV epidemic in this region [2].

T. marneffei (formerly known as *Penicillium marneffei*) [3] is an opportunistic pathogen that causes an invasive fungal infection among immune-suppressed patients and is characteristically thermally dimorphic. It grows as a mycelium at 25°C, but at 37°C it grows as yeast with a unique pink or red pigment on blood agar. This pathogen was initially isolated from the liver of a bamboo rat in 1956 [4]; however, the first clinical case of disseminated talaromycosis in a patient with lymphoma was reported by DiSalvo and colleagues in 1973 [5].

It is endemic in most countries of Southeast Asia, especially Thailand, India, China, Hong Kong, Vietnam, and Taiwan [6, 7]. In fact, *T. marneffei* is identified as one of the leading causes of mortality among the HIV population in South-East Asia [6]. Therefore, talaromycosis is an important differential to consider in febrile HIV patients who have a history of travel to or residence in Asia. This is especially true in the case of this patient as exposure to invasive endemic mycosis such as *Talaromyces* includes any travel to or contact with fomites from an endemic area, no matter how remote that travel history may be [3]. Epidemiological data from Bangladesh are severely lacking, but a recent case report was published in 2022 about their first confirmed case of talaromycosis, presenting as non-resolving pnemonia [8]. However, rarely it can occur in non-endemic regions also as illustrated by Yo et al., who have described a case of disseminated *T. marneffei* infection in an African HIV patient who did not have any history of exposure to endemic regions [9]. Although talaromycosis is not an uncommon AIDS-defining illness in endemic regions, especially in patients who have a CD4+ cell count of <100 cells/μL, yet it remains unheard of in the Middle East [10].

Although the exact route of acquiring the infection is unknown, it is postulated to be transmitted via inhalation or rarely, by direct inoculation of the pathogen. No cases of human-to-human transmission have been documented [11].

This condition is increasingly being recognized among immune-competent individuals also. Immune-competent persons in endemic regions are likely to acquire a subclinical infection. This was demonstrated by a serological survey performed by Vanittanakom et al. [12] in northern Thailand, where 10% of population had evidence of latent infection with *T. marneffei*.

Common clinical manifestations of disseminated *T. marneffei* infection are non-specific and include fever, weight loss, cough, lymphadenopathy, hepatosplenomegaly. The classical umbilicated cutaneous lesions resembling molluscum contagiusum are the hallmark of this infection.

Since a lumbar puncture was not done in our case, the neurological symptoms could be secondary to sepsis or uraemic encephalopathy rather than CNS involvement with talaromycosis. In fact, cases of disseminated *T. marneffei* with central nervous system involvement are relatively

uncommon. In a recent review, Thuy et al. have described a retrospective series of 21 HIV patients who presented with *T. marneffei* infection of the central nervous system (out of 677 registered cases of talaromycosis). The CSF culture was positive for *T. marneffei* in all these cases [13].

The gold standard method for diagnosis is to culture the fungus from the blood or biopsies of the bone marrow, lymph node, liver, and cutaneous lesions. It typically takes four to 7 days to grow in culture [14]. The characteristic thermal dimorphism and production of red pigment can easily be demonstrated in the lab. Serodiagnosis and nucleic acid assays are not routinely used in clinical practice [9].

The disease is associated with high mortality because of delay in diagnosis, initiation of appropriate antifungal therapy, and misdiagnosis with other infections. Untreated cases of invasive *T. marneffei* are all fatal. In patients with severe disseminated infection, the ideal therapeutic regimen includes induction therapy with amphotericin for 2 weeks, followed by oral itraconazole for 10 weeks [15, 16]. This is also the recommended regimen in patients with talaromycosis who might have central nervous system involvement as well [13]. Since relapse of *T. marneffei* infection is common, secondary prophylaxis with antifungals is recommended until the CD4+ cell count is >100 cells/μL for at least 6 months. The secondary prophylaxis can be reinitiated once the CD4+ cell count falls below 100 cells/μL [17].

We describe the first case of *T. marneffei* infection in the Middle East, in a patient with advanced HIV disease. He was of Bangladeshi background and, despite aggressive medical therapy, eventually succumbed to carbapenem-resistant *Klebsiella* pneumonia and multiorgan failure secondary to sepsis.

Statement of Ethics

The case was done, according to the guidelines of Helsinki Declaration. Hence the condition of the patient's consciousness does not allow the physician to obtain consent, and there were no relatives. For the importance of the case for science, a letter from the patient's most responsible physician was obtained for publication of this case and any accompanying images. Moreover, patient consent was waived by the Dubai Scientific Research Ethics Committee (DSREC), decision number DSREC-GL07-2021, dated October 27, 2021.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.H. has drafted the content, with an extensive literature review, and took the lead in writing the manuscript. S.H. assisted in the production and critical revision of the report. L.D., Z.O.D., and R.A. oversaw the creation of the report, provided critical feedback, and were also involved in the direct care of the patient.

Data Availability Statement

All data generated during this case report are included in this paper. However, further details are available by writing to the corresponding author.

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