CASE REPORT

Visceral leishmaniasis (kala-azar) and malaria coinfection in an immigrant in the state of Terengganu, Malaysia: A case report

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Malaria is endemic in Malaysia. Leishmaniasis is a protozoan infection rarely reported in Malaysia. Here, a 24-year-old Nepalese man who presented with prolonged fever and hepatosplenomegaly is reported. Blood film examination confirmed a Plasmodium vivax malaria infection. Despite being adequately treated for malaria, his fever persisted. Bone marrow examination showed presence of Leishman-Donovan complex. He was successfully treated with prolonged course of amphotericin B. The case highlights the importance of awareness among the treating physicians of this disease occurring in a foreign national from an endemic region when he presents with fever and hepatosplenomegaly. Coinfection with malaria can occur although it is rare. It can cause significant delay of the diagnosis of leishmaniasis.

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Introduction

Malaysia is a tropical country and located in the region of Southeast Asia. Malaria is endemic in this region, whereas leishmaniasis is not. Malaysia is considered free of endemic Leishmania species although few species of Malaysian sandflies have been described, possibly because the sandflies are not largely anthropophilic.1,3 However, with the advancement of world travel today, including migration of refugees or workers from endemic regions, visceral leishmaniasis (VL) has emerged as an increasingly important and imported infection in many countries. Cases of cutaneous leishmaniasis have doubled and tripled in the Netherlands.
and the United Kingdom, respectively, in the past decade, whereas cutaneous leishmaniasis and VL cases in Australia have increased in significant numbers over the past few years. Therefore, this condition needs to be suspected in someone who presents with prolonged fever and has history of recent travel or among the immigrants originated from endemic area.

Here, we report a case of a foreign worker who had been referred to us from a district hospital for the management of prolonged fever after successful treatment of malaria infection.

**Case report**

The patient was a 24-year-old apparently healthy gentleman from Nepal, arrived in Malaysia in August 2007 after being successfully secured an employment as a construction worker in one of the states in Malaysia. His problem started 2 weeks after his arrival, with insidious onset, on and off moderate grade of fever. Subsequently, he developed vague abdominal pain, which was mild and intermittent in nature. He stayed in an overcrowded temporary hostel with other new immigrant workers from various countries of origin. He ate the same food with others. He denied any history of vomiting or diarrhea.

At the second week of illness, his condition got worse, with more persistent fever. The left-sided abdominal pain persisted and became more intense and unbearable. At this point, he decided to seek for medical treatment. He admitted himself at one of the district hospital in the state of Terengganu, one of the 14 states in Malaysia. Septic workup, including blood culture, blood film for malaria parasite, urine culture, typhus serology, and typhoid serology was carried out.

The blood film result was positive for *Plasmodium vivax* with a parasite density of 8,000/μL (Fig. 1). Oral chloroquine (600 mg) was given initially as a loading dose, followed by another 300 mg 6 hours later and subsequently 300 mg daily for 2 more days. Oral primaquine (15 mg daily) was then added on (after reviewing his glucose-6-phosphate dehydrogenase profile). Oral primaquine was given for a total of 14 days.

After 7 days of adequate antimalarial therapy, he still has persistent spikes of temperature and did not look well. His appetite remained poor. Posttreatment blood films for malaria parasite were negative for *plasmodium* parasite.

He was referred to Hospital Sultanah Nur Zahirah (HSNZ) during the second week of treatment. HSNZ is located in Kuala Terengganu, the capital city of Terengganu. HSNZ serves as a referral and secondary hospital for the state of Terengganu.

At presentation to HSNZ, he looked lethargic but not ill. His vital signs were in the normal range. His body temperature was 38.3°C. He appeared pale but not jaundiced. His skin looked normal. The spleen was visibly enlarged, crossing the umbilical line, and firm but nontender. He was also noted to have enlarged liver, approximately 6 cm below the right subcostal margin (Fig. 2).

Ultrasound study of the abdomen and pelvis was normal. A 2D echocardiography was carried out to look for evidence of bacterial endocarditis, which was later found to be normal. He had another cycle of septic workup mentioned above, and the results were all negative.

Because of worsening pancytopenia (Table 1), he underwent a diagnostic bone marrow aspiration procedure, and the result of marrow aspirate is shown in Fig. 3A and B.

With the above findings, daily intravenous infusion of amphotericin B deoxycholate was started. He became afebrile on Day 5 of the treatment and remained well until the day he was discharged home. He received a total cumulative dose of 1.26 g or 21 mg/kg of amphotericin B. His renal function was monitored at biweekly interval. Serum creatinine and serum potassium were normal throughout the course of treatment with amphotericin B. Serial follow-up of full blood counts during the course of treatment showed spontaneous recovery of all the three cell lines (Table 2). Six months after discharge, he was seen again at the clinic. He was otherwise well and asymptomatic. No repeat bone marrow examination was carried out.

**Discussion**

Differential diagnoses in patient with massive hepatosplenomegaly, fever, and pancytopenia are not many.
Chronic myeloid leukemia, myelofibrosis, non-Hodgkin lymphoma, and Gaucher disease are some of the recognized noninfectious causes of these conditions. Infectious causes of massive splenomegaly in tropical countries and malarial endemic area are chronic malaria and tropical splenomegaly. Little information exists on the true incidence of leishmaniasis in Malaysia, especially among the immigrants coming from the endemic region, because it is not a notifiable disease in this country. Physicians generally are not aware of this disease, and the lack of experience and knowledge in managing this illness may lead to unnecessary delay in the treatment initiation. To our knowledge, this is the second case of VL reported in Malaysia. The first case of VL in Malaysia was reported in a young immigrant suspected to have hematological malignancy in 1995.4

The Leishmania donovani complex includes Leishmania chagasi and Leishmania infantum and causes VL, a disseminated and potentially fatal form of leishmaniasis. It is transmitted by indigenous sandflies, which is the only vector responsible for the transmission of the parasite. Leishmaniasis is considered to be endemic in many countries, including India, Nepal, and Bangladesh. India alone may contribute as many as 40% to 50% of the world’s cases.5

The confirmatory diagnosis of leishmaniasis relies on either the microscopical demonstration of Leishmania amastigotes in the relevant tissue aspirates or the biopsies, such as bone marrow, spleen, lymph nodes or liver, slit skin smears or biopsies, or in the peripheral blood Buffy coat. Splenic aspiration appears to be more sensitive than bone marrow aspirate with Leishman-Donovan bodies found in 90% and 76% to 85%, respectively.6,7 However, the safety of splenic aspiration procedure is operator dependant. It is not widely used as a diagnostic procedure in this country. Bone marrow aspiration is widely practiced here for the diagnosis of other disease conditions. It is considered as a more acceptable mode of diagnosis, less hazardous with no major complications, although it has a sensitivity of about 50% to 60%.7

Apart for diagnostic purposes, bone marrow biopsy findings can also be helpful for assessing the prognosis of VL patients, in terms of recovery of affected marrow cells. The outcome of treatment seems to be excellent in cases of hypercellular marrow. The presence of extensive fibrosis and necrosis of the marrow associated with very poor outcome, whereas granuloma if present is usually resulted in moderate response.8 In the above-mentioned case, the marrow architecture was hypercellular, without the presence of significant necrosis or granuloma. We expected that he will have a good chance of total recovery with regard to the marrow profiles.

The direct agglutination test (DAT) is a highly specific and sensitive test. It is cheap and simple to perform, making it ideal for both field and laboratory use. DAT in various studies has been found to be 91% to 100% sensitive and 72% to 100% specific.7 For long time, DAT remained first-line diagnostic tool in resource poor countries. However, polymerase chain reaction has been proven to be the most specific and sensitive technique (100% and 80–93.3%, respectively), albeit limited to tertiary care hospitals and research laboratories.7

Table 1 Series of full blood count results showing worsening leucopenia, anemia, and thrombocytopenia during malaria treatment in Hospital Sultanah Nur Zahirah

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<tr>
<td>TWC (10⁹/L)</td>
<td>1.6</td>
<td>1.5</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
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<td>7.9</td>
<td>6.6</td>
<td>6.8</td>
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<td>Platelet (cells/mm³)</td>
<td>141,000</td>
<td>134,000</td>
<td>69,000</td>
<td>63,000</td>
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Hb = hemoglobin; TWC = total white blood cell count.

Figure 3. (A) Marrow aspirate of the patient showing numerous extracellular amastigotes (thick arrow). (B) Intra-macrophage amastigotes of Leishmania (Leishman-Donovan bodies) (thin arrow).
Pentavalent antimony (Sb) like sodium stibogluconate and meglumine antimoniate remains the first-line treatment in all regions of the developing world because of decades of clinical experience. It has proven efficacy with greater than 90% of long-term cure rate with acceptable cost.

The development of resistance to first-line therapy necessitated the use of even more expensive and more toxic second-line drugs like amphotericin B. Data from the immunocompetent European VL patients demonstrated that 100% cure rate was achieved if treated with a total dose of greater than 21 mg/kg of amphotericin B. More commonly now, at least in India, infusions of 1 mg/kg given either daily for 20 days or on alternate days (15 infusions over 30 days) for a total dose of 15 mg/kg are used, resulting in uniformly high efficacy with long-term cure rate of greater than or equal to 96%, A more recent study by Sundar et al. in 2007 found that amphotericin B can be effectively and safely given at a lower dose, that is, 0.75 mg/kg daily for 15 days (total dose, 11.25 mg/kg) with comparable cure rates (≥96%) and shorter duration of hospital stay.

Results from another study in India demonstrated that lipid formulation amphotericin, that is, AmBisome and Abelcet produced an overall cure rates similar to conventional amphotericin B (amphotericin B >96%, AmBisome >96%, and Abelcet >92%), with fewer infusion-related reactions and little toxicity. However, the cost of these drugs is expensive, thus limiting its potential use in the treatment of leishmaniasis in many countries.

For the case under discussion, conventional amphotericin B was chosen because it is more readily available and comparatively much cheaper than the lipid formulation amphotericin. Pentavalent antimony is not available here. Lipid formulation amphotericin is expensive and not readily available in most government hospitals in Malaysia. He completed a total cumulative dose of 21 mg/kg of intravenous infusion of amphotericin B. Close monitoring of the renal function and serum electrolyte as well as ensuring good hydration status were carried out during the treatment period, hence minimizing the risk of amphotericin-related toxicity.

VL with chronic malaria in undernourished children was known as malarial cachexia in Imperial India, although presently, concomitant infection is rarely reported. Only few human cases of concomitant malaria and leishmaniasis have been reported. In previously reported case of malaria coinfection, marked pancytopenia with severe neutropenia was noted, as what had happened to our patient. However, the abnormalities were self-limited and improved dramatically with the initiation of therapy.

Chronic VL is known to cause CD4 lymphopenia and a low CD4:CD8 ratio, whereas blood CD4:CD8 ratio remains unaltered during malarial paroxysms. The study by Rohatgi et al. in leishmaniasis patients found that the pretreatment CD4 cell count was depressed in the peripheral blood of acute and chronic VL cases but higher in the bone marrow. An influx of CD4 cells to the bone marrow and spleen might account for the fall in the CD4:CD8 cell ratio in the blood observed. Studies using experimental models of malaria in immune-deficient mice and chickens have shown that resistance to blood-stage infection is mediated by protective antibodies and T cell-dependent cell-mediated mechanisms of immunity. Therefore, it seems that leishmaniasis-mediated CD4 lymphopenia may have nullified the protective effect against malaria.

Leishmaniasis is not endemic in this region. However, it is becoming important to recognize this disease, especially among the migrants from endemic regions or those who had recently traveled to those countries. Because of the issue of safety and familiarity with the procedure, bone marrow examination remained the preferred method of parasite identification. The treatment of VL is long and expensive. In many countries, including Malaysia, conventional amphotericin B still has a role in the treatment of VL. With close and regular monitoring of renal function and ensuring good hydration status of the patient, its toxicity effect can be minimized. Coinfection with malaria is rare, but it may have significant impact on the delay of diagnosis. A high clinical suspicion is necessary among the primary care practitioners about the threat of imported infectious disease, especially among the patients who presented with prolonged febrile illness and hepatosplenomegaly.

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**References**