Case report

Fatal septicemic shock associated with Strongyloides stercoralis infection in a patient with angioimmunoblastic T-cell lymphoma: A case report and literature review


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A B S T R A C T

Introduction: Strongyloides stercoralis infection can persist in the host for several decades, and patients with cancer and other clinical conditions who are exposed to immunosuppressive therapy are at risk of developing hyperinfection.

Case report: This is a case of angioimmunoblastic T-cell lymphoma (AITL) in a patient with lymphadenopathy and bulky neck mass. Severe sepsis and episodes of diarrhea were observed upon the first cycle of cyclophosphamide, doxorubicin, oncovin (vincristine) and prednisone (CHOP) regime chemotherapy preceded by high dose of dexamethasone. There was Klebsiella pneumoniae bacteremia and moderate eosinophilia. Rhabditiform S. stercoralis larvae were observed in the stool, and this was confirmed by real-time PCR. Strongyloides-specific IgG and IgG4 were also positive. The patient was treated with oral albendazole (400 mg/day) for 3 days and intravenous tazocin (4.5gm/6 hours) for 5 days; however he succumbed following multi-organ failure.

Conclusion: This is likely a case of Strongyloides hyperinfection with secondary bacteraemia.

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1. Introduction

Strongyloides stercoralis infects 50–100 million people in 70 countries in tropical and subtropical regions [1]. Low socioeconomic backgrounds and habits that facilitate parasitic transmission are the major risk factors for acquiring the infection which can be long-term, sometimes for life [1–3]. Human infection occurs when the infective filariform larvae in contaminated soil actively penetrate the intact skin of feet sole, hand or oral cavity through direct contact.

In Malaysia, strongyloidiasis among fishermen in Penang was found to be 1.2% [4]. In a more recent study, Strongyloides larvae were detected in 7.1% of soil samples from Selangor, Malaysia [5]. In the USA, 347 cases of strongyloidiasis-associated deaths occurred within 15 years were identified [6], and among cancer patients who are infected with strongyloidiasis, 52.0% of them had solid organ malignancy and the remaining had hematologic malignancy [7]. Meanwhile in Columbia, 3.6% of immunocompromised patients were found to be infected with S. stercoralis [8].

Strongyloides can cause acute infection, autoinfection and chronic intestinal infection, hyperinfection syndrome and dissemination syndrome. Hyperinfection syndrome develop in cases of impaired cellular immunity due to viral infection, hypogammaglobulinemia syndrome, malnutrition and immune suppressive drug intake for treatment of various types of cancers, organ transplantation or autoimmune diseases. The hallmark of hyperinfection is the development or exacerbation of gastrointestinal and pulmonary symptoms [9]. It is frequently accompanied by secondary fungal or bacterial infection [10], which is the primary cause of death in most patients [11]. In the present report we describe a case of disseminated strongyloidiasis in a lymphoma patient in Malaysia and review previous similar reports.

2. Case description

We present a case of a 79-year-old man who was admitted on 7th September 2010 to a tertiary hospital of Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, with generalized lymphadenopathy and bulky neck mass. He had speech and breathing difficulties. Diagnosis of angioimmunoblastic T-cell lymphoma (AITL) was made according to standard histological and immunohistochemical examinations of the excised lymph nodes on 10th October 2010. He was planned for six cycles of cyclophosphamide, doxorubicin, oncovin (vincristine) and prednisone (CHOP) chemotherapy which included intravenous (IV) cyclophosphamide (IV, 750 mg/m²), doxorubicin (IV, 50 mg/m²), and oncovin (vincristine) (IV, 1.4 mg) for 1 day, and prednisone (oral, 100 mg) for 5 days for every 21 days. Prior to the first cycle, the patient was given dexamethasone (IV, 8 mg) every
8 hours for rapid reduction of the neck mass. He tolerated the first cycle of chemotherapy infusions well on 1st November 2010 and was discharged for daily prophylactic granulocytes colony stimulating factor (GCSF) in the day care center.

The patient had two episodes of mild and self-limiting diarrhea about a week after the first cycle of chemotherapy. This was thought to be associated with GCSF since the diarrhea ceased after the treatment was stopped. On 2nd December 2010, the following week after his second cycle chemotherapy, he became tired and was noted to be pale. The total white blood cells count was 32.2×10^9/L with 1.40×10^9/L, respectively. Serum from blood sample was tested to be pale. The total white blood cells count was 32.2×10^9/L with 1.40×10^9/L, respectively. Serum from blood sample was tested to be pale. The total white blood cells count was 32.2×10^9/L with 1.40×10^9/L, respectively. Serum from blood sample was tested to be pale. The total white blood cells count was

Blood and stool samples were sent on 6th December 2010 for culture and microscopic examination. The blood culture grew Klebsiella pneumoniae and was found to be sensitive for amikacin, amoxicillin-clavulanic acid, cefotaxime, ciprofloxacin, and gentamicin. Parasitological diagnosis was performed by microscopic examination of direct fecal smear, which showed one to three S. stercoralis larvae per low power field (10× magnification). This was subsequently confirmed by a strong positive result by real-time polymerase chain reaction using Strongylides primers and probe based on a previous protocol from our group [12]. A low Ct value of 26.77 was obtained (positive Ct < 40.0) which indicated presence of substantial amount of Strongylides DNA in the sample. No investigation for the presence of Strongylides larvae in other clinical specimens was made. The patient was treated with albendazole (oral, 400 mg/day) for 3 days and tazocin (IV, 4.5 g every 6 hours) for 5 days. Unfortunately, despite the treatment, the patient succumbed following multiorgan failure on 9th December 2010.

3. Case review

Literature search for the case review was performed using 'PubMed' and 'Google Scholar'. Lymphoma is the most common hematologic malignancy associated with the occurrence of Strongylides hyperinfection syndrome [13]. In a retrospective study which involved 253 patients with hematological malignancies (mostly lymphomas), Strongylides hyperinfection was recorded in 53 (21.0%) patients and was found to be sensitive for amikacin, amoxicillin-clavulanic acid, cefotaxime, ciprofloxacin, and gentamicin. Parastisological diagnosis was performed by microscopic examination of direct fecal smear, which showed one to three S. stercoralis larvae per low power field (10× magnification). This was subsequently confirmed by a strong positive result by real-time polymerase chain reaction using Strongylides primers and probe based on a previous protocol from our group [12]. A low Ct value of 26.77 was obtained (positive Ct < 40.0) which indicated presence of substantial amount of Strongylides DNA in the sample. No investigation for the presence of Strongylides larvae in other clinical specimens was made. The patient was treated with albendazole (oral, 400 mg/day) for 3 days and tazocin (IV, 4.5 g every 6 hours) for 5 days. Unfortunately, despite the treatment, the patient succumbed following multiorgan failure on 9th December 2010.

A summary of previous reports of strongyloidiasis in lymphoma patients is shown in Table 1. There was an old report of three Jamaican patients with Hodgkin’s lymphoma in 1973. Two of the patients presented with intestinal symptoms abdominal pain, weight loss and diarrhea for 3 months. The other patient presented with weight loss, weakness and night sweat for 6 weeks. The patients who succumbed to the infection showed widespread infiltration of filarialm form larvae into the small intestinal lumen, lymph nodes and spleen at necropsy [16]. In another case, a man with follicular lymphoma had dyspnea and non-productive cough of acute onset associated with subjective fevers and fatigue. He deteriorated within 3 days of admission needing intensive care support. Bronchoalveolar lavage yielded motile larvae confirming the diagnosis of disseminated strongyloidiasis. He was treated with a combination of ivermectin and thiabendazole, and survived the course of illness [17]. A Venezuelan female patient with mantel cell lymphoma was admitted to a hospital with clinical signs of meningitis, fever and productive cough. The meningitis was due to Staphylococcus warneri and was treated accordingly. Three weeks later symptoms of intestinal pseudo-obstruction and pneumonia prompted readmission and examination of feces and expectoration revealed the presence of abundant filarialm form larvae of Strongylides stercoralis [18].

The Hospital Universiti Sains Malaysia in Kelantan had recorded several cases of strongyloidiasis in the past years; these included a case of strongyloidiasis in an adult patient with non-Hodgkin’s lymphoma [15]. The patient had completed chemotherapy regimen and he presented to our hospital with fever and bilateral pleural effusion. On laboratory examination, Strongylides larva was detected from the pleural fluid.

In most cases illustrated above, majority of the patients were adult male and numerous larvae were observed from stool and other body fluid samples of these patients.

4. Discussion

The Hospital Universiti Sains Malaysia in Kelantan, where the patient was admitted, had recorded several cases of strongyloidiasis in the past years; these included two cases of strongyloidiasis in an adult patient with diabetes on immunosuppressive drugs [19] and in a non-Hodgkin’s lymphoma patient [15]. Recently, there were two cases of S. stercoralis infection in immunocompromised children at our hospital (unpublished data). We have also reported the detection of S. stercoralis larvae in water used to wash common herbs and vegetables in a main central market in the state of Kelantan, a very popular shopping destination among the population in this area [20]. In addition, Strongylides larvae were reported in 60% of stool samples collected from aborigine children in Kelantan [21]. In Southern Thailand, which neighbors the state of Kelantan, 1.8% of the school children were reported to be infected with S. stercoralis. Thus there are ample evidences to show that Strongylides is endemic in

### Table 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Number of cases</th>
<th>Age (years) and gender</th>
<th>Type of lymphoma</th>
<th>Country of origin</th>
<th>Strongylides diagnosis</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1</td>
<td>62, male</td>
<td>Non-Hodgkin lymphoma</td>
<td>Malaysia</td>
<td>Larva in pleural fluid</td>
<td>Dead</td>
<td>[15]</td>
</tr>
<tr>
<td>2.</td>
<td>3</td>
<td>27, male 22, male 46, male</td>
<td>Hodgkin lymphoma</td>
<td>Jamaica</td>
<td>Larva in stoll Histological diagnosis at necropsy</td>
<td>Survived</td>
<td>Dead</td>
</tr>
<tr>
<td>3.</td>
<td>1</td>
<td>31, male</td>
<td>Follicular lymphoma</td>
<td>TX, USA</td>
<td>Larva in bronchoalveolar lavage sample</td>
<td>Survived</td>
<td>[17]</td>
</tr>
<tr>
<td>4.</td>
<td>1</td>
<td>59, female</td>
<td>Mantel cell lymphoma</td>
<td>Venezuela</td>
<td>Abundant larvae in stool and expectoration</td>
<td>Survived</td>
<td>[18]</td>
</tr>
</tbody>
</table>
the area where the patient resided. Meanwhile Stewart et al. [22] reported disseminated strongyloidiasis in patient with leukemia co-infected with HTLV-1. In addition, there was a report of a case of meningitis due to S. warneri secondary to S. stercoralis hyperinfection in a patient with lymphoma [18].

Glucocorticoids are the most widely used and the most specifically associated with transformation of chronic strongyloidiasis to hyperinfection [23], which is associated with a two- to three-fold increase in the risk of developing hyperinfection syndrome [14]. In general, steroids can lead to life threatening hyperinfection which has about 50% mortality due to Gram-negative bacterial sepsis [24]. Hyperinfection may result from high-dose steroids, low-dose steroid, high levels of endogenous adrenocorticotropicin, locally injected steroids and pharmacologically administered adrenocorticotropicin. One likely explanation for the ability of glucocorticoids to induce hyperinfection is their acute suppression of eosinophilia and lymphocyte activation. Some authors have suggested that glucocorticoids may also have a direct effect on the parasites themselves, accelerating the transformation of rhabditiform to invasive filariform larvae or rejuvenating reproductively latent adult females [9].

Seven cases of disseminated strongyloidiasis were studied retrospectively in Hong Kong over ten years. Six out of seven patients were immunosuppressed by means of prednisolone alone or along with chemotherapy. Two patients developed fatal secondary bacterial sepsis; S. stercoralis larvae were isolated form stool, duodenal and gastric biopsies, and pulmonary samples. Thibendazole was administrated in all patients, and five patients passed away [25].

Prednisone and dexamethasone were steroids that were given to the patient in the present report. The first drug was included in the CHOP regime and the second drug was previously given during oral surgery. A single cycle of CHOP and the dexamethasone dose were probably sufficient to suppress the patient’s immune system and re-activate the autoinfection cycle of Strongyloides. In addition, oncovic (vincristine) in the CHOP regime has been proposed to exert a toxic effect on myenteric neurons, decreases the intestinal motility and increases the amount of time available for rhabditiform larvae to molt into invasive filiform larvae. A number of case reports had documented Strongyloides hyperinfection among patients who received vincristine [9]; therefore this drug could be an additional risk factor for development of Strongyloides hyperinfection in this patient.

Autoinfection and chronic strongyloidiasis develop when the acute infection did not completely clear. The persistent infection maintains the larval migration through the organs and can remain undetected for decades [11]. Our patient’s previous occupation as an army staff had probably exposed him to an asymptomatic and lifelong chronic strongyloidiasis before the immunosuppression episodes caused by hematological cancer, chemotherapy and steroid treatment. Thus screening of high risk individuals or empiric anti-helminth treatment in suspected patients with or without eosinophilia is warranted prior to immunosuppression to prevent the severe morbidity and mortality associated with hyperinfection syndrome [7,22,24,25].

Once diagnosed, strongyloidiasis warrants treatment particularly among the high risk patients. A combination therapy of albendazole (oral, 400 mg twice daily) for 7 days and ivermectin (oral, 200 mg/kg daily) for 1–2 days is recommended for the treatment in immunosuppressed patients [9]. In the case of disseminated strongyloidiasis, albendazole and ivermectin should be continued until there is evidence of complete parasite clearance [26]. In this patient, a three-day course of albendazole was administered without addition of ivermectin due to unavailability of the latter at our hospital.

In conclusion, strongyloidiasis with secondary bacteremia was the complication in this immunosuppressed patient. Despite the unavailable data on larval presence in clinical samples other than stool, our patient was likely a case of Strongyloides hyperinfection based on the consistent clinical presentations and demonstration of S. stercoralis larva in stool and strong real-time PCR positivity. Thus, this condition must be diagnosed and treated early as its case fatality rate is high. Although ivermectin is the recommended drug of choice for strongyloidiasis, it is currently not available in health services in Malaysia. With the rising number of immunocompromising conditions, awareness on the importance of early diagnosis and treatment of strongyloidiasis must be increased in clinicians. It is crucial that in future ivermectin is made available for strongyloidiasis management in endemic areas.

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