Symptomatic chronic strongyloidiasis in children following treatment for solid organ malignancies : case reports and literature review

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Abstract. Strongyloidiasis is an infection caused by the intestinal nematode *Strongyloides stercoralis*. Infected healthy individuals are usually asymptomatic, however it is potentially fatal in immunocompromised hosts due to its capacity to cause an overwhelming hyperinfection. Strongyloidiasis could be missed during routine screening because of low and intermittent larval output in stool and variable manifestations of the symptoms. We present two cases of strongyloidiasis occurring in children with solid organ malignancies suspected to have the infection based on their clinical conditions and treatment history for cancer. Both patients were diagnosed by molecular and serological tests and were successfully treated. Thus, strongyloidiasis in patients undergoing intensive treatment for malignancies should be suspected, properly investigated and treated accordingly.

INTRODUCTION

Strongyloidiasis is a disease caused by the female *Strongyloides stercoralis* or also commonly known as thread worm. The infection is widespread in tropical and subtropical countries including India, Indonesia, Malaysia, Northeast Australia, Africa and Americas (Daubenton *et al.*, 1998; Ozturk *et al.*, 2008). Transmission routes of the parasite are through trans-cutaneous and faecal-oral route. Strongyloidiasis has variable manifestations from asymptomatic to acute hyperinfection, chronic or disseminated infection. Most common presentations are usually related to the gastrointestinal tract. In acute infection patient may have cutaneous, pulmonary or gastrointestinal symptoms (Aregawi *et al.*, 2009; Ganesh & Cruz, 2011). Fifty percent of chronically infected individuals as well

as immunocompetent subjects are asymptomatic. However, severe opportunistic strongyloidiasis can occur in patients with underlying illness such as cancers, autoimmune syndromes and those with chronic illnesses on steroids or other immunosuppressive agents (Ozturk *et al.*, 2008; Azira & Zeehaida, 2010). Strongyloidiasis has also been reported in those with rheumatoid arthritis, bronchial asthma, diabetes mellitus, chronic renal failure and following total body irradiation (Altintop *et al.*, 2010). The prevalence of *S. stercoralis* infection was found to be higher in those with low socioeconomic status and male gender (Siddiqui & Berk, 2001).

In general, strongyloidiasis is not an infection that a doctor usually considers when treating children with hematological and solid organ malignancies. Hence screening for *S. stercoralis* is not a routine

procedure in cancer patients, and anti-helminthic drug administration is also not a routine procedure prior to commencement of chemotherapy. Diarrhoea and abdominal pain are common non-specific symptoms and their aetiologies are very broad. Mild eosinophilia and occasional presence of larvae in stool may be the only indications of the infection. However eosinophilia is also not specific for strongyloidiasis. Furthermore, screening of asymptomatic patients is often unsuccessful due to the low sensitivity of available assays or low excretion of *S. stercoralis* larvae in stool (Bialek, 2005; Azira & Zeehaida, 2010). Nevertheless, one needs to be aware that latent asymptomatic infection might become symptomatic due to accelerated autoinfection, leading to hyperinfection syndrome during immunosuppression state in children with cancer, thereby resulting in severe illness and also mortality (Bialek, 2005).

Thus, more sensitive methods are necessary to improve the diagnosis of strongyloidiasis so as to enable recommendations to be made on the necessity of *S. stercoralis* screening among immunocompromised children who are at risk of developing hyperinfection prior to commencement of chemotherapy (Marty, 2009). We present two cases of strongyloidiasis in immunocompromised children in paediatric oncology ward at Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia. In both cases, diagnosis were negative by routine direct microscopic examination, however the infection was detected by molecular diagnostic and serological methods.

CASE REPORT

First case: A three and half year old Malaysian boy of Indian origin was diagnosed with relapse hepatoblastoma. The initial diagnosis of the disease was made at the age of 2 years old when he presented with 3 months history of right hypochondrial mass. His growth was at 50th percentile as per growth chart. Diagnosis was confirmed by tissue biopsy and histology. He was treated with chemotherapy using SIOPEL 3 high risk hepatoblastoma protocol and underwent extensive right hepatectomy to remove the tumor. There was no history of steroid administration. SIOPEL 3 protocol comprised of cisplatin 80 mg/m^2, doxorubicin 60 mg/m^2 and carboplatin 500mg /m^2.

Six months after completion of chemotherapy, the patient again presented with abdominal distension. Computerized tomography (CT) scan of the abdomen and thorax confirmed relapsed hepatoblastoma with portal vein invasion and lung metastasis. ICE protocol comprising ifosfamide 1.8 gm/m^2/day, carboplatin 400 mg/m^2 and etoposide 100 mg/m^2 /day was commenced. Etoposide was given half of the recommended dose in view of raised liver enzyme in this patient. During treatment with chemotherapy following hepatectomy, he started to develop frequent episodes of diarrhoea. His diarrhoea was up to more than 10 times a day and extended to more than two weeks. Sometimes he had episodes of febrile neutropenia accompanying the diarrhoea. He was given multiple antibiotics including amikacin, tazocin, imipenem, metronidazole and amphotericin B for the febrile episodes. Among positive blood cultures detected during his febrile episodes were Gram negative bacilli and *Enterobacter* species.

Routine laboratory culture and microscopic investigations of his recurrent diarrhoeic stool revealed negative findings, except on one occasion where *Salmonella* species was isolated. Stool test for reducing sugar was also negative. The highest absolute eosinophil count was 400 cells/µL. Serum and stool samples were then sent for *S. stercoralis* investigations. Serum samples were tested for presence of *S. stercoralis*-specific antibodies using commercial enzyme-linked immunosorbant assay (ELISA) kit for IgG (Strong-96 ELISA, IVD, USA), and laboratory-based indirect ELISAs for IgG, IgG4, and IgE. The laboratory-based ELISAs were established using *S. stercoralis* larvae lysate. The stool sample was tested using wet mount direct microscopic examination and real-time polymerase chain reaction (PCR).

The laboratory results are presented in Table 1. The serological result for anti-*Strongyloides* IgG (using laboratory-based indirect ELISA) was positive, while the other serological tests were negative. Repeat direct stool microscopy did not reveal any *S. stercoralis* larva. However, positive result for *S. stercoralis* was obtained by real-time PCR of the stool with (cycle threshold) Ct value of 34 (Figure 1), based on published protocol (Basuni *et al.*, 2011).

Retrospectively, the boy's mother claimed that he hardly played outdoors and never went out barefooted. In view of the frequent and prolonged episodes of diarrhoea and positive laboratory investigations, the patient was given syrup albendazole 400 mg for three days. His diarrhoea resolved and repeat samples of stool and blood were taken five weeks post-treatment. The repeat serum sample showed positive anti-*Strongyloides* IgG antibodies using both laboratory-based and commercial ELISAs and other serological tests were negative. Real-time PCR on the repeat stool sample was also negative. Titration of the anti-*Strongyloides* IgG antibodies (using lab-based ELISA) showed that the titer was 6400 before treatment and decreased to 1600 after treatment.

Second case: A three year-old Malay boy was diagnosed with atypical teratoid/ rhabdoid tumour of the brain after he presented with history of a fall from a chair and vomited for three days. There was a right temporoparietal lesion noted on CT scan of brain. He underwent a right fronto-temporo-parietal craniotomy, temporal lobectomy and tumour excision with fascioduraplasty. Brain tissue histology was consistent with atypical teratoid/rhabdoid tumour WHO grade IV.

The patient also had underlying infrequent episodic asthma on syrup salbutamol and history of allergy to pethidine. His growth was always below the 3rd percentile. He was commenced on 31 cycles of radiotherapy following the operation. He received 18 Gray in the first phase and 38 Gray in the second phase of his radiotherapy regime. During radiotherapy treatment he had several episodes of diarrhoea and clinical sepsis which resolved after commencing antibiotic. Among the bacteria isolated were methicillin-resistant coagulase-negative staphylococci (MRCONS) from blood culture and *Proteus mirabilis* from urine sample.

Stool and blood samples were taken for *S. stercoralis* investigations when the patient was febrile and had diarrhoea. Both samples were investigated for *S. stercoralis* using the same test panel as the first case. The laboratory results are presented in Table 1. Only laboratory-based ELISA for IgG and real-time PCR (Ct value of 35, Figure 2) were

Table 1. Results of serological tests and PCR for both patients pre and post treatment

Test	Pre-treatment Case 1	Post-treatment Case 1	Pre-treatment Case 2	Post-treatment Case 2
Lab-based ELISA IgG4 (*COV: 0.21)	-0.0102 Neg	-0.0121 Neg	0.0732 Neg	0.0096 Neg
Lab-based ELISA IgG (COV: 0.34)	2.8004 Pos	1.4037 Pos	1.2948 Pos	0.9820 Pos
Lab-based ELISA IgE (COV: 0.2)	0.1363 Neg	0.0609 Neg	0.1030 Neg	0.041 Neg
Commercial ELISA IgG (COV: 0.2)	0.1160 Neg	0.6707 Pos	0.1139 Neg	0.2427 Pos
Real time PCR	Pos (Ct Value: 34)	Neg	Pos (Ct Value: 35)	Neg

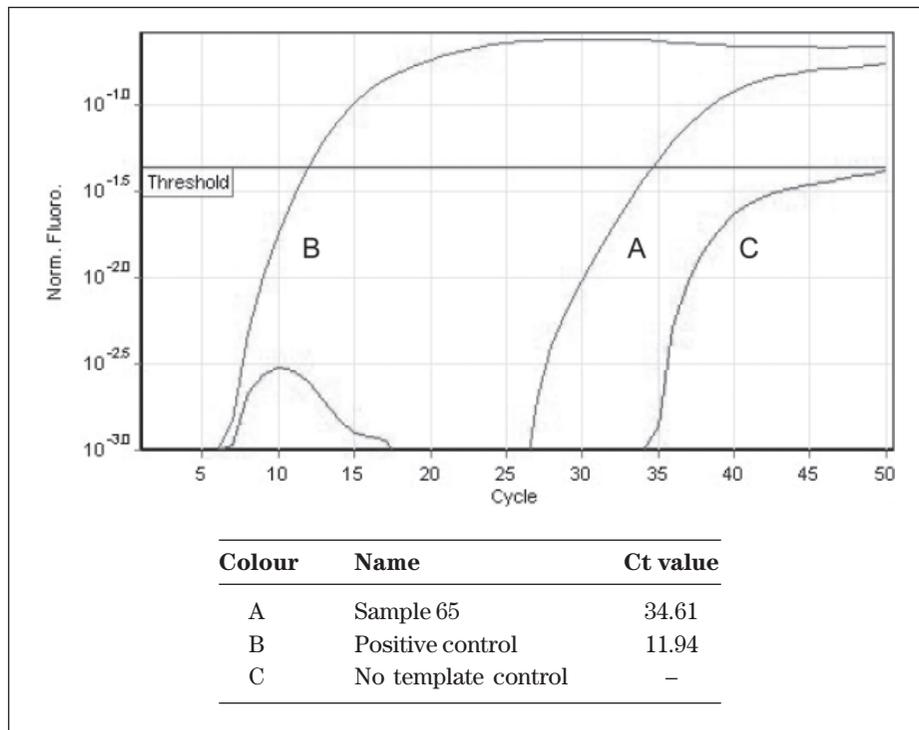Note: The ELISA results are expressed as optical density (OD) values
*COV: cut-off OD value

Colour	Name	Ct value
A	Sample 65	34.61
B	Positive control	11.94
C	No template control	–

Figure 1. Real-time PCR of the stool showing amplification plots for detection of *S. stercoralis* in pre-treatment for case 1

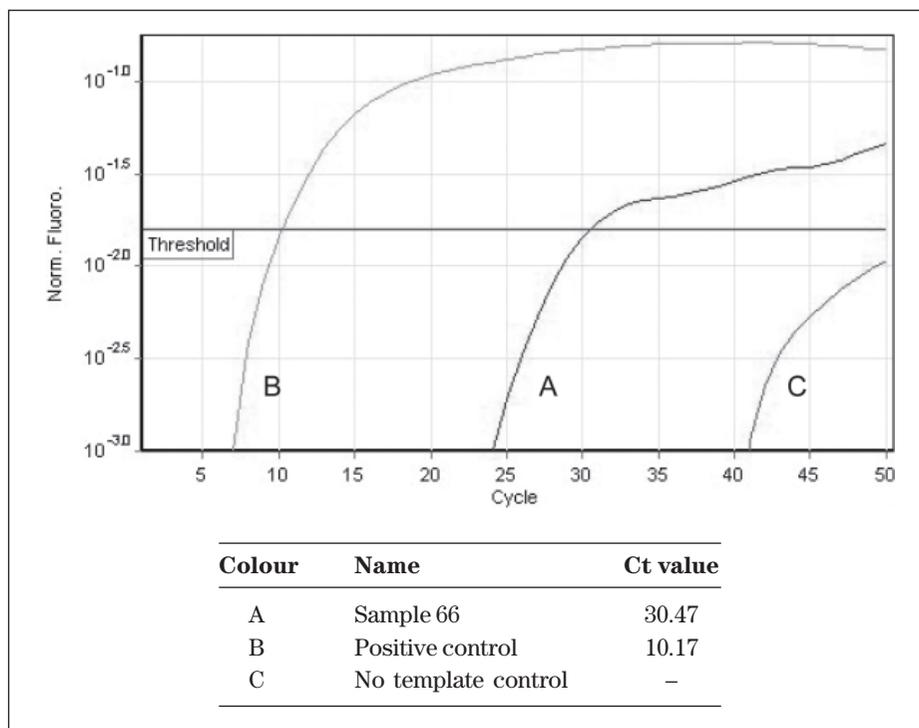| Colour	Name	Ct value
A	Sample 66	30.47
B	Positive control	10.17
C	No template control	–

Figure 2. Real-time PCR of the stool showing amplification plots for detection of *S. stercoralis* in pre-treatment for case 2

positive, while the remaining tests were negative. The highest absolute eosinophil count in this patient was 580 cells/µL. Other than local cranial radiotherapy, he received oral prednisolone as a pre-medication prior to CT scan and MRI of his brain, at 20 mg per dose at 13 hours, 8 hours and one hour prior to CT scan and MRI as per local protocol. Retrospectively, the child had first episode of diarrhoea at the age of 2½ year. There was a history of playing barefooted outside his caretaker's home. His stool was described as very smelly and bubbly, and was then given one stat dose of anti-helminthic drug.

In view of several episodes of diarrhoea and positive laboratory investigations, the patient was given syrup albendazole 400 mg for three days. Following the treatment, he still had a few episodes of diarrhoea accompanied by fever and clinical sepsis. Repeat serum sample taken five weeks post-treatment showed positive anti-*Strongyloides* IgG antibodies using both laboratory-based and commercial ELISAs and other serological tests were negative. Real-time PCR on the repeat stool sample was also negative. Titration of the anti-*Strongyloides* IgG antibodies (using lab-based ELISA) showed that the titre was 400 before treatment and slightly increased to 800 after treatment.

DISCUSSION

Enteric parasitic infections, particularly soil transmitted helminthes, are prevalent in a tropical country like Malaysia. Kelantan is a state located in the north-east of peninsular Malaysia where majority of people live in rural areas. Many parts of this region are endemic for soil-transmitted helminthes, such as *Ascaris lumbricoides, Trichuris trichiura* and hookworm. *Strongyloides stercoralis* is also a soil-transmitted helminth, and it is likely to be also endemic in this part of Malaysia (Menon *et al.*, 1999). There are several studies and case reports that had documented detection of chronic strongyloidiasis among immunocompetent as well as immunocompromised children in Kelantan (Daubenton *et al.*, 1998).

A preliminary study of the prevalence of intestinal parasites in immunocompromised children and adult patients showed that 47.7% did not present with any clinical manifestation associated with the gastro-intestinal tract, while 52.3%, presented with abdominal pain, diarrhoea or flatulence. Only 11.3% of patients without associated gastrointestinal manifestations were positive for intestinal parasites recognized as human pathogens, based on faecal samples. The overall prevalence of potentially pathogenic parasites was 32.4% which include *Entamoeba histolytica* (9.9%), *Giardia lamblia* (7.1%), *S. stercoralis* (3.6%), *T. trichiura* (3.6%) and others (8.2%) (Botero *et al.*, 2003). In another study, the analysis of patients of various age groups at a comprehensive cancer centre in the United States demonstrated that among cancer patients infected with strongyloidiasis, 52.0% of them had solid organ malignancy and the remaining had hematologic malignancy (Safdar *et al.*, 2004). Clinical presentations in children in relation to strongyloidiasis and solid organ malignancies have not been adequately discussed.

Children presented with abdominal symptoms suggesting of worm infection are given anti-helminthic treatment in most clinics or hospitals in Malaysia. In general, the main complaints by the parents are abdominal pain, abdominal distension, very foul smelling or bubbly stools. Sometimes the worm comes out from the anus or could be seen in the stool or the patient may vomit out the worm together with food substance. Foul smelling and bubbly stool which are not described in the literature are often the only reasons for parents to seek anti-helminthic treatment for their children and in most cases, no investigation is performed to verify the diagnosis of the infection. For paediatric oncology patients, diarrhoea is one of the presentations following sepsis or complication of chemotherapy. Extensive investigations for sepsis are carried out which include stool investigations. However, if the first stool sample is negative for ova and larvae the chance of treating the patients with anti-helminthic is rare. Most of the time only one stool sample would be sent for

investigation, and the stool is examined by wet mount examination under light microscopy. Menon *et al.* (1999) reported in her study in HUSM, Kelantan that 42.0% of children with cancer were positive for stool parasites. The parasites identified were *T. trichiura*, *A. lumbricoides*, *G. lamblia*, *Blastocystis hominis*, hookworm and *Cryptosporidium* species. No *S. stercoralis* larvae were reported. Intermittent or low secretion of *S. stercoralis* larvae could have contributed to the low detection of *S. stercoralis*. Furthermore direct wet mount microscopy used in this centre has very low sensitivity to detect *S. stercoralis* larvae. According to the HUSM data, the yield of *S. stercoralis* larvae is only 0.1 to 0.3% of stool specimens examined by microscopy per year (unpublished data). In the HUSM, only a few cases of strongyloidiasis were recorded in the past years and this included a single case of strongyloidiasis in an adult patient with diabetes on immunosuppressive drugs (Azira & Zeehaida, 2010) and another case in a patient with non-Hodgkin lymphoma (Win *et al.*, 2011).

Does strongyloidiasis coexist, precipitate or aggravate sepsis in children with malignancy? There is no clear answer as this group of patients is always at risk of septicemia or has infections in other parts of the body. For the child with rhabdoid/teratoid tumour, he had a few episodes of sepsis with diarrhoea. Among organisms identified were MRCONS from blood and *P. mirabilis* detected in the urine on two separate occasions respectively. The patient with hepatoblastoma also had a few episodes of proven sepsis together with diarrhoea. However stool for *S. stercoralis* was negative. Among microorganisms isolated from his blood were Gram negative bacilli and *Enterobacter* species, and in one occasion his stool was positive for *Salmonella* species. In both cases, stool microscopic examinations were negative for *Strongyloides*, but detection for the helminth was positive by molecular and serological methods. Hence being immunocompromised increases the possibility for *S. stercoralis* activation that leads to polymicrobial sepsis. Therefore this shows that the choice of the diagnostic

method to detect *S. stercoralis* infection is important. If only wet mount examination of the stool under light microscopy was used, *S. stercoralis* would have been missed in these two cases.

In the second case report, the patient had history of playing bare footed outside the caretaker's home, and his first diarrhoea started months before he was diagnosed to have tumour. It is known that *S. stercoralis* is transmitted transcutaneously from contaminated stool or soil. In addition raw vegetables and herbs have been shown to be the sources of *S. stercoralis* (Zeehaida *et al.*, 2011). Hence fecal oral contamination through food preparation or eating contaminated food are possible in cases where there was no history of playing outdoor, as in the first patient.

A previous study had been performed to find the occurrence of *S. stercoralis* among 227 children who presented with diarrhoea, and their nutritional status was also investigated. All of them were immuno-competent and 12 (5.3%) of the children with diarrhoea were found to have *S. stercoralis*. All the infected children were malnourished, while none of the normal nourished children had the infection. Thus, malnutrition was the risk factor for strongyloidiasis complications that caused diarrhoea in these patients (Dada-Adegbola & Bakare, 2004). Our second case is under 3rd percentile in terms of growth while the boy with hepatoblastoma had an average growth at 50th percentile.

The first and second cases had eosinophils of 400 and 580/L respectively. Eosinophilia is defined as the absolute peripheral eosinophil count of >400 cells/L. The absence of eosinophilia does not exclude hyperinfection especially in patient with malignancy (Safdar *et al.*, 2004). In fact in the study by Vaiyavatjamai *et al.* (2008), they had shown a significant low peripheral eosinophil blood count in a group of HIV patients with strongyloidiasis.

Both cases that we presented had solid tumors and diarrhoea. Safdar *et al.* (2004) reported that strongyloidiasis in patients with solid organ malignancies remained localized to the intestine and there was no systemic dissemination observed. This seemed to

concur with the patients in this report where there was no evidence of disseminated infection.

Treatment of strongyloidiasis is directed against circulating filariform larvae during the autoinfection cycle, which is reported to be highly drug resistant (Siddiqui & Berk, 2001). Albendazole (400 mg/day for 3 days) has an important role in the treatment of chronic strongyloidiasis and it is routinely administered (Venkatesan, 1998). However, ivermectin (200 µg/kg body weight given daily for 1 to 2 days) is the best drug for the treatment of *S. stercoralis* infection and sometimes it is combined with albendazole for successful cure (Adenusi *et al.*, 2003). In our centre, ivermectin is not available; hence we rely on albendazole for treatment.

Both children had surgery as part of cancer treatment, and both had episodes of gastrointestinal symptoms. The first patient, who suffered from recurrent diarrhoea was under ICE chemotherapy protocol. This protocol comprised of ifosfamide, carboplatin and etoposide. Ifosfamide and etoposide used in treating cancer patient had been previously associated with *Strongyloides* hyperinfection (Tabacof *et al.*, 1991). He was treated with albendazole. The antihelminthic treatment was repeated once again in view of persistent gastrointestinal symptoms and this patient is still under follow-up. The infection pathogenesis is similar and correlated with previous literatures (Daubenton *et al.*, 1998; Clyti *et al.*, 2004) in which the chemotherapy causes immunesuppression leading to accelerated autoinfection cycle resulting in severe gastrointestinal symptoms such as diarrhoea.

There were several cases reported of active strongyloidiasis in patients exposed to total body irradiation for organ or stem cell transplantation to avoid graft-versus-host-disease (Rodrigues, 2007). Total body irradiation causes total suppression of blood cells production, thus decreasing the immunity. In this condition, the patient is at risk for developing strongyloidiasis activation and complications, a mechanism that resembles the chemotherapy-induced active strongyloidiasis. However, a search of the literature failed to reveal any previous reports on the occurrence of *S. stercoralis* complications in patients receiving local radiotherapy.

In our second case, the patient had completed 31 cycles of local (cranial) radiotherapy. Few episodes of diarrhoea accompanied with neutropenia had occurred during the radiotherapy course. Although local radiotherapy does not decrease body immunity and does not activate the egg-lying' adult worms in the intestine, active strongyloidiasis was diagnosed in the patient. The probable interpretation could be linked with the doses of oral prednisolone (steroid) that were given to the patient for CT scan and MRI as the patient was a known asthmatic. This may have caused a few episodes of immunesuppression leading to accelerated *S. stercoralis* autoinfection causing diarrhoea. However, further studies should be performed to investigate the relationship between active strongyloidiasis and local radiotherapy treatment combined with steroid given for any cause. In addition, screening for *S. stercoralis* in cancer patients, who are under local radiotherapy treatment and suspected to be exposed to immunesuppression caused either by steroid or admission for second-line chemotherapy, may introduce a new perspective on when strongyloidiasis should be screened in cancer patients.

Strongyloides stercoralis larvae in stool can be directly examined microscopically in wet mounts preparation by suspending stool sample with physiological saline (0.9% NaCl) or with Lugol's iodine stain (Siddiqui & Berk, 2001). Although it is the definitive diagnosis, direct microscopic examination of stool specimens is insensitive in asymptomatic individual due to low larval output (<25 larvae per gram of stool) (Wirk & Wingard, 2009). It is reported that in up to 70% of cases, a single stool examination fails to detect larvae (Koosha *et al.*, 2004). Absolute eosinophil count could serve as an alternative indicator for the investigation of *S. stercoralis* infection, including in patients who presented with mild eosinophilia (0.4-1.5x10^9/L) (Siddiqui & Berk, 2001). Nevertheless eosinophil count does not provide sufficient diagnosis of strongyloidiasis because the elevation in count is mild and is nonspecific. In addition,

eosinophilia may not develop in immuno-compromised hosts, and thus it is not helpful in excluding strongyloidiasis in the differential diagnosis (Kazura, 2008).

Immunological diagnosis of strongyloidiasis is often based on serology that investigates anti-*Strongyloides* antibodies circulating in serum of patient (Loutfy *et al.*, 2002). Serological test has been shown to correlate with active infection of *S. stercoralis* and the level of antibody correlates with the infection stage whether it is acute, chronic, hyperinfection, after treatment (treatment follow-up), and cure (Rodrigues, 2007; Marcos *et al.*, 2008). In spite of immunesuppression, both patients had positive lab-based ELISA IgG. In both cases, there was a change in antibody titres post-treatment, the first case showed a reduced titer post-treatment while in the second case the titre increased slightly after treatment. The latter may be due to a slight increase in antibody production triggered by the antigens released when the larvae were killed upon treatment. During the acute phase of the infection, up to 95% of infected patients have circulating IgG (IgG-total and subclass 1) and IgE, and can be detected by serological methods. However, after elevation, the level of IgG1 and IgE were reported to decline, while the level of IgG4 remains elevated throughout the duration of infection until successful treatment (Rodrigues, 2007). However in the two patients in our case reports, anti-*Strongyloides* IgE and IgG4 antibodies were not detected.

There are some limitations of ELISA that may affect the results including cross-reactions with other nematode infections; variable sensitivity and specificity; and inability to differentiate between acute or chronic infection (Siddiqui & Berk, 2001). In addition, the sensitivity of serology is reported to be good in individuals with chronic infection but is lower in those who become infected after travelling to endemic areas (Lindo & Lee, 2001).

The detection of parasitic DNA in fecal samples using real-time PCR has been proven to be a sensitive and specific method for the diagnosis of intestinal protozoan and helminthic infections especially in returning travelers (Verweij *et al.*, 2009). Real-time PCR is preferred over other methods for stool sample analysis, due to its improved rapidity, sensitivity and reproducibility. In both cases, real-time PCR was used as the confirmatory assay that formed the basis for initiation of treatment. However the relatively high cost and the technical skill required may not make real-time PCR feasible in most hospitals in under developed countries.

In conclusion, a standard agreement on the screening assays for *Strongyloides* infection in suspected patients is still needed for early detection and cure.

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