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## Disseminated strongyloidiasis: a retrospective study of clinical course and outcome

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**Abstract** A retrospective study was carried out to evaluate the clinical course and outcome of disseminated strongyloidiasis treated in a regional hospital in Hong Kong over a 10-year period. Seven cases were identified, and the case history of each patient was analysed. The most common presenting symptom was fever (100%). Five (71%) patients had gastrointestinal symptoms, the most common being abdominal pain and diarrhoea. Three (42%) patients had a significant drop in haemoglobin. Six (85%) patients had bronchoalveolar infiltrates on chest radiographs. Most patients were immunosuppressed by means of steroid treatment for their underlying primary disease. One patient was diabetic, and another had lymphoma and was receiving chemotherapy. *Strongyloides* larvae were identified in stool specimens in two patients, in sputum smears in two patients, and in gastric biopsies in three patients. Five (71%) of the patients with lung involvement progressed to respiratory failure and died. Two (29%) cases were complicated by gram-negative bacterial infection. No patient had eosinophilia on presentation. All patients received antihelminthic treatment of variable duration. The case fatality rate in the cohort was 71% despite aggressive supportive therapy. Pulmonary and bowel symptoms were prominent in our series. In conclusion, the diagnosis of disseminated strongyloidiasis is often delayed because of nonspecific presenting symptoms. Early diagnosis relies on a high index of clinical suspicion, especially in immunocompromised hosts. Screening for *Strongyloides* infection before the initiation of immunosuppressive therapy should be considered, especially in endemic areas.

### Introduction

*Strongyloides stercoralis* was first identified in 1876 as the aetiological agent of Cochin China diarrhoea in French troops returning from Southeast Asia [1]. It is endemic in many tropical and subtropical areas, and its prevalence ranges up to 11% in areas of Southeast Asia [2]. In Hong Kong, the reported incidence in faecal specimens is 0.1–0.3%, and there have only been isolated cases of clinical strongyloidiasis reported. Intestinal strongyloidiasis is a mild infection associated with few symptoms and a small worm load. Patients usually are asymptomatic and able to control the proliferation of the larvae, though not eradicate them. However, the parasite is capable of autoinfection, by which it can multiply in the same host in the absence of further exogenous infestation. Although autoinfection is limited by an intact immune response, a low level of autoinfection may permit the organism to persist for decades and cause clinical manifestations long after the initial infection. This process is accelerated under conditions of impaired cellular immunity, resulting in disseminated strongyloidiasis, which is associated with high mortality. We report here a series of cases of disseminated strongyloidiasis in seven immunocompromised patients over the past 10 years in our institution.

### Patients and methods

In the present retrospective study, we included all adult patients with disseminated strongyloidiasis diagnosed in Tuen Mun Hospital during a period of 10 years from January 1995 to December 2004. All diagnoses were made on the basis of clinical presentation suggestive of strongyloidiasis and were confirmed by the identification of *Strongyloides* larvae in tissue specimens. The medical records of the patients were reviewed and the clinical parameters, including sex, age, underlying comorbid conditions, medication history, clinical presentation, site of involvement, and clinical outcome, collected for each patient.

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## Results

Seven patients, five men and two women, were identified. The mean age of the subjects was 58.7 years. The characteristics of the patients are summarised in Table 1.

### Case 1

Case 1 was a 36-year-old woman with a history of systemic lupus erythematosus. She presented to our hospital because of repeated vomiting, abdominal distension, and watery diarrhoea. She was born in mainland China and moved to Hong Kong at the age of 20. At the time of hospitalization, she was on oral prednisone 60 mg/day and monthly intravenous cyclophosphamide for her lupus nephritis. She was afebrile on admission. Laboratory investigations showed a leucocyte count of  $8 \times 10^9/l$ , a haemoglobin level of 10.5 g/dl, and normal liver and renal functions. Radiographs of the chest and abdomen were normal. During hospitalization, she developed a low-grade fever and her diarrhoea persisted, but repeated stool cultures were negative. Her condition deteriorated, and 2 weeks after admission she developed high fever and mental confusion. Computed tomography of brain was normal, and examination of cerebrospinal fluid obtained by lumbar puncture yielded normal findings. She was treated empirically with intravenous cefuroxime for her sepsis. The prednisone dosage was maintained at 30 mg/day for her systemic lupus. Her haemoglobin dropped to 8.5 g/dl at this time, although there was no evidence of malaena. Oesophagogastroduodenoscopy was performed and showed gastritis endoscopically. Shortly afterwards, the patient went into septicaemic shock. Examination of the gastric biopsy obtained during oesophagogastroduodenoscopy later showed evidence of *S. stercoralis* infection. A subsequent repeat chest radiograph showed progressive

alveolar infiltrates over both lung fields, and the patient soon required inotropic support and mechanical ventilation. Stool and sputum specimens were both positive for *Strongyloides* larvae at this stage. The patient was treated with thiabendazole and intravenous ceftazidime, but she died 2 days later despite intensive supportive care. Post-mortem examination confirmed the diagnosis of disseminated strongyloidiasis affecting multiple organs.

### Case 2

Case 2 was a 56-year-old man with non-Hodgkin's lymphoma who was admitted for fever, diarrhoea, and abdominal distension. He was born in mainland China and had come to Hong Kong 30 years earlier. He had received two courses of chemotherapy consisting of cyclophosphamide, vincristine, prednisolone, and epirubicin for his lymphoma. His leucocyte count at presentation was  $9.4 \times 10^9/l$ . His chest radiograph was normal, and his abdominal radiograph showed dilated bowels suggestive of intestinal ileus. He was given supportive therapy that included intravenous fluid, nasogastric tube aspiration, and intravenous cefuroxime to cover for possible bacterial infection. Repeated cultures of blood, stool, and urine were all negative. He had a fluctuating fever that did not respond to the intravenous antibiotic. The intestinal obstruction persisted, and he then started to complain of shortness of breath. A repeat chest radiograph showed bilateral ill-defined radio-opacities. Examination of stool for ova and cysts was positive for *S. stercoralis*. At the same time, cytological examination of sputum was positive for strongyloides larvae. Therapy was switched to thiabendazole 1.5 g b.i.d. for 3 days together with intravenous cefoperazone for 1 week. Subsequently, the patient made an uneventful recovery with resolution of the chest shadows and intestinal obstruction.

**Table 1** Characteristics of the seven patients with disseminated strongyloidiasis

| Case no. | Age/sex | Underlying disease           | Immunosuppressive therapy or condition                | Initial presenting symptoms                        | Diagnostic method      | Site(s) of involvement | Outcome  |
|----------|---------|------------------------------|---|--|------------------------|------------------------|----------|
| 1        | 36/F    | Systemic lupus erythematosus | Prednisone  | Intestinal ileus, epigastric pain, vomiting        | Gastric biopsy         | CNS, lung, GI tract    | Died     |
| 2        | 56/M    | Lymphoma                     | Cyclophosphamide, vincristine, epirubicin, prednisone | Intestinal ileus, fever, epigastric pain, vomiting | Stool                  | GI tract               | Survived |
| 3        | 55/M    | Nephrotic syndrome           | Prednisone  | Intestinal ileus, fever, epigastric pain, vomiting | Duodenal biopsy        | GI tract, lung         | Survived |
| 4        | 74/M    | COPD                         | Prednisone  | Pulmonary infection with fever                     | Sputum examination     | GI tract, lung         | Died     |
| 5        | 57/M    | Diabetes mellitus            | Diabetes mellitus                                     | Intestinal ileus, fever, epigastric pain, vomiting | Gastric biopsy         | GI tract, lung         | Died     |
| 6        | 61/F    | Microscopic polyarteritis    | Prednisone  | Pulmonary infection with fever, loose stool        | Bronchoalveolar lavage | GI tract, lung         | Died     |
| 7        | 72/M    | COPD                         | Prednisone  | Meningitis with fever, abdominal pain              | Stool                  | GI tract, lung         | Died     |

CNS central nervous system, COPD chronic obstructive pulmonary disease, GI gastrointestinal

## Case 3

Case 3 was a 55-year-old male who was admitted to hospital with fever, abdominal distension, and watery diarrhoea. He had underlying nephrotic syndrome secondary to minimal-change glomerulonephritis and had been put on prednisolone 60 mg/day 2 months prior to this admission. His leucocyte count at presentation was  $20 \times 10^9/l$ . Abdominal radiograph showed dilated small bowel without fluid level. Lung fields were clear on the chest radiograph. Blood and stool cultures were negative. He was treated for intestinal ileus with intravenous fluid, nasogastric tube aspiration, and intravenous cefuroxime to cover possible sepsis. Oesophagogastroduodenoscopy, performed to determine the cause of repeated vomiting and a decreasing haemoglobin level, showed gastritis and duodenal erosion. The patient developed a high fever, and a repeat chest radiograph showed increasing bilateral lower-zone radio-opacities. At this time, *S. stercoralis* infection was identified in the duodenal biopsy. Subsequently, stool and sputum samples were examined for *S. stercoralis* larvae and were also positive. Thiabendazole 1.5 g b.i.d. was given for 1 week, during which time his fever responded and diarrhoea subsided. Moreover, there was a corresponding resolution of the dilated bowel on the abdominal radiograph. Interestingly, the patient's nephrotic syndrome also remitted after the treatment, and proteinuria decreased to only 0.3 g/day.

## Case 4

Case 4 was a 74-year-old man who was hospitalised with fever and productive cough. He had a 5-year history of severe chronic obstructive pulmonary disease (COPD) and had received repeated short courses of oral prednisolone to control the COPD exacerbations. His leucocyte count at presentation was  $14.4 \times 10^9/l$ , and chest radiograph showed emphysematous changes with bilateral patchy alveolar consolidation over both lower zones. He was treated for an acute infective exacerbation of COPD and was given intravenous amoxicillin/clavulanic acid and inhalational bronchodilators. Meanwhile, sputum was sent for bacterial culture, acid-fast bacilli smear, and cytological examination. Five days later, the patient developed a high fluctuating fever accompanied by hypotension, which required inotropic and ventilatory support. By this time, *S. stercoralis* larvae had been identified in sputum by cytological examination. Although treatment with thiabendazole and intravenous ciprofloxacin was initiated, he continued to deteriorate and died 1 day later.

## Case 5

Case 5 was a 57-year-old man who was hospitalised in our surgical department due to weight loss, vomiting, and abdominal pain. He was on gliclazide to control his

diabetes mellitus but otherwise did not take any medications. On admission, he did not have diarrhoea and was afebrile. His leucocyte count at presentation was  $8 \times 10^9/l$ , and his abdominal radiograph was unremarkable. Oesophagogastroduodenoscopy showed inflamed gastric mucosa suggestive of gastritis. Gastric biopsy confirmed the presence of *Strongyloides* infection. Treatment with mebendazole 100 mg b.i.d. was initiated, and the patient was transferred to another hospital for convalescence. Several days later, however, his condition deteriorated and he was readmitted to our medical ward in a comatose state with fever and shock. The chest radiograph showed bilateral lower zone patchy consolidations. He was found to be in diabetic ketoacidosis with plasma glucose levels of up to 30 mmol/l. A diagnosis of disseminated strongyloidiasis complicated by diabetic ketoacidosis was made, and he was placed on inotropic support and mechanical ventilation. Therapy with thiabendazole and intravenous ceftazidime was commenced, but he died 2 days later. Postmortem examination confirmed the diagnosis of disseminated strongyloidiasis with multiple organ involvement.

## Case 6

Case 6 was a 60-year-old woman with a history of hypertension and mild renal impairment secondary to membranous glomerulonephritis, for which she had been treated with prednisolone and cyclophosphamide. She was admitted 2 months after the initiation of immunosuppressive therapy with fever and cough of 1 week's duration. The chest radiograph showed bilateral lower-zone opacities. Initial leucocyte count was  $8.5 \times 10^9/l$ . She was given intravenous ceftazidime for the pneumonia, and cyclophosphamide therapy was stopped. Her fever responded initially, but her renal function deteriorated to a level that necessitated dialysis support. Repeated blood and sputum cultures were negative. The lung infiltrates persisted, however, and she developed fever and shock 2 weeks later. She continued to deteriorate clinically and was placed on inotropic and ventilatory support because of hypoxaemia. A repeat chest radiograph showed progressive deterioration with dense consolidation. The antibiotic regimen was changed to intravenous piperacillin/tazobactam, amikacin, and cotrimoxazole. Sputum cultures remained negative for bacteria, but examination of bronchoalveolar lavage fluid revealed *Strongyloides* larvae, and viral culture grew cytomegalovirus. The patient died before the finding of *Strongyloides* in lavage fluid was available.

## Case 7

Case 7 was a 72-year-old man who was admitted to hospital because of fever and headache. He had a history of hypertension and COPD, the latter of which was controlled with inhaled salbutamol and beclomethasone. On admission, the examination was remarkable for neck rigidity.

Lumbar puncture was performed, and examination of cerebrospinal fluid showed findings suggestive of meningitis, with a leucocyte count of  $1,700/\text{mm}^3$ , a protein level of 2.3 g/dl, and a glucose level of 3.5 mmol/l with a corresponding blood glucose level of 6.8 mmol/l. He was treated empirically with a course of penicillin and cefotaxime. However, bacterial antigen tests and culture of cerebrospinal fluid were subsequently found to be negative. At the same time, the patient was also given a short course of prednisolone for an exacerbation of COPD during his hospital stay.

One week after discharge from the hospital, the patient was readmitted for exacerbation of COPD and respiratory failure that required intubation and mechanical ventilation. The chest radiograph showed bilateral patchy infiltrates. He was given intravenous piperacillin/tazobactam, inhalational bronchodilators, and hydrocortisone for his pulmonary condition. During his stay in the intensive care unit, he developed bloody diarrhoea, and stool examination showed *Strongyloides larvae*. There were also abundant *Strongyloides larvae* in the endotracheal tube aspirate. In addition, herpes simplex virus and *Pseudomonas aeruginosa* were isolated from the endotracheal aspirate. The patient was treated with a complete course of thiabendazole, ceftazidime, and ciprofloxacin for *Strongyloides* hyperinfection and bacterial infection. His mental state then deteriorated suddenly, and examination of cerebrospinal fluid obtained by lumbar puncture showed a leucocyte count of  $4,500/\text{mm}^3$ , a protein level of 1.7 g/l, and a glucose level of 0.4 mmol/l. Repeat culture of cerebrospinal fluid was positive for *Enterococcus faecalis*. The patient's overall condition was compatible with bacterial meningitis complicated by *Strongyloides* hyperinfection. Despite treatment with broad-spectrum antibiotics and aggressive resuscitation, he eventually died of pseudomonal pneumonia.

## Discussion

*S. stercoralis* is a small intestinal nematode that normally resides in the mucosal crypts of the duodenum and jejunum. Infection begins when the infective filariform larvae penetrate the human skin or mucous membrane. The larvae then migrate via the bloodstream to the lungs, ascend the bronchi and trachea, and are subsequently swallowed, reaching the small intestine. Chronic infection is often asymptomatic. *Strongyloides* is unique among the human helminths in its capability for autoinfection. In this process, the adult female produces eggs, which will hatch into rhabditiform larvae. Some of these will transform into the infective filariform larvae, which reside in the colon and may penetrate the intestinal mucosa to infect the same host. This phenomenon explains why people may present with disseminated strongyloidiasis years after leaving an endemic area. Strongyloidiasis is not endemic in Hong Kong. In our series, all of the patients left mainland China, where strongyloidiasis is endemic and where the infestations

were thought to have taken place, more than 20 years before their clinical presentations appeared.

The autoinfection usually remains quiescent and does not cause significant morbidity. However, rapid multiplication of the parasite can occur when the host's defence mechanism is disrupted, resulting in hyperinfection and extensive tissue invasion. Disseminated strongyloidiasis has been reported in patients with AIDS [3], underlying malignancy, malnutrition, or alcoholism as well as in those treated with corticosteroid or cytotoxic drugs. In our series, six of seven patients (86%) had received immunosuppressive drugs, including prednisolone and cyclophosphamide, and one patient with lymphoma had been exposed to multiple chemotherapy treatments. The remaining patient (case 5) had not received any immunosuppressive drugs, but he nevertheless had diabetes mellitus, which resulted in a depressed immune status. Genta [4, 5] noted that 70% of cases of systemic strongyloidiasis occurred in immunosuppressed hosts, while the remaining 30% occurred in persons with severe malnutrition.

In the hyperinfection syndrome, multiple organs can be affected, including the lungs, liver, heart, kidneys, and central nervous system, but in most cases the presentations involve the gastrointestinal and pulmonary tracts. The most common manifestations are fever, nausea, vomiting, diarrhoea, abdominal pain, cough, dyspnoea, bronchospasm, and haemoptysis [6]. Another notable clinical feature of systemic strongyloidiasis is that 30–45% of cases are complicated by gram-negative septicaemia [6]. This association with bacterial infection has been attributed to the invasion of the gut by colonic flora secondary to the penetration of the colonic mucosa by the *Strongyloides larvae*.

In our series, all patients presented with fever. Five (71%) had gastrointestinal symptoms, the most common being abdominal pain and diarrhoea; three (42%) had a significant drop in the haemoglobin level. Six (85%) patients had bronchoalveolar infiltrates on the chest radiograph that could be attributed to either pulmonary strongyloidiasis or secondary bacterial pneumonia; of these six patients, five died of progressive lung disease. In two (29%) of our patients, disseminated strongyloidiasis was complicated by gram-negative bacterial infection, which is in agreement with previous reports by other investigators. The patient in case 6 developed *Acinetobacter pneumonia*, and in case 7 strongyloidiasis was complicated by *E. faecalis meningitis* and later by *P. aeruginosa pneumonia*.

Patients with systemic strongyloidiasis often present a diagnostic challenge. The key to prompt diagnosis is a high index of suspicion, especially in those who are immunosuppressed. Unexplained gastrointestinal and pulmonary symptoms in a high-risk patient should alert the physician to the possibility of systemic strongyloidiasis. One might expect parasitic infestation to be associated with eosinophilia; however, it has been shown that eosinophilia may be absent in parasitic infections, even in cases of disseminated strongyloides infection [7]. In our present series, no patient had an elevated eosinophil count at presentation. A possible explanation may be the presence of concomitant

pyogenic infection or the administration of immunosuppressive drugs in our patients. A definitive diagnosis of strongyloidiasis is based on the finding of *Strongyloides* larvae in the faeces, in the sputum, in bronchial washings, in a duodenal aspirate, or in gastric or jejunal biopsies in hyperinfection syndrome [8]. Gastric involvement has rarely been reported in the literature but was common in our series. Although the acid environment in the stomach is not suitable for *Strongyloides stercoralis*, reduced gastric acid secretion by proton pump inhibitors might raise the pH sufficiently to allow infection and invasion of the stomach to take place [9]. Wurtz et al. [10] reported that achlorhydria as a result of histamine-2 blockers or proton pump inhibitors may facilitate gastric strongyloidiasis. Five (70%) patients in our series were receiving either histamine-2 blockers or proton pump inhibitors, and three (42%) of them had documented gastric involvement, the diagnosis of which was made unexpectedly by gastric biopsy because of the presenting symptoms of anaemia and abdominal pain.

Thiabendazole is the drug most commonly used to treat disseminated strongyloidiasis. It is given orally at a dosage of 25 mg/kg b.i.d. for at least 7–14 days. However, complete eradication of the parasite is often difficult. The cure rates for immunocompetent patients and immunocompromised patients are only 70% and 59%, respectively, even if the drug is given for a prolonged period [11], and some authorities have recommended giving periodic short courses of thiabendazole as maintenance therapy. Ivermectin at a dosage of 25 µg/kg/day for one or two doses is an effective and better-tolerated alternative to thiabendazole. It may be necessary to prolong or repeat therapy in immunocompromised patients with disseminated disease. The efficacy of therapy can be documented by repeated examination of stool or other body fluids.

The mortality rate of disseminated strongyloidiasis is exceptionally high, ranging from 50 to 80% in previous reports. Early and active treatment may improve the outcome, but the mortality rate still ranges up to 30–40% [6]. In our series, the case fatality rate was 71%, which is probably related to the late diagnosis. The time to diagnosis ranged from 7 to 28 days in our series. Therefore, screening for *Strongyloides* infection before the initiation of immunosuppressive therapy may be essential, especially in endemic areas. Stool examination can be negative in infected patients because of sporadic passage of the larvae, and therefore repeated stool examinations are recom-

mended, which can increase the sensitivity up to 80% [12]. Serological testing by the ELISA method has been found to have 100% sensitivity and specificity [13]. However, this method is not widely available or useful in the confirmation of parasite eradication. Periodic stool examination for *Strongyloides* remains the method of choice to ensure successful treatment. In summary, physicians should be alert to include strongyloidiasis in the differential diagnosis when immunocompromised patients present with fever and gastrointestinal and/or pulmonary symptoms.

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