

# *Strongyloides* Hyperinfection in a Patient with Hypogammaglobulinaemia

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## Abstract

*Strongyloides* hyperinfection is a potentially fatal infection in immunocompromised patient. We report a case of *Strongyloides* hyperinfection in a patient with hypogammaglobulinaemia and suspected Good syndrome (thymoma-related adult-onset immunodeficiency). The patient presented with symptoms of gastroenteritis and developed respiratory failure shortly after admission. The *Strongyloides* hyperinfection was controlled by a prolonged course of ivermectin therapy. Owing to the profound immunodeficiency, the patient was also suffering from multiple opportunistic infections and eventually died of aspergillosis.

## Introduction

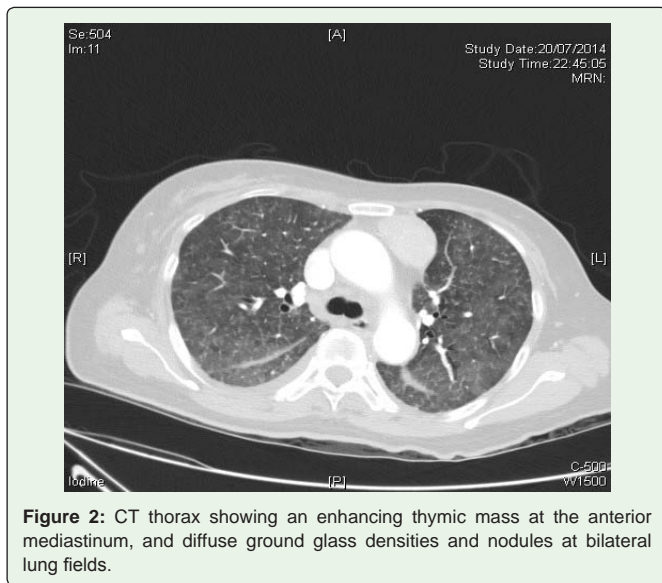
Strongyloidiasis, a human parasitic disease, is caused by *Strongyloides stercoralis*, or sometimes *S. fullebroni*. Infection in immunocompetent people causes mostly mild diseases. *Strongyloides* hyperinfection and disseminated strongyloidiasis are uncommon but potentially fatal conditions, affecting primarily immunocompromised patients. There are few locally reported cases of *Strongyloides* hyperinfection and disseminated strongyloidiasis, where affected patients were those with metastatic malignancies or receiving immunosuppressive therapies [1,2,3]. In the literature, there were only 2 cases of *Strongyloides* hyperinfection associated with hypogammaglobulinaemia [4,5]. We report a case of *Strongyloides* hyperinfection in an elderly lady with hypogammaglobulinemia and suspected Good syndrome. Her *Strongyloides* hyperinfection was refractory to prolonged antihelmintic therapy and she eventually died from disseminated opportunistic infections.

## Case

A 74-year-old lady, who had history of hypertension only and no recent use of steroid or other immunosuppressive therapies, presented to the Emergency Department for symptoms of gastroenteritis with fever, vomiting and watery diarrhea for 4 days in July 2014. The initial complete blood picture showed normal hemoglobin and platelet levels, but a White Cell Count (WCC) of  $14.2 \times 10^9/L$  (reference range:  $3.9$  to  $10.7 \times 10^9/L$ ). The WCC differential revealed neutrophilia, lymphopenia and normal eosinophil count. Her random blood glucose level, renal and liver functions were normal. She developed respiratory distress shortly after admission. Her chest X-ray showed bilateral diffuse infiltrates (Figure 1) Computed Tomography (CT) of abdomen was performed and showed diffuse mucosal wall thickening with edematous changes at the ascending and transverse colon suggestive of colitis. CT scan of thorax showed diffuse ground glass densities and multiple nodules over bilateral lungs, with an incidental finding of a thymic mass (Figure 2). Empirical treatment with ceftriaxone and metronidazole was given on admission and antibiotic regimen was later escalated to piperacillin and tazobactam for suspected hospital acquired pneumonia. In view of her persistent abdominal distension and dilated bowels on abdominal X-ray, CT scan of abdomen was repeated on day 10<sup>th</sup> which showed dilated small bowels without definite obstruction and oedematous large

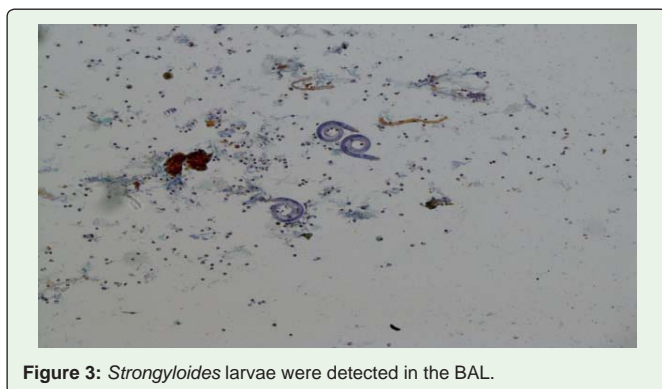


**Figure 1:** Chest X-ray images of the patient (Left) on admission showing clear lung fields and bilateral infiltrates after admission (Right).



**Figure 2:** CT thorax showing an enhancing thymic mass at the anterior mediastinum, and diffuse ground glass densities and nodules at bilateral lung fields.

bowel from caecum to distal transverse colon. Colonoscopy was done on day 15<sup>th</sup> and showed diffuse colitis with mucosal atrophy and loss of haustration in transverse colon. Biopsy of transverse colon showed chronic inflammation but no histological evidence of Cytomegalovirus (CMV) colitis. She was admitted to Intensive Care Unit (ICU) in the fourth week of hospital stay for respiratory failure, septic shock and acute renal failure requiring mechanical ventilation support, escalating dose of inotropes and also renal replacement therapy. Her sputum eventually grew Extended Spectrum Beta Lactamase (ESBL) positive *Klebsiella* species and her antimicrobial therapy was changed to Meropenem. However, she responded poorly to the antimicrobial therapy and further investigations were performed to look for another septic source. Bronchoalveolar Lavage (BAL) was done and it grew ESBL positive *Klebsiella* species, *Stenotrophomonas maltophilia* and *Candida tropicalis*. *Strongyloides* larvae were detected in the BAL and stool specimen (Figure 3). Peripheral blood CMV pp65 was elevated (206 / 2 x 10<sup>5</sup> WCC). Micafungin, levofloxacin, ganciclovir and ivermectin were prescribed based on the culture results. The larvae were detectable in stool until day 10 of oral ivermectin treatment (12mg daily) but were still present in tracheal aspirates despite 2 weeks of ivermectin treatment. Albendazole (400mg twice daily) was added after discussion with microbiologists. Daily tracheal aspirates showed persistent presence of larvae until day 27<sup>th</sup> of ivermectin and day 12<sup>th</sup> of albendazole treatment. Ivermectin and albendazole



**Figure 3:** *Strongyloides* larvae were detected in the BAL.

were discontinued 2 days after the larvae had been cleared from the tracheal aspirates. Another 2-day course of ivermectin treatment was given 2 weeks after the clearance of larva in tracheal aspirates. Generalized petechial skin rash was noticed and skin biopsy showed non-specific inflammation only without any larva detected. A total 14-day course of ganciclovir was prescribed for her CMV infection and was stopped after the peripheral blood CMV pp65 was confirmed to be negative. However, she suffered from recurrent CMV infection with positive CMV pp65 level (31 / 2 x 10<sup>5</sup> WCC) 2 weeks after cessation of ganciclovir treatment. Thus, ganciclovir was restarted and the peripheral blood CMV pp65 returned negative 3 weeks after the antiviral therapy. Other microbiology tests including sputum acid fast bacilli, urine legionella antigen and PCR tests of nasopharyngeal aspirate for influenza, human metapneumovirus, *Bordetella pertussis*, *Chlamydia pneumonia* and *Mycoplasma pneumonia* were all negative. In view of the presence of multiple opportunistic infections, further investigations for possible underlying immune compromised state were done and revealed normal complement (C3 and C4) levels and no antibodies for anti-nuclear antibodies, anti-neutrophil cytoplasmic antigen, Human T-Lympho tropic Virus-1 (HTLV-1) and Human Immunodeficiency Viruses (HIV). However, the anti-acetylcholine receptor antibody was found to be positive (0.71 nmol/L; reference range: <0.45 nmol/L). Workup of her Immune status showed diminished B cells, T cells (CD3 and CD4), immunoglobulin G and M levels. (Table 1) Good syndrome was suspected in view of the presence of a thymic mass with radiological features suggestive of thymoma together with her immune deficient state. Intravenous Immunoglobulin (IVIG) was prescribed monthly as immunoglobulin replacement treatment. Trimethoprim-sulfamethoxazole was started as prophylaxis therapy for *Pneumocystis jiroveci* infection. Pyridostigmine was prescribed in view of possible underlying myasthenia gravis.

In the 6<sup>th</sup> week of ICU stay, the patient developed an episode of convulsion. CT brain showed multiple foci of hyper dense lesions at bilateral frontal lobes and right parietal lobe which were confirmed

**Table 1:** Lymphocyte subset profile by flow cytometry and immunoglobulin levels of the patient.

Lymphocytesubset profile	Value	Reference range
B-cells CD19	2/uL 0.3%	160-708 /uL 6.6-22.6 %
T-cells CD3	578/uL 96.0%	716-2011 /uL 47.2-79.4 %
T helper cells CD4	337/uL 56.5%	415-1418 /uL 23.1-46.1 %
T-suppressor/cytotoxic cells CD8	233/uL 39.0%	292-1258 /uL 17.7-41.1 %
CD4:CD8 ratio	1.45	0.62-2.70
Natural killer cells CD16/56	14/uL 2.3%	158-1156 /uL 8.5-41.8 %
<b>Immunoglobulins</b>		
A	1.32 g/L	0.70-4.00 g/L
G	2.27 g/L	7.00-16.00 g/L
M	0.19 g/L	0.40-2.30 g/L

to be late sub acute haematomas in follow-up magnetic resonance imaging. Her cerebrospinal fluid analysis showed absence of *strongyloides* larva, and no evidence of bacterial and fungal infections. The cause of intracranial hemorrhage was unknown. She didn't have episode of hypertensive crisis. Her platelet count was normal and her clotting profile was not grossly deranged. Parenteral nutritional support was started for poor nutritional status. She required prolonged mechanical ventilation due to muscle weakness, poor coughing effort and lung abscess complicating *Escherichia coli* infection. Tracheostomy was subsequently performed. Her condition gradually improved with medical treatments. Her renal function recovered eventually. Her muscle power improved slowly with physiotherapy but she remained bed-ridden. Definitive surgery for her thymic mass was not done owing to her suboptimal pulmonary condition. She was discharged to general ward after 2 months of ICU care. The patient eventually developed invasive pulmonary aspergillosis and died after 4 months of hospitalization.

## Discussion

*S.stercoralis* is a soil-transmitted helminth endemic in humid tropical and subtropical regions, including Africa, Southeast Asia and Latin America. *S.fuelleborni* is another species of *Strongyloides* which can cause human strongyloidiasis, but it is less common and is found mainly in Africa and Papua New Guinea. *Strongyloides* has a complex biology with 2 separate life cycles- the free-living cycle (environment) and the parasite cycle (in human) [6]. The infective filariform larvae inside the soil can penetrate intact human skin to start the parasitic cycles. After entering the circulation, the larvae are transported to the lungs where they can penetrate the alveolar space and ascend along the bronchial tree. When they are being coughed out of the trachea, they are swallowed to reach the small bowel. The female worms embed in the duodenal mucosa and lay eggs which hatch and release the rhabditiform larvae. The rhabditiform larvae are either passed into feces or mature into the filariform larvae which restart the parasitic cycle by penetrating the intestinal mucosa or the skin of the perianal region. Infection by *Strongyloides* can persist for years through the process of auto-infection [6]. Strongyloidiasis can cause wide spectrum of diseases including chronic infection, symptomatic or asymptomatic autoinfection, acute infection with Löfller's syndrome, hyperinfection syndrome and disseminated strongyloidiasis.

Human response against *Strongyloides* infection depends on the T cells immune system in which the T helper 2 (Th-2) cells play the most important role to kill the penetrating infective larvae. Two Th-2 dependent mechanisms are involved including the mast cell degranulation and direct killing of the parasite by eosinophils [7]. Strongyloidiasis in immunocompromised hosts, particularly patients with impaired cell-mediated immunity, can transform into fatal hyperinfection syndrome with dissemination. From a systematic review of 244 reported cases of severe strongyloidiasis (171 cases of hyperinfection and 73 cases of dissemination) from 1991 to 2011, steroid therapy represented the main trigger predisposing to severe strongyloidiasis (67%). Other triggers include organ transplant, haematological malignancies, HIV and HTLV-1 infections, rarely chronic alcoholism and malnutrition [8]. Strongyloidiasis triggered by hypogammaglobulinemia has rarely been reported [9].

Good syndrome is a rare adult-onset immunodeficiency condition associated with thymoma. From our literature search; there

is no previous case report of strongyloidiasis associated with Good syndrome. In contrast to common variable immune deficiency, Good syndrome is characterized by hypogammaglobulinaemia and defects in both humoral and cellular immunities with low or absence of peripheral B-cells [10]. The pathogenesis of Good syndrome remained unclear and has been proposed to be related to the defect in the bone marrow. Patients with Good syndrome are susceptible to various opportunistic infections including *Candida* infections, CMV disease, Herpes simplex virus infection, *Pneumocystis jiroveci* pneumonia, tuberculosis [11] and mucormycosis [12]. In addition, there are also variable T cells abnormalities in patients with Good syndrome [13] and this could increase the susceptibility of strongyloidiasis. Although our patient did not have a histological confirmation of a thymoma, Good syndrome is a possible diagnosis in view of the immunological picture, occurrence of multiple opportunistic infections and the absence of other causes for her immune compromised state. Immunoglobulin replacement treatment is recommended to maintain appropriate immunoglobulin G levels and has been reported to improve infection control, reduce hospitalization and use of antibiotics. Surgical removal of thymoma, however, cannot reverse the immunodeficiency state in patients with Good syndrome [13].

*Strongyloides* hyper infection is a condition describing an accelerated autoinfection by *Strongyloides*, occurring mostly in patients with impaired immune state. In hyper infection, there is exacerbation of gastrointestinal and pulmonary symptoms, with the detection of an increased number of larvae in stool and sputum. Disseminated infection refers to migration of larvae to organs beyond the range of the pulmonary auto infective cycle, for example, the central nervous system [9]. The mortality rates of hyper infection and disseminated strongyloidiasis are more than 60% [8]. Patients with *Strongyloides* hyperinfection commonly present with fever and gastrointestinal symptoms including abdominal pain, diarrhea, constipation, anorexia and weight loss. Mucosal ulceration can occur at any level from the esophagus to the rectum mimicking inflammatory bowel disease. Common pulmonary manifestations include cough, dyspnea and hemoptysis. Chest X-ray frequently shows interstitial infiltrates, either bilateral or focal. The onset of symptoms may be acute or insidious [9]. Eosinophilia was only present in one-fourth of the reported cases [8].

To diagnose strongyloidiasis, stool can be examined for the presence of rhabditiform larvae in direct fecal smears. However, the sensitivity of stool examination with a single sample is as low as 30 to 50%. The sensitivity can be improved by multiple repeated stool examinations. Enzyme-Linked Immunosorbent Assays (ELISA) to detect antibodies to filariform larvae in serum has high sensitivity (83-93%) and specificity (95-98%), but the test is unable to differentiate current infection from past infection [6]. Larvae can also be detected in intestinal and lung tissues biopsy.

Treatment options for strongyloidiasis include albendazole and ivermectin. Ivermectin has a higher cure rate of 94 to 100% and is more preferable. On the other hand, albendazole has low efficacy of only 38 to 45% cure rate and is associated with higher risk of relapse. Our patient has a refractory *Strongyloides* hyperinfection requiring a prolonged course of ivermectin and albendazole treatment. Unfortunately, the patient eventually died of invasive aspergillosis due to severe immunodeficiency despite successful treatment of strongyloidiasis and IVIG therapy.

In summary, *Strongyloides* infection should be considered in patients with immune-deficient state. The infection can be insidious and symptoms are always non-specific. *Strongyloides* hyperinfection and disseminated strongyloidiasis carry high mortality and treatment with oral ivermectin should be initiated. In patients with *Strongyloides* infection with no obvious cause of immunodeficiency, immune profile should be analyzed and CT thorax for a thymoma should be considered as Good syndrome is a possible cause of adult immunodeficiency.

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