

## Strongyloides Hyperinfection and Hypogammaglobulinemia

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**We report strongyloides hyperinfection in two patients with generalized hypogammaglobulinemia from multiple myeloma and nephrotic syndrome, despite a significant strongyloides-specific immunoglobulin G (IgG) response. In contrast to reports on animals, where human IgG was shown to be a protective antibody, our observation suggests that in humans, immunity to the infective-stage larvae is not protective against the autoinfective larvae, which are the causative agents of strongyloides hyperinfection.**

**Case reports. (i) Patient 1.** A 55 year-old Chinese male with immunoglobulin A( $\kappa$ ) [IgA( $\kappa$ )] multiple myeloma developed constipation and nonspecific abdominal pain after receiving vincristine, adriamycin, and dexamethasone as part of his chemotherapeutic regimen. The clinical examination was initially unremarkable, and both chest and abdominal radiographs were normal. A complete blood count revealed leukocytosis, total white cells,  $12.1 \times 10^9$ /liter (eosinophils, 0.3%), with normal hemoglobin (14.3 g/dl) and platelet ( $220 \times 10^9$ /liter) levels. Electrolyte assay was significant for hyponatremia (sodium, 119 mmol/dl) and was otherwise unremarkable (potassium, 4.7 mmol/dl; blood urea, 4.9 mmol/liter; creatinine, 32  $\mu$ mol/dl; glucose, 7.2 mmol/liter). Liver function test was normal, apart from albumin of 26 g/liter and globulin of 20 g/liter. Serum and urine osmolality were consistent with the syndrome of inappropriate antidiuretic hormone production. His initial symptoms had responded partially to laxatives.

Two days later, he became hypotensive and a repeat complete blood count showed a fall in the hemoglobin level to 9.1 g/dl. Emergency gastroscopy revealed an area of erythematous and granular mucosa in the second part of the duodenum resembling lymphangiectasia with no evidence of bleeding. This was biopsied. His conditions stabilized after fluid resuscitation. However, he became acutely dyspneic and hypoxicemic the following day. A repeat chest radiograph showed increased pulmonary infiltrates bilaterally. He was ventilated and managed in the intensive care unit. Bronchoalveolar lavage was performed.

The duodenal biopsy revealed multiple filariform larvae of *Strongyloides stercoralis* within the glandular crypts, with marked surrounding inflammatory infiltrates. Microscopic examination of the smears obtained by bronchoalveolar lavage also showed a large number of larvae. The detection of larvae in both the duodenum and by bronchoalveolar lavage confirmed strongyloides hyperinfection in this patient. Strongyloides-specific IgG antibody (by an enzyme-linked immunosorbent assay method against the soluble antigen derived from processed *S. stercoralis* larvae L3) was elevated at 4.74 (normal, <1.00) (IVD Research, Carlsbad, CA). Tests for other

strongyloides-specific immunoglobulin subclasses were not performed. Human immunodeficiency virus and human T-lymphotropic virus type 1 tests were negative. Oral ivermectin (200  $\mu$ g/kg) was prescribed for 10 days with good clinical and radiological recovery. He was discharged 12 days later, and his subsequent antimyeloma chemotherapy was continued without further complications.

**(ii) Patient 2.** A 51-year-old Thai male presented to the neurology service with acute left hemiparesis, motor power of Medical Research Council grade 3/5 in both upper and lower limbs. CT head was significant for a right internal capsule infarct. He was initiated on aspirin and received early inpatient rehabilitation. Baseline complete blood count revealed total white cells at  $7.32 \times 10^9$ /liter (eosinophils, 12.3%), hemoglobin at 14.1 g/dl, and platelets at  $335 \times 10^9$ /liter. Urea and creatinine were elevated, at 16.1 mmol/liter and 138  $\mu$ mol/dl, respectively. Apart from a serum albumin of 23 g/liter and a globulin of 32 g/liter, the remaining liver function was normal. Lipid profile was abnormal (total cholesterol, 10.21 mmol/dl; triglyceride, 1.89 mmol/dl; high-density lipoprotein, 1.25 mmol/dl; low-density lipoprotein, 8.11 mmol/dl). Thrombophilia (antithrombin, protein C, protein S, and lupus anticoagulant) and autoimmune (antinuclear antibodies, anti-double-stranded DNA antibodies, complements 3 and 4) screening was unremarkable. Repeat biochemistry revealed improvement but not normalization of the serum urea and creatinine results. He was discharged 4 days later.

Two days later, he was readmitted with colicky abdominal pain and watery diarrhea of 1 day's duration. The clinical examination was significant for bipedal edema and basal crepitations. The abdominal and digital rectal examinations were unremarkable. Repeated laboratory investigations disclosed rising urea and creatinine levels, 19.5 mmol/liter and 236  $\mu$ mol/dl, respectively. Protein was observed on a urine dipstick. Twenty-four-hour urine total protein excretion was 6.44 g/day, consistent with the nephrotic syndrome.

He was febrile 2 days later and was empirically treated with intravenous ceftriaxone. Blood cultures subsequently yielded *Escherichia coli*. Stool investigations were significant for *S. stercoralis*. Strongyloides-specific IgG antibody (by enzyme-linked immunosorbent assay method against the soluble antigen derived from processed *S. stercoralis* larvae L3) was elevated at 3.24 (normal, <1.00) (IVD Research, Carlsbad, CA). Tests for other strongyloides-specific immunoglobulin sub-

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TABLE 1. Comparison of patients described in this paper with those described in the literature

Patient	1	2	3	4	5
Reference	This study	This study	8	2	1
Age at presentation (yr)	55	51	27	17	28
Gender	Male	Male	Male	Male	Female
Clinical feature(s)	Constipation, abdominal pain	Diarrhea, abdominal pain	Recurrent abdominal pain-diarrhea, weight loss	Recurrent diarrhea	Recurrent diarrhea, abdominal pain, fatigue
Etiology	IgA( $\kappa$ ) multiple myeloma	Nephrotic syndrome	IgA deficiency	Primary hypogammaglobulinemia	Primary hypogammaglobulinemia
Diagnostic method	Duodenal biopsy, stool, strongyloides-specific IgG	Stool, strongyloides-specific IgG	Duodenal biopsy, stool	Stool	Stool
Treatment and duration	Ivermectin, 200 $\mu$ g/kg, 10 days	Ivermectin, 200 $\mu$ g/kg, 5 days	Mebendazole, 100 mg, twice daily, 4 weeks	Thiabendazole, 1.5 g, 58 weeks	Thiabendazole, 1.5 g, twice daily, 5 days; ivermectin, 200 $\mu$ g/kg, 9 courses
Outcome	Recovery	Recovery	Recovery	Persistent blood eosinophilia	Persistent strongyloides in stool

classes were not performed. The proportions of IgG, IgA, IgM, and IgE were within normal limits. Human immunodeficiency virus and human T-lymphotropic virus type 1 tests were negative.

He was progressively dyspneic the following day. Chest radiographs revealed increased basal infiltrates, and the arterial blood gas recording was consistent with type 1 respiratory failure. Intravenous diuretics and oral ivermectin (200  $\mu$ g/kg for 5 days) were prescribed, with improvement of clinical and radiological features 3 days later. Bronchoscopy was not performed. His abdominal symptoms resolved, and his lower limb edema improved with diuretic treatment. He was discharged 10 days from admission. He admitted to the use of traditional Chinese medication after his initial admission for ischemic stroke.

He was reviewed in the outpatient clinic, where serum urea and creatinine were documented to have normalized. Repeat stool examination did not demonstrate the presence of strongyloides. He declined renal biopsy and had opted to return to his own country for further management.

**Discussion.** Strongyloides hyperinfection is unique among the parasitic infections because of its ability to autoinfect the host without a soil or intermediate host. The detection of increased numbers of larvae in stool and/or sputum is a hallmark of hyperinfection that normally occurs as a result of an alteration in immune status. Hyperinfections are often complicated by infections caused by gut flora that gain access to intestinal sites, presumably through ulcers induced by the filariform larvae (6).

We report strongyloides hyperinfection in two patients where strongyloides-specific IgG was demonstrated, despite generalized hypogammaglobulinemia from multiple myeloma and nephrotic syndrome, respectively. Strongyloides hyperinfection is likely triggered by the use of steroids as part of the chemotherapeutic regimen in patient 1 and traditional Chinese medication in patient 2. Although the medicaments he took

were not available for analysis, traditional Chinese medications are well known to contain synthetic steroidal compounds (4). A review of the literature and comparison of previously reported cases suggested that recovery in patients with strongyloidiasis and primary hypogammaglobulinemia was often prolonged and refractory (Table 1) (1, 2, 8). This was in contrast to cases of strongyloidiasis and secondary hypogammaglobulinemia that respond readily to conventional anti-strongyloides treatment.

Protective immunity to larval *S. stercoralis* has been shown to be dependent on antibody, complement, and granulocytes (7). The importance of the humoral response of the B cell in controlling *S. stercoralis* infection in humans is suggested by a more severe course of strongyloidiasis among patients with hypogammaglobulinemia (1, 2) and the protective role of B cells in the immunity against strongyloides infection in mice (5). Following treatment with ivermectin and thiabendazole, a fall in strongyloides-specific immunoglobulin IgG, IgA, and IgE has been observed in patients infected with strongyloides (9) and in males, an elevation of the strongyloides-specific IgG4 antibody titer has been associated with resistance to treatment of strongyloides infection (10).

The significance of an elevated strongyloides-specific IgG and hyperinfection in our patients is uncertain. The development of strongyloides hyperinfection would suggest that the strongyloides-specific IgG response was not protective and that other IgA and IgE responses may be more important in the humoral response against strongyloides infection, when in fact it might have been nonspecific for the autoinfective stage of strongyloides hyperinfection. It has been reported that immunity to the infective-stage larvae does not protect animals from the autoinfective larvae, which are the causative agents of disseminated strongyloidiasis (3).

To conclude, hypogammaglobulinemia is an important risk factor to the development of strongyloides hyperinfection. In contrast to reports in animals where human IgG was shown to

be a protective antibody, our observation suggests that in humans, immunity to the infective-stage larvae is not protective against the autoinfective larvae, which are the causative agents of strongyloides hyperinfection. Further studies are needed to confirm this observation.

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