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(κ) [IgA(κ)] multiple myeloma developed constipation and nonspecific abdominal pain after receiving vincristine, adriamycin, and dexamethasone as part of his chemotherapy 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 × 109/liter (eosinophils, 0.3%), with normal hemoglobin (14.3 g/dl) and platelet (220 × 109/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 μmol/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 hypoxemic the following day. A repeat chest radiograph showed increased urea and creatinine levels, 19.5 mmol/liter and 236 μmol/dl, respectively. Repeated laboratory investigations disclosed 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 μmol/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 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 μg/kg) was prescribed for 10 days with good clinical and radiological recovery. He was discharged 12 days later, and his subsequent antymyeloma 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 × 109/liter (eosinophils, 12.3%), hemoglobin at 14.1 g/liter, and platelets at 335 × 109/liter. Urea and creatinine were elevated, at 16.1 mmol/liter and 138 μmol/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 (anti-thrombin, 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.

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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 IgG response was not protective and that other IgA and IgE responses may be more important in the immunity against strongyloides infection in mice (5) and in males, an elevation of the strongyloides-specific IgG response was not protective and that other IgA and IgE responses may be more important in the immunity against 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 strongyloidiasis hyperinfection. Further studies are needed to confirm this observation.

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REFERENCES