

CASE REPORT

STRONGYLOIDIASIS WITH GASTRIC MUCOSAL INVASION PRESENTING WITH ACUTE INTERSTITIAL NEPHRITIS

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Abstract. We report an atypical occurrence of invasive *Strongyloides stercoralis* infection of the stomach mucosa in an elderly female patient from Bangka Island, northwestern Indonesia. The patient presented with severe epigastric pain, edema of the legs, proteinuria and severe hypoalbuminemia. Gastric and duodenal biopsies found eggs, larval and adult forms present in the superficial mucosa with mild inflammation. The Harada-Mori filter paper culture technique revealed *S. stercoralis* filariform larvae and free-living adult worms, corroborating the diagnosis. The infection was associated with acute interstitial nephritis. The patient showed rapid and dramatic improvement after treatment with mebendazole.

INTRODUCTION

The threadworm, *Strongyloides stercoralis* (Bavey, 1876) Stiles and Hassall, 1902, is a cosmopolitan intestinal nematode parasite of humans, infecting an estimated 30 million worldwide (Genta, 1989), particularly people residing in warm, humid tropical and subtropical regions. This parasite is typically found in low prevalence (< 1%), even in more endemic tropical regions. However, in some tropical areas, prevalence of infection can exceed 30% of the population, especially in areas where hookworm (*Necator*, *Ancylostoma*) infection does not occur (Beaver *et al*, 1984; Ashford and Crewe, 1998; Myers *et al*, 2000). Human infections normally involve adult female

worms residing in the mucosa of the duodenum and upper jejunum. The majority of infections are clinically asymptomatic and only discovered as a serendipitous incidental finding. Occasionally, low-grade eosinophilia may be the only sign of infection (Liu and Weller, 1993).

Typically, the female parasitic stage is buried in the mucosal crypts of the small intestine, where they lay uninucleate eggs that embryonate in the tissue. After hatching, rhabditiform larvae migrate into the intestinal lumen and eventually pass out with the feces. Rhabditiform larvae can either molt to the infective filariform stage directly or develop into facultative free-living stages in the soil, ultimately producing (indirectly) infective filariform larvae that are able to penetrate the skin of a susceptible host. Parasitic filariform larvae will migrate via the blood to the lungs and other organs of the body, eventually migrating to the intestines. Skin invasion can cause pruritic urticarial rash and secondary bacterial infection, whereas migration can result in a transient eosinophilic pneumonitis (Loffler's syndrome).

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Symptomatic *S. stercoralis* is normally the result of intestinal inflammation and irritation that can promote abdominal pain and a non-bloody diarrhea (Jones, 1950). Occasionally, autoinfection occurs wherein rhabditiform larvae can develop into filariform larvae while still in the intestine, and invade the ileum and colon. This may lead to recurrent migratory-associated symptoms or disseminated strongyloidiasis (hyperinfection syndrome) involving many organs in the body, particularly the lungs (Igra-Siegmán *et al*, 1981; Mahmoud, 2000; Myers *et al*, 2000). In cases of massive worm burdens and untreated hyperinfection, extensive larval infiltration of the small bowel and migration to other organs can result in severe complications and death (Adedayo *et al*, 2001). These exceptional presentations have been observed mostly in immunosuppressed patients, in particular those receiving prolonged corticosteroid therapy for various afflictions (Cruz *et al*, 1966; Purtilo *et al*, 1974; Suvajdzic *et al*, 1999). Herein, we report an unusual occurrence of invasive *S. stercoralis* of the gastric mucosa that contributed to severe symptomatic illness requiring hospitalization.

CASE REPORT

A 68-year-old, acutely ill, female with a history of rheumatoid arthritis from Bangka Island off the eastern coast of Sumatra, Indonesia, was admitted to the hospital in Jakarta presenting with severe epigastric pain, anorexia, significant bilateral lower extremity edema, persistent nonproductive cough and wheezing. She had complained of chronic episodic diarrhea and abdominal pain while in Bangka and had been unable to find relief from health care providers on the island. Chest radiographs were unremarkable and repeated sputum examination was negative. The patient was severely hypoalbuminemic (0.9 g/dl), and urinalysis revealed heavy proteinuria and pyuria (100-120 leukocytes per 100x field). Repeated

blood examination ruled out malaria, and she had no frank eosinophilia. Fresh diarrheic stool was examined microscopically and revealed heavy *S. stercoralis* infection (5-10 larvae/100x microscopic field), which was confirmed using a Harada-Mori culture technique (Ash and Orihel, 1987). No other helminthic or protozoal infections were detected. Before initiating treatment, stool culture was achieved by smearing patient fecal material onto a filter paper strip and placing it in a plastic bag containing a small amount of water held at ambient room temperature (25-30 °C). Rhabditiform larvae migrated down the paper into the water within 1-2 days of exposure and free-living adults were seen after 3-4 days. Culture of fresh stool produced second-stage rhabditiform larvae, free-living male and female adult worms and infective filariform larvae. Typical first-stage rhabditiform (both first and second stage forms) larvae were also detected in fresh stool, having a characteristic small buccal cavity and large genital primordium relative to morphology of hookworm species (Fig 1).

Exploratory esophagogastroduodenoscopy with biopsy of the gastric antrum and duodenum revealed numerous nodular lesions on the inner surface of the superficial gastric and duodenal mucosa. Formalin-fixed biopsy specimens were examined histologically. Paraffin-embedded gastric and duodenal tissue were sectioned at 5 µm thickness and stained with hematoxylin-eosin (H&E) and toluidine blue. Microscopic tissue examination indicated an invasive helminthic infection (Gardiner and Poynton, 1999). At high-powered magnification, numerous adults, immature rhabditoid worms and embryonated eggs conforming to *S. stercoralis* were identified. Worms and eggs were located in the superficial gastric mucosa and crypts within lymphatic vessels and gland lumina (Figs 2-4). There was no evidence of submucosal invasion of the duodenum or stomach. Pathology was unremarkable; epi-

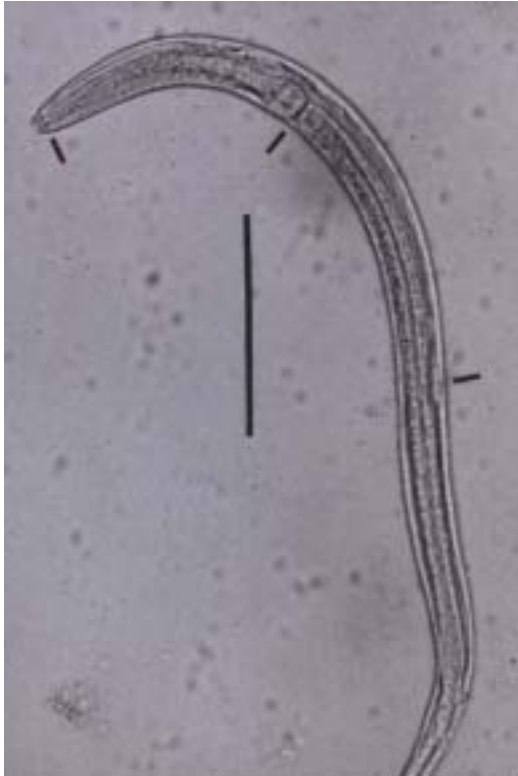


Fig 1—*Strongyloides stercoralis* infection in a naturally infected human from Bangka Island, Indonesia. Unstained, formalin-preserved first-stage rhabditiform larvae (~250 x 15 μ m) isolated in fresh stool from patient (original magnification 100X) demonstrating short, cuticle-lined buccal cavity, a clearly demarcated rhabditiform esophagus, and the prominent mid-level genital primordium (dash lines from anterior end, respectively). Measurement bar = 40 μ m.

thelial mucosal architecture was fairly well preserved without necrosis, ulceration or abscess formation. Histological sections did not show significant acute inflammatory cell infiltrates or well developed eosinophilic granulomas surrounding parasite-containing mucosa. Tissue obtained from percutaneous needle renal biopsy was also fixed and sectioned at 2 μ m thickness, stained with H&E, periodic acid-Schiff (PAS), Masson trichrome and PAS-silver methanamine. Renal biopsy showed a chronic,

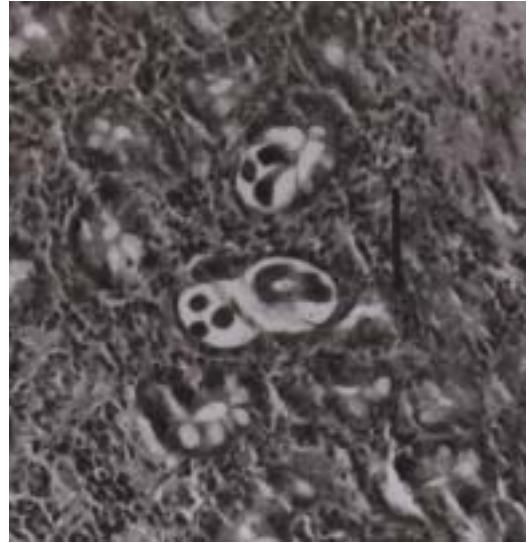


Fig 2—*S. stercoralis* ova in gastric superficial mucosa (crypts) containing developing rhabditiform larvae (original magnification 50X). Measurement bar = 50 μ m.

non-specific interstitial nephritis with normal glomeruli. Although a definitive association between nephritis and strongyloidiasis is difficult to make, other known causes for interstitial nephritis (eg, concurrent medication, hypercalcemia) were not identified.

DISCUSSION

Because more effective drugs, like albendazole, ivermectin and thiabendazole, were not readily available in Jakarta, the patient was treated with mebendazole (500 mg bid) for 3 consecutive days, and provided a second full course shortly thereafter. A stool sample on day 4 post-treatment showed no evidence of active *Strongyloides* infection (ie, rhabditiform larvae); the stool contained only parasitic adult female *S. stercoralis*. After only a few days of treatment, the patient's symptoms rapidly subsided. Although mebendazole is no longer recommended for the treatment of strongyloidiasis because of inconsistent efficacy compared to other drugs (Pelletier and Baker,

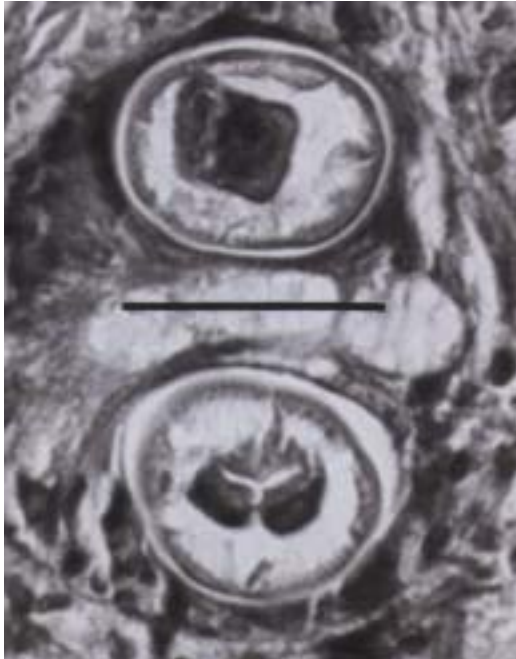


Fig 3—Cross section of adult female *S. stercoralis* in gastric epithelial burrow showing esophageal lumen (upper section) and paired ovarian uteri and intestine (lower section) surrounded by a hypodermis layer and musculature projecting into the pseudocoelom (pulled slightly away from outer cuticle) (original magnification 400X). Measurement bar = 40 μ m.

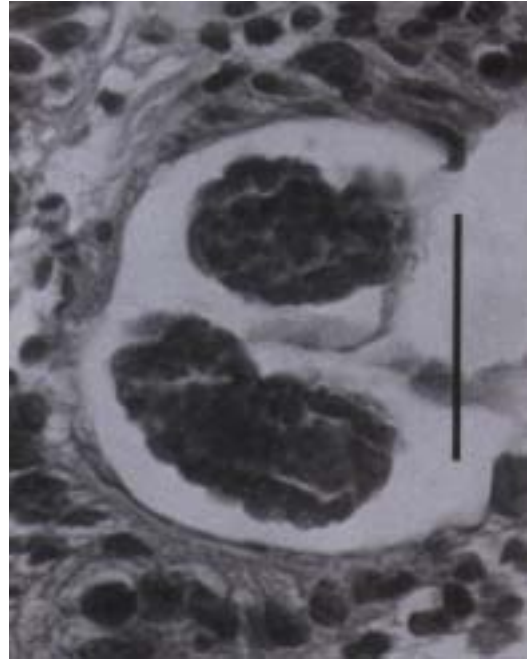


Fig 4—Paired, thin-shelled embryonated ova of *S. stercoralis* in gastric mucosa (original magnification 400X). Measurement bar = 40 μ m.

1987; The Medical Letter, 2000; Pornsuriyasak *et al*, 2004), this patient appeared to respond extremely well to therapy. Unfortunately, further follow-up after treatment was not possible as the patient returned home to Bangka; therefore, complete cure or possible relapse could not be reported.

Strongyloidiasis can persist for many years in untreated patients or cases failing to respond to chemotherapy (Pelletier, 1984). Often associated with intermittent creeping eruption, urticaria and gastrointestinal symptoms (heartburn, indigestion, diarrhea and abdominal pain), chronic intestinal infections may also result in recurrent colitis (Berry *et al*, 1983), intestinal malabsorption and low-grade

eosinophilia (Stemmermann, 1967). In chronic infections, adult worms have been reported to invade the superficial gastric mucosa, causing gastritis and perhaps ulceration (Stemmermann, 1967; Than, 1979; Myers *et al*, 2000). We report another case of gastric tissue involvement by *S. stercoralis* in a patient with apparent chronic strongyloidiasis.

Invasion by *S. stercoralis* of the stomach mucosa is not that unusual, but seldom reported. In this case report, gastric involvement by *S. stercoralis* could have resulted from one or more sources. An initial infection from the free-living cycle in the soil could result in external autoinfection involving perianal re-invasion of filariform larvae developing in the colorectal area. It is also possible that she suffered from a low-grade chronic strongyloidiasis, caused either by repeated exposure to contaminated soil or internal autoinfection, a condition by which larvae rapidly mature within

the lumen of the gut, producing filariform larvae that penetrate the intestinal mucosa and invade the blood stream directly. Low-grade immunosuppression could have predisposed the patient to the latter mechanism of infection.

Disseminated hyperinfection usually develops only in severely immunosuppressed patients (Armignacco *et al*, 1989). The patient reported here showed no significant pulmonary involvement other than cough and mild shortness of breath upon hospital admission. She had no documented history of clinical immunosuppression. However, she admitted having rheumatoid arthritis and treated the condition regularly with a combination of modern and traditional medicines, which she could not specify or provide for identification. Glucocorticoids are commonly used in Indonesia for the treatment of rheumatoid arthritis, and these anti-inflammatory drugs can impair cell-mediated immunity. Loss of intact cellular immunity is believed to be partly responsible for allowing conversion of rhabditiform to infectious filariform larvae and thus promoting systemic infection.

The association between the patient's *Strongyloides* infection and acute presentation with interstitial nephritis remains unclear. A link between nephrotic syndrome and disseminated strongyloidiasis infection has been postulated (Morimoto *et al*, 2002), although the evidence appears tenuous. The fact that her nephritis resolved rapidly after beginning therapy along with apparent clinical recovery from her strongyloidiasis suggests such an association. Although not specifically reported in connection with strongyloidiasis, interstitial nephritis has been linked with immune response to infection (Owada *et al*, 1999). However, interstitial nephritis has also been associated with the ingestion of aristolochic acid contained in some herbal medicines (Yang *et al*, 2000). Her nephritis could have resolved due to the withdrawal of an offending herbal

agent during treatment of strongyloidiasis. Therefore, a definitive link between *Strongyloides* infection and her presentation with acute nephritis cannot be established.

The patient's long history of abdominal pain and intermittent diarrhea in the setting of acute presentation with mild pulmonary symptoms and gastric mucosa involvement strongly suggested that she suffered from chronic strongyloidiasis. Although the patient did not have a significant eosinophilia at admission, eosinophilia is not considered a reliable diagnostic sign for strongyloidiasis in many cases. In severe disease there may be no eosinophilia seen at all. Whether her acute renal dysfunction and interstitial nephritis were a direct result of hyperinfection could not be established with certainty. However, her rapid improvement after beginning treatment suggests that she was suffering from mild hyperinfection with multi-organ involvement. Her predisposing factor is speculated to be glucocorticoids used in the treatment of rheumatoid arthritis.

Clinical symptoms ultimately attributable to strongyloidiasis appear in a variety of forms that can be misleading. Moreover, accurate diagnosis of *Strongyloides* infection can often be difficult (Sato *et al*, 1995; Siddiqui and Berk, 2001; Sudarshi *et al*, 2003). The most common diagnostic methods are microscopic examination of feces by either direct smear or formalin-ether concentration and filter paper or agar plate culture techniques (Myers *et al*, 2000), followed by serologic testing (Gyorkos *et al*, 1990). In general, stool examinations underestimate and serological testing overestimates infection prevalence (Joseph *et al*, 1995). Often found sympatric with hookworm infection, it is important that an accurate diagnosis be made to differentiate hookworm (*Necator* and *Ancylostoma* spp) infection from *S. stercoralis*, since the treatment, follow-up and clinical considerations are predicated on the particular parasite present and the patient's condition. Moreover, accurate diag-

nosis is critical before beginning immunosuppressive corticosteroid treatment, because undiagnosed *S. stercoralis* infection can result in a fatal outcome due to disseminated hyperinfection (Suvajdzic *et al*, 1999).

Indonesia and neighboring countries in Southeast Asia seldom report a high prevalence of *S. stercoralis* infection in human populations (Oemijati, 1989; Liu and Weller, 1993; Anantaphruti *et al*, 2000; Widjana and Sutisna, 2000). Under most conditions, prevalence rates rarely exceed 5% of sampled populations. This apparent low prevalence is likely a reflection of gross underreporting because of high frequency of latent infections and the insensitive detection techniques often used in community surveys and clinical settings (Sato *et al*, 1995). It is imperative that health care providers remain aware of the seriousness this nematode poses, especially in the elderly, immunosuppressed individuals, or before beginning immunosuppression therapy, and to ensure accurate diagnosis (*ie*, use of more than one method), appropriate treatment and careful follow-up of cases.

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REFERENCES

- Adedayo AG, Grell GA, Bellot P. Case study: Fatal strongyloidiasis associated with human T-cell lymphotropic virus type 1 infection. *Am J Trop Med Hyg* 2001; 65: 650-1.
- Anantaphruti MT, Nuamtanong S, Muennoo C, *et al*. *Strongyloides stercoralis* infection and chronological changes of other soil-transmitted helminthiasis in an endemic area of southern Thailand. *Southeast Asian J Trop Med Public Health* 2000; 31: 378-87.
- Armignacco O, Capecchi A, De Mori P, Grillo LR. *Strongyloides stercoralis* hyper-infection and acquired immunodeficiency syndrome. *Am J Med* 1989; 86: 258.
- Ash LR, Orihel TC. Parasites: A guide to laboratory procedures and identification. Chicago: American Society of Clinical Pathologists Press, 1987: 59-62.
- Ashford RW, Crewe W. The parasites of *Homo sapiens*. Liverpool: Liverpool School of Tropical Medicine, 1998: 66-67.
- Beaver PC, Jung RC, Cupp EW. Clinical parasitology. 9th ed. Philadelphia: Lea & Febiger, 1984: 253-68, 750.
- Berry AJ, Long EG, Smith JH, *et al*. Chronic relapsing colitis due to *Strongyloides stercoralis*. *Am J Trop Med Hyg* 1983; 32: 1289-93.
- Cruz T, Reboucas G, Rocha H. Fatal strongyloidiasis in patients receiving corticosteroids. *N Engl J Med* 1966; 275: 1093-6.
- Gardiner CH, Poynton SL. An atlas of metazoan parasites in animal tissues. Washington DC: Armed Forces Institute of Pathology, 1999.
- Genta RM. Global prevalence of strongyloidiasis: critical review with epidemiologic insights into the prevention of disseminated disease. *Rev Infect Dis* 1989; 11: 755-767.
- Gyorkos TW, Genta RM, Viens P, *et al*. Seroepidemiology of *Strongyloides* infection in the Southeast Asian refugee population in Canada. *Am J Epidemiol* 1990; 132: 257-64.
- Igra-Siegman Y, Kapila R, Sen P, *et al*. Syndrome of hyperinfection with *Strongyloides stercoralis*. *Rev Infect Dis* 1981; 3: 397-407.
- Jones CA. Clinical studies in human strongyloidiasis. I. Semeiology. *Gastroenterol* 1950; 16: 743-56.
- Joseph L, Gyorkos TW, Coupal L. Bayesian estima-

- tion of disease prevalence and the parameters of diagnostic tests in the absence of a gold standard. *Am J Epidemiol* 1995; 141: 263-72.
- Liu LX, Weller PF. Strongyloidiasis and other intestinal nematode infections. *Infect Dis Clin North Am* 1993; 7: 655-82.
- Mahmoud AAF. Intestinal nematodes (roundworms). In: Mandell G, Douglas R, Bennett J, eds. Principles and practice of infectious diseases. Vol 2. Philadelphia: Churchill Livingstone, 2000: 2938-43.
- Morimoto J, Kaneoka H, Sasatomi Y, et al. Disseminated strongyloidiasis in nephrotic syndrome. *Clin Nephrol* 2002; 57: 398-401.
- Myers WM, Neafie RC, Marty AM. Strongyloidiasis. In: Myers WM, ed. Pathology of infectious diseases. Vol 1. Helminthiasis. Washington DC: Armed Forces Institute of Pathology, 2000: 341-52.
- Oemijati S. Important nematode infections in Indonesia. *Bull Health Stud (Indonesia)* 1989; 17: 29-33.
- Owada K, Kurihara S, Osono E, et al. A case of interstitial nephritis induced by super antigen produced by methicillin-resistant *Staphylococcus aureus* (MRSA) presenting as acute renal failure. *Nippon Jinzo GakkaiShi* 1999; 41: 89-94.
- Pelletier LL. Chronic strongyloidiasis in World War II Far East ex-prisoners of war. *Am J Trop Med Hyg* 1984; 33: 55-61.
- Pelletier LL, Baker CB. Treatment failures following mebendazole therapy for chronic strongyloidiasis. *J Infect Dis* 1987; 156: 532-3.
- Pornsuriyasak P, Niticharoenpong K, Sakapibunnan A. Disseminated strongyloidiasis successfully treated with extended duration ivermectin combined with albendazole: A case report of intractable strongyloidiasis. *Southeast Asian J Trop Med Public Health* 2004; 35: 531-4.
- Purtilo DT, Meyers WM, Connor DH. Fatal strongyloidiasis in immunosuppressed patients. *Am J Med* 1974; 56: 488-93.
- Sato Y, Kobayashi J, Toma H, Shiroma Y. Efficacy of stool examination for detection of *Strongyloides* infection. *Am J Trop Med Hyg* 1995; 53: 248-50.
- Siddiqui A, Berk S. Diagnosis of *Strongyloides stercoralis* infection. *Clin Infect Dis* 2001; 33: 1040-7.
- Stemmermann GN. Strongyloidiasis in migrants. *Gastroenterology* 1967; 53: 59-70.
- Sudarshi S, Stumpf R, Armstrong M, et al. Clinical presentation and diagnostic sensitivity of laboratory tests for *Strongyloides stercoralis* in travelers compared with immigrants in a non-endemic country. *Trop Med Int Health* 2003; 8: 728-32.
- Suvajdzic N, Kranjic-Zec I, Jovanovic V, Popovic D, Colovic M. Fatal strongyloidiasis following corticosteroid therapy in a patient with chronic thrombocytopenia. *Haematologia* 1999; 29: 323-6.
- Than K. *Strongyloides* gastritis – report of a case. *J Trop Med Hyg* 1979; 82: 21-2.
- The Medical Letter. Drugs for parasitic infections. New Rochelle, NY: The Medical Letter, Inc, 2000.
- Widjana DP, Sutisna P. Prevalence of soil-transmitted helminth infections in the rural population of Bali, Indonesia. *Southeast Asian J Trop Med Public Health* 2000; 31: 454-9.
- Yang CS, Lin CH, Chang SH, Hsu HC. Rapidly progressive fibrosing interstitial nephritis associated with Chinese herbal drugs. *Am J Kidney* 2000; 35: 213-8.