Relapse of Overwhelming Strongyloidiasis After Therapy with Mebendazole or Albendazole: Report of Two Cases

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Abstract

Two cases of overwhelming strongyloidiasis complicating psoriasis and systemic lupus erythematosus during corticosteroid therapy were described. Mebendazole 400 mg per day was prescribed for three days in the first case when stool examination disclosed numerous larvae of *S. stercoralis*. Nine days later, he experienced hemoptysis. Chest-roentgenogram showed diffuse bilateral pulmonary infiltration. *S. stercoralis* larvae were demonstrated in sputum and stool. In another case, albendazole 400 mg per day was given for twelve days to treat disseminated strongyloidiasis. *Strongyloides* larvae disappeared from sputum and stool in six days after treatment and the patient clinically improved. *Strongyloides* larvae appeared again in sputum and stool 2 weeks after cessation of therapy. Both were dead in respiratory distress syndrome. Mebendazole and albendazole appeared ineffective in eradicating disseminated strongyloidiasis in these two cases.
**Strongyloides stercoralis** infection is asymptomatic in approximately 50% of the cases. The classic symptoms are epigastric and upper abdominal pain, nausea, vomiting, and diarrhea. In cases of overwhelming infections, the diarrhea becomes increasingly severe with hypoproteinemia, hypokalemia, shock and death. Malnutrition, debilitating disease, and immunosuppressive drugs are known to contribute to exacerbation of *Strongyloides* infection with development of a massive endoautoinfection cycle. Prevalence of intestinal strongyloidiasis in patients with chronic renal disease at Siriraj Hospital is 7 per cent and 0.5-2 per cent in people living in rural areas. Therefore it can be foreseen that strongyloidiasis will be continuously encountered at this hospital as well as in other medical centres in Thailand. Its presenting symptoms may mimic other common diseases or occasionally be very bizarre manifested as arthritis, brain abscess or periumbilical purpura. Consequently, diagnosis of disseminated strongyloidiasis is inevitably eluded under these conditions. Thiabendazole has long been recommended for therapy of all forms of strongyloidiasis.

Mebendazole and a newer synthetic benzimidazole, albendazole are broad-spectrum anthelmintics used in the treatment of various round worm infestations. They act by blocking glucose uptake by the susceptible helminths. These two drugs are preferable in the treatment of various round worm infestations. Though mebendazole and albendazole are well recognized for their poor gastrointestinal absorption, scattered reports of mebendazole's and albendazole's effectiveness in strongyloidiasis appeared in the journals and also in the advertisement leaflet of the drugs. Since mebendazole and albendazole are newer drugs and better tolerated, both are increasingly prescribed for therapy of intestinal strongyloidiasis and accordingly substituted for thiabendazole which is older but so far, the best anthelmintic among several hundred benzimidazole compounds. We reported herein two cases of disseminated strongyloidiasis treated with mebendazole and albendazole because of patients' intolerance to thiabendazole.

**CASES OF REPORT**

Case 1 A 26 year-old Thai male was admitted to Siriraj Hospital in June 1977 for evaluation of weight loss for 10 kilograms in one month. He was suffered from psoriasis vulgaris confirmed by skin biopsy with joint involvement since November 1976. He was treated with prednisolone and methotrexate intermittently with improvement. He did well until June 1977 when he noticed the onset of progressive fatigue, anorexia and weight loss for 10 kilograms in one month. He also complained of occasional tetany, chest oppression, nausea, vomiting and abdominal pain. On admission physical examination revealed an emaciated patient with moderate pallor. The blood pressure was 110/80 torr, the pulse rate 98 per minute, the temperature 36.4°C and the respiratory rate 20 per minute. Dry skin was noted over extremities with scattered area of hyperpigmented and hypopigmented lesions of subsided psoriasis. There was mild generalized tenderness over abdomen. Other physical examination was unremarkable. The haematocrit was 33 per cent, the white cells count was 8,050 per cu. mm with 1 per cent of eosinophil, serum potassium and calcium were 1.7 meq per litre and 7.0 mg per cent respectively. Serum albumin and globulin were 1.9 and 2.3 gm per cent respectively.

He was treated with antacid for abdominal tenderness without clinical improvement. Chronic adrenal insufficiency was further suspected and 60 mg of prednisolone was added without benefit. Three weeks after admission he developed watery diarrhea and stool examination revealed numerous *Strongyloides* larvae. Mebendazole 400 mg per day for three days was prescribed. Nine days later, he developed hemoptysis and the film of the chest showed bilateral miliary infiltration. We were consulted to see the patient and sputum as well as stool examination revealed numerous living larvae of *Strongyloides*. Thiabendazole 25 mg per kilogram, twice daily was initiated but he expired on that day. Hemoculture and spinal fluid culture taken before death were sterile. Autopsy was not permitted.

Case 2 A 15-year-old woman (HN. 93276-30, AN. 2-25296-30) with birth and early residence in Ubonratchanee Province was relatively well until three month prior to admission when she began to note leg edema. She was diagnosed nephrotic syndrome but did not respond to medication given at the district hospital and subsequently developed dyspnea. She was transferred to Siriraj Hospital and systemic lupus erythematosus with nephrotic syndrome was diagnosed based on positive anti DNA antibody, positive ANF (fine speckle type), 1+ Coomb's test, proteinuria 3+, albumin 1.9 mg/dl, globulin 2.2 gm/dl, cholesterol 398 mg/dl. Prednisolone, 60 mg per day was initially prescribed for one month with slight improvement. However, urinalysis still revealed numerous red cells and proteinuria 3+. Cellulitis and fever suddenly developed two days before hospitalization and followed by an acute onset of abdominal pain and diarrhea. She had experienced three to four bowel movements per day, each preceded by low crampy abdominal pain. The stools were watery and contained mucus but no blood. There was no nausea or vomiting.

Physical examination revealed a somewhat confused and markedly undernourished female with blood pressure 120/70 torr, pulse rate 120 per
minute, respiratory rate 24 per minute, temperature 39.2°C. She was slightly pale, edematous and showed cushingoid face due to corticosteroid treatment. Cellulitis was noted in left leg. Cardiovascular and respiratory examination were unremarkable. Abdomen was distended but not tender. Bowel sounds were normoactive. No stiffneck was detected but Kernig's sign was equivocal. On the day of hospitalization, she was given prednisolone 40 mg per day. Two days later, Hookworm ova and Strongyloides larvae were demonstrated in stool examination. Two tablets of thiabendazole were initiated but patient developed nausea and vomiting and unable to take further medication by oral route. However, stool examination was negative for Strongyloides larvae four days later. Cellulitis was treated with penicillin G sodium 6 million units for five days and replaced by cefotaxime when cerebrospinal fluid disclosed 90 per cent of neutrophil out of total cell count of 1250 per cu. mm. Urine and blood culture on admission were reported later to be positive for E. coli. She clinically improved and was maintained with prednisolone 40 mg per day. However hematocrit dropped from 21 to 14 per cent in 10 days without evidence of gross blood loss or hemolysis and Coomb's test was negative. She was transfused with two units of packed red cell. Therapy of E. coli septicemia with possible bacterial but culture-negative meningitis with cefotaxime was maintained for three weeks. Strongyloides larvae appeared again in stool examination and she was given albendazole 400 mg per day for twelve days because of better tolerance and stool examination was negative for Strongyloides larvae six days later. Twelve days later, while on therapy with prednisolone 60 mg per day, she gradually developed dyspnea and chest roentgenogram revealed bilateral diffuse infiltration. Sputum examination revealed numerous living larvae of Strongyloides and thiabendazole 1 gm per day was administered together with cefotaxime and gentamicin. Her condition deteriorated and she succumbed nine days later in respiratory failure.

**DISCUSSION**

Overwhelming infection with Strongyloides stercoralis in the immunocompromised host is a well known entity. The larvae of this nematode usually produce asymptomatic infections or mild disease in normal hosts. However, in the patients with immunocompromised disease or corticosteroid therapy, acceleration of the phenomenon of autoendoinfection and excessive metamorphosis of rhabditiform to invasive filariform larvae may occur. As a result, the larvae may disseminate and involve many organs, causing increased morbidity and mortality. Recent studies of experimentally induced S. stercoralis infection in dogs and monkeys have shed light on the mechanism of hyperinfection in humans.\(^{14-16}\) When chronically infected animals are given high-dose steroid therapy, fulminant fatal hyperinfection occurs with vague clinical signs. It is evident that corticosteroid therapy alters the host-parasite relationship in favour of the parasite. Numerous reported cases including ours who subsequently developed disseminated strongyloidiasis during corticosteroid therapy, substantiate the finding in these animals' experiments. Also it is not uncommon that the diagnosis of disseminated strongyloidiasis was not entertained in many cases before death or autopsy since corticosteroid is such powerful in retardation of inflammatory process that various clinical signs of parasitic and bacterial infections are not apparent until shortly before death. It can not be overemphasized that stool, sputum, gastric content as well as other specimens should be frequently examined for this larvae in immunocompromised patients since it is the only reliable and accurate method for reaching to the diagnosis.

The first cases had psoriasis as underlying disease and died of respiratory failure very likely due to massive infection of Strongyloides larvae in lung parenchyma. Respiratory failure also intervened in the second case and is the terminal event before death. However, florid manifestation of disseminated strongyloidiasis was only seen in the second cases which included E. coli septicemia upon admission, abdominal pain with watery diarrhea, culture-negative neutrophilic meningitis, a significant reduction of haematocrit without obvious evidence of blood loss or hemolysis, hypoproteinemia and hypokalemia. Progressive anemia without obvious cause in immunocompromised host should always arouse one's suspicion of Strongyloides hyperinfection and stool examination for S. stercoralis must be undertaken without delay. The presence of multiple cerebral abscesses' or meningitis\(^{17}\) in a patient with strongyloidiasis has been described. In our second reported case, we feel that our patient's meningitis may be due to S. stercoralis though active SLE process or bacterial infection can not be entirely ruled out.

In our cases, mebendazole and albendazole failed in eradicating disseminated strongyloidiasis in spite of appropriate dosages of both drugs were employed. Since they are newer broad-spectrum anthelmintics with least side effect and better tolerance compared to thiabendazole, the formers may be prescribed for therapy of strongyloidiasis in stead of the latter. Since mebendazole and albendazole are practically non-absorbable, they can be expected to be ineffective for therapy of systemic strongyloidiasis. In the first case, larvae of S. stercoralis were continuously found in sputum. In the second case, the larvae reappeared in sputum and stool twelve days later after cessation of albendazole administration.
Thus, mebendazole and albendazole can not replace thiabendazole in this regard. However, mebendazole and albendazole have been studied and claimed to be moderately effective in the treatment of intestinal strongyloidiasis in healthy host. The scope of the efficacy study of both anthelmintics never extends to immunocompromised patient with disseminated strongyloidiasis. Thus, one might be misled to use thiabendazole and albendazole in this condition which is potentially dangerous to the patients. Removal of strongyloidiasis from the indication of thiabendazole or albendazole therapy appeared in the advertisement leaflet is one way to prevent inappropriate use of both drugs in this condition.

The therapeutic effect of thiabendazole for strongyloidiasis is estimated to be at least 90% in healthy host. When host-defence mechanism to eradicate strongyloidiasis is no longer dependable as happened during corticosteroid therapy, the therapeutic success rate is strongly related to the susceptibility of the larvae to thiabendazole. Although the susceptibility of *Strongyloides* larvae to thiabendazole is not exactly known, it can be anticipated that minimal "parasitcidial" concentrations of the drug varies from strain to strain and in *vitro* susceptibility test for larvae is non-existent. Thus, the recommended dosage of thiabendazole should be at maximum to cover the broadest spectrum of *S. stercoralis*. Therapy should be prolonged and response may require several days. At present, 25 mg per kg orally twice a day for 5-10 days are suggested as optimal dose for treatment of disseminated strongyloidiasis. After initial and successful treatment, the patient must be followed up closely and stool examination must be performed at least once a week for one month to ensure that patients remain in the "parasite-free" stage. If corticosteroid is to be administered again in patient who ever developed disseminated strongyloidiasis, physician must be alert for this condition. Alternatively, thiabendazole may be given at the appropriate interval in patients who need prolonged corticosteroid therapy and reside in endemic area where close follow up is not feasible. However, thiabendazole administration can not be substituted for stool examination especially in area where microscope is available and close follow up is easily achieved. Thiabendazole should not be easily abandoned if patients are initially intolerated to the drug. Alternatively, mebendazole and albendazole might be initially used to reduce the "worm load" and hence the inflammatory process at the gastrointestinal mucosa. This may render patients better tolerate thiabendazole if subsequently administered at full dose.

In conclusion, disseminated strongyloidiasis is anticipated to be prevalent in immunocompromised hosts as well as malnourished patients who ever resided in rural areas. This overwhelming complication should be suspected in those patients who developed respiratory or abdominal symptoms without identified cause. Direct microscopic examination of the following specimens i.e., stool, sputum, bronchial lavage, gastric content, peritoneal fluid, is the rapid, accurate and simple method for diagnosis of hyperinfection with *S. stercoralis*. Mebendazole and albendazole are unreliable drugs to eradicate disseminated strongyloidiasis but can temporarily reduce intestinal "Worm-load" in the severely ill patients. Thiabendazole remains the only drug of choice for all forms of strongyloidiasis. However, when corticosteroid is re-instituted, one should always remember that recurrence of strongyloidiasis is not uncommon which is possibly due to unsuccessful previous therapy with anthelmintics or new acquisition of *S. stercoralis* larva in endemic area. Under these conditions, repeated courses of treatment with thiabendazole is required to prevent hyperinfection with *S. stercoralis*.

REFERENCES


