Fever, Petechiae, and Pulmonary Infiltrates in an Immunocompromised Peruvian Man

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The diagnostic considerations raised by immunocompromised patients with opportunistic infection continue to expand. When such patients harbor latent or persistent infection acquired in a tropical environment, the diagnostic challenge is even greater. The Infectious Disease Service at Yale–New Haven Hospital was asked to see a middle-aged man from Peru with known T-cell lymphoma who had recently completed a course of chemotherapy. He presented to the hospital with fever, petechial skin rash, pulmonary infiltrates, and neutropenia. Ultimately this case illustrated the necessity for careful evaluation of such patients, looking, in particular, for evidence of opportunistic parasitic infection.

CASE PRESENTATION

DR. CHARLES BERENSON (Infectious Disease Fellow): A 58-year-old Peruvian man was admitted to Yale–New Haven Hospital with new pulmonary infiltrates, fever, and a petechial rash, which occurred two weeks after completing a course of chemotherapy for lymphoma. He first presented to us in October 1984, with unusual skin lesions, diagnosed by skin biopsy as manifestations of polyarteritis nodosa. He was treated with prednisone and cyclophosphamide through December 1984. There was no previous history of active tuberculosis, but a chest radiograph taken at that time (Fig. 1A) showed questionable apical scarring. Multiple sputum examinations were negative for acid-fast organisms. Hematocrit was 42.8 percent; white blood count was 15.8/mm³, with 11 percent eosinophils, prompting evaluation of two stool specimens for ova and parasites. Both were negative. By February 1985, he had returned with massive lymphadenopathy, pancytopenia, and fever. Lymph node biopsies demonstrated a stage IV T-cell lymphoma. He completed a course of cyclophosphamide, Adriamycin, vincristine, and prednisone (CHOP) fourteen days prior to admission. Two days prior to admission he developed tachypnea and a cough productive of blood-streaked sputum. Abdominal discomfort gradually developed and was treated with antacids and cimetidine. On the day of admission he became lethargic and febrile. Emergency

CASE PRESENTATION

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Abbreviations: CHOP: cyclophosphamide, Adriamycin, vincristine, and prednisone   DIC: disseminated intravascular coagulation

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medical technicians administered intravenous fluids to correct a blood pressure of 50/30, and rapidly transported him to Yale–New Haven Hospital. The patient had worked as a field laborer in Peru and was most recently employed in a local hotel kitchen. He had no history of travel since emigrating from Peru in February 1984.

On admission he was arousable and appropriate, with a temperature of 102.4°F, a blood pressure of 90/60, a pulse of 140/minute, and a respiratory rate of 30/minute. He had pale conjunctivae, palpable cervical lymphadenopathy, and a supple neck. Bibasilar rales were heard, but cardiac examination was unremarkable. Diminished bowel sounds and mild, diffuse, epigastric tenderness were noted. A non-blanching petechial rash containing a few pustules was noted on his abdomen. Stool did not contain occult blood. The chest radiograph taken on admission showed bilateral pulmonary infiltrates (Fig. 1B).

DR. MARY JEAN AHERN (Associate Clinical Professor of Medicine): There are diffuse interstitial infiltrates, most prominent in the lower lobes. Although diffuse, they do not resemble miliary tuberculosis. Evidence of congestive heart failure is not present since neither cardiomegaly nor increased vascular markings have appeared since the previous radiograph.
DR. BERENSON: Laboratory values included a hemoglobin of 4.7 gm/dl, hematocrit of 14.2 percent, platelet count of 189,000/µl, and a white blood count of 1,100/µl, with 37 polymorphonuclear leukocytes, 15 bands, 36 lymphocytes, 10 monocytes, and 2 metamyelocytes. Chemistries included serum sodium concentration 129 meq/L, potassium 5.0 meq/L, chloride 94 meq/L, CO₂ 24.6 meq/L, blood urea nitrogen 25 mg/dl, and creatinine 1.1 mg/dl. Transaminase (SGOT) was 92 IU (normal, less than 40), but other liver function parameters were normal. Prothrombin time was 13.2 seconds (control, 11.5 seconds) and partial thromboplastin time was two minutes. Arterial blood gas values obtained with the patient breathing room air were pH 7.57, pCO₂ 23 torr, pO₂ 39 torr, which rose to 7.50, 27 torr, and 101 torr, respectively, while he received 100 percent oxygen by mask. He was intubated because of persistent respiratory distress.

Skin lesions were biopsied by the dermatology consultants. Their differential diagnosis included leukocytoclastic angiitis, septic vasculitis, and disseminated intra-vascular coagulation (DIC). Gram stain of skin pustule contents demonstrated neither bacterial organisms nor cells.

A PHYSICIAN: His rash could represent meningococcemia. Although one might explain his lethargy by anemia and/or anoxia, a lumbar puncture would be indicated.

DR. BERENSON: A lumbar puncture was performed and showed clear cerebrospinal fluid with no white blood cells, four red blood cells, and normal glucose and protein concentrations.

DR. THOMAS GRECO (Assistant Clinical Professor of Medicine): Was there any known exposure to ticks? Rocky Mountain spotted fever or another rickettsial disease within the spotted fever or typhus group could cause shock, a petechial rash, and pulmonary infiltrates.

DR. BERENSON: He had no known exposure to ticks or wooded areas.

DR. FRANK BIA (Associate Professor of Medicine): Epidemiologically, that would be very important information. In addition, endemic typhus from exposure to rat fleas has been seen in the United States in restaurant and food workers. Was there any evidence of disseminated intravascular coagulation?

DR. BERENSON: His platelet count remained normal. Measurement of fibrin degradation products and review of peripheral blood smear did not suggest that DIC was occurring.

DR. GRECO: His hematocrit dropped enough that one must be concerned about either a hemolytic event or a bleeding diathesis. His peripheral blood smear did not suggest hemolysis, however, and his stool showed no evidence of occult gastrointestinal bleeding. That brings up the possibility of retroperitoneal bleeding, which unfortunately would not explain either his dermatological or pulmonary processes.

DR. BERENSON: Abdominal ultrasound examination and computerized tomographic scans showed no evidence of retroperitoneal bleeding, although retroperitoneal lymphadenopathy was present. Following blood transfusions, his hematocrit remained stable.

DR. AHERN: I would like to direct this discussion toward consideration of his pulmonary infiltrates. While his neutrophil count was slightly above 500/µl, we must still consider those opportunistic infections which affect neutropenic patients.
DR. ROBERT BALTIMORE (Associate Professor of Pediatrics and Epidemiology): While bacterial pneumonias commonly infect neutropenic patients, the diffuse nature of these infiltrates makes a bacterial pneumonia less likely. This pattern is more suggestive of \textit{Pneumocystis carinii} pneumonia [1]. In addition, lymphoma patients can develop diffuse infiltrates as a result of cytomegalovirus or \textit{Herpes zoster} infections.

DR. GRECO: Legionella pneumonia has also been described in this setting and deserves consideration. \textit{Mycoplasma pneumoniae} is not a common cause of pneumonia in compromised hosts, but the diffuse pattern makes it worth considering. Both possibilities should be covered by including erythromycin in any empiric antibiotic coverage used while awaiting results of diagnostic tests.

DR. JOHN MELLORS (Assistant Professor of Medicine): Fungal infections have not been commented upon. Most commonly Candida, and Aspergillus, but also Mucor species, are recognized causes of fungal pneumonia in neutropenic patients [2]. Usually, Aspergillus pneumonia presents as wedge-shaped infiltrates; however, diffuse infiltrates are possible. Diagnosis of these entities might require bronchoscopy or an open-lung biopsy, but I would like to know the results of a sputum Gram stain first.

DR. BERENSON: Endotracheal suctioning yielded modest amounts of blood-tinged pulmonary secretions. Occasional inflammatory cells were seen scattered among some larger unidentifiable Gram-variable objects, thought at first to represent mucous plugs. Acid-fast and potassium hydroxide preparations were not helpful. The patient was started empirically on antibiotics which included mezlocillin, an aminoglycoside, erythromycin, and trimethoprim-sulfamethoxazole to cover the range of clinical possibilities raised thus far in our discussion. Sputum was sent for Legionella direct fluorescent antibody staining, viral cultures, bacterial cultures, and both acid-fast and silver stains; however, a wet mount of sputum revealed the material shown in Fig. 2. These objects were best seen under low power. They were clearly mobile and readily identified as filariform larvae of the nematode, \textit{Strongyloides stercoralis}.

DR. BIA: At this point, the previous sputum Gram stain was re-evaluated. Under low power, the large Gram-variable objects seen in the sample were recognized as filariform larvae (Fig. 3) albeit somewhat obscured by the stain. It is a mistake to overlook performing low-power evaluation of Gram-stained specimens. Had a more
careful low-power evaluation of this specimen been done, the organisms might have been identified on Gram stain. The utility of Gram stains for diagnosis of pulmonary strongyloidiasis has recently been reported [3]. Still, their appearance and motility makes their identification on a wet preparation of sputum somewhat easier.

The absence of peripheral eosinophilia should not preclude this diagnosis. It is taught that disseminated strongyloidiasis, and other parasitic infections, commonly present with eosinophilia. In fact, even patients with overwhelming disseminated strongyloidiasis who are not neutropenic often demonstrate eosinopenia [4].

DR. BERENSON: An interesting laboratory finding was noted by the lab technicians responsible for working on the patient’s sputum culture. The growth pattern of *Staphylococcus aureus* in the culture seemed to follow tiny serpiginous tracks caused by movement of the larvae through the agar, a laboratory phenomenon recently reported by others [5,6].

Histological examination of skin biopsies was largely unremarkable; however, in a few sections, larvae were visible near dermal blood vessels (Fig. 4). The patient was
begun on thiabendazole, 3 grams/day, via a nasogastric tube. Antibacterial coverage with mezlocillin and an aminoglycoside agent was continued.

DR. MELLORS: Although a clear-cut bacterial infection was not demonstrated, it would be appropriate to maintain coverage for enteric organisms under these circumstances. In disseminated strongyloidiasis, enteric flora may reach the circulation by larval disruption of the bowel wall, or possibly by being “piggy-backed” across the gut or within the migrating larvae. Hematogenous spread of bacteria can result in systemic bacterial infection such as pneumonia or Gram-negative bacillary meningitis [7].

DR. BERENSON: In fact, on the ninth day of hospitalization, he became more lethargic, and meningismus was present. A repeat lumbar puncture revealed cloudy cerebrospinal fluid with 480 red blood cells/μl and 220 white blood cells/μl (99 percent polymorphonuclear leukocytes). Protein and glucose concentrations remained normal; Gram stain, cryptococcal antigen determination, and India ink preparation were negative. Cultures yielded no growth. As Dr. Mellors has suggested, a partially treated meningitis of enteric origin was suspected, although cases of central nervous system strongyloidiasis have also been reported [8]. After several days of therapy with parenteral cefotaxime, 12 grams/day, cerebrospinal fluid pleocytosis resolved.

Partial ileus and large gastric residual volumes made administration of thiabendazole difficult, interrupting therapy. As the ileus improved, stool specimens showed enormous numbers of filariform larvae (Fig. 5). Therapy with thiabendazole was continued over 25 days, until stool and sputum specimens were free of larvae.

During therapy, bilirubin and transaminase levels rose. Possible causes included thiabendazole toxicity, recurrent lymphoma, or hepatic larval infiltration. Rapidly worsening lymphadenopathy represented failure to induce remission of the underlying lymphoma. Further attempts at chemotherapy were considered unwise. Despite improvement of his parasitic infection, he succumbed to his malignancy after six weeks of hospitalization. A post-mortem examination was not performed.

DISCUSSION

DR. BERENSON: We can summarize the life cycle of this interesting nematode in the following manner. Free-living Strongyloides stercoralis adults live in the soil where their ova hatch into rhabditiform larvae. These larvae undergo several moult
become invasive filariform larvae, which can penetrate the skin of humans to cause local cutaneous lesions, called *larvae currens*. Larvae then enter the lymphatic system and travel through veins to the right heart and lungs, where they penetrate into alveolar spaces. They are coughed up and swallowed, arriving at the duodenum and proximal jejunum. Filariform larvae than burrow into gut mucosa, where they develop into adults. Each female lays about 40 eggs per day. Ova then hatch into rhabditiform larvae, which are expelled with feces [4].

**DR. BIA:** In contrast to other nematode infections such as hookworm, one almost never finds *S. stercoralis* ova in the stool of patients with strongyloidiasis. One finds larvae instead. Finding filariform larvae in feces is one means of distinguishing between *Strongyloides stercoralis* infections and those caused by other nematodes [9]. If, however, a stool sample contains hookworm ova and sits for a period of time before being examined, the ova can hatch. The larvae are difficult to distinguish from Strongyloides larvae, which have a somewhat shorter buccal cavity than do hookworm larvae (Fig. 5).

**DR. BERENSON:** If filariform larvae actually develop within the gut, they may reinvade it or penetrate the perianal skin to reinfect the same host in a process called autoinfection. Occasionally, a large number of larvae become invasive and produce a heavy nematode burden for the infected host. This is referred to as the “hyperinfection syndrome.” It may include gastrointestinal problems such as nausea, vomiting, and diarrhea, and respiratory complaints such as wheezing and hemoptysis [7].

Scowden et al. distinguish this from “disseminated strongyloidiasis,” in which autoinfection is profound and large numbers of filariform larvae disseminate to many organs including liver, central nervous system, heart, lymph nodes, and kidneys. Both brain and meningeal involvement have been documented. Hepatic invasion, while unusual, is suggested by elevations of bilirubin and/or alkaline phosphatase [4].

Both of these syndromes overlap considerably, each predisposing to bacteremia caused by enteric organisms. The lungs and meninges are sites of metastatic bacterial infections. Damage to intestinal lymphatics causes bowel edema, malabsorption, and ileus, making therapy of this illness with the currently available oral medication (thiabendazole) somewhat difficult.

About half of all patients with intestinal strongyloidiasis have no symptoms referable to the infection. Most of the remainder have only vague or mild gastrointestinal complaints. Patients with intact cell-mediated immunity do not progress to develop either dissemination or hyperinfection. Many conditions predispose to disseminated strongyloidiasis, including lymphomas, treated leukemias, renal transplantation, systemic lupus erythematosus, and nephrotic syndrome. Depressed cell-mediated immunity may also result from alcoholism, chronic renal failure, malnutrition, and carcinomas, in addition to chemotherapeutic agents which depress cell-mediated immunity [4,10].

During autoinfection, transformation from rhabditiform to filariform larvae occurs in the gut. Corticosteroids may encourage penetration of the gut wall by reducing local inflammation [4]. In addition, autoinfection is enhanced by azathioprine and cyclophosphamide. While it has been assumed that cyclosporine A might produce a similar predisposition, experimental evidence in rats suggests that it might actually protect against strongyloidiasis [11].

Clinical observations suggest an important defensive role for eosinophils and antibodies against *S. stercoralis* larvae. Patients with severe intestinal infections have
been noted to have lower serum IgG levels and lower eosinophil counts than their asymptomatic counterparts [12]. In another study, immunosuppressed patients with strongyloidiasis, including some with disseminated disease, all had elevated IgG levels. Hyperinfected patients had lower IgE levels, however, as well as lower eosinophil counts than did non-hyperinfected patients. While not conclusive, a possible protective role for IgE and eosinophils is suggested [13].

Current therapy for uncomplicated intestinal strongyloidiasis is a two-day course of thiabendazole (25 mg/kg twice a day for two days; maximum, 3 g/day), which is given orally. It is the only recommended medication for disseminated disease. Cambendazole, a thiabendazole derivative, may be superior for intestinal strongyloidiasis [14], but it has not been evaluated for efficacy against disseminated disease and is not readily available in the U.S. The duration of therapy for disseminated disease is not at all clear, but a minimum of five days' therapy is suggested. Repeated stool examinations are probably the best parameter of successful therapy. One should remove, if possible, those factors responsible for compromising cell-mediated immunity, such as immunosuppressive drugs.

The complicated course followed by our patient clearly illustrates several of the issues discussed. He manifested both the hyperinfection state and disseminated strongyloidiasis and probably suffered from enteric bacteremia with bacterial seeding of the meninges. The latter seems more likely than meningeal infection by nematodes since cerebrospinal fluid pleocytosis rapidly resolved with antibacterial therapy. His elevated serum bilirubin and transaminase, with normal alkaline phosphatase levels, is uncharacteristic of hepatic infection by nematodes.

Exposure to S. stercoralis larvae need not have been in the recent past. Laboratory evaluations performed in veterans of World War II have demonstrated persistent strongyloidiasis acquired during their 1940s military service in southeast Asia [15,16]. This case dictates a need to search exhaustively for intestinal evidence of strongyloidiasis in asymptomatic patients from endemic areas, particularly if eosinophilia exists, prior to institution of immunosuppressive therapy.

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