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A 65-year-old man with progressive shortness of breath

A 65-YEAR-OLD RETIRED coal miner presented to a tertiary care center complaining of progressive shortness of breath over the past 4 months. He reported audible wheezing and intermittent cough productive of scant, thin, yellow sputum but denied fever, chills, or hemoptysis. He had been diagnosed with "black lung" and emphysema in 1992 and treated with bronchodilators, with which he had not been compliant. He also had hypertension and type 2 diabetes mellitus. He said he was up-to-date in his immunizations for influenza and pneumonia and had never had thromboembolic disease.

TABLE 1

The patient's laboratory data

TEST	VALUE	NORMAL RANGE
Hemoglobin	10.8 g/dL	13.5–17.5
Hematocrit	33%	40–52
White blood cell count	8.24×10^9/L	4–11
Neutrophils	90.2%	40–70
Lymphocytes	5%	15–45
Monocytes	4.5%	2–10
Basophils	0.1%	0–1
Eosinophils	0.2%	0–2
Platelets	170×10^9/L	150–400
Sodium	131 mmol/L	135–146
Blood urea nitrogen	93 mg/dL	10–25
Creatinine	3.9 mg/dL	0.7–1.4
Aspartate aminotransferase	28 U/L	7–40
Alanine aminotransferase	64 U/L	0–30
Albumin	4.5 g/dL	3.5–5.0
International normalized ratio	0.98	0.9–1.1

Four months earlier, the patient had begun to experience gross hematuria. He was diagnosed with rapidly progressive glomerulonephritis (RPGN) on the basis of a renal biopsy at another hospital and was treated with cyclophosphamide and high-dose prednisone (60 mg/day). In the months that followed he was hospitalized twice for shortness of breath and treated for community-acquired pneumonia. After his last admission 3 weeks earlier, he was started on oxygen therapy (2 L/minute continuously per nasal cannula) and transferred to a pulmonary rehabilitation facility, from which he was discharged 2 days before his current admission.

The patient quit smoking 4 years ago after a 20 pack-year history. He worked as a coal miner for 14 years and was disabled by his lung disease. His current home was in northern Ohio, but he grew up in rural Appalachia. He said he had not traveled outside the United States, had not been exposed to tuberculosis, and had never been in the military. He had an extensive family history of lung disease: his father had "black lung" and emphysema, and four siblings had died of lung cancer.

Physical examination

The patient was morbidly obese. He was tachypneic (22 breaths per minute) but not cyanotic. His blood pressure was 134/65 mm Hg and his pulse was 100 beats per minute. Cardiac examination revealed an accentuated S_2 and an S_4 gallop. Auscultation of his lungs was notable for decreased air entry and diffuse expiratory wheezes. He had a distended, soft abdomen, petechiae on his lower extremities, clubbing of his fingers, and pedal edema (1+) without calf tenderness. Homans sign (pain on passive dorsiflexion of the foot; a sign of throm-

bosis of the deep calf veins) was not present.

The patient's initial laboratory data are shown in TABLE 1. His chest radiograph is shown in FIGURE 1.

WHAT IS THE DIAGNOSIS?

1 Which is the *least* likely diagnosis?

- ❑ Acute exacerbation of chronic obstructive pulmonary disease (COPD)
- ❑ Pulmonary-renal syndrome
- ❑ Pulmonary thromboembolism
- ❑ Opportunistic lung infection
- ❑ Congestive heart failure
- ❑ Coal workers' pneumoconiosis

Congestive heart failure is the least likely, based on the absence of signs and symptoms of either left or right heart failure.

COPD is the fourth leading cause of death in the United States. Exacerbations can be ascribed to many factors, including smoking, air pollution, allergens, occupational exposure, and infection.

If a patient with COPD continues to smoke, his or her forced expiratory volume in 1 second (FEV_1) declines more rapidly: 90 to 150 mL/year compared with the yearly physiologic decline of 30 mL/year. Our patient quit smoking more than 4 years earlier, which may have slowed the rate of decline to normal, though beginning at a lower baseline level of function.

If presumed exacerbations of COPD do not respond adequately to bronchodilator and anti-inflammatory therapy, one should promptly seek other diagnoses, particularly because such patients have poor pulmonary reserve.

Pulmonary thromboembolism. Chronic thromboembolic pulmonary hypertension occurs in a minority of patients following acute pulmonary embolism. It is due to repeated episodes of emboli (occult or clinically evident) or to failure of emboli to resolve. A patient may initially have an asymptomatic period of months to years followed by worsening exertional dyspnea, hypoxemia, and right ventricular failure. Ventilation-perfusion mismatch suggests chronic thromboembolic pulmonary hypertension, but the definitive diagnosis is made by pulmonary angiography. The disease is underdiagnosed and should be considered in any patient with dyspnea in whom no compelling cause can be established.

The patient's chest radiograph

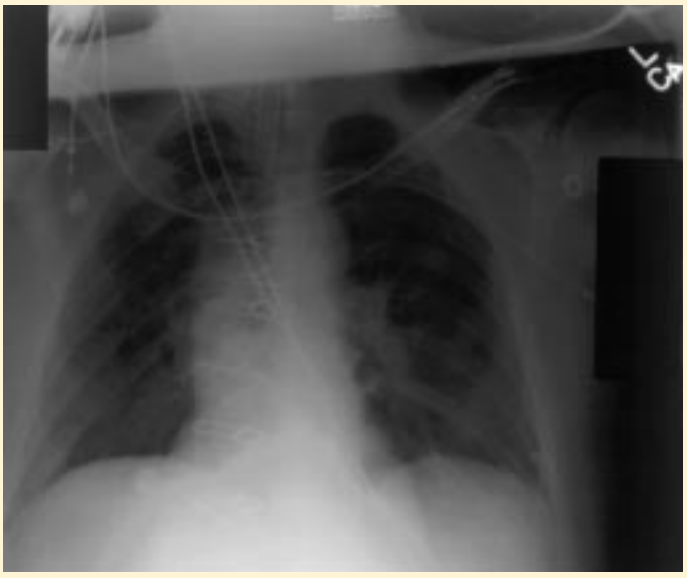

FIGURE 1. The patient's chest radiograph shows left hilar and subcarinal calcifications suggestive of old granulomatous disease but no evidence of parenchymal lung disease.

Lung function falls 3 to 4 times faster in COPD patients who smoke

Coal workers' pneumoconiosis (CWP), commonly known as "black lung," is associated with coal dust inhalation. Simple CWP, previously diagnosed in our patient, is recognized by its radiographic features (multiple, small, rounded opacities on the chest radiograph) along with a typical exposure history (more than 10 years in coal mines). In contrast, complicated CWP is associated with significant respiratory impairment and more pronounced chest radiographic findings.

Progression from simple to complicated CWP requires continued industrial exposure. Our patient's initial chest radiograph is not consistent with the diagnosis of simple CWP. Even if present, CWP does not explain his rapidly progressive respiratory decompensation nor the evolution of his radiographic findings.

Pulmonary-renal syndrome is characterized by renal failure and lung hemor-

The patient's chest CT scan

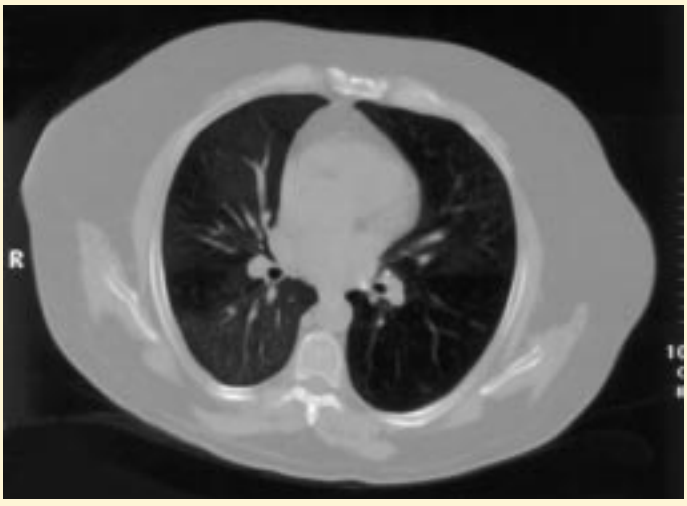

FIGURE 2. Ground-glass appearance suggestive of alveolitis with relative sparing of the left lower lobe.

The highest rates of *Strongyloides* infection are in the South

rhage. It encompasses immune-complex vasculitides (systemic lupus erythematosus), pauci-immune vasculitides (Wegener granulomatosis, microscopic polyarteritis nodosa), antiglomerular basement membrane disease (Goodpasture syndrome), and other entities.

Opportunistic infection will be considered later in this discussion.

Other factors. Anemia and deconditioning might have added to our patient's dyspnea. He had no overt signs of hypothyroidism nor evidence of myopathy related to glucocorticoid use. His morbid obesity was a contributing factor, causing an increased mechanical load, reduction of his chest wall compliance, and decreased respiratory drive (obesity-hypoventilation syndrome).

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

2 Which of the following is true about rapidly progressive glomerulonephritis (RPGN)?

- ❑ RPGN is a clinicopathologic entity
- ❑ Clinically, RPGN is characterized by subacute renal failure, active urine sediment, and variable degrees of hypertension, edema, oliguria, and proteinuria
- ❑ It includes antiglomerular basement membrane disease, pauci-immune glomerulonephritis, and immune complex glomerulonephritis, but more than 50% of cases are idiopathic
- ❑ The classic pathologic correlate of RPGN is crescent formation involving most glomeruli
- ❑ All of the above

All of the above are true of RPGN.[1]

CASE CONTINUED: FEVER, WORSENING STATUS

Review of the patient's kidney biopsy revealed infiltration by monocytes, prominent interstitial fibrosis, and widespread tubular injury but no crescents consistent with the histologic diagnosis of chronic interstitial nephritis. Consequently, the cyclophosphamide was stopped and the prednisone was tapered.

A duplex ultrasound scan of the lower extremities showed no evidence of deep venous thrombosis, and a ventilation-perfusion scan failed to demonstrate a mismatch.

A transthoracic echocardiogram revealed normal systolic function, hypertrophy with early-stage diastolic dysfunction, and mild right ventricular dysfunction.

Spirometry could not be performed because of the patient's condition. Spriometric tests in December 1999 showed a forced vital capacity of (FVC) of 1.63 L (45% of predicted) and an FEV_1 of 0.67 L (26% of predicted); both improved by more than 20% with bronchodilators.

The patient developed a low-grade fever, and his respiratory status began to deteriorate: his dyspnea worsened and he needed more oxygen. The possibility of opportunistic lung infection was considered, and empiric broad-spectrum antibiotic therapy was started, including coverage for fungal organisms. A computed tomographic (CT) scan of the chest demonstrated a ground-glass appearance suggestive of alveolitis (FIGURE 2).

Bronchoscopy was performed, and transbronchial biopsy showed interstitial pneumonitis and nematode larvae suggestive of *Strongyloides stercoralis* infection (FIGURE 3).

HOW IS *STRONGYLOIDES* TRANSMITTED?

3 What is the most common mode of transmission of *Strongyloides stercoralis*?

- ❑ Inhalation of infective eggs
- ❑ Ingestion of infective larvae
- ❑ Skin contact with soil contaminated with infective larvae
- ❑ Ingestion of pork that contains infective cysts
- ❑ Venereal transmission

The usual route of infection with *S stercoralis* is through skin contact with soil contaminated with infective (filariform) larvae by human feces. Transmission depends on poor sanitation and the suitability of the soil and climate conditions. The fecal-oral route of infection is very uncommon in healthy, noninstitutionalized adults. Venereal transmission in the homosexual community has been described.[2]

S stercoralis, though less common than other intestinal parasites, is endemic in tropical and subtropical regions. The highest prevalence rates in the United States occur in the South (0.4%–4%) and Appalachia (where our patient spent his childhood), in immigrants from endemic areas, and in those with occupational exposure (including military veterans) in endemic areas.[3]

Life cycle of *S stercoralis*

The life cycle of *S stercoralis* is not completely understood. Filariform larvae living in soil penetrate human skin and migrate hematogenously to the lungs, where they break into the alveolar spaces, ascend to the glottis, are swallowed, and enter their final habitat in the upper small intestine. The larvae mature into adult worms that burrow into the duodenal mucosa, where they may live for up to 5 years. The adult worms produce eggs that either are excreted with the feces or transform themselves into noninfective (rhabditiform) larvae within the gastrointestinal tract. These noninfective forms can transform into filariform infective larvae during their passage through the gastrointestinal tract, resulting in cycles of autoinfection (FIGURE 4).

Strongyloides stercoralis on lung biopsy

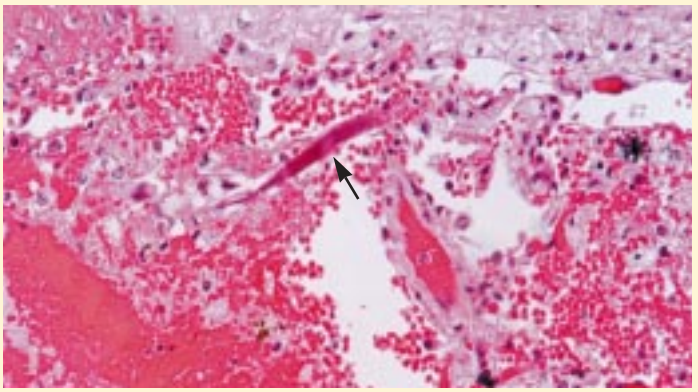

FIGURE 3. Filariform larvae of *Strongyloides stercoralis* (arrow) in lung (× 20).

Low levels of autoinfection help sustain the infection in immunocompetent humans. The autoinfection cycle accelerates in the presence of immunosuppression and may result in a lethal hyperinfection.

Larval forms may persist in the body up to 40 or 50 years.[1,4]

CLINICAL FEATURES OF STRONGYLOIDIASIS

4 Which of the following clinical features is pathognomonic of strongyloidiasis?

- ❑ Nausea and epigastric discomfort
- ❑ Eosinophilia with pulmonary symptoms of cough, dyspnea, and wheezing
- ❑ Larva currens
- ❑ Urticaria
- ❑ Duodenitis

All of the above are features of *S stercoralis* infections, but larva currens ("running larva") is pathognomonic. This is a serpiginous skin eruption consisting of pruritic, raised, erythematous lesions that advance as rapidly as 10 cm/hour along the course of larval migration, and can be easily seen by observers.

Approximately one third to one half of patients with strongyloidiasis have no symptoms. Clinical features range from asymptomatic latent infestation to the hyperinfection syndrome (TABLE 2).[3,5]

Strongyloides larvae may persist in the body for 40 to 50 years

Life cycle of *Strongyloides stercoralis*

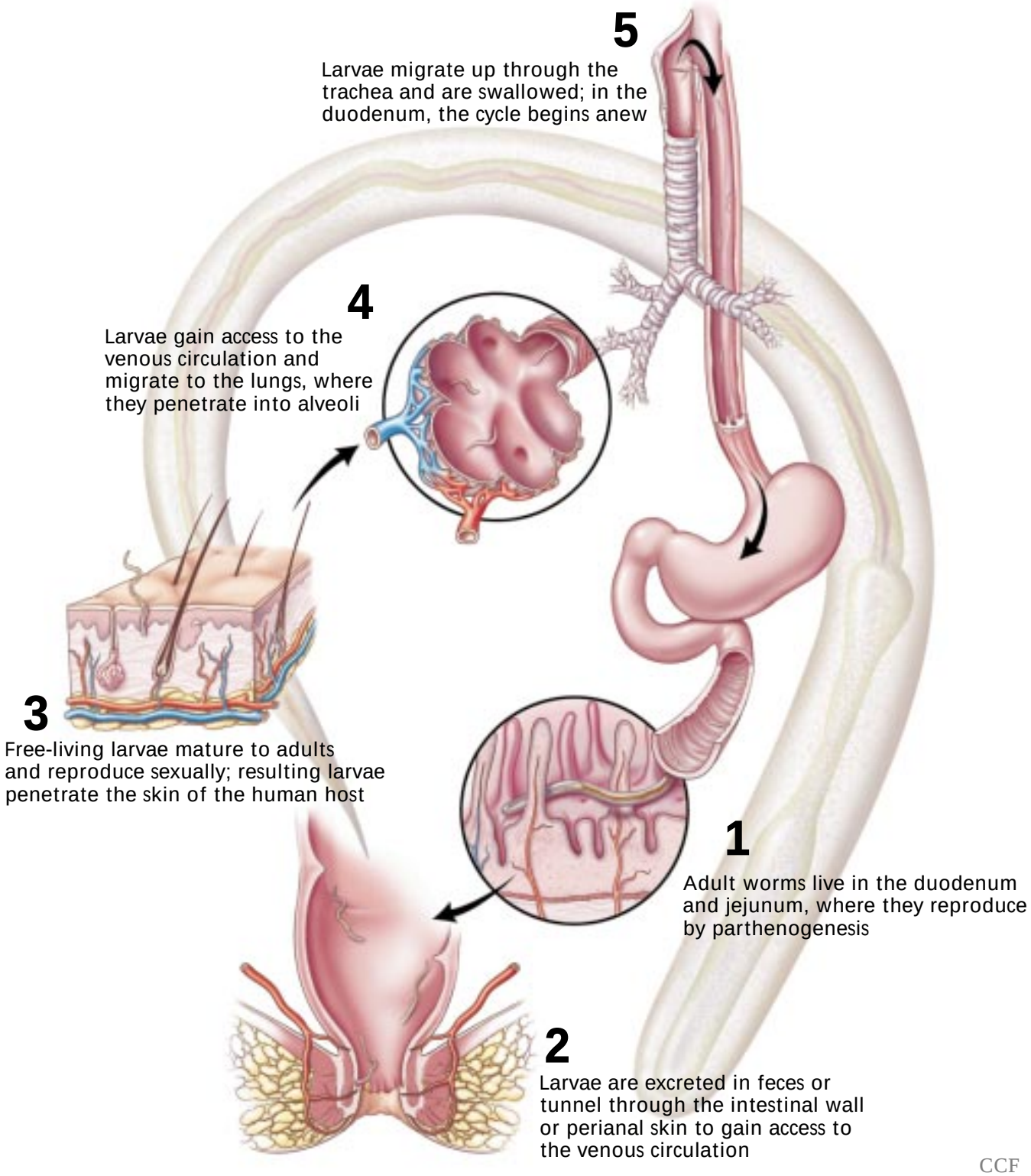

FIGURE 4

TABLE 2

Clinical features of *Strongyloides stercoralis* infection

Abdominal involvement

Adult parasites burrow into the duodenal mucosa causing burning, and sometimes colicky abdominal pain, nausea and vomiting, diarrhea, and passage of mucus or a chronic enterocolitis with protein losing enteropathy

Skin involvement

Usually recurrent urticaria involving the buttocks and wrists (most common)

When larvae penetrate the skin (usually the feet), cutaneous reactions may include inflammation, urticarial rash, and severe pruritus

Larva currens is pathognomonic

Lung involvement

Transpulmonary migration of larvae can produce cough, throat irritation, wheezing, hemoptysis, and, rarely, a Loeffler-like syndrome with eosinophilia

Peripheral blood

Eosinophilia is common, though levels may fluctuate, and is often absent in disseminated strongyloidiasis (especially in patients treated with corticosteroids)

Disseminated infection (the hyperinfection syndrome)

Immunocompromise can lead to disseminated infection

The ongoing autoinfection cycle of strongyloidiasis is normally constrained by the host immune system. However, whenever cellular-mediated immunity is compromised (due to malignancy, malnutrition, alcoholism, or immunosuppressive therapy), disseminated infection can occur. In particular, it is speculated that steroids may also induce differentiation of the larvae into their infective forms.

The massive dissemination of filariform larvae to various organs may result in symptomatic failure of the organs involved, including the central nervous system, peritoneum, liver, and kidney. Moreover, bacteremia may develop due to entry of enteric flora through disrupted mucosal barriers. Consequently, gram-negative sepsis, pneumonia, or meningitis may complicate or dominate the clinical course.[2,6]

DIAGNOSIS OF STRONGYLOIDIASIS

5 Which is the *least* sensitive diagnostic test for strongyloidiasis?

- ❑ Stool examination
- ❑ Sampling intestinal fluid
- ❑ Enzyme-linked immunosorbent assay (ELISA)
- ❑ String test (Enterotest)

Stool examination is the least sensitive test. In uncomplicated strongyloidiasis, the finding of rhabditiform larvae in feces is diagnostic, but approximately 25% to 60% of infected patients have negative stool examinations. Serial examinations may be needed to improve the sensitivity of stool diagnosis. The use of the (Enterotest) string method and duodenojejunal sampling by aspiration of fluid or biopsy may be alternatives.

A highly sensitive and specific ELISA serologic test has proven valuable in detecting strongyloidiasis.

Whenever disseminated infection is suspected, stool and other specimens from suspected sites of infection (sputum, bronchoalveolar lavage, and peritoneal fluid) should be examined for filariform larvae.[2,5]

Gram-negative sepsis, pneumonia, or meningitis may complicate strongyloidiasis

TREATMENT OF STRONGYLOIDIASIS

6 Which one of the following statements about the treatment of strongyloidiasis is true?

- ❑ Thiabendazole is the treatment of choice
- ❑ Treatment should be focused on symptomatic patients
- ❑ Thiabendazole is 100% effective in eradicating infection

***Strongyloides stercoralis* in duodenal tissue**

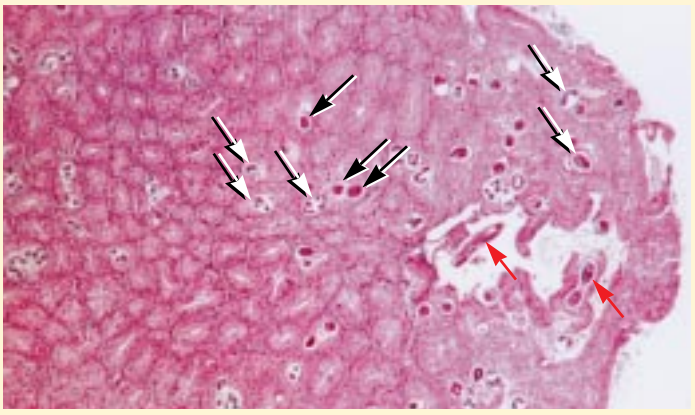

FIGURE 5. Eggs (black arrows), eggs with developing larvae (white arrows), and adult worms (red arrows) of *Strongyloides stercoralis* in duodenal tissue obtained at autopsy (× 4).

- ❑ There is no need for posttreatment clinical and test monitoring

Mortality in *Strongyloides* hyperinfection syndrome is as high as 90%

Thiabendazole is generally considered the drug of choice for strongyloidiasis, but treatment failure is well described. There is increasing interest in the use of ivermectin and, to a lesser extent, albendazole.[7,8] Even patients without symptoms should undergo treatment because of the risk of hyperinfection. The duration of drug treatment for intestinal disease is only 2 days, but disseminated infection may require days to weeks of treatment until the parasite is eradicated. Stool examinations and monitoring of clinical symptoms should be continued following treatment.[2,9]

CASE CONTINUED: IN SPITE OF THERAPY, THE PATIENT DIED

Our patient was started on intravenous thiabendazole. Prednisone, which had been tapered, was subsequently stopped to reduce suppression of cell-mediated immunity and, possibly, to decrease autoinfection. In spite of therapy, his clinical status deteriorated and he subsequently died. Postmortem examination showed disseminated strongyloidiasis with panlobar pulmonary infestation and patchy large-bowel and small-bowel strongyloidiasis (FIGURE 5).

Screening is suggested for patients at risk before undergoing immunosuppression

Among the earliest cases of fatal strongyloidiasis described are five cases from Brazil in 1966.[10] All of these cases occurred in the presence of high-dose glucocorticoid therapy. Fatality rates from hyperinfection syndrome as high as 80% to 90% have been reported. In view of the mortality risk, screening has been suggested for patients at increased risk for strongyloidiasis before they receive immunosuppressive therapy. These include patients who have at any time resided in endemic areas and patients with unexplained eosinophilia.

ELISA has proven to be both highly sensitive and specific in detecting strongyloidiasis.

Though an uncommon infection, strongyloidiasis should be considered in immunocompromised patients with unexplained worsening of respiratory status.

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