The Missing Piece

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In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows.

A 21-year-old man presented to the emergency department after a 2-day history of increasing pain in the right lower quadrant. The pain was dull and nonradiating, was not exacerbated by eating, and was unrelated to bowel movements. The patient's appetite was normal, and he had not had fever, chills, night sweats, weight loss, headache, nausea, diarrhea, or constipation. He had had exertional dyspnea and a cough productive of scanty yellow sputum for a month.

Lower abdominal pain and respiratory symptoms may be the consequence of a single clinical problem, or they may represent two separate processes. In an attempt to find a unifying diagnosis, it is important to consider disorders that typically are first manifested by respiratory symptoms but could involve coexisting abdominal pain, as well as disorders in which abdominal pain is typically the presenting symptom but that could have respiratory manifestations. The first category includes infections such as lower-lobe pneumonia with radiation of pain to the abdomen and tuberculosis with abdominal involvement, such as mesenteric lymphadenitis. Patients with disorders such as inflammatory bowel disease typically present with abdominal pain, but they may also have airway or pulmonary parenchymal disease. Other diagnostic considerations include an intraabdominal neoplasm with pulmonary metastasis, a primary abdominal process complicated by pulmonary emboli, and vasculitis.

The patient had no surgical history, and his medical history was unremarkable. He did not take any medications or herbal supplements. He had previously been employed as a sushi chef, but he had not worked for 3 months. He had not ingested raw shellfish but had prepared raw crayfish and crab for restaurant patrons. He was born and raised in the United States, but 4 years before presentation, he had spent 3 months visiting relatives in rural areas of South Korea.

Sushi chefs are at risk for parasitic infections from raw fish, such as Clonorchis sinensis, which characteristically causes disease in the biliary tract but not in the pulmonary system, and anisakis, which invades the submucosa of the gastrointestinal tract and causes acute abdominal pain, nausea, vomiting, and occasionally, urticaria. Travel to Korea and other parts of East Asia can be associated with various infections that might explain the patient’s presenting symptoms, including malaria, paragonimiasis, amebiasis, and tuberculosis.

On physical examination, the patient appeared well; he was afebrile, with normal vital signs. There were decreased breath sounds at both lung bases, with dullness to percussion. He had mild tenderness in the right lower quadrant that was traced to a...
firm, slightly mobile subcutaneous nodule, 2 by 3 cm, with no warmth or fluctuance. The results of a rectal examination were normal, with no fecal occult blood.

Decreased basilar breath sounds and dullness to percussion suggest either bilateral pleural effusions or elevated hemidiaphragms. The abdominal examination shows that the pain in the right lower quadrant is not intraabdominal, but rather caused by a more superficial, subcutaneous nodule. Such a nodule often represents a benign proliferation of subcutaneous tissue, such as a lipoma or fibroma, although these proliferations typically are not painful. Alternatively, the nodule could reflect infiltration with either malignant cells (metastatic tumor) or inflammatory cells (a phlegmon or abscess caused by an infectious agent) or a granulomatous inflammation resulting from tuberculosis or sarcoidosis. An uncommon mechanism for a tender subcutaneous nodule is panniculitis, an inflammation of the subcutaneous adipose tissue, which occasionally complicates cases of alpha-1-antitrypsin deficiency. Erythema nodosum causes painful nodules, but a single nodule on the abdominal wall would be unusual in patients with this condition. Finally, infection with gnathostoma causes tender, migratory subcutaneous nodules and is associated with the ingestion of raw fish.

Laboratory analysis revealed a white-cell count of 20,000 per cubic millimeter, with 56% eosinophils (normal range, 0 to 6). The hematocrit was 45%, and the platelet count was 459,000 per cubic millimeter. Levels of serum electrolytes, tests of hepatic and renal function, urinalysis, and findings on electrocardiography were all normal. A chest radiograph demonstrated pleural effusions in both lungs, with a peripheral opacity in the left upper lobe (Fig. 1).

The patient has a striking peripheral-blood eosinophilia, accompanied by a chest radiograph showing moderate-sized, bilateral pleural effusions. Although the broad differential diagnosis of peripheral eosinophilia is commonly categorized with the catchphrase, “worms, wheezes, and weird diseases,” bilateral pleural effusions are not typically associated with any of these possibilities. An interesting possibility is infection with Paragonimus westermanni, which is associated with a marked peripheral eosinophilia and can be accompanied by bilateral pleural effusions that are related to the migration of the worm through the diaphragm and into the pleural space.

Acute fascioliasis caused by either Fasciola hepatica or F. gigantica should also be considered, although it is rare in the United States. Infection typically involves the bile ducts; however, larvae can also migrate to the skin and lungs.

I am puzzled about the relationship of the sub-
cutaneous nodule to the peripheral eosinophilia and the bilateral pleural effusions. If intraabdominal disease is the cause of pain in the right lower quadrant (even though the tenderness of the subcutaneous nodule apparently reproduced the pain), the abdominal process could be secondarily complicated by ascites and bilateral pleural effusions. At this point, I would perform a diagnostic thoracentesis.

Thoracentesis revealed straw-colored fluid with a pH of 7.41, a white-cell count of 3900 per cubic millimeter, and a red-cell count of 630 per cubic millimeter. The differential count included 38% eosinophils, 28% mononuclear cells, and 12% lymphocytes. The lactate dehydrogenase (LDH) level was elevated (4780 U per liter), and the glucose level was 3 mg per deciliter (0.2 mmol per liter).

Analysis of the pleural fluid reveals an exudative effusion (defined by an LDH level that is more than two thirds of the normal serum value) with a prominent eosinophilia and an extremely low glucose level. Eosinophilic pleural effusions, defined by an eosinophil count of 10% or higher, often occur when there is air or blood in the pleural space, but neither seems to be present in this case. Other miscellaneous causes of pleural fluid eosinophilia include drug reactions, benign asbestos-related effusions, collagen vascular diseases, pulmonary embolism, and parasitic infections (paragonimiasis, echinococcosis, filariasis, and toxocariasis). Sometimes no cause is found, and the effusion is considered idiopathic. In this patient, another possibility is that the eosinophilia in the pleural fluid may be mirroring the striking number of eosinophils in the peripheral blood, without the diagnostic implications usually attributed to a selective accumulation of eosinophils within pleural fluid.

Extremely low glucose levels in the pleural fluid (less than 10 mg per deciliter [0.6 mmol per liter]) are typically associated with either empyema or rheumatoid pleural effusions. However, the white-cell differential count in the pleural fluid rules out a diagnosis of empyema, and there is no clinical evidence to suggest the presence of a rheumatoid effusion.

Although a parasitic infection affecting the pleural space, specifically paragonimiasis, is a rare entity, it is one diagnosis that might account for both the clinical picture and the pleural fluid findings. Pleural effusions secondary to infection with paragonimus are typically eosinophilic and have a strikingly low glucose level. In retrospect, perhaps even the subcutaneous nodule in the abdominal wall can be explained by this diagnosis, since such nodules can result from subcutaneous immature flukes.

The serum IgE level was elevated at 742 U per milliliter (normal value, less than 165). Blood cultures were negative. Computed tomography (CT) of the chest, abdomen, and pelvis revealed large, bilateral pleural effusions; a nodular consolidation in the left upper lobe; several small, hypodense lesions, 5 to 10 mm, in the right hepatic lobe; and prominence of the subcutaneous tissue overlying the muscles of the right abdominal wall (Fig. 2).

The CT findings confirm the radiographic finding of bilateral pleural effusions, but they also indicate that the abnormality in the left upper lobe seen on the chest radiograph represents a pleura-based parenchymal infiltrate rather than loculated pleural fluid. The hepatic and subcutaneous abnormalities seen on abdominal CT are nonspecific and suggest an inflammatory process in the affected areas. However, the CT findings in all three areas (lung, liver, and abdominal wall) are consistent with paragonimus infestation. In most disorders in which a pleural effusion accompanies a pleural-based infiltrate, the effusion is due to extension of the parenchymal disease to the visceral pleural surface; in the case of paragonimiasis, however, the parenchymal involvement results from migration of flukes from the pleural space into the peripheral lung parenchyma.

Although an alternative diagnosis for the nodular infiltrate in the left upper lobe is tuberculosis, pleural effusions accompanying either primary or reactivation tuberculosis are generally unilateral rather than bilateral. In addition, the patient had no fever or other constitutional symptoms that commonly accompany tuberculosis, and the finding of such striking eosinophilia in the pleural fluid and peripheral blood would be distinctly unusual.

Because my concern about the possibility of paragonimiasis remains high and because the diagnosis can potentially be made by noninvasive methods, I would next obtain sputum for cyologic examination and ask the cytopathologist to...
look specifically for eggs in the sputum. I would also perform serologic testing for antibodies against paragonimus.

Cultures and stains of the pleural fluid, sputum, and stool were negative for bacteria, fungi, acid-fast bacilli, and ova and parasites. Bronchoscopy revealed normal airways. Stains and cultures of bronchoalveolar-lavage fluid were negative for acid-fast bacilli, fungi, ova, and parasites. Serologic tests for *Entamoeba histolytica*, *strongyloides*, and *ascaris* were negative.

The negative results of the bronchoalveolar-lavage stains and cultures do not dissuade me from the diagnosis of paragonimiasis, since early in the course of pulmonary infection, the flukes in the lung are still immature and may not yet produce eggs that can be recovered from the airways.

An immunoblot assay for paragonimus was positive, and the patient was treated with a 2-day course of praziquantel. One month later, he felt well and had complete resolution of the nodule in the abdominal wall, leukocytosis, and eosinophilia. His right-sided pleural effusion had also resolved, but he had a persistent large, left-sided pleural effusion, which eventually required open thoracotomy and decortication. Samples of the pleural tissue were negative for ova and parasites. He recovered completely from the surgery.

I suspect that this patient was infected during his recent employment as a sushi chef. Although he could have been exposed to *P. westermani* in Asia, his clinical presentation is most consistent with the presence of acute paragonimiasis in which symptoms develop 2 to 3 months after exposure.

**Commentary**

Studies of clinical problem-solving suggest that a clinician's approach depends largely on the nature of the clinical problem and the expertise of the clinician. One of the most effective strategies involves pattern recognition, in which the clinician breaks the case down into manageable pieces and compares features of the current case with ones he or she has seen in the past. New cases are then recognized as similar or identical to old ones that have already been solved. In the case under discussion, the clinician focused on two patterns of disease...
with which he was familiar: abdominal pain and respiratory disease. As more information became available, he was able to identify more specific patterns, including pleuroparenchymal lung disease and subcutaneous nodules. The patient's striking peripheral-blood eosinophilia proved to be the sentinel clue, pointing to a parasitic infection with gastrointestinal and pulmonary involvement as the likely diagnosis. From that point, targeted and specific diagnostic tests were obtained to verify paragonimus as the causative agent.

Paragonimiasis, a food-borne parasitic infection caused by numerous species of lung flukes, infects an estimated 22 million people worldwide. The most common species, *P. westermani*, is responsible for human infection in Asia. Other paragonimus species are endemic to Asia, Africa, and the Americas. Adult lung flukes can live in the human host for as long as 20 years, highlighting the need for clinicians in areas where the disease is not endemic to become familiar with it when evaluating an immigrant.

Humans are infected when they ingest raw or partially cooked crab or crayfish containing paragonimus metacercariae. After the metacercariae hatch in the duodenum, the young flukes travel to the pleural cavity by penetrating the intestinal wall, mesentery, and diaphragm. During migration, the flukes may travel to ectopic foci in the peritoneal cavity, subcutaneous tissue, muscle, and brain. Within a few weeks, most worms penetrate the lung, where, enclosed in a pseudocapsule, they grow into adults. Adult flukes live within a pulmonary cyst, where they lay eggs that pass into the alveoli and are expectorated with sputum or swallowed and passed in feces. On reaching water, the eggs hatch into miracidia, which penetrate snails. Cercariae form in the snails, reemerge into water, and encyst in the gills, liver, or muscles of crayfish or crabs as metacercariae.

This case is most consistent with the presence of an acute infection. Since the lung is the target organ, patients typically present with respiratory symptoms such as cough and dyspnea. Fever, night sweats, weight loss, hemoptysis, and pleuritic chest pain may also be present, making the clinical presentation difficult to distinguish from other pulmonary infections. Ectopic foci in the subcutaneous tissues and brain can result in palpable, tender subcutaneous nodules; headaches; and seizures.

Chest radiographs may show infiltrates, cavitary lesions, pleural effusions, pleural thickening, or pneumothorax. Analysis of the pleural fluid reveals an exudative process with a white-cell count that is usually less than 2000 per cubic millimeter and marked pleural-fluid eosinophilia. As was seen in this case, the glucose level in the pleural fluid is commonly less than 10 mg per deciliter, and the LDH level is often greater than 1000 U per liter.

Paragonimiasis is diagnosed by the finding of eggs in the patient’s sputum, gastric washings, pleural fluid, or feces or by the demonstration of adult flukes or eggs in tissue specimens obtained at biopsy. If eggs or flukes are not found, an immunoblot assay, which is reported to have a sensitivity of 96% and a specificity of 99%, can be performed at the Division of Parasitic Diseases, Centers for Disease Control and Prevention, in Atlanta. Cure rates approach 100% with 3 days of praziquantel therapy. Pulmonary disease is rarely fatal. However, cerebral disease can cause an increased risk of seizures and dementia, and its treatment should be closely supervised.

Striking peripheral-blood eosinophilia, with an eosinophil count that is commonly as high as 25%, is one of the hallmarks of paragonimus infection. Other causes of peripheral-blood eosinophilia (defined by an absolute eosinophil count of more than 350 cells per cubic millimeter) include allergic disorders, autoimmune disease, adrenal insufficiency, medications, and hematologic cancer, such as acute leukemia. Globally, parasitic infections are the most common cause, although medications and allergic conditions are more common causes in industrialized countries. In the absence of allergic disease and medications that could be the source of the peripheral-blood eosinophilia, the initial diagnostic evaluation of a patient such as this one should include serial stool examination for ova and parasites to identify intestinal roundworms (e.g., hookworm and *Strongyloides*), schistosomiasis, paragonimiasis, fascioliasis, and other infections caused by trematodes. More extensive evaluation, including tests of the urinary sediment to identify schistosoma, chest radiography and sputum examination to identify paragonimus, serologic tests, and tissue biopsy should be guided by the patient’s history.

This patient’s history was notable both for travel to Korea, a region where paragonimus is endemic, 4 years before his illness and for his employment as a sushi chef, in which he handled raw fish, crayfish, and crabs. Although the adult paragonimus fluke can live in its human host for
many years, we suspect that this patient, because of his acute presentation, was probably infected while working as a sushi chef. Although he had not eaten raw crabs or crayfish, he may have had an accidental transfer of the fluke by handling infected crustaceans during food processing.10 Cases of paragonimiasis contracted in the United States are extremely rare, but they do occur.11

The clinical presentation of pleuropulmonary paragonimiasis may be difficult to distinguish from that of pulmonary tuberculosis.1,11-14 Tuberculosis is common in regions of the world where paragonimiasis is endemic, and patients with paragonimiasis have been treated erroneously for tuberculosis.1,14 In this case, the presence of marked peripheral-blood eosinophilia provided the missing piece to the puzzle, allowing the pattern to become clear.

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REFERENCES

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