# Case 9-2013: A 9-Year-Old Boy with Fever, Cough, Respiratory Distress, and Chest Pain

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## PRESENTATION OF CASE

*Dr. Sarita U. Patil* (Allergy and Immunology): A 9-year-old boy was admitted to this hospital because of fever, cough, respiratory distress, and chest pain.

The patient had been well until 8 days before admission, when cough, red and watery eyes, and a temperature of 37.2°C developed. Two days later, on a winter holiday, he vomited and did not want to open his presents. The temperature rose to 38.9°C, and he became increasingly lethargic. The next day, he saw his pediatrician. On examination, the temperature was reportedly 39.4°C, the right periorbital region and cheek were erythematous, and a cervical lymph node on the left side was enlarged. A rapid screening test for streptococcal pharyngitis was negative; supportive care was advised, and the patient returned home.

The next day, 4 days before admission, shortness of breath and tachypnea developed. The patient was seen in the emergency department at another hospital, where a chest radiograph was reportedly normal. A diagnosis of acute otitis media was made, and a 5-day course of azithromycin was prescribed. During the next 3 days, cough and occasional vomiting persisted. On the morning of admission, he returned to his pediatrician. The patient and his family reported that he had worsening cough, midsternal chest pain with deep inspiration, and weight loss of 1.8 kg in 1 week. On examination, the temperature was 40.3°C, and he appeared to be in respiratory distress. Acetaminophen was administered, and he was sent to this hospital.

The patient's family reported decreased cervical lymphadenopathy in the patient as compared with earlier in the week; however, cough and shortness of breath had worsened. He did not have diarrhea, jaundice, rash, tongue or lip swelling, or abdominal or joint pain.

The patient had been delivered by cesarean section because of failure to progress after 42 weeks of uncomplicated gestation; umbilical-cord separation occurred in a normal time frame. Between the ages of 6 and 9 years, he had had five episodes of streptococcal pharyngitis, three episodes of otitis media, and four episodes of cellulitis (most recently, caused by methicillin-resistant *Staphylococcus aureus*, sensitive to trimethoprim–sulfamethoxazole). One year earlier, he had been evaluated in the pulmonary clinic at this hospital because of a cough of 3 months' duration, which occurred during the day but not during sleep. At that time, the

physical examination was normal. T-cell subsets were normal; other test results are shown in Table 1. Specific IgE antibodies to environmental allergens were not detected by immunoassays. Antibody titers to the 23-valent pneumococcal polysaccharide vaccine were not at protective levels. Pneumococcal vaccine was administered, with improvement in the antibody titers to pro-

tective levels. Spirometry was normal. Nasal fluticasone was administered for 1 month, without improvement, but the cough gradually resolved spontaneously.

The patient had attention deficit–hyperactivity disorder, had had molluscum contagiosum in the past, and approximately 5 years earlier, had lymphopenia that had resolved spontaneously,

| Variable | Reference Range, Age-Adjusted† | 1 Yr before Admission | On Admission | 2nd Hospital Day | 3rd Hospital Day |
|---|---|---|---|---|---|
| **Table 1. Laboratory Data.\*** | | | | | |
| Hematocrit (%) | 35.0–45.0 | 36.9 | 37.2 | 30.3 | 28.2 |
| Hemoglobin (g/dl) | 11.5–15.5 | 13.1 | 12.6 | 10.1 | 9.2 |
| White-cell count (per mm³) | 4500–13,500 | 3700 | 18,000 | 13,100 | 13,300 |
| Differential count (%) | | | | | |
| Neutrophils | 33–59 | 42 | 92 | 92 | 93 |
| Lymphocytes | 33–50 | 49 | 4 | 3 | 3 |
| Monocytes | 4–11 | 7 | 3 | 3 | 2 |
| Eosinophils | 0–8 | 1 | 1 | 2 | 2 |
| Basophils | 0–3 | 1 | | | |
| Erythrocyte sedimentation rate (mm/hr) | 0–11 | | 46 | 53 | 57 |
| Protein (g/dl) | | | | | |
| Total | 6.0–8.3 | | 6.8 | 5.8 | 5.7 |
| Albumin | 3.3–5.0 | | 3.2 | 2.6 | 2.7 |
| Globulin | 2.6–4.1 | | 3.6 | 3.2 | 3.0 |
| Bilirubin (mg/dl) | | | | | |
| Total | 0.0–1.0 | | 2.3 | 1.6 | 1.3 |
| Direct | 0.0–0.4 | | 1.2 | 0.7 | 0.8 |
| Phosphorus (mg/dl) | 4.5–5.5 | | 3.3 | 2.4 | 3.3 |
| Alkaline phosphatase (U/liter) | 15–350 | | 458 | 344 | 350 |
| Aspartate aminotransferase (U/liter) | 10–40 | | 69 | 51 | 45 |
| Alanine aminotransferase (U/liter) | 10–55 | | 91 | 72 | 64 |
| C-reactive protein (mg/liter) | <8.0 | | 123.2 | | |
| Lactate dehydrogenase (U/liter) | 110–210 | | | 254 | |
| Lactate (mmol/liter) | 0.5–2.2 | | 1.0 | | |
| Immunoglobulins | | | | | |
| IgE (IU/ml) | 0–100 | 16 | 76 | | |
| IgA (mg/dl) | 45–233 | 220 (ref 33–199) | | | 275 |
| Total IgG (mg/dl) | 585–1509 | 1028 | | | 738 |
| IgG1 (mg/dl) | 400–1080 | 605 | | | |
| IgG2 (mg/dl) | 85–410 | 333 | | | |
| IgG3 (mg/dl) | 13.0–142.0 | 27.2 | | | |
| IgG4 (mg/dl) | ≤189.0 | 269.0 | | | |
| IgM (mg/dl) | 49–229 | 107 | | | 74 |

| Variable | Reference Range, Age-Adjusted† | 1 Yr before Admission | On Admission | 2nd Hospital Day | 3rd Hospital Day |
|---|---|---|---|---|---|
| **Table 1. (Continued.)** | | | | | |
| Serum protein electrophoresis | | | | | Normal pattern |
| Complement | | | | | |
| Total (U/ml) | 63–145 | | | | 169 |
| C3 (mg/dl) | 93–202 | | | | 143 |
| C4 (mg/dl) | 13–51 | | | | 30 |
| Blood gases | | | | | |
| Specimen | | | Venous | Venous | Arterial |
| Inspired oxygen (liter/min by nasal cannula) | | | 1 | 1 | 1 |
| Partial pressure of oxygen (mm/Hg) | 35–50 (venous), 80–100 (arterial) | | 74 | 47 | 109 |
| Partial pressure of carbon dioxide (mm/Hg) | 38–50 (venous), 35–42 (arterial) | | 43 | 35 | 29 |
| pH | 7.30–7.40 (venous), 7.35–7.45 (arterial) | | 7.38 | 7.44 | 7.48 |
| Base excess (mmol/liter) | | | –1.0 | –0.5 | –2.0 |
| Bicarbonate (mmol/liter) | 24–30 | | 24 | 23 | 21 |

\* To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for IgE to micrograms per liter, multiply by 2.40.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are age-adjusted and are for patients who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

with no clinical sequelae. He did not have a history of failure to thrive, night sweats, recurrent lower respiratory tract disease, or severe or unusual infections. Medications on admission included ibuprofen, acetaminophen, and azithromycin. Immunizations, including the influenza A (H1N1) vaccine, were current, but he had not received the seasonal influenza vaccine. He had no known allergies.

The patient lived with his parents, a sibling, two dogs (one with a newly diagnosed roundworm infection), a cat (less than 1 year of age), and a snake. His home was heated with forced hot water, and his parents had recently noted mold in the basement. The home had recently been sprayed with permethrin for eradication of lice. Moles had been seen in the backyard where the patient played. He had been exposed to relatives with pneumonia 1 month earlier. He had not traveled internationally or to the midwestern or southwestern United States. His father worked in construction, smoked in the home, and had recurrent skin abscesses. The patient's mother and sister were carriers of cystic fibrosis, a maternal aunt had environmental allergies, and a paternal aunt had rheumatoid arthritis. His parents were of western European ancestry, with no history of consanguinity.

On examination, the patient was alert and oriented. He appeared ill. The temperature was 38.6°C, the blood pressure 110/64 mm Hg, the pulse 109 beats per minute, the respiratory rate 30 breaths per minute, and the oxygen saturation 95% while he was breathing ambient air. The weight was 32.3 kg. Conjunctival injection with edema (chemosis), mild erythema of the right upper cheek and the left tympanic membrane, dry mucous membranes, and a mildly enlarged and mobile nontender anterior cervical lymph node were present, and the trachea was midline. There was no nasal flaring or suprasternal retraction on inspiration, there were mild intercostal and subcostal retractions, and the abdomen protruded on inspiration. Air entry was good (with poor inspiratory effort because of chest pain), and there were coarse breath sounds, without crackles or wheezes; the remainder of the examination was normal.

The platelet count and blood levels of electrolytes, calcium, magnesium, glucose, total protein, globulin, amylase, and lipase were normal, as were the results of renal-function tests; other test results are shown in Table 1. Rapid screening of a nasal swab for influenza viruses A and B, parainfluenza, adenovirus, and respiratory syncytial virus was negative, as was testing for influenza A (seasonal and H1N1) nucleic acid. Urinalysis revealed clear amber fluid with 2+ albumin, 1+ urobilinogen, and 2+ bilirubin; 3 to 5 red cells, 5 to 10 white cells, and many bacteria per high-power field; 3 to 5 hyaline casts per low-power field; and mucin. An electrocardiogram revealed sinus tachycardia and nonspecific T-wave changes in the inferior leads. A chest radiograph showed hilar lymphadenopathy and multiple nodular opacities throughout both lungs, more prominent in the middle and lower zones. Normal saline (a total of 1500 ml) was infused in three boluses. Cultures of the blood and urine were obtained and remained sterile. Vancomycin was administered intravenously.

The patient was admitted to the pediatric intensive care unit, and the administration of meropenem (intravenously) and azithromycin and trimethoprim–sulfamethoxazole (orally) was added. Ten hours after presentation, computed tomography (CT) of the chest, performed after the administration of intravenous contrast material, revealed multifocal ill-defined nodular opacities throughout all lung lobes, superimposed areas of consolidation, scattered ground-glass opacities, and mediastinal and hilar lymphadenopathy.

On the second day, ultrasonography of the abdomen revealed a small pleural effusion on the right side and was otherwise normal. Ultrasound examination of the neck showed bilateral cervical lymphadenopathy, more prominent on the right side; there was no evidence of deep venous thrombosis in the neck. During the second night, while the patient was sleeping, oxygen saturation decreased to 58%, with cyanosis on examination; saturation improved with arousal and rose to 93 to 95% with the administration of oxygen (1 liter per minute by nasal cannula). The maximal temperature was 38.4°C. A chest radiograph was unchanged. A skin test for tuberculosis was negative at 48 hours. Other test results were pending.

On the third day, a diagnostic test was performed.

## DIFFERENTIAL DIAGNOSIS

*Dr. Mary Shannon Fracchia:* All the discussants are aware of the diagnosis in this case. Dr. Sagar, may we see the imaging studies?

*Dr. Pallavi Sagar:* The chest radiograph (Fig. 1) shows multiple nodular and fluffy opacities distributed throughout the lungs. The hilar prominence is suggestive of lymphadenopathy. A CT scan obtained after the administration of intravenous contrast material (Fig. 2) shows multifocal patchy nodular opacities bilaterally, without internal cavitations. There are areas of more focal consolidation with adjacent ground-glass opacities. There is both hilar and mediastinal lymphadenopathy. There is no pleural effusion, pneumothorax, pulmonary cysts, or areas of air trapping. In this clinical context, the findings suggest infectious causes, including multifocal pneumonia or septic emboli. Noninfectious considerations include pulmonary edema, vasculitis with pulmonary hemorrhage, and metastatic disease; however, these are less likely in this clinical context.

*Dr. Fracchia:* This child was acutely ill with a respiratory process. Infectious diseases were primary considerations, and Dr. El Saleeby will discuss the differential diagnosis from the infectious diseases perspective.

### DIFFERENTIAL DIAGNOSIS OF INFECTIOUS DISEASES

*Dr. Chadi M. El Saleeby:* The diagnosis of pediatric pneumonias is best approached by a multifactorial evaluation, which involves the characteristics of the host (e.g., age and immune status), potential exposures including epidemiologic considerations, and the radiographic appearance of the pulmonary process.

The panoply of microbes associated with community-acquired pediatric pneumonias is closely related to the age of the patient, which is not the case in adults.[1] Viruses are most common in infants and young children, but in this patient's age group, atypical bacteria predominate. Pneumococcal pneumonia is a possibility, despite the patient's immunization; one study showed the incidence of uncomplicated infection to be essentially unaffected by vaccination in the group 5 to 17 years of age.[2] Primary or acquired immunologic impairments are generally associated with specific microorganisms, depending on which component of the immune
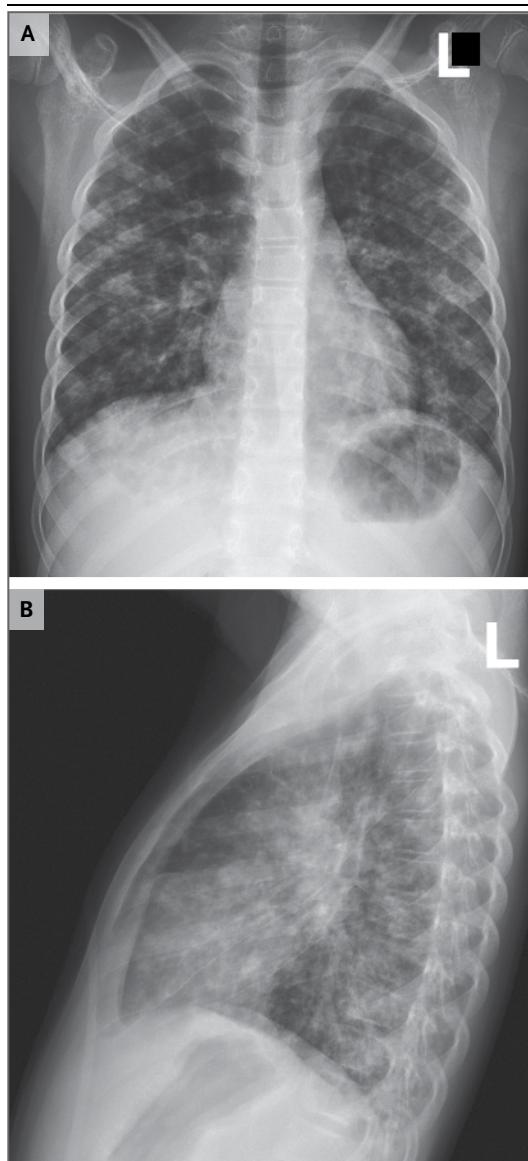
**Figure 1. Chest Radiographs.**

The frontal (Panel A) and lateral (Panel B) chest radiographs show multiple nodular opacities throughout both lungs and hilar prominence, features suggestive of hilar lymphadenopathy.



**Figure 2. CT Images of the Chest.**

CT images of the chest viewed in lung windows (Panel A) and soft-tissue windows (Panel B) after the administration of intravenous contrast material show multifocal patchy nodular opacities and areas of consolidation throughout all lung lobes, with mediastinal and hilar lymphadenopathy (arrow).

system is affected. A detailed immunologic investigation of this patient was not available to us at the time of presentation, but the relative rarity of primary immunodeficiencies argues against them in this case, as do the absence of recurrent, persistent, or serious infections; sinopulmonary disease; failure to thrive; and a suggestive family history. The patien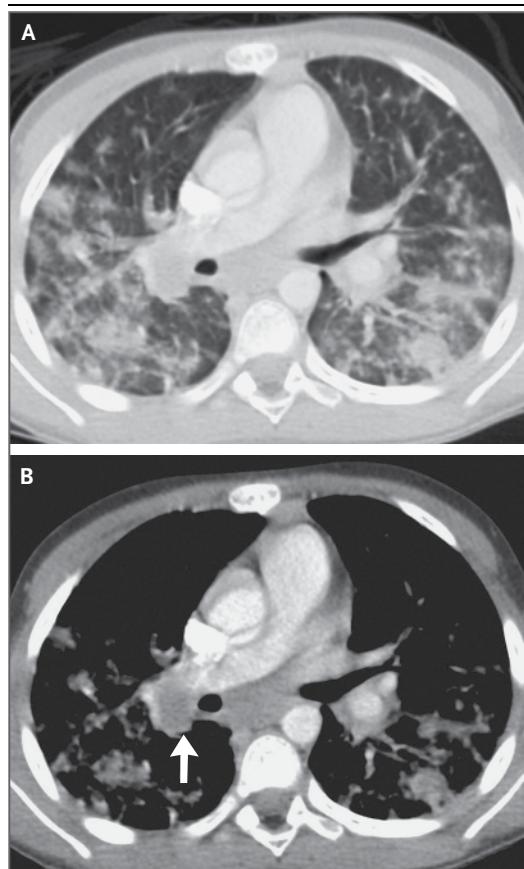t's history of lymphopenia might indicate infection with the human immunodeficiency virus, but the lymphopenia had resolved spontaneously and he has no history of opportunistic infections.

We also considered the endemic mycoses (histoplasmosis, coccidioidomycosis, and blastomycosis), which may have a nodular appearance on radiographs and can affect persons regardless of their immune status. However, this patient had not traveled to areas where these pathogens are endemic, and person-to-person transmission does not occur. The family had a young cat; exposure to kittens is a risk factor for infection with *Bartonella henselae*, the causative agent of cat scratch disease. Pneumonia due to *B. henselae* is exceedingly rare. It is usually preceded by regional lymphadenopathy draining the

site of the scratch and is commonly associated with extrapulmonary manifestations,[3] which were not documented in this patient. Exposure to a contaminated water supply may cause legionellosis, but clinically significant disease is rare in immunocompetent children.[4] This patient had no known risk factors for tuberculosis, and a tuberculin skin test was negative at 48 hours.

Cognizance of the time of year at presentation is also important, since many respiratory pathogens, particularly viruses, show a predictable epidemiology.[5] A nasal swab for rapid screening for influenza virus, parainfluenza virus, adenovirus, and respiratory syncytial virus antigens was negative in this case, as was testing for influenza A (seasonal and H1N1) virus nucleic acid.

Finally, the radiographic appearance of the pulmonary process can narrow the differential diagnosis. Nodular infiltrates indicate endobronchial and bronchiolar spread of infection, which is commonly seen in bacterial pneumonias, especially those associated with aspiration, respiratory viruses, tuberculous and nontuberculous mycobacteria, endemic mycoses, *Pneumocystis jirovecii* pneumonia, aspergillosis, and nocardiosis. Angioinvasive aspergillosis is seen exclusively in immunocompromised hosts. Although nocardiosis is uncommon in children, it can occur in persons with a competent immune system, manifesting as a subacute respiratory illness. It requires no specific exposures and may cause nodular infiltrates on imaging. Septic emboli may also be nodular in appearance. In this case, multiple blood cultures and echocardiography to evaluate for infectious endocarditis were negative. An ultrasound examination of the neck showed no evidence of deep venous thrombosis, ruling out Lemierre's syndrome.

Most puzzling illnesses are atypical presentations of common diseases. After initial evaluation of the patient, our leading diagnoses were an infection with an atypical bacteria, a viral infection (recognizing the limitations of diagnostic methods for the upper airways), or a bacterial superinfection of a viral pneumonia. Less likely possibilities included abscesses or septic emboli, perhaps from an endovascular focus, or infection with nocardia species. The administration of broad-spectrum antimicrobial agents to cover these potential pathogens was begun. We ad-

vised the primary care team to consider noninfectious causes. Pediatric pulmonary consultation was requested.

### DIFFERENTIAL DIAGNOSIS FROM THE PULMONARY MEDICINE PERSPECTIVE

*Dr. Fracchia:* What aspects of this patient's presentation are of importance to a pediatric pulmonologist? Cough, weight loss, and fever were clinically significant, as was tachypnea. A normal respiratory rate for a 9-year-old boy is similar to the adult rate of approximately 15 breaths per minute, whereas this patient's rate was double that. The chest pain on inspiration was also a concern. Why was he having pleuritic chest pain? Two layers of pleura are separated by a thin layer of fluid to prevent friction during breathing. When the pleura is inflamed or irritated, the fluid is adsorbed, resulting in pain with inspiration. The differential diagnosis of pleuritic chest pain includes infection, emboli, malignant tumors, and autoimmune inflammatory processes.

### EMBOLI

Tachypnea, tachycardia, and chest pain would be consistent with embolic disease, as are the radiographic findings. Septic emboli from Lemierre's syndrome were considered in light of the cervical lymphadenopathy, but cervical ultrasonography did not reveal thrombi. Pulmonary emboli from a deep venous thrombosis or fat emboli were less likely in view of the absence of trauma, immobility, and a coagulation disorder and in view of the constitutional symptoms.

### MALIGNANT TUMORS

Lung tumors in children are typically metastases from a primary tumor outside the lung, and we had not found evidence of a primary tumor in this patient. The weight loss and radiographic findings were consistent with cancer, but the patient's presentation was more dramatic and acute than is typical for cancers. Langerhans'-cell histiocytosis of the lungs can be associated with dyspnea, tachypnea, and weight loss, as seen in this patient, as well as pulmonary nodules and lymphadenopathy, which were seen on imaging. Pulmonary Langerhans'-cell histiocytosis is typically seen in adults with a history of smoking, whereas bone and pituitary lesions are more common in Langerhans'-cell histiocytosis in children.[6]

### AUTOIMMUNE AND INFLAMMATORY PROCESSES

After infection, autoimmune and inflammatory processes were at the top of my differential diagnosis. Patients with vasculitides, particularly the Churg–Strauss syndrome and granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis), may have clinical features that are similar to those of this patient, and nodules and lymphadenopathy may be apparent on imaging. Patients with Churg–Strauss syndrome, however, typically have wheezing and eosinophilia.[7] This patient had neither the upper-airway involvement nor the renal involvement typically seen in granulomatosis with polyangiitis. Another consideration was sarcoidosis; in patients who are between 10 and 40 years of age, it tends to manifest as bilateral infiltrates and hilar lymphadenopathy, as seen in this patient. Children with sarcoidosis, however, are usually asymptomatic or present with eye or skin findings.[8] Aspiration pneumonitis was unlikely, since the patient was neurologically intact and did not have a history of reflux or choking on liquids. We also considered hypersensitivity pneumonitis, but the patient had not been exposed to birds or farm animals.

### CYSTIC FIBROSIS

As a pediatric pulmonologist, I always consider cystic fibrosis in a child with lung disease. The patient's mother and sister were carriers of the most common mutated form of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, ΔF508-CFTR. Although the patient's father was negative for this mutation, it is still possible that he was a carrier of 1 of the 1800 mutations not tested for on the basic genetic panel, so that this patient could have inherited the ΔF508-CFTR mutation from his mother and another mutation from his father. However, his newborn screening test was negative, and cystic fibrosis tends not to present in such an acute manner. A sweat test was negative, which made cystic fibrosis unlikely.

A bronchoscopy was initially deferred, because the patient was becoming hypoxemic, and I was concerned about impending respiratory failure. A hypersensitivity panel was sent for analysis. Dr. Murali will discuss the case from an immunologic perspective.

### HYPERSENSITIVITY PNEUMONITIS

*Dr. Mandakolathur R. Murali:* Hypersensitivity pneumonitis (also known as extrinsic allergic alveoli-

**Table 2. Diagnostic Criteria for Hypersensitivity Pneumonitis.***

**Major criteria**

A history of symptoms compatible with hypersensitivity pneumonitis (e.g., weight loss, cough, breathlessness, febrile episodes, and fatigue)

Evidence of exposure to the offending antigen in patient's history or through detection of precipitins (IgG and IgM antibodies) in serum or bronchoalveolar-lavage fluid

Radiographic changes consistent with hypersensitivity pneumonitis (fleeting, micronodular, and interstitial infiltrates, in the middle and lower lung zones)

Lymphocytosis in bronchoalveolar-lavage fluid (CD4:CD8 T-cell ratio, <1.0)

Histologic changes consistent with hypersensitivity pneumonitis on lung biopsy

A positive natural challenge or a controlled inhalational challenge that produces symptoms or objective abnormalities on reexposure to the offending environment

**Minor criteria**

Bibasilar rales

Decreased carbon monoxide diffusing capacity

Arterial hypoxemia at rest or with exertion

* The presence of any four major criteria and at least two minor criteria establishes a definitive diagnosis of hypersensitivity pneumonitis. Data are from Schuyler and Cormier.[9]

tis) is a noninfectious, immune, inflammatory interstitial lung disease with a broad clinical spectrum that must be in the differential diagnosis in this case. Many infectious and other causes of pulmonary infiltrates in this case appear to have been ruled out. Because of the heterogeneity of hypersensitivity pneumonitis and the lack of a single diagnostic test, many diagnostic criteria have been proposed for the disease. Schuyler and Cormier developed criteria that integrate the various aspects of the disease[9]; the presence of any four major criteria and at least two minor criteria establishes a definitive diagnosis of hypersensitivity pneumonitis (Table 2). This patient has symptoms and radiographic findings compatible with this diagnosis, including hypoxemia.

The detection of precipitin antibodies in the serum (on the hypersensitivity panel) is a useful noninvasive diagnostic test.[10] Examination of the gel (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) reveals that this patient has precipitins to both *Aspergillus fumigatus* and *A. flavus*. This suggests that he has circulating antibodies that can form immune complexes in the alveoli and interstitium when the fungal antigens are present in the alveoli. The ensuing antigen–anti-

body complexes are instrumental in initiating the vascular and cellular phase of inflammation resulting in the spectrum of hypersensitivity pneumonitis.[11] The immune complexes lead to the production of kinins,[12,13] activation of the classical complement cascade, and generation of anaphylatoxins and chemotactic peptides, which contribute to the vascular phase of inflammation and recruit neutrophils and macrophages. Both CD4+ and CD8+ T cells contribute to the immunopathogenesis of hypersensitivity pneumonitis,[14] with CD4+ cells and immune complexes predominating in acute forms of the disease and CD8+ cells in subacute and chronic forms of the disease. Although neutrophils are the predominant cells in bronchoalveolar lavage in the acute phase, CD8+ cells predominate in the subacute and chronic phases of the disease. This is reflected in bronchoalveolar lavage by lymphocytosis with an altered ratio of CD4+ T cells to CD8+ T cells, which is a major diagnostic criterion.[9]

It is important to know which of three recognized phases of hypersensitivity pneumonitis the patient is in so that his response to therapy and overall prognosis can be predicted. The acute phase is an immune-complex alveolitis that is manifested on chest imaging as a ground-glass infiltrate; patients present with fever, chills, cough, and hypoxemia 4 to 48 hours after exposure to the antigen. The subacute phase is seen after weeks or several months of exposure to the antigen and is characterized by peribronchiolar inflammation and granulomas; imaging reveals micronodules and air trapping. The clinical manifestations are cough, dyspnea, and bibasilar rales. This patient has fever, cough, dyspnea, bibasilar rales, and hypoxemia, and both nodular and ground-glass opacities are evident on imaging. Therefore, the clinical criteria for a diagnosis of an acute exacerbation of subacute hypersensitivity pneumonitis are met.

In patients with either acute or subacute hypersensitivity pneumonitis, elimination of the antigen results in a good outcome. Persistent exposure to the antigen for months or years results in the chronic phase, with progressive dyspnea, cough, fatigue, and weight loss, as well as radiologic features of interstitial fibrosis, honeycombing, and emphysema. In patients in the chronic phase, inflammation is less amenable to therapy and the prognosis is poor. In this patient, bronchoscopy with bronchoalveolar lavage was performed, as was transbronchial lung biopsy, to confirm the diagnosis and determine the phase of the disease.

## CLINICAL DIAGNOSIS

Acute exacerbation of subacute hypersensitivity pneumonitis caused by exposure to *Aspergillus fumigatus* and *A. flavus*.

## PATHOLOGICAL DISCUSSION

*Dr. Mari Mino-Kenudson:* The transbronchial-biopsy specimen from this patient shows bronchiolo-centric inflammation that obscures pulmonary arteries and respiratory bronchioles (Fig. 3A through 3D). There are histiocytic aggregates in the alveolar spaces, along with activated pneumocytes and scattered lymphocytes and eosinophils. In addition, a few multinucleated giant cells are present in the alveolar walls. Peripheral alveolar walls are well visualized, and there is no notable fibrosis. This constellation of findings (bronchiolocentric inflammation, histiocytic collections, and giant cells without interstitial fibrosis) is consistent with subacute hypersensitivity pneumonitis. The other possible diagnosis is aspiration pneumonitis, which can be ruled out on the basis of the patient's clinical course.

In this case, there is also prominent acute inflammation consisting of scattered neutrophils in the alveolar walls, which is not a feature of subacute hypersensitivity pneumonitis (Fig. 3E). The presence of an interstitial neutrophilic infiltrate in this context indicates acute exacerbation of hypersensitivity pneumonitis.[15]

Bronchoalveolar lavage revealed most of the cells to be granulocytes (including neutrophils), corresponding to the biopsy findings; the ratio of CD4+ T cells to CD8+ T cells was low, at 0.7. These findings, together with the results of serologic testing, are consistent with acute exacerbation of subacute hypersensitivity pneumonitis caused by exposure to *A. fumigatus* and *A. flavus*.

## MANAGEMENT AND FOLLOW-UP

*Dr. Sarita U. Patil* (Allergy and Immunology): We strongly suspected that the patient's exposure was in his home. During the patient's hospitalization, investigation of the residence by state of-
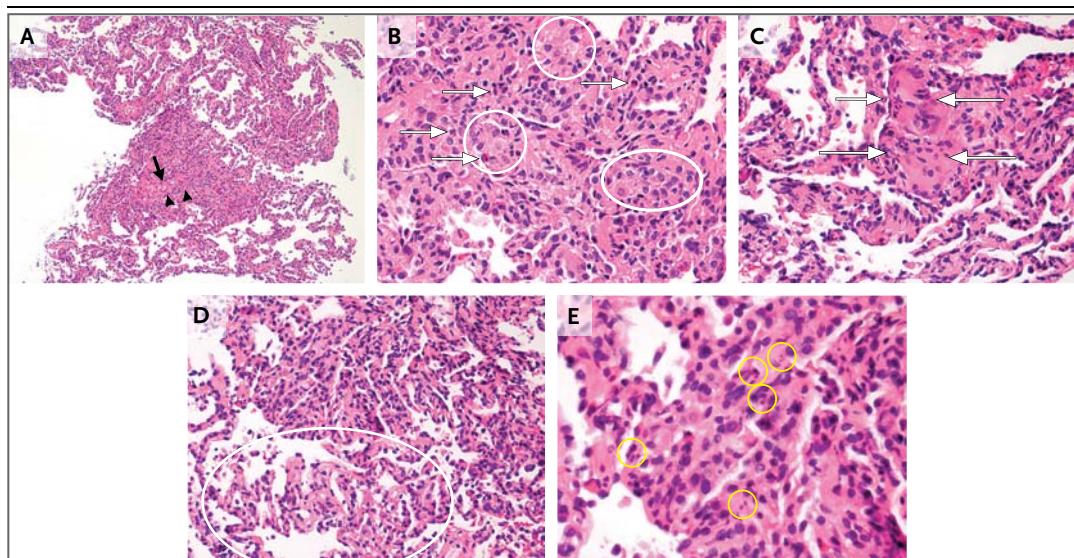
**Figure 3. Transbronchial-Biopsy Specimen (Hematoxylin and Eosin).**

The transbronchial-biopsy specimen (Panel A) shows bronchiolocentric inflammation that obscures pulmonary arteries (arrow) and respiratory bronchioles with a lining of low-columnar epithelial cells (arrowheads). A view at high magnification (Panel B) shows histiocytic aggregates in the alveolar spaces (encircled areas), along with activated pneumocytes and scattered lymphocytes and eosinophils (arrows), resulting in a cellular appearance. A few multinucleated giant cells (Panel C, arrows) are present in the alveolar walls. Peripheral alveolar walls are well visualized (Panel D, encircled area), and there is no notable fibrosis. There is also prominent acute inflammation consisting of scattered neutrophils in the alveolar walls (Panel E, circles). This acute inflammation is not a feature of subacute hypersensitivity pneumonitis and therefore, in this context, indicates acute exacerbation of hypersensitivity pneumonitis.

ficials and a company specializing in indoor-mold remediation revealed that there was a malfunction of the venting system in the basement, with visible mold. The venting system misdirected warm air into the patient's room, resulting in a warm and humid environment, and a high density of aspergillus was found in the patient's bedroom carpet.

As the first-line therapy for hypersensitivity pneumonitis is removal or minimization of antigen exposure, the patient was discharged to an alternate residence, where he has continued to reside. Pharmacologic management of hypersensitivity pneumonitis with glucocorticoid therapy is directed at the inflammatory component of the disease. Acute hypersensitivity pneumonitis can be treated with a 2-to-4-week regimen of glucocorticoids, whereas subacute to chronic cases can require weeks or months of treatment with variable doses and responses. The use of steroid-sparing therapies (e.g., azathioprine and macrolide antibiotics) has also been described.[16,17]

After a 3-month course of treatment with glucocorticoids, the patient regained normal pulmonary function. He is an avid soccer player today and has had no further episodes of hypersensitivity pneumonitis.

*A Physician:* Since fungi such as aspergillus are ubiquitous, do we know the risk factors and why the disease develops in only a few persons?

*Dr. Murali:* Hypersensitivity pneumonitis, like many immune disorders, is an outcome of environmental stimuli interacting with the human host genes. Most fungal spores are eliminated by alveolar macrophages. Genetic predilection to hypersensitivity pneumonitis has been mapped to polymorphisms of tumor necrosis factor α, the genes that modulate the structure of HLA class I (e.g., the *TAP* [transporter associated with antigen processing] genes), proteasome genes involved in antigen processing, and polymorphisms of the tissue inhibitors of metalloproteinase.[18,19]

## ANATOMICAL DIAGNOSIS

Hypersensitivity pneumonitis, subacute, with features suggestive of acute exacerbation, caused by *Aspergillus fumigatus* and *A. flavus* exposure.

This case was discussed at the postgraduate course, Primary Care Pediatrics; course directors: Ronni L. Goldsmith, M.D., Peter T. Greenspan, M.D., Ronald E. Kleinman, M.D., Janice A. Lowe, M.D., and John Patrick T. Co, M.D., M.P.H., sponsored by the Department of Continuing Education, Harvard Medical School.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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