CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 16-2020: A 47-Year-Old Woman with Recurrent Melanoma and Pulmonary Nodules

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PRESENTATION OF CASE

Dr. Justine V. Cohen: A 47-year-old woman with malignant melanoma was seen in the pulmonary clinic of this hospital because of new abnormal findings on chest imaging.

The patient had observed routine quarterly surveillance imaging after resection of right axillary melanoma, radiation therapy, and initiation of pembrolizumab therapy 3 years earlier. The most recent imaging was performed 6 days before this evaluation.

Dr. Jo-Anne O. Shepard: Computed tomography (CT) of the chest, performed after the administration of intravenous contrast material, revealed a patchy consolidation in the left upper lobe, bilateral hilar and mediastinal lymphadenopathy, and numerous bilateral scattered solid pulmonary nodules with associated ground-glass halos (Fig. 1A through 1D). These findings were new relative to the most recent imaging performed 3 months earlier. Other pulmonary nodules, measuring 2 to 4 mm in greatest dimension, in the right upper lobe that had been noted on imaging studies obtained during the previous 3 years were stable. Changes in the right upper lobe that had resulted from radiation therapy were also stable relative to previous imaging studies. CT of the abdomen and pelvis, performed after the administration of intravenous contrast material, revealed a hemangioma in the right hepatic lobe that measured 9 mm in greatest dimension and a cyst in the left hepatic lobe that measured 15 mm in diameter; both were unchanged from previous imaging studies. Magnetic resonance imaging (MRI) of the head, performed after the administration of intravenous contrast material, was normal.

Dr. Cohen: The patient was referred by her oncologist for urgent evaluation in the pulmonary clinic of this hospital. On evaluation, the patient reported no symptoms, specifically no fever, weight loss, night sweats, fatigue, malaise, headache,

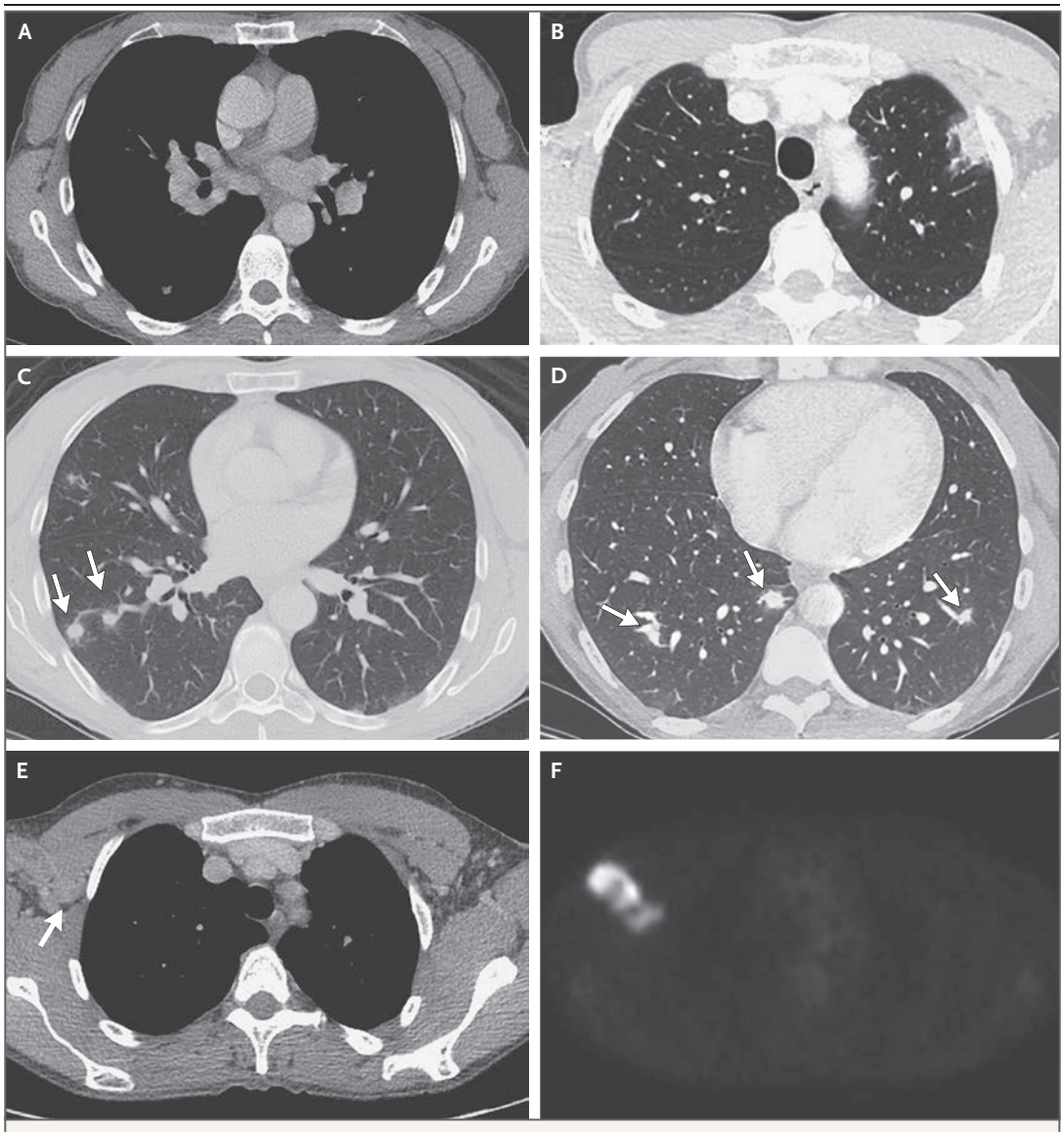

Figure 1. Imaging Studies of the Chest.

Six days before evaluation at this hospital, CT of the chest was performed after the administration of intravenous contrast material; the scan shows new bilateral hilar and subcarinal lymphadenopathy (Panel A), a new peripheral patchy consolidation in the left upper lobe (Panel B), and new bilateral pulmonary nodules (Panels C and D, arrows). Positron-emission tomography and CT had been performed 3 years before the current evaluation; the scan shows a 3.5-cm right axillary soft-tissue nodal mass (Panel E, arrow) with foci of intense ^{18}F-fluorodeoxyglucose uptake (Panel F) and no other sites of avidity.

chest pain, cough, hemoptysis, new or changed skin lesions (except a mild traumatic abrasion on the right arm), pruritus, or new masses.

The patient's medical history was notable for superficial spreading melanoma on the right upper back that had initially been diagnosed two decades before this evaluation and had been surgically excised, with clear pathological margins. Eleven years later, an in situ superficial spreading melanoma developed on the left upper back and was completely excised.

Dr. Shepard: Three years before the current evaluation, locally advanced melanoma in the right axilla was diagnosed on the basis of a positron-emission tomographic and CT image that showed a 3.5-cm right axillary nodal con-

glomerate mass with multiple foci of intense ^{18}F-fluorodeoxyglucose (FDG) uptake; no other sites of FDG avidity were seen (Fig. 1E and 1F). Multiple pulmonary nodules, measuring 2 to 4 mm in greatest dimension, in the right lobe and hypodense hepatic lesions, measuring 9 mm in the right lobe and 10 mm in the left lobe, were noted. MRI of the abdomen suggested that the hepatic lesion in the right lobe corresponded to a hemangioma and the hepatic lesion in the left lobe a cyst. MRI of the head, performed before and after the administration of intravenous contrast material, was normal.

Dr. Cohen: At that time, dissection of the right axillary lymph nodes was performed, and examination of the specimens revealed metastatic melanoma in 25 of 39 lymph nodes, with a high degree of extracapsular extension. Molecular profiling identified the BRAF V600E mutation. The patient received radiation therapy to the right axilla and supraclavicular fossa (total dose of 4800 cGy over a period of 5 weeks), followed by pembrolizumab every 3 weeks for the next 12 months. During this course of treatment, lichenoid nodules developed on the fingers of both hands, tenosynovitis developed in the right ankle, and hypothyroidism was diagnosed, for which treatment with levothyroxine was initiated. These findings were attributed to adverse effects of the immune checkpoint inhibitor therapy. The plan for surveillance imaging included CT of the chest, abdomen, and pelvis, which was to be performed every 3 months, and MRI of the head, which was to be performed annually.

The patient's medical history also included bilateral ovarian cysts, osteopenia, and a melanocytoma of the left optic disc that had been stable for at least 13 years. A Papanicolaou smear and testing for high-risk human papillomavirus performed 3 years before this evaluation had been negative. Routine screening mammography performed 1 month before this evaluation had revealed dense breast tissue with bilateral calcifications that appeared to be benign; no suspicious lesions were noted. Medications included calcium carbonate, cholecalciferol, and levothyroxine. There were no known drug allergies.

The patient was born on the northern coast of South America and had immigrated to the United States as a child. She lived in New England with her husband, two children, and two cats. She worked in the health care industry. She drank one or two glasses of wine per day and did not smoke tobacco or use illicit drugs. One month before this evaluation, she and her family had traveled to the northern coast of South America for 1 week. On the trip, the patient spent most her time outdoors, including taking trips to the jungle and swimming in fresh water, and ate local cuisine, such as water chestnuts. When she returned home with her family, her husband and one of her children had generalized myalgias and malaise that resolved spontaneously.

The patient's mother had breast cancer, melanoma, and basal-cell carcinoma; her father had prostate cancer; and her daughter had mixed connective-tissue disease. Her maternal grandfather had colon cancer, her paternal grandmother had breast cancer, and her maternal cousin had melanoma.

On examination, the temperature was 37.0°C, the blood pressure 123/68 mm Hg, the pulse 56 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 20.8. She appeared well, and the lungs were clear on auscultation. Examination showed fair skin, multiple nevi without suspicious features, and healed scars at the sites of previous surgical procedures. There were lichenoid nodules on the fingers of both hands. The remainder of the physical examination was normal.

The levels of electrolytes, glucose, and lactate dehydrogenase were normal, as were results of renal- and liver-function tests. The complete blood count and differential count were also normal. Blood samples were obtained for culture. An interferon-γ release assay for *Mycobacterium tuberculosis* was negative, and the level of 1,3-β-D-glucan was less than 31 pg per milliliter (reference value, <60).

Diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Katrina A. Armstrong: The construction of a differential diagnosis and selection of diagnostic tests are two steps in the cycle of clinical decision making that underlies much of medicine (Fig. 2). Often, this cycle begins with defin-

ing the problem representation (typically a one-sentence summary that describes the important features of a case), which then leads to developing the list of possible diagnoses and estimating the probability of each diagnosis. This list, together with information about the accuracy and risks of possible diagnostic tests, then leads to a diagnostic testing strategy that informs the decision about possible treatments. Although I will focus on the decision about diagnostic testing, the cycle does not end with the test or even with the treatment; rather, it depends on longitudinal assessment of response and the potential to redefine the problem representation and enter the cycle again if diagnostic uncertainty increases.

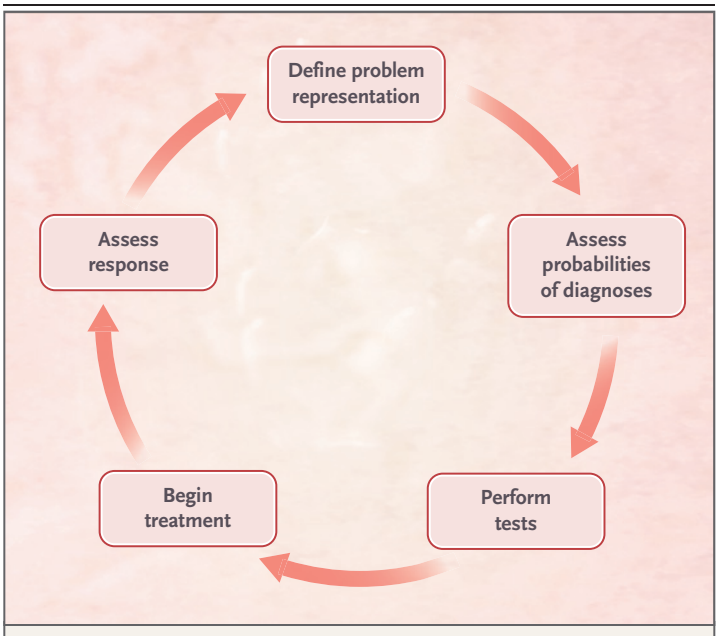

Figure 2. Diagnostic and Clinical Decision-Making Cycle.

PROBLEM REPRESENTATION

Following this paradigm, the problem representation in this case includes key facts about the patient (i.e., she is in her 40s, she received immunotherapy for metastatic melanoma, and she recently traveled to South America) and key signs and symptoms (i.e., finding of bilateral pulmonary nodules, hilar and mediastinal lymphadenopathy, and left upper lobe infiltrate without associated symptoms). Timing is also important, with key dates showing that the patient had completed pembrolizumab treatment 2 years before the current presentation and had not had lung disease or evidence of melanoma since that time.

ASSESSING PROBABILITIES OF DIAGNOSES

Ideally, once we have defined the problem representation, we should be able to translate the representation into probabilities of various diagnoses. Finding that information can be surprisingly challenging. Most clinical studies describe patients with a given diagnosis, thereby enabling the assessment of the probability that, for example, patients with sarcoidosis have hilar lymphadenopathy, but not the probability that patients with hilar lymphadenopathy have sarcoidosis. Useful information can sometimes be found in studies evaluating new diagnostic tests. Two studies that evaluated the use of endobronchial ultrasound-guided transbronchial needle aspiration in determining the underlying causes of hilar or mediastinal lymphadenopathy provide information about the final diagnoses of the patients.[1,2] In the two studies, the final diagnosis was reactive lymphadenopathy in 29% and 48% of the patients, sarcoidosis in 43% and 20%, carcinoma or lymphoma in 21% and 13%, and granulomatous infections (i.e., tuberculosis or fungus) in 5% and 18%. Reactive lymphadenopathy occurs when a patient has an underlying pulmonary process, such as chronic obstructive pulmonary disease, interstitial lung disease, or bronchiectasis, all of which are unlikely diagnoses in this patient, given her normal imaging studies before this presentation. Rare diseases that were diagnosed in these studies included silicosis, amyloidosis, and Castleman's disease.

Although the studies provide some sense of the relative likelihood of the various diagnoses, the probability of a particular diagnosis in this patient depends on the specifics of her presentation. One of the two studies provides information about the characteristics of the patients, according to diagnosis.[2] For example, all the patients who had carcinoma had symptoms at presentation — most commonly, weight loss (86%). In contrast, only 75% of the patients with sarcoidosis had symptoms on presentation. This information can be used to determine the probability of a specific diagnosis given this patient's problem representation. For example, when the absence of weight loss at presentation is included in the calculation for probability, the result is a 97% chance that the lymphadenopathy is not a

manifestation of cancer, information that is greatly reassuring in this patient with a history of metastatic melanoma. Interestingly, the presence of both hilar and mediastinal lymphadenopathy has little effect on the probabilities of the various diagnoses. Although lymphadenopathy is always seen in patients with sarcoidosis, it is also relatively common in patients with other diagnoses. On the basis of this information, the likelihood that the lymphadenopathy represents reactive lymphadenopathy or cancer is low, leaving sarcoidosis and granulomatous infection as the most likely diagnoses in this case.

Distinguishing between sarcoidosis and a granulomatous infectious process can be challenging, since they are driven by a similar immune reaction to one or more antigens. The challenge may be particularly great in this patient, given the previous treatment with pembrolizumab, a programmed death 1 (PD-1) inhibitor.[3] PD-1 inhibitors prevent down-regulation of the immune response, particularly the activation of CD4+ and CD8+ T cells, enabling an immune response against cells that express PD-1 ligands, with the primary target being cells from tumors such as melanoma. However, PD-1 inhibition is also associated with an array of autoimmune syndromes in which activated T cells attack normal cells.[4] These syndromes can affect almost any organ and may explain the development of hypothyroidism and tenosynovitis in this patient. Notably, the use of pembrolizumab has been associated with a sarcoidosis-like syndrome with bilateral hilar and mediastinal lymphadenopathy and the finding of noncaseating granulomas on biopsy of lymphoid tissue.[5,6] Few patients in whom the sarcoidosis-like syndrome was reported had pulmonary nodules or parenchymal involvement, but approximately one third had cutaneous manifestations. Nearly all these autoimmune syndromes were reported to have developed while the patients were receiving pembrolizumab treatment, with the caveat that available follow-up data after treatment remained limited; in one patient, cutaneous sarcoidosis was reported to have developed months after treatment ended. Given that there were 2 years between the time of this patient's presentation and the last dose of PD-1 inhibitor therapy, a sarcoidosis-like syndrome associated with a PD-1 inhibitor is unlikely.

If this patient's presentation is unlikely to represent an autoimmune complication of PD-1 inhibitor therapy, then a granulomatous infection becomes a more likely diagnosis. The most common pulmonary infections that are manifested by hilar and mediastinal lymphadenopathy are tuberculosis and fungal infections, primarily coccidioidomycosis and histoplasmosis and, less commonly, blastomycosis and cryptococcal disease. Pulmonary infiltrates with lymphadenopathy are commonly seen with primary tuberculosis but not with reactivation of the disease. However, primary tuberculosis is uncommon in immunocompetent adults and generally manifests with cough, fever, and fatigue. Furthermore, given the patient's negative interferon-γ release assay for tuberculosis, the probability of this diagnosis is low.

Both coccidioidomycosis and histoplasmosis can be manifested by pulmonary infiltrates, nodules, and lymphadenopathy in immunocompetent hosts.[7,8] With both infections, pulmonary nodules can have ground-glass halos on CT — a finding associated with an adjacent area of hemorrhage or tissue injury. However, a halo sign occurs with other conditions, and information about its predictive ability is hard to find. Patients who have either coccidioidomycosis or histoplasmosis are usually asymptomatic, but 40% of patients with coccidioidomycosis have an influenza-like illness with fever, cough, and fatigue. Distinguishing between these infections often depends on a patient's history of exposure. Exposure to the fungi that cause either infection is unlikely in the northeastern region of the United States, making this patient's trip to South America her most likely source of exposure — a hypothesis that is supported by the presence of the concomitant mild febrile illnesses of her family members. Histoplasmosis is far more common than coccidioidomycosis in that region.[9] A negative 1,3-β-D-glucan test lowers the probability of both diagnoses but does not rule out either one.[10] Thus, histoplasmosis becomes the most likely diagnosis in this case.

In the end, the decision is not which diagnosis is correct but whether further diagnostic testing is needed and, if so, which tests should be done. In this case, considerable diagnostic uncertainty remains, in part because the effect of previous PD-1 inhibitor treatment on subsequent immune responses is largely unknown. Possible diagnostic tests include measurement of the

blood level of angiotensin-converting enzyme (ACE), assays for fungal antigens and antibodies, and a biopsy of the lymphadenopathy, probably with the use of endobronchial ultrasound-guided transbronchial needle aspiration, given its greater yield than traditional transbronchial needle aspiration. Although ACE testing has limited predictive ability, it could be considered, since it is safe, has a low cost, and, if the result is normal, lowers the probability that the diagnosis is sarcoidosis.[11] Histoplasma antigen testing is helpful in both ruling out and confirming histoplasmosis with clinically significant disease, is safe and inexpensive, and should be performed in this case.[10] If histoplasma antigen testing is unrevealing or if diagnostic uncertainty remains after these tests, a biopsy should be performed.

CLINICAL IMPRESSION

Dr. Cohen: Given the aggressive nature of this patient's melanoma and her high nodal burden of disease before surgery, as well as extranodal extension, I was most concerned about recurrence of metastatic disease. Alternatively, late immune-related adverse effects from immunotherapy were a consideration, but this patient's clinical course did not reflect the typical pattern of immune-related pneumonitis. She underwent an extensive workup for infectious causes because of her recent travel to South America, and while waiting for those results, she underwent a bronchoscopy.

CLINICAL DIAGNOSIS

Metastatic melanoma.

DR. KATRINA A. ARMSTRONG'S DIAGNOSIS

Histoplasmosis.

INTERVENTIONAL PULMONARY APPROACH

Dr. Erik E. Folch: In cases such as this one, in which enlarged mediastinal and hilar lymph nodes are present, as well as multiple peripheral lung lesions, we favor diagnostic approaches that provide access to both the mediastinum and the lung parenchyma. Ideally, we would obtain adequate tissue for histopathological and microbiologic analysis during the same episode of anesthesia. Initially, we considered accessing the mediastinal and hilar lymph nodes by means of linear endobronchial ultrasonography, followed by the use of electromagnetic navigation bronchoscopy or robotic bronchoscopy to access the parenchymal pulmonary nodules. However, during a careful review of this patient's imaging studies, we identified parenchymal lesions amenable to esophageal access by means of endoscopic ultrasonography and by endoscopic ultrasonography with a bronchoscope. We presumed that the lymphadenopathy and the pulmonary nodules were probably caused by the same process, but the diagnostic yield of infection is not as high as that of cancer.[12]

We performed a flexible bronchoscopy with endobronchial ultrasound-guided transbronchial needle aspiration of the lymph nodes in the mediastinum and hila (stations 11R, 7, and 11L) (Fig. 3). The rapid on-site evaluation of the specimens revealed no cancer cells, so we proceeded with obtaining parenchymal lung-biopsy specimens through the esophagus. We used endoscopic ultrasonography with a bronchoscope to obtain a biopsy specimen of the pulmonary nodule that had been noted in the right lower lobe near the esophagus (Fig. 3).

PATHOLOGICAL DISCUSSION

Dr. Jonathan A. Stefely: Histologic examination of the lung-biopsy specimen revealed a granulomatous cellular infiltrate (Fig. 4A). This finding could suggest metastatic melanoma, given the patient's history and the diverse histologic appearances of this disease. However, on immunohistochemical analysis, the lung-biopsy specimen did not show the melanoma markers HMB45 and S100.

The lymph node–biopsy specimen also contained numerous granulomas (Fig. 4B), a nonspecific finding that can indicate infection, autoimmune disease, or cancer. In this case, the presence of focal necrosis increased suspicion for infection. A stain for acid-fast bacteria showed no mycobacteria. However, Gomori methenamine silver staining highlighted numerous yeast cells, measuring 2 to 4 μm in diameter, with narrow-based budding (Fig. 4C), which could

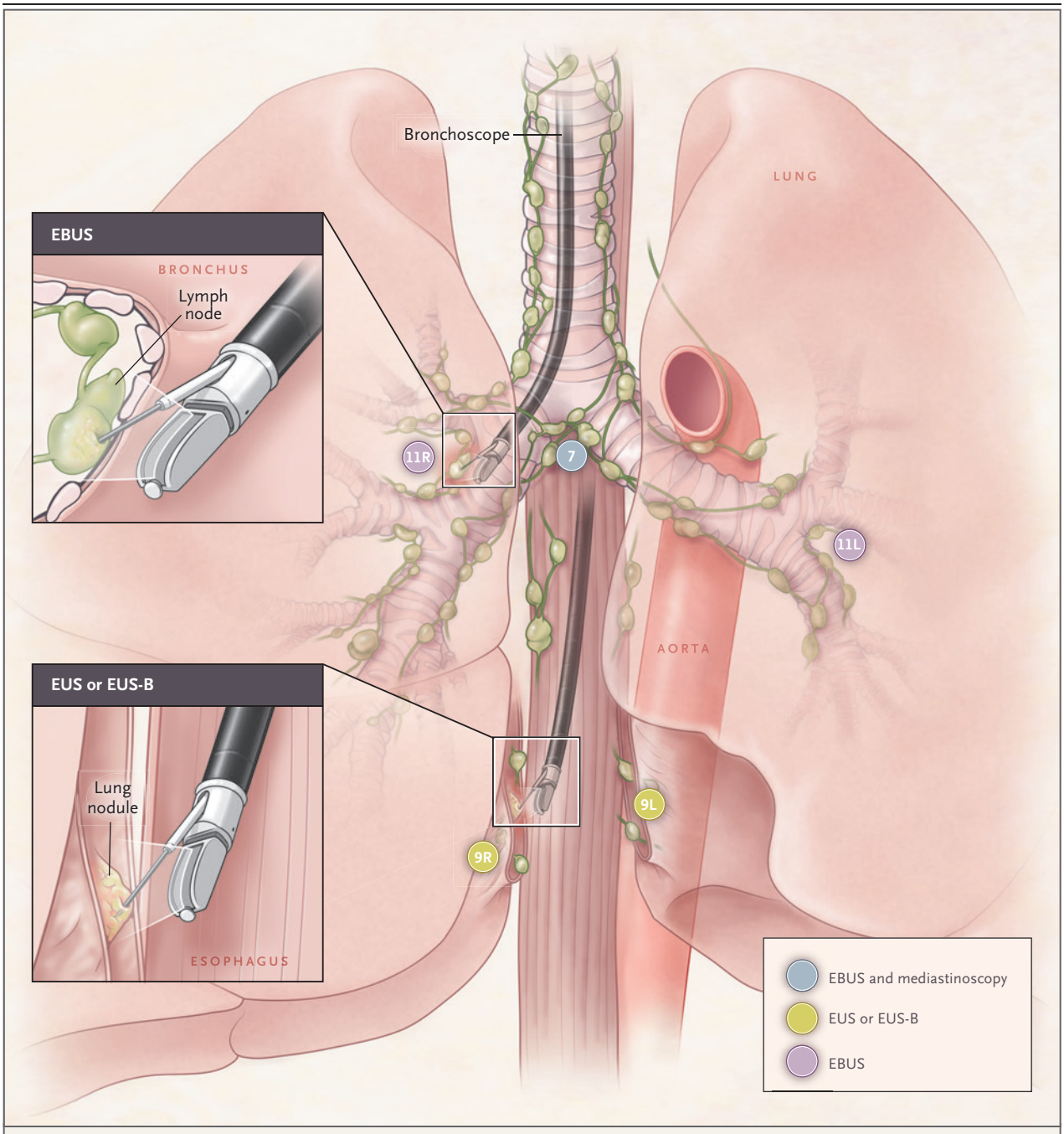

Figure 3. Interventional Diagnostic Strategies.

Mediastinal and hilar lymph nodes can be accessed by means of a variety of procedures, including endobronchial ultrasonography (EBUS), endoscopic ultrasonography (EUS), and mediastinoscopy. In this case, lymph nodes at stations 11R, 7, and 11L were accessed by means of EBUS, and a pulmonary nodule in the right lower lobe near the pulmonary ligament (9R) was accessed through the esophagus by means of endoscopic ultrasonography with a bronchoscope (EUS-B). The insets show the manner in which EBUS, EUS, or EUS-B can be used to sample structures that are in proximity to the wall of the trachea, bronchi, or esophagus with real-time ultrasound guidance.

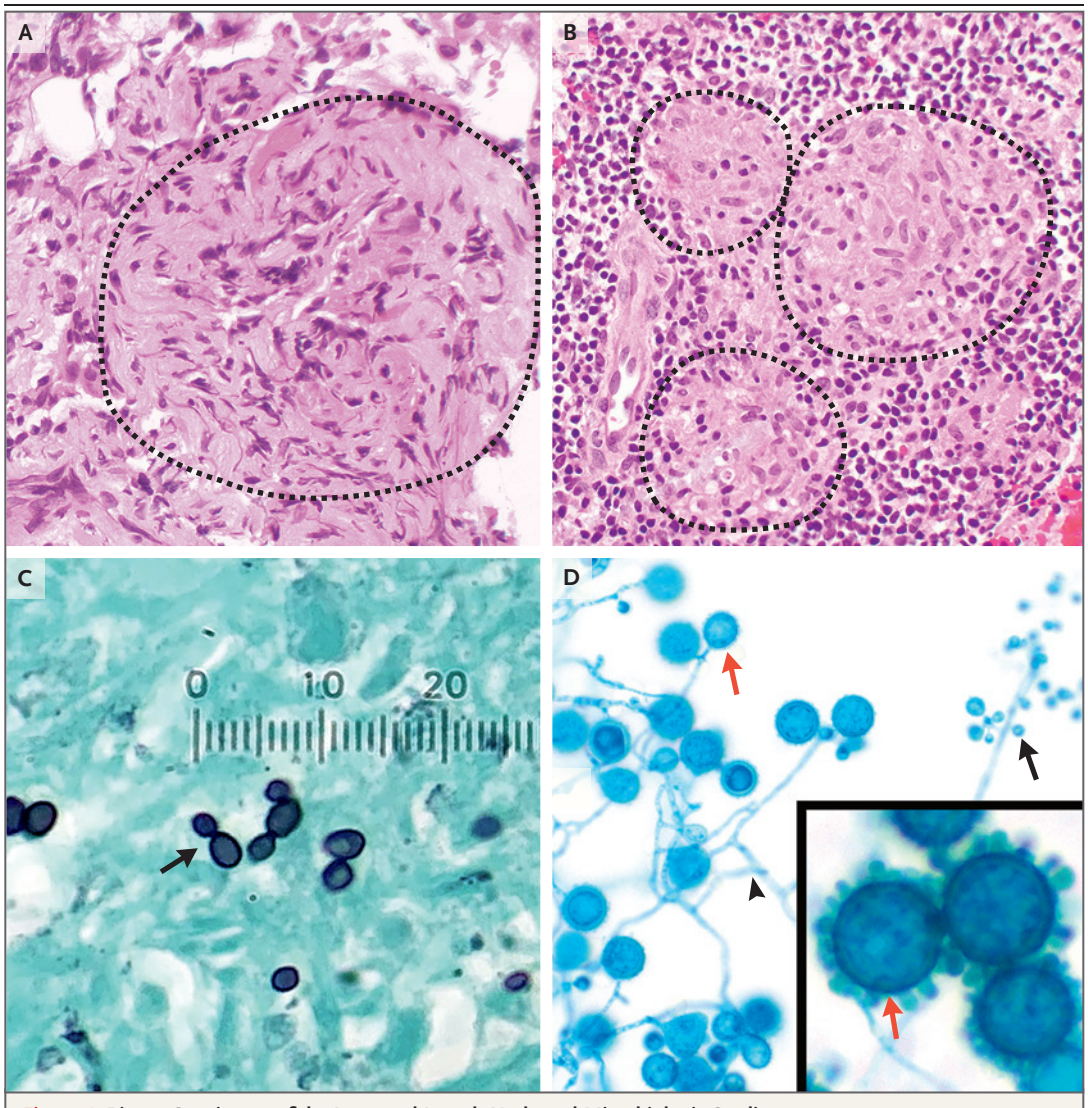

Figure 4. Biopsy Specimens of the Lung and Lymph Node and Microbiologic Studies.

Hematoxylin and eosin staining of biopsy specimens of the lung (Panel A) and the lymph node (Panel B) shows granulomas (outlined by dashed lines). Gomori methenamine silver staining of the lymph-node specimen (Panel C) highlights yeast cells, measuring 2 to 4 μm in diameter, with narrow-based budding (arrow; micrometer ruler units). Lactophenol cotton-blue staining of the cultured mold (Panel D) shows slender septate hyphae (arrowhead), microconidia (black arrow), and conidia (red arrow); the inset shows a magnified view of conidia with characteristic tubercles (protrusions).

represent either *Candida glabrata*[13] or *Histoplasma capsulatum*.[14]

A microbiologic evaluation performed in parallel revealed growth of a tan-white mold after 12 days of incubation at 30°C. Microscopic examination with lactophenol cotton-blue stain showed slender septate hyphae, microconidia, and conidia with characteristic protrusions called tubercles that lend a flower-like appearance (Fig. 4D). Notably, this mold grew from a tissue specimen containing yeast, indicating that it was a dimorphic fungus. Dimorphic fungi include *H. capsulatum*, *Blastomyces dermatitidis*, *Sporothrix schenckii*, coccidioides species, *Paracoccidioides brasil-*

iensis, and *Penicillium marneffei*, with *H. capsulatum* being the most likely in this case, given its 2-to-4-μm size. Additional molecular testing with a chemiluminescent DNA probe that targets *H. capsulatum* ribosomal RNA was positive. In isolation, this finding could indicate either of two variants — *H. capsulatum* var. *capsulatum* or *H. capsulatum* var. *duboisii* — but *H. capsulatum* var. *duboisii* is found only in Africa and those cells typically measure 6 to 12 μm in diameter.[15] Taken together, the findings indicate infection by *H. capsulatum* var. *capsulatum*. In addition, a blood test for histoplasma antigen, an indirect marker of histoplasmosis burden, was low-positive (i.e., the antigen was detectable but below the limit of quantification).

PATHOLOGICAL DIAGNOSIS

Histoplasma capsulatum var. *capsulatum* infection.

DISCUSSION OF MANAGEMENT

Dr. Michael K. Mansour: The first question we considered in the management of this patient's condition was whether antifungal therapy was warranted. The clinical manifestations of *H. capsulatum* infection can be quite varied, and symptoms can include fever, anorexia, and cough. Patients can present with acute pulmonary infection, chronic disease, or pulmonary cavitation. That said, this patient was completely asymptomatic. Clinically, her exercise tolerance was excellent, her weight was stable, and she had no pulmonary symptoms whatsoever. Laboratory evaluation was normal, with no evidence of end-organ involvement.

Although the patient's test for histoplasma antigen was positive, studies that have evaluated the natural course of this fungal marker indicate a very slow decline in the level over time, suggesting a long half-life that may require several months to become undetectable.[16,17] Despite these observations, one may argue that this patient should be treated conservatively with itraconazole for the possibility of invasive *H. capsulatum* infection. Although it is standard practice to carefully monitor for azole-related side effects, complications associated with the use of this antifungal drug can still occur. In an initial study of itraconazole, gastrointestinal disturbance, blood abnormalities, and hepatitis developed in approximately one third of the patients.[18]

After extensive discussion with the patient, and because of the possibility of drug-related toxic effects, the decision was made to observe this patient without administration of antifungal treatment. Currently, 8 months after the initial imaging studies were performed, she is doing well and has no evidence of active fungal disease. If relapse or worsening disease develops, or if there is an anticipated need for additional immunomodulating therapy, we will reconsider the risks and benefits of initiating antifungal therapy.

Dr. Shepard: One month after the patient's presentation, follow-up CT of the chest revealed that the hilar and mediastinal lymphadenopathy had resolved, and a radiographically significant decrease in both the degree of consolidation in the left upper lobe and the size and number of bilateral pulmonary nodules was observed.

PATIENT PERSPECTIVE

The Patient: I had my routine surveillance scans on a Monday, and I was supposed to see Dr. Cohen on Thursday, but she called on Tuesday. When her number appeared on my phone, I knew something was wrong. She immediately said to me, "How are you feeling? Are you okay? Do you have a cough? Do you feel sick? Do you have a fever?" And I said, "No, I feel great. I feel awesome."

She then went on to ask me a bunch of questions about where I had traveled and whether I had eaten water chestnuts and all sorts of crazy things. She explained that my scans showed multiple nodules on my lungs, and there was concern about whether this was recurrent melanoma or whether it was a fungal infection, which is what one radiologist thought it could be. So, they were exploring these options, since recurrent cancer would be horrible. That was the nature of our initial conversation, and then it took some time before I had my bronchoscopy and then got the results, which showed histoplasmosis.

At that point, Dr. Cohen called and said, "I never thought I'd be so happy to tell a patient that they have a fungal infection." When we discussed starting itraconazole, I remembered that I have a friend whose daughter had been taking itraconazole for cystic fibrosis, and she had had bad reactions involving her liver and other bad side effects. I didn't want to put something into my body that I didn't have to, especially after having

already gone through radiation and a year of pembrolizumab treatment and getting scans every 3 months. Then I wanted to know more about histoplasmosis, so I went online and started reading about it — things like what happens if it disseminates to the various organs and the death rate.

What had the biggest impression on me was that I had been in South America with several friends and family members, and the only reason I found out about the histoplasmosis was because I get scans every few months for melanoma surveillance. Otherwise, because I was asymptomatic, nobody would have ever known I had histoplasmosis. That was my argument: "Okay, I don't have any symptoms, and it's obviously not disseminating at this point. Let's see if it starts to resolve itself," which happens in a lot of patients. So, that was my argument for not wanting to have treatment.

FINAL DIAGNOSIS

Pulmonary histoplasmosis.

This case was presented at the Medicine Case Conference.

Dr. Cohen reports receiving consulting fees from Sanofi Genzyme and Bristol-Myers Squibb; Dr. Folch, receiving grant support from Intuitive Surgical and consulting fees from Medtronic, Boston Scientific, and Cook Medical; and Dr. Mansour, receiving consulting fees from Vericel, SmartPharm Therapeutics, Pulsethera, GenMark Diagnostics, and Global Life Sciences, grant support from Thermo Fisher Scientific, advisory board fees from Celularity, and holding a pending patent (15/999,463) on cellular therapy for infections. No other 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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