Case Presentation. A 69-year-old veteran presented with an intermittent, waxing and waning cough. He had never smoked and had no family history of lung cancer. His primary care physician ordered a chest radiograph, which revealed a nodular opacity within the lingula concerning for a parenchymal nodule. Further characterization with a chest computed tomography (CT) demonstrated a 1.4-cm left upper lobe subpleural nodule with small satellite nodules (Figure 1). Given these imaging findings, the patient was referred to the pulmonary clinic.

Lauren Kearney, MD, Medical Resident, VA Boston Healthcare System (VABHS) and Boston Medical Center. What is the differential diagnosis of a solitary pulmonary nodule? What characteristics of the nodule do you consider to differentiate these diagnoses?

Renda Wiener, MD, Pulmonary and Critical Care, VABHS, and Assistant Professor of Medicine, Boston University School of Medicine. Pulmonary nodules are well-defined lesions < 3 cm in diameter that are surrounded by lung parenchyma. Although cancer is a possibility (including primary lung cancers, metastatic cancers, or carcinoid tumors), most small nodules do not turn out to be malignant. Benign etiologies include infections, benign tumors, vascular malformations, and inflammatory conditions. Infectious causes of nodules are often granulomatous in nature, including fungi, Mycobacterium tuberculosis, and nontuberculous mycobacteria. Benign tumors are most commonly hamartomas, and these may be clearly distinguished based on imaging characteristics. Pulmonary arteriovenous malformations, hematomas, and infarcts may present as nodules as well. Inflammatory causes of nodules are important and relatively common, including granulomatosis with polyangiitis, rheumatoid arthritis, sarcoidosis, amyloidosis, and rounded atelectasis.

To distinguish benign from malignant etiologies, we look for several features of pulmonary nodules on imaging. Larger size, irregular borders, and upper lobe location all increase the likelihood of cancer, whereas solid attenuation and calcification make cancer less likely. One of the most reassuring findings that suggests a benign etiology is lack of growth over a period of surveillance; after 2 years without growth we typically consider a nodule benign. And of course, we also consider the patient’s symptoms and risk factors: weight loss, hemoptysis, a history of cigarette smoking or asbestos exposure, or family history of cancer all increase the likelihood of malignancy.

Dr. Kearney. Given that the differential diagnosis is so broad, how do you think about the next step in evaluating a pulmonary nodule? How do you approach shared decision making with the patient?

Dr. Wiener. The characteristics of the patient, the nodule, and the circumstances in which the nodule were discovered are all important to consider. Incidental pulmonary nodules are often found on chest imaging. The imaging characteristics of the nodule are important, as are the patient’s risk factors. A similarly appearing nodule can have very different implications if the patient is a never-smoker exposed to endemic fungi, or a long-time smoker enrolled in a lung cancer screening program. Consultation with a pulmonologist is often appropriate.

It’s important to note that we lack high-quality evidence on the optimal strategy to evaluate pulmonary nodules, and there is no single “right answer” for all patients. For patients with a low risk of malignancy (< 5%-10%)—which comprises the majority of cases—surveillance is appropriate. For higher-risk patients, more aggressive evaluation may be necessary.
of the incidental nodules discovered—we typically favor serial CT surveillance of the nodule over a period of a few years, whereas for patients at high risk of malignancy (> 65%), we favor early surgical resection if the patient is able to tolerate that. For patients with an intermediate risk of malignancy (~5%-65%), we might consider serial CT surveillance, positron emission tomography (PET) scan, or biopsy. The American College of Chest Physicians guidelines for pulmonary nodule evaluation recommend discussing with patients the different options and the trade-offs of these options in a shared decision-making process.

Dr. Kearney. The patient’s pulmonologist laid out options, including monitoring with serial CT scans, obtaining a PET scan, performing CT-guided needle biopsy, or referring for surgical excision. In this case, the patient elected to undergo CT-guided needle biopsy. Dr. Huang, can you discuss the pathology results?

Qin Huang, MD, Pathology and Laboratory Medicine, VABHS, and Assistant Professor of Pathology, Harvard Medical School (HMS). The microscopic examination of the needle biopsy of the lung masses revealed rare clusters of atypical cells with crushed cells adjacent to an extensive area of necrosis with scarring. The atypical cells were suspicious for carcinoma. The Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) stains were negative for common bacterial and fungal microorganisms.

Dr. Kearney. The tumor board, pulmonologist, and patient decide to move forward with video-assisted excisional biopsy with lymphadenectomy. Dr. Huang, can you interpret the pathology?

Dr. Huang. Figure 2 showed an hematoxylin and eosin (H&E)-stained lung resection tissue section with multiple caseating necrotic granulomas. No foreign bodies were identified. There was no evidence of malignancy. The GMS stain revealed a fungal microorganism oval with morphology typical of *Histoplasma capsulatum* (Figure 3).

Dr. Kearney. What are some of the different ways histoplasmosis can present? Which of these diagnoses fits this patient’s presentation?

Judy Strymish, MD, Infectious Disease, VABHS, and Assistant Professor of Medicine, HMS. Most patients who inhale histoplasmosis spores develop asymptomatic or self-limited infection that is usually not detected. Patients at risk of symptomatic and clinically relevant disease include those who are immunocompromised, at extremes of ages, or exposed to larger inoculums. Acute pulmonary histoplasmosis can present with cough, shortness of breath, fever, chills, and less commonly, rheumatologic complaints such as erythema nodosum or erythema multiforme. Imaging often shows patchy infiltrates and enlarged
Clinical Takeaways

• Most solitary pulmonary nodules are not malignant. The differential diagnosis for solitary pulmonary lesions includes infections, benign tumors, vascular malformations, and inflammatory conditions. Several features of pulmonary nodules on imaging can indicate increased likelihood of benign or malignant etiologies.
• There is no single right way to work up a solitary pulmonary nodule. The evaluation can vary from surveillance imaging to invasive diagnostic procedures. Discussion with patients regarding the benefits and risks of these options in a shared decision-making process is vital.
• Histoplasmosis can take a variety of forms, including asymptomatic self-limited infection, acute pulmonary infection, subacute or chronic pulmonary disease, or progressive disseminated disease. This depends largely on the characteristics of the host. For patients with solitary histoplasmosma and a normal immune system, treatment with antifungal therapy is often not required.
• Open and honest communication between physicians and patients is of paramount importance. The workup of solitary pulmonary nodules includes discussion of possible etiologies, including malignancy and approach to evaluation.

IUDS are the most common cause of deaths in women aged 15-44 due to complications of induced abortion. This is true for women in the United States and in many developing countries. The vast majority of these deaths occur in developing countries, where access to safe abortion services is limited. The ratio of deaths from abortion complications to deaths from all causes in women aged 15-44 is highest in Africa and the Eastern Mediterranean region. The ratio is lowest in North America, Europe, and Australia. The United States has the second highest ratio of deaths from abortion complications to deaths from all causes in women aged 15-44. The ratio is highest in the United States and in many developing countries, where access to safe abortion services is limited. The ratio is lowest in North America, Europe, and Australia. The United States has the second highest ratio of deaths from abortion complications to deaths from all causes in women aged 15-44. The ratio is highest in the United States. The ratio is lowest in North America, Europe, and Australia.

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distress during the period of radiographic surveillance. Reassuringly, high-quality patient-clinician communication was associated with lower distress and higher adherence to pulmonary nodule evaluation.4

Dr. Kearney. The patient was educated about his diagnosis of solitary histoplasmosa. Given that the patient was otherwise well appearing with no complicating factors, he was not treated with antifungal therapy. After an 8-month-long workup, the patient was relieved to receive a diagnosis that excluded cancer and did not require any further treatment. His case provides a good example of how to proceed in the workup of a solitary pulmonary nodule and on the importance of communication and shared decision making with our patients.

Author disclosures
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Disclaimer
All patients or their surrogate decision makers understand and have signed appropriate patient release forms. This article has received an abbreviated peer review.

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References