A Recurrent Problem

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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 50-year-old woman from Texas had nasal stuffiness, postnasal drip, myalgias, cough, and hoarseness in early winter. She attributed her symptoms to “cedar fever,” a common environmental allergic reaction in Texas, which she had every winter for 3 to 6 weeks. The nasal stuffiness, postnasal drip, and myalgias had resolved within 6 weeks, but the nonproductive cough and hoarseness persisted. She reported no fever, chills, night sweats, joint pain, weight loss, nausea, vomiting, abdominal pain, chest pain, or rash. She also reported no contact with sick people.

The initial symptoms are characteristic of a viral upper respiratory tract infection, although 6 weeks of persistent symptoms is unusual. Hoarseness is commonly caused by acute laryngitis due to upper respiratory infection or vocal overuse, both of which are self-limited. Ongoing hoarseness suggests gastroesophageal reflux disease, chronic vocal overuse, tobacco exposure, benign vocal-fold nodules, hypothyroidism, or laryngeal carcinoma. Less common causes include recurrent-laryngeal-nerve injury and infiltrative diseases such as amyloidosis or sarcoidosis. After a targeted history taking and physical examination, direct visualization of the larynx by an otolaryngologist is often necessary. Chronic cough has a broad differential diagnosis, including tobacco smoking, use of angiotensin-converting–enzyme inhibitors, postnasal drip, gastroesophageal reflux disease, and reactive airway disease. The combination of cough and hoarseness brings to mind conditions characterized by both laryngotracheal and pulmonary involvement, including recurrent aspiration, squamous-cell carcinoma, tuberculosis, fungal infections (e.g., coccidioidomycosis or histoplasmosis), and inflammatory conditions such as Wegener’s granulomatosis.

The patient had been in excellent health. Her medical history included a benign mass in the left breast 2 years earlier, mitral-valve prolapse, and osteoarthritis of the cervical spine (C5 level). Her medications included a dehydroepiandrosterone (DHEA) supplement, calcium carbonate, and vitamin D. She had consumed two alcoholic drinks per day for years and had never smoked cigarettes. There was a family history of pancreatic cancer, melanoma, and colon cancer. Within the past 3 years, she had vacationed in the British Virgin Islands and had traveled to nearly every state in the contiguous United States as part of her marketing job.

The presence of mitral-valve disease raises the remote possibility of enlargement of the left atrium, leading to compression of the recurrent laryngeal nerve. Sustained alcohol consumption and the family history of cancer raise concern about laryngeal carcinoma or an intrathoracic cancer involving the recurrent laryngeal nerve. The patient’s extensive travel suggests the possibility of an endemic fungal infection; tuberculosis is unlikely on the basis of the areas she has visited.
The patient described her voice as weak, breathy, and easily fatigued, and noted difficulty speaking over background noise. She was not aware of any aggravating or relieving factors. The hoarseness was constant throughout the day and was not associated with pain. She adapted to initial episodes of choking while swallowing by taking more time to eat and drink. Her husband, an otorhinolaryngologist, performed flexible laryngoscopy and noted paralysis of the left vocal cord. Computed tomography (CT) of the neck, abdomen, and pelvis showed no abnormalities. CT of the chest revealed a 10-mm spiculated nodule in the medial segment of the left upper lobe (Fig. 1). No mediastinal or hilar adenopathy was noted. The patient was referred to a tertiary medical center for further evaluation.

Breathiness suggests excessive air escaping between incompletely apposed vocal cords. Vocal-cord paralysis raises the possibility that the spiculated mass in the lung may be impinging on or invading the recurrent laryngeal nerve (a branch of the vagus nerve). The cause of the lung mass in a nonsmoker could be primary or metastatic cancer, granuloma, or hamartoma. Although imaging did not reveal a primary visceral cancer that may metastasize to the lung (e.g., colon or renal cancer), a careful examination is required to rule out other cancers with a predilection for lung metastases, including breast cancer, melanoma, and sarcoma. Infections or cancers that involve the skull base and cervical spine should also be considered.

The patient was seen by an otorhinolaryngologist at the referral center for persistent hoarseness and nonproductive cough. There was no history of ear discharge, hearing problems, balance abnormalities, or tinnitus. She reported no rhinorrhea, sneezing, sore throat, difficult or painful swallowing, heartburn, stridor, hemoptysis, or shortness of breath. There was no history of thyroid disease or of exposure to tuberculosis.

The patient appeared well. The temperature was 36.4°C, the heart rate 84 beats per minute, the blood pressure 112/62 mm Hg, and the respiratory rate 18 breaths per minute. Her head and neck examination was normal. Her voice was breathy and weak. There was no cervical or supraclavicular lymphadenopathy, thyromegaly, or neck mass. Cardiac, respiratory, abdominal, and neurologic examinations were normal.

Flexible videolaryngoscopy revealed normal-appearing vocal cords without any lesions, atrophy, or inflammation. However, abduction and adduction of the left vocal cord was severely diminished, confirming paralysis. The epiglottis, false vocal cords, and aryepiglottic folds were normal; there was no pooling of secretions in the hypopharynx (see the video, available with the full text of this article at NEJM.org).

The patient was also seen by an oncologist. Her general physical examination was unchanged. The white-cell count was 6400 per cubic millimeter, with 64% neutrophils, 25% lymphocytes, 5% monocytes, 4% eosinophils, and 2% basophils. The hemoglobin level was 13.1 g per deciliter, and the platelet count was 279,000 per cubic millimeter. Serum electrolyte, blood urea nitrogen, serum creatinine, liver enzyme, serum bilirubin, and lactate dehydrogenase levels were all normal. Measurements of serum tumor markers (CA 27-29 and carcinoembryonic antigen) were normal. Positron-emission tomography–computed tomography (PET-CT) from the skull base to midtigh revealed asymmetric uptake in the right vocal cord, which was consistent with paralysis of the left vocal cord (i.e., an overworked right vocal cord). Enhanced uptake was also noted in a 10-mm nodule in the left upper lobe of the lung (standardized uptake value, 4.3) and in an adjacent 8-mm mediastinal lymph node in the aortopulmonary window.
When a lung nodule is present, the focus of the physical examination is to uncover evidence of a systemic disease or to find any potential site for culture or biopsy that might avert more invasive pulmonary sampling. Neither was found. At this point, the findings are compatible with an infection (e.g., tuberculosis or fungal infection), a malignant condition (e.g., pulmonary adenocarcinoma), or an inflammatory process (e.g., sarcoidosis). The hypermetabolic activity on PET scanning is compatible with any of these processes. Measurements of tumor markers are not recommended in the diagnostic evaluation of a solitary pulmonary nodule and are not helpful in this case.

A diagnosis of pulmonary neoplasm with mediastinal lymph-node metastasis, involvement of the left recurrent laryngeal nerve, and vocal-cord paralysis was suspected. Magnetic resonance imaging of the breasts revealed no evidence of tumor. Colonoscopy performed 5 years earlier had shown no abnormalities. A pulmonologist prescribed a 2-week course of oral moxifloxacin for possible pulmonary infection. A tuberculin skin test was negative.

Because the clinical course and imaging studies appear to be inconsistent with bacterial infection, antibiotic therapy seems unnecessary. Furthermore, antituberculous activity of quinolones can render subsequent mycobacterial cultures falsely negative. Sputum culture for fungal and mycobacterial pathogens would have been indicated before antibiotic therapy was initiated.

Moxifloxacin therapy had no effect on the patient’s symptoms. On repeat CT of the chest 3 weeks later, the nodule in the left upper lobe had increased to 22 mm, with adjacent ground-glass opacification; the lymph node in the aortopulmonary window had enlarged to 12 mm (Fig. 2). A new 6-mm superior mediastinal lymph node and three new lung nodules (<5 mm) were identified in the left apex, left lower lobe, and right lower lobe.

The rapid growth of the initial nodule (which doubled in size in 3 weeks) is compatible with a high-grade lymphoma. The imaging characteristics of pulmonary lymphomas are varied, but spiculated masses are uncommon. Small-cell lung cancer could grow this fast but is less likely in a non-smoker than in a smoker. An occult intraabdominal cancer that was not detected on the initial CT scan with pulmonary metastases should also be considered. Since multiple pulmonary nodules have developed, endocarditis with septic emboli warrants consideration, although other clinical features of endocarditis are absent. Infections caused by parasites that migrate to the lung, such as *Strongyloides stercoralis* or *Ascaris lumbricoides*, can develop after travel to the tropics or certain regions of the United States; however, such an infection is unlikely in this case, given the radiologic findings and the absence of eosinophilia.

After 3 months of progressive pulmonary nodular disease with lymphadenopathy, the absence of systemic symptoms or disease outside the lungs...
is surprising. Metastatic melanoma and carcinoma of unknown primary origin are possibilities. Progressive pulmonary fungal infection, such as histoplasmosis, can mimic carcinoma and may be clinically silent.

Patients with lymphoma or sarcoidosis may present with radiographic evidence of disease in the absence of symptoms. However, the predominance of nodules over lymphadenopathy is atypical for both disorders, and the rapid growth of the nodules is uncharacteristic of sarcoidosis.

The patient underwent a CT-guided percutaneous biopsy of the enlarging nodule in the left upper lobe of the lung. Histopathological examination revealed spherules that were consistent with coccidioides species (Fig. 3) and focal organizing pneumonia with eosinophilia. There was no evidence of cancer.

If the patient lives in west Texas, she may have acquired locally endemic coccidioidomycosis. It would be of interest to learn where she traveled, particularly whether she was in areas where coccidioidomycosis is hyperendemic, such as Arizona. Compression of the recurrent laryngeal nerve by a lymph node or the primary nodule is probably responsible for the unilateral vocal-cord paralysis.

The patient was referred to a specialist in infectious diseases. The serum coccidioides complement-fixation antibody titer was negative. Fluconazole at a dose of 400 mg daily was prescribed. A chest CT scan obtained 3 weeks later revealed shrinkage of the nodule in the left upper lobe and of the lymph node in the aortopulmonary window; the smaller lung nodules had resolved. Her cough subsided, the vocal-cord paralysis resolved, and her voice normalized 6 weeks after the start of fluconazole therapy. A chest CT scan obtained 3 months later revealed a stable, 15-mm nodule in the left upper lobe; mediastinal lymphadenopathy was no longer evident.

Persistent vocal-cord paralysis stemming from an enlarging pulmonary nodule and compressive mediastinal lymphadenopathy was the basis for antifungal therapy in this case.

Five months after the initiation of fluconazole therapy, the patient sought a second opinion from a specialist with expertise in coccidioidomycosis. She had traveled to Arizona several times over the past 5 years; her most recent trip was 4 weeks before the onset of symptoms. Serologic tests for coccidioidal antibodies revealed IgG and IgM antibodies on enzyme-linked immunoassay, whereas the results of complement-fixation and immunodiffusion assays were negative. Fluconazole was discontinued. At follow-up 10 months later, the patient remained asymptomatic, and repeat chest CT revealed further shrinkage of the nodule in the left upper lobe.

**Commentary**

Our patient presented with hoarseness, a common symptom with a wide range of causes, including local irritants (e.g., alcohol, tobacco, inhaled glucocorticoids, gastroesophageal reflux disease, voice overuse), aspiration, seasonal allergy, infections, neoplasms, neuromuscular disorders, vocal-cord trauma, and injury to the recurrent laryngeal nerve. The initial evaluation of hoarseness entails a thorough history taking, subjective assessment of voice quality, and a detailed physical examination with particular attention to the head and neck. Unexplained hoarseness lasting longer than 2 weeks necessitates a more detailed voice evaluation (e.g., pitch, degree of dysphonia, and quantification of vocal disability) and examination of the larynx by direct or indirect laryngoscopy. The larynx serves four important functions (breathing, swallowing, coughing, and phonation).
that require an intact recurrent laryngeal nerve.

The axons of the recurrent laryngeal nerve travel with the vagus nerve in the neck. In the superior mediastinum, the left recurrent laryngeal nerve loops around the aorta, ascends within the tracheoesophageal groove, and enters the larynx. The right recurrent laryngeal nerve loops around the right subclavian artery. Because the left recurrent laryngeal nerve has a longer intrathoracic course (Fig. 4), it is more susceptible to injury.\(^2,3\) Injury to or compression of the recurrent laryngeal nerve may result in vocal-cord paralysis (unilateral or bilateral) and temporary or permanent. Unilateral vocal-cord paralysis can cause dysphonia, breathy and low-pitched voice, vocal fatigue, dysphagia, and choking. With bilateral paralysis, phonation can be nearly normal; however, inspiratory stridor and complete respiratory obstruction may necessitate an emergency tracheotomy.\(^3\)

Paralysis of the recurrent laryngeal nerve may be caused by extrathoracic or intrathoracic processes. In the neck, thyroid surgery, anterior surgical approaches to the cervical spine, carotid endarterectomy, and skull-base operations are the most common causes of damage to the recurrent laryngeal nerve.\(^2\) Thyroid goiters, benign or malignant neoplasms (e.g., lymphomas or skull-base tumors), neurologic disorders, toxins, chemotherapeutic agents, radiation, viral infections, and endotracheal intubation can also damage this nerve.\(^2\) Approximately 15% of cases of paralysis of the recurrent laryngeal nerve are idiopathic.\(^2\)

Noninfectious intrathoracic causes of injury to the recurrent laryngeal nerve include lung and esophageal cancer, mediastinal metastases, lymphoma, sarcoidosis, silicosis, surgical procedures, and cardiovascular disorders (aortic-arch aneurysm, pulmonary hypertension, and mitral stenosis with left atrial dilatation [Ortner’s syndrome]).\(^5\) Tuberculosis is the most common intrathoracic infection causing paralysis of the recurrent laryngeal nerve (as a result of compression by mediastinal lymph nodes, or entrapment or traction due to apical fibrosis).\(^5,5\) Histoplasmosis, aspergillosis, mucormycosis, syphilitic aortitis, and salmonella-related mycotic aneurysm of the aorta have also been implicated.

Coccidioidomycosis (or valley fever) is a systemic mycosis that is endemic to the southwestern United States and parts of Central and South America. It results from inhaling the sporelike arthroconidia of *Coccidioides immitis* or *C. posadasii*. Sixty percent of patients with primary infection are asymptomatic; the rest have fever, night sweats, cough, pleuritic chest pain, arthralgias, rash, headache, or some combination of these symptoms 1 to 3 weeks after exposure. Primary coccidioidomycosis is manifested as consolidation, nodules, or opacities on chest imaging, with concurrent hilar adenopathy in up to 40% of patients.\(^7,8\) Mediastinal lymphadenopathy is less common.\(^8\) Dissemination occurs in about 1% of immunocompetent patients; the most common extrapulmonary sites are the meninges, skin, and skeletal system.\(^9\)

The diagnosis can be established by serologic tests, histopathological identification of characteristic spherules, or growth of coccidioides species in culture. In patients with solitary pulmonary nodules, culture of respiratory secretions has a low yield and is not recommended as the sole means of ruling out the diagnosis. The sensitivity of serologic testing for coccidioidomycosis depends on the length of time since primary infection, the immune status of the host, the extent of infection, and prior therapy.\(^10\) Among healthy, immunocompetent patients who underwent coccidioidal serologic testing within a year after the onset of symptoms, enzyme immunoassay was positive in 87%, complement-fixation assay in 75%, and immunodiffusion assay in 73%; at least one of these tests was positive in 95% of patients.\(^10\) Positive results of serologic tests may indicate recent or remote coccidioidomycosis (symptomatic or silent); tissue biopsy may still be necessary, particularly in patients who have risk factors for cancer.

Most patients with uncomplicated primary coccidioidomycosis do not require antifungal therapy; symptoms resolve spontaneously over a period of several weeks.\(^9\) Antifungal therapy is indicated in patients with disseminated disease, concurrent immunosuppression, or pregnant or postpartum status, as well as in older people and those with severe primary infection (as indicated by ongoing weight loss, persistent night sweats, infiltrates involving more than half of one lung or portions of both lungs, persistent lymphadenopathy, or a complement-fixation titer $\geq 1:16$).\(^9\) Antifungal therapy led to the resolution of vocal-cord paralysis in our patient.

Guidelines from the American College of Chest Physicians recommend PET scanning in patients with a low-to-moderate pretest probability of cancer and an indeterminate solitary nodule in the lung.\(^11\) Although a pulmonary-nodule doubling
Figure 4. Anatomical Relationships of the Recurrent Laryngeal Nerve.
The left recurrent laryngeal nerve loops around the aortic arch and has a longer intrathoracic course than does the right recurrent laryngeal nerve.
time of less than 3 weeks reduces the likelihood of cancer, a tissue diagnosis is still recommended for solitary nodules with clear evidence of growth. Even in areas where coccidioidomycosis is endemic, coccidioidal pulmonary nodules are often diagnosed by means of tissue biopsy or surgical excision because of the low sensitivity of serologic testing in patients with isolated nodules (38%) and the need to rule out cancer (which would be suggested by underlying risk factors, a history of cancer, or suspicious findings on CT or PET imaging). Empirical antibiotic therapy is strongly discouraged for patients with solitary pulmonary nodules.

Our patient probably acquired coccidioidomycosis during her trip to Arizona 4 weeks before the onset of symptoms. The overlap between her symptoms and those of cedar fever delayed the initial evaluation for persistent hoarseness. Suspicious abnormalities on chest imaging, paralysis of the recurrent laryngeal nerve, and the absence of systemic symptoms raised concern about cancer. During evaluation for suspected cancer, patients should be educated regarding the possibility of benign and less ominous diagnoses in order to mitigate undue stress and anxiety. Knowledge of the clinical and radiographic manifestations of endemic infections and careful attention to a travel history can facilitate timely diagnosis of geographically restricted illnesses.

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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REFERENCES