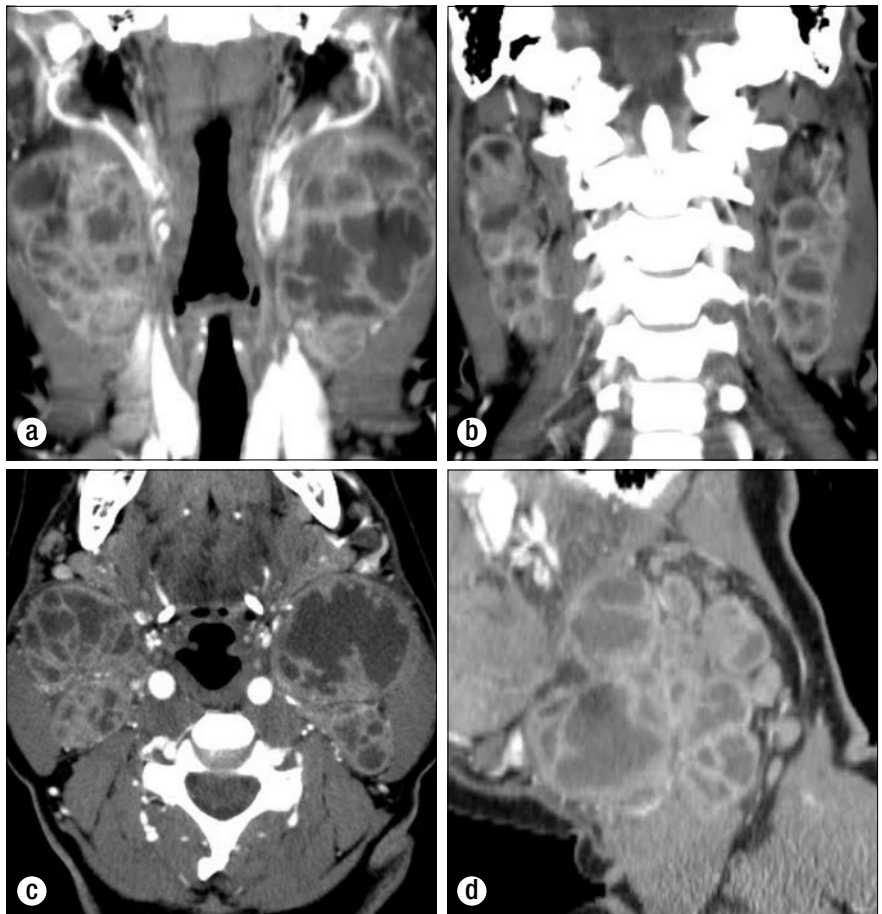


## Bilateral lymphadenopathy in a young woman

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A 20-year-old woman presented to the emergency department with bilateral tender neck masses that had been increasing in size for 2 months. Associated symptoms included weakness, headaches, neck pain, dysphagia, and left-sided earache. In the previous week, she had developed a cough productive of white sputum, chest pain, and shortness of breath. She denied fevers, night sweats, and myalgias but did have occasional chills. She had developed a rash on her arms and lower extremities 3 weeks prior, which was now resolving, and tingling in her feet. She had minimal weight loss secondary to decreased appetite over the previous few months. Several weeks prior to admission, she had been diagnosed with mumps. She was also given a 5-day course of azithromycin that did not alleviate her symptoms. She reported that 6 months earlier, her boyfriend and another good friend had been treated for tuberculosis, but she had not been tested. She received standard vaccinations as a child. She denied alcohol, tobacco, and intravenous drug use. Her family history was significant for lung cancer and thyroid disease. She had not recently traveled outside of the United States, and she had been exposed to dogs but not to cats.

Physical examination revealed a healthy appearing young woman with significant bilateral cervical lymphadenopathy that was tender to palpation. The skin over the masses was not discolored and did not have draining sinus tracts. Her oropharynx was clear and nonerythematous. Her lungs were clear. She had a resolving rash on her extremities. The remainder of her examination was normal. A posteroanterior and lateral chest radiograph revealed no abnormalities in her lungs. A computed tomography (CT) scan of the neck demonstrated large, bilateral, necrotic lymph nodes extending from the high to low internal jugular lymph node chains (*Figure*).



**Figure.** Contrast-enhanced CT images of the neck. **(a)** Coronal image demonstrating multiple large necrotic lymph nodes. **(b)** Coronal image at a more posterior level, showing involvement of nodes in levels 2 to 4. Nodes are centrally hypodense, representing necrosis, and enhance peripherally. **(c)** Axial image showing medial displacement of major vascular structures. **(d)** Sagittal reconstruction showing the confluent nature of the necrotic cervical lymphadenopathy.

*What are the differential diagnostic considerations? What is the most likely diagnosis? What tests can confirm the diagnosis?*

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**DIAGNOSIS:** Infectious cervical lymphadenitis, or scrofula, likely caused by *M. tuberculosis*.

The most likely etiology, considering exposures, age, and symptoms, was cervical tuberculous lymphadenitis, or scrofula. However, the broad differential diagnosis of enhancing cervical lymphadenopathy in an adult includes metastatic squamous cell carcinoma, metastatic papillary thyroid carcinoma, lymphoma, tuberculous and nontuberculous mycobacterial lymphadenitis, cat-scratch disease, Kaposi's sarcoma, AIDS-related lymphadenopathy, Kimura's disease, Castleman's disease, and Kikuchi's disease. Fungal and viral infections, such as Epstein-Barr virus, cytomegalovirus, and rubella, also may present with bilateral diffuse lymphadenopathy.

Imaging of the chest, abdomen, and pelvis revealed no systemic lymphadenopathy or other abnormalities. A tuberculin skin test (purified protein derivative [PPD]) was positive. Acid-fast bacilli (AFB) and fungal blood cultures were negative. An HIV antibody test, monospot, and cytomegalovirus polymerase chain reaction (PCR) test were negative. Her angiotensin-converting enzyme level was within normal limits, an antinuclear antibody screen was minimally positive at 1:80, her sedimentation rate was elevated at 40 mm/h (reference range, 0–20), and her lactic acid dehydrogenase level was elevated at 248 U/L (reference range, 135–214). Lymph node sampling by fine-needle aspiration showed caseating granulomatous inflammation, but AFB and fungal smears and *Mycobacterium tuberculosis* (MTB) PCR results were negative. This sample eventually grew pansensitive MTB, also identifiable by MTB probe. A QuantiFERON-TB Gold test was sent and returned with a positive result.

## DISCUSSION

The presentation of enlarging bilateral neck masses can be a diagnostic challenge, requiring not only a comprehensive history and physical exam, but radiologic imaging, multiple laboratory studies, and, often, cervical node biopsy. Scrofula is difficult to diagnose because it mimics other pathologic processes and yields inconsistent physical and laboratory findings. Further differentiation of tuberculous versus nontuberculous etiology is vital to proper treatment, as the former is best treated with systemic medical therapy, while the latter is amenable to surgical intervention. Timely diagnosis requires a high index of suspicion and knowledge of the spectrum of clinical and radiologic features of this disease.

Scrofula, or infectious cervical lymphadenitis, is a term predominantly applied to tuberculous and nontuberculous mycobacterial infections affecting the cervical lymph nodes. The word *scrofula* is from the Latin for “glandular swelling” and, later, from the French for “full-necked sow” (1). Scrofula has been recognized for at least 3000 years; it was described by Hippocrates in ancient Greece. In the Middle Ages, the disease was known as “the king's evil” because it was believed that the “royal touch” of the monarch was curative. This act was associated with the doctrine of the king's divine rights and thus important politically until the 19th century. In 1882, Robert Koch demonstrated mycobacteria in lymph nodes, linking scrofula to tuberculosis. Soon after this, reports of nontuberculous mycobacteria (NTM)

were described, and in the 1950s, large series confirmed that NTM were also human pathogens (2).

Mycobacteria are bacilli characterized microscopically by their dense lipid capsules which are “acid fast,” as they resist decoloration by acid alcohol after staining. These capsules protect the bacteria from lysis and promote a strong cell-mediated response in the host. Humans are the only reservoir for *M. tuberculosis*. Other tuberculous mycobacteria that cause disease in humans are *M. bovis* and *M. africanum*, which most often cause extrapulmonary disease. NTM are ubiquitous and commonly reside in the soil. They can be found in contaminated water, dairy products, eggs, dust, and even tap water (3). While *M. tuberculosis* is spread by airborne droplets that infect the host through the airways, the majority of NTM infections that cause cervical lymphadenopathy spread directly from the oral mucosal cavity.

Approximately 95% of adult scrofula cases are caused by *M. tuberculosis*, while the remaining 5% are caused by NTM, such as *M. avium intracellulare*, *M. scrofulaceum*, *M. kansasii*, and *M. chelonae*. In children, this statistic is reversed, with NTM responsible for up to 92% of scrofula cases (3). Prevalence of mycobacterial species, and therefore distribution of causative organisms, varies geographically.

## Clinical findings

Scrofula produces lymph nodes that are discrete, firm, and typically nontender, in contrast with the lymphadenopathy associated with acute infection, which is often tender. A firm mass of matted nodes may become visible with disease progression, and untreated lymphadenopathy can become fluctuant with draining fistulas. Enlarging nodes may compress the esophagus, causing dysphagia. The presence of systemic symptoms is variable and is more likely in immunocompromised patients.

## Imaging findings

Cervical lymph nodes enlarge in response to neoplastic, inflammatory, and systemic disease. Lymph nodes with central lucency on CT are always abnormal, reflecting either pathologic necrosis or tumor infiltration. Peripheral contrast enhancement reflects hyperemia of the inflamed lymph node capsule or increased lymph node vascularity. In general, inflammatory nodes have thick, irregular, enhancing margins, while metastatic nodes tend to have a thin rim of contrast enhancement.

Scrofula presents with a variable imaging appearance depending upon the stage of the disease. Tuberculous lymphadenitis may be unilateral (90% in adults) or bilateral and is usually found in the internal jugular nodal chains (levels 2–4) and the spinal accessory chains (levels 5a and 5b). In the early infectious phase, nonnecrotic nodes have homogeneous signal intensity and enhance homogeneously with contrast on both CT and magnetic resonance (MR) imaging. As the disease progresses and nodes become necrotic, CT images demonstrate characteristic central low density, representing necrosis, with a thick rim of enhancement. On MR images, the necrotic center of the nodes will show intermediate signal intensity on T1-weighted images and low signal intensity on

T2-weighted images and will enhance with contrast. The surrounding granulation tissue, with its inflammatory hypervascularity and increased vascular permeability, will be markedly hyperintense on T2-weighted images. The nodes may become multiloculated and matted, simulating metastatic cervical disease both on imaging and clinically. Despite extensive necrosis, infiltration of adjacent fat planes is minimal, which may differentiate this process from other infections or malignant nodal disease. Chronic or posttreatment nodes are characterized by fibrous and calcific elements that are easily identified on CT. Calcification can also be seen in scrofula caused by NTM. On MR, treated nodes are homogeneously hypointense on both T1- and T2-weighted images and do not enhance with contrast (4, 5).

### Diagnostic testing and treatment

Once scrofula is diagnosed, it is important to determine the exact etiology, as tuberculous and NTM infections are treated differently. Differentiation can be difficult because there is PPD cross-reactivity between TB and some NTM antigens (e.g., *M. kansasii*, mycobacterium avium complex). The QuantiFERON-TB Gold serology test for MTB is a relatively new enzyme-linked immunosorbent assay that detects the release of interferon-gamma in the blood of sensitized individuals after incubation with mixtures of synthetic peptides that simulate *M. tuberculosis* proteins. These proteins, ESAT-6 and CFP-10, are secreted by all *M. tuberculosis* and pathogenic *M. bovis* strains but are absent from all bacille Calmette-Guérin vaccine strains. These proteins are also present in the NTM species *M. kansasii*, *M. szulgai*, and *M. marinum* (6). The gold standard for diagnosis is tissue sampling, which allows for histological evaluation, AFB species identification, and sensitivity testing. The sensitivity of fine-needle aspiration is 52.9% when used alone but up to 82% when combined with PCR (7). Demonstration of epithelioid histiocytes, necrotic cells, AFB, and Langhans multinucleated giant cells is indicative of tuberculous scrofula. Once AFB are growing in the lab, highly specific DNA probe tests are available for MTB, *M. kansasii*, mycobacterium avium complex, and *M. goodnae*.

The current standard drug regimen for scrofula caused by sensitive *M. tuberculosis* consists of isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for a total of 6 to 12 months. Lymphadenopathy may initially worsen during antituberculous therapy, representing an immune response to killed mycobacteria.

Surgical intervention is reserved for complications such as abscess formation and draining sinuses.

NTM infections can be addressed locally and are amenable to surgical intervention. The treatment of choice is complete surgical excision of all affected tissue. However, the proximity of lesions to the facial nerve or its branches may necessitate the use of aspiration or curettage in combination with antibiotic therapy. Simple incision and drainage can be associated with prolonged postoperative wound discharge and hypertrophic scarring (8). The overlying skin can be excised when there is a fistula, necrosis, or scar formation.

### Conclusion

The clinical and radiologic manifestations of scrofula often mimic those of other diseases. A high degree of suspicion is required, especially in high-risk populations. Although in many cases, biopsy or culture specimens are still needed to yield the definitive diagnosis, it is important to understand the spectrum of imaging features associated with scrofula in order to make an early diagnosis and begin proper treatment.

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