Case Report/Case Series

Histoplasmosis Mimicking Malignant Adenopathy During Diagnostic Thyroid Lobectomy

Paul N. Frank, BS; Miguel Fernando Palma Diaz, MD; Daniel Z. Uslan, MD; Michael W. Yeh, MD

IMPORTANCE Benign granulomatous disease may mimic malignant disease in the evaluation of mediastinal or pulmonary lesions. However, histoplasmosis as a cause of cervical lymphadenopathy is relatively rare. We report the first case of Histoplasma infection mimicking malignant adenopathy discovered during diagnostic thyroid lobectomy.

OBSERVATIONS A 2.5-cm, calcified, right paratracheal lymph node intimately involving the recurrent laryngeal nerve was discovered during lobectomy for a follicular lesion of undetermined significance with a positive NRAS mutation. Although metastatic thyroid cancer was the most probable diagnosis, results of gross inspection of the bisected thyroid node suggested a benign process. Partial removal of the node, sparing the nerve, established the diagnosis of Histoplasma capsulatum infection.

CONCLUSIONS AND RELEVANCE Histoplasmosis is a rare cause of cervical adenopathy that should be considered in cases in which a discordance arises between the malignant gross appearance of the adenopathy and the benign gross appearance of an associated thyroid nodule.

Report of a Case

A middle-aged white man presented with a 5.4-cm right thyroid nodule on physical examination. Ultrasonographic findings confirmed a solitary thyroid nodule and no other abnormalities. Results of fine-needle aspiration biopsy revealed a follicular lesion of undetermined significance (Bethesda category III). Molecular profiling revealed an NRAS (HGNC 7989) mutation.

The patient underwent diagnostic right thyroid lobectomy performed by one of us (M.W.Y.). A fleshy, well-circumscribed right thyroid nodule was found, and the lobectomy proceeded uneventfully. In addition, a 2.5-cm heavily calcified right paratracheal lymph node was discovered. The node was densely adherent to the right recurrent laryngeal nerve, and the gross appearance was highly suggestive of a lymph node affected by metastatic thyroid cancer. Complete removal of the lymph node would have required sacrifice of the nerve. The surgeon paused the operation at this point, given the unexpected findings that were likely to have a significant effect on the patient's overall treatment.

The thyroid nodule was bisected. On gross examination, the surgeon deemed the nodule to be most likely benign, given its well-defined margins and soft consistency without granularity or internal punctate calcifications. Therefore, the lymph node was partially removed for diagnostic purposes while sparing the recurrent laryngeal nerve. Frozen section of the lymph node was attempted but ultimately not possible owing to the heavy calcification. The operation was concluded.

In the recovery room, the patient was questioned regarding potential exposures to infectious agents. He had grown up in rural Illinois and had spent a significant amount of time on a dairy farm amid fields of grain. Although the patient had no significant medical history as a child or as an adult, he did report that calcium deposits had been identified in his chest on a radiograph when he was a teenager. A tentative clinical diagnosis of histoplasmosis was made based on the history and operative findings.

Final pathological evaluation of the right paratracheal calcified lymph node performed by one of us (M.F.P.D.) revealed calcified granuloma associated with yeast forms, morphologically consistent with Histoplasma capsulatum (Figure 1 and Figure 2). Final pathological evaluation of the thyroid nodule revealed a benign follicular adenoma. A follow-up chest radiograph revealed multiple diffuse globular calcifications within the mediastinum and hilar regions and scattered parenchymal lung calcifications most prominent within the right upper lobe consistent with residuals of old granulomatous disease (Figure 3). The patient was referred to an infectious disease specialist (D.Z.U.) for evaluation. Testing of urine and serum samples for Histoplasma antigen (MiraVista Diagnostics) and immunodiffusion and complement fixation for Histoplasma capsulatum antigen (Histo-
plasma antibodies yielded negative findings. Computed tomography of the chest revealed extensive calcified mediastinal and hilar lymphadenopathy consistent with old granulomatous disease.

Discussion

Differential Diagnosis of Cervical Lymphadenopathy

The differential diagnosis of cervical lymphadenopathy is broad. Possible causes include infection, malignant disease, lipid storage disease, and immunologic disorders. In the present patient with a mutation-positive thyroid nodule, malignant disease was the most likely diagnosis. Infection was a distant second. Autoimmune disease (Hashimoto thyroiditis) was also considered, although calcified adenopathy is uncommon in this scenario.

Clinical Features of Histoplasmosis

*Histoplasma capsulatum* is a dimorphic fungus endemic to the Ohio and Mississippi River Valleys and may be found in soil containing bird or bat excrement. Inhalation of spores can cause infection that is asymptomatic or minimally symptomatic in more than 99% of patients. Most symptomatic cases are characterized by acute pulmonary histoplasmosis, a self-limited illness with the symptoms of atypical pneumonia, including fever, malaise, headache, substernal chest discomfort, and dry cough. Early chest radiography will show patchy pulmonary infiltrates and hilar and mediastinal lymphadenopathy, whereas later-stage chest radiography will show only hilar lymphadenopathy.

Even in patients who are asymptomatic and otherwise healthy, *Histoplasma* will disseminate throughout the reticuloendothelial system via macrophages that have engulfed the yeast. The infection is controlled and ultimately eliminated when T lymphocytes activate against the *Histoplasma* antigen and stimulate macrophages to kill the engulfed yeast. Patients who have a defect in T-cell immunity will not be able to mount this response and may develop disseminated histoplasmosis, which may manifest with fever, anorexia, weight loss, hepatosplenomegaly, pancytopenia, and mucosal ulcerations. Disseminated histoplasmosis can also lead to sepsis and acute respiratory distress.
Published Cases
Benign granulomatous disease may mimic malignant disease quite often in the evaluation of mediastinal or pulmonary lesions, particularly in geographic areas where Histoplasma infection is endemic.2 However, histoplasmosis as a cause of cervical lymphadenopathy is relatively rare. A study of 239 pediatric patients with lymphadenopathy in any anatomic site who underwent lymph node biopsy identified histoplasmosis as the cause in just 4 of them. Three of these lymph nodes were in the cervical chains and one was in the submental region.3 Results of 73 biopsies in that study identified other granulomatous diseases (e.g., mycobacterial infection, toxoplasmosis) as the cause of lymphadenopathy.3

At least 10 cases of histoplasmosis presenting as a neck mass have been described in the literature.4 Most of these patients had mediastinal lymph node involvement in addition to cervical lymph node involvement. Cutaneous fistula tracts complicated 6 of these published cases.4 Six cases were diagnosed surgically, and 2 were diagnosed by results of fine-needle aspiration biopsy.4 Histoplasma infection has also been reported, in rare instances, to cause neck abscess,5 infection of the thyroid gland,6 and lingual mucosal ulceration.7 Our report is the first, to our knowledge, to describe cervical adenopathy owing to histoplasmosis concomitant with a thyroid nodule suggestive of a malignant process.

Lessons Learned
Based on our patient’s history of growing up in rural Illinois and the imaging findings, we concluded that he had a remote history of histoplasmosis. Yeast elements may be visible in calcified lesions even in inactive disease. Based on the negative findings of serologic and antigen studies, no antifungal therapy was prescribed.

Intraoperative discovery of the calcified lymph node necessitated the rapid formulation of a differential diagnosis and action plan. The likelihood of a malignant cause in a thyroid nodule positive for an NRAS mutation is as great as 87%,8 thus identifying malignant disease as the most likely cause of the adenopathy. Mutation of NRAS can be found in follicular carcinomas, follicular-variant papillary thyroid carcinomas, and follicular adenomas. In this case, the surgeon’s gross assessment of the thyroid nodule contributed to the decision-making process by reducing suspicion of a classic papillary carcinoma or a widely invasive follicular carcinoma. Uncertainty regarding a possible follicular-variant papillary carcinoma remained. The absence of a frankly invasive primary lesion made a positive lymph node less likely, leading to the consideration of infectious causes in the differential diagnosis.

This decision-making path spared the patient a permanent recurrent laryngeal nerve injury. The decision to remove only as much of the node as possible without damaging the recurrent laryngeal nerve achieved the optimal outcome: allowing for pathological examination of the specimen without causing unilateral vocal cord paralysis. If metastatic thyroid cancer had been found within the node at permanent section, the patient would have required reoperation consisting of completion thyroidectomy and central neck dissection. Although such a reoperation would have been risky, the risk was balanced by the certainty of nerve injury had an initial oncologic resection been pursued.

Conclusions
Histoplasmosis is a rare cause of cervical adenopathy. It should be considered in cases such as these with discordance between the malignant gross appearance of the adenopathy and the benign gross appearance of an associated thyroid nodule.