

Micronodular Radiographic Pulmonary Pattern in Metastatic Medullary Thyroid Carcinoma

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Medullary carcinoma of the thyroid is a rare form of all thyroid malignancies, thereby limiting the clinical nature and the ability to optimize diagnostic tools. We present two cases of a micronodular radiographic pulmonary pattern in metastatic medullary thyroid cancer to enhance awareness of the disease process. We reviewed the literature to examine the ideal methods to establish a diagnosis.

Key words: thyroid ■ cancer ■ metastasis ■ pulmonary pattern ■ lung ■ diagnostic methods

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INTRODUCTION

Tumor identification is crucial for overall survival of patients with medullary thyroid carcinoma. Metastasis is commonly seen with this type of aggressive tumor. Early diagnosis of the disease, along with identification of particular characteristic patterns and monitoring response to therapy, is extremely important. Metastases of medullary thyroid cancer to the lung generally exhibit a macronodular pattern, whereas radiographic findings with micronodular patterns appear more with metastatic papillary thyroid cancer.¹ It is important to note that micronodular patterns can be sometimes be confused with an infectious etiology—namely, tuberculosis. The following two cases present evidence to support that metastatic medullary thyroid carcinoma is an important diagnosis to consider when presented with patients exhibiting radiographic findings of a micronodular pulmonary pattern.

CASE 1

A 33-year-old woman referred to our clinic in July 2002 complained of persistent right neck swelling for the past 10 years. The swelling had progressively in-

creased in size within the last three years. She admitted to an unintentional 12-lb weight loss over a two-month period. She denied any associated pain, fevers, chills, night sweats, anorexia or early satiety. Physical examination demonstrated a normotensive, afebrile 5'3", 127-lb female. She had oxygen saturation of 97% on room air. Examination of the neck revealed a firm right thyroid nodule. No lymphadenopathy was appreciated. Decreased bibasilar breath sound on lung auscultation was without rales, rhonchi, wheezes, egophony, tactile fremitus or stridor. Heart sounds revealed a sinus rate and regular rhythm. Abdomen was soft, and there was no organomegaly.

Laboratory Data

Thyroid function testing indicated a thyroid-stimulating hormone of 25.50 uIU/mL (reference range: 0.4–5.0 uIU/mL), thyroglobulin 9.0 ng/mL (reference range: 5–50 ng/mL) and thyroglobulin antibody 30 IU/mL (reference range: 1–10 IU/mL). Thyroid ultrasonography revealed a heterogeneous mass with calcifications involving the entire right lobe. Analysis of a fine-needle aspiration was consistent with medullary thyroid cancer. Serum preoperative calcitonin level was significantly elevated at 19,950 pg/mL (reference range: 0.0–8.4 pg/mL). The patient underwent a total thyroidectomy with bilateral neck dissection and ultimately cancer was determined to be at stage 3 (T3N1bMx). Laboratory and radiographic evaluations were devoid of any metastatic lesions. Postoperative calcitonin level decreased to 35 pg/mL. Oncogene and family genetic testing indicated that this carcinoma was of a sporadic nature.

Follow-Up

She presented a year later with progressive worsening of a productive cough with whitish sputum, but no fever, chills or night sweats. Plain chest radiograph then discovered a diffuse micronodular pattern in both lung fields (Figure 1). Sputum culture grew normal flora. Aerobe and anaerobe blood cultures were also negative. A computed tomography (CT) of the thorax revealed innumerable pulmonary nodules, suggestive of inflamma-

tory process versus metastasis. The thyroid-stimulating hormone was normal as were thyroglobulin and thyroglobulin antibody; however, the serum calcitonin level had increased to 15,100 pg/mL.

Bronchoscopy revealed no gross pathology. Examination of the transbronchial biopsy of the left lower lobe indicated pathological evidence for metastasis of the medullary thyroid carcinoma. Immunohistochemistry studies confirmed the presence of calcitonin. A negative Grocott's methenamine stain (GMS) and acid-fast bacilli (AFB) stain ruled out invasive fungal infections and *Mycobacterium tuberculosis*.

Case 1 was presented at the American College of Physicians Region II Meeting as a poster presentation, October 2003.

CASE 2

A 23-year-old asymptomatic man was referred to the clinic in May 2006 for evaluation of an incidental finding of a diffuse bilateral micronodular pattern seen on chest radiograph (Figure 2). His past medical history was significant for multiple endocrine neoplasia 2B for which he had a total thyroidectomy and multiple neck dissections for regional recurrences. His only medication included L-thyroxine. Physical exam demonstrated a normotensive, afebrile 5'7", 120-lb male. He had oxygen saturation of 98% at room air. Lips and tongue showed multiple mucosal neuromas. Examination of the neck revealed well-healed incision scars. Lung were clear, and he had no egophony. Tactile fremitus was nor-

mal. Heart sounds were in normal sinus rate and regular rhythm. Abdomen was soft and showed no organomegaly. There were no hemodynamic variations or any other signs to suspect active pheochromocytoma.

Laboratory Data

Sputum culture grew normal flora. Serum calcitonin level was 47,318 pg/mL with normal values for thyroid-stimulating hormone, thyroglobulin and thyroglobulin antibody. No gross bronchoscopic findings were appreciated, and the patient successfully underwent a transbronchial biopsy of the left lower lobe. The presence of polyhedral neoplastic cells cluster, with visualization of calcitonin on immunohistochemistry studies, confirmed our concerns for metastatic medullary thyroid carcinoma. A negative GMS and AFB stain ruled out invasive fungal infections and *M. tuberculosis*.

DISCUSSION

Medullary carcinoma of the thyroid accounts for 3–10% of all thyroid malignancies. It is an aggressive calcitonin-producing neuroendocrine tumor that arises from parafollicular C cells. Most cases are sporadic in nature, making early detection very difficult but extremely important to overall survival, since 10-year survival rates average only 40–50%. Age and tumor stage are indicative of survival.² Total thyroidectomy with meticulous triple compartment nodal dissection correlates with the highest cure rate.³ Therefore, aggressive methods of early detection of tumor behavior and characterization are

Figure 1. Chest radiograph showing a diffuse, bilateral micronodular pattern.



Figure 2. Chest radiograph showing diffuse bilateral micronodular disease pattern



the best approach for increasing the cure rate.

However, diagnosing metastasis of medullary carcinoma of the thyroid is generally challenging due to poor identification by conventional imaging. Radionuclide techniques are sometimes used for superior detection. Thallium-201 chloride single-photon emission CT optimally detects metastatic differentiated thyroid carcinoma foci as small as 1.0 cm in the neck and 1.5 cm in the lung that are undetectable by planar imaging.⁷ Variable radiotracer uptake and limited spatial resolution make these techniques suboptimal, especially with small lesions. A short review by Nanni et al.⁸ shows fluorodeoxyglucose positron emission tomography (FDG-PET) has a superior sensitivity for detection of medullary carcinoma of the thyroid compared to conventional imaging methods, particularly in the neck and mediastinal structures. Like most diagnostic tools, FDG-PET can have false positives, particularly in the neck, due to localized inflammation. Additionally, some studies indicate that FDG-PET cannot adequately detect micronodular lung metastases <6 mm in size. Even with its limitations, it appears to be the superior method for detection at the present time. The current methods of obtaining histopathological tissue remain unchanged. It is recommended to first undergo a transbronchial or a CT-guided biopsy. If the tissue does not yield an adequate diagnosis, as it does in 40% of cases, the patient should undergo video-assisted thoracic surgery or an open-lung biopsy.

Although medullary carcinomas of the thyroid commonly exhibit a macronodular pattern, also known as "cannonball" appearance, the two cases presented here indicate that micronodular patterns can also occur with the disease. Unfortunately, a micronodular pulmonary pattern can also be easily mistaken for tuberculosis, pulmonary eosinophilic granuloma or sarcoidosis, complicating the diagnosis of medullary carcinoma of the thyroid even further. In the review of the literature, only one other case has been reported to have a micronodular pattern.⁴ Other descriptive characterizations of medullary carcinoma of the thyroid noted in the literature are calcified pulmonary metastases^{5,6} and reticulonodular perihilar lesions.⁴

Approximately half of all cases of medullary carcinoma of the thyroid demonstrate distant metastasis either to the liver, lung or bone. Traditional therapies with systemic chemotherapy and radiotherapy are generally ineffective. Advances in radionuclide therapy include strategies using pretargeted radioimmunotherapy, bispecific monoclonal antibodies and iodine-131-labeled bivalent haptens. Twenty-nine patients with metastatic medullary carcinoma of the thyroid underwent radioimmunotherapy using a bispecific anti-CEA monoclonal antibody and iodine-131-labeled hapten.⁹ The only

group that showed a gain in overall survival was that of patients who had calcitonin doubling time <2 years (overall survival 159 vs. 109 months for untreated controls). Adverse reactions to this method include neutropenia, thrombocytopenia and myelodysplastic syndrome. Additional target directed therapies used are tyrosine kinase inhibitors (RET kinase activity), and the inhibition of vascular endothelial growth factor receptor KDR are currently being conducted.¹⁰

CONCLUSION

Medullary thyroid carcinoma exhibiting a macronodular pulmonary metastatic pattern represents a relatively small number of all differentiated thyroid tumors. An even smaller fraction of thyroid carcinomas presents as a micronodular pattern. It is imperative to use all available resources to appropriately diagnose and cure this type of aggressive tumor. We have presented two cases of medullary thyroid carcinoma with micronodular radiographic pulmonary metastases to increase awareness for this uncommon mode of progression of this aggressive disease. In addition to early detection, it is anticipated that improved diagnostic tools and target directed therapies will greatly improve the survival of patients and increase the cure rates.

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