Not all that is miliary is tuberculosis: metastatic medullary thyroid carcinoma mimicking miliary tuberculosis

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Abstract

Medullary thyroid carcinoma (MTC) typically manifests as a solitary thyroid nodule, and a miliary pattern on conventional chest imaging is not commonly observed. Here, we report a 58-year-old woman with constitutional symptoms, and innumerable small nodules on chest imaging, mimicking miliary tuberculosis. Pathologic findings confirmed a diagnosis of metastatic MTC.

Background

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine primary thyroid tumor, originating from the parafollicular C-cells of the thyroid gland. These aggressive cancers constitute approximately 3-10% of all primary thyroid malignancies, and are mainly sporadic (75%) [1,2]. Sporadic cases of MTC are usually diagnosed within the fourth to sixth decades of life and commonly manifest as a solitary thyroid nodule [3]. In about 5-10% of patients with MTC who have a palpable thyroid nodule, distant metastatic disease is present at presentation [1,4,5]. These tumors tend to metastasize to the kidneys, liver, lungs, bones, and less frequently, to the brain and skin [6,7]. Lung metastases occur in 33% of patients with locally advanced or metastatic MTC [8] and usually have a macronodular appearance; however, calcified pulmonary metastases, reticulonodular perihilar lesions and micronodular lesions have also been reported in several studies [9,10]. According to the literature, micronodular densities are more often associated with papillary thyroid carcinoma [10]. Here, we report the case of a middle-aged woman with metastatic medullary carcinoma of the thyroid presenting with an unusual miliary pattern on chest imaging mimicking that of miliary tuberculosis.

Case presentation

A 58-year-old woman presented with a history of shortness of breath, fever, chills and productive cough with non-blood-stained sputum. Her symptoms had initiated approximately 8 months prior to admission and had progressed during the last 2 weeks. She did not complain of excessive perspiration at night, dysphagia or hoarseness. However, she mentioned unintentional weight loss of about 25 kilograms within the last 6 months. The patient did not have a history of head and neck irradiation, but was a passive smoker. She denied exposure to tuberculosis and similar symptoms in any of her close family members. Her past medical history was only significant for hypothyroidism for which she received medication (levothyroxine 100 mcg once daily). She had no family history of malignancy or pulmonary disease. The patient was referred to our hospital for further investigation due to the lack of clinical response to anti-tuberculosis therapy that had been initiated after a suspicion of miliary tuberculosis in another center. On physical examination, she was hemodynamically stable with a blood pressure of 130/80 mmHg. She had a normal respiratory rate (12 breaths/min), a body temperature of 37.8 °C, was not tachycardic (pulse rate 84/bpm) and had an oxygen

blood saturation of 98% on room air. No thyroid nodule was discovered by palpation and no mass, swelling or cervical lymphadenopathy was detectable on examination of the neck. Pulmonary exam revealed clear lungs on auscultation.

In our hospital, a diagnostic work-up was performed for the patient following admission. Laboratory examinations revealed a TSH of 0.08 (normal range, 0.35-4.9 mU/L), a fT4 of 0.7 (normal range, 0.76-2.24 ng/dL) and an elevated serum calcitonin level (128 pg/mL). Other blood tests were within normal limits. On imaging, chest radiography demonstrated bilateral diffuse micronodules with a miliary pattern, characterized by multiple, small 1-3 mm nodular infiltrates (Fig 1). Considering the most probable differential diagnoses of miliary tuberculosis, primary lung cancer or metastatic malignancies, non-contrast-enhanced computed tomography (CT) of the chest was performed, which showed numerous small lung nodules with a random distribution, and a confluent mass within the right lung (Fig 2). Furthermore, results were negative for acid-fast bacilli (AFB) smear and culture, *mycobacterium tuberculosis* was not detected by polymerase chain reaction (PCR), and blood cultures conveyed negative results for infectious diseases. These findings as well as the right-sided mass on CT made miliary tuberculosis a less likely diagnosis. Later, the patient underwent thyroid ultrasonography. On ultrasound, a left-sided solid hypoechoic nodule measuring 5 x 4.5 mm in size with irregular borders, a taller-than-wide shape and multiple punctuate echogenic foci were observed, compatible with Thyroid Imaging Reporting and Data System (TI-RADS) 5 [11]. Also, bilateral malignant-looking cervical lymph nodes were detected within zones 2 and 3. These findings prompted an ultrasound-guided fine-needle aspiration (FNA) biopsy, and cytological examination showed isolated and loose clusters of ovaloid atypical cells (Fig 3).

The patient also underwent bronchoscopy with trans-bronchial lung biopsy, which demonstrated atypical cells infiltrating the lung parenchyma. These cells showed a positive reaction for CK7, TTF1, CD56, CEA, chromogranin, and calcitonin by immunohistochemistry (IHC) (Fig 4). Regarding the histological and cytological findings, a diagnosis of MTC stage IV was confirmed, and the patient underwent treatment with sorafenib 400mg twice daily. Unfortunately, about two and a half months after diagnosis, the patient died of disease.

Discussion and Conclusion

Although miliary tuberculosis is the most known cause of miliary infiltrates on chest imaging, other differential diagnoses including pneumoconiosis, fungal infections, sarcoidosis, histoplasmosis, primary lung cancer, and hematogenous spread of non-pulmonary malignancies [12] can mimic this radiographic finding. Rarely, primary lung adenocarcinoma could be the etiology of miliary nodules on chest radiography [13]. While renal cancers are the most likely solid organ malignancies that can manifest with a miliary pattern on chest imaging [14], primary cancers of the thyroid, melanoma, trophoblastic tumors and sarcomas also can display a similar radiologic feature. Chest CT has the highest sensitivity for detecting lung metastases in patients with suspected metastatic MTC [3]. The distribution of miliary nodules on chest CT can be centrilobular, perilymphatic or random [15]. Random micronodular patterns are seen in entities such as hematogenous spread of malignancies, in line with the case reported here. Moreover, micronodules that are seen in hematogenous spread of malignancies to the lungs mainly have a basal predominance. This finding was also observed on the chest radiography and CT scan of this patient. In patients with MTC, lung metastases are commonly accompanied with mediastinal lymph node metastases [3]; however, no mediastinal lymphadenopathy was evident on chest imaging of our patient.

Non-specific clinical symptoms such as, fever, chills, cough, and weight loss can be associated with infectious diseases other than*mycobacterium tuberculosis* as well as malignancies. Patients with MTC may present with systemic symptoms such as diarrhea and flushing due to the secretion of serum calcitonin, calcitonin gene-related peptide and other hormones from parafollicular C-cells [16]. In this specific case, our patient was mistakenly treated with anti-tuberculosis drugs since her clinical symptoms as well as radiologic findings were compatible with a diagnosis of miliary pulmonary tuberculosis. Taken together, establishing a diagnosis of miliary tuberculosis should be based on the combination of radiologic, histologic and microbiologic examinations. Nevertheless, it is worthy to note that a negative AFB sputum smear result should not

exclude a diagnosis of miliary tuberculosis as this test is only positive in a small percentage of patients with disseminated disease [15].

Thyroid FNA is a useful and reliable tool with a diagnostic yield of 50 to 80% for medullary thyroid carcinoma [17-19]; however, this percentage is increased with the addition of immunohistochemical staining for calcitonin [20,21]. Among the secretory products of C-cells, calcitonin and carcinoembryonic antigen (CEA) are the most valuable biomarkers in patients with MTC. Studies have shown that the concentration of these tumor biomarkers in patients' sera is associated with the C-cell mass [3]. Unlike calcitonin, CEA does not play a role in the early diagnosis of MTC; in fact, baseline serum CEA levels are measured preoperatively for determining the extent of disease after surgery [22]. Histologically, MTC cells are usually round, spindle-shaped or polyhedral and are arranged in the shape of sheets or nests with peripheral palisading. Moreover, MTC cells are typically discohesive or weakly cohesive on aspiration cytology [2,3]. Our observations were consistent with these findings.

The significant prognostic value of tumor stage in patients with MTC [23,24] underlines the importance of early detection of this aggressive tumor. The 10-year overall survival rate for patients with stage IV disease is reported to be as low as 21%. Some patients, however, may survive for longer years [24]. Considering the increasing number of cases with MTC presenting with miliary nodules on conventional chest imaging, observation of this radiologic pattern should prompt a possible diagnosis of metastatic MTC, even in cases without clinically palpable thyroid nodules. MTCs appearing with a miliary pattern on radiography could be erroneously diagnosed as miliary tuberculosis, leading to a delay in the detection of cancer and ultimately higher stages of disease.

Ethics approval and consent to participate: This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report, including accompanying images.

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Author contributions:

Elham Askari: designed the study, performed the literature search, critically revised the manuscript, and supervised the study.

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Neda Khalili: designed the study, performed the literature search, and drafted the manuscript.

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Figure legends

Fig. 1 Frontal chest x-ray shows bilateral innumerable nodules with a miliary pattern resembling miliary tuberculosis. No evidence of hilar lymphadenopathy is seen.

Fig. 2 Axial images of non-contrast enhanced computed tomography of both lungs show numerous small lung nodules with a random distribution, and a confluent mass within the right lung, indicating disseminated lung metastasis (a-d).

Fig. 3 FNA biopsy of solid thyroid nodule demonstrates isolated and loose clusters of ovaloid atypical cells.

Fig. 4 Trans-bronchial lung biopsy (TBLB) shows that lung parenchyma is infiltrated by sheets and nests of rather monotonous atypical cells with round to oval nuclei, inconspicuous nucleoli, finely dispersed chromatin and moderate amount of eosinophilic cytoplasm. These cells are strongly positive for CK7 (a) and TTF1 (b) by immunohistochemistry (IHC). Atypical cells exhibit a strong and diffuse positive reaction for CEA (c), chromogranin (d), calcitonin (e) and CD56 (f). IHC for P63, Pax8 and NapsinA did not show a positive reaction.