

CASE REPORT

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

Elham Askari¹ | Mihan Pourabdollah Toutkaboni¹ | Sara Haseli¹ | Mitrasadat Rezaei² | Payam Tabarsi³ | Majid Marjani³ | Afshin Moniri² | Neda Khalili⁴ 

¹Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

²Virology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

³Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁴School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Correspondence

Neda Khalili, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
Email: nedakhalili44@gmail.com

Funding information

This study did not receive funding from any sources

Abstract

Medullary carcinoma of the thyroid should be considered in the differential diagnosis of miliary pattern of micronodules on chest imaging, irrespective of clinical features.

KEYWORDS

case report, computed tomography, immunohistochemistry, medullary thyroid carcinoma, miliary tuberculosis

1 | BACKGROUND

Medullary thyroid carcinoma (MTC) is a calcitonin-secreting primary tumor of the thyroid gland. This rare tumor typically manifests as a solitary thyroid nodule, but may be metastatic at presentation. MTC most likely metastasizes to the kidneys, lungs, and bones. A miliary pattern on conventional chest imaging, however, is not commonly observed among patients with lung metastases. Here, we report a 58-year-old woman presenting with constitutional symptoms and productive cough, and innumerable small nodules on chest imaging, mimicking miliary tuberculosis. Histological and cytological examinations along with immunohistochemical staining confirmed a diagnosis of metastatic MTC in this patient.

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 MTC⁸ 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.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

2 | CASE PRESENTATION

A 58-year-old woman presented with a history of shortness of breath, fever, chills, and productive cough with nonblood-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 antituberculosis 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 examination 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 (Figure 1). Considering the most probable differential diagnoses of miliary tuberculosis, primary lung cancer or metastatic malignancies, noncontrast-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 (Figure 2). Furthermore, results were negative for acid-fast bacilli (AFB) smear and culture, and *Mycobacterium tuberculosis* was not detected by polymerase chain reaction (PCR), and blood cultures conveyed negative results for infectious diseases. These findings and 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 and multiple punctuate echogenic foci were observed, compatible with Thyroid Imaging Reporting and Data System (TI-RADS) 5¹¹ (Figure 3). Also, bilateral malignant-looking



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

cervical lymph nodes were detected within zones 2 and 3, but no calcification was seen. These findings prompted an ultrasound-guided fine-needle aspiration (FNA) biopsy, and cytological examination showed isolated and loose clusters of ovaloid atypical cells (Figure 4).

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) (Figure 5). 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.

3 | 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 nonpulmonary malignancies¹² 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

FIGURE 2 Axial images of noncontrast-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)

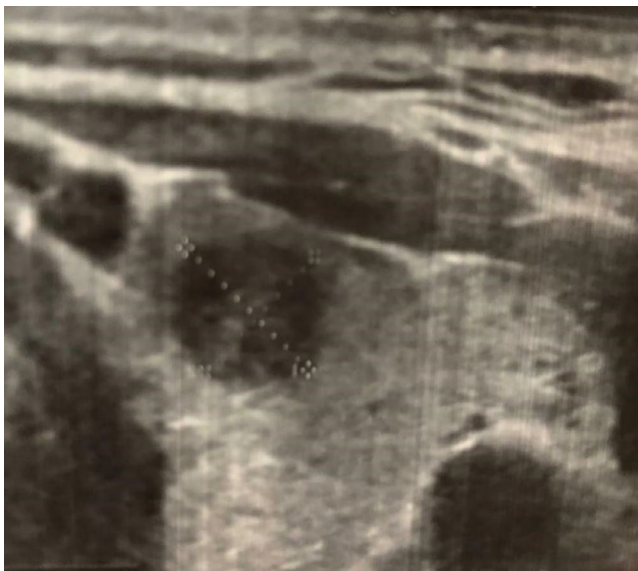
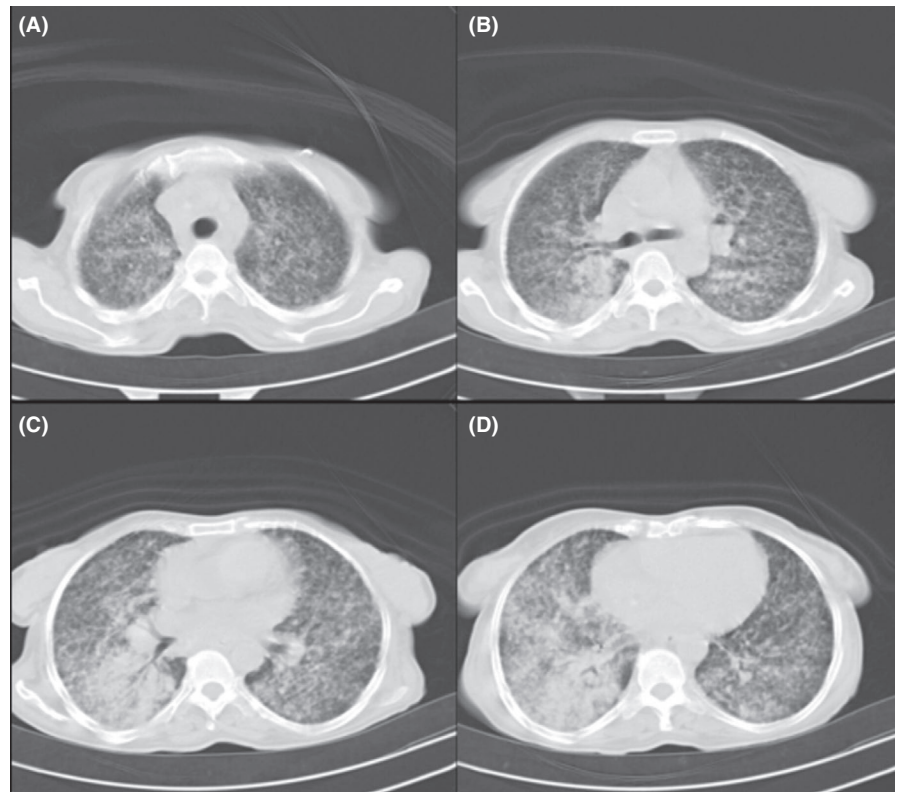


FIGURE 3 Thyroid ultrasound shows a left-sided solid hypoechoic nodule measuring 5 x 4.5 mm in size with irregular borders and multiple punctuate echogenic foci, compatible with Thyroid Imaging Reporting and Data System (TI-RADS) 5

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

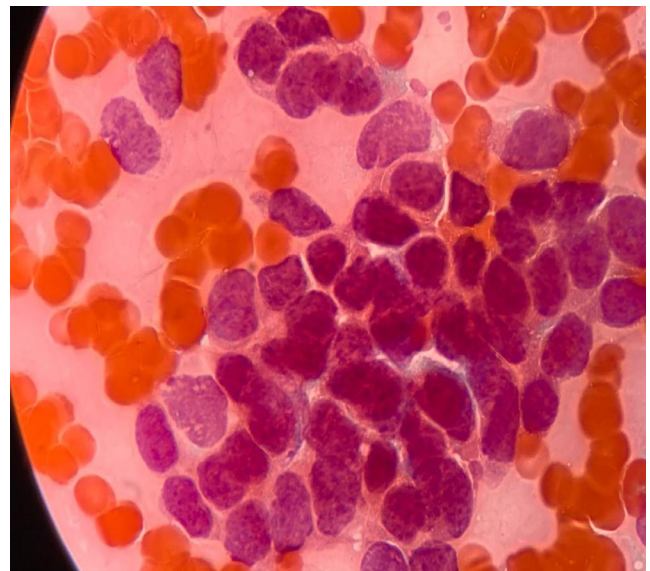


FIGURE 4 FNA biopsy of solid thyroid nodule demonstrates isolated and loose clusters of ovaloid atypical cells

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 metastases³; however, no mediastinal lymphadenopathy was evident on chest imaging of our patient.

Nonspecific clinical symptoms such as fever, chills, cough, and weight loss can be associated with infectious diseases other than *mycobacterium tuberculosis* and malignancies.

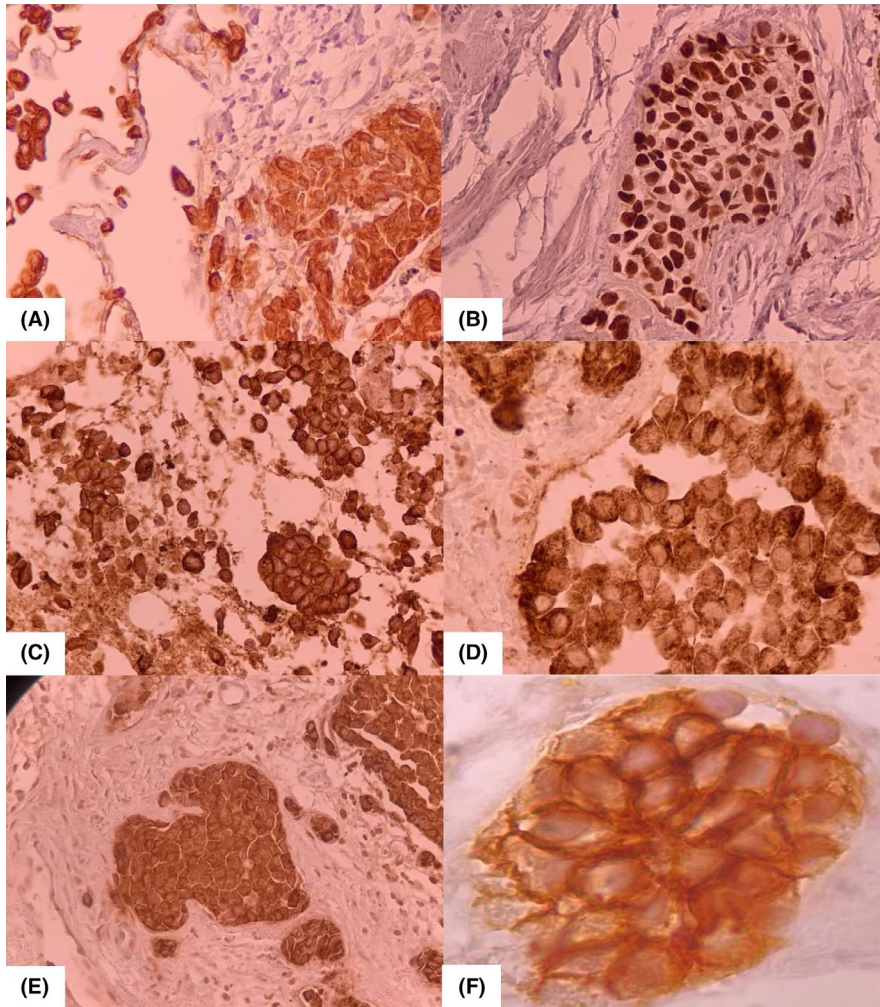


FIGURE 5 Trans-bronchial lung biopsy (TBLB) shows that lung parenchyma is infiltrated by sheets and nests of rather monotonous atypical cells with round to oval nuclei, inconspicuous nucleoli, finely dispersed chromatin, and moderate amount of eosinophilic cytoplasm. These cells are strongly positive 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

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 antituberculosis drugs since her clinical symptoms and 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 carcinoma¹⁷⁻¹⁹; 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 dis-cohesive 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.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Elham Askari: designed the study, performed the literature search, provided the images and data, critically revised the manuscript, and supervised the study. Miham Pourabdollah Toutkaboni: critically revised the manuscript, provided the images and data, and supervised the study. Sara Haseli, Mitrasadat Rezaei, Payam Tabarsi, Majid Marjani, and Afshin Moniri: critically revised the manuscript, and provided the images and data. Neda Khalili: designed the study, performed the literature search, and drafted the manuscript. All authors have read and approved the final version of the manuscript.

ETHICAL APPROVAL

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.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Neda Khalili  <https://orcid.org/0000-0001-8415-8996>

REFERENCES

- Cohen EG, Shaha AR, Rinaldo A, Devaney KO, Ferlito A. Medullary thyroid carcinoma. *Acta Otolaryngol.* 2004;124(5):544-557.
- Blankenship DR, Chin E, Terris DJ. Contemporary management of thyroid cancer. *Am J Otolaryngol.* 2005;26(4):249-260.
- Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid.* 2015;25(6):567-610.
- Pacini F, Castagna MG, Cipri C, Schlumberger M. Medullary thyroid carcinoma. *Clinical oncology.* 2010;22(6):475-485.
- Moley JF. Medullary thyroid carcinoma: management of lymph node metastases. *J Natl Compr Canc Netw.* 2010;8(5):549-556.
- Smit J. Treatment of advanced medullary thyroid cancer. *Thyroid Res.* 2013;6(Suppl 1):S7.
- Schlumberger M, Bastholt L, Dralle H, Jarzab B, Pacini F, Smit JWA. 2012 European thyroid association guidelines for metastatic medullary thyroid cancer. *Eur Thyroid J.* 2012;1(1):5-14.
- van Heerden JA, Grant CS, Gharib H, Hay ID, Ilstrup DM. Long-term course of patients with persistent hypercalcitoninemia after apparent curative primary surgery for medullary thyroid carcinoma. *Ann Surg.* 1990;212(4):395-401.
- Jimenez JM, Casey SO, Citron M, Khan A. Calcified pulmonary metastases from medullary carcinoma of the thyroid. *Comput Med Imaging Graph.* 1995;19(4):325-328.
- Afshar K, Alalawi R, Boylen CT. Micronodular radiographic pulmonary pattern in metastatic medullary thyroid carcinoma. *J Natl Med Assoc.* 2007;99(5):575-577.
- Russ G. Risk stratification of thyroid nodules on ultrasonography with the French TI-RADS: description and reflections. *Ultrasonography.* 2016;35(1):25-38.
- Salahuddin M, Cherian S, Patel RAJ, Estrada-Y-Martin R. Etiology of miliary nodules. *Chest.* 2018;154(4):583A.
- Khan D, Danjuma M, Saddique MU, Murshed KAH, Yassin MA. Adenocarcinoma of the lung mimicking miliary tuberculosis. *Case Rep Oncol.* 2020;13(1):139-144.
- Manko AG, Shilo K, McCallister JWA. Case of diffuse miliary pulmonary infiltrates in a 35 year-old man. *American Thoracic Society.* <https://www.thoracic.org/professionals/clinical-resources/clinical-cases/08-14.php>. Accessed June 12, 2020.
- Kimmig L, Bueno J. Miliary nodules: not always tuberculosis. *Ann Am Thorac Soc.* 2017;14(12):1858-1860.
- Abe K, Adachi I, Miyakawa S, et al. Production of calcitonin, adrenocorticotrophic hormone, and beta-melanocyte-stimulating hormone in tumors derived from amine precursor uptake and decarboxylation cells. *Can Res.* 1977;37(11):4190-4194.
- Trimboli P, Treglia G, Guidobaldi L, et al. Detection rate of FNA cytology in medullary thyroid carcinoma: a meta-analysis. *Clin Endocrinol.* 2015;82(2):280-285.
- Papaparaskeva K, Nagel H, Droese M. Cytologic diagnosis of medullary carcinoma of the thyroid gland. *Diagn Cytopathol.* 2000;22(6):351-358.
- Bugalho MJ, Santos JR, Sobrinho L. Preoperative diagnosis of medullary thyroid carcinoma: fine needle aspiration cytology as compared with serum calcitonin measurement. *J Surg Oncol.* 2005;91(1):56-60.
- Trimboli P, Cremonini N, Ceriani L, et al. Calcitonin measurement in aspiration needle washout fluids has higher sensitivity than cytology in detecting medullary thyroid cancer: a retrospective multicentre study. *Clin Endocrinol.* 2014;80(1):135-140.
- Bhanot P, Yang J, Schnadig VJ, Logroño R. Role of FNA cytology and immunochemistry in the diagnosis and management of medullary thyroid carcinoma: report of six cases and review of the literature. *Diagn Cytopathol.* 2007;35(5):285-292.
- Wells SA, Haagenen DE, Linehan WM, Farrell RE, Dilley WG. The detection of elevated plasma levels of carcinoembryonic antigen in patients with suspected or established medullary thyroid carcinoma. *Cancer.* 1978;42(3 Suppl):1498-1503.
- Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. *Cancer.* 2000;88(5):1139-1148.
- Modigliani E, Cohen R, Campos JM, et al. Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. The GETC Study Group. Groupe d'étude des tumeurs à calcitonine. *Clin Endocrinol.* 1998;48(3):265-273.

How to cite this article: Askari E, Pourabdollah Toutkaboni M, Haseli S, et al. Not all that is miliary is tuberculosis: Metastatic medullary thyroid carcinoma mimicking miliary tuberculosis. *Clin Case Rep.* 2021;9:e04231. <https://doi.org/10.1002/ccr3.4231>