


Thyroid sarcoidosis: a rare entity in the differential diagnosis of thyroid cancer

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Summary

We present two cases of thyroid sarcoidosis that were misdiagnosed as thyroid cancer. In the first patient, fine needle aspiration cytology (FNAC) of a suspicious thyroid nodule indicated the presence of papillary thyroid cancer, and the patient underwent thyroid surgery. However, histopathology identified a sarcoid granuloma, without any sign of malignancy. The second patient had a history of papillary microcarcinoma with suspicious lymph nodes diagnosed years after the initial diagnosis and was referred for assessment of cervical lymphadenopathy. Fine needle aspiration cytology (FNAC) of the suspicious lymph nodes erroneously indicated metastasis from thyroid cancer, and lateral modified lymph node dissection was performed, based on FNAC and ultrasonographic features. Histopathology excluded malignancy and identified non-caseating granulomas. Sarcoidosis of the thyroid may have a clinical presentation similar to well-differentiated thyroid carcinoma and, although rare, should be considered in the differential diagnosis, especially when other signs of the disease are already present. In these cases, FNAC provided a false diagnosis of papillary thyroid carcinoma and lymph node metastases that led to unnecessary surgery.

Learning points:

- Sarcoidosis may share clinical and ultrasonographic features with papillary thyroid carcinoma.
- Fine needle aspiration cytology is helpful in the diagnosis of both conditions; however, the overlapping cytological characteristics may lead to erroneous diagnosis.
- The present cases illustrate the importance of cytological identification of these difficult cases. Every piece of information provided by the clinician is essential to the cytologist.

Background

Sarcoidosis is a multisystemic disease characterized by the presence of non-caseating granulomas. Various sites may be affected by sarcoidosis, most commonly the lungs (90%), skin (20%), and eyes (15%) (1). Thyroid involvement is rare with a prevalence of 1–4% in case series of autopsied patients with systemic sarcoidosis (2). Thyroid sarcoidosis usually manifests as a gradual enlargement of the gland, eventually causing compressive symptoms, but may also present as a multinodular goiter or as cold solitary thyroid

nodules, with or without cervical lymphadenopathy (3). Hyper- or hypothyroidism and autoimmune thyroid disease may also be present and, according to some case series, even associated with sarcoidosis of the thyroid (4).

The differential diagnosis between a sarcoid granuloma of the thyroid and a primary thyroid carcinoma is challenging, as they may appear with similar ultrasonographic features. When cervical lymphadenopathy is present, extreme caution is needed

when determining its inflammatory or metastatic nature before leading the patient to the operating room. Two cases of thyroid sarcoidosis will be presented subsequently, demonstrating that thyroid sarcoidosis can both mimic and coexist with thyroid carcinoma, thus highlighting the importance of correctly diagnosing this rare thyroid condition when treating thyroid cancer.

Case presentation

Patient 1

A 70-year-old woman presented to her physician with generalized fatigue and malaise that first presented 1 month prior to the visit. She had an unremarkable medical history apart from a family history of coronary artery disease and heart failure. Physical examination indicated nothing of note except for a palpable nodule of the left thyroid lobe. She was referred to an endocrinologist.

Patient 2

A 74-year-old woman was referred to the endocrinology department for follow-up after total thyroidectomy and right modified radical neck dissection. Her histological report showed bilateral numerous non-caseating sarcoid-like granulomas, consisting of epithelioid cells and multinucleated giant cells. In the left lobe, a papillary microcarcinoma of 3 mm with extrathyroidal extension was identified. A lymph node adhering to the left lobe showed metastatic infiltration from thyroid cancer (stage T3pN1pMx according to the TNM classification). In addition to those findings, a Hürthle cell adenoma of the right lobe was evident, along with multiple lymphocytic infiltrates indicative of Hashimoto's thyroiditis. Non-necrotising granulomas were present in 10 of 14 resected lymph nodes in total.

The patient underwent radioiodine ablation therapy postoperatively. Post-treatment whole body scan showed uptake in the neck. Stimulated thyroglobulin (Tg) levels were low (0.45 ng/mL). In addition, further examinations to evaluate other organ involvement from sarcoidosis were recommended. A chest CT revealed bilateral hilar enlargement and ground glass opacities in the lower lung segments bilaterally. A bronchoalveolar lavage showed an elevated percentage of lymphocytes (26%) with a decreased percentage of neutrophils (4%) and a significantly elevated CD4+/CD8+ ratio of 1.36, all supportive of sarcoidosis (5).

Investigation

Patient 1

The patient was found clinically and biochemically euthyroid. Thyroid ultrasound revealed a hypoechoic mixed nodule of the left lobe, 36 mm × 23 mm × 29 mm in size, with increased vascularity, microcalcifications, and smooth margins (Thyroid Imaging Reporting and Data System — TI-RADS: 4B), as well as multiple not suspicious thyroid nodules smaller than 1 cm (Fig. 1). No suspicious lymph nodes were detected. A fine needle aspiration cytology (FNAC) of the suspicious nodule demonstrated a three-dimensional papillary architecture of follicular cells with micronucleoli, intranuclear inclusions and grooves, basophilic cytoplasm, and eccentric nuclei. In addition, psammoma bodies and giant cells were present in the sample. The sample was diagnostic for malignancy and was classified according to the Bethesda system as category VI.

Patient 2

During the patient's follow-up and 2 years after her initial surgery, a neck ultrasound indicated suspicious lymph nodes in the left lateral neck compartment with loss of fatty hilum and round shape. Tg levels remained low on TSH suppression (0.25 ng/mL). The FNAC suggested metastasis from thyroid carcinoma, describing some medium-sized malignant cells in groups with hyperchromatic nuclei, often overlapping. The Tg level measured in the washout of the aspirate was 0.73 ng/mL.

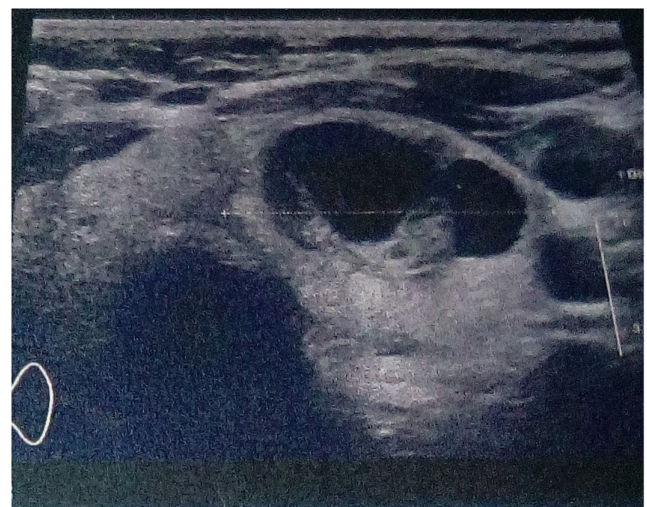


Figure 1

Ultrasongraphic appearance of sarcoid granuloma of the thyroid resembling a suspicious thyroid nodule. The FNAC of the above-depicted lesion was erroneously classified as Bethesda VI.



The biochemical and hormonal data of the two patients at the time of the initial evaluation are presented in [Table 1](#).

Treatment

Patient 1

The patient underwent a total thyroidectomy and central and left neck dissection including compartments III, IV, and VI, as surgeons identified enlarged lateral lymph nodes and decided to perform additional lateral neck dissection. Multiple nodular formations were evident in both lobes, and the largest one was located in the left lobe measuring 3.2 cm. Also, a total of 30 lymph nodes were excised. Microscopically, the nodular parenchyma showed cystic degeneration and fibrous tissue, with foci of papillary and follicular hyperplasia. In both the thyroid gland and lymph nodes, several congregating non-caseating granulomas were identified, composed of epithelioid histiocytes and Langhans giant cells. Ziehl-Nielsen and periodic acid-Schiff stains were negative for any microorganisms. Therefore, the findings indicated sarcoidosis of the thyroid with cervical granulomatous lymphadenitis, without any signs of malignancy.

Postoperatively, the patient was started on levothyroxine and was referred for further investigation regarding the involvement of other organs. While the preoperative chest X-ray showed mild hilar enlargement, a chest CT of the patient also revealed multiple pulmonary small nodules (pulmonary sarcoidosis stage II).

Patient 2

Upon suspicion, a left neck dissection was performed. The histopathology report described 17 lymph nodes in total, all of which presented non-caseating granulomas

Table 1 Biochemical and hormonal data of the two patients.

Parameter	Reference values	Patient 1	Patient 2
TSH, mIU/L	0.3–4.4	2.25	0.31
FT4, pmol/L	7.8–19.4	12.32	16.56
Anti-Tg, IU/mL	<70	10	28
Anti-TPO, IU/mL	<50	15	5.73
Calcium, mg/dL	8.4–10.2	9.4	10.4
ALB, g/dL	3.5–5	4.3	4.3
PTH, pg/mL	<65	25	60
25(OH)D3, ng/mL	25–50	37	22

ALB, albumin; Anti-Tg, antithyroglobulin antibodies; Anti-TPO, anti-thyroid peroxidase antibodies; FT4, free thyroxine; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; 25(OH)D3, 25-hydroxyvitamin D3.

composed of epithelioid cells and multinucleated giant Langhans cells. No signs of malignancy were evident ([Fig. 2](#)).

Outcome and follow-up

Patient 1

After a 2-year follow-up, the patient is stable without need for treatment for pulmonary sarcoidosis.

Patient 2

After a 3-year follow-up, the patient shows no signs of metastatic disease. In regard to her sarcoidosis, the radiologic findings of bilateral hilar lymphadenopathy remain present, but the patient did not require treatment.

Discussion

Sarcoidosis of the thyroid is extremely rare. It may present with clinical characteristics mimicking papillary adenocarcinoma (6), diffuse multinodular goiter, or painful thyroid nodule (3) and more commonly with symptoms of dysphagia and/or dyspnea due to gradual enlargement of the gland. While the differential diagnosis of thyroid sarcoidosis can pose a serious challenge, it has been shown that it can also coexist or be associated with other thyroid disorders, namely Hashimoto's disease, Grave's disease, and resistant thyrotoxicosis (4). The association with Hürthle cell hyperplasia or adenoma is scanty in the literature (7). To the authors' knowledge and to this

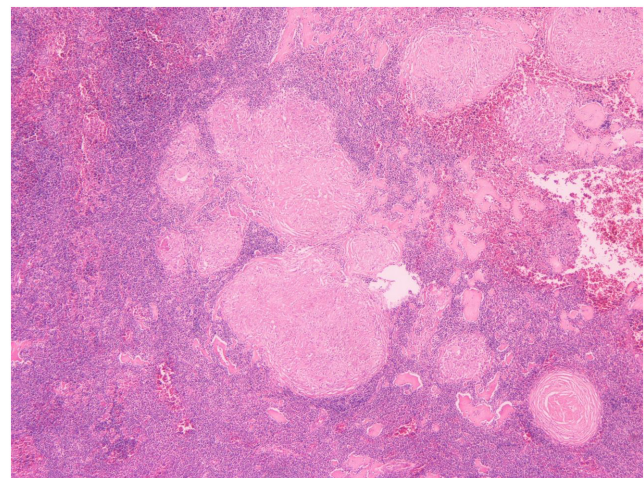


Figure 2 Cervical lymph node specimen with sarcoid granulomas lacking caseous necrosis (hematoxylin and eosin stain, ×100).



date, no case of histopathologically proven coexistence of papillary thyroid carcinoma, Hashimoto's disease, Hürthle adenoma, and sarcoidosis of the thyroid has been reported, as in the second case.

Apart from the difficult differential diagnosis between thyroid sarcoidosis and other thyroid diseases, its diagnosis remains elusive, when other causes of granulomatous inflammation are contemplated, such as tuberculosis, fungal infections, DeQuervain thyroiditis, and non-Hodgkin's lymphoma. The variations of the clinical presentation of the disease may add to the diagnostic difficulty. Fine needle aspiration is indisputably an invaluable tool in the differential diagnosis of thyroid nodules and especially in accurately detecting thyroid malignancy, being a technique with proven high specificity and sensitivity. However, in both our cases, FNAc erroneously indicated thyroid malignancy instead of sarcoidosis. This is not a unique phenomenon in the literature, although a clear explanation for the cytological confusion has not been given. One possible explanation might be the scattered pattern of granulomatous infiltration, which can therefore be missed by FNAc (3). In addition, the reactive follicular cells, forming hyperplastic papillary structures, along with giant cells due to sarcoidosis, can mimic a papillary thyroid carcinoma. Lastly, condensed colloid in the papillary structures can be erroneously interpreted as psammoma bodies. Core needle biopsy (CNB), on the other hand, has been reported to detect non-caseating granulomas of the thyroid, when used as an alternative method to transbronchial biopsy in patients with thyroid and pulmonary sarcoidosis (8).

The second case reported in this article raises a discussion regarding the management of cervical lymphadenopathy in patients with known sarcoidosis. Granulomatous infiltration of cervical lymph nodes may have a radiographic appearance mimicking nodal metastases. This radiographic similarity, along with an FNAc reporting malignancy, due to reactive lymphocytes in aggregates, can falsely lead to surgery. In the reported case, immunohistochemistry for thyroid transcription factor-1, T_g, and cytokeratin-19 was not diagnostic due to limited cytologic material. Spiekerman *et al.* discussed the diagnostic and therapeutic dilemma posed by the coexistence of sarcoidosis and metastatic lesions, reviewing 59 patients with history of sarcoidosis and solid malignant tumors reported in the literature, eight of which had thyroid carcinomas. In addition to bioptical evaluation of suspicious lymph nodes, the authors suggested the use of F18-labeled 3'-deoxy-3'-fluorothymidine-PET scan as a helpful tool to discriminate

between inflammatory lymphadenitis and metastatic lesions, thus achieving avoidance of unnecessary surgery or insufficient treatments, although more research is needed in this regard (9). More recently, Wenter *et al.* extensively discussed the challenges of differentially diagnosing lesions in 16 patients with concomitant thyroid carcinoma and sarcoidosis, with cytology or histology needed for a definitive diagnosis in most cases (10).

In conclusion, sarcoidosis involving the thyroid gland is a rare entity and may pose a diagnostic challenge. It can coexist with other thyroid disorders including thyroid carcinomas. Granulomatous diseases, although very rare, should be considered when patients present with a neck mass and cervical lymphadenopathy. In cases of inconclusive FNAc results, a CNB could be a useful diagnostic tool, in order to avoid misdiagnosis and overtreatment.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent for publication of the clinical details was obtained from both patients.

Author contribution statement

The authors provide hereby affirmation of the originality of this article and of the participation of all listed authors in this work in a substantive manner. Surgeons Katsamakos M and Zafeiriou G and surgical resident Tzitzili E performed the above-mentioned surgical interventions. Endocrinologists Boudina M and Chrisoulidou A initially evaluated and conducted the follow-up of the patients presented. Kiziridou A was the pathologist who examined the surgical specimens and Valeri R. was the cytologist who assessed the FNAc specimens.

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