



The Diagnostic Dilemma of Metastatic Papillary Thyroid Carcinoma vs Tubercular Cervical Lymphadenitis

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ABSTRACT

Papillary thyroid cancer (PTC) often leads to cervical lymph node metastasis, occurring in 50–70% of cases. This high prevalence can sometimes cause clinicians to overlook other potential causes of cervical lymphadenopathy, especially in regions where tuberculosis (TB) is common. Distinguishing between these conditions can be challenging as they appear similar on ultrasound and cytology. However, examination of paraffin-embedded sections is the most effective way to differentiate between the two. We present a case series of three interesting patients where differentiation between the two conditions posed a diagnostic challenge. In two patients, the diagnosis was made after surgery, while in one patient, the diagnosis was made before surgery, preventing the patient from undergoing an unnecessary procedure.

Keywords: Case report, Diagnostic dilemma, Metastasis, Papillary thyroid carcinoma, Tubercular lymphadenitis.

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INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for about 80–85% of cases. It is the most common malignant tumor of the thyroid in countries with adequate or excessive iodine intake. These tumors are usually slow-growing and have a good prognosis, with a survival rate of over 95% at 25 years.¹ Regional lymph node metastases occur in approximately 50% of cases, even in the early stages of the disease. However, some patients with enlarged cervical nodes may not have metastatic thyroid cancer and may have a different disease, especially in regions where tuberculosis (TB) is common.² A small percentage of PTC patients with enlarged lymph nodes may have TB rather than metastasis. Globally, about 35% of patients with TB have TB lymphadenitis.³ Diagnosing these patients is challenging and often relies on fine-needle aspiration cytology (FNAC), which has a 70–80% sensitivity.⁴ Therefore, it can be a diagnostic dilemma. When it comes to treating metastatic cervical nodes, neck dissection is the preferred method, but it can cause complications. On the other hand, treating TB lymphadenitis with anti-tuberculosis medication is a much simpler option than surgery. This study discussed three challenging cases of PTC with cervical tubercular lymphadenitis diagnosed at various management stages.

CASE SERIES

Case 1

A 48-year-old woman noticed a swelling on the left side of her neck, which gradually increased without any accompanying symptoms. She was evaluated elsewhere and diagnosed with PTC, measuring 2.5 cm in the largest dimension. Following this diagnosis, she underwent a left hemithyroidectomy at that center, and the pathology report confirmed the presence of PTC without any high-risk features. Three-month post-surgery, she received radioactive iodine (RAI) therapy and was started on a suppressive dose of thyroxine. During the COVID-19 pandemic, the patient did not follow-up for 3 years. She then presented to

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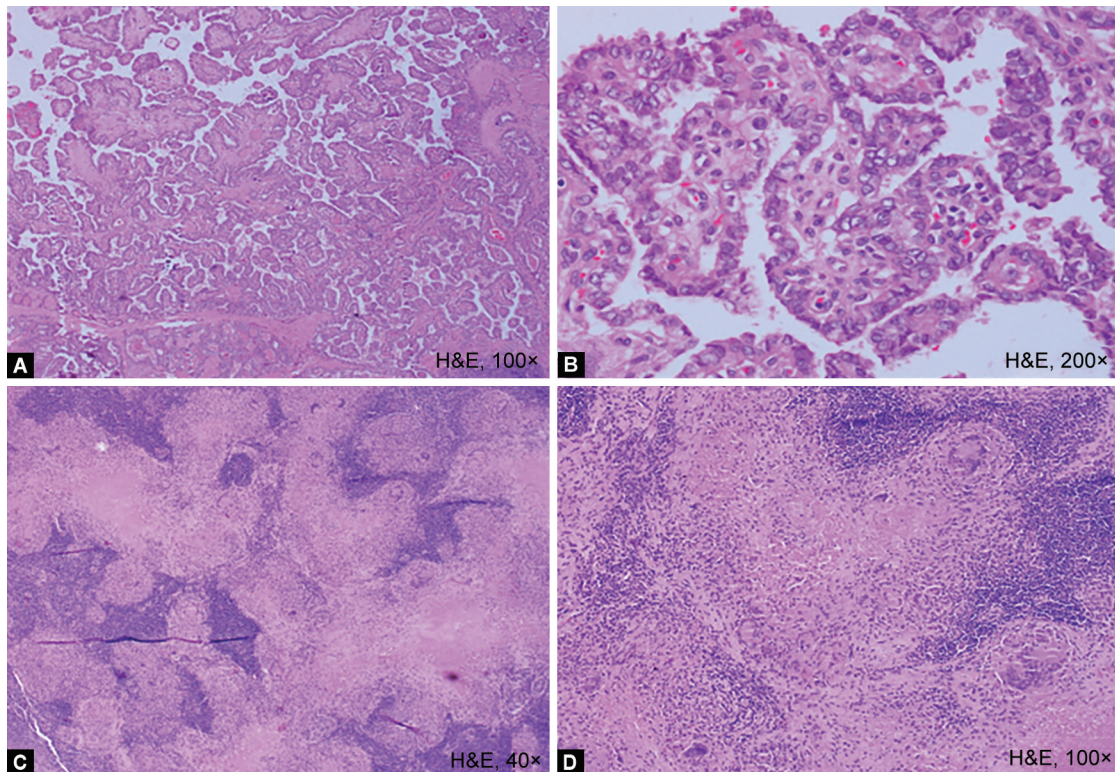
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our hospital with swelling in the left cervical lymph nodes. The diagnostic process involved a neck ultrasound (USG) followed by USG-guided FNAC from a suspicious lymph node, confirming the presence of PTC. A PET scan indicated metabolic activity in the left cervical lymph nodes, with no evidence of distant metastasis. The case was discussed in the MDT, and the patient was planned for left selective lymph node dissection (SND). The surgical findings revealed 2–3 enlarged, dark-colored nodes at levels II, III, and IV. Histopathological examination (HPE) of 15 lymph nodes showed that two nodes exhibited non-necrotizing epithelioid granulomas only, with no evidence of tumor involvement. These features were indicative of granulomatous lymphadenitis. A chest X-ray was done to rule out concomitant pulmonary TB, and screening for human immunodeficiency virus (HIV) was performed to assess the immunocompromised status. Consequently, the patient was started on anti-tubercular treatment (ATT) and completed the treatment with no recurrence at the last follow-up visit.



Figs 1A to D: (A and B) (H&E 100× and 200×) Sections from the thyroid show a papillary patterned tumor; tumor cells are arranged in papillae having fibrovascular cores, showing nuclear elongation, focal nuclear overlapping, overcrowding, and clearing with few intranuclear grooves and intranuclear cytoplasmic inclusions; (C and D) (H&E 40× and 100×) Sections from the lymph node depicting multiple necrotizing epithelioid cell granulomas with Langerhans giant cells surrounded by a collar of lymphocytes suggestive of TB

Learning Point

Every cervical lymphadenopathy in a case of PTC is not metastasis, especially if there are no high-risk features.

Case 2

A 13-year-old girl with down syndrome visited our outpatient department with a swelling in the front of her neck that had been present for the last 2 years. The swelling started as a small lump and gradually increased in size with no other accompanying symptoms. A firm generalized thyroid swelling and a 2 × 1 cm left level 1b lymph node were observed upon clinical examination. Ultrasound examination revealed a heterogeneously enlarged thyroid with no discrete nodule and multiple necrotic lymph nodes in the neck at levels 1b, 2, and 3, with the largest measuring 2.7 × 1.3 cm in the left level 1b, suggesting possible metastatic involvement. Subsequent ultrasound-guided FNAC from the thyroid and the lymph node suggested PTC. However, this was suspected to be incorrect as the thyroid had no discrete nodules visualized on the ultrasound.

Further, contrast-enhanced computed tomography (CECT) of the neck revealed enlarged thyroid lobes with nodular margins and lymphadenopathy in the neck, mediastinum, and internal mammary locations. The suspicion of other pathologies, such as lymphoma or TB, was considered at this point. Therefore, the patient was planned for an excisional cervical lymph node biopsy and a simultaneous core-needle biopsy of the thyroid under general anesthesia. Histopathological examination of the lymph node sections revealed necrotizing granulomatous lymphadenitis,

consistent with TB. The thyroid biopsy revealed lymphocytic thyroiditis. Chest X-ray and HIV testing were unremarkable. The patient was initiated on ATT and exhibited a clinically complete response. The thyroid swelling normalized on follow-up.

Learning Point

This case highlights the importance of a core-needle biopsy of the thyroid gland, which saved this girl an unwarranted thyroidectomy. Also, it showcases the role of excisional biopsy of the lymph node for an unequivocal diagnosis of TB.

Case 3

A 47-year-old woman, previously in good health, noticed a swelling on the left side of her neck a year ago. A neck ultrasound revealed a large cystic lesion with internal echoes and a peripheral nodular solid lesion with small calcifications. Multiple hypoechoic lesions were also observed in the thyroid. A CECT of the neck showed a well-defined multiloculated cystic lesion measuring 41 × 42 × 59 mm with mild hypodense eccentric soft tissue in the left thyroid lobe and no cervical lymphadenopathy. Ultrasound-guided fine-needle aspiration (FNA) from the solid cystic lesion revealed follicular cell clusters with nuclear enlargement, and the solid nodule was suggestive of PTC. The patient was planned for a total thyroidectomy. However, intraoperatively, a few central compartment nodes and the left lateral compartment nodes were enlarged. These were sent for a frozen section, which reported them to be positive for the tumor. Thus, central compartment lymph node dissection (CCLND) and left SND were performed. However, the final histopathology report from the left thyroid lobe confirmed

the presence of PTC (Figs 1A and B). However, the SND specimen yielded seven lymph nodes, and the CCLND specimen yielded one lymph node, all free of tumors but three lymph nodes (2 from SND and one from CCLND) exhibiting multiple non-necrotizing epithelioid granulomas (Figs 1C and D). Consequently, the patient was started on ATT for extrapulmonary TB.

Learning Point

Prophylactic CCLND in T3 and T4 is still debatable, and performing an intra-operative frozen section guides the individualized treatment protocol.

DISCUSSION

Papillary thyroid cancer is the most common type of thyroid cancer and is known for its tendency to spread to cervical lymph nodes.^{5,6} Diagnosing metastatic PTC involves FNAC examination of the suspicious lymph node, typically done with ultrasound guidance. On the other hand, extrapulmonary TB often presents with lymph node involvement, particularly in the neck.³ Diagnosis of this condition is based on clinical presentation, inflammatory markers, and excisional biopsy of the affected node, sometimes including polymerase chain reaction (PCR) based tests.⁷ Occasionally, in areas where TB is common, enlarged lymph nodes in patients with known papillary thyroid cancer may not be due to cancer metastasis but instead because of TB. In such cases, a diagnostic challenge may arise. A case series from a country with endemic TB reported that 72% of cases of papillary thyroid cancer with cervical lymphadenopathy were found to have TB upon postoperative histopathology.⁸ Our case series presents three cases where the authors encountered a diagnostic dilemma.

The diagnostic challenge begins with similar ultrasound features of the affected lymph nodes. Metastatic cervical lymph nodes show peripheral calcifications, intranodal cystic necrosis, lack of an echogenic hilum, a minimum axial diameter of the lymph node >6 mm for the rest of the neck, and >7 mm for level II, hyperechogenicity around the surrounding muscles, and lack of an echogenic hilum.⁹ The most distinctive features are the lymph node's calcification and cystic necrosis.⁹ Lymph nodes in TB lymphadenitis have similar characteristics, such as hypoechoic, round sonographic features, intranodal cystic necrosis, and calcification.¹⁰

All the suspicious nodes are sampled with ultrasound-guided FNAC. Papillary thyroid carcinoma is a cyto-morphologically diverse entity due to its numerous subtypes and the absence of characteristic nuclear features in some of the subtypes. Tubercular lymphadenitis displays epithelioid cells with or without giant cells on the FNAC, which can give a similar pattern and confuse the diagnosis. For example, the preoperative FNAC reported PTC in the first case, but the postoperative HPE revealed tubercular lymphadenitis. The proposed strategy to differentiate these two entities on the lymph node FNAC sample is to either perform an FNA wash of thyroglobulin to confirm the diagnosis of metastatic PTC or combine the FNAC with PCR for mycobacterium detection.^{11,12} Fine-needle aspiration-based QuantiFERON tests may be helpful in the detection of cervical lymph node tuberculous infection.¹³ Studies have reported PCR positivity rates ranging from 40 to 90% in these patients' FNA samples.¹⁴ Therefore, it is advisable to establish a standardized protocol for systematically screening all cases of PTC with cervical lymphadenopathy. This protocol should include conducting fine needle aspirate PCR, specifically utilizing Gene Xpert technology, to detect mycobacterium TB. Chest X-ray imaging and

HIV screening should also be integrated into this comprehensive screening approach.

Another option is to perform an excisional biopsy of the palpable node under local/general anesthesia and send it for histopathology to confirm the diagnosis. This approach is uncommon among clinicians because it causes discomfort to the patient and results in two surgical procedures instead of one. In the second case, the LN biopsy was performed under general anesthesia. This also allowed the team to perform a core-needle biopsy of the thyroid because the diagnosis was PTC, which was not clinically suspected due to the absence of discrete nodules identified on the ultrasound scan.

There is increasing interest in the role of the frozen section of the lymph nodes to identify the metastasis. Kim et al. reported that all 28 individuals with cervical lymphadenopathy and a preoperative diagnosis of PTC, along with radiographic features suggesting metastasized lateral neck nodes, did not have lymph node dissection (LND) based on the findings of intraoperative frozen sections. Out of the eight patients who had LND, seven had metastases along with tuberculous lymphadenopathy, while the other patients had no metastasis.¹⁵ However, in our third case, a similar situation arose when a patient planned for total thyroidectomy had enlarged lymph nodes intra-operatively, and those were sent for the frozen section. It was reported positive for the tumor, but on final histopathology, it was reported as tubercular lymphadenitis. This was highly unusual, and the probable reason for this is that the sectioning was done from the non-representative part of the lymph node, which showed just the epithelioid cells without the necrosis or the giant cells.

Treatment of metastatic PTC involves upfront surgery of the resectable disease followed by radio-iodine ablation of any residual/distant disease. In the case of recurrent, radio-refractive cases, the role of multikinase inhibitors is evolving. At the same time, treatment regimens for pulmonary and extrapulmonary TB are generally similar. This highlights the importance of early diagnosis and timely initiation of appropriate treatment to mitigate the morbidity and mortality associated with TB, particularly in individuals with comorbidities like HIV.¹⁶

As endocrine surgeons in a country endemic to TB, it is essential to be aware of such a dilemma, and further studies should be performed at a multi-institutional level to determine its prevalence. We should also know the evolving strategies to differentiate between these two close differentials preoperatively. This includes FNA wash thyroglobulin, FNA AFB, FNAC PCR, and FNA QuantiFERON. Intraoperative frozen section is an option for clinically suspicious cases.

CONCLUSION

Tubercular lymphadenitis can coexist with PTC and resemble PTC on ultrasound and cytology. Intraoperative frozen sections and paraffin-embedded histopathology can assist in confirming the diagnosis. In TB endemic areas, patients with PTC and lymphadenopathy should be investigated for coexistent TB. The role of TB work-up in patients with PTC and lymphadenopathy should be evaluated in well-designed prospective studies.

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