

PTH washout as a decisive biochemical tool in a diagnostic dilemma: Ectopic parathyroid adenoma mimicking metastatic disease

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TO THE EDITOR,

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia and most commonly caused by parathyroid adenomas [1]. Accurate preoperative localization of hyperfunctioning parathyroid tissue has become increasingly important with the widespread use of minimally invasive surgical approaches. Although ultrasonography and Tc-99m sestamibi scintigraphy are routinely used as primary imaging modalities, they may not provide sufficient diagnostic accuracy in some cases. Imaging findings may be particularly inconclusive or conflicting in parathyroid lesions with ectopic localization or accompanying thyroid pathologies [2].

PTH washout (PTH-WO) analysis is a biochemical confirmation method based on measuring parathyroid hormone (PTH) levels in aspiration material obtained under ultrasonographic guidance and may be particularly useful when imaging studies are inconclusive [3,4]. Herein, we present a rare case of an ectopic parathyroid adenoma located at the level of the carotid bifurcation in a patient with lung adenocarcinoma, mimicking metastatic cervical lymphadenopathy, and highlight the contribution of PTH-WO analysis to the diagnostic process.

A 61-year-old woman scheduled for radiotherapy because of lung adenocarcinoma was found to have persistent hypercalcemia during oncological follow-up. It was learned that the patient had elevated serum calcium levels for approximately 1.5 years. Biochemical evaluation demonstrated serum calcium levels ranging between 11.5 and 12.8 mg/dL, while serum PTH levels increased up to 958 pg/mL. These biochemical findings were considered more consistent with PHPT rather than malignancy-associated hypercalcemia. The patient's biochemical and hormonal laboratory findings are summarized in Table 1.

In this patient with an indication for curative parathyroid surgery because of PHPT, multiple imaging modalities were used for preoperative lesion localization. Neck ultrasonography demonstrated multiple thyroid nodules consistent with multinodular goiter, exhibiting Thyroid Imaging Reporting and Data System (TI-RADS) 3–4 features. In addition, a heterogeneous lesion measuring 33 × 28 × 15 mm was identified in the left level III region, superolateral to the left thyroid lobe. Based on its ultrasonographic characteristics, the lesion was initially considered to represent ectopic thyroid tissue; however, the possibility of metastatic cervical lymph node involvement could not be excluded because of the accompanying history of lung adenocarcinoma. Tc-99m sestamibi scintigraphy demonstrated mild focal uptake posterior to the inferior pole of the left thyroid lobe, although the findings were insufficient for reliable localization of hyperfunctioning parathyroid tissue. Ultrasonographic evaluation also failed to demonstrate the typical features of parathyroid adenoma. Therefore, imaging modalities did not clearly support a parathyroid origin for the lesion, and metastatic lymph node, ectopic thyroid tissue, and ectopic parathyroid adenoma were all considered in the differential diagnosis.

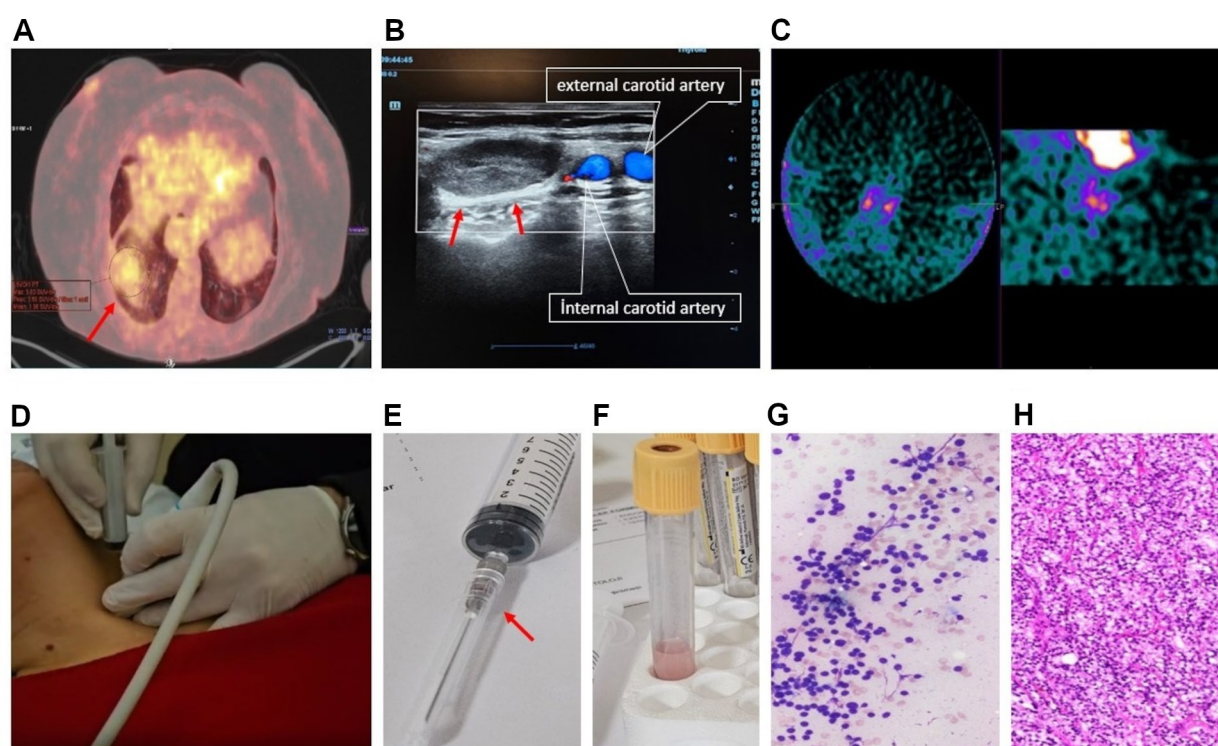
Fine-needle aspiration biopsy (FNAB) of the suspicious cervical lesion was performed by interventional radiology. Cytological examination demonstrated mature lymphoid cells in a hemorrhagic background, and the findings were reported as benign cytology consistent with a reactive lymph node. In addition, the presence of persistent indeterminate cytology in the nodule inferior to the left thyroid lobe raised the possibility that the lesion in the left level III region could represent metastasis from thyroid malignancy. However, despite repeated cytological evaluations, the origin of the lesion could not be definitively determined.

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Table 1. Clinical biochemical findings during the diagnostic and postoperative period

Parameter	Preoperative	Postoperative	Reference Range
Calcium (mg/dL)	12.8	9.3	8.4 – 10.2
Phosphate (mg/dL)	2.6	4.6	2.5 – 4.5
PTH (pg/mL)	585 – 958	47.6	15 – 65
PTH washout (pg/mL)	3,677	—	Not available*
Thyroglobulin washout (µg/L)	0.04	—	Not available*
Alkaline phosphatase (U/L)	185	78	35–105
Vitamin D (ng/mL)	5.02	8.7	30 – 50 ng/mL
TSH (mIU/L)	1.58	2.2	0.27 – 4.2
Creatinine (mg/dL)	0.49	0.62	0.50 – 0.90
eGFR (mL/min/1.73 m ²)	105	98	> 60
24-hour urinary calcium (mg/day)	303	—	Female: < 250 Male: < 300

The symbol “—” indicates parameters that were not re-evaluated postoperatively because repeat measurement was not considered clinically necessary. *No universally accepted reference ranges are available for PTH or thyroglobulin washout analyses [10]. Abbreviations: PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; eGFR, estimated glomerular filtration rate.

**Figure 1. Diagnostic workup, biochemical confirmation, and histopathological diagnosis of an ectopic parathyroid adenoma mimicking metastatic disease**

(A) FDG PET/CT image of the patient demonstrating a hypermetabolic lesion corresponding to lung adenocarcinoma in the right lower lobe of the lung (SUVmax: 4.56, red arrow). **(B)** B-mode ultrasonography showing a lesion measuring approximately 3.3 × 2.8 cm in the left level III region, containing central cystic and hyperechoic components (red arrows). On initial evaluation, the lesion was interpreted as ectopic thyroid tissue; however, metastatic lymphadenopathy could not be excluded because of the patient's history of lung adenocarcinoma. Doppler ultrasonography demonstrated that the lesion was located at the carotid bifurcation adjacent to the internal and external carotid arteries. No prominent vascular Doppler findings typically characteristic of parathyroid adenomas were identified within the lesion. **(C)** Tc-99m sestamibi/SPECT pinhole images demonstrating radioactive uptake corresponding to the localization of the left inferior thyroid nodule, which was cytologically reported as Bethesda category III. Therefore, the findings were initially interpreted in favor of a thyroid nodule, and the ectopic parathyroid lesion could not be differentiated. **(D)** Ultrasonography-guided fine-needle aspiration and PTH washout procedure. **(E–F)** Demonstration of the hemorrhagic intralesional aspirate obtained using a 23-gauge needle (red arrow), which was washed with 1 mL saline solution and transferred into a biochemistry tube. PTH washout analysis provided biochemical confirmation of the parathyroid origin of the lesion. **(G)** Giemsa-stained fine-needle aspiration cytology smear demonstrating scattered mature lymphoid cells in a hemorrhagic background, initially interpreted as a benign reactive lymph node (×200). **(H)** Histopathological examination of the surgically excised lesion confirming the diagnosis of ectopic parathyroid adenoma (H&E stain, ×10). Abbreviations: PET/CT, positron emission tomography/computed tomography; SPECT, single-photon emission computed tomography; SUVmax, maximum standardized uptake value; PTH, parathyroid hormone; H&E, hematoxylin and eosin.

Because of persistent diagnostic uncertainty, the patient was referred to the endocrinology clinic. Ultrasonographic evaluation demonstrated that the lesion had an atypical localization, exhibited ultrasonographic features similar to thyroid tissue, and lacked the typical vascularity pattern of parathyroid adenoma. Since conventional imaging modalities and cytological examinations remained diagnostically insufficient, thyroglobulin washout and PTH-WO analyses were performed during the same session. Fine-needle aspiration of the lesion was performed using a 23-G needle under real-time ultrasonographic guidance, and the obtained aspiration material was washed at least three times in 1 mL of saline solution for simultaneous biochemical analyses, according to our institution's standard PTH washout protocol [3]. The aim of thyroglobulin washout analysis was to evaluate whether the lesion represented ectopic thyroid tissue or possible metastatic thyroid malignancy. The detection of a very low thyroglobulin level (0.04 µg/L) largely excluded thyroid tissue. In contrast, the markedly elevated PTH-WO level (3677 pg/mL) strongly supported the parathyroid origin of the lesion. In this case, where imaging modalities and cytological examinations yielded conflicting results, PTH-WO analysis became the key biochemical confirmation method leading to the diagnosis.

The patient underwent simultaneous total thyroidectomy and parathyroidectomy because of concomitant multinodular goiter and indeterminate thyroid cytology. Intraoperative frozen-section examination was consistent with parathyroid tissue, and final histopathological evaluation confirmed ectopic parathyroid adenoma. Multinodular goiter and lymphocytic thyroiditis were identified in the thyroidectomy specimen, while no malignancy was observed. Immunohistochemical examination demonstrated positivity for PTH together with negativity for thyroglobulin and TTF-1, supporting the diagnosis of parathyroid adenoma. Marked reductions in serum calcium and PTH levels were observed postoperatively, and biochemical cure was achieved. Representative imaging findings, cytological examination, PTH washout analysis, and histopathological features are presented in Figure 1.

In this case, marked discordance was observed between ultrasonography and Tc-99m sestamibi scintigraphy findings because of an ectopically located parathyroid adenoma. Due to the atypical localization of the lesion at the level of the carotid bifurcation, its ultrasonographic features resembling thyroid tissue, and the accompanying history of lung adenocarcinoma, the lesion was initially considered to represent either metastatic cervical lymph node involvement or ectopic thyroid tissue. This situation highlights the importance of

biochemical confirmation methods in cases where conventional imaging modalities remain insufficient [2–4]. In our case, PTH-WO analysis was the biochemical method that made a major contribution to confirming the parathyroid origin of the lesion.

Ectopic parathyroid adenomas may demonstrate a broad anatomical distribution because of embryological migration anomalies and can therefore create substantial diagnostic challenges [5]. Concomitant conditions such as multinodular goiter, chronic lymphocytic thyroiditis, and cervical lymphadenopathies may further complicate the interpretation of ultrasonography and sestamibi scintigraphy findings [3,6]. Similarly, in our case, the coexistence of multinodular goiter, indeterminate thyroid cytology, and an atypical cervical lesion reduced the reliability of radiological evaluations [5].

Cytological evaluation alone may yield insufficient or misleading results in suspicious parathyroid lesions [7]. Parathyroid aspiration material is often hypocellular and has been reported to potentially cytomorphologically resemble thyroid tissue, lymphoid tissue, papillary thyroid carcinoma, or Hürthle cell neoplasms [8,9]. Supporting this, mature lymphoid cells were observed on the initial FNAB in our case, and the lesion was interpreted as a benign reactive lymph node. This finding demonstrates that cytological evaluation should be supported by biochemical confirmation methods.

In recent years, PTH-WO analysis has emerged as a complementary biochemical confirmation method with high sensitivity and specificity, particularly in cases where imaging modalities and cytological evaluation are inadequate. In addition, simultaneous thyroglobulin analysis may contribute to the evaluation of thyroid-origin lesions such as exophytic thyroid nodules, ectopic thyroid tissue, or differentiated thyroid carcinoma metastasis, thereby providing additional biochemical support in the differential diagnosis [4,10]. In our case, although ultrasonography and sestamibi scintigraphy failed to provide definitive localization, the markedly elevated PTH-WO level (3,677 pg/mL) biochemically supported the parathyroid origin of the lesion. Furthermore, the simultaneously low thyroglobulin washout level contributed to excluding the possibility of ectopic thyroid tissue or metastatic thyroid malignancy.

One of the major advantages of the PTH-WO method is that it is minimally invasive and enables biochemical confirmation of potential parathyroid tissue. Particularly in patients with a history of malignancy and imaging findings that may be confused with metastatic disease, the PTH-WO method may help prevent unnecessary advanced and costly imaging studies or extensive surgical interventions.

The success of the method may be influenced by several factors, including aspiration technique, lesion localization, and accompanying thyroid pathologies. In addition, variability in standard cut-off values may complicate the interpretation of results [10,11]. On the other hand, data regarding the histopathological safety of the PTH-WO procedure remain limited, and cell seeding along the needle tract with subsequent development of parathyromatosis is considered among the theoretical complications [12–14]. Therefore, large-scale prospective studies are needed to better evaluate the clinical contribution, potential disadvantages, and long-term safety profile of this method.

We report this case to highlight a rare but clinically relevant diagnostic challenge and to share our experience with the use of PTH washout analysis, which may assist clinicians and laboratorians in the evaluation of similar cases.

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None.

AUTHORS' CONTRIBUTION

İÇ – Conceived and designed the study; managed the patient; performed ultrasonographic evaluation and PTH washout procedures; collected and interpreted the clinical and biochemical data; conducted the literature review; drafted and critically revised the manuscript.

MÇ – Performed and interpreted the nuclear medicine imaging studies; contributed to diagnostic evaluation and clinical interpretation; critically reviewed the manuscript.

All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

None to declare.

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ETHICS STATEMENT

Written informed consent was obtained from the patient before all diagnostic and interventional procedures and for publication of the clinical data and accompanying images included in this letter. Ethical committee approval was not required according to institutional policy.

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