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Ectopic parathyroid adenoma in a patient with multiple endocrine tumours

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Ectopic parathyroid adenomas (EPA) are a relatively common cause of primary hyperparathyroidism (PHPT), occurring with an incidence of up to 25% [1]. Ectopic parathyroid glands may arise from abnormal migration during embryogenesis, or they can be acquired, due to the influence of gravity in an enlarged parathyroid gland [2]. Regarding the anatomical location of EPA, an analysis of 26 studies enrolling 7005 patients with PHPT showed that only 4.3% of parathyroid glands were located in the mediastinum, and the majority were thymic [3]. Paraesophageal EPAs are rarely encountered, comprising 2.7% of EPAs found in a series of 231 patients with PHPT [4], of whom 16% had EPAs. Additionally, EPAs are more commonly seen in patients with multiple endocrine neoplasia (MEN) syndromes than in patients with sporadic hyperparathyroidism [5].

A 62-year-old female reported a history of multiple episodes of nephrolithiasis in the past 8 years, treated with lithotripsy and multiple surgeries. She complained of memory loss and difficulty focusing. Also, she had had high blood pressure since age 47, computed tomography (CT) scans showed a solitary pulmonary nodule with 10 mm, which had been stable for 6 years, and a 25 mm non-functioning right adrenal nodule that remained stable for 2 years.

Laboratory analysis was compatible with PHPT, with serum levels of calcium 11.2 mg/dL [normal range (NR): 8.4–10.2], phosphate 2.1 mg/dL (NR: 2.3–4.7), and intact parathyroid hormone (iPTH) of 236 pg/ml (NR: 12.0–65.0). Renal function and 25-OH vitamin D were within the reference intervals.

Neck ultrasonography (US) revealed a solid, hypoechogenic thyroid nodule with irregular borders and micro calcifications, which was 11 mm at its greatest dimension. However, it did not show nodules suggestive of parathyroid adenomas. Hence, a parathyroid gland scintigraphy was performed using [^{99m}Tc]Tc-hexakis-(2-methoxy-2-isobutyl isonitrile) ([^{99m}Tc]Tc-MIBI) in a single-tracer, dual-phase protocol. It revealed a right upper paraesophageal lesion with sustained radiotracer uptake, consistent with EPA, measuring 31 × 21 × 16 mm (anteroposterior × transverse × craniocaudal) (Fig. 1).

A fine needle aspiration biopsy of the suspicious thyroid nodule was performed, and the cytological analysis suggested a papillary thyroid carcinoma (PTC). Therefore, the patient underwent a combined surgery that included total thyroidectomy and excision of both the paraesophageal lesion and the pulmonary nodule. A right inferior parathyroid gland was also removed due to its abnormal appearance in the intraoperative examination; however, PTH

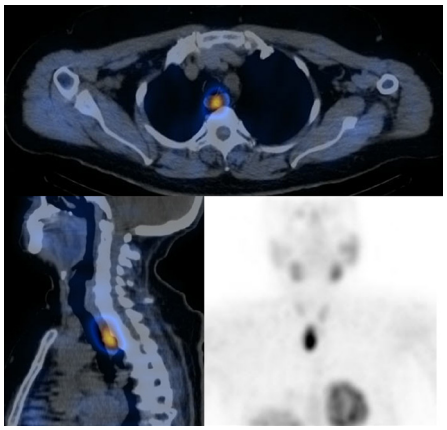

Figure 1. *[^{99m}Tc]Tc-MIBI single-photon emission computed tomography combining computed tomography (SPECT/CT) scintigraphy showing the paraesophageal lesion with sustained radiotracer uptake on the delayed images.* **AB.** *Axial and sagittal SPECT/CT images;* **C.** *Maximum intensity projection image*

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Table 1. *Calcaemia and phosphataemia evolution during follow-up*

	Before surgery	D1 post-op	D3 post-op	D5 post-op	D10 post-op	1M post-op	6M post-op	12M post-op*	15M post-op	Normal range
Calcium [mg/dl]	11.2	8.3	7.6	7.2	8.3	7.4	8.9	8.1	8.5	8.4–10.2
Phosphate [mg/dl]	1.2	3.2	3.5	3.4	5.1	3.6	3.2	3.5	3.1	2.3–4.7
iPTH [pg/ml]	236				< 3			27.5	41.2	12.0–65.0
GFR [ml/min/1.73 m^2]	93						74	84	56	> 90
Urinary calcium [mg/24 h]	340						106			100–300

D — day; M — month; iPTH — intact parathyroid hormone; GFR — glomerular filtration rate; *With no oral supplementation of calcium or vitamin D

levels remained elevated (216 pg/ml). After excision of the paraesophageal lesion, intra-operative PTH gradually decreased from 216 pg/ml to a minimum of 6.5 pg/ml at 30 minutes.

Pathology confirmed that the paraesophageal lesion was indeed a parathyroid adenoma. The pulmonary nodule was a grade 2 neuroendocrine tumour (NET) with 2 mitosis/ 2 mm^2 and a proliferation index Ki-67 of 3%, measuring 1.5 cm, defining an intermediate-grade atypical carcinoid. Histological analysis of the thyroid specimen documented a multifocal and angioinvasive PTC with a greatest dimension of 12 mm.

After surgery, the patient developed hungry bone syndrome, with a symptomatic hypocalcaemia that worsened during the following week despite increasing doses of oral calcium carbonate and calcitriol, with a transient requirement of intravenous calcium gluconate. She was discharged 10 days after surgery with oral supplementation of calcium and calcitriol, and although a gradual tapering was possible, permanent hypoparathyroidism was established. At the time of last medical visit, 15 months after surgery, the patient still required a low dose of calcium carbonate and calcitriol, and at this time serum calcium and iPTH levels were 8.5 mg/dL and 41.2 pg/mL, respectively (Tab. 1).

Regarding staging of the pulmonary NET, the patient underwent [^{68}Ga-DOTA^0-NaI^3] octreotide ([^{68}Ga] Ga-DOTA-NOC) positron emission tomography with computed tomography (PET/CT), which documented an increased uptake in an intracranial lesion in the left frontal region. MRI confirmed an intracranial lesion 8 × 3 mm, suggestive of a meningioma. During follow-up, chromogranin A was undetectable, and neuron-specific enolase (NSE) decreased from 13.9 to 5.5 ng/dL (NR < 11).

Given that the PTC was at intermediate risk of recurrence, the patient underwent radioiodine therapy with 3700 MBq iodine-131. Post-therapy whole-body scan showed no distant foci of uptake. She had no evidence of disease at her last medical visit.

Although no family history of hypercalcaemia or other known endocrine tumour was reported, the patient underwent genetic testing. However, no mutations were found in the *MEN1*, *CDC73*, *AIP*, *GCM2*, *CASR*, *RET*, *CDKN1A*, *1B*, *2B*, or *2C* genes.

We report a very rare case of a paraesophageal EPA. This infrequent location combined with the coexistence of a pulmonary NET and an adrenal tumour raised the possibility of a phenocopy. Because meningioma is one of the most common intracranial tumours and has only been described in patients with MEN syndrome who also have a pituitary adenoma, we cannot draw clear conclusions of an association in this case report.

Nevertheless, this case emphasizes the challenges of distinction between phenocopies from MEN 1 and MEN 4 syndromes based on clinical criteria.

Also, this report highlights [^{99m}Tc] Tc-MIBI SPECT/CT scintigraphy as an effective method to detect and locate EPAs in patients with PHPT, mainly in cases where lesions are not identified in US.

Conflict of interests

The authors have no conflicts of interest to disclose.

Statements of ethics

The research was conducted in accordance with the World Medical Association Declaration of Helsinki. Data were collected retrospectively.

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