

## A Giant Cystic Ectopic Parathyroid Adenoma of the Anterior Mediastinum Mimicking a Mediastinal Tumor: A Diagnostic Challenge

Irida Pano<sup>1</sup>, Vasileios Leivaditis<sup>2</sup>, Chrysa Andrikopoulou<sup>3</sup>, Elias Liolis<sup>4</sup>, Christos Sachpekidis<sup>5</sup>, Dimitrios Apostolopoulos<sup>6</sup>, Vasiliki Androutsopoulou<sup>7</sup>, Konstantinos Nikolakopoulos<sup>8</sup>, Ioannis Panagiotopoulos<sup>9</sup>, Artemisia Papadima<sup>10</sup>, Zafeiria Papathanassiou<sup>11</sup>, Efstratios Koletsis<sup>12</sup>, Francesk Mulita<sup>13\*</sup>

<sup>1</sup>Department of Clinical Subject, University of Medicine Tirana, Tirana, Albania

<sup>2</sup>Department of Cardiothoracic and Vascular Surgery, Westpfalz Klinikum, Kaiserslautern, Germany

<sup>3</sup>Department of Surgery, General Hospital of Aigio, Aigio, Greece

<sup>4</sup>Department of Oncology, General University Hospital of Patras, Patras, Greece

<sup>5</sup>Department of Nuclear Medicine, School of Medicine, Democritus University of Thrace, Alexandroupolis, Greece

<sup>6</sup>Department of Nuclear Medicine, General University Hospital of Patras, Patras, Greece

<sup>7</sup>Department of Cardiothoracic Surgery, Faculty of Medicine, University of Thessaly, Biopolis, Larissa, Greece

<sup>8</sup>Department of Vascular Surgery, General University Hospital of Patras, Patras, Greece

<sup>9</sup>Department of Cardiac Surgery, Hippokration General Hospital of Athens, Greece

<sup>10</sup>Department of Anesthesiology, Hippokration General Hospital of Athens, Greece

<sup>11</sup>Department of Radiology, General University Hospital of Patras, Patras, Greece

<sup>12</sup>Department of Cardiothoracic Surgery, General University Hospital of Patras, Patras, Greece

<sup>13</sup>Second Department of Surgery, Medical School, Democritus University of Thrace, Alexandroupolis, Greece

### \*Corresponding author:

Asst Prof Francesk Mulita, Second  
Department of Surgery, Medical School  
Democritus University of Thrace  
Alexandroupolis, Greece  
E-mail: oknarfmulita@hotmail.com

### Rezumat

*Un adenom paratiroidian ectopic chistic gigantic al mediastinului anterior care imită o tumoră mediastinală: o provocare diagnostică*

**Introducere:** Adenoamele paratiroidiene ectopice reprezintă o cauză mai puțin frecventă, dar clinic semnificativă, de hiperparatiroidism primar, în special atunci când sunt localizate în mediastin. Diagnosticul lor poate fi dificil, mai ales în prezența unei patologii tiroidiene concomitente, care poate obscura interpretarea imagistică și poate duce la studii de localizare înșelătoare.

**Prezentare caz:** Prezentăm cazul unui bărbat în vârstă de 63 de ani care s-a prezentat cu răgușeală persistentă și s-a constatat că are hipercalcemie marcată și niveluri crescute de parahormon, compatibile cu hiperparatiroidismul primar. Ecografia cervicală a demonstrat gușă multinodulară, în timp ce scintigrafia cu dublu trasor cu perțehnetat de tehneciu-99m și sestamibi de tehneciu-99m cu SPECT/CT a sugerat un adenom tiroidian funcțional și a ridicat suspiciunea unei posibile leziuni paratiroidiene în glanda tiroidă. Aspirația cu ac fin cu eliminarea parahormonului nu a confirmat o origine paratiroidiană intra-tiroidiană. Imagistica transversală ulterioară a relevat o masă chistică mare în mediastinul anterior superior, care comprimă structurile adiacente. După stabilizarea medicală cu cinacalcet, pacientul a fost supus unei excizii chirurgicale printr-o toracotomie axilară dreaptă. Constatările intraoperatorii și

biochimice au confirmat leziunea ca sursă a secreției excesive de parahormon. Examinarea histopatologică și imuno-histochimică a stabilit diagnosticul de adenom paratiroidian ectopic chistic. Postoperator, nivelurile serice de calciu și parahormon s-au normalizat, iar pacientul a rămas fără dovezi biochimice de boală recurentă pe durata perioadei de urmărire disponibile.

**Concluzie:** Acest caz evidențiază complexitatea diagnostică a adenoamelor paratiroidiene ectopice mediastinale, în special la pacienții cu gușă multinodulară coexistentă și constatări scintigrafice neconcludente. Medicii ar trebui să mențină un indice ridicat de suspiciune pentru țesutul paratiroidian ectopic în cazurile de hiperparatiroidism inexplicabil cu imagistică cervicală negativă sau discordantă, deoarece localizarea precisă este esențială pentru un tratament chirurgical definitiv.

**Cuvinte cheie:** hiperparatiroidism primar, adenom paratiroidian ectopic, masă mediastinală, scintigrafie cu sestamibi, gușă multinodulară, SPECT/CT

## Abstract

**Background:** Ectopic parathyroid adenomas represent an uncommon but clinically significant cause of primary hyperparathyroidism, particularly when located in the mediastinum. Their diagnosis may be challenging, especially in the presence of concomitant thyroid pathology, which can obscure imaging interpretation and lead to misleading localization studies.

**Case Presentation:** We report the case of a 63-year-old man who presented with persistent hoarseness and was found to have marked hypercalcemia and elevated parathormone levels consistent with primary hyperparathyroidism. Neck ultrasonography demonstrated multinodular goiter, while dual-tracer technetium-99m pertechnetate and technetium-99m sestamibi scintigraphy with SPECT/CT suggested a functional thyroid adenoma and raised suspicion for a possible parathyroid lesion within the thyroid gland. Fine-needle aspiration with parathormone washout did not confirm an intrathyroidal parathyroid origin. Subsequent cross-sectional imaging revealed a large cystic mass in the anterior superior mediastinum compressing adjacent structures. After medical stabilization with cinacalcet, the patient underwent surgical excision through a right axillary thoracotomy. Intraoperative and biochemical findings confirmed the lesion as the source of excessive parathormone secretion. Histopathological and immunohistochemical examination established the diagnosis of a cystic ectopic parathyroid adenoma. Postoperatively, serum calcium and parathormone levels normalized, and the patient remained free of biochemical evidence of recurrent disease during the available follow-up period.

**Conclusion:** This case highlights the diagnostic complexity of mediastinal ectopic parathyroid adenomas, particularly in patients with coexisting multinodular goiter and inconclusive scintigraphic findings. Clinicians should maintain a high index of suspicion for ectopic parathyroid tissue in cases of unexplained hyperparathyroidism with negative or discordant cervical imaging, as accurate localization is critical for definitive surgical management.

**Keywords:** primary hyperparathyroidism, ectopic parathyroid adenoma, mediastinal mass, sestamibi scan, multinodular goiter; SPECT/CT

## Introduction

Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders and represents the leading cause of persistent hypercalcemia in the outpatient setting. Its incidence increases with age and is higher in women, although clinically significant disease may occur in both sexes (1). In the majority of cases, PHPT is caused by a solitary parathyroid adenoma, whereas multiglandular hyperplasia and parathyroid carcinoma account for a smaller proportion of cases (2).

Accurate preoperative localization has become increasingly important in the era of focused and minimally invasive parathyroid surgery. Conventional

imaging modalities, including ultrasonography and technetium-99m sestamibi scintigraphy, are routinely employed for this purpose. However, their diagnostic accuracy may be limited in cases of ectopic glands, small lesions, multiglandular disease, or coexisting thyroid pathology (3).

Ectopic parathyroid glands are reported in up to 20% of patients and may be located anywhere along the embryologic migration pathway, from the angle of the mandible to the mediastinum. Mediastinal ectopic adenomas represent a particular diagnostic and surgical challenge, especially when they are large, cystic, or radiologically indistinguishable from other mediastinal masses (4). In such cases, differentiation from thymic lesions, germ cell tumors, or other anterior

mediastinal pathologies may not be straightforward, particularly when nuclear imaging findings are inconclusive.

We report a case of a large cystic ectopic parathyroid adenoma located in the anterior superior mediastinum, presenting with discordant scintigraphic findings in the setting of concomitant multinodular goiter. The case highlights the diagnostic pitfalls associated with cystic degeneration and coexisting thyroid disease, and underscores the importance of multimodality imaging and careful clinicopathologic correlation.

## Case Presentation

### *Patient Information and Clinical Findings*

A 63-year-old man with a medical history of bipolar disorder was referred to our hospital for further evaluation of persistent hoarseness. He denied dysphagia, dyspnea, nephrolithiasis, bone pain, pathological fractures, gastrointestinal symptoms, or prior cervical surgery. There was no known family history of endocrine disorders. Laryngoscopic examination revealed right vocal cord paresis. Physical examination demonstrated a diffusely enlarged thyroid gland without palpable cervical lymphadenopathy or clinically evident mediastinal mass.

### *Laboratory Evaluation*

Biochemical investigation revealed marked hypercalcemia with a serum calcium level of 13.3 mg/dL in the presence of normal serum albumin (4.3 g/dL). Serum parathormone (PTH) was significantly elevated at 350 pg/mL, establishing the diagnosis of primary hyperparathyroidism. Serum vitamin D was 30.3 ng/mL and calcitonin were 1.24 pg/mL. Thyroid function tests demonstrated subclinical hyperthyroidism, with a serum thyrotropin (TSH) level of 0.58 mU/L, normal free thyroxine (fT4) of 1.4 ng/dL, and normal triiodothyronine (T3) of 1.2 ng/mL. Anti-thyroid peroxidase antibodies were negative. The remainder of laboratory investigations, including renal and liver function tests, were within normal limits.

### *Imaging Studies*

Neck ultrasonography demonstrated a multinodular goiter. An isoechoic nodule measuring 4 × 2.6 cm was identified in the upper portion of the right thyroid lobe, a second isoechoic nodule measuring 2.6 × 1 cm was in the isthmus, and an additional smaller nodule was present in the lower part of the left lobe.

Dual-tracer scintigraphy with technetium-99m

pertechnetate and technetium-99m methoxyisobutylisonitrile (99mTc-MIBI), combined with SPECT/CT, revealed increased uptake in the isthmus nodule, compatible with a functional thyroid adenoma. The lesion in the upper right lobe was interpreted as suspicious for a parathyroid adenoma (Figs. 1, 2).

Fine-needle aspiration cytology of the right and left thyroid nodules demonstrated benign thyroid nodules (Bethesda category II). Measurement of PTH in the needle washout fluid was lower than the correspon-

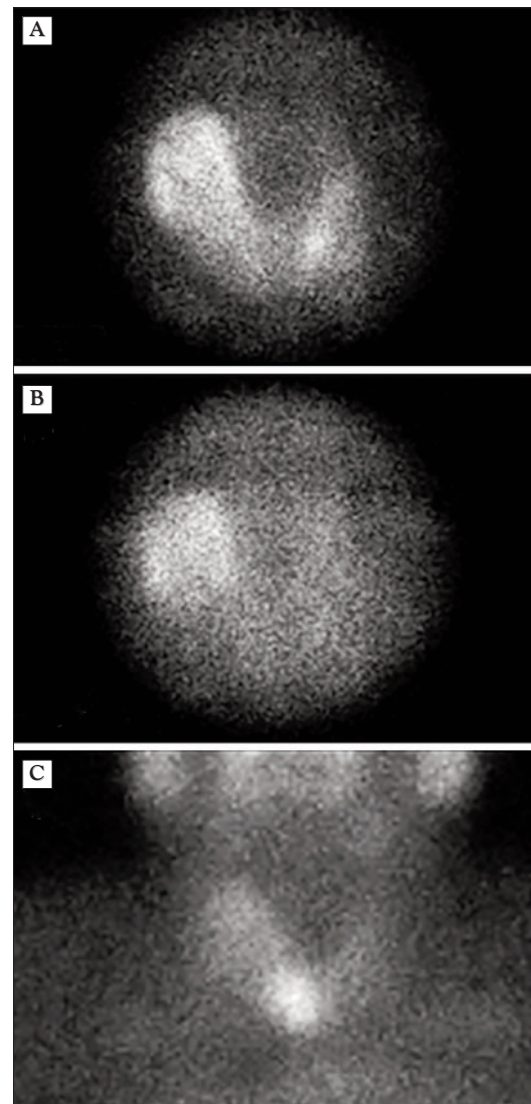
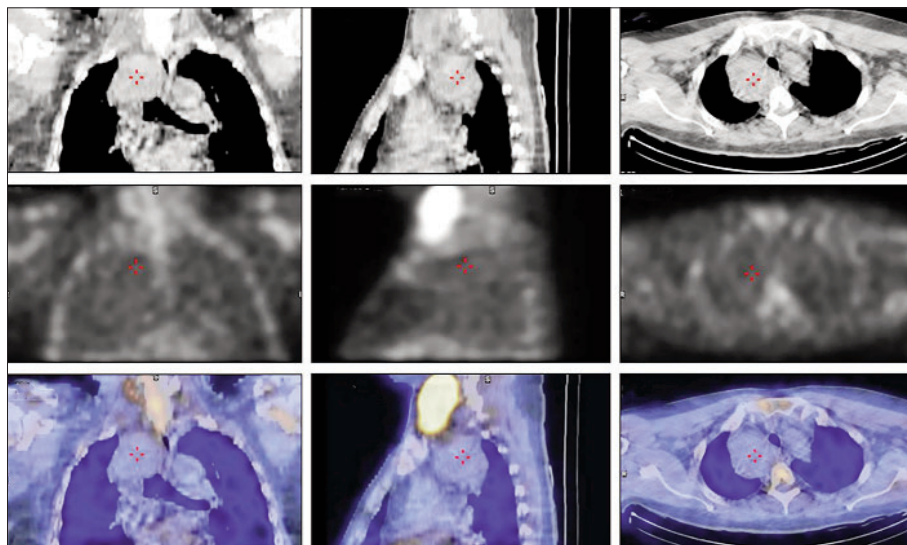


**Figure 1.** <sup>99m</sup>Tc-Sestamibi and <sup>99m</sup>Tc-Pertechnetate images of the neck. (A) early (10 min post injection), (B) late Sestamibi view (2 hours post injection), (C) <sup>99m</sup>Tc-Pertechnetate anterior view. A large lesion at the upper pole of the right thyroid lobe shows intense early uptake and late retention of Sestamibi (A and B). Pertechnetate images (C) reveal a functioning thyroid nodule at the isthmus, with depression of tracer uptake in the rest thyroid parenchyma.

**Figure 2.**  $^{99m}\text{Tc}$ -Sestamibi SPECT/CT study in the thorax. A large mass in the upper mediastinum is recognized on low-resolution CT images. However, there is no uptake of Sestamibi in the lesion.



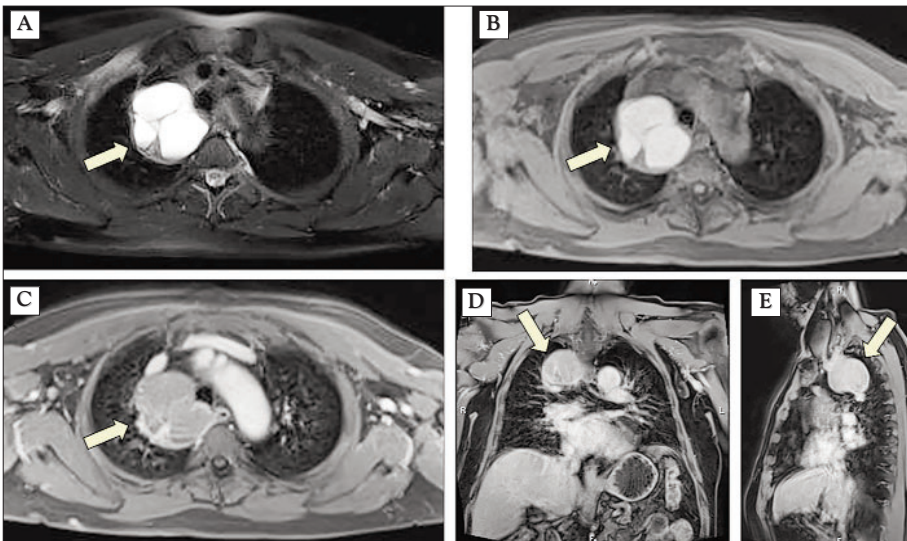
ding serum PTH level, arguing against an intra-thyroidal parathyroid lesion. Consequently, the source of excess PTH secretion remained unidentified.

Contrast-enhanced computed tomography of the chest demonstrated a  $67 \times 63$  mm well-circumscribed, low-attenuation mass in the superior mediastinum, causing compression of the trachea and esophagus without obvious vascular invasion. Differential diagnosis included mediastinal germ cell tumor, thymic cystic lesion, or an ectopic parathyroid tumor (adenoma or carcinoma).

Magnetic resonance imaging of the thorax (1.5 T) revealed a multilobulated mass in the anterior superior mediastinum with internal septations

measuring  $67 \times 63$  mm. The lesion was hyperintense on T2-weighted sequences (*Fig. 3A*), of intermediate signal intensity on T1-weighted images (*Figs. 3 B-E*), and demonstrated diffusion restriction. Following intravenous contrast administration, enhancement of the septations was observed, more prominent in the inferior portion of the lesion. No fat component was detected. The mass caused pressure on the trachea and esophagus was near the lower pole of the thyroid gland but showed no evidence of arising from it. It was adjacent to the superior vena cava without signs of vascular infiltration. Serum alpha-fetoprotein and beta-human chorionic gonadotropin levels were within normal limits.

**Figure 3.** Magnetic resonance imaging of the thorax demonstrating a large multilobulated cystic mass in the anterior superior mediastinum (arrows). (A) Axial T2-weighted turbo spin-echo fat-suppressed image showing marked hyperintensity of the lesion with internal septations. (B) Axial T1-weighted gradient-echo fat-suppressed image demonstrating intermediate signal intensity. (C) Axial contrast-enhanced T1-weighted gradient-echo fat-suppressed image showing enhancement of the internal septations, most prominent in the inferior portion of the lesion. (D) Coronal contrast-enhanced T1-weighted gradient-echo fat-suppressed image illustrating the relationship of the mass to the superior mediastinal structures. (E) Sagittal contrast-enhanced T1-weighted gradient-echo fat-suppressed image demonstrating the cranio-caudal extension of the lesion within the anterior superior mediastinum. The mass was adjacent to the lower pole of the thyroid gland but showed no evidence of arising from it.



Overall, the diagnostic strategy followed a stepwise approach. Initial biochemical testing established the diagnosis of primary hyperparathyroidism, while cervical ultrasonography and dual-tracer scintigraphy were performed as first-line localization studies. Because the scintigraphic findings were discordant and fine-needle aspiration with PTH washout failed to confirm an intrathyroidal parathyroid lesion, further cross-sectional imaging was undertaken. Computed tomography and magnetic resonance imaging sub-

sequently identified a large cystic mediastinal mass anatomically separate from the thyroid gland. In the setting of persistent biochemical evidence of primary hyperparathyroidism, absence of an alternative endocrine source, and the presence of a resectable mediastinal lesion causing local compressive symptoms, surgical excision was considered both diagnostically and therapeutically indicated. A diagnostic algorithm summarizing the diagnostic pathway has been added as *Fig. 4*.

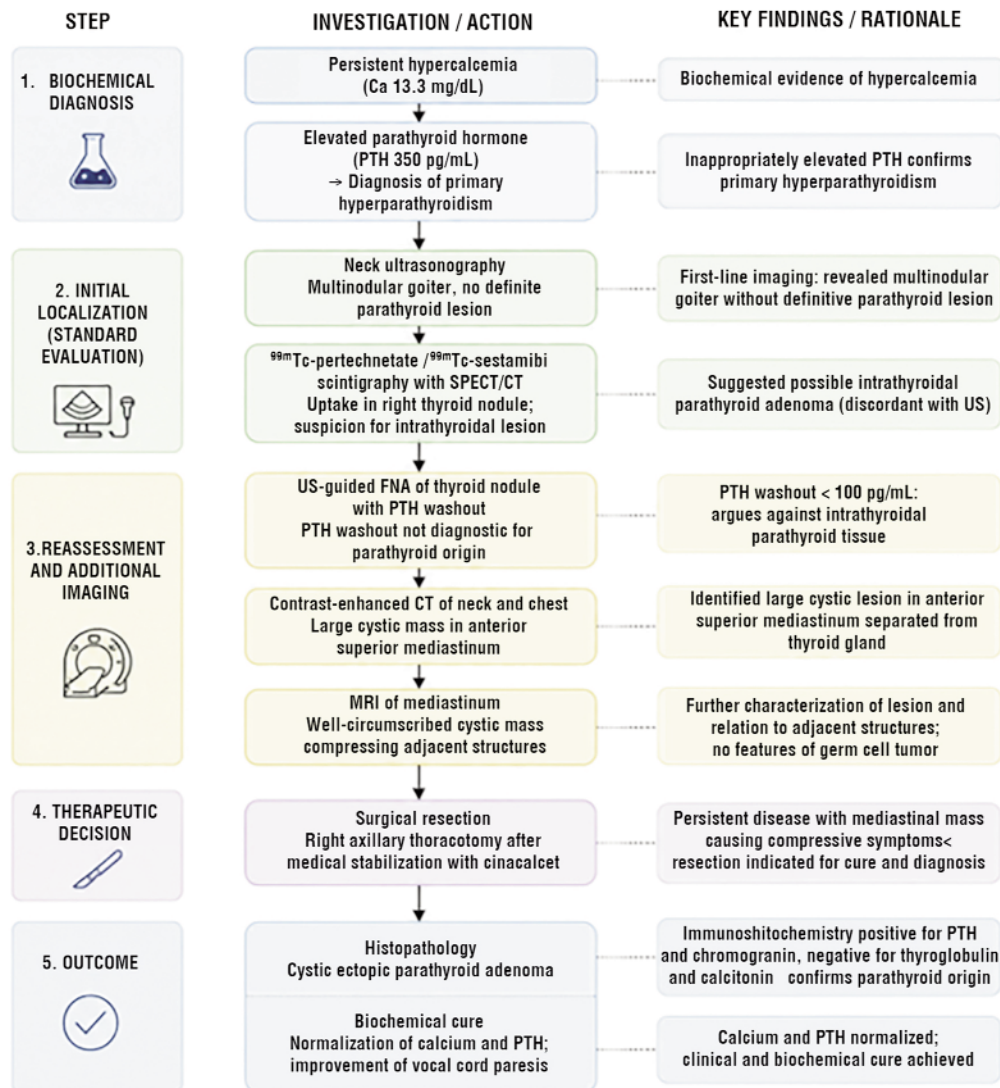


**Figure 4.** Diagnostic pathway and clinical decision-making process leading to the diagnosis and treatment of a cystic ectopic mediastinal parathyroid adenoma. The flowchart summarizes the sequential diagnostic evaluation from biochemical confirmation of primary hyperparathyroidism through first-line localization studies, additional cross-sectional imaging, surgical management, and final histopathological diagnosis. The case illustrates how discordant scintigraphic findings, concomitant multinodular goiter, and cystic degeneration contributed to diagnostic uncertainty and necessitated a multimodality imaging approach

### Therapeutic Intervention

The patient was initiated on cinacalcet at a dose of 60 mg twice daily, resulting in gradual normalization of serum calcium levels. After biochemical stabilization, surgical excision of the mediastinal mass was undertaken. A right curved axillary thoracotomy through the fourth intercostal space was performed. Intraoperatively, a large cystic lesion extending from the thoracic inlet to the level of the azygos vein was identified within the space bounded anteromedially by the trachea, superior vena cava, and innominate artery, and posteromedially by the esophagus and vertebral column. Careful dissection allowed complete excision of the mass without intraoperative complications.

Washout fluid obtained from the excised lesion revealed markedly elevated PTH levels exceeding 5000 pg/mL, confirming its parathyroid origin. Intraoperative PTH monitoring demonstrated a decline greater than 50% within 15 minutes following excision. The remaining cervical parathyroid glands were not grossly enlarged.

### Pathological Findings

Gross examination demonstrated a well-circumscribed multilocular soft cystic mass measuring  $5.5 \times 5.5 \times 4$  cm and weighing 59 g. The cut surface was predominantly cystic and hemorrhagic, with a whitish nodular

area measuring  $3.5 \times 2.0 \times 1.5$  cm located in the wall of a cystic cavity.

Microscopically, most of the lesion consisted of fibrotic and degenerative hemorrhagic cystic spaces. The nodular component was composed of uniform cells arranged in nodular, trabecular, and pseudofollicular solid patterns separated by thick fibrous septa. The tumor cells exhibited abundant water-clear cytoplasm and bland cytologic features, without nuclear atypia, necrosis, or mitotic activity. Immunohistochemistry demonstrated strong expression of parathyroid hormone and chromogranin, while thyroid transcription factor-1, thyroglobulin, and calcitonin were negative. The Ki-67 proliferation index was less than 2%, and Galectin-3 expression was negative. No vascular or perineural invasion was identified. Although the lesion focally approached the surgical margins, definitive histopathological criteria for parathyroid carcinoma were absent. The overall findings were consistent with a cystic ectopic parathyroid adenoma (Fig. 5).

### Follow-up and Outcomes

The postoperative course was uneventful. Serum calcium normalized on the first postoperative day (9.4 mg/dL), and serum PTH decreased to 45 pg/mL. Cinacalcet therapy was discontinued. At three-month follow-up, calcium and PTH levels remained within

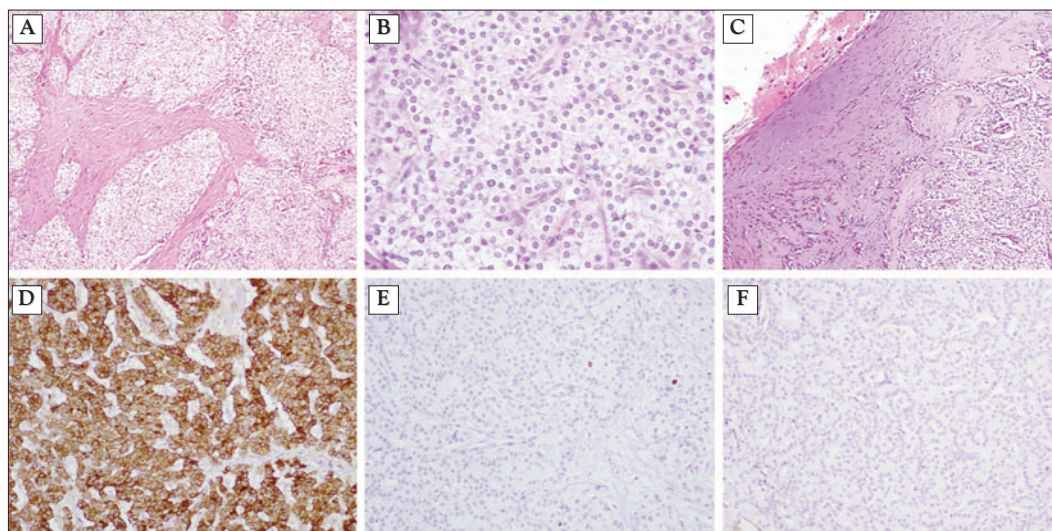


**Figure 5.** (A, B, C) Hematoxylin and eosin staining (A,B). Cellular lesion composed of nodules of uniform cytological bland cells with water clear cytoplasm separated by fibrous septa (A x 100, B x 400) (C). Area of hemorrhagic and cystic degeneration (x 100) (D, E, F). Immunohistochemical staining showing positive strong expression of PTH (x 200) in chief cells (D), low Ki67 labelling index by immunohistochemistry (x 200) (E) and negative Galectin-3 expression (x 200) (F).



**Figure 6.** Timeline of clinical presentation, diagnostic work-up, treatment, and follow-up of a patient with a cystic ectopic mediastinal parathyroid adenoma. The figure summarizes the chronological sequence of symptoms, biochemical findings, imaging studies, multidisciplinary evaluation, therapeutic interventions, surgical treatment, histopathological diagnosis, and postoperative outcome. The timeline highlights the diagnostic challenges posed by discrepant scintigraphic findings, concomitant multinodular goiter, and extensive cystic degeneration, ultimately leading to identification and successful resection of an ectopic parathyroid adenoma.

Abbreviations: AFP, alpha-fetoprotein; -hCG, beta-human chorionic gonadotropin; CT, computed tomography; MRI, magnetic resonance imaging; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; SPECT/CT, single-photon emission computed tomography/computed tomography.

normal limits (9.2 mg/dL and 48 pg/mL, respectively), indicating biochemical cure. The patient's hoarseness improved progressively, with complete resolution of right vocal cord paresis during follow-up.

The chronological sequence of clinical presentation, diagnostic investigations, therapeutic interventions, and postoperative evolution is summarized in Fig. 6.

### Discussion

Primary hyperparathyroidism (PHPT) is most frequently caused by a solitary parathyroid adenoma, accounting for approximately 80–85% of cases (5). Ectopic parathyroid glands are encountered in 10–20% of patients and result from aberrant embryologic migration of the third and fourth pharyngeal pouches (6). Inferior parathyroid glands, which descend in association with the thymus, are particularly prone to ectopic localization along the thymic migration pathway and may ultimately reside within the anterior mediastinum (6,7). Contemporary surgical series continue to report mediastinal localization as one of the most common sites of ectopic glands requiring non-cervical approaches (8).

Although mediastinal ectopic glands are recognized, large cystic adenomas in the anterior superior mediastinum remain uncommon. In the present case, the lesion extended from the thoracic inlet to the level of the azygos vein and was closely related to major mediastinal structures. Its substantial cystic degeneration and size (> 6 cm) are atypical for conventional parathyroid adenomas. Radio-

logically, the mass closely resembled a primary anterior mediastinal tumor. Large cystic lesions in this compartment are more commonly attributed to thymic cysts, thymomas, or germ cell tumors rather than endocrine pathology (9). This overlap significantly contributed to the initial diagnostic uncertainty.

The choice of surgical approach deserves consideration in such cases. While video-assisted thoracoscopic surgery (VATS) and robotic-assisted techniques have become increasingly utilized for selected mediastinal parathyroid adenomas, their applicability depends largely on lesion size, location, and relationship to adjacent structures. In the present case, the mass measured more than 6 cm, extended from the thoracic inlet to the level of the azygos vein, and was closely associated with the trachea, superior vena cava, innominate artery, and esophagus. Given these anatomical characteristics, an open right axillary thoracotomy was considered the safest approach, providing optimal exposure for meticulous dissection and vascular control while minimizing the risk of injury to major mediastinal structures. Furthermore, because the exact nature of the lesion remained uncertain preoperatively and differential diagnoses included other mediastinal neoplasms, complete en bloc resection through an open approach was considered preferable. Although median sternotomy could also have provided adequate exposure, the predominantly right-sided location of the lesion favored a right axillary thoracotomy. The operation was completed without complications, confirming the suitability of the selected strategy.

Preoperative localization remains critical in PHPT management. Technetium-99m sestamibi (99mTc-MIBI) scintigraphy combined with SPECT/CT continues to be widely used, with reported sensitivity exceeding 80% in solitary adenomas (10). However, recent literature emphasizes that its diagnostic accuracy declines in the presence of multiglandular disease, small adenomas, cystic degeneration, or concomitant thyroid pathology (11). In our patient, dual-tracer scintigraphy suggested a functional thyroid adenoma and raised suspicion of an intra-thyroidal parathyroid lesion, findings not confirmed by cytology and PTH washout. 99mTc-Sestamibi scintigraphy was misleading in this case. It indicated a possible large parathyroid adenoma at the upper pole of the right thyroid lobe, which was proved a benign thyroid nodule. There was no Sestamibi uptake at the large mediastinal parathyroid adenoma, probably because of the extensive cystic degeneration and fibrotic changes of the tumor.

Cystic degeneration is known to reduce viable chief cell mass and mitochondrial density, resulting in

diminished radiotracer uptake and potential false-negative imaging (12). The extensive cystic component observed in this case likely impaired sestamibi retention. Furthermore, multinodular goiter represents a recognized cause of false-positive uptake. Hyperfunctioning or mitochondria-rich thyroid nodules may accumulate sestamibi and obscure parathyroid tissue (13). Recent imaging reviews stress that coexisting thyroid disease remains a significant confounder in nuclear parathyroid imaging (11,14). Technical limitations of SPECT/CT - including reduced spatial resolution in deep mediastinal locations and attenuation from surrounding structures - may further compromise detection (10).

The mechanisms underlying false-negative and false-positive sestamibi findings are multifactorial. Uptake of 99mTc-MIBI depends primarily on mitochondrial content, cellular viability, and regional perfusion. Consequently, lesions with extensive cystic degeneration, hemorrhage, fibrosis, or reduced chief-cell density may demonstrate diminished tracer accumulation and accelerated washout, resulting in false-negative examinations. Conversely, false-positive uptake may occur in hypercellular thyroid nodules, Hürthle-cell lesions, thyroid adenomas, inflammatory thyroid disease, and other mitochondria-rich tissues. Comparative imaging studies have consistently shown lower localization accuracy of sestamibi scintigraphy in patients with concomitant nodular thyroid disease than in those with isolated parathyroid adenomas. In the present case, the combination of extensive cystic degeneration within the ectopic adenoma and coexisting multinodular goiter likely contributed simultaneously to reduced visualization of the true lesion and misleading uptake within the thyroid gland.

In cases of inconclusive scintigraphy, contemporary guidelines increasingly support the use of contrast-enhanced CT, 4D-CT, or even PET/CT with novel tracers for improved localization (8,14). Recent evidence indicates that four-dimensional computed tomography (4D-CT) offers superior spatial resolution and higher sensitivity compared with conventional sestamibi scintigraphy, particularly in cases of ectopic glands and prior negative imaging. Reported sensitivities for 4D-CT range from 80% to 90% for solitary adenomas, with improved localization accuracy in deep cervical and mediastinal positions (11). Furthermore, 18F-fluorocholine (FCH) PET/CT has emerged as a highly sensitive modality in primary hyperparathyroidism, especially in patients with negative or discordant first-line imaging. Several contemporary series report detection rates exceeding 90%, even in small, ectopic, or multiglandular disease. These advanced imaging techniques may therefore

represent valuable second-line options when conventional ultrasonography and sestamibi-based imaging are inconclusive (15). In retrospect, the use of 18F-fluorocholine PET/CT might have facilitated earlier and more accurate localization of the ectopic lesion, potentially reducing the diagnostic delay observed in this case. It is important to recognize, however, that the potential benefit of advanced imaging in this case would likely have been primarily diagnostic rather than therapeutic. Given the presence of severe biochemical hyperparathyroidism, a large mediastinal mass causing compressive symptoms, and the absence of an alternative source of excess PTH secretion, surgical resection would almost certainly have remained indicated regardless of the imaging modality used. Nevertheless, earlier implementation of 4D-CT or 18F-fluorocholine PET/CT might have improved diagnostic confidence, reduced uncertainty regarding an intrathyroidal origin, shortened the diagnostic pathway, and facilitated preoperative planning by more clearly defining the relationship of the lesion to adjacent mediastinal structures. Thus, while the ultimate management strategy may not have changed, the diagnostic process could potentially have been streamlined. This consideration underscores the evolving role of advanced molecular imaging in complex presentations of primary hyperparathyroidism. In the present case, cross-sectional thoracic imaging ultimately revealed the ectopic lesion and clarified the source of excess PTH secretion.

Beyond its diagnostic complexity, the present case offers several features that distinguish it from previously reported mediastinal cystic parathyroid adenomas. First, the lesion produced discordant localization findings, with scintigraphy suggesting a possible intrathyroidal source in the setting of multinodular goiter, while the actual pathology originated from a large ectopic mediastinal adenoma. Second, extensive cystic degeneration further reduced the diagnostic performance of conventional sestamibi-based imaging, creating a clinically relevant scenario in which both thyroid pathology and cystic transformation acted as confounding factors. Finally, the case illustrates the importance of integrating biochemical findings, PTH washout analysis, cross-sectional imaging, and multidisciplinary assessment when first-line localization studies are misleading. These features highlight a practical diagnostic pitfall and reinforce the growing role of advanced imaging strategies in the evaluation of complex ectopic parathyroid disease.

The differential diagnosis of a cystic anterior mediastinal mass is broad. Several radiologic and clinical findings helped narrow the differential diagnosis before surgery, although none were

individually diagnostic. The lesion was well circumscribed, predominantly cystic, and lacked imaging features suggestive of aggressive behavior such as vascular invasion, infiltrative growth, or associated lymphadenopathy. Germ cell tumors were considered because of the anterior mediastinal location; however, the absence of a fat-containing component on MRI and normal serum alpha-fetoprotein and beta-human chorionic gonadotropin levels made this diagnosis less likely. Similarly, although thymic cysts and cystic thymic neoplasms remained plausible considerations, the presence of marked hypercalcemia and substantially elevated serum PTH levels strongly suggested an endocrine source. The case was reviewed within a multidisciplinary setting involving endocrinology, radiology, thoracic surgery, and pathology, and the overall clinicoradiologic profile favored resection for both definitive diagnosis and treatment.

Germ cell tumors must be considered, particularly in male patients, although normal tumor markers argued against this possibility (9). Thymic cysts and cystic thymomas are additional frequent considerations. From an endocrine perspective, parathyroid carcinoma must be contemplated in cases of marked hypercalcemia and significantly elevated PTH levels (16,17). Although rare, carcinoma may occasionally demonstrate cystic changes and large tumor size (18). Multiglandular hyperplasia also enters the differential when histologic findings are not unequivocal. In the present case, the markedly elevated PTH level in cyst fluid (>5000 pg/mL) combined with prompt postoperative biochemical normalization strongly supported a solitary ectopic parathyroid source.

Distinguishing parathyroid adenoma from carcinoma remains challenging. Parathyroid carcinoma accounts for less than 1% of PHPT cases and is defined primarily by invasive growth, vascular or perineural invasion, or metastatic spread rather than cytologic atypia alone (17,18). Recent reviews emphasize that no single immunohistochemical marker is diagnostic, and clinicopathologic correlation is essential. In our case, the lesion was well circumscribed, cytologically bland, and devoid of necrosis or mitotic activity. No vascular or perineural invasion was identified. The low Ki-67 proliferation index (<2%) and absence of Galectin-3 expression further supported a benign diagnosis (19,20).

Nevertheless, the interpretation of immunohistochemical markers in parathyroid neoplasia requires caution. Although low Ki-67 labeling indices and absent Galectin-3 expression are generally more consistent with benign lesions, neither marker alone reliably distinguishes parathyroid adenoma from atypical adenoma or low-grade parathyroid carcinoma.

Recent studies have demonstrated considerable overlap in immunophenotypic profiles among these entities, limiting the diagnostic value of individual biomarkers when considered in isolation. Additional markers such as parafibromin, APC, and PGP9.5 have been investigated, although none has achieved universal acceptance as a standalone discriminator of malignancy. Consequently, contemporary pathological assessment continues to rely primarily on conventional histomorphologic criteria, including evidence of invasive growth, vascular or perineural invasion, and metastatic potential, with immunohistochemistry serving as a complementary rather than definitive diagnostic tool. In the present case, the overall clinicopathologic findings favored a benign adenoma despite the recognized limitations of currently available biomarkers. Early postoperative biochemical remission further supports a benign diagnosis, although continued follow-up remains necessary.

The principal value of the present case lies not in the rarity of mediastinal ectopic parathyroid tissue itself, but in the convergence of several diagnostic pitfalls within a single patient. First, concomitant multinodular goiter generated potentially misleading scintigraphic findings suggestive of an intrathyroidal lesion. Second, extensive cystic degeneration reduced the diagnostic performance of sestamibi-based imaging and complicated radiologic interpretation. Third, the lesion presented as a large anterior mediastinal mass with imaging characteristics overlapping those of more common mediastinal pathologies, including thymic and germ cell lesions. Finally, despite clear biochemical evidence of primary hyperparathyroidism, localization remained uncertain until cross-sectional imaging identified the ectopic source. Together, these factors illustrate how multiple confounding variables may coexist and obscure the diagnosis of ectopic parathyroid disease, emphasizing the need for careful integration of biochemical, radiologic, and clinical findings.

This case provides several important clinical insights. Ectopic parathyroid adenoma should be suspected in patients with persistent hypercalcemia and elevated PTH levels even when cervical imaging is negative or discordant. The presence of a mediastinal mass in the context of biochemical hyperparathyroidism warrants evaluation for ectopic parathyroid tissue. Measurement of PTH levels in cyst fluid or needle washout material remains a highly valuable diagnostic adjunct in ambiguous cystic lesions (21). Finally, clinicians should avoid overreliance on sestamibi imaging alone, particularly in patients with cystic degeneration or concomitant

thyroid disease. Multimodality imaging and careful histopathological evaluation are essential for accurate diagnosis and appropriate management.

A limitation of the present report is the relatively short duration of postoperative follow-up. Although serum calcium and PTH levels normalized promptly after resection and remained within normal limits at three months, this interval is insufficient to definitively exclude late biochemical recurrence. This consideration may be particularly relevant in large cystic lesions and in cases where the tumor approaches the surgical margins. Nevertheless, the marked intraoperative decline in PTH levels together with sustained early postoperative biochemical remission strongly supports successful removal of the hyperfunctioning tissue. Continued long-term clinical and biochemical surveillance remains warranted.

## Conclusions

Ectopic parathyroid adenomas of the anterior mediastinum, particularly when large and cystic, represent an uncommon but clinically significant cause of primary hyperparathyroidism. Their presentation may mimic primary mediastinal tumors and create substantial diagnostic uncertainty, especially in the presence of concomitant thyroid pathology and discordant scintigraphic findings.

This case highlights the limitations of sestamibi-based localization in the setting of cystic degeneration and multinodular goiter, underscoring the importance of maintaining clinical suspicion when biochemical evidence of hyperparathyroidism persists.

Multimodality imaging, combined with measurement of parathyroid hormone levels in cyst fluid when appropriate, may be essential for accurate localization.

Complete surgical excision remains the definitive treatment and is associated with prompt biochemical normalization when the ectopic source is successfully removed. Careful histopathologic evaluation is crucial to exclude malignancy and to guide follow-up. A multidisciplinary approach integrating endocrinology, radiology, pathology, and thoracic surgery is key to achieving accurate diagnosis and durable cure in complex presentations of ectopic parathyroid disease.

## Authors' Contributions

All authors contributed to the clinical management of the patient, data collection, literature review, manuscript drafting, and approval of the final version.

## Competing Interests

The authors declare that they have no competing interests.

## Funding

No funding was received for the preparation of this case report.

## Consent for Publication

Written informed consent for publication of this case report and accompanying images was obtained from the patient.

## Availability of Data and Materials

All relevant data are included in the manuscript. Additional information is available from the corresponding author upon reasonable request.

## References

1. Yeh MW, Ituarte PH, Zhou HC, Nishimoto S, Liu IL, Harari A, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *J Clin Endocrinol Metab.* 2013;98(3):1122–1129.
2. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: 2022 update. *J Clin Endocrinol Metab.* 2022;107(10):3119–3146.
3. Ghaffar T, Kanwal S, Aamir AH, Din N. Diagnostic accuracy of ultrasonography and 99m-Technetium Sestamibi scintigraphy for the preoperative localization of Parathyroid Adenoma keeping histopathological findings as reference standard. *Pak J Med Sci.* 2024;40(10):2405–2409.
4. Wei CH, Harari A. Ectopic parathyroid adenomas: surgical implications and management strategies. *J Thorac Dis.* 2020;12(12):7645–7652.
5. Bilezikian JP, Bandeira L, Khan A, Cusano NE. Hyperparathyroidism. *Lancet.* 2018;391(10116):168–178.
6. Noussios G, Anagnostis P, Goulis DG, Lappas D, Natsis K. Ectopic parathyroid glands and their anatomical, clinical and surgical implications. *Exp Clin Endocrinol Diabetes.* 2012;120(10):604–610.
7. Phitayakorn R, McHenry CR. Incidence and location of ectopic abnormal parathyroid glands. *Am J Surg.* 2006;191(3):418–423.
8. Alesina PF, Moka D, Mahlstedt J, Walz MK. Thoracoscopic removal of mediastinal parathyroid adenomas: surgical indications and results. *Surg Endosc.* 2008;22(3):671–675.
9. Carter BW, Benveniste MF, Madan R, Godoy MC, de Groot PM, Truong MT, et al. ITMIG classification of mediastinal compartments and multidisciplinary approach to mediastinal masses. *Radiographics.* 2017;37(2):413–436.
10. Lavelly WC, Goetze S, Friedman KP, Leal JP, Zhang Z, Garret-Mayer E, et al. Comparison of SPECT/CT, SPECT, and planar imaging with single - and dual-phase 99mTc-sestamibi parathyroid scintigraphy. *J Nucl Med.* 2007;48(7):1084–1089.
11. Kluijfhout WP, Pasternak JD, Gosnell JE, Shen WT. Role of 4D-CT and novel imaging modalities in parathyroid localization. *Endocr Pract.* 2020;26(6):690–700.
12. McCoy KL, Yim JH, Zuckerbraun BS, Ogilvie JB, Carty SE. Cystic parathyroid lesions: functional and nonfunctional parathyroid cysts. *Surgery.* 2009;146(6):1173–1181.
13. Rubello D, Casara D, Giannini S, Piotta A, Pelizzo MR, Shapiro B. Clinical role of 99mTc-sestamibi scintigraphy in primary hyperparathyroidism. *Eur J Endocrinol.* 2002;147(6):717–727.
14. Rodrigo JP, Hernandez-Prera JC, Randolph GW, Zafero ME, Hartl DM, Silver CE, et al. Contemporary management of parathyroid carcinoma. *Head Neck.* 2021;43(6):1991–2006.
15. Quak E, Cavarec M, Ciappuccini R, Girault G, Rouzier R, Lequesne J. Detection, resection and cure: a systematic review and meta-analysis of 18F-choline PET in primary hyperparathyroidism. *Q J Nucl Med Mol Imaging.* 2023;67(2):122–129.
16. Hindié E, Ugur Ö, Fuster D, O'Doherty M, Grassetto G, Ureña P, et al. 2009 EANM parathyroid guidelines. *Eur J Nucl Med Mol Imaging.* 2009;36(7):1201–1216.
17. DeLellis RA. Parathyroid carcinoma: an overview. *Adv Anat Pathol.* 2005;12(2):53–61.
18. Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: IARC; 2017.
19. Erickson LA, Jin L, Wollan P, Thompson GB, van Heerden JA, Lloyd RV. Parathyroid hyperplasia, adenomas, and carcinomas: differential expression of Cyclin D1 and Ki-67. *Mod Pathol.* 1999;12(4):412–419.
20. Bergero N, De Pompa R, Sacerdote C, Gasparri G, Volante M, Bussolati G, et al. Galectin-3 expression in parathyroid carcinoma: an immunohistochemical study of 26 cases. *Hum Pathol.* 2005;36(8):908–914.
21. Abdelghani R, Noureldine SI, Gooi Z, Tufano RP, Kandil E. The diagnostic value of parathyroid hormone washout in parathyroid lesions. *Surgery.* 2014;156(6):1621–1627.