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Severe Hypercalcemia Complicating a Giant Mediastinal Parathyroid Compressive Cyst- A Case Report.

Pierre Yves Marcy*, Florent Carsuzaa, Quentin Holay, Jean Baptiste Morvan

IMASUD Radiology, PolyClinics Medipole SUd ELSAN Group, France

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***Corresponding author:** Pierre Yves Marcy, IMASUD Radiology, PolyClinics Medipole Sud ELSAN, Polyclinique les Fleurs, Quartier Quiez, 83189- Ollioules, France

ASTRACT

Introduction: Primary hyperparathyroidism (PHPT) is an endocrine condition caused by a single parathyroid adenoma (PTA) in 80-85%, multiple PTAs or PT gland hyperplasia in 15%; exceptionally a PT carcinoma (<1%). The final diagnosis includes hypercalcemia, raised or inappropriate PTH, and concordance between significant focal uptake at functional imaging and morphological features at US and/or MDCT assessment. According to literature data, a giant PTA is defined as weighing more than 350mg.

Case report: A 62-year-old female patient presented with progressive hoarseness and expiratory dyspnea; nasofibroscopy revealed right vocal cord paralysis, FDG -PET ruled out any suspicious cervico- mediastinal mass uptake, F-choline PET-CT disclosed a 37 mmx 21mm x 30mm (12.2ml) cyst of the upper right mediastinum, MDCT showed focal tiny contrast enhancement of solid lower part that could be in favor of cystic PT adenoma. Two months later on, patient presented with sudden worsening of dyspnea, and severe hypercalcemia Surgical resection (combined head & neck and thoracic surgery) of the mass was successfully performed without complication.

Conclusions: The diagnosis of a mediastinal functional cystic PTA is highly challenging because of the frequent negative result on parathyroid tracer scintigraphy. Surgical resection of the mass and postoperative histopathological diagnosis are necessary even if the clinical diagnosis of a PTA cannot be often obtained preoperatively. Decreases in the PTH and serum calcium level indicate successful resection of the functional PTA. Cystic FNA PTH wash -out under image- guidance could definitely make -up the full diagnosis pre operatively. Alternatives minimally invasive therapies will be discussed.

Keywords: Calcium; Cyst; Giant parathyroid adenoma; Incidentaloma; Parathormone; Parathyroid adenoma; Parathyroid tumor; Parathyroidectomy; Primary hyperparathyroidism; Mediastinal tumor; Vitamin D; Percutaneous ethanol injection.

INTRODUCTION

Parathyroid adenomas (PTA) are benign neoplasms of parathyroid gland producing excess parathyroid hormone (PTH). PTA are the most common cause of primary hyperparathyroidism (PHPT) in 80-85% of the cases,

followed by PT gland hyperplasia or multiple PTAs in 15%, and malignant PT tumor in less than 1% of the cases [1]. The best diagnostic clue is functional imaging showing focal uptake of18F-fluorocholine positron emission tomography/computed tomography (F- PET-CT)) within PTA [2-4]. The basics for successful PT surgery is preoperative planning of the diseased PT gland(s). Indeed, the surgeon definitely needs concordant diagnosis between functional imaging and morphological imaging means (neck ultrasonography first, MDCT of the neck and mediastinum as second option) in order to precisely detect and localize the single (or multiple) PTA(s), thus preventing persistent post-operative HPTH and related complications and further surgical reintervention [5,6]. Moreover, a new paradigm has progressively raised over the past few decades, shifting from bilateral neck exploration to minimally unilateral invasive parathyroidectomy, on a minimal hospital in-patient stay.

Giant cystic mediastinal mass of parathyroid origin is extremely rare; its diagnosis is challenging indeed.

CASE PRESENTATION

A 62-year-old female patient presented with progressive hoarseness and expiratory dyspnea on exertion. Patient was given beclomethasone dipropionate (BDP) aerosol spray. Clinical examination confirmed right vocal cord paralysis due to recurrent laryngeal nerve paresis, without any pharyngolaryngeal or thyroid lesion. Neck ultrasonography did not disclose any mass of the neck. MDCT of the neck and chest ruled out mass syndrome of the pharynx, larynx, trachea, oesophagus, or schwannoma of the vagus nerve. MDCT confirmed the laryngeal nerve paralysis, and disclosed a giant cystic mass in the upper right mediastinum. Biological profile was consistent with PHPT. FDG -PET ruled out any suspicious cervico- mediastinal mass uptake for malignancy, F-choline PET-CT disclosed a 45mm x 55mmx 70mm giant cystic mass of the upper right mediastinum, MDCT showed focal tiny contrast enhancement of solid lower part that could be in favor of cystic PT adenoma (Figure 1).

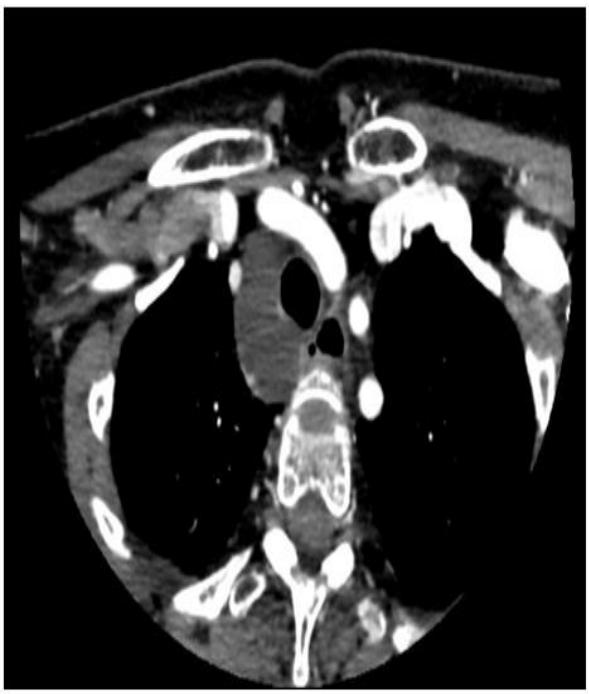


Figure 1A

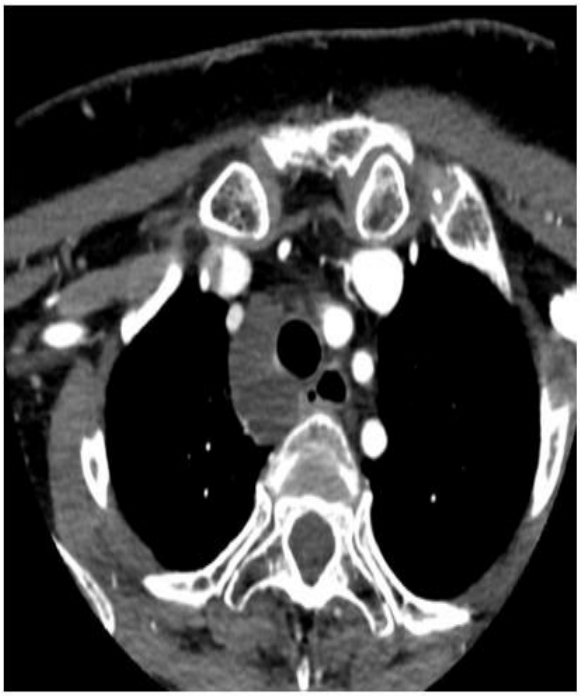


Figure 1B

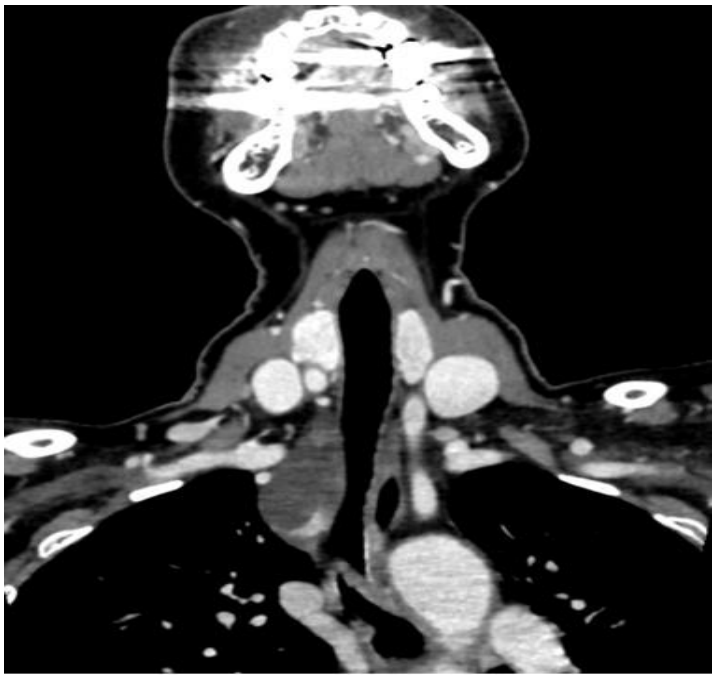
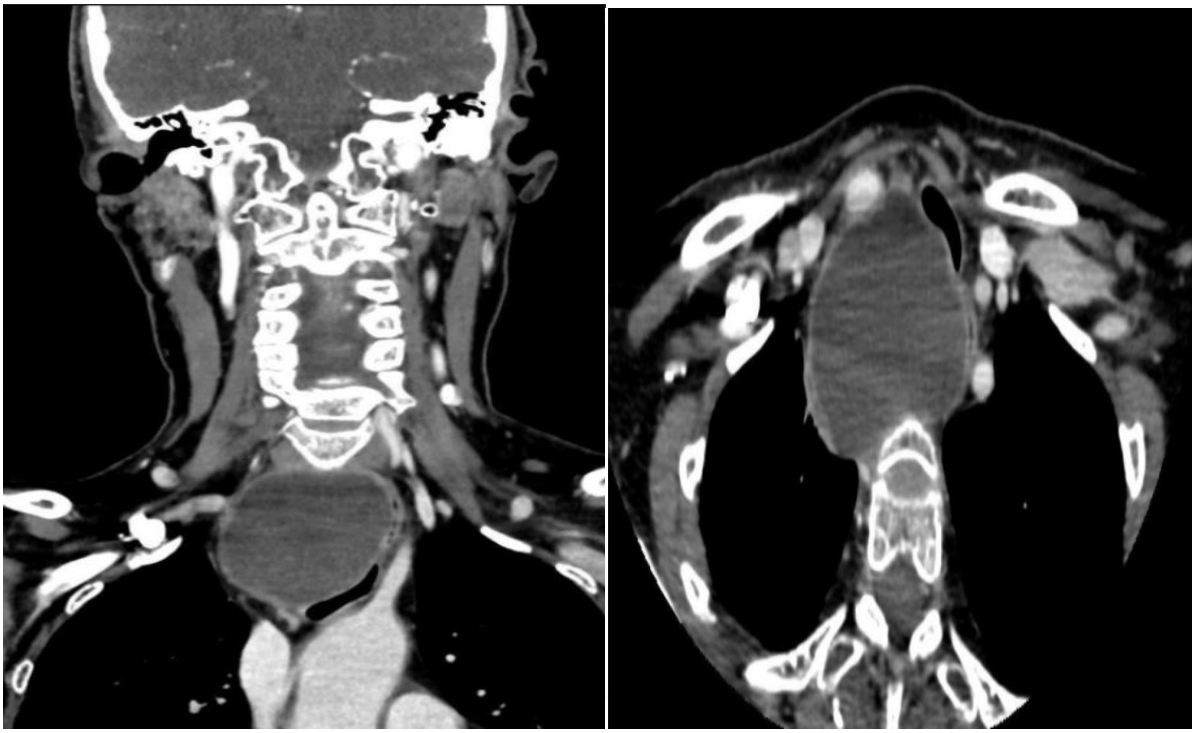


Figure C

Figure 1A, B, C: Triphasic cervico-thoracic MDCT showed at arterial phase (45sec) a 35ml cystic (21HU) mass at the upper right mediastinum, slightly displacing and compressing the tracheal lumen and oesophagus laterally. A focal solid mural part enhanced at the lower medial part of the cyst: attenuation 33 HU (0sec) < 169 HU (45sec) > 169HU (70sec), with no wash out (<20%). Note the low attenuation cystic homogeneous component, focal arterial contrast peripheral enhancement, the ovale shape, the absence of local invasion of innominate veins or of the aorta & mediastinal fat.



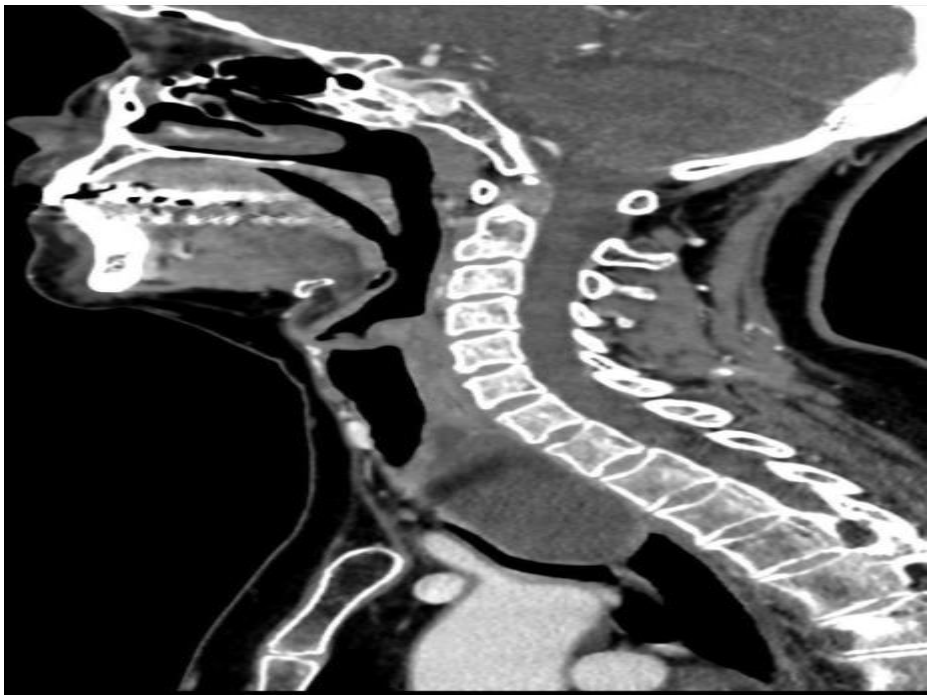


Figure 2: Cervico-thoracic contrast enhanced- MDCT sagittal, axial coronal reformations, performed one month later on, showed at arterial phase (45sec) the sudden increase in size of the mass measuring 45 x 55 x 77mm =100ml (extending from Cervical body C7 to Thoracic vertebrae T3) that strongly displaced and compressed the trachea & oesophagus laterally. Calcemia 3.17mMol/L, PTH 208ng/L, serum phosphorus 0.57mMol/L; Vitamine D 13.9 ng/ml.

Combined head & neck and thoracic surgery was planned to perform surgical excision of the upper mediastinal right mass. After having identified lower right thyroid lobe, and targeted the upper part of the cyst at the lower right neck, gentle dissection was performed to remove the mass from the tracheal wall medially, oesophagus on the left, common carotid artery on the right, pre vertebral muscles posteriorly, subclavian artery anteriorly, the right pleura laterally and inferiorly. Fine needle aspiration (FNA) of the cyst revealed thick brown chocolate -like liquid. Concomitant sternotomy was not performed as complete removal of the mass was eventually performed by using the sole cervical approach. Chest x-ray ruled out post-operative pneumothorax. FNAC assessment disclosed siderophages and multinuclear cells, fibrin deposition and epithelial cells, with no malignant or suspicious cells. Histopathology definitely ruled out malignancy, showing a 100ml cystic mass, thin cystic wall with a necrotic area consistent with a PT gland remnant, few epithelial benign cells. Immuno-histological staining showed positive for CD163 Ab + (macrophage), Cytokeratine + (necrosis area, epithelial cells), and negative for P40 Ab -.

Histopathological final diagnosis was giant mediastinal parathyroid adenoma with total post infarction cystic degeneration. The post-operative serum calcium & phosphorus and PTH levels decreased to normal ranges: 2.27 mMol/L (2.2-2.55) & 0.96 mMol/L (0.81-1.45) and 39.9 ng/L (14.9-56.9) respectively. Post-operative clinical examination noted progressive release of right vocal paresis, and progression of right arytenoid cartilage mobility during follow-up, at 2, 4 and 6 months clinical evaluation. Patient is still free of HPTH disease at six months follow-up. MDCT of chest and neck at three and six months did not show any local recurrence.

DISCUSSION

According to the extensive review of literature by Schulte et al, a total of 436 cases of mediastinal PTA have been identified from 221 articles including 42 small case series and 179 case reports published over a forty- year time period, between 1980-2020 [7]. Cystic giant mediastinal PTA are very rare and compressive PTAs presenting with severe hypercalcemia are even rarer. Precise knowledge of the anatomy and embryology of PT glands may explain the imaging feature and location of this pathology. As a matter of fact, there are commonly four PT endocrine glands that are located posteriorly in the vicinity of the thyroid gland. Thanks to the huge development of cervical high frequency ultrasound, normal PT glands are nowadays depicted on routine daily practice with a 75% detection rate at the lower pole of the thyroid gland and in the infra-thyroid region. Mean grand axis and mean volume of normal PT glands respectively of 5.7 mm (± 1,42 mm) and 33.3 mm3 (± 17.75 mm3) have been reported by Marchand et al [8]. The inferior « PT3 » glands and thymus arise from the third (« PT3 ») branchial pouch whereas the superior « PT4 » glands arise from the fourth (« PT4 ») pharyngeal pouch, along with the lateral thyroid gland. The inferior PT3 glands migrate down to the lower posterior aspect of the thyroid gland in the great majority of the cases. Owing to their longer embryonic migration course compared to the superior PT glands, they may often be reported in ectopic locations. Such ectopic PT3 gland may develop in any region of the migration pathway of the thymus gland, starting from the angle of the jaw to the pericardium layer, as reported by Ceriani et al [9]. Some patients may also exhibit supernumerary glands in about 2.5%-22%; namely the aorta pulmonary window has been reported as one of them into the mediastinum [10]. The most common location of inferior PT glands is the posterolateral aspect of the inferior pole of the thyroid gland. Other locations may include the thyrothymic ligament, the carotid bifurcation, intrathyroidal or intrathymic glands, the vagus nerve; and even the anterior mediastinum and pericardium [9-12].

In the present case, differential diagnoses were clearly challenging, including cystic plunging mediastinal goiter, thymic cyst, and cystic mediastinal adenomegaly. The latter including tuberculosis lymphadenopathy, prevalent level VI cystic adenopathy related to primary papillary thyroid carcinoma or to lymphophilic head & neck carcinomas was easily ruled out [13]. Regarding the possibility of a thymic cyst, this includes cystic thymic epithelial benign & also malignant tumors. Water attenuation is typically <31HU in benign thymic cyst with no significant enhancement between pre and post- contrast medium sequences on MDCT & MRI, and a frequent median anterior location; whereas age >60y, mean diameter > 17.2 mm, mediastinal lymph node enlargement and adjacent mediastinal organ invasion & anterolateral position are in favor of a thymic carcinoma, with a high specificity but low sensitivity [14,15]. Interestingly, the median volume doubling time was 324 days in benign thymic cysts versus 641 days in thymic carcinomas, according to Kim et al [16].

Regarding the last differential diagnosis of right plunging mediastinal goiter, MDCT features of the mass (Figure 1, solid focal peripheral tissue) [17,18] favored the diagnosis a benign neoplasm; however, differentiating PTA from thyroid nodule was not feasible. According to Ernst et al [19] there were two typical MDCT features out of three in favor of PTA including spontaneous attenuation and arterial phase attenuation of the solid peripheral part. The spontaneous attenuation may help differentiating between PTA and thyroid gland nodule: 33HU << 80HU threshold (mean values of 45HU in PTA vs 80HU in thyroid nodule), the attenuation of 169HU > 120 HU threshold at the arterial phase (mean value 170UH in PTA vs 80HU in lymph nodes), but lack of significant decrease of 20% wash out at 70seconds (mean 60HU in PTA) [19].

Given the biological and clinical context, the diagnosis of parathyroid adenoma infarction was the most likely [20]. Indeed, the acute worsening of compressive symptoms (dyspnea, dysphagia) that was concomitant with acute swelling of the mass, the cystic degeneration and presence of fibrin deposit & siderophages (considered as a hallmark of hemorrhagic infarction of PTA) at FNAC assessment, were all in favor of this diagnosis. Moreover, histopathology of the PTA showed central necrosis and hemorrhage and cells present in the periphery of the adenoma that may regenerate the adenoma (corresponding to the focal hyper vascular spot, (Figure 1) (20,21). The latter may explain the potential recurrence of hypercalcemia in case of spontaneous remission [22]. Acute HPT due to PTA' s infarction has been reported for the first time by Norris et al in 1946 [20] and should be beared in mind in case of sudden event in HPTH context.

In the present case, there was dysphonia due to stretching compression of the right laryngeal recurrent nerve by the giant cystic mass. But also, there was severe compression of the trachea and oesophagus (Figure 2) due to PTA's massive infarction related swelling. In 2018, Paparamidis et al collected data from a total of 218 articles reporting 359 cystic PTAdenomas [23]. Mean age of patients was 49years and the male/female ratio was 1/1.85. The most common locations included the left thyroid lobe (31.6%), and superior mediastinum (19.3%). Most common symptoms were neck mass (42%), compressive symptoms (21%) and hyperparathyroidism (17.5%). In 62% of the cases, the cystic PTA were non-functioning. Mean diameter was 49 mm. Recurrences occurred in 27/97 patients (28%). No deaths due to parathyroid cysts were mentioned in the literature to date. Mediastinal location includes anterior in 4.5%, middle compartment in 3.6%, and posterior compartment in 1.1% [23].

Malignant HPT accounts for less than 1% of the PHPT, and usually is associated with severe hypercalcemia, and invasive symptoms (trachea, oesophagus, venous invasion, loco regional tumor spread to level VI lymph nodes, and distant metastasis) [7]. The malignancy rate reached 7.1% of all cases. Interestingly, no malignant transformation of cystic PTA has been reported to date.

In solid PTA of mediastinal location, Schulte et al proposed « the 3 + 3 rule », to accurately predict malignancy in the majority of such patients. Patients presenting with mediastinal PT neoplasms > 30mm (mean size 42.5mm, median age 56.5years old, SR M/F 1.5) and with hypercalcemia > 3mMol/L (median calcemia 3.6mMol/L) were found positive for malignancy with a 63% accuracy rate [7]. In case of cystic PTA, subacute infarction and subsequent acute release of PTH into the patient's blood circulation may explain the sudden onset of hypercalcemia of benign origin.

Lastly, even very large mediastinal PTAs may be incidentally diagnosed as non-functional parathyroid cysts on MDCT (24), as reported by Mossinelli et al [25].

Interestingly, minimally invasive diagnostic means such as PTH assay in preoperative image- guided fine needle aspiration FNA-PTH washout fluid should be used when facing negative or discordant functional/ morphological image findings.

Moreover, percutaneous thermal ablation and/ or ethanol injection therapy (PEIT) of cystic PTAs under ultrasound/MDCT guidance may represent an alternative procedure in polymorbid elderly patients presenting with increased surgical risk or contraindication for surgery. Major complications include hypocalcemia, hoarseness, and Claude Bernard Horner syndrome [26,27].

To best of our knowledge, percutaneous minimally invasive therapy (PEI) has not been evaluated in mediastinal cystic PTA.

CONCLUSIONS

Giant mediastinal PT cysts can be misleading namely when discovered incidentally, or presenting as retrosternal cystic goiter, or compressive mass. Severe hypercalcemia is reported in solid malignancy or infarction cases. Combined pre-operative functional & MDCT imaging is mandatory. The surgeon's skills on complete resection of the PTA are of prime importance for a definitive treatment. Decrease in the PTH and serum calcium levels are successful markers of complete resection of functional ectopic parathyroid adenoma. FNA-PTH washout fluid is accurate to reach the full diagnosis in negative or discordant functional/ morphological image findings.

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