



# A Rare Case of Recurrent Mediastinal Malignant Paraganglioma of Thyroid Origin: a Case Report

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## Abstract

Paraganglioma is a neuroendocrine tumor that originates from extraadrenal chromaffin cells. Primary thyroid paraganglioma is an extremely rare neoplasm. In this study, an exceptionally uncommon case of recurrent mediastinal malignant paraganglioma with primary origin from thyroid gland is presented. Median re sternotomy, resection of left brachiocephalic vein, and extirpation of the mediastinal tumor were performed successfully. Commonly, it is preoperatively misdiagnosed and has unpredictable biological behavior. Incorrect diagnosis results in disastrous consequences for the patient, and consequently, correct pre- and postoperative diagnoses promise an optimal treatment plan and good prognosis. Long-term follow-up is indicated in all patients due to the risk of recurrence and distant metastases.

## Keywords

recurrent mediastinal malignant paraganglioma, re sternotomy, thyroid gland, surgery

## INTRODUCTION

Paraganglioma (PG) is a neuroendocrine tumor that originates from extraadrenal chromaffin cells. Primary thyroid paraganglioma (PTPG) is an extremely rare tumor described for first time by van Miert in 1964.<sup>[1]</sup> PTPG accounts for 0.04% of all thyroidectomy procedures. It presents with compressive symptoms, local aggressiveness, and despite invasion of adjacent structures, surgical resection can achieve a long disease-free interval.<sup>[2]</sup> PTPG has a rate of <1% of all extra-adrenal paragangliomas.<sup>[3]</sup> The aim of this study is to present an exceptionally uncommon case of recurrent mediastinal malignant paraganglioma with primary origin from thyroid gland and make a brief review of literature.

## CASE REPORT

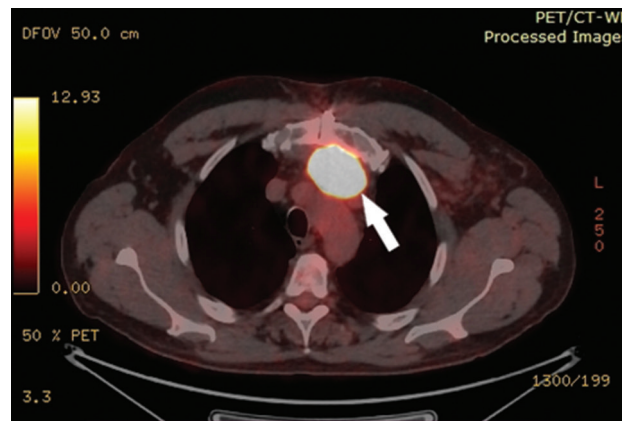
A 54-year-old man was admitted to the Department of Thoracic Surgery for the second time with a one-month history of left upper limb edema. Nine months prior, the same patient underwent surgery in this department for a malignant paraganglioma of the left thyroid lobe, which descended into the superior mediastinum. A neck collar incision with proximal partial sternotomy, total thyroidectomy, and thorough unilateral left lymph node dissection on groups 2A, 3, 4, 5A, B and 6 on the left side were performed. The left paratracheal lymph nodes were removed too. Metastases were confirmed in five left paratracheal lymph nodes. After a multidisciplinary board discussion, the patient was referred for radiotherapy, but he had another consultation with another radiotherapist, who considered it unnecessary, and eventually, he did not

undergo radiotherapy. A magnetic resonance imaging (MRI) was performed six months later and there was no evidence of recurrence. At the second admission, all paraclinical tests were within normal ranges. On physical examination, abundant venous collaterals on the left hemithorax and left upper extremity were found, as the last one was also edematous.

A CT scan performed nine months after the first surgery revealed an oval soft-tissue mass in the superior-anterior mediastinum (Fig. 1). It was with the following dimensions: crano-caudal – 62 mm, antero-posterior – 37 mm, medio-lateral – 53 mm. The tumor was relatively homogeneous during the native study with density of 45 HE, and after intravenous application of contrast material, it raised its density moderately and non-homogenously up to 96 HE with the presence of relatively hypodense zones. The posterior wall of the lesion was lying closely to the left brachiocephalic vein, and it was compressed and stenosed to a minimal diameter of 2.5 mm. It reached the aortic arch without evidence of invasion. Post-operative fibrous changes around the left brachiocephalic and subclavian vein were detected. The right jugular vein was dilated up to 32 mm. The left jugular vein was lightly stenosed up to 5 mm in the distal segment. The left subclavian vein was contrasted, but in the segment before the influx in the left brachiocephalic vein, there was a mural thrombus. Single small lymph nodes in the mediastinum and neck region were revealed. Conclusion for a recurrent formation was made.

A PET/CT scan detected a metabolic active soft-tissue-equivalent lesion with dimensions of 62×36×60 mm, SUV max 41.5, located in the anterior mediastinum. Ventrally, it was located closely to the sternum without evidence of infiltration, and dorsally, it contacted with the aortic arch on a wide area, distally, it was clearly distinguished from the pulmonary trunk. Close to the lesion, we found disseminated small nodular densities, including disseminated lymph nodes with dimensions up to 7/10 mm without metabolic activity. Conclusion for a recurrent disease without lymph node or distant dissemination was made (Fig. 2).

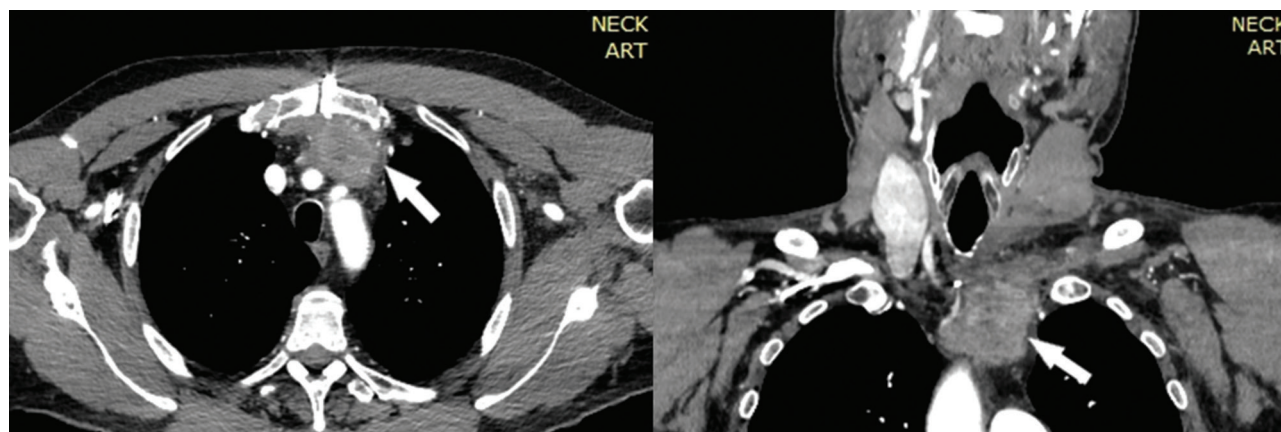
The patient was presented at a multidisciplinary board discussion, and it was suggested that it was most likely a recurrent malignant PG. The probability of tumor being an



**Figure 2.** PET/CT scan before surgery showing a highly metabolic oval mass in superior-anterior mediastinum.

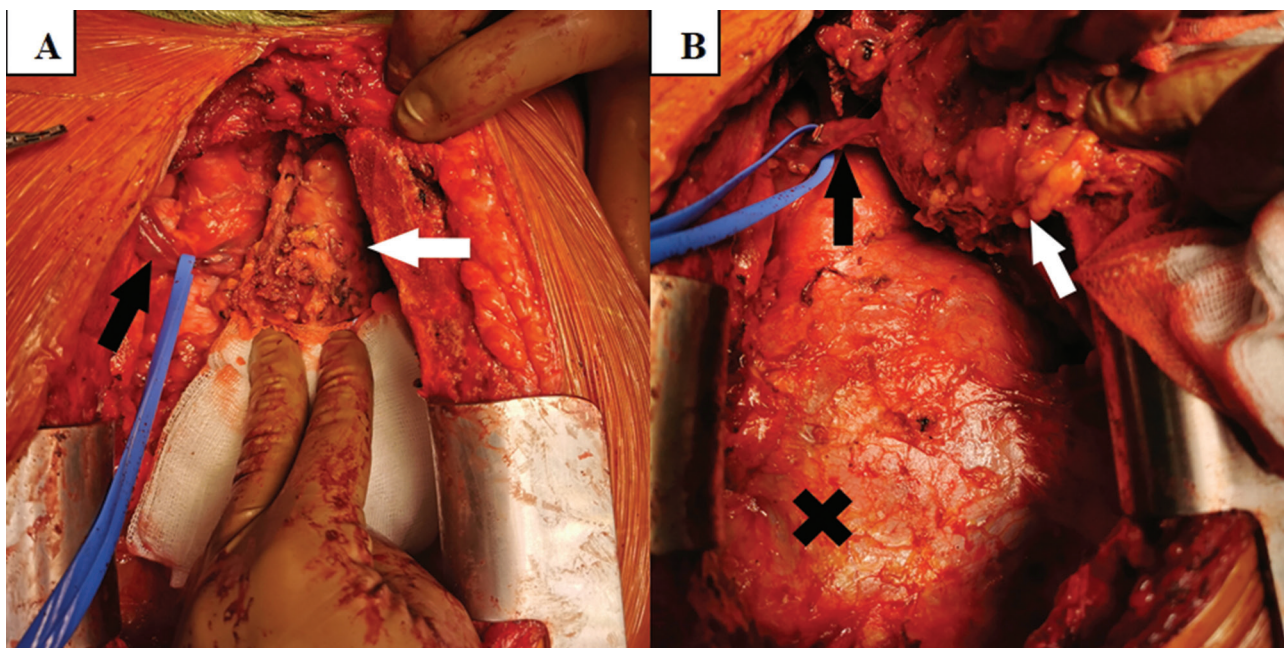
enlarged metastatic lymph node was excluded because of the same locoregional emergence as the primary PG and imaging data excluding metastases. The patient was referred for operative treatment.

A total midline re sternotomy was performed (Fig. 3A). A dense-elastic lesion was found in the superior-anterior mediastinum with dimensions of 70×50 mm, intimately adjacent to the manubrium and mainly to the left of it, anterior pericardial wall, aortic arch, brachiocephalic trunk, left carotid artery, and anterior tracheal wall. By sharp dissection of the lesion together with the surrounding prepericardial fat tissue, several visibly unchanged lymph nodes around the right board of the brachiocephalic trunk and from the aorto-pulmonary window were removed (Fig. 3B). Mobilization of the posterior wall of the lesion revealed an infiltration of the anterior-superior wall of the middle part of the left brachiocephalic vein. The latter was resected on the right side before the influx into the superior vena cava and on the left side after the left venous angle between the subclavian vein and the internal jugular vein, and in this area, the influx of an intact left vertebral vein was established. After careful dissection of the lesion in crano-caudal direction, the latter was totally extirpated en-bloc with the resected left brachiocephalic



**Figure 1. A, B.** CT with intravenous contrast administration before surgery, revealing an oval heterodense mass (marked with a white arrow).





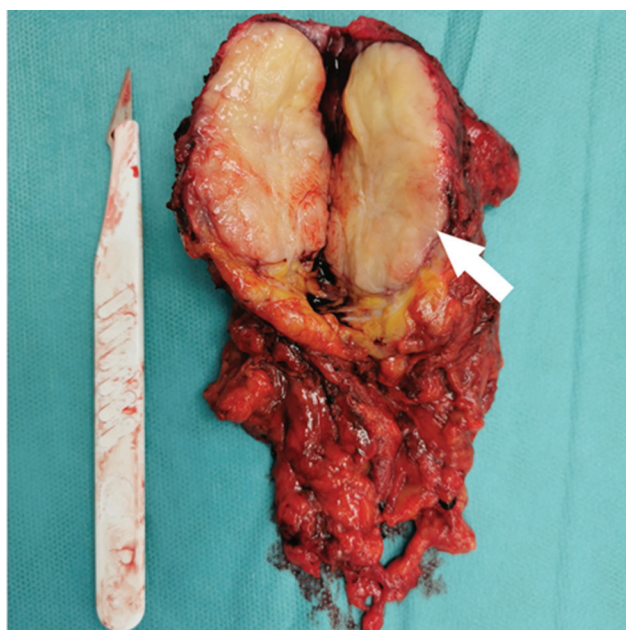
**Figure 3.** Intraoperative imaging. **A.** Median re-sternotomy and tumor in the superior-anterior mediastinum (white arrow shows the tumor). A vessel loop is placed around the left brachiocephalic vein (the vein is marked with a black arrow). **B.** Anterior pericardial wall after dissection of the lesion (marked with X).

vein, surrounding adipose tissue and lymph nodes from the aorto-pulmonary window and the right board of the brachiocephalic trunk. Sternotomy was closed.

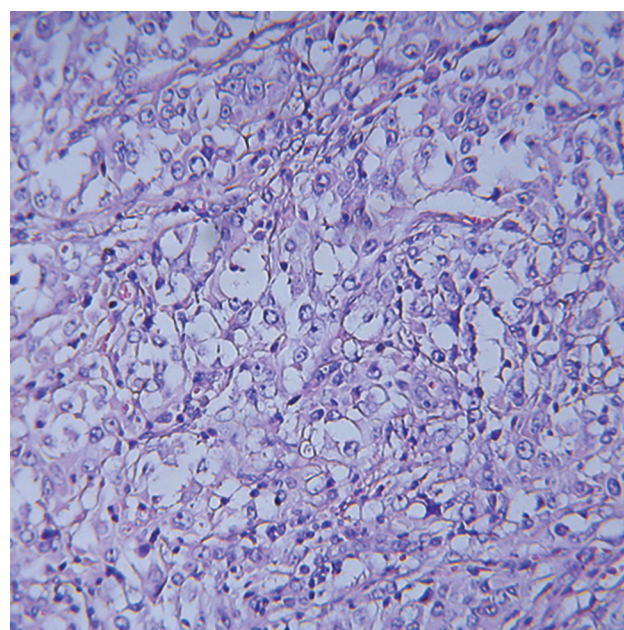
The lesion was well demarcated with macroscopic dimensions of 60×40×55 mm (Fig. 4). The cut surface was white, smooth and without macroscopic evidence for necrosis.

Microscopically, the formation had solid nest structure composed by oval cells with abundant eccentric eosinophil

cytoplasm and large polymorphous vesicular nuclei with visible large nucleoli (Fig. 5). Cells with multiple nuclei were also seen. There were zones of necrosis and slight-to-moderate infiltration of the stroma with lymphocytes, mixed with plasma cells and neutrophils in places. Comparison with the previous biopsy confirmed the morphological diagnosis. Final pathological decision was for mediastinal recurrent malignant PG without lymph node metastases.



**Figure 4.** Postoperative specimen after cutting (white arrow shows the tumor).



**Figure 5.** Histopathological images with hematoxylin and eosin staining of a recurrent mediastinal malignant paraganglioma with origin from thyroid gland (magnification ×20).



Immunohistochemistry revealed positive expression of tumor cells for CD56, chromogranin and synaptophysin, and positive expression of sustentacular cells for S-100, which proved recurrent PG (Fig. 6).

The patient was discharged five days postoperatively with the postoperative period being uneventful. He received adjuvant radiotherapy. Eight months later, he was in excellent general condition and without local recurrence or distal metastases.

## DISCUSSION

We present the first reported case of a recurrent malignant mediastinal PG arising from thyroid gland.

PTPG are thought to originate from the inferior laryngeal paraganglia, which are pulled down by the recurrent laryngeal nerve and lie outside the thyroid or are buried inside the gland.<sup>[4]</sup> PTPG have female predominance, typically occurring between the ages of 40 and 60 and presenting as an asymptomatic solitary thyroid nodule.<sup>[5]</sup> The present case was a 54-year-old man with complaints of right upper limb edema and abundant venous collaterals on the left hemithorax and left upper extremity due to left brachiocephalic vein stenosis and left subclavian vein thrombosis.

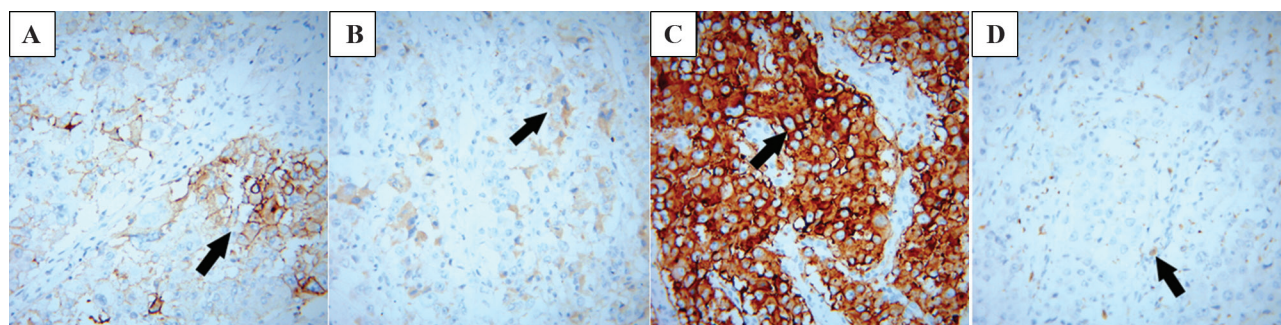
PGs are often misinterpreted on fine-needle aspiration biopsy like other relatively common primary thyroid tumors such as follicular or medullary thyroid carcinoma, metastatic neuroendocrine tumor, or even benign thyroid nodule because of architectural similarities.<sup>[6]</sup> In PTPGs, criteria for malignancy are controversial and include necrosis, metastasis, uniform cytological atypia, and vascular invasion, and unlike malignant neoplasms elsewhere, local infiltration, as it was reported by Ferri et al., does not indicate malignant disease.<sup>[7]</sup> Because of a mediastinal localization of the lesion, dense adhesions, close proximity to central vessels and high imaging suspicion for recurrence, preoperative core needle biopsy was not performed. Histologically, these lesions are composed of polygonal chief cells and elongated sustentacular cells, as tumor cells exhibit a characteristic nesting or organoid growth pattern (Zellballen) that resembles the normal paraganglion's architecture.<sup>[3]</sup> According to a study, true thyroid PGs have

positive immunohistochemical staining for chromogranin A, synaptophysin, S-100 and neuron-specific enolase.<sup>[8]</sup> In our case the tumor showed also positive expression for chromogranin, synaptophysin, S-100 and CD56. Differential diagnosis includes hyalinizing trabecular thyroid adenoma (or so called paraganglioma-like adenoma) and medullary thyroid carcinoma, particularly in case of nesting (paraganglioma-like) growth pattern.<sup>[7]</sup>

PGs located in the base of the skull, head, neck and thyroid are usually clinically asymptomatic due to minimal or no synthesis of catecholamines (non-secretory).<sup>[9]</sup> Clinically and biochemically asymptomatic PGs can cause hemodynamic instability during surgery, as well as approximately 4% of head and neck PGs are found to be hyperfunctional, and therefore empiric low dose adrenergic blockade should be considered.<sup>[10]</sup> The patient presented here was also a non-secretor and had no symptoms of hyperproduction of catecholamines.

On contrast enhanced CT, PTPG is very similar to carotid body PG: intense homogeneous enhancement (because of nodular hypervascularity) with splaying of peri-nodular vasculature; although heterogeneous enhancement is also present in case of internal hemorrhage or thrombosis.<sup>[4]</sup> CT scan of the reported case showed an oval soft-tissue-equivalent formation in the superior-anterior mediastinum in close proximity to the left brachiocephalic vein. It was relatively homogeneous in the native study with density of 45 HE, and after intravenous application of contrast material, it raised its density moderately and non-homogeneously up to 96 HE in the presence of relatively hypodense zones. A thrombosis of the left subclavian vein was also found.

Surgery is the cornerstone in the treatment of PTPGs. Practically, the resection may be very risky due to the increased vascularity and fragility of the lesion, which can also be densely attached to the adjacent tissues.<sup>[5]</sup> Lobectomy or total thyroidectomy are the preferred treatment alternatives for PTPG and an elective radical neck dissection is usually not indicated due to its mostly benign nature.<sup>[11]</sup> In case of confirmed malignant degeneration, it is advised to perform radical resection with regional lymph node dissection, followed by radio-chemotherapy. Reznick et al. described the first PTPG with clearly malignant behavior, local recurrence, regional lymph node, and distant



**Figure 6.** Immunohistochemistry images of a recurrent mediastinal malignant paraganglioma with origin from thyroid gland. Positive expression of CD56 (A), chromogranin (B), synaptophysin (C) and S-100 (D) (marked with black arrows).

metastases.<sup>[12]</sup> Our team also proceeded with total thyroidectomy and thorough unilateral left lymph node dissection on groups 2A, 3, 4, 5A, B, and 6 on the left during the first surgery. Five paratracheal lymph nodes were confirmed to be metastatic. Due to the malignant nature of the tumor and lymphatic spread, adjuvant radiotherapy was suggested. The non-conduction of radiotherapy is the most probable reason for the locoregional recurrence in the presented case. As a result, on the second hospitalization, a median re sternotomy was performed, as well as excision of the left brachiocephalic vein due to malignant infiltration and successful extirpation of the mediastinal tumor. The operation was really complex due to the dense adhesions to the adjacent main vessels because of the previous surgery and the invasive nature of the tumor. Also, the lesion was well vascularized and the risk of hemorrhage was highly increased. Again, the patient was sent for radiotherapy and eight months later there was no evidence of recurrences or metastases. For inoperable cases, treatment with radioisotopes and chemotherapy may be helpful, as well as long-term follow-up is recommended as these tumors can develop late metastasis and have unpredictable behavior.<sup>[9]</sup>

## CONCLUSIONS

PTPG is a rare tumor with commonly preoperative misdiagnosis and unpredictable biological behavior. Mediastinal malignant PTPG is extremely rare and only few cases were described in literature and this article is the first description of a recurrent tumor with this localization. Incorrect diagnosis results in disastrous consequences for the patient and the correct pre- and postoperative diagnoses promise an optimal treatment plan and good prognosis. Long-term follow-up is indicated in all patients due to the risk of recurrence and distant metastases.

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## Competing Interests

The authors have declared that no competing interests exist.

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# Редкий случай рецидивирующей злокачественной параганглиомы средостения тиреоидного происхождения: описание случая

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## Резюме

Параганглиома – нейроэндокринная опухоль, развивающаяся из экстранадпочечниковых хромоаффинных клеток. Первичная параганглиома щитовидной железы – крайне редкое новообразование. В данном исследовании представлен исключительно редкий случай рецидивирующей злокачественной параганглиомы средостения с первичным происхождением из щитовидной железы. Срединная рестернотомия, резекция левой плечеголовой вены и экстирпация опухоли средостения были успешно выполнены. Обычно в предоперационном периоде она диагностируется неправильно и имеет непредсказуемое биологическое поведение. Неправильный диагноз приводит к катастрофическим последствиям для пациента, а, следовательно, правильный до- и послеоперационный диагноз сулит оптимальный план лечения и хороший прогноз. Длительное наблюдение показано всем пациентам из-за риска рецидива и отдалённых метастазов.

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## Ключевые слова

рецидив злокачественной параганглиомы средостения, рестернотомия, щитовидная железа, хирургия

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