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Caso Clínico

# Poorly Differentiated Thyroid Carcinoma: A Diagnostic and Therapeutic Challenge

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A B S T R A C T

Poorly differentiated thyroid carcinoma is a rare entity. This aggressive thyroid cancer is biologically situated between well-differentiated and anaplastic thyroid carcinoma. This article reports a case of a poorly differentiated thyroid carcinoma in a 41-year-old female. The patient underwent treatment with surgery and radioiodine therapy. Metastases were detected during early follow-up. Faced with a persistent, aggressive disease unresponsive to radioiodine, the patient started lenvatinib. With this therapy, there was a significant metastasis size reduction. The patient completed two and a half years of follow-up, without the appearance of new lesions, although with evidence of slow disease progression. Poorly differentiated thyroid carcinoma is an aggressive lesion with poor median disease-free survival. Its treatment includes surgery and radioiodine treatment. Tyrosine kinase inhibitors are an option in disease relapse or progression, iodine resistance and metastatic disease. Close monitoring is essential given the high risk of relapse.

## Carcinoma Pouco Diferenciado da Tiroide: Um Desafio Diagnóstico e Terapêutico

R E S U M O

O carcinoma pouco diferenciado da tiroide é uma entidade rara. Este carcinoma agressivo está biologicamente situado entre o carcinoma bem diferenciado da tiroide e o anaplásico. Este artigo relata o caso raro de um carcinoma da tiroide pouco diferenciado, diagnosticado numa mulher de 41 anos. A doente foi submetida a cirurgia e iodo radioativo. Foram detetadas metástases durante o follow-up precoce. Perante uma doença persistente, agressiva e não responsiva ao iodo radioativo, a doente iniciou lenvatinib. Com esta terapia houve redução dimensional das metástases. A doente completou dois anos e meio de seguimento, sem surgimento de novas lesões, mas com evidência de progressão lenta da doença. O carcinoma pouco diferenciado da tiroide é uma lesão agressiva com uma sobrevida média livre de doença curta. O seu tratamento inclui cirurgia e terapêutica com iodo radioativo. Os inibidores da tirosina cinase são uma opção na recidiva ou progressão da doença, na resistência

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## Introduction

Poorly differentiated thyroid carcinoma (PDTC) was only recognized as a distinct entity by the World Health Organization in 2004. In 2006, the Turin criteria were published, establishing the current histologic criteria for PDTC diagnosis: the presence of a solid/trabecular/insular pattern of growth; and at least one of the following features: convoluted nuclei, mitotic activity ≥3 × 10 HPF, and tumour necrosis.[1] Studies on PDTC have been limited due to its rarity and heterogeneity of inclusion criteria before the Turin criteria.

PDTC accounts for 3%–5% of all thyroid carcinomas and has an intermediate biological behaviour, between well-differentiated and anaplastic carcinoma.[2,3] At presentation, the majority of patients with PDTC have advanced locoregional disease, and distant metastasis eventually appear during follow-up in up to 85% of cases, being the cause of most disease-related deaths.[3-5]

The cytological diagnosis of PDTC on fine needle aspiration (FNA) samples is challenging, and histological examination is usually required; immunohistochemistry increase the diagnostic accuracy (TTF1 positivity) but molecular testing as a diagnostic tool has not yet a role, due to the vast overlap mutations and the lack of specific ones.[2-4,6]

There is no standardized treatment for PDTC to date. Surgery with removal of all gross disease can achieve satisfactory locoregional control and adjuvant treatment with high-dose radioiodine is recommended, however this treatment is only successful in a subset of patients owing to variable levels of iodine uptake, about 15% of cases has a decreased iodine uptake limiting the success of this treatment.[3,5-7] Other adjuvant treatment includes external beam radiotherapy and systemic chemotherapy in selected cases.[3,7]

Disease-free survival is less than a year and the mean survival is about 60 months, which gives this entity an important clinical significance.[7] In a 2014 series of Ibrahimpasic, with a total of 91 patients with PDTC treated by surgery with or without adjuvant therapy, the 5-year overall survival and disease-free survival were 62% and 66%, respectively and locoregional and distant control at 5 years was 81% and 59%, respectively.[8] Disease-specific deaths have occurred due to distant metastases and rarely due to uncontrolled locoregional recurrence.

Recently, tyrosine kinase inhibitors (TKIs) have been used in PDTC patients with radiodine-resistent progressive, recurrent or metastatic disease.[7]

The objective of this work is to draw attention for the existence of this entity, reporting a clinical case of metastatic PDTC, its approach and treatment.

## Case Report

A 41-year-old female, medicated with trazodone 150 mg and escitalopram 10 mg for depression, presented to our General Surgery – Endocrine Pathology consultation, due to a follicular tumour (Bethesda IV) in a 55 mm nodule in the left thyroid lobe.

The patient underwent left hemithyroidectomy in November 2020, uneventfully. Pathological examination revealed that the 4.5 x 3.3 x 5.7 cm tumour had morphological and immunohistochemical alterations compatible with PDTC (Fig.1). The patient underwent totalization one month after the first surgery, in December 22, 2020, with no evidence of neoplasia in the resected specimen.

At the follow-up visit, in January 20, 2021, a left supraclavicular lesion was identified (Fig. 2). Ultrasound revealed two pericentimetric lesions in the left lobectomy site and a supraclavicular

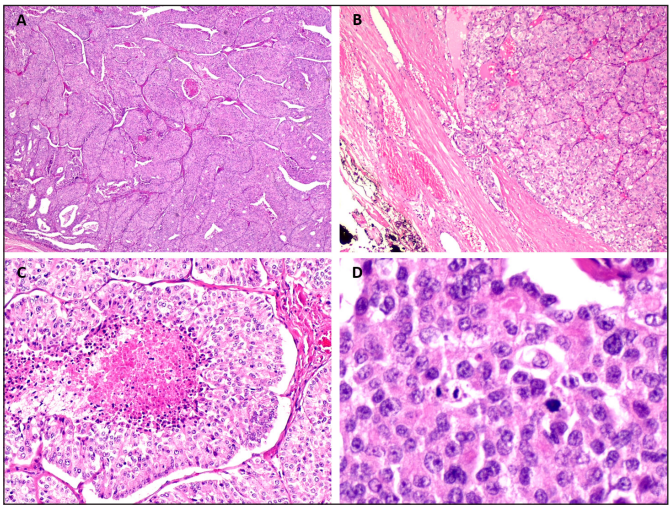


*Figure 1.* Hemithyroidectomy histopathological findings. On hematoxylin and eosin staining, a neoplasm with a predominantly trabecular to solid growth pattern was found. (A - H&E, 40x). The tumour was encapsulated, with areas of capsular invasion (B - H&E, 40x). Foci of necrosis were also present (C - H&E, 100x). On a higher magnification, this malignancy was comprised of cells with an eosinophilic cytoplasm and round, hyperchromatic to vesicular nuclei. Several mitosis were readily identifiable (D - H&E, 100x).

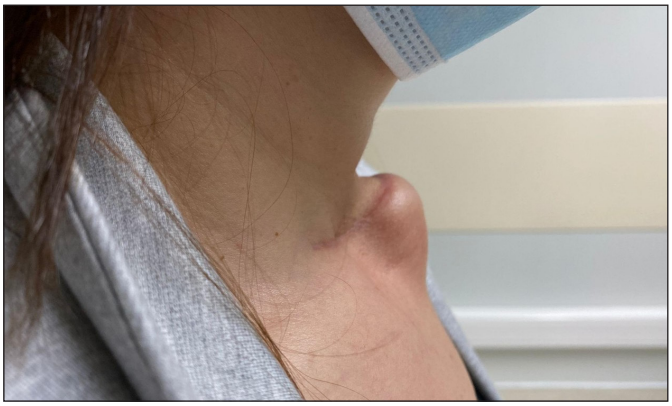

*Figure 2.* Left supraclavicular lesion identified during early follow-up.

lesion (with a solid appearance and nonspecific characteristics) measuring approximately 18 mm. The patient underwent radioiodine treatment in February 24 (iodine-131 162 mCi), after thyroid hormone withdraw. The day before, the lab work-up reveal a stimulated thyroglobulin level of 94.50 ng/mL.

Whole-body scintigraphy with radioiodine-131 revealed a conglomerate of two adjacent foci of slightly increased fixation in the anterior cervical region between the sternal furcula and the chin, in the midline.

A cervical computed tomography (CT) scan, in March, revealed a small solid nodular image with 8 mm in the left lobectomy site, poorly delimited (Fig. 3a). A vaguely nodular image in the region of the medial end of the clavicle, poorly delimited with an elongated configuration, approximately 2 cm in diameter, with peripheral uptake and a central cystic component was apparent (Fig. 3b). There was no evidence of lymphadenopathy in the cervical ganglionic chains. The supraclavicular node was biopsied, the cytology was positive for malignant cells and immunostaining was positive for thyroid transcription factor-1.

In April, the FDG PET/CT scan showed an area of densification in the left lobectomy site measuring 12 x 6 mm with greatly increased uptake; nodular formation in the subcutaneous tissues

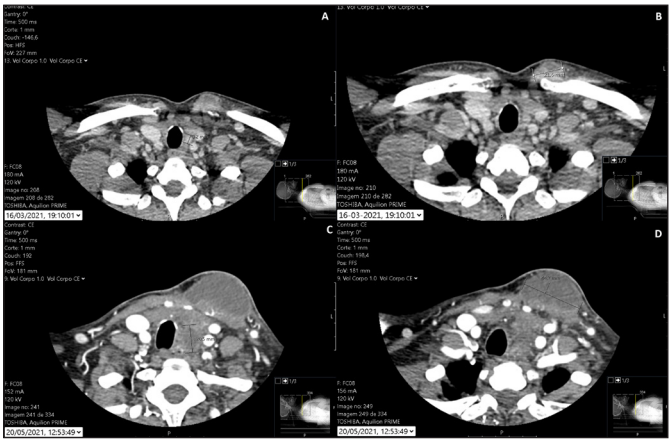

*Figure 3.* Axial plane of cervical CT showing a nodular image in the left lobectomy site (A) and a nodular image in the region of the medial end of the clavicle (B), and their growth in two months (C and D, respectively).

of the left lower cervical region measuring 23 x 18 mm with intense uptake suggestive of metastases from thyroid neoplasia and at least three nodules in both lungs with slight but significant avidity, suggestive of pulmonary metastization (Fig. 4). At this time the lab work-up reveal an unstimulated thyroglobulin level of 29.10 ng/mL.

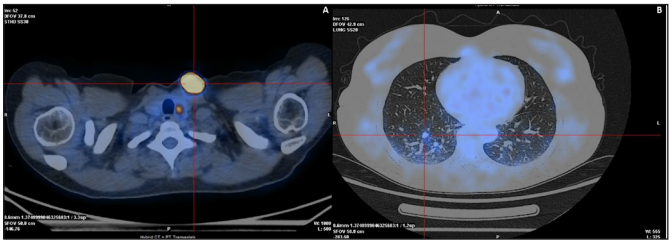

*Figure 4.* FDG PET/CT showing an area of densification in the left lobectomy site with greatly increased uptake and a nodular formation in the subcutaneous tissues of the left lower cervical region with intense uptake suggestive of metastases (A) and pulmonary nodules with significant avidity, suggestive of pulmonary metastization (B).

Faced with a persistent, aggressive disease unresponsive to iodine, the patient started lenvatinib 24 mg daily, in May 13, 2021.

On May 20, 2021, the patient underwent a follow-up CT scan which revealed, compared to the March and April exams, a dimensional increase both in the nodule located in left lobectomy site (21 mm) and in the clavicular node (45 mm) (Figs. 3c and 3d). In the lung parenchyma, multiple rounded nodular lesions were identified, with central necrosis, compatible with metastases, the largest with dimensions between 6 and 8 mm, all significantly larger than in the previous evaluation. Numerous millimetric nodular lesions also appeared, suggesting diffuse pulmonary metastasis. Two weeks after starting lenvatinib, unstimulated thyroglobulin was 20.5 ng/mL. About a month after starting therapy, there was clinical improvement with marked reduction of the clavicular implant and unstimulated thyroglobulin was 0.71 ng/mL. Cervical and thoracic CT scan, in July, revealed dimensional reduction of pulmonary metastases and reduction of the lesion in the left lobectomy site, and the supraclavicular lesion disappeared (Fig. 5a). In September we received the genetic study report, not having found any mutation or rearrangement in the *EGFR*, *KRAS*, *NRAS*, *BRAF*, *MET*, *HER2*, *HER4*, *PIK3CA*, *ALK*, *RET*, *ROS1* or *NTRK* genes. A mutation in the *HER3* gene was identified, which is not associated with any targeted therapy. At this time, on physical examination we could only identify a small scar at the left clavicular implant site (Fig. 5b).

During treatment with lenvatinib, dosage adjustments were necessary, given the side effects of this drug. The patient had nausea, anorexia, intense asthenia, high blood pressure, headaches and proteinuria that led to a dose reduction to 20 mg in September 2021, and even discontinuation of the drug for two weeks in December 2021. The patient resumed treatment at a dose of 14 mg.

In the reassessment by imaging in July 2022 (1 year and 8 months of follow-up), there was an increase in the lesion located at the left lobectomy site and a dimensional increase in pulmonary metastatic lesions. CT scan was repeated 6 months later, the disease was found to be slowly progressing. Therefore, it was decided to increase the dose of lenvatinib to 18 mg. During this monitoring period, there was also a gradual increase in thyroglobulin, the last value in May 2023 being 5.09 ng/mL.

Currently, the patient is taking lenvatinib 18 mg during the week and discontinuing it on the weekend due to its adverse effects. The patient completed two and a half years of follow-up, without the appearance of new lesions, but with evidence of slow disease progression.

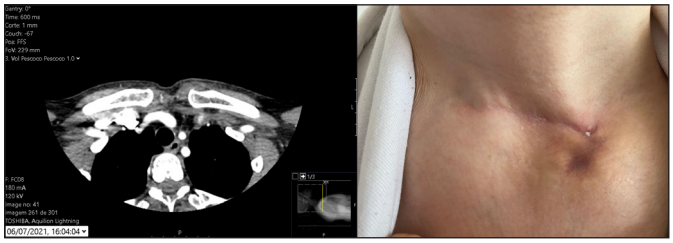

*Figure 5.* Axial plane of cervical CT showing supraclavicular lesion disappearance (A). Small scar at the left clavicular implant site (B).

## Discussion

PDTC is a rare but aggressive subtype of thyroid cancer with poor overall prognosis and challenging management.

A lump neck with rapid growth is the most common symptom of PDTC, along with symptoms of advanced diseased as hoarse voice, dyspnoea and dysphagia.[4] We report the case of a 41-year-old female that did not exhibited this typical presentation. The cytological analysis of the FNA sample suggested a follicular tumour (Bethesda IV). Indeed it is described, in published series, that only 27% of cases of PDCT are correctly diagnosed on FNA, whereas most of the remaining cases are put into the category follicular neoplasm.[7] According to the FNA result we proposed to the patient a lobectomy, and since the pathology report revealed a PDCT, the patient underwent totalization.

According to American Thyroid Association guidelines, thyroid lobectomy is the recommended initial approach for a cytologically indeterminate nodule, such as those classified as Bethesda IV.[9] This approach can be modified based on clinical or sonographic characteristics, but the patient's nodule was not suspicious on palpation or in ultrasound, the patient had no alarm symptoms, history of thyroid carcinoma, or radiation exposure. The nodule was large (>4 cm) but after discussion in a multidisciplinary consultation and considering that the estimated risk of malignancy of Bethesda IV lesions is 15%-30%, it was decided to proceed with a more conservative approach to preserve thyroid function and minimize morbidity. However, given the final histopathological diagnosis, the patient underwent totalization.

One month after totalization, a cystic lesion was identified close to the scar. At this point, our first suspicion was that the lesion was a seroma, so we requested an ultrasound for better clarification. It was decided to maintain the indication for treatment with radiodine because even considering that the cystic cervical lesion could be a local recurrence/persistent disease, this treatment modality could be effective and less aggressive than a surgery with increased risk, as it would be a third intervention. The lesion was only biopsied after treatment with radiodine, because we believed that it would not change our therapeutic strategy.

Although there is no standardized treatment for this PDCT, total thyroidectomy and clearance of all gross disease can achieve a satisfactory locoregional control with excellent 5-year locoregional control rate of 81%.[4]

PDTC generally presents at an older age (median age of 59 years) and with a higher male-to-female ratio than differentiated thyroid cancer and shows a more aggressive course, with a higher propensity for local recurrence and distant metastasis.[5,6] In this clinical case report, the patient presented at an earlier age than documented, but in fact the disease developed very quickly with very early local recurrence. Several factors have been associated with poor prognosis namely age ≥ 45 years, large tumour size ≥ 5 cm, evidence of extrathyroidal extension at surgery , distant metastasis at presentation, and some imunohistochemical markers.[7] Positive thyroglobulin post-surgery was also demonstrated to have prognostic value, in a retrospective analyses conducted on 38 patients with PDTC concluded that thyroglobulin levels after surgery and RAI appear to predict a higher rate of death and recurrence.[10]

In the presented case, larger tumour size was present and the thyroglobulin after surgery and radioiodine treatment was detectable.

Given the aggressiveness of PDTC and the poor survival rates, a multimodality treatment approach is required. Radioiodine treatment is only successful in a subset of patients with PDTC, and disease in our patient was unfortunately resistant to this therapy. The patient started therapy with lenvatinib, an oral multi-kinase inhibitor that has shown improvement in the progression-free survival and response rate among patients with iodine refractory thyroid cancer, including PDTC.[11,12] The patient had an excellent initial response, but with the need for frequent dose adjustments due to its difficult-to-manage side effects, and the disease eventually progressed. A close monitoring is required to improve outcome and to adjust treatment according to the patient´s tolerance.

The role of tyrosine kinase inhibitors is evolving and can act against different altered pathways implicated in the pathogenetic process of aggressive types of thyroid cancer. As well as lenvatinib, other multi-target kinase inhibitors, namely sorafenib and cabozantinib, have been approved for the therapy of aggressive radioiodine-resistant thyroid cancer, representing therapeutic options in disease progression.[13] Management of treatment with multi-targeted kinase inhibitors must involve a multidisciplinary team in order to maximize the benefit of these therapies, manage adverse effects and improve treatment compliance.

This clinical case is a paradigmatic example of the diagnostic and therapeutic difficulty of this entity.

## Contributorship Statement / Declaração de Contribuição:

BC: Conceptualization, data collection, writing original draft, and final approval.
DAJ: Provided pathologic figure and description.
ARF, JV, DAJ: Review and final approval.
SG, GR, AP, CS, MJO, MO: Supervision, review and final approval.

BC: Conceptualização, recolha de dados, redação do projeto original e aprovação final.
DAJ: Forneceu a figura patológica e a descrição.
ARF, JV, DAJ: Revisão e aprovação final.
SG, GR, AP, CS, MJO, MO: Supervisão, revisão e aprovação final.

## Responsabilidades Éticas

**Conflitos de Interesse:** Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
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**Confidencialidade dos Dados:** Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
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**Proveniência e Revisão por Pares:** Não comissionado; revisão externa por pares.

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**Patient Consent:** Consent for publication was obtained.
**Provenance and Peer Review:** Not commissioned; externally peer reviewed.

## References / Referências

1. Volante M, Collini P, Nikiforov YE, Sakamoto A, Kakudo K, Katoh R, et al. Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. Am J Surg Pathol. 2007;31:1256-64. doi: 10.1097/PAS.0b013e3180309e6a.
2. Bellini MI, Biffoni M, Patrone R, Borcea MC, Costanzo ML, Garritano T, et al. Poorly differentiated thyroid carcinoma: single centre experience and review of the literature. J Clin Med. 2021;10:5258. doi: 10.3390/jcm10225258.
3. Roque J, Nunes Silva T, Regala C, Rodrigues R, Leite V. Outcomes of lenvatinib therapy in poorly differentiated thyroid carcinoma. Eur Thyroid J. 2023;12:e230003. doi: 10.1530/ETJ-23-0003.
4. Tong J, Ruan M, Jin Y, Fu H, Cheng L, Luo Q, et al. Poorly differentiated thyroid carcinoma: a clinician's perspective. Eur Thyroid J. 2022;11:e220021. doi: 10.1530/ETJ-22-0021.
5. Ibrahimpasic T, Ghossein R, Shah JP, Ganly I. Poorly Differentiated Carcinoma of the Thyroid Gland: Current Status and Future Prospects. J Clin Endocrinol Metab. 2014;99:1245-52. doi: 10.1210/jc.2013-3842.
6. Cherkaoui GS, Guensi A, Taleb S, Idir MA, Touil N, Benmoussa R, et al. Poorly differentiated thyroid carcinoma: a retrospective clinicopathological study. Pan Afr Med J. 2015;21:137. doi: 10.11604/pamj.2015.21.137.6720.
7. Dettmer MS, Schmitt A, Komminoth P, Perren A. Poorly differentiated thyroid carcinoma : An underdiagnosed entity. Pathologe. 2020;41:1-8. doi: 10.1007/s00292-019-0600-9.
8. Ibrahimpasic T, Ghossein R, Carlson DL, Nixon I, Palmer FL, Shaha AR, et al. Outcomes in patients with poorly differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2014;99:1245-52. doi: 10.1210/jc.2013-3842.
9. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26:1-133. doi: 10.1089/thy.2015.0020.
10. Nunes da Silva T, Limbert E, Leite V. Poorly differentiated thyroid carcinoma patients with detectable thyroglobulin levels after initial treatment show an increase in mortality and disease recurrence. Eur Thyroid J. 2018;7:313-8. doi: 10.1159/000491996.
11. Prete A, Matrone A, Gambale C, Torregrossa L, Minaldi E, Romei C, et al. Poorly differentiated and anaplastic thyroid cancer: insights into genomics, microenvironment and new drugs. Cancers. 2021;13:3200. doi: 10.3390/cancers13133200.
12. Molinaro E, Viola D, Viola N, Falcetta P, Orsolini F, Torregrossa L, et al. Lenvatinib administered via nasogastric tube in poorly differentiated thyroid cancer. Case Rep Endocrinol. 2019;2019:6831237. doi: 10.1155/2019/6831237.