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Poorly differentiated and undifferentiated (anaplastic) carcinoma of thyroid with diagnostic challenges: A case series

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ABSTRACT

Poorly differentiated thyroid carcinoma (PDTC) and anaplastic or undifferentiated thyroid carcinomas (ATC) are uncommon malignancies of the thyroid. Anaplastic thyroid cancers represent only 1–2% of all thyroid cancer diagnoses; however, they contribute to 14–50% of fatalities associated with thyroid cancer, with a median survival duration ranging from 3 to 5 months. The majority of patients diagnosed with this disease are aged 65 years or older. Most patients exhibit a rapidly enlarging neck mass, difficulties in swallowing, or alterations in their voice. The 2022 World Health Organization classification introduced PDTC as a subtype of high-grade follicular cell-derived thyroid carcinoma (HGFCTC), whereas also renaming ATC as anaplastic follicular cell-derived thyroid carcinoma. There are evidence which suggests stepwise molecular progression from well-differentiated carcinoma to HGFCTC to ATC manifested by alteration in the MAPK pathway especially BRAF and RAS mutations and gain of secondary aggressive molecular signatures. PDTCs and ATCs are difficult to diagnose due to their rarity and previous equivocal diagnostic criteria. The aim of this study is to present a series of rare and interesting cases of PDTC and undifferentiated/anaplastic thyroid carcinoma accompanied by a concise literature review.

Key words: Thyroid; Carcinoma; Anaplastic; Poorly differentiated; Ki67

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INTRODUCTION

Poorly differentiated thyroid carcinoma (PDTC), an uncommon neoplasm accounts for 4–7% of all thyroid malignancies.[1] The term PDTC was first coined by Sakamoto et al., in 1983.[2] It gained recognition after inclusion in the World Health Organization (WHO) classification of endocrine tumors in 2004.[3] Lately in 2006 after the consensus meeting in Turin, Italy, regarding the diagnostic criteria, this rare malignancy has been acknowledged as a distinct pathological entity.[4] Undifferentiated/anaplastic thyroid cancer (ATC) is an uncommon malignancy of the thyroid. Only 1–2% of thyroid cancers are anaplastic, but the disease contributes to 14–50% of the mortality with a median survival of 3–5 months. Most patients diagnosed with this disease are 65 years of age or older. The incidence of anaplastic thyroid cancer is decreasing worldwide. Most patients present with a rapidly growing neck mass, dysphagia, or voice change.[5]

Recent WHO classification of thyroid tumors has included another entity of differentiated high-grade thyroid carcinoma (DHGTC), morphologically similar to PDTC, however, can be differentiated based on mitotic count and the presence of tumor necrosis.[4] These tumors also have similar low-grade nuclear features.[4,6] Moreover, the classification system lacks a universal grading system. Thus, it poses difficulty in the categorization and grading of follicular cell origin

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Table 1: Details of all cases

Case	Age	Sex	Presentation	USG Findings	FNAC	OT	Gross	Histology	Extra-thyroidal extension	Necrosis	LVSI	PNI	Stage	Ki 67 Li
1	63 years	M	Diffuse midline neck swelling for 6 months, non-tender, firm, progressively increase in size. Chronic cough for 4 months.	Enlarged thyroid compressing trachea and esophagus	Suspicious for malignancy BETHESDA-V	Total thyroidectomy	Specimen measures 6 cm × 4 cm ×1 cm	Poorly differentiated thyroid carcinoma	Present	+ (Focal)	+	+	$pT_{3b}N_X$	High
2	23 years	F	Right anterior neck swelling for 3 years, progressively increasing in size.	Well-defined nodule in the right lobe of the thyroid	Follicular lesion of undetermined significance BETHESDA-III	Right hemi-thyroidectomy	Nodule measures 3.5 cm × 2.7 cm × 1.8 cm	Poorly differentiated thyroid carcinoma arising from follicular carcinoma	Absent	+ (Focal)	+	+	pT_2N_X	Low
3	51 years	F	Diffuse midline neck swelling for 9 months, progressively increasing in size. Mild pain and dysphagia	Large complex thyroid with central node	Atypia of undetermined significance BETHESDA-III	Total thyroidectomy with central neck node dissection	The specimen measures 6.5 cm × 3.5 cm × 1 cm C/S – greyish-white with few colloid cysts multiple lymph nodes measuring 0.5 cm ×1 cm also received	Poorly differentiated thyroid carcinoma 2/4 lymph nodes positive for tumor deposits	Present	+ (large area)	+	+	$pT_{3b}N_2$	High
4	64 years	F	History of Anterior neck swelling for 10 years, recently complaining of rapid increase in swelling, hoarseness of voice, and shortness of breath.	Enlarged thyroid with lateral displacement of trachea by the tumor	Undifferentiated (Anaplastic) carcinoma BETHESDA-VI	Total thyroidectomy	Specimen measures 6 cm × 3 cm × 1.5 cm	Undifferentiated (Anaplastic) carcinoma, NOS, with predominantly Sarcomatoid morphology. 2/2 lymph nodes positive for tumor deposits.	Present	+ (large area)	+	+	$pT_{3b}N_2$	High
5	55 year	F	Right anterior neck swelling for 5 years, progressively increasing in size	Nodule in the right lobe of the thyroid	Suspicious for malignancy BETHESDA-V	Right hemi-thyroidectomy	Specimen measures 5.5 cm × 3.5 cm × 1 cm	Undifferentiated (Anaplastic) carcinoma, NOS, with predominantly Sarcomatoid morphology.	Present	+ (Focal)	+	+	$pT_{3b}N_X$	High
6	58 years	F	Diffuse midline neck swelling for 1 year, non-tender, firm with pain and dysphagia	Enlarged thyroid compressing trachea and esophagus	Poorly differentiated carcinoma of the thyroid BETHESDA-VI	Total thyroidectomy (multiple fragmented)	Multiple fragmented, altogether measuring 5.5 cm × 3.2 cm × 3 cm	Undifferentiated (Anaplastic) carcinoma, NOS, with predominantly Sarcomatoid morphology. 1/2 lymph nodes positive for tumor deposits	Present	+	+	+	$pT_{3b}N_1$	High

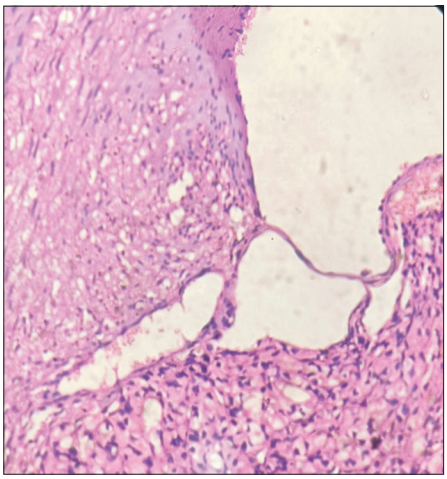

Figure 1: Lymphovascular invasion in poorly differentiated thyroid carcinoma arising from follicular carcinoma (×10)

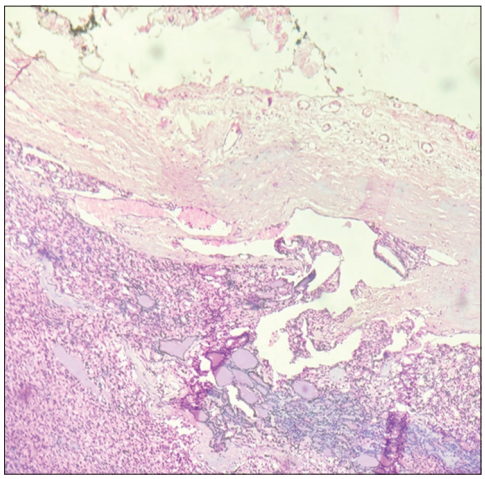

Figure 2: Capsular invasion in poorly differentiated thyroid carcinoma arising from follicular carcinoma (×10)

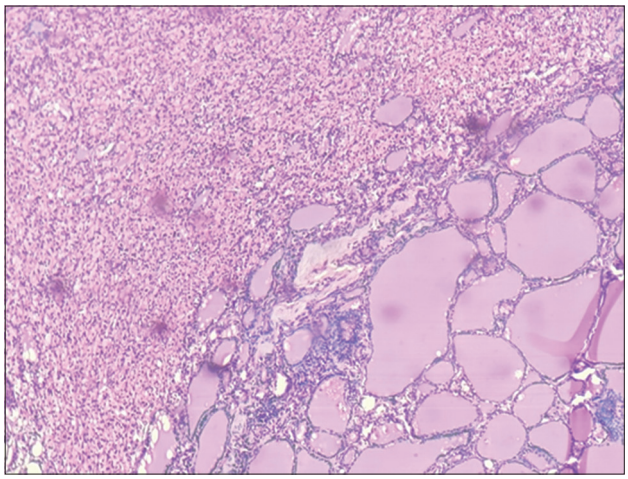

Figure 3: Follicular insular carcinoma transformation zone (×10)

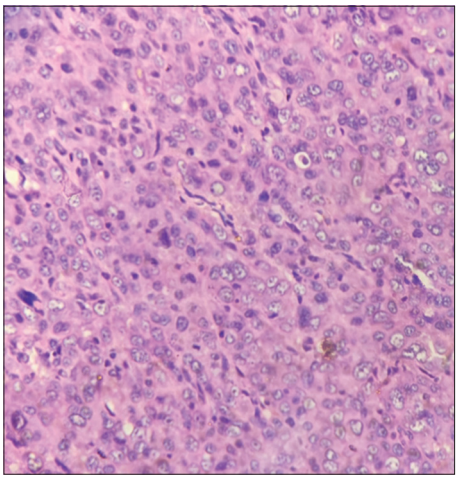

Figure 4: Polygonal area of anaplastic carcinoma (×40)

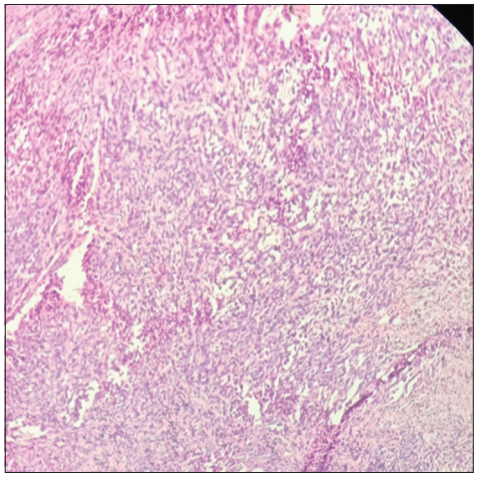

Figure 5: Sarcomatoid area in anaplastic carcinoma (×10)

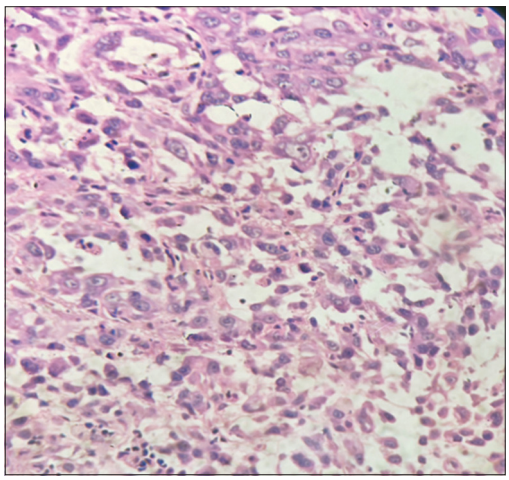

Figure 6: Sarcomatoid area with mitosis (×40)

tumors, as well as differentiating between PDTC and DHGTC. On the other hand, tumors with a high nuclear grade can be categorized as ATC, however, the cell of origin is not always confirmed by morphology alone. Immunohistochemistry (IHC) may be required to identify whether the tumor originated from follicular cells or C cells.

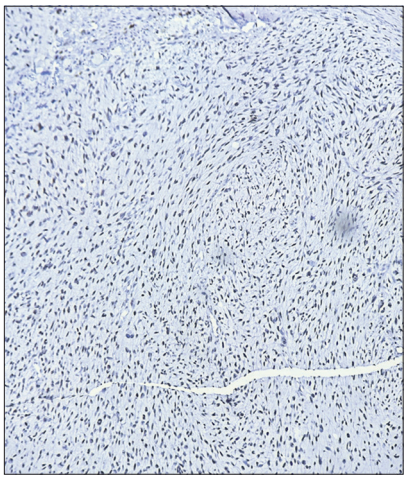

Figure 7: Ki67 expression in anaplastic carcinoma (×10)

CASE PRESENTATION

A record-based observational study was conducted in the pathology department of the College of Medicine and Sagore Dutta Hospital, Kolkata, West Bengal from February 2023 to February 2024 to present a series of rare and interesting cases of PDTC and undifferentiated/anaplastic thyroid carcinoma (ATC) with a brief review of the literature. This cross-sectional study consisted of surgically resected thyroid specimens of six cases of PDTC and ATC received in the department of pathology over 1 year. Records of clinical, radiological, cytological, and laboratory data were retrieved and analyzed [Table 1]. Cases diagnosed on ultrasound, clinically, and on gross thyroid specimen examination were studied which included three cases of undifferentiated/ATC and three cases of PDTC among which one case of PDTC arising from follicular thyroid carcinoma. Before reaching the final diagnosis, two pathologists independently evaluated the gross and histopathological features of each case [Figures 1-6]. The TNM staging system was used to determine tumor staging.[5] The presence of lymphovascular space invasion (LVSI), perineural invasion (PNI), mitotic activity, and extra-thyroidal extension were also evaluated.

Sections measuring 3 μm in thickness from tissues that were formalin-fixed and paraffin-embedded were mounted on slides coated with poly-L-lysine in preparation for IHC staining. The primary antibody employed was Ki-67 (Rabbit monoclonal antibody). The sections were analyzed using a high magnification. Ki-67 Labeling Index (LI) was expressed as the percentage of positively staining nuclei [Figure 7] among the total number of nuclei in the area scored in ×400 magnification. For proper grouping of results, cases were categorized into: Cases with low Ki-67 LI: 0–2%≤5% positive nuclei, intermediate Ki-67 LI: 2–5% positive nuclei, and cases with high Ki-67 LI: >5% positive nuclei, according to Miyauchi et al.[6]

Hemithyroidectomy was conducted in 33.33% of the cases (2/6), whereas the remaining patients underwent total thyroidectomy. All the cases of PDTC and ATC (6/6, 100%) showed evidence of LVSI and PNI. The majority of cases (5/6, 83.33%) showed necrosis whereas PDTC arising from follicular carcinoma showed no evidence of necrosis. All the cases except PDTC arising from follicular carcinoma (5/6, 83.33%) showed extra-thyroidal extension to the strap muscles. Among all cases, 16.66% (1/6) of cases were in stage II at the time of diagnosis. 83.33% (5/6) were in stage IV at the time of diagnosis. All cases of ATC (3/3) and 66.66% (2/3) cases of PDTC showed a high Ki67 LI (five out of six cases), whereas one case of PDTC arising from follicular carcinoma showed a low Ki67 LI.

DISCUSSION

The malignant tumors of the thyroid encompass a range, with the slow-growing well-differentiated thyroid carcinoma (WDTC) including papillary and follicular carcinoma on one side and the aggressive anaplastic/undifferentiated thyroid carcinoma (ATC) on the other.[4] PDTC falls in between WDTC and ATC in terms of characteristics, behavior, and prognosis.

PDTC was first characterized in 1983, and since that time, these tumors have been the focus of ongoing discussions regarding their morphological diagnostic characteristics, molecular profile, and clinical evolution. Initially, it was characterized as a tumor with intermediate characteristics between ATC and differentiated thyroid carcinoma, which was included as a new entity in the WHO classification of endocrine tumors.[5] Subsequently, additional features and diagnostic criteria were put forward by the Memorial Sloan Kettering Cancer Centre in 2006 and were incorporated into the Turin proposal to establish universal diagnostic criteria.[3]

At present, there is no established stratification system for tumors associated with PDTC. The 8th edition of the AJCC/UICC staging system is frequently employed, classifying both PDTC and ATC under stage IV.[7] The American Thyroid Association has provided guidelines for treating these thyroid tumors based on the staging system and molecular profile.

Controversies surrounding PDTC have arisen due to the absence of clearly defined diagnostic criteria.[8] Based on the WHO classification 2004, the diagnosis was based on the architectural pattern, such as insular, trabecular, and solid, in an otherwise malignant thyroid lesion. It also involved infiltrative growth pattern, necrosis,

increased mitosis as other high-grade features, along with mild cytologic atypia. However, it is concerning that the solid, trabecular, and insular patterns can frequently occur mixed within the same lesion and are even observed to coexist with differentiated components of the papillary and follicular types. Extensive sampling and thorough microscopic examination are essential to establish a precise histological diagnosis. The literature reviewed encompasses various studies on high-grade characteristics, such as the presence of necrosis and high mitotic activity, which have been shown to be associated with a poor prognosis. Therefore, these features are considered hallmark features in the diagnosis of PDTC.[5] Hence, it can be deduced that the WHO criteria were hard to put into practice and exhibited some duplication in their classifications.[8] A consensus meeting held in Turin, Italy resulted in the formulation of the "Turin proposal," which presents a structured methodology along with diagnostic criteria intended for practical application.[3] The fifth iteration of the WHO histologic classification of thyroid neoplasms, released in 2022, presents recently recognized tumor types, subtypes, and a grading scheme. In the classification system, PDTC is categorized as a member of the "high-grade follicular-derived carcinomas."[4]

ATC is acknowledged as one of the most aggressive forms of thyroid cancer, frequently resulting in unfavorable overall survival rates. It generally manifests as a rapidly growing thyroid mass, predominantly impacting individuals in their sixth and seventh decades of life. The fifth edition of the WHO histologic classification of thyroid neoplasms, published in 2022, introduces a new nomenclature for ATC, which is now referred to as "Anaplastic follicular cell-derived thyroid carcinoma."[4] It is crucial to correctly assess and identify these cases promptly, since individuals with ATC and tumors smaller than 5 cm, along with no spread to the lymph nodes, tend to have higher average survival times than those with larger tumors or disease that has spread to the lymph nodes.

The prognosis rates vary significantly among WDTC, PDTC, and ATC. PDTC has a poorer prognosis compared to WDTCs, but it is still better than ATCs, with an average 5-year survival rate of 50% for patients. As a result, an early diagnosis before metastasis and subsequent surgery can be extremely beneficial.

Ki-67 is an antigen associated with cell proliferation, expressed in all stages of the cell proliferative cycle except the G0 phase.[3] Ki-67 evaluation is commonly performed immunohistochemically to determine the LI in tissue samples. A high Ki-67 LI has been linked to a negative prognosis in patients with breast carcinoma, prostate carcinoma, and thyroid carcinoma. IHC was utilized to identify cell cycle-specific antigens, allowing for the assessment of cell proliferative activity.

Ki-67 is frequently employed as a marker to assess the proliferative capacity of tumor cells. Increased levels of Ki-67 expression have been correlated with enhanced invasiveness in numerous cancer types. Consequently, identifying Ki-67 in clinical settings can prove advantageous for managing and predicting outcomes for individuals with thyroid cancer.

CONCLUSION

Poorly differentiated and undifferentiated (anaplastic) thyroid carcinoma presents significant diagnostic challenges owing to their uncommon occurrence and the ambiguity of prior diagnostic criteria. Consequently, it is essential to identify, distinguish, and recognize these histological variants to ensure appropriate management and improve prognosis.

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