

Rare Entities of Thyroid Gland: A Series of Twelve Cases

MILI THOMAS¹, NIKITA JAMES², LILLIKUTTY POTHEN³, MEETA THOMAS⁴, REBECCA MATHEWS⁵

ABSTRACT

Thyroid disorders are frequently encountered in clinical practice, with hypothyroidism and hyperthyroidism representing the most common manifestations. However, beyond these frequently diagnosed disorders exists a group of rare thyroid lesions that present unique and often formidable diagnostic and therapeutic challenges. Despite their infrequent occurrence, these rare lesions carry significant clinical importance due to their potential for misdiagnosis, variable behaviour, and the complexity of their management. This retrospective case series examines a diverse group of rare thyroid lesions diagnosed over three years, in a tertiary care centre in South Kerala, to underscore their clinical relevance and emphasise the necessity for heightened diagnostic vigilance. In this series, the author explores 12 different conditions, which include a variety of uncommon pathologies such as dysmorphogenetic goitre and follicular adenoma with bizarre nuclei, along with several histological variants of Papillary Thyroid Carcinoma (PTC), including the tall-cell, columnar-cell, Warthin-like, and diffuse sclerosing subtypes. In addition, authors also describe cases of rare thyroid malignancies, such as the papillary variant of Medullary Thyroid Carcinoma (MTC), collision tumours, cribriform morular thyroid carcinoma, high-grade follicular carcinoma, poorly differentiated carcinoma, and anaplastic carcinoma. These cases were observed in patients ranging from 14 to 77 years of age, highlighting that such lesions can occur across a broad age spectrum. Due to their overlapping clinical and cytological features with more common thyroid conditions, accurate diagnosis of these rare lesions depends heavily on comprehensive histopathological examination, meticulous tissue sampling, and adjunctive Immunohistochemical (IHC) studies. Failure to recognise these entities can lead to misdiagnosis, delayed treatment, and suboptimal patient outcomes. This case series emphasises the critical need for increased awareness among clinicians and pathologists regarding the presentation and management of rare thyroid lesions. Early identification and tailored therapeutic strategies are essential to improving prognostic outcomes. By shedding light on these infrequent but clinically significant conditions, this study advocates for the integration of detailed histological analysis and advanced diagnostic techniques into routine thyroid pathology assessments.

Keywords: Collision, Histopathology, Neoplasm, Thyroid disorders

INTRODUCTION

The thyroid gland plays a pivotal role in maintaining homeostasis through its regulation of metabolism, growth, and development. Disorders of the thyroid are frequently encountered in clinical practice, with hypothyroidism and hyperthyroidism representing the most common manifestations. However, beyond these prevalent conditions lies a spectrum of rare thyroid disorders that, while infrequent, present substantial diagnostic and therapeutic challenges. These include congenital anomalies such as thyroid agenesis, thyroglossal duct cysts, and ectopic thyroid tissue [1]; uncommon autoimmune thyroid diseases such as Riedel's thyroiditis and Hashimoto's thyroiditis; and a variety of rare malignancies [2]. The latter encompasses primary thyroid lymphomas, anaplastic carcinomas, sarcomas, and metastatic involvement of the thyroid from extrathyroidal primaries. These lesions often defy typical clinical and radiological patterns, making them difficult to distinguish from more common thyroid pathologies.

The atypical presentations of these rare entities, ranging from rapidly enlarging neck masses to compressive symptoms and systemic manifestations, necessitate a high index of suspicion. Misdiagnosis or delayed diagnosis can lead to suboptimal treatment strategies and poor prognoses. As such, their identification requires a multidisciplinary approach involving clinical evaluation, imaging, cytopathology, histopathology, and, in certain cases, molecular studies [3,4].

This article presents a retrospective review of rare thyroid lesions diagnosed over three years at a tertiary care centre. By analysing these unusual cases, the review aims to underscore their clinical relevance despite their rarity. The objective is to raise awareness among clinicians and pathologists, encourage early recognition, and facilitate timely, appropriate management that can significantly

influence patient outcomes. Through this focussed examination, the article contributes to the growing body of literature that seeks to refine diagnostic criteria and improve the overall understanding of these uncommon but important thyroid conditions.

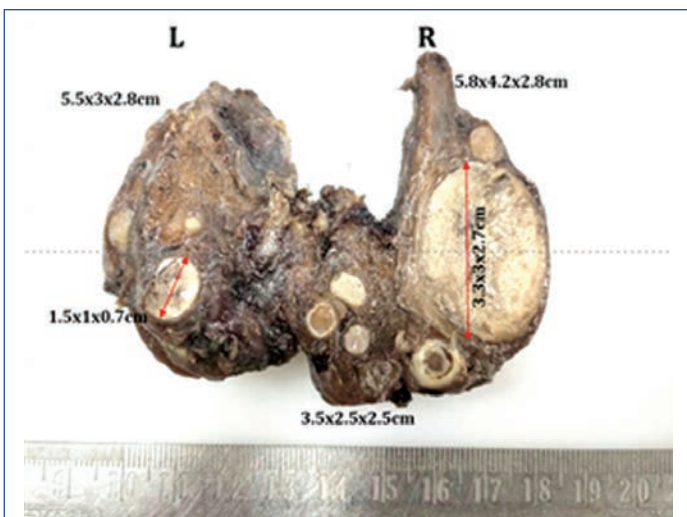
CASE SERIES

Case 1

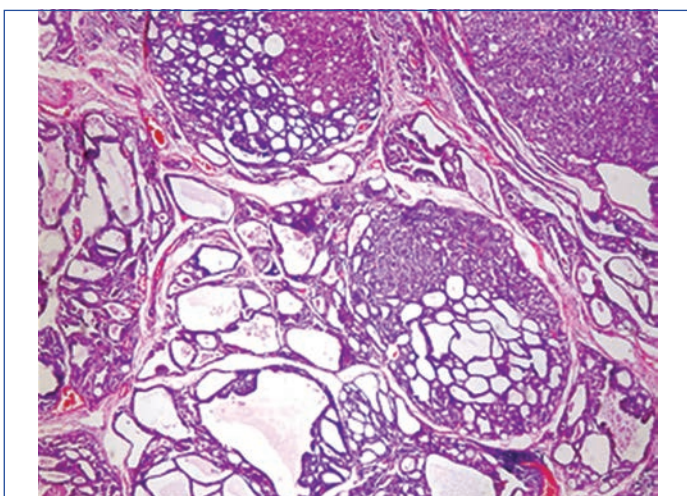
A 29-year-old female with hypothyroidism since age 7, came with complaints of swelling in the front of the neck for two years. Ultrasonography (USG) revealed the presence of multiple ACR-TR4 and TR3 nodules on both thyroid lobes, and Fine Needle Aspiration Cytology (FNAC) was reported as atypia of undetermined significance - nuclear atypia. Thyroidectomy was done, and macroscopic examination revealed multiple pale white nodules [Table/Fig-1]. Microscopy showed multiple nodules of varying sizes, with a predominant microfollicular pattern and no/minimal colloid [Table/Fig-2]. Extensive sampling showed no evidence of malignancy. The final diagnosis was dysmorphogenetic goitre. The patient was started on supportive thyroid hormone replacement therapy and is on regular follow-up.

Case 2

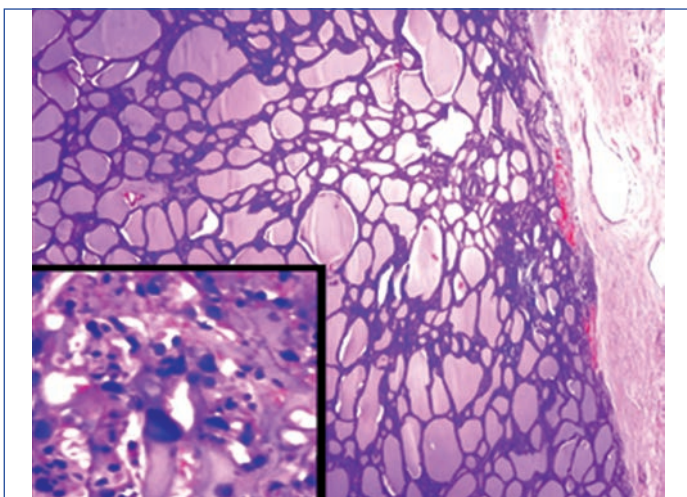
A 51-year-old female came with complaints of swelling in the front of the neck for the past 10 years. USG revealed a bulky right lobe with an ACR-TR4 nodule. The patient underwent total thyroidectomy. Microscopy revealed an encapsulated neoplasm composed of varying-sized colloid-filled follicles lined by oncocytic epithelium showing moderate to marked anisonucleosis and nuclear hyperchromasia in focal areas, along with the presence of bizarre cells [Table/Fig-3].



[Table/Fig-1]: Macroscopy - Multiple nodules involving both lobes and isthmus.



[Table/Fig-2]: Microscopy – Dysmorphogenetic goitre (Haematoxylin and Eosin (H&E) 10x).

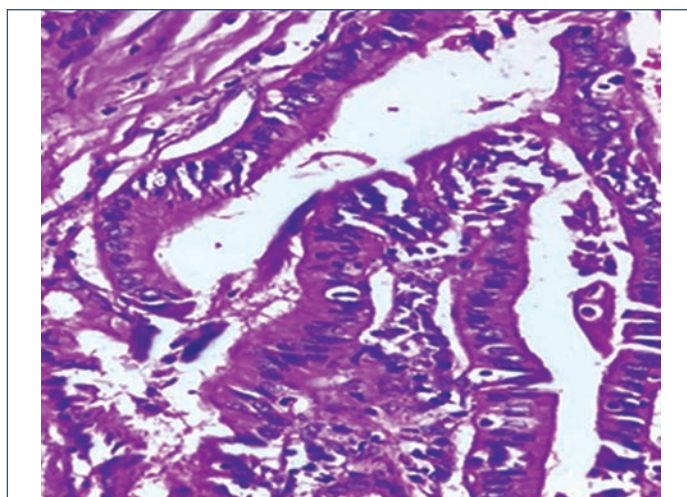


[Table/Fig-3]: Follicular adenoma with bizarre nuclei (H&E, 10x). (Inset- Cells with bizarre nuclei (H&E, 40x)

With these features, a diagnosis of follicular adenoma with bizarre nuclei was made. The patient is doing well postoperatively and is on regular follow-up.

Case 3

A 17-year-old adolescent came with complaints of neck swelling for the past two weeks, which on USG was identified as an ACR-TR4 nodule in the left lobe. Gross examination revealed the presence of an irregular, pale white lesion. Microscopy showed tall columnar cells on parallel placed slender papillae with predominant papillary-like nuclear features [Table/Fig-4].

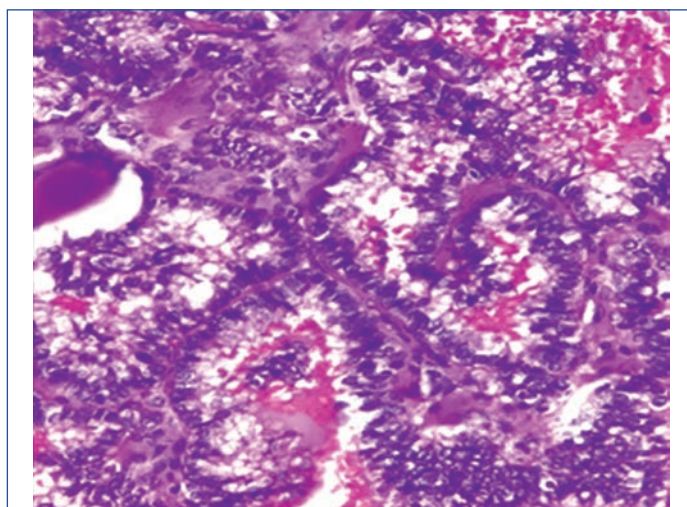


[Table/Fig-4]: Papillary carcinoma of thyroid - Tall-cell variant (H&E, 40x).

The final diagnosis was papillary carcinoma of the thyroid- Tall-cell subtype. The patient was directed to an alternative tertiary oncology centre for continued treatment owing to limited financial resources.

Case 4

A 77-year-old male came with complaints of cervical lymphadenopathy for three days. Clinical evaluation revealed the presence of thyroid swelling. Total thyroidectomy with central neck dissection was performed. Microscopic examination of the thyroid lesion showed a papillary neoplasm with columnar cells showing pseudo-stratification, hyperchromatic nuclei and prominent supranuclear vacuolations [Table/Fig-5]. Lymph nodes showed metastatic deposits from the above lesion. The case was diagnosed as papillary carcinoma of thyroid-columnar-cell subtype. The patient was doing well post radiotherapy and was later lost to follow-up.



[Table/Fig-5]: Papillary carcinoma of thyroid - Columnar-cell variant (H&E, 40x).

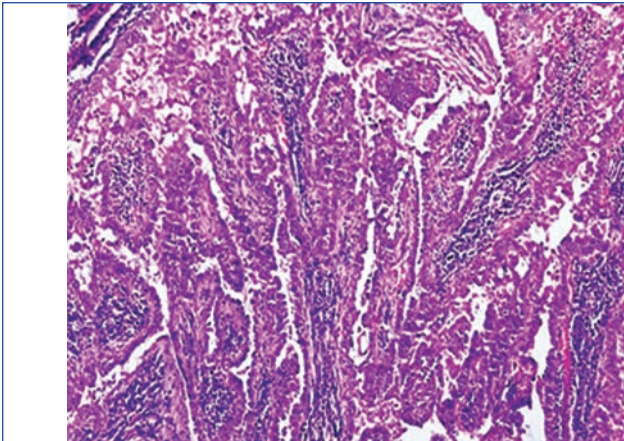
Case 5

A 14-year-old female came with complaints of neck swelling noticed incidentally two days before, which on USG was revealed to be an ACR-TR4 nodule. Thyroidectomy was done and the microscopic examination revealed an infiltrating papillary neoplasm lined by oncocytic epithelium with stroma showing dense lymphoplasmacytic infiltrate [Table/Fig-6]. A diagnosis of papillary carcinoma thyroid-Warthin-like subtype was made, taking into account all the features.

The patient is doing well postoperatively and is on regular follow-up.

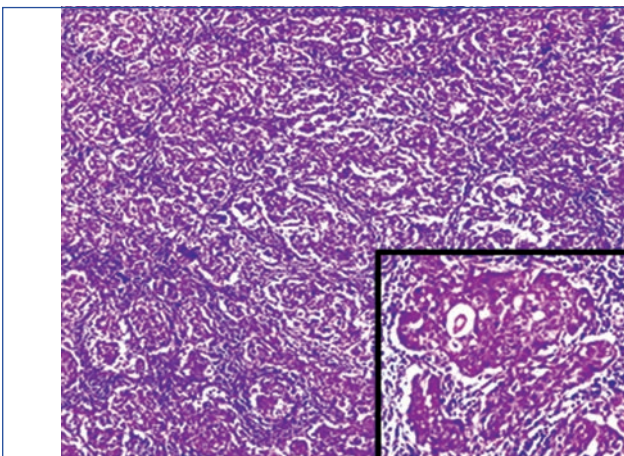
Case 6

A 21-year-old female came with complaints of a recent onset of neck swelling and cervical lymphadenopathy. Total thyroidectomy was done and gross examination revealed a grey white irregular



[Table/Fig-6]: Papillary carcinoma thyroid - Warthin-like variant (H&E, 10x).

lesion. Microscopy revealed a diffusely infiltrating neoplasm with papillary pattern and solid nests separated by sclerotic stroma, along with extensive squamous metaplasia [Table/Fig-7].

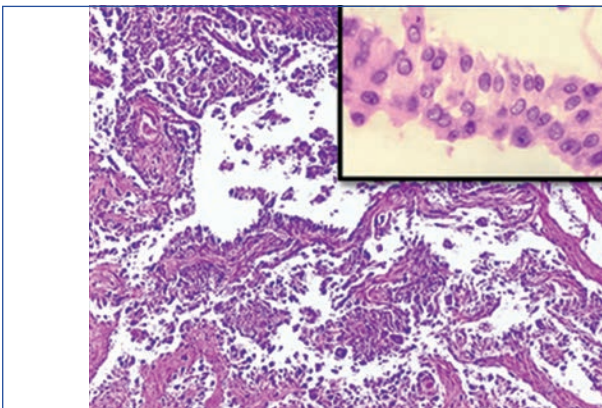


[Table/Fig-7]: Papillary carcinoma thyroid - Diffuse sclerosing variant (H&E, 10x). (Inset showing squamous morules (H&E, 40x).

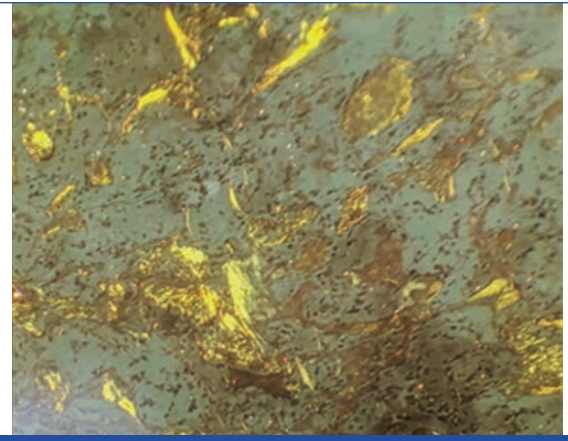
The case was diagnosed as papillary carcinoma thyroid-diffuse sclerosing subtype. The patient is doing well postoperatively and is on regular follow-up.

Case 7

A 49-year-old female with thyroid swelling and pressure symptoms. Gross examination of the thyroidectomy specimen revealed the presence of a grey white granular lesion at the junction of the left lobe and the isthmus. Microscopy showed the presence of an encapsulated papillary neoplasm lined by cells with stippled chromatin and extensive areas of congophilic material deposition [Table/Fig-8] with apple green birefringence under polarised light [Table/Fig-9]. IHC confirmation was done (synaptophysin, chromogranin, calcitonin - strong positive; TTF1 - dim positive).



[Table/Fig-8]: Papillary variant of Medullary Thyroid Carcinoma (MTC) (H&E, 10x). (Inset- nucleus with stippled chromatin. (H&E, 100x).

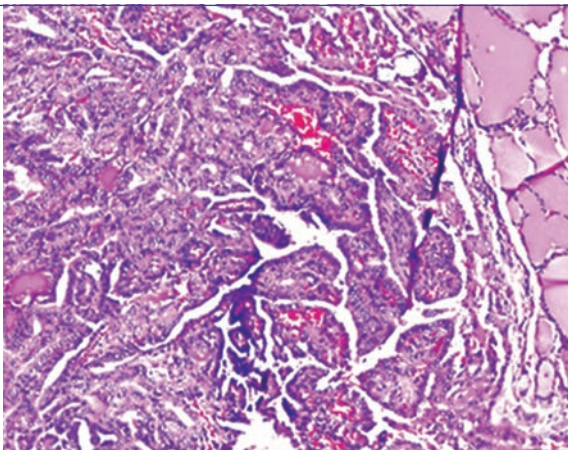


[Table/Fig-9]: Apple green birefringence under polarised light.

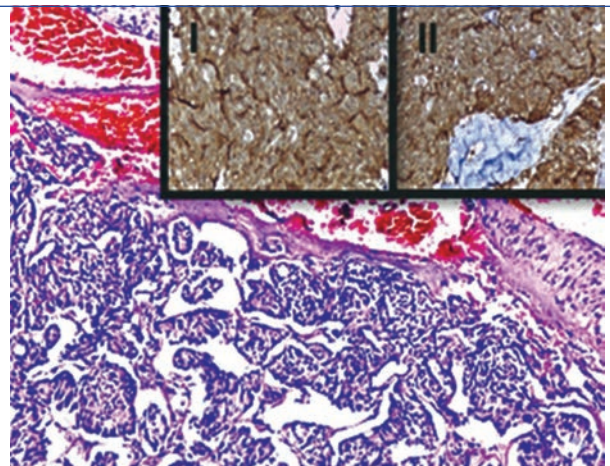
The final diagnosis was confirmed as a papillary variant of MTC. The patient was directed to an alternative tertiary oncology centre for continued treatment owing to limited financial resources.

Case 8

A 27-year-old female came with complaints of neck swelling for the past two weeks. USG of the neck was done, which revealed the presence of an ACR-TR5 nodule in the right lobe and an ACR-TR4 nodule in the left lobe. Gross examination of the thyroidectomy specimen revealed two lesions, one on each lobe. On microscopy, the lesion on the right lobe was identified as Papillary carcinoma thyroid [Table/Fig-10] and the lesion on the left lobe was identified as medullary carcinoma thyroid (IHC confirmed) [Table/Fig-11].



[Table/Fig-10]: Collision tumour: Papillary carcinoma thyroid in right lobe (H&E, 10x).

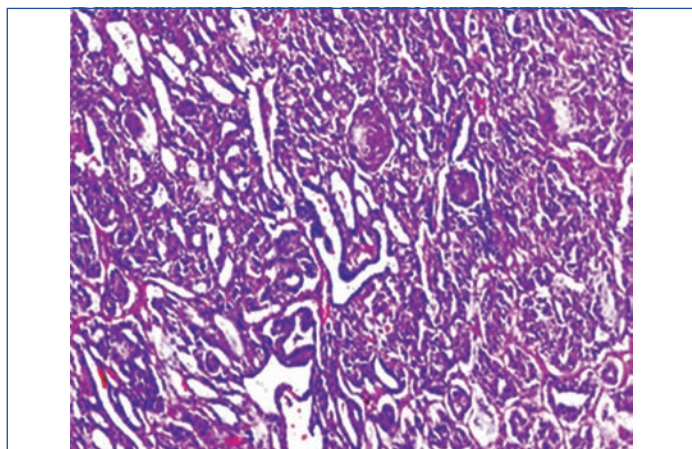


[Table/Fig-11]: Medullary carcinoma thyroid (H&E, 10x). (inset: synaptophysin and chromogranin immunostaining).

Thus, it was diagnosed as a collision tumour: Right lobe - Papillary carcinoma thyroid; Left lobe - Medullary carcinoma thyroid. Post-thyroidectomy, the patient was lost to follow-up.

Case 9

An 18-year-old female came with complaints of swelling in the front of the neck for two years and a sudden increase in size over the past two months. USG revealed the presence of a heterogeneous, well-defined isoechoic ACR-TR5 nodule in the left lobe. Microscopy revealed the presence of an encapsulated neoplasm with prominent cribriform architecture and squamous morule formation [Table/Fig-12].

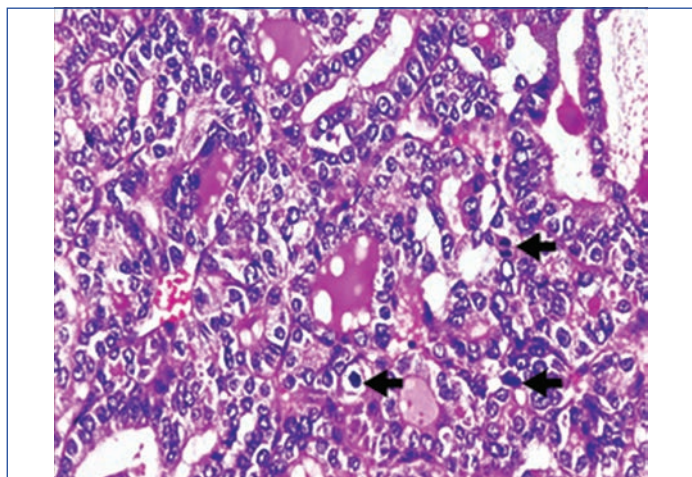


[Table/Fig-12]: Cribriform morular thyroid carcinoma (H&E, 10x).

This was a classic case of cribriform morular thyroid carcinoma. Post-thyroidectomy, the patient was lost to follow-up.

Case 10

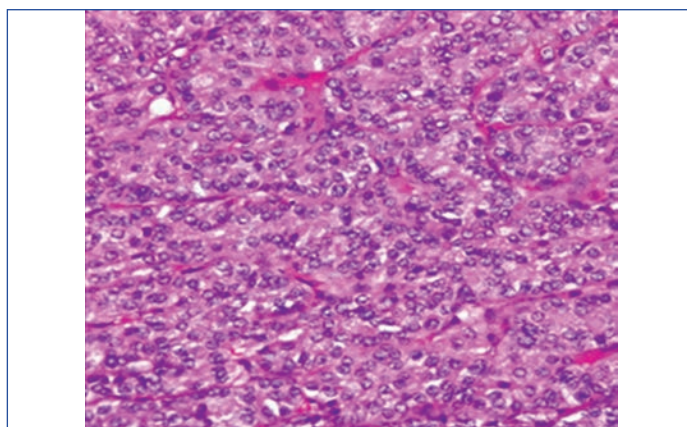
A 61-year-old female came with complaints of thyroid swelling and pressure symptoms for three weeks. Total thyroidectomy was done, and the microscopic examination showed the presence of a neoplasm with microfollicles and macrofollicles with papillary-like nuclear features and increased mitotic activity [Table/Fig-13]. The final diagnosis was high-grade follicular thyroid carcinoma. The patient was directed to an alternative tertiary oncology centre for continued treatment owing to limited financial resources.



[Table/Fig-13]: High-grade follicular thyroid carcinoma (arrow- mitotic figures) (H&E, 40x)

Case 11

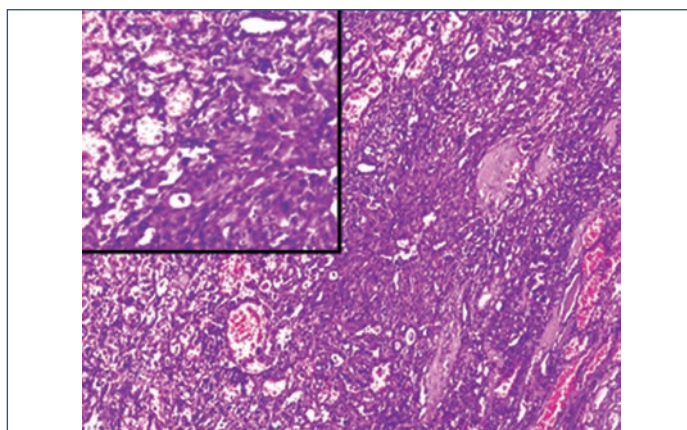
A 59-year-old female who is a known case of hypothyroidism came with complaints of an increase in the size of her neck swelling over the past four months. USG showed the presence of an ACR-TR4 nodule. Microscopy of the thyroidectomy specimen revealed the presence of a neoplasm composed of cuboidal cells with moderate eosinophilic cytoplasm and a round to oval convoluted nucleus, arranged in solid, trabecular, and insular patterns, and increased mitosis [Table/Fig-14]. Diagnosis was poorly differentiated thyroid carcinoma. Due to financial constraints, the patient was referred to another tertiary oncology centre for further treatment.



[Table/Fig-14]: Poorly differentiated thyroid carcinoma (H&E, 40x)

Case 12

A 62-year-old man came with complaints of rapidly enlarging thyroid swelling, which was noticed a week before. Total thyroidectomy was done and the specimen was sent for histopathological examination. Macroscopically, identified as an ill-circumscribed lesion with a necrotic cut-surface. Microscopy showed an infiltrating neoplasm with undifferentiated areas- markedly pleomorphic cells, brisk mitosis and necrosis; and differentiated areas - papillary-like nuclear features [Table/Fig-15]. The case was diagnosed as anaplastic carcinoma of the thyroid. The patient was referred to another tertiary oncology centre for further management. All the cases are summarised in [Table/Fig-16].



[Table/Fig-15]: Anaplastic carcinoma of the thyroid (H&E, 10x) (inset- H&E, 40x).

DISCUSSION

Commonly encountered thyroid lesions include thyroid follicular nodular disease, Hashimoto thyroiditis, follicular neoplasms, and papillary carcinomas. Rare lesions, often atypical and uncommon, present challenges in diagnosis and treatment

Dyshormonogenetic goitre: An extremely rare, autosomal recessive disorder, occurring in one in 30,000 to 50,000 live births. It involves enzyme defects in thyroid hormone synthesis, leading to congenital hypothyroidism and goitre. Familial screening is crucial upon diagnosis. The condition can mimic malignancies like follicular or papillary carcinoma, but is distinguished by specific histological features. It may also be associated with Pendred syndrome [5]. Our case had a classical presentation and microscopy, but unlike other published cases, lacked familial and syndromic associations.

Follicular adenoma with bizarre nuclei: A rare subtype of follicular adenoma featuring atypical cells with large, irregular, hyperchromatic nuclei. Despite the unusual appearance, these tumours lack features of malignancy such as mitotic activity, necrosis, and invasion, confirming their benign nature [6]. The bizarre nuclei are attributed to hyperfunctioning adenomas or can result from exposure to ionising radiation. The presence of clear encapsulation and a lack of invasion in our case supports the benign nature of the lesion.

Case	Age / Gender	Chief Complaint	Final Diagnosis	IHC Findings
1	29 / F	Neck swelling×2 years	Dyshormonogenetic goitre	NA
2	51 / F	Neck swelling×10 years	Follicular adenoma with bizarre nuclei	NA
3	17 / F	Neck swelling	Papillary thyroid carcinoma – Tall-cell subtype	NA
4	77 / M	Cervical lymphadenopathy	Papillary thyroid carcinoma – Columnar-cell subtype	NA
5	14 / F	Neck swelling	Papillary thyroid carcinoma – Warthin-like subtype	NA
6	21 / F	Neck swelling and cervical lymphadenopathy	Papillary thyroid carcinoma – Diffuse sclerosing subtype	NA
7	49 / F	Thyroid swelling, pressure symptoms	Papillary variant of medullary thyroid carcinoma	Synaptophysin+, Chromogranin+, Calcitonin+, TTF1 (dim)+
8	27 / F	Neck swelling×2 weeks	Collision tumor: Right lobe – Papillary; Left lobe – Medullary	IHC confirmed medullary component
9	18 / F	Neck swelling×2 yrs, rapid growth in 2 months	Cribiform morular thyroid carcinoma	NA
10	61 / F	Thyroid swelling, pressure symptoms	High-grade follicular thyroid carcinoma	NA
11	59 / F	Increasing neck swelling×4 months	Poorly differentiated thyroid carcinoma	NA
12	62 / M	Rapidly enlarging thyroid swelling	Anaplastic carcinoma of thyroid	NA

[Table/Fig -16]: Summary of all cases.

Papillary Thyroid Carcinoma (PTC)- rare subtypes:

- i **Tall-cell subtype:** Aggressive with >30% tall cells, requiring aggressive treatment and close follow-up. Even the presence of small foci of tall cell components should be mentioned separately in the report, as such cases are associated with a poorer prognosis [7,8].
- ii **Columnar subtype:** Rare (0.15-0.4%) and aggressive variant lacking the typical nuclear features of papillary carcinoma and should be differentiated from metastatic adenocarcinomas [8].
- iii **Warthin-like subtype:** Rare lesion (0.06-1.9%) with favourable prognosis and is so named because it resembles Warthin tumour of the salivary gland. It may be missed out, especially in the background of Hashimoto thyroiditis [9,10].
- iv **Diffuse sclerosing subtype:** Uncommon (0.7-2%), with diffuse thyroid involvement, lymphatic infiltration, extrathyroidal extension and increased risk of distant metastasis [8,11].

Papillary variant of medullary carcinoma thyroid is a very rare form of MTC, first reported by Kakudo K et al., in 1979 [12]. It is characterised by the presence of true or artefactual papillae due to tissue fragmentation [13]. This variant can mimic other papillary thyroid lesions, making careful histomorphological analysis and the use of IHC markers crucial for diagnosis. We were able to prove the medullary nature with the help of IHC markers which was not done in older reports.

Collision tumours are rare neoplastic lesions where two distinct cell populations co-exist, each maintaining separate borders. Histopathological examination is the most reliable diagnostic method allowing clear identification of distinct tumour components. Molecular and genetic testing is also essential as the lesions may result from different genetic mutations, providing insights into

the tumour’s origin and behaviour. Our case was that of papillary carcinoma in one lobe and medullary carcinoma in the other [14,15]. The bilaterality of the lesions is a rare occurrence with reported cases having adjacent lesions or overlapping tumour zones.

Cribiform morular thyroid carcinoma is an uncommon thyroid neoplasm with uncertain histogenesis, previously considered a subtype of PTC but now classified separately in the 2022 World Health Organisation (WHO) classification [8]. It is often associated with Familial Adenomatous Polyposis (FAP) or Gardner syndrome and linked to germline mutations in the APC gene and somatic mutations activating the Wnt/β-catenin pathway. Diagnosis involves identifying cribriform, follicular, papillary, and trabecular patterns with morular structures. Genetic testing is crucial to assess potential familial implications [16]. APC mutation and FAP screening were not done in this case due to non-compliance, citing financial constraints.

High-grade follicular carcinoma of the thyroid is characterised by retaining the distinctive architectural and cytomorphological features of differentiated thyroid carcinomas but exhibiting aggressive characteristics such as a high mitotic rate (>5 mitoses per 2 mm²) or tumour necrosis. Adverse prognostic factors include larger tumour size, age over 45, extra thyroidal extension, extensive necrosis, lack of encapsulation, and distant metastasis. This category includes aggressive carcinomas that do not meet the criteria for poorly differentiated or anaplastic thyroid carcinomas [17]. Our case fits the updated WHO classification, highlighting high mitotic rate and necrosis as criteria.

Poorly differentiated thyroid carcinomas account for 0.3-6.7% of thyroid carcinomas. They exhibit intermediate clinical behaviour between well-differentiated and anaplastic thyroid carcinomas, with limited follicular cell differentiation. Diagnosis is determined using the Turin consensus criteria, which include a solid, trabecular, or insular growth pattern, the absence of papillary-like nuclear features, and at least one of the following: convoluted nuclei, ≥3 mitoses per 10 High-Power Fields (HPF), or tumour necrosis [18].

Anaplastic carcinoma is the most aggressive thyroid malignancy, with an incidence of 1-2% of all thyroid malignancies and a>90% mortality rate. It is rapidly growing and widely invasive, thus necessitating the need for early diagnosis [8]. The usual presentation with the lesion arising from a dedifferentiated PTC or follicular thyroid carcinoma could not be established in our case, as the patient did not have any prior history.

CONCLUSION(S)

Rare thyroid disorders, though uncommon, present significant diagnostic and therapeutic challenges. Accurate histopathological evaluation with extensive sampling and heightened clinical awareness are essential for proper diagnosis and management. Timely recognition of these conditions can improve patient outcomes and reduce the risk of misdiagnosis, ultimately guiding effective treatment strategies.

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