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Case Report of Three Saudi Pediatric and Adolescent Patients with Poorly Differentiated Thyroid Cancer: A Unique and Challenging Entity

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Abstract

Poorly Differentiated Thyroid Cancer (PDTC) is an infrequent and aggressive form of thyroid malignancy, characterized by histological features that lie between those of well-differentiated and anaplastic thyroid cancers. PDTC in pediatric and adolescence is even more rare and its clinical manifestations, histological features and outcomes are not well known. This case series of pediatric and adolescent PDTC provides a comprehensive examination of the clinical manifestation, diagnostic challenges, therapeutic approaches, and outcomes linked to PDTC, as shown by three unique cases from a single tertiary care center in Saudi Arabia.

Keywords: Thyroid cancer; Poorly differentiated thyroid cancer; Clinical management; Prognosis

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Introduction

Thyroid malignancies are largely categorized according to their histological characteristics, which include well-differentiated subtypes (papillary and follicular), medullary subtype, and anaplastic subtype [1]. Poorly Differentiated Thyroid Cancer (PDTC) classified as a distinct entity, characterized by a more aggressive phenotype compared to Well-Differentiated Thyroid Cancer (WDTC), although displaying a less aggressive behavior than Anaplastic Thyroid Cancer (ATC) [2]. PDTC is relatively rare, accounting for a small percentage about (5%) of all TCs. It commonly affects individuals in their late adulthood and has a slight tendency for females [3].

Individuals diagnosed with PDTC often have neck masses that demonstrate fast growth [4]. These masses may manifest with or without accompanying symptoms [5]. Clinical manifestations such as hoarseness of voice, dysphagia, and Shortness of Breathing (SOB) are indicative of compressive consequences or local invasions. The diagnostic procedure often incorporates ultrasonography, fine-needle aspiration biopsy, and sophisticated imaging techniques such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) [5]. The histopathological examination conducted subsequent to surgical resection plays a crucial role in establishing a clear diagnosis [5].

The usual aggressive behavior of PDTC, along with the absence of established treatment procedures, makes it difficult to treat and maintain the condition [5]. Surgery, radioactive iodine therapy, thyroid hormone suppression therapy, and the selective use of external beam radiation therapy and multitargeted kinase inhibitors or mutation-specific kinase inhibitors are the main components of treatment for PDTC [5].

The overall prognosis of PDTC is often more unfavorable compared to WDTC, however it is more favorable when compared to ATC [6]. Prognostic indicators include several variables such as tumor size, amount of invasion, metastatic dissemination, and the age of the patient. It is essential to conduct long-term surveillance in order to effectively manage the heightened likelihood of

recurrence and metastatic dissemination [7,8].

This case report presents three pediatric and adolescent patients who have been diagnosed with PDTC at our hospital. The primary objective is to further demonstrate the broad spectrum of clinical manifestations, diagnostic complexities, treatment strategies, and associated outcomes related to this highly aggressive form of thyroid cancer. We seek to enhance the understanding and treatment of PDTC in this unique population through the documentation and analysis of these cases.

Case Series

Case 1: A 15-year-old female

The patient presented to our outpatient clinic with a history of goiter for 2 months duration that was incidentally detected. There was no history of associated medical problems. The patient did not report any history of hoarseness, SOB or dysphagia. There was no family history of thyroid cancer.

The physical examination revealed a prominent and solid mass located in the anterior region of the neck, mostly on the left side. The mass exhibited movement while swallowing and did not exhibit any signs of changes in the skin. The laboratory findings indicated a Thyroid-Stimulating Hormone (TSH) level of 1.4 mIU/L, a free Thyroxine (T4) level of 13.2 pmol/L, and an increased Thyroperoxidase (TPO) antibody level of 455 IU/mL. The ultrasound examination of the thyroid gland detected a nodule in the left lobe measuring 4.16 cm × 3.04 cm × 4.4 cm that is solid, hyperechoic, had a smooth margin with no detected calcifications. In addition, there was a nodule in the right lobe measuring 1.09 cm × 0.6 cm × 1.13 cm which seemed to be cystic (Figure 1).

A Fine Needle Aspiration (FNA) procedure was performed on the left thyroid nodule, providing a finding of Atypia of Undetermined Significance (AUS) that is Bethesda category III. The patient underwent a total thyroidectomy where the histopathological evaluation showed a papillary thyroid cancer, specifically located in the left lobe. This particular carcinoma was found to be of the encapsulated oncocytic follicular subtype/variant, with a poorly differentiated component comprising 5% of the tumor. The tumor has a maximum dimension of 4.5 cm, accompanied by two additional foci of papillary microcarcinoma measuring a maximum dimension of 0.3 cm each. There was no evidence of angioinvasion, extrathyroidal extension, or lymphatic invasions. Four lymph nodes were taken out and were benign the tumor shows encapsulated follicular neoplasm with atypical nuclear features including nuclear enlargement, clearing, and grooving with multifocal areas of capsular invasion. There is focal area of dedifferentiation around 5% of entirely submitted tumor contain solid/trabecular growth with increase mitotic figures (4/10HPF) (Figure 2).

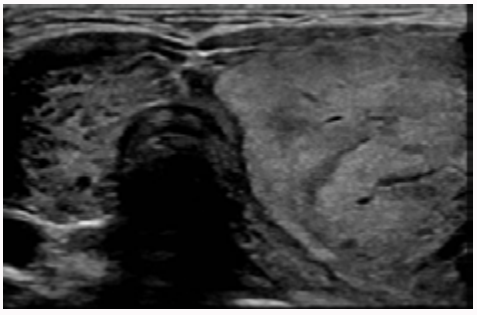

Figure 1: Ultrasound of the thyroid gland showed diffuse heterogeneous echotexture with an enlarged solid left lobe nodule measuring 4.16 cm × 3.04 cm × 4.4 cm that is hyperechoic with a smooth margin and no detected calcifications.

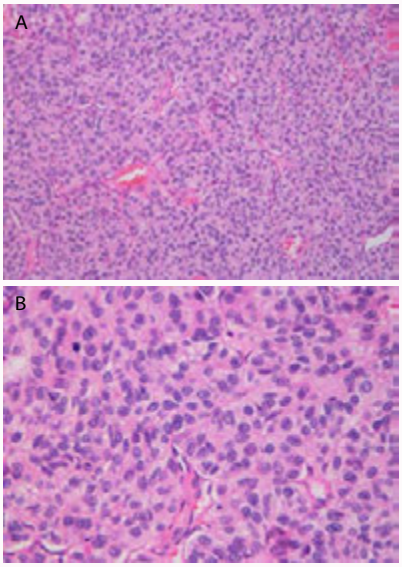

Figure 2: A) Solid/ trabecular growth pattern of poorly differentiated components. B) Solid/trabecular pattern with small round nucleus and lack the nuclear features of well differentiated papillary thyroid carcinoma with foci of mitosis.

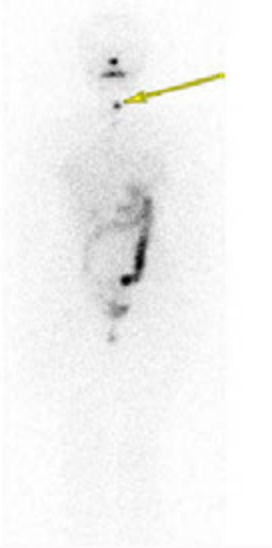

Figure 3: Whole Body Iodine Scan (WBIS) showed iodine avid left thyroid bed activity (yellow arrow) likely compatible with remnant thyroid tissue.

The patient received Radioactive Iodine (RAI) therapy at a dosage of 30 millicuries (mCi). Seven days following the treatment, a Whole-Body Iodine Scan (WBIS) was conducted which revealed a little iodine avid activity in the left thyroid bed (Figure 3). The levels of stimulated thyroglobulin were <0.09 ug/l while the thyroglobulin antibody level was elevated (557.27 IU/mL). The patient is now undergoing routine monitoring and care at the thyroid oncology clinic.

Case 2: A 9-year-old male

This was a 9-year-old male patient who was referred to pediatric

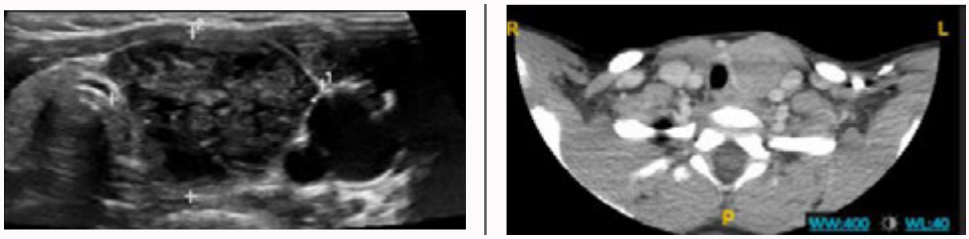

Figure 4: A) US thyroid showed large heterogeneous irregular left thyroid lobe nodule. B) CT neck showed ill-defined heterogeneous lesion occupying the left thyroid lobe measures approximately 2.5 cm × 2.5 cm × 3 cm causing mild compression and displacement on the trachea.

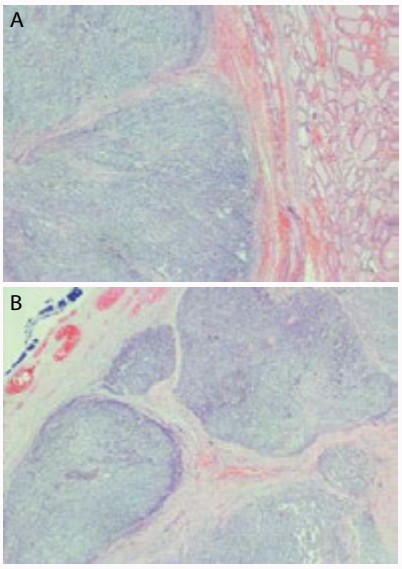

Figure 5: A) Histologic feature of the encapsulated solid growth and B) nodular growth of poorly differentiated.

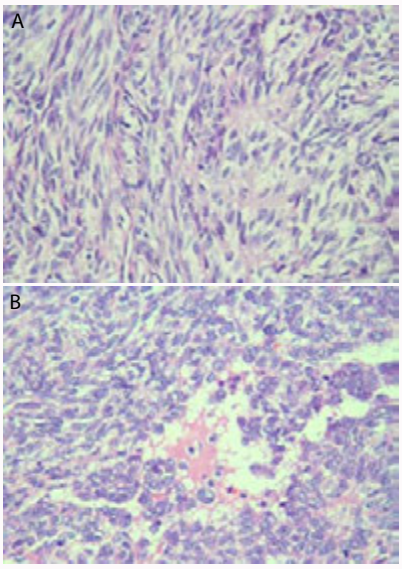

Figure 6: Solid/trabecular pattern with small round nucleus and lack the nuclear features of well differentiated papillary thyroid carcinoma (A&B).

endocrinology clinic at the age of 6 for evaluation of a left thyroid lobe nodule. The observation of the nodule was brought to attention by his parents that has exhibited a rapid enlargement over a span of three months. The patient did not have any additional noteworthy symptoms, including but not limited to weight loss, diaphoresis, alterations in appetite or physical exertion, heat or cold intolerance, tremors, or changes in bowel habits. The patient exhibited no prior radiation exposure, although a familial predisposition to hypothyroidism was observed on the paternal lineage.

Following a comprehensive evaluation, the individual presented a state of overall wellness, exhibiting unremarkable vital signs within the expected range. The subject exhibited a weight of 23.8 kg, positioning him within the 75th percentile of the weight distribution. Additionally, his height was measured at 120.7 cm, placing him at the 50th percentile of the height distribution. An observable swelling on the left side of the neck was noted, exhibiting movement in synchrony with the act of swallowing. The observed swelling exhibited a diameter of approximately 3 cm and displayed a firm consistency upon palpation, devoid of any signs of tenderness. Additionally, a notable increase in size was observed in the lymph node located in the posterior region of the cervical area on the left side, with a measured diameter of approximately 0.5 cm. The observed lymph node exhibited a palpable softness and demonstrated a commendable degree of mobility. No additional lymph node enlargements were detected during the examination.

The laboratory tests yielded findings that fell within the established range of normal values. A thyroid ultrasound examination revealed the presence of a substantial, varied, and asymmetrical nodule within the left thyroid lobe, measuring approximately 2 cm × 2 cm × 3.5 cm in size. The observed nodule exhibited characteristics consistent with fibroid morphology, displaying a lobulated structure and demonstrating a limited presence of internal blood vessels (Figure 4A). The right thyroid lobe exhibited a normal appearance. Upon conducting a CT scan of the neck, it was observed that there exists an ill-defined heterogeneous lesion occupying the left thyroid lobe. This lesion measures approximately 2.5 cm × 2.5 cm × 3 cm in size. The lesion exhibited a mild degree of compression and displacement on the trachea, without causing complete obstruction (Figure 4B).

FNA was conducted on the left thyroid nodule, resulting in the extraction of a highly cellular aspirate containing a multitude of round cells arranged in disseminated rosette formations. The observed results were deemed to be atypical, thereby eliciting a heightened sense of suspicion for the presence of malignancy. Following the initial evaluation, the individual underwent a comprehensive surgical procedure for a total thyroidectomy.

The histopathological analysis of the excised thyroid tissue unveiled the presence of poorly differentiated thyroid carcinoma. The neoplasm exhibited unifocality and was situated on the left side, measuring 3.6 cm in its greatest dimension. Observation of the specimen revealed a notable presence of angioinvasion and lymphatic invasion, while the absence of extrathyroidal extension was noted. Additionally, two out of five lymph nodes (2/5) showed metastasis.

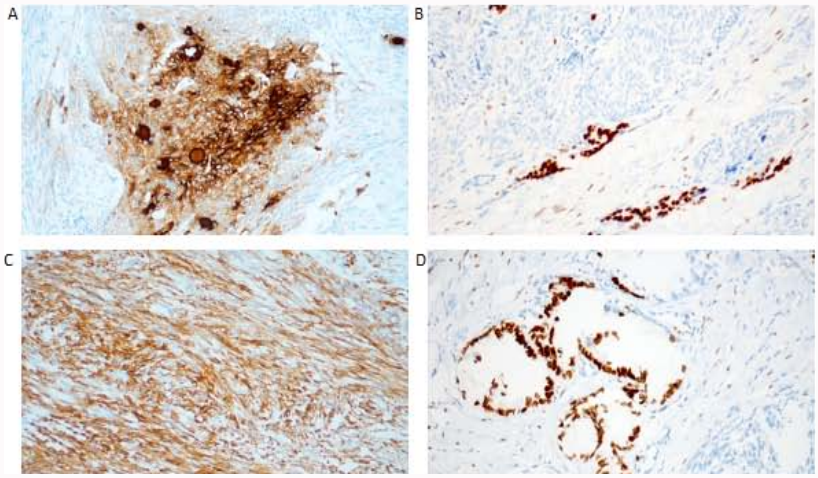

Figure 7: A) Histologic features showed thyroglobulin positive in well differentiated and reduce/lack expression in poorly differentiated components. B) PAX8 positive in well differentiated papillary thyroid carcinoma. C) CAM5.2 is positive in poorly differentiated components. D) TTF1 positive in well differentiated.

These represented a small proportion of tumor cells (around 1%) and showed strong reactivity for TTF-1 and PAX-8 transcription factors. This finding supports a part of differentiated papillary carcinoma, like giving rise to a predominant poorly differentiated component with no to very focal reactivity for thyroid-specific transcription factors. Additionally, Ki-67 proliferation index is high (approximately 45% of tumor cells). Moreover, focal areas of necrosis and extensive venous invasion were noted. This was coupled with increased mitotic activity (Figures 5-7).

Molecular testing was conducted to evaluate and analyze targeted genetic mutations. The findings revealed the absence of any mutations in the *BRAF*^{V600E}, *KRAS*, and *NRAS* genes. Furthermore, the Fluorescence *in situ* Hybridization (FISH) analysis conducted to detect the presence of SS18 translocation yielded negative results.

Follow up imaging utilizing Positron Emission Tomography (PET) scan (Figure 8) and CT of the abdomen unveiled the presence of extensive and diffuse metastatic lesions in the pulmonary, hepatic (Figure 9) and renal regions, thereby signifying a notable advancement of the disease.

During the past three years, the patient has experienced multiple admissions due to persistent hypercalcemia, despite undergoing various lines of therapy.

Considering the advanced stage of the disease, the patient and his family sought a second opinion in the United States. The reason for seeking a second opinion was to explore alternative treatment options, as the patient was not deemed a candidate for radiation therapy or chemotherapy.

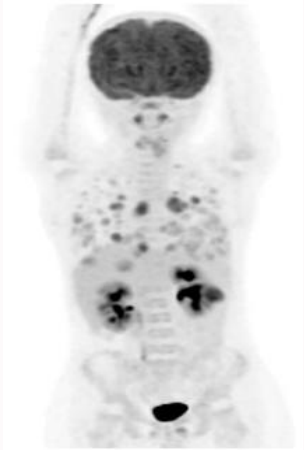

Figure 8: PET F-18 whole body showing Bilateral moderately hypermetabolic miliary pulmonary lesions, metastatic.

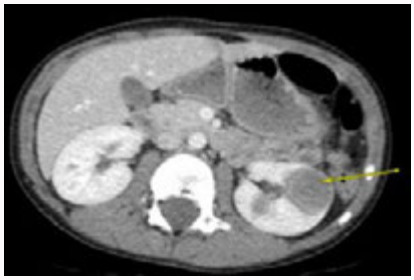

Figure 9: CT abdomen shows metastatic left renal lesions (yellow arrow).

Case 3: A 15-year-old female

This is a 15-year-old female who had a known history of toxic multinodular goiter that had been undergoing a five-year course of treatment with carbimazole. The patient presented with obstructive symptoms, namely dysphagia and nocturnal dyspnea. There was no history of radiation exposure or familial occurrences of thyroid cancer. During the physical examination, a large firm right neck mass was palpated. No clinical manifestations indicative of hypothyroidism or hyperthyroidism were observed; however, the Pemberton's sign was positive.

The laboratory investigations unveiled a marginally increased TSH level measuring 5.5 (mIU/L), accompanied by Free Thyroxine (FT4) and Free Triiodothyronine (FT3) levels measuring 7.7 and 4.5 (pmol/L), respectively. Thyroid ultrasound demonstrated diffuse enlargement of the right thyroid lobe with a heterogeneous exophytic texture measuring around 5.5 cm × 3.3 cm × 8.0 cm with a total expected volume of 75.8 mL. Multiple hypoechoic nodules and microcalcifications were observed, with the largest nodule measuring 1.6 cm × 1.2 cm. The left thyroid lobe appeared normal. Additionally, bilateral prominent cervical lymph nodes were identified (Figure 10).

The cervical CT scan has successfully supported the presence

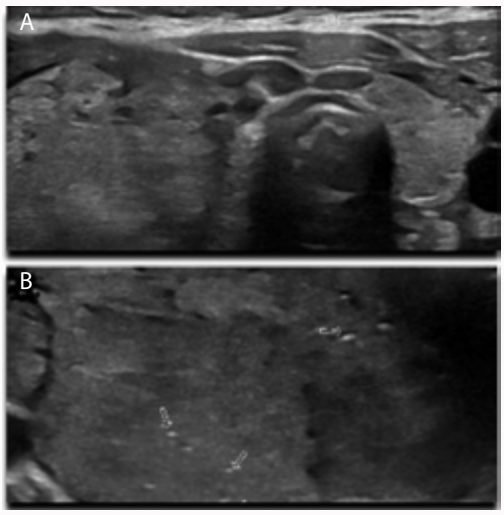

Figure 10: A) Transverse view of the thyroid gland US showed enlarged right thyroid lobe, deviating trachea and normal left thyroid lobe. B) Longitudinal view of the right thyroid lobe US showed enlarged right thyroid lobe with microcalcifications.

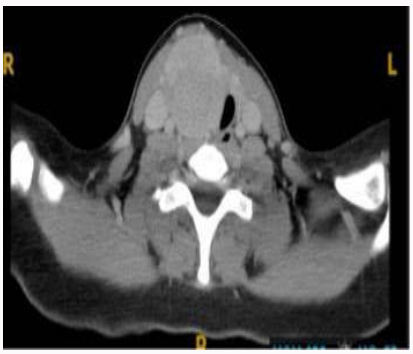

Figure 11: CT scan of the neck revealed diffuse enlargement of the right thyroid lobe which demonstrate heterogenous density with significant mass-effect and displacement of the trachea to the left.

of diffuse enlargement in the right thyroid lobe, exhibiting a heterogeneous density pattern, accompanied by regions of nodularity and localized calcification. The dimensions of the mass were quantified as 5.6 cm × 5.4 cm × 8 cm, representing the maximum extent of its size. The observed findings indicate a notable leftward displacement of the subglottic larynx and trachea, which can be attributed to the presence of a mass exerting pressure (Figure 11).

Based on the notable clinical indicators, the patient underwent total thyroidectomy where the histopathology revealed a thyroid carcinoma of poorly differentiation, characterized by the presence of an encapsulated neoplasm measuring 6 cm in its maximum dimension located in the right lobe exhibited a growth pattern characterized by insular and trabecular structures, accompanied by sporadic regions of tissue death, indicative of a transition towards PDTC. The neoplasm exhibited characteristics consistent with its origin from a follicular adenoma and demonstrated complete encapsulation with localized penetration of the capsule. There were no angioinvasion, lymphatic invasion or extrathyroidal extension detected (Figure 12).

Genetic analysis revealed the absence of any discernible mutations in the BRAF/NRAS genes.

After the complete surgical removal of the thyroid gland, the patient underwent RAI therapy of 100 mCi. After a nine-month treatment regimen, the patient exhibited a highly favorable response (excellent response), as evidenced by a negative uptake by WBIS as well as undetectable levels of Thyroglobulin (Tg) (<0.09 ug/L), and negative levels of Thyroglobulin Antibody (TgAb) (<3.0).

Discussion

Poorly Differentiated Thyroid Cancer (PDTC) is a neoplastic condition that represents only about 5% of the total cases of Thyroid Cancers (TC) [7]. Due to its infrequent manifestation and the variability in the criteria of this disease, PDTC poses a considerable diagnostic challenge [9]. PDTC may appear in many various ways in children and adolescents, as seen by the three cases described here. The rarity of PDTC in the pediatric and adolescent population and the limited literature that is currently available make the diagnosis and management of it a bit challenging [10]. Therefore, our report here may help fill in the gaps in our understanding of the full range of PDTC that may affect younger people. PDTC can presented with unusual symptoms and clinical courses in young population, accordingly, physicians must have a high index of suspicion and investigate a wide differential diagnosis.

Based on our clinical experience, the diagnosis of PDTC can pose significant challenges owing to its infrequent occurrence and potential overlap with other thyroid pathologies [1]. The comprehensive evaluation of a patient's condition typically necessitates the integration of clinical assessment, imaging studies, histopathological and genetic analysis. FNA cytology, while undoubtedly a valuable diagnostic tool, may not invariably yield conclusive results, necessitating the consideration of a surgical resection to ensure an accurate and

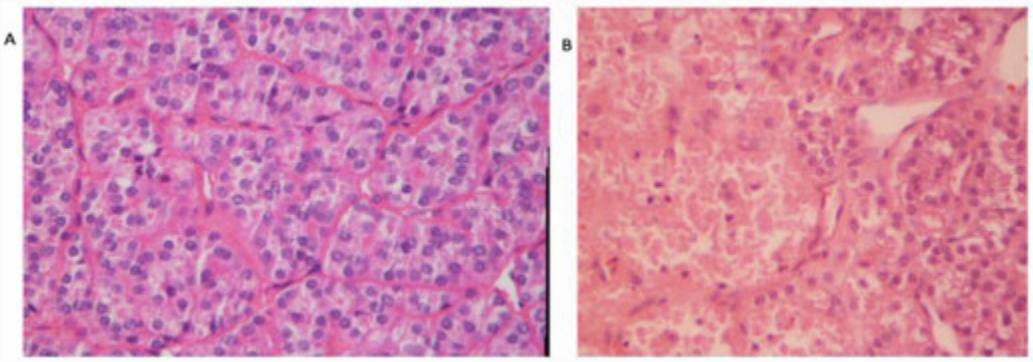

Figure 12: A) Histopathology shows solid/trabecular pattern with small round nucleus and lack the nuclear features of well differentiated papillary thyroid carcinoma and B) Foci of necrosis.

Table 1: Summary of clinical and pathological features.

Case	Age (Years)	Sex	Tumor Size (cm)	Differentiated component	ETE	LVI	Lymph Node Involvement	Distant Metastasis	Necrosis	RAI therapy
1	15	Female	4.5	Papillary carcinoma, follicular variant	No	No	No	No	No	30 mCi
2	9	Male	3.6	No	No	Yes	Yes, 2 LN	Lung, liver and kidney	Yes	No
3	15	Female	6	No	No	No	No	No	Yes	100 mCi

ETE: Extrathyroidal Extension; LVI: Lymphovascular Invasion; RAI: Radioactive Iodine Therapy

definitive diagnosis.

The effects on patient outcomes are substantial, notwithstanding the rarity of such presentations. Our report explains why a thorough and interdisciplinary approach to treatment is necessary, as well as the difficulties encountered and the possibility of misdiagnosis. While each case we see is unique, the therapies used give valuable insight into the potential for pediatric and adolescent patients to respond favorably to novel and aggressive therapeutic strategies when standard procedures fail to alleviate their symptoms. We observed that the prognosis for PDTC is variable, and generally less favorable outcome than well-differentiated thyroid cancers. However, children and adolescents tend to have better outcomes compared to adults [1].

It is clear from these cases presented here that more investigations into the etiologies, genetic and molecular pathogenesis, and best treatment options for PDTC in young children are urgently required [11]. More researches would add to our body of information, and ultimately will increase our chances of making advances in accurate diagnosis, support our decision making for therapeutic options, and help in understanding the prognosis.

Conclusion

In conclusion, the learning obtained from these cases reported here has broad implications for clinical practice and offers a platform for future investigative endeavors. As an uncommon disease, PDTC in pediatric and adolescent patients necessitates a high index of suspicion and an individualize treatment strategy. Even while the treatments available now may be helpful, more advanced diagnostic instruments along with targeted medications are still required. And further investigation into the biological processes behind PDTC will be essential to the development of these advances. With more research into this disease, we may be able in the future to combine comprehensive treatment with tailored therapy to better serve this group. Furthermore, it is only through meticulous reporting and analysis of such rare cases that we can hope to improve our understanding and management of pediatric and adolescent PDTC, which, though rare, present a significant challenge to patients and healthcare providers alike.

Despite the rarity of pediatric thyroid carcinomas, researchers are making progress in decoding their molecular landscape. Embracing the potential of the molecular characteristics for diagnosis, prognostication, and therapeutics opens up exciting opportunities for multi-institutional studies utilizing sensitive and high-performance molecular techniques. Finally, in order to gain a more comprehensive understanding of the most effective treatment strategies for PDTC in this distinct population, it is imperative to conduct extensive multicentral investigations.

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