A Rare Event of Unmasking Anaplastic Transformation in Pre-Existing Papillary Thyroid Carcinoma - A Case Report

Dr Govardhani V [1], Dr Kalaivani Amitkumar [2], Dr Balaji Radhakrishnan [3], Dr Meethu Rappai [4]

[1] *Postgraduate, Department: Department of pathology, SRM Medical College Hospital and Research Centre, SRMIST, Kattankulathur, Tamil Nadu, India. Email id: govardhaniv7@gmail.com*
[2] *Professor and HOD, Department: Department of pathology, SRM Medical College Hospital and Research Centre, SRMIST, Kattankulathur, Tamil Nadu, India. Email id: drkalaivani1980@gmail.com*
[3] *Associate Professor, Department: Department of pathology, SRM Medical College Hospital and Research Centre, SRMIST, Kattankulathur, Tamil Nadu, India. Email id: balajir11@srmist.edu.in*
[4] *Assistant Professor, Department of pathology, SRM Medical College Hospital and Research Centre, SRMIST, Kattankulathur, Tamil Nadu, India. Email id: meethur@srmist.edu.in*

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Anaplastic thyroid carcinoma, Undifferentiated thyroid carcinoma, adjuvant chemo-radiotherapy.

ABSTRACT
Anaplastic thyroid carcinoma (ATC) is a rare, aggressive thyroid cancer accounting for only 1–2% of thyroid cancers but responsible for 14–50% of thyroid cancer-related deaths, with a median survival of 3–5 months. The origin of anaplastic carcinoma remains debated - whether it arises independently or evolves from well-differentiated carcinoma through anaplastic transformation or dedifferentiation, driven by genetic mutations like TP53. It predominantly affects individuals aged 65 and older and is more common in females. Nearly all ATC cases originate within the thyroid gland, rarely arising outside it. The disease is typically locally advanced, invading nearby structures such as blood vessels, skin, and surrounding organs in the neck. Paraneoplastic symptoms may occur. Approximately 50% of patients present with distant metastases, most frequently to the lungs and brain. Diagnosis requires comprehensive sampling, expert pathological interpretation, and additional immunohistochemical and molecular analyses. In our study we have diagnosed, A 65 year male patient with right lobe ATC (Undifferentiated carcinoma) – NOS - major component - predominantly sarcomatoid with other varying patterns. Dedifferentiation from preexisting papillary carcinoma- infiltrating follicular subtype. Right parathyroid gland showing extensive infiltration. This case posits a diagnostic dilemma as there are overlapping features with other thyroid malignancy like medullary thyroid carcinoma- spindle cell variant and poorly differentiated. Careful correlation with clinical details and knowledge of these unique presentations is important for reaching the correct diagnosis. For localized disease diagnosed after primary surgical treatment, adjuvant chemo-radiotherapy is recommended.

1. Case Presentation

A 65-year-old male presented with a three-month history of a progressively enlarging swelling on the anterior neck. Initially small, it rapidly grew to its current size. He reported a 3 kg weight loss during this period and had a one-year history of diabetes mellitus, controlled with regular medication. He denied symptoms such as hoarseness, dyspnea, dysphagia, or breathlessness.

On examination, a 4x4 cm firm, non-tender, mobile swelling was noted on the right side of the neck, moving with deglutition, does not move with protrusion of tongue, without cervical lymphadenopathy. Left side of the neck was normal. Preoperative thyroid function tests indicated euthyroid status (free T3: 3.04 pg/mL, free T4: 0.97 ng/dL, TSH: 1.076 µIU/mL). CECT scan showed a 6.2x5.3x5.2cm heterogeneously enhancing hypodense lesion arising from the right thyroid lobe, likely neoplastic [Table/Fig-1]. Carotid doppler was done which showed the mass lesion partly encasing the right common carotid artery without thrombosis or significant luminal narrowing.

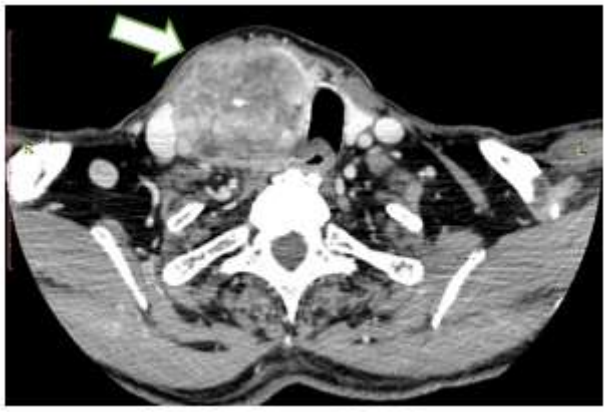

Fig. 1: CECT of neck revealed a heterogeneously enhancing hypodense lesion of size 6.2x5.3x5.2cm arising from the right lobe of thyroid (white arrow).

An initial USG-guided FNAC yielded a haemorrhagic, inconclusive aspirate, and a repeat FNAC was reported as Bethesda category I due to sparse cellularity. Total thyroidectomy was planned with a clinical and radiological suspicion of papillary thyroid carcinoma. Subtotal thyroidectomy was performed due to encasement of the right internal jugular vein and carotid artery over the right lobe. Specimen was sent for histopathological examination. Gross examination of thyroidectomy specimen, weighing 93 grams, showed an enlarged right lobe (7.5x5.5x5 cm) with irregular, nodular, grey-white, partly capsulated features. The cut surface revealed an ill-defined grey-white lesion with focal cystic changes. The left lobe and isthmus appeared grossly normal, except for focal grey-white areas [Table/Fig-2 a,b].

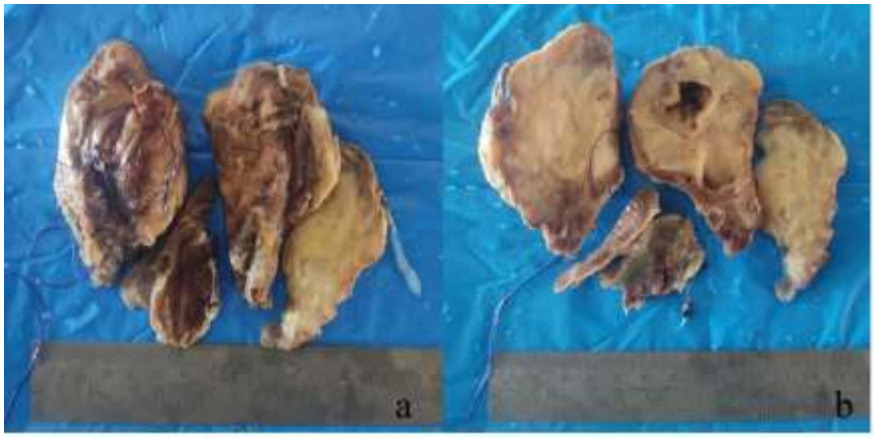

Fig. 2: Gross features of retroperitoneal mass: a) External surface of the right lobe appears irregularly enlarged, nodular, bosselated, partly capsulated and left lobe appears normal; b) Cut surface shows an ill-defined grey white lesion with focal yellowish areas. Focal cystic areas noted

Histopathology revealed a highly infiltrative malignant tumor in the right lobe, showing marked pleomorphism and varied morphologies, including sarcomatoid patterns, areas resembling liposarcoma and pleomorphic sarcoma, epithelioid areas with high vascularity, hemorrhage, and calcification. Mitotic activity was >20/10 HPF. [Table/Fig-3 a,b,c]Tumour shows sheets of lymphocytes in the advancing margin. Residual papillary thyroid carcinoma features were identified, with enlarged orphan Annie nuclei arranged in sheets and focal follicular patterns. The tumor extensively invaded the right parathyroid gland [Table/Fig-4 a,b,c]. No perineural invasion or lymphovascular emboli noted. The left lobe and isthmus displayed adenomatous hyperplasia [Table/Fig-5], and the left parathyroid gland was free of tumor. Based on the histopathological features, the differential diagnosis of poorly differentiated thyroid carcinoma, anaplastic thyroid carcinoma, medullary thyroid carcinoma (spindle cell variant) was considered.

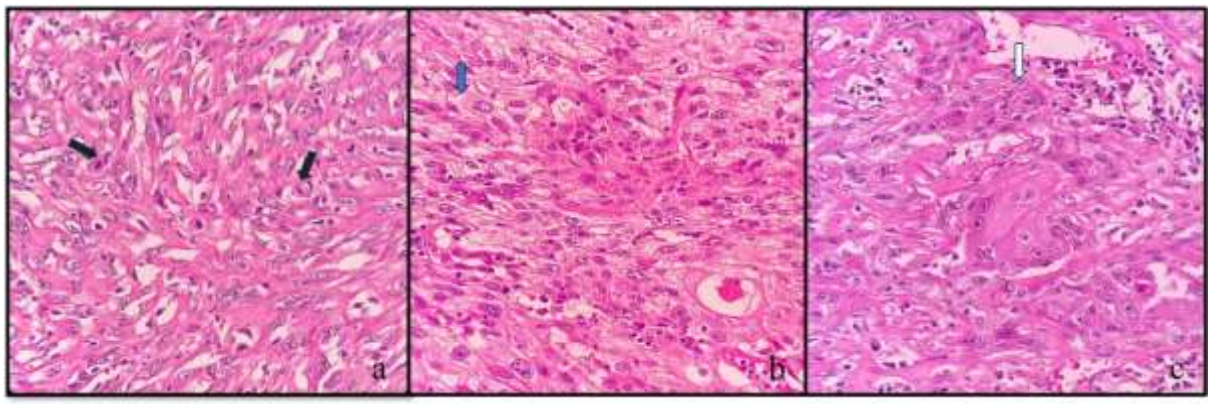

Fig. 3: Right thyroid lobe histology a) Malignant tumor exhibiting sarcomatoid pattern with black arrows showing high mitotic activity (H&E 400x); b) areas resembling liposarcoma (blue arrow) (H&E 400x); c) epithelioid areas (white arrow) (H&E 400x)

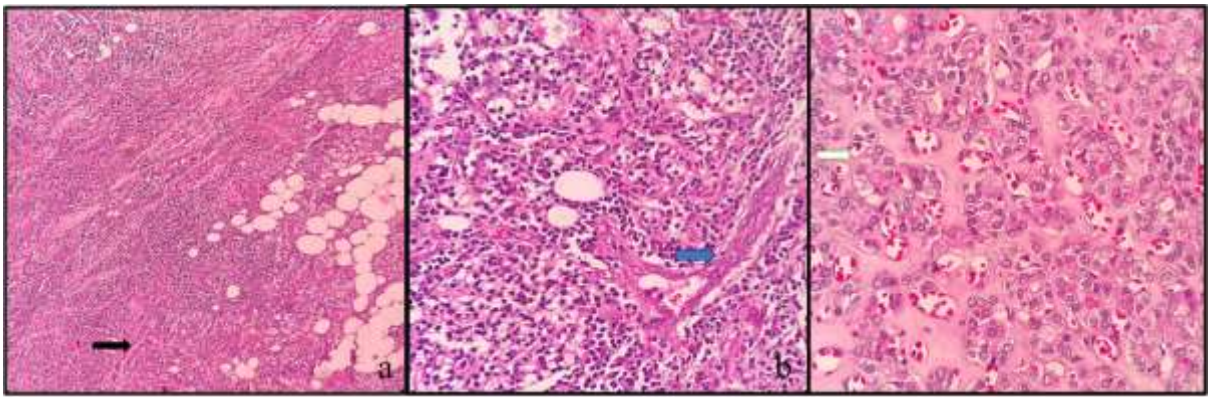

Fig. 4: a,b)Right parathyroid showing tumor infiltration (black arrow) (H&E 100x), (blue arrow) (H&E 400x); c) Right lobe of thyroid showing follicular variant of papillary thyroid carcinoma with orphan annie nuclei (white arrow) (H&E 400x)

Immunohistochemistry revealed strong cytoplasmic positivity for PanCK, Vimentin and negative for TTF-1 [Table/Fig-5], strong nuclear positivity for p53, and a high Ki67 proliferation index (60%). Chromogranin was negative [Table/Fig-6].

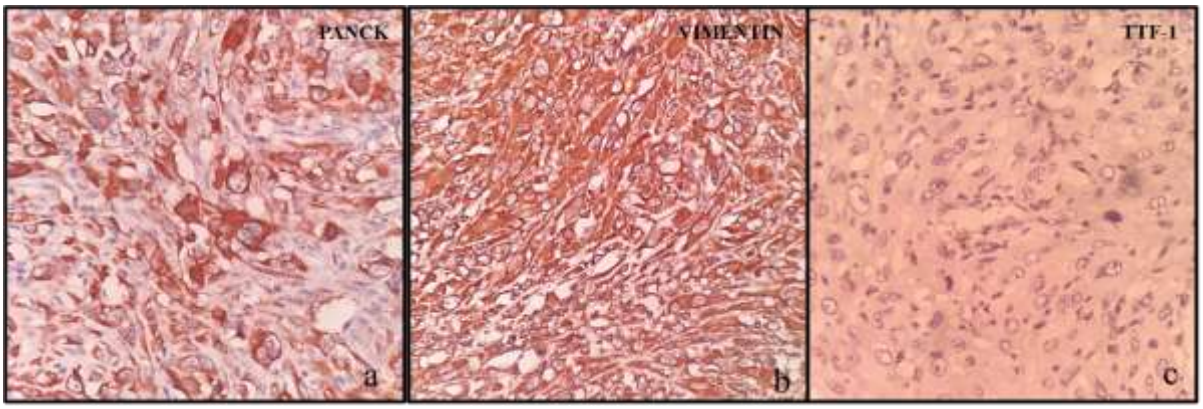

Fig. 5: Immunohistochemical studies a) PanCK showing strong and diffuse cytoplasmic positivity in tumor cells (PanCK stain 400x); b) Vimentin showing strong and diffuse cytoplasmic positivity in tumor cells (Vimentin stain 400x); c) TTF-1 negative in tumor cells (TTF-1 stain 400x)

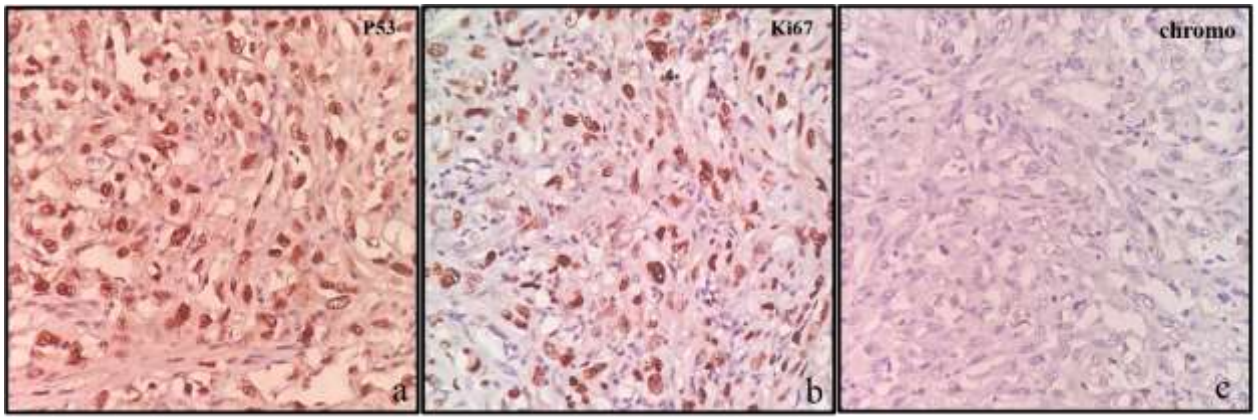

Fig. 6: Immunohistochemical studies a) P53 showing strong nuclear positivity in tumor cells (P53 stain 400x); b) Ki67 showing high proliferative index, 60% positivity in the tumor cells (Ki67 stain 400x); c) Chromogranin negative in tumor cells (chromogranin stain 400x)

Based on the above-mentioned histopathological and IHC findings, the diagnosis of Anaplastic thyroid carcinoma (ATC) was confirmed. Post surgery, patient was advised adjuvant Radiotherapy after oncology opinion. Patient is on regular radiotherapy and completed 30 cycles till date. He is on regular follow-up for the past 4 months without any symptoms and continues to be actively monitored.

2. Discussion

PanCK positivity indicated epithelial differentiation, while Vimentin showed strong, diffuse positivity in spindle-shaped tumor cells, consistent with dedifferentiation seen in ATC. TTF-1 was negative, ruling out poorly differentiated carcinoma and is usually negative in anaplastic carcinoma of thyroid. p53 demonstrated strong nuclear positivity, ruling out poorly differentiated thyroid carcinoma, which shows only focal positivity. The high Ki67 proliferation index (60%) further excluded poorly differentiated thyroid carcinoma, typically exhibiting only 10-30% positivity. Serum calcitonin range was 4pg/ml and chromogranin was negative, ruling out medullary thyroid carcinoma. Based on histopathology and IHC findings, a diagnosis of anaplastic thyroid carcinoma (ATC) was confirmed.

ATC is a rare but highly fatal thyroid cancer, with an incidence of 0.9–1.2 cases per 1,000,000 and a median survival of 3–4 months, according to SEER data [1]. It predominantly affects females, with 75% of cases occurring in patients over 65 years old [2]. Most patients present with a neck mass, while fewer report symptoms like hoarseness, dyspnea, dysphagia, weight loss, or pain secondary to metastasis [3]. Tumors are usually large, averaging 5–6 cm [4]. At diagnosis, less than 10% of cases are confined to the thyroid, while most show extrathyroidal extension (~70%), lymph node metastases (40–45%), or distant metastases (~50%) [5]. The occurrence of both papillary thyroid carcinoma (PTC) and anaplastic thyroid carcinoma (ATC) in the same patient is exceptionally uncommon. At present, no standardized method exists to predict which thyroid neoplasms may progress to anaplastic transformation.[6] Only one case of anaplastic thyroid carcinoma with a dedifferentiated follicular variant of papillary thyroid carcinoma has been reported so far [7]. While direct proof of stepwise progression from well-differentiated to anaplastic carcinoma is lacking, studies show that over 60% of cases contain a well-differentiated component, making up most of the tumor (8). Various theories have been suggested to explain the anaplastic transformation in PTC, emphasizing the role of genetic alterations. Mutations in genes such as BRAF, TERT, RAS, TP53, and those in the Wnt signaling pathway are believed to contribute to the progression to ATC. Other research has indicated that being over 65 years old and having a history of radiation exposure to the neck and prolonged goiter, as possible risk factors for ATC, suggesting that the combination of these factors can contribute to the appearance of the transformation to ATC [6,9]. ATC exhibits several primary histologic patterns, including spindle cell, pleomorphic giant cell, and epithelioid or squamoid morphologies. Tumors are often heterogeneous, displaying more than one of these patterns within the same lesion [10]. While these typical patterns are almost always present in ATC, it is essential to recognize that less common histologic variants can also occur, such as rhabdoid cytomorphology or the paucicellular variant of ATC [11,12]. Atypical mitoses, tumor necrosis are common features of ATC, being observed in 85%, 77% of tumors respectively [1]. Additionally, there are reports in the literature describing cases where ATC has mimicked other conditions, including Riedel's thyroiditis, squamous cell carcinoma, and even benign histiocytic

proliferation [13]. Anaplastic thyroid carcinoma is positive for cytokeratin (Lam et al.,2001; Lam, 2017, 2020) where pankeratin was more positive in differentiated component than anaplastic component (Ragazzi et al., 2020) [2]. P53 overexpression is seen in over half of ATC and the Ki67 proliferative index is virtually always over 30% [14]. Numerous studies have demonstrated that radiotherapy, either alone or in combination with surgery, can achieve effective local control [15]. The study found no significant difference in survival among patients with pure ATC, those with ATC containing a differentiated thyroid carcinoma component, and those with ATC developing in the context of a history of DTC. However, disease-specific survival was notably better for patients whose tumors had only a minor ATC component. Reported 1-year, 2-year, and 5-year survival rates for the combined group of patients with pure ATC, ATC with a differentiated thyroid carcinoma component, and ATC arising from a history of DTC were 34%, 29%, and 14%, respectively [9].

3. Conclusion

ATC arising from papillary thyroid carcinoma is rare and carries a poor prognosis. Due to overlapping histological and radiological features with other thyroid malignancies, accurate differentiation is crucial, as treatment, survival, and prognosis differ. Diagnosis relies on histopathology and IHC. This study emphasizes the importance of identifying co-existence of histological features which impact the patient survival.

References

[1] Amin, S., Polich, Xu B, Fuchs T, Dogan S, Landa I, Katabi N, Fagin JA, Tuttle RM, Sherman E, Gill AJ, Ghossein R. Dissecting Anaplastic Thyroid Carcinoma: A Comprehensive Clinical, Histologic, Immunophenotypic, and Molecular Study of 360 Cases. Thyroid. 2020 Oct;30(10):1505-1517. doi: 10.1089/thy.2020.0086. Epub 2020 May 8. PMID: 32284020; PMCID: PMC7583343.

[2] Abe I, Lam AK. Anaplastic thyroid carcinoma: Updates on WHO classification, clinicopathological features and staging. Histol Histopathol. 2021 Mar;36(3):239-248. doi: 10.14670/HH-18-277. Epub 2020 Nov 10. PMID: 33170501.

[3] Akaishi J, Sugino K, Kitagawa W, Nagahama M, Kameyama K, Shimizu K, Ito K, Ito K. Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma. Thyroid. 2011 Nov;21(11):1183-9. doi: 10.1089/thy.2010.0332. Epub 2011 Sep 21. PMID: 21936674.

[4] Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. Cancer. 2005 Apr 1;103(7):1330-5. doi: 10.1002/cncr.20936. PMID: 15739211.

[5] Glaser SM, Mandish SF, Gill BS, Balasubramani GK, Clump DA, Beriwal S. Anaplastic thyroid cancer: Prognostic factors, patterns of care, and overall survival. Head Neck. 2016 Apr;38 Suppl 1:E2083-90. doi: 10.1002/hed.24384. Epub 2016 Feb 19. PMID: 26894506.

[6] Lyu YS, Hong R, Oh J. Anaplastic Transformation in Papillary Thyroid Carcinoma: A Case Report. Ear Nose Throat J. 2024 Jan 20:1455613231225872. doi: 10.1177/01455613231225872. Epub ahead of print. PMID: 38243815.

[7] Ragazzi M, Torricelli F, Donati B, Ciarrocchi A, de Biase D, Tallini G, Zanetti E, Bisagni A, Kuhn E, Giordano D, Frasoldati A, Piana S. Coexisting well-differentiated and anaplastic thyroid carcinoma in the same primary resection specimen: immunophenotypic and genetic comparison of the two components in a consecutive series of 13 cases and a review of the literature. Virchows Arch. 2021 Feb;478(2):265-281. doi: 10.1007/s00428-020-02891-9. Epub 2020 Jul 18. PMID: 32683537.

[8] Rapkiewicz A, Roses D, Goldenberg A, Levine P, Bannan M, Simsir A (2009) Encapsulated anaplastic thyroid carcinoma transformed from follicular carcinoma: a case report. Acta Cytol 53:332–336

[9] Jannin A, Escande A, Al Ghuzlan A, Blanchard P, Hartl D, Chevalier B, Deschamps F, Lamartina L, Lacroix L, Dupuy C, Baudin E, Do Cao C, Hadoux J. Anaplastic Thyroid Carcinoma: An Update. Cancers (Basel). 2022 Feb 19;14(4):1061. doi: 10.3390/cancers14041061. PMID: 35205809; PMCID: PMC8869821.

[10] Yang J, Barletta JA. Anaplastic thyroid carcinoma. Semin Diagn Pathol. 2020 Sep;37(5):248-256. doi: 10.1053/j.semdp.2020.06.005. Epub 2020 Jun 24. PMID: 32624319.

[11] Canos JC, Serrano A, Matias-Guiu X. Paucicellular variant of anaplastic thyroid carcinoma: report of two cases. Endocr Pathol. 2001 Summer;12(2):157-61. doi: 10.1385/ep:12:2:157. PMID: 11579681.

[12] Lai ML, Faa G, Serra S, Senes G, Daniele GM, Boi F, Mariotti S, Beauchemin M, Asa SL. Rhabdoid tumor of the thyroid gland: a variant of anaplastic carcinoma. Arch Pathol Lab Med. 2005 Mar;129(3):e55-7. doi: 10.5858/2005-129-e55-RTOTTG. PMID: 15737050.

[13] Mo JH, Tan D, Zhao XS, Tjoa T, Wang BY. Anaplastic Thyroid Carcinoma Histologically Mimicking a Plasmacytoma. Diagnostics (Basel). 2020 Jan 8;10(1):29. doi: 10.3390/diagnostics10010029. PMID: 31936233; PMCID: PMC7168172.

[14] SanitàD, Al E. WHO Classification of tumours of endocrine organs. Lyon: International Agency for Research On Cancer; 2017.

[15] Nagaiah G, Hossain A, Mooney CJ, Parmentier J, Remick SC. Anaplastic thyroid cancer: a review of epidemiology, pathogenesis, and treatment. J Oncol. 2011; 2011:542358. doi: 10.1155/2011/542358. Epub 2011 Jun 12. PMID: 21772843; PMCID: PMC3136148.