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Case Report

Unraveling Thyroid Angiosarcoma: A Rare Case and Systematic Review of the Literature

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Case Presentation

A 74-year-old man, heavy smoker and with a history of low risk localized prostate cancer treated by surgery in 2009, presented to the clinic with severe and rapidly progressive alteration in his general status with fever, weight loss and anorexia.

A whole-body CT scan revealed only a 36 mm hypodense nodule in the right thyroid lobe. Upper endoscopy and colonoscopy were normal.

Blood tests showed a PSA level of 0.64 ng/ml, normal thyroid function tests thyroglobulin elevated at 136 ng/mL, normal Calcitonin and CEA levels and a slightly elevated WBC.

A PET-CT scan identified a suspicious thyroid mass and enlarged centimetric cervical lymph nodes.

Fine Needle Aspiration (FNA) of the thyroid was performed, yielding satisfactory material for analysis. The cytology was suspicious for malignancy (Bethesda Category V, 2023).

The patient underwent a total thyroidectomy and cervical lymph nodes dissection. Histological examination reveals a tumor proliferation composed of cellular sheets interspersed with irregular slit-like spaces. The tumor cells exhibit an epithelioid appearance, with large nuclei centered by prominent nucleoli and a moderately abundant cytoplasm. Numerous mitotic figures are observed. The stroma is fibrous and hemorrhagic, with areas of tumor necrosis. Immunohistochemically, the tumor cells show diffuse positivity for CD31 and ERG, with heterogeneous expression of CD34, cytokeratin AE1/AE3, and p53. They are negative for PAX8, TTF-1, calcitonin, EMA, S100, Melan-A, and BRAF. The proliferation index (Ki-67) is markedly elevated. These findings are consistent with a diagnosis of thyroid angiosarcoma.

Unfortunately, the pathology report showed positive margins.

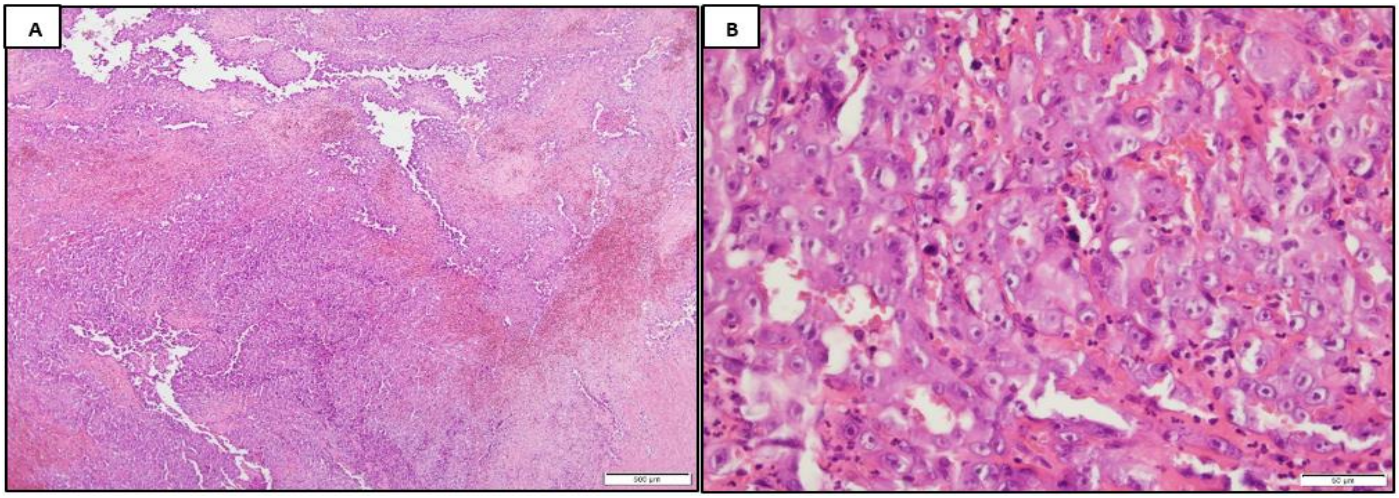

Figure 1: A. H&E x4. The tumor shows a diffuse architecture with large areas of necrosis and Irregularly shaped anastomosing vascular channels. B. H&E x40 Higher power shows atypical epithelioid cells with large nuclei, prominent nucleoli and numerous mitotic figures.

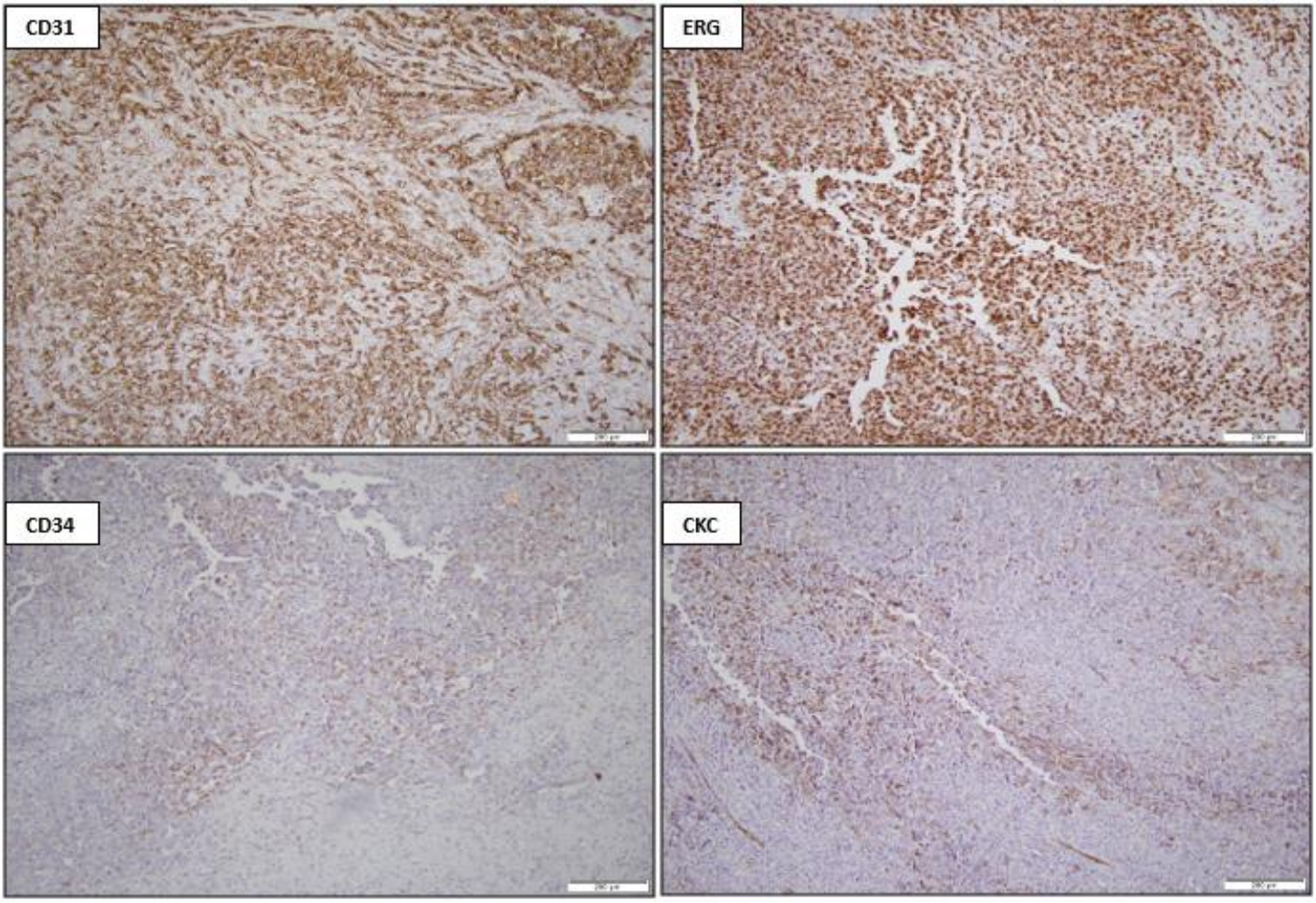

Figure 2: x10. The tumor cells are positive for CD31 and ERG in a diffuse pattern. CD34 and Cytokeratin AE1/AE3 are focally expressed.

Molecular analysis with Next Generation Sequencing of the tumor showed a microsatellite stable disease with a tumor mutational burden of 4 Muts/Mb, PDL1 CPS score of 0 concluding for no targeted therapies or clinical trials associated with his gene alterations.

A few months later, the patient passed away before receiving any further treatment or radiation therapy.

Discussion and literature review

Primary thyroid angiosarcomas (TAS) are extremely rare, accounting for less than 1% of primary thyroid cancers worldwide [1]. However, they exhibit a notably higher prevalence in alpine regions such as Switzerland, Austria, and northern Italy, where they can represent up to 16% of all malignant thyroid tumors [2]. The exact etiology of TAS remains unknown, but its incidence is associated with iodine deficiency and endemic goiter, and a history of exposure to ionizing radiation, polyvinyl chloride, and thorium dioxide. Typically presenting in patients aged 50 to 80, TAS predominantly affects females, with a female-to-male ratio of approximately 3:1 [1,3].

Among all histological types, angiosarcoma is the most common and most lethal mesenchymal malignancy of the thyroid, often leading to metastasis in bones, lungs, lymph nodes, and soft tissues [4]. Despite being first described in English literature in 1953, the existence of TAS as a primary tumor has been debated due to its unusual pathological findings [4]. The World Health Organization classifies TAS as a distinct entity within vascular tumors, highlighting its unique pathological profile, which may arise from malignant transformation in goitrous nodules following recurrent intranodular hemorrhagic events [5]

Our patient presented with a decline in overall health, characterized by weight loss, fatigue, and anorexia. While these manifestations are consistent with the paraneoplastic syndromes frequently observed in TAS, they are not the typical initial presentation. The majority of patients present with neck compressive symptoms or clinical signs of distant metastases, highlighting the aggressive nature of the disease.

Differentiating TAS from other thyroid malignancies based on imaging and laboratory findings remains challenging. While ultrasound, CT, and MRI provide valuable information on tumor characteristics, they are not specific for TAS. Ultrasound typically reveals non- homogeneously hypoechoic lesions with indistinct margins and hyperechoic zones, while CT and MRI often show heterogeneous lesions with variable density and intensity [6]. However, these findings overlap with other aggressive thyroid tumors, such as anaplastic carcinoma. Laboratory markers, particularly thyroglobulin, may aid in

differentiation, as TAS is consistently negative for thyroglobulin, whereas anaplastic carcinoma may exhibit weak positivity [7]. Despite these tools, definitive diagnosis requires histopathological and immunohistochemical analysis following biopsy or thyroidectomy.

The diagnosis of thyroid angiosarcoma (TAS) often requires a comprehensive analysis of surgical specimens, with fine needle aspiration cytology (FNAC) being the most common diagnostic tool. FNAC demonstrates a sensitivity of 93.4% and a specificity of 74.9% [6]. However, the complexity of its cytological features can sometimes lead to misdiagnosis.

Histologically, TAS is characterized by anastomosing vascular channels lined by atypical endothelial cells, extensive necrosis, and a high mitotic rate [8]. Immunohistochemically, TAS is strongly positive for endothelial markers, particularly CD31, which is the most sensitive and specific marker, along with CD34 and ERG. In contrast, anaplastic carcinoma typically expresses PAX8 and shows focal positivity for smooth muscle actin and p63, markers that are absent in TAS [9].

Molecularly, TAS lacks TP53 and TERT promoter mutations, which are commonly found in anaplastic carcinoma. Moreover, TAS is negative for mutated p53 and PAX8, whereas anaplastic carcinoma frequently harbors these alterations. Beyond IHC and genetic profiling, differences in thyroglobulin mRNA expression further support the distinction between these two entities. In a study using radioactive in situ hybridization, TAS demonstrated an almost complete absence of thyroglobulin mRNA expression, while anaplastic carcinoma exhibited weak but detectable levels (mean counts: 9.6 vs. 35.7 arbitrary units, $P<0.01$) [10]. This significant difference suggests that thyroglobulin mRNA quantification may serve as an additional diagnostic tool for accurately distinguishing TAS from anaplastic carcinoma.

Considering these distinct differences, we recommend the routine use of CD31 IHC, thyroglobulin staining, TP53 mutation analysis, and thyroglobulin mRNA expression assessment as reliable tools for accurately distinguishing TAS from anaplastic carcinoma.

Given the high risk of lymphatic and distant metastasis, early diagnosis is crucial. Lymph node involvement should be closely monitored, and sentinel lymph node biopsy may be considered to assess disease spread. In patients with pathologically confirmed metastatic lymph nodes, multimodal therapy, including lymph node dissection, may improve disease-free survival [8]. However, treatment efficacy remains highly variable due to the rarity and heterogeneity of TAS.

Surgical resection remains the cornerstone of TAS treatment, aiming for negative margins due to the tumor's aggressive nature and high recurrence risk. Total thyroidectomy is the standard approach, often combined with sentinel lymph node dissection or systemic lymph node dissection in advanced cases [4]. However, the high vascularity of TAS raises concerns about intraoperative and postoperative hemorrhage.

Adjuvant radiotherapy (RT) is considered in cases of high recurrence risk, particularly when total doses of 53–65 Gy are used [1]. While TAS exhibits some radio-resistance, its high mitotic index and vascularity may enhance responsiveness to high-dose radiation [4]. In unresectable cases, RT serves as a sole treatment modality, though its effectiveness is limited, especially for visceral metastases.

Systemic chemotherapy is used in neoadjuvant, adjuvant, or metastatic settings, but its efficacy remains uncertain. Agents such as taxanes, epirubicin, ifosfamide, and doxorubicin are commonly employed, with some benefit in tumor control. However, recurrence rates remain high despite systemic treatment [11].

Given TAS's vascular nature, anti-angiogenic agents targeting the VEGF pathway, including bevacizumab, and tyrosine kinase inhibitors (TKIs) such as sunitinib, and pazopanib, have been explored. Results remain inconsistent, but these therapies may offer potential benefits in slowing disease progression [4].

Emerging immunotherapeutic approaches, including immune checkpoint inhibitors, are being studied for TAS. However, evidence remains limited, and their effectiveness in improving survival outcomes is yet to be established.

In our patient's case, the evolution was very fast so he just could benefit from the surgical approach without having sufficient time to receive radiation or systemic therapy.

Despite multimodal treatment, TAS carries a poor prognosis, with most patients surviving less than six months after diagnosis, regardless of intervention. Metastatic disease and capsular invasion are the strongest negative prognostic factors, significantly reducing survival. While rare long-term survival has been reported, such as a 5-year survival rate of 33.3% in one study, outcomes remain highly unfavorable [12].

In conclusion, despite aggressive treatment approaches, including surgery, radiotherapy, and chemotherapy, the overall prognosis for TAS remains poor, with most patients succumbing to the disease within months to years. The development of personalized therapies based on the molecular profiles of the tumors is a promising avenue for future research and treatment strategies.

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