

CASE REPORT



Primary thyroid angiosarcoma in a non-endemic region – a rare case

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Abstract

Thyroid angiosarcoma (AS) is a specific type of vascular tumor that arises from the endothelial cells, being highly aggressive, with increased recurrence rates and metastasis. It is characterized by positive endothelial markers and co-positive markers for cytokeratins and epithelial membrane antigen. We are describing the case of a 76-year-old patient who presented to the hospital for dyspnea and asthenia. The clinical and paraclinical investigations confirmed the presence of a right large thyroid nodule, which turned out positive at immunostaining for AS. Even if thyroid AS is a rare type of tumor, mainly described in the Alps, one has to take into account that it can evolve in any other regions and should be considered as a differential diagnosis.

Keywords: thyroid, angiosarcoma, epithelioid.

Introduction

Thyroid nodules are found in general in routine clinical practice, most of the time during physical examination, but also fortuitously, during different imaging procedures. Because they have malignant potential, a rigorous evaluation must be done [1]. Up to 7% of the world population has thyroid nodules, but the majority of patients (80%) have benign lesions, such as colloid cysts and thyroiditis. Five percent of the patients are diagnosed with malignant tumors of the thyroid gland that are described in almost all the cases as primary and epithelial [2].

Vascular thyroid lesions represent a disputed subject in thyroid pathology for many years [3]. The two main categories are the benign neof ormation lesions, such as hemangiomas, and malignant tumors, like angiosarcoma (AS) and angiosarcomatoid carcinoma [2]. AS of the thyroid gland is a rare malignant tumor of endothelial differentiation, which has its highest incidence in the European Alpine mountains and specific in Switzerland,

Austria and Northern Italy [4], where they can account for up to 16% of all malignant thyroid tumors. The high incidence in this region is considered to be due to the lack of iodine, which leads to chronic multinodular goiter and hemorrhagic nodules [5].

Most commonly, the thyroid AS affects female patients, being reported in advanced ages (median age 65 years) [2]. It arises from the vascular parts of the thyroid gland, being histopathologically defined by the unusual endothelial differentiation [6]. This can be highlighted by the expression of vascular markers – cluster of differentiation 31 (CD31), cluster of differentiation 34 (CD34) and factor VIII (FVIII)-related antigen. CD31 is by far the most sensitive and specific marker [4]. The vascular canals are revealed at the microscopic examination [6].

This particular type of thyroid tumor is very aggressive. Its systemic metastases appear in a short period of time, especially at lymph nodes, lung, skin and bones [7]. The optimal treatment consists in a very wide surgical excision,

if the tumor is removable. Adjuvant chemoradiotherapy may be effective as further therapeutic option [6]. The prognosis is very poor, most of the patients die within six months after diagnosis [7].

Due to the rarity of this tumor, a standardized protocol of treatment is not available. A review published in 2013 by Kaur *et al.* identified a number of only 48 published cases of thyroid AS [8], while five years later, in 2018, another review published by De Felice *et al.* identified 61 patients [9]. So, only 13 new patients were identified in five years. The results of the reviews lacked statistical significance regarding the best therapeutic management although they concluded that surgical resection should be the gold standard. These patients should be referred to a specialized center in the treatment of sarcomas to ensure the optimal results [8, 9].

Out of 452 excised thyroid samples that were assessed over a period of almost five years (between January 2015 and September 2019) at the Department of General Surgery, Prof. Dr. Agrippa Ionescu Clinical Emergency Hospital, Bucharest, Romania, only one case of AS was encountered.

Aim

The current study reports a case of thyroid AS, being add, in this way, to the available literature of rare and atypical subtype of sarcomas.

Case presentation

A 76-year-old male patient presented to the Department of Endocrinology, Prof. Dr. Agrippa Ionescu Clinical Emergency Hospital, complaining of dyspnea, dysphonia and asthenia. Thyroid gland high-resolution ultrasonography showed an enlargement of the right lobe and the presence of a nodular lesion. In contrast, the left lobe was of normal size and normal structure. Family history was negative regarding malignancies and thyroid disease.

The thyroid function was evaluated by measuring serum levels of free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH, thyrotropin). The results of thyroid function tests were within the normal range.

The patient was a heavy smoker, with arterial hypertension, atrial fibrillation and type 2 diabetes mellitus. At that time, blood test results revealed a serum creatinine of 2.3 mg/dL, serum hemoglobin (Hb) 10.1 g/dL, iron 21 µg/dL, white blood cells 12 100/µL with 72.6% neutrophils.

The patient was transferred to the Department of General Surgery.

The fine-needle aspiration (FNA) was performed, but it was not significant. The cytology result pointed “suspicious for malignancy”. Before biopsy, a local ethical agreement and informed consent of the patient were obtained.

Surgical management was decided after iron supplementation and normalization of the serum Hb value. The intraoperative examination revealed a large nodule of the right lobe, with the invasion of the infrahyoid muscles. Enlarged local adenopathies were not identified at exploration. The capsule of the tumor was extremely friable and bled easily at dissection. A total thyroidectomy was performed, with the excision of the affected muscles. The tissue fragment was sent to Department of Pathology for the ultimate diagnosis.

The right thyroid lobe measured 82/60/40 mm, presenting an encapsulated nodule. It was firm and yellow-grey, measuring 38/36 mm, being identified by hemorrhagic areas in the central part, but also by the large necrotic tissue areas (almost 40%).

The histopathological (HP) assessment showed malignant proliferation characterized by epithelioid, large rounded cells with relatively high nuclear grade (Figure 1). The cells had abundant eosinophilic cytoplasm and prominent nucleoli. Atypical mitoses were present (Figure 2). Moreover, the cells grow in sheets and lined abnormal vascular spaces that contained erythrocytes (Figures 3 and 4). There were areas of necrosis, hemorrhage, sclerosis and calcification.

Regarding the immunohistochemical profile, the neoplastic cells were strongly positive for CD31 (Figure 5), erythroblast transformation-specific related gene (ERG) (Figure 6) and CD34. The cytoplasm of epithelioid cells was intense positive for FVIII-related antigen. Epithelial differentiation markers, such as cytokeratin, thyroid transcription factor-1 (TTF-1), thyroglobulin and epithelial membrane antigen (EMA) were negative.

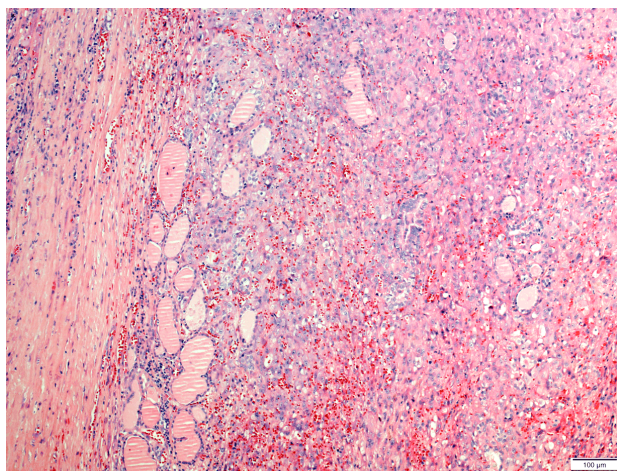


Figure 1 – Hematoxylin–Eosin (HE) staining (×100) shows the histological features of angiosarcoma, with normal tissue of the thyroid gland in the peripheral edge and areas with large epithelioid cells.

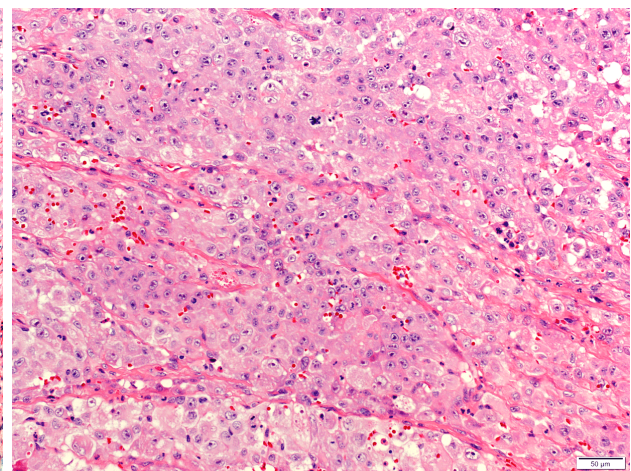


Figure 2 – HE staining (×200) highlights tumor cells with eosinophilic cytoplasm and large, vesicular nuclei with prominent nucleoli. Numerous atypical mitoses are present.

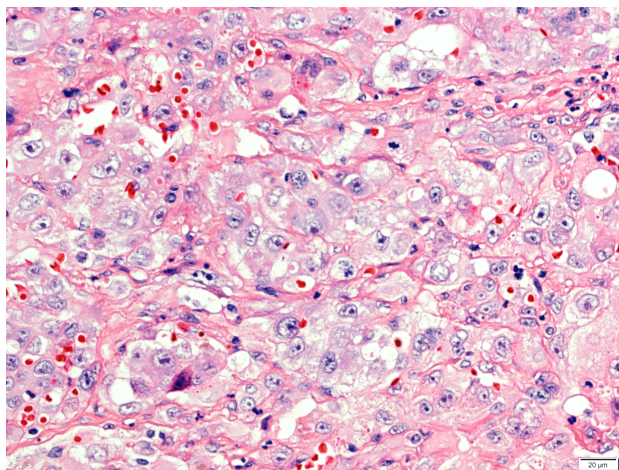


Figure 3 – HE staining ($\times 400$) shows numerous vascular channels bordered by the epithelioid cells.

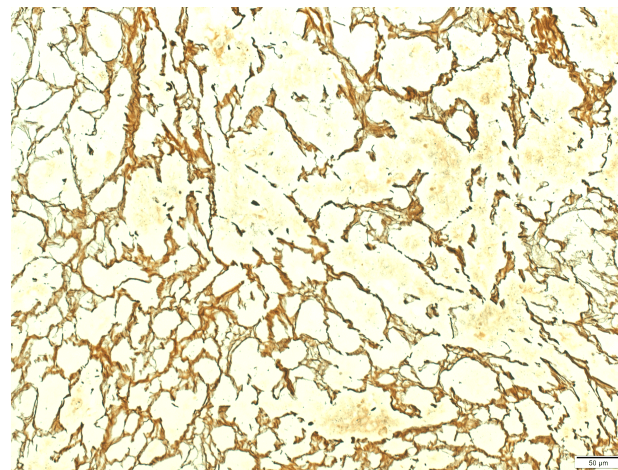


Figure 4 – Silver staining ($\times 200$) shows the vasoformation architecture.

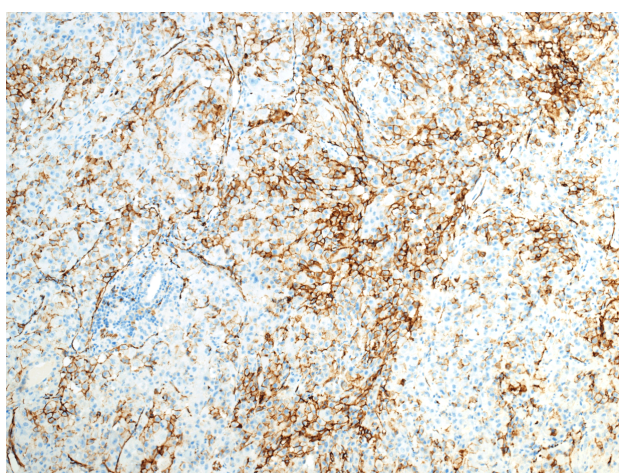


Figure 5 – Immunohistochemical staining ($\times 100$) shows strong diffuse immunoreactivity for anti-CD31 antibody. CD31: Cluster of differentiation 31.

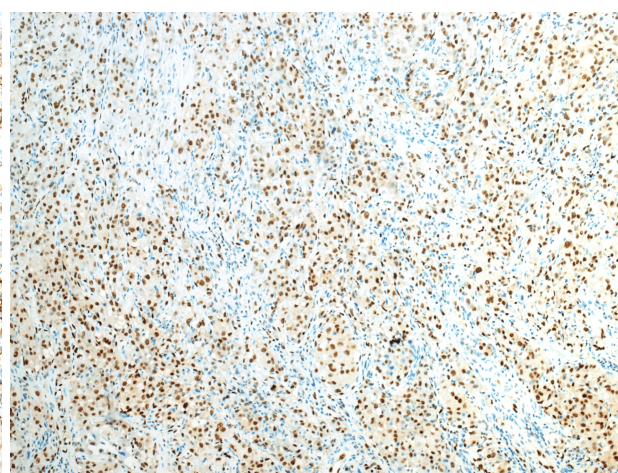


Figure 6 – Immunohistochemical staining ($\times 100$) shows strong immunoreactivity for anti-ERG antibody. ERG: Erythroblast transformation-specific related gene.

The final histological report was primary epithelioid AS of the thyroid, grade 3 according to *Fédération Nationale des Centres de Lutte Contre le Cancer* (FNCLCC).

Postoperatively, the patient presented a wound dehiscence that was treated with special dressings. The evolution was favorable. Total body computed tomography was performed after surgical intervention and no metastatic lesions were detected. The patient fully recovered after seven days of hospitalization and left the Department in a good clinical condition. He received hormonal substitution therapy.

☞ Discussions

AS is a rare and highly aggressive mesenchymal tumor [6]. The main predisposing factors are the chronic lymphedema and radiation exposure. Most commonly, it has been described on the skin and superficial soft tissues. However, lesions of the heart, breast, liver, bone and spleen were encountered. ASs are characterized by locoregional recurrence, nodal and distant metastases, having poor prognoses [10, 11].

We reported the case of a male patient, from a non-Alpine region (Bucharest, Romania), diagnosed with AS of the thyroid gland.

This kind of tumor can develop on a substrate of chronic thyroid affection, such as multinodular goiter [2]. Iodine deficiency is the main cause for endemic thyroid goiter [12]. This was not the case of our patient because in Romania all salts commercialized are supplemented with iodine, a fact required by the law.

FNA biopsy is considered to be the main diagnostic tool for thyroid nodules, being an important factor in deciding the surgical strategy [13]. However, for our patient, its result was not significant. The general surgeon performed the total thyroidectomy. Although there is not a standard surgical treatment for these tumors, one must respect the oncological principles of surgery. Therefore, wide local excision of the lesion represents the “gold standard”. Primary the surgical intervention the patient was seen to the diabetologist, because of his comorbidities. A nutrition plan was established to prevent the evolution of the disease [14]. He had an early stage of diabetic nephropathy, caused by the advanced age, high levels of arterial pressure and smoking [15].

Postoperatively, our patient presented a wound dehiscence. Silver dressings were used to accelerate the healing [16]. Nowadays, there are many types of modern wound dressings that reduce pain and promote healing [17].

The HP examination validates the diagnosis. Most commonly, epithelioid AS affects the deep soft tissues of the extremities, thyroid gland being involved extremely rare. It is described by large, pleomorphic epithelioid cells, arranged in sheets, cellular islands or cords [18], with eosinophilic cytoplasm, central nuclei and prominent nucleoli [19]. Because the nucleus has the chromatin in the peripheral part, its aspect is vesicular. Sporadic, cells with intracytoplasmic lumina containing erythrocytes can be seen. Papillary appearance can be designed by the cellular stratification, in the malignant vascular areas. The vasoformative lesions are undoubtedly signaled by reticulin staining [18]. All over the tumor, there are highlighted increased mitotic activity, varying degrees of hemorrhage and necrosis, but also anastomosing vascular channels [19]. The histological features of the epithelioid AS define easily a clear diagnosis on routine Hematoxylin–Eosin (HE) staining [18].

Tumor cells stains positively for anti-CD31 antibody [platelet endothelial cell adhesion molecule-1 (PECAM-1)], which is a sensitive marker that characterizes all the cases of epithelioid AS [20]. CD31 expression has become known as the “gold standard” for endothelial differentiation in ASs. CD34 is a marker of vascular endothelial progenitor cells, but it is not specific [21]. Nowadays, it is demonstrated the importance of ERG, another sensitive marker of endothelial differentiation, expressed in vascular tumors [22]. Moreover, the tumor immunostainings for FVIII-related antigen [2]. Carcinomas do not stain for endothelial markers – FVIII, CD31 and CD34 [18].

The diagnosis is indicated also by the immunonegativity for thyroglobulin [4].

The thyroid AS can invade rapidly the cervical lymph nodes, producing early metastasis to the lung, brain, duodenum and small bowel [23].

Because there is not a validated therapeutic management after the surgical intervention, adjuvant or neo-adjuvant chemotherapy with or without local radiotherapy may increase the overall survival. New treatment solutions are under investigation, involving the vascular endothelial growth factor and its receptor, but also tyrosine kinase inhibitors [7].

☒ Conclusions

Angiosarcoma of the thyroid gland is a rare, aggressive vascular tumor characterized by sheets of epithelioid endothelial cells. CD31 and ERG immunohistochemistry are identified to be valuable in the differential diagnosis. Having a poor prognosis, a multidisciplinary collaboration would be a more feasible approach.

☒ Conflict of interests

None to declare. All authors participated in the case of the patient, documentation, writing and corrections of the article.

Authors' contribution

Adrian Daniel Tulin, Adelaida Avino, Laura Răducu, Maria Daniela Tănăsescu and Dorin Ionescu are main authors.

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