ABSTRACT:

Introduction: Thyroid Angiosarcoma is a rare malignant condition of the thyroid gland with higher incidence reported in mountainous Alpine regions (Switzerland, Austria and northern Italy), featured with poor prognosis. Case presentation: A 76 years old male patient presented in our hospital complaining about difficulty in breathing, altered voice (hoarseness), fatigue and dysphagia. Careful observation of the frontal neck region revealed hemorrhaging petechiae and purpura, while palpation indicated a large nodule movable with deglutition, presumably derived by the thyroid gland. Serum biochemical thyroid function tests were normal. Ultrasound of the thyroid gland showed enlargement of the right lobe with a nodular lesion. FNAC indicated a “suspicious for malignancy” lesion. After patient’s consensus, total thyroidectomy took place accompanied by excision of infiltrated infrahyoid muscles. The cytopathologic results were positive for primary thyroid angiosarcoma. Patient’s postoperative condition was regular, but he died of disease progression 6 months later. Discussion: Angiosarcomas are malignant neoplasms arising from endothelial cells of blood vessels. They are most commonly found in skin, soft tissue, breast, bone, liver and spleen. Angiosarcomas tend to be highly hemorrhaging and invasive. Thyroid gland is a rare location of development. Cytopathologically they are grossly characterized by freely anastomosing vascular channels lined by atypical endothelial cells unusually enlarged, often multinucleated with many nucleoli and vacuoles into the cytoplasm containing fragments of erythrocytes. The immunohistological identity of angiosarcomas are endothelial line markers (CD31, CD34 and vimentin). Surgical excision when feasible is the first line treatment while adjuvant radio-and/or chemo-therapy are ambiguous. Infiltration of surrounding tissues and distant metastasis (lymph nodes and lungs) are negative prognostic factors.

KEYWORDS: Thyroid cancer, angiosarcoma, surgery.
Case Presentation

A 76 year old male patient presented in our hospital complaining about difficulty in breathing, altered voice (hoarseness), fatigue and dysphagia. Careful observation of the frontal neck region revealed hemorrhaging petechiae and purpura, while palpation indicated a large nodule movable with deglutition, presumably derived by the thyroid gland. Serum biochemical thyroid function tests were normal. Ultrasound of the thyroid gland showed enlargement of the right lobe with a nodular lesion. Fine needle aspiration indicated a “suspicious for malignancy” lesion. After patient’s consent, total thyroidectomy took place accompanied by excision of infiltrated infrahyoid muscles.

The thyroid gland was fixed in buffered 4% formaldehyde solution and sections was embedded in paraffin blocks. Sections 3mm of thickness were stained by the usual haematoxylin-eosin staining.

For immunohistochemistry the automatic system of platform Ventana Benchmark XT was used. The antibodies and their dilutions were: Vimentin (DACO) 1:50, CD31 (Thermo Scientific) 1:150, CKAE1/AE3 (DACO) 1:50, Calcitonin (Thermo Scientific) 1:150, TTF1 (Leica) 1:80, CD34 (Immunologic) 1:400 and PAX8 (Biocare) predilution.

Histopathological examination revealed that the tumor was a high grade malignant neoplasm. The tumor cells frequently were large, epithelioid with severe nuclear atypia and many mitoses. Focally giant tumor cells were observed. The tumor cells are arranged in solid aggregates or irregular clefts. Extensive invasion by the tumor of both lobes and isthmus was observed. Also, gross extrathyroid invasion of soft tissue was observed.

Immunohistochemical the tumor cells were positive for Vimentin, CD31, CD34, CKAE1/AE3 and negative for TTF1, PAX8 and Calcitonin. Thus, the diagnosis of an epithelioid angiosarcoma was confirmed. In the rest of the thyroid parenchyma lesions of multinodular goiter were observed. (Figures 1-6).

Figure 1. Invasion of thyroid parenchyma by the angiosarcoma with epithelioid cells (H&E x 100).

Figure 2. Invasion of thyroid parenchyma by the angiosarcoma with epithelioid cells (H&E x 200).
Figure 3. The tumor cells are epitheloid with severe nucleus atypia in solid arrangement or in irregular clefts (H&E x 400).

Figure 4. The tumor cells are positive for Vimentin (IHC x 400).

Figure 5. The tumor cells are positive for CD31 (IHC x 400).
Discussion

Thyroid angiosarcoma is extremely rare in non-Alpine regions, and as a differential diagnosis we should consider a high-grade epithelioid neoplasm of the thyroid.

There are pathological differences between thyroid angiosarcoma.

Therefore, we must have precision diagnosis.

Several immunohistochemical stains are necessary, including at least two endothelial markers PAX-8, should always be done in order to make the differential diagnosis.

Moreover, the use of immunohistochemical stains have several issues with antibodies, and observers.

There is also a limitation with the survival of these patients because of the relatively limited follow-up durations in some reports.

Additionally, several heterogeneous treatment approaches and regimens are observed with inconsistent follow-up data of patients with primary thyroid angiosarcomas add to false prognostic statistics.

Angiosarcomas may be positive for cytokeratins, especially in the epithelioid variant.

In one study weak prevalence thyroglobulin mRNA (TG mRNA) expression in anaplastic carcinoma of the thyroid was observed which is rare in angiosarcomas, this observation supports the fact that angiosarcomas are not derived from follicular lineage but they are sarcomas [8].

Previous studies have been performed in order to understand the tumorigenesis of angiosarcoma [9-11].

Vascular endothelial growth factor (VEGF) and its receptor, Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2), mutations of p53 gene, and activation of phosphoinositide-3-kinase catalytic alpha polypeptide/v-akt murine thymoma viral oncogene homolog/mechanistic target of rapamycin (PIK3CA/AKT/mTOR) pathways were associated with angiosarcomas in several different tissues [11].

It has been investigated that angiosarcomas do not have follicular lineage origin [8].

Furthermore, in a previous study it was suggested that these tumors had possibly a common neoplastic cell of origin.

Angiosarcoma of the thyroid has been associated with female preponderance (male/female=1:1.47).

Epidemiologic studies presented data where thyroid angiosarcoma has poor prognosis and observed mortality rate close to 90% [12].

Thyroidectomy with or without radiotherapy has been the tip of the arrow for most cases.

Radioactive iodine is rarely used as therapy for angiosarcoma because it is not effective to thyroid cancer cells.

However; radiotherapy for angiosarcomas of the head and neck surgery as adjunctive treatment has shown improvement outcome to survival, and therefore it is recommended.

Chemotherapy alone is not as effective as the combination of both chemotherapy and radiotherapy [13-15].

Nowadays newer treatments with drugs targeting vascular endothelial growth factor/vascular endothelial factor receptor pathway (bevacizumab) and tyrosine kinase inhibitors with activity against VEGFR (pazopanib and sunitinib) are under development.
Several phase II trials have showed effectiveness of these drugs. However, further studies are needed to confirm these findings [16].

Current data indicate that in the head and neck region, thyroidectomy and radiotherapy either alone or in combination are an efficient treatment approach as in our case.

Consent
Consent was acquired from the patient in order to publish the case report and all accompanying material.

Conflict of Interest
None to declare

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