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Case Report

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Primary Epithelioid Angiosarcoma of the Thyroid: Long-Term Survival Case Report and Literature Review

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ABSTRACT

Thyroid angiosarcoma is a rare neoplasm of debated clinical management. In addition, the epithelioid variant poses microscopic challenges due to its close resemblance to poorly differentiated carcinoma. Only 63 cases of thyroid angiosarcoma have been published in English literature. Due to its rarity, the limited clinical experience can make its management complex. We report a new case of primary thyroid angiosarcoma showing preponderant epithelioid features characterized by an exceptional long survival. We also provide a discussion on the role of radiotherapy in tumor treatment and a brief review of the pertinent literature.

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Introduction

Thyroid malignancy tumors arise most commonly from follicular cells (papillary or follicular carcinoma) or neuroendocrine C cells. Sarcomas are, on the other hand, very rare [1,2]. Thyroid angiosarcoma originates from endothelial cells, it's characterized by an aggressive behavior often associated with early metastatic dissemination and poor prognosis. A significant number of cases have been described in European mountainous regions of the Alps (Austria, Switzerland and northern Italy) and are likely related to iodine deficiency and long-standing goiter, endemic in these regions. Nevertheless, sporadic cases have been described in non-Alpine regions [3,4]. Although, thyroid neoplasms characterized by angiomatoid features have been reported since more than a century, only 63 cases have been documented in English literature and the number of cases with confirmatory immunohistochemistry and/or electron microscopy is even 50 smaller [5,6].

We report a case of primary epithelioid thyroid angiosarcoma showing an exceptionally long-term survival and address the potential role of radiotherapy in tumor treatment. A brief review of the pertinent literature is also provided especially focusing on the role of radiotherapy.

Case Report

A 58-year-old man was referred to our hospital for a rapidly growing thyroid mass, clinically he experienced progressive severe dyspnea and dysphonia occurred in few months. Except for type II diabetes, his past medical history was unremarkable. There was no history of goiter, alcohol, or tobacco abuse. Physical examination showed abnormal enlargement of the thyroid gland. A CT scan revealed an increased (7 x 5cm), non-homogeneous, multi-nodular right thyroid lobe and a dominant solid nodular lesion with micro-calcifications. On the 2nd of July 2003 the patient underwent surgery, and a complete thyroidectomy was performed. The left lobe size was within the normal limits with instrumental evidence of smaller nodular lesions and micro-calcifications. The trachea was displaced to the left. There was no evidence of cervical lymph node involvement.

Grossly, the thyroid showed confluent, haemorrhagic, greyish nodules up to 5,5 cm in largest dimension with ill-defined border and infiltrative aspect (Figure 1).

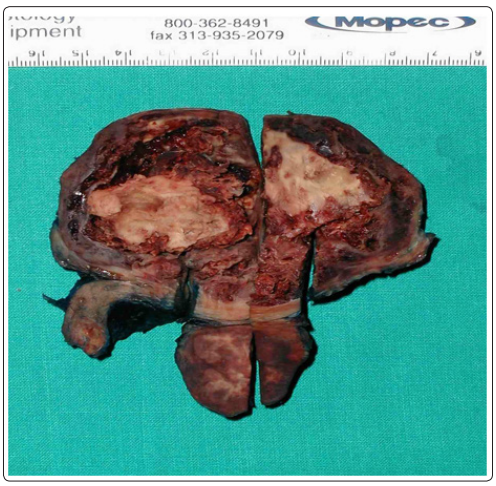

Figure 1: Macro: confluent, hemorrhagic, greyish nodules up to 5,5 cm in largest dimension with ill-defined border and infiltrative aspect.

Histologically, tumour cells were arranged in anastomosing cords, strands, and single cells embedded within a distinctive hyaline stroma. Occasionally, solid nests were present. Abortive vascular channels and intra-luminal papillae with a hyaline core were often noticed (Figure 2).

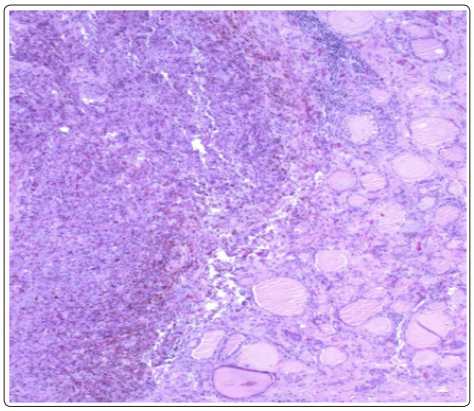

Figure 2: Haematoxylin/Eosin (E/E) 10 x tumour structure arrangement with anastomosing cords, strands, and single cells embedded within a distinctive hyaline stroma.

Preponderant tumor cells featured plump polygonal to stellate cells with characteristic pale to pink, glassy cytoplasm, although focal spindling could be seen.. The nuclei were either round, or horse-shaped/folded, and possessed vesicular chromatin with scattered macro-nucleoli. Intra-cytoplasmic vacuoles were common (Figure 3).

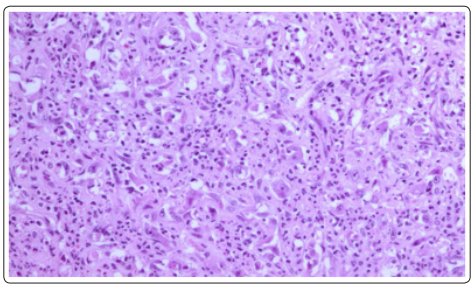

Figure 3: E/E 40x Preponderant tumor cells featured plump polygonal to stellate cells with characteristic pale to pink, glassy cytoplasm, although focal spindling.

Tumour cells showed CD31, CD34, Factor VIII and ERG immunoreactivity; epithelial markers (panCK, EMA) were negative. At the first follow-up, 2 months after thyroidectomy, the disease relapsed locally, in the thyroid lodge, no distant metastases were detected. The chosen treatment was an adjuvant concomitant chemo-radiotherapy strategy, it was started in November 2003. The 1st line chemotherapy regimen combined Epirubicin and Ifosfamide up to IV cycles. The concurrent radiotherapy treatment, it was delivered over 6 weeks with the thyroid lodge and lymphatic drainage received a prophylactic irradiation dose of 46Gy in a 13 daily fractions scheme, while the total dose to the tumor bed was boosted up to 60Gy (2Gy each fraction). Treatment was completed in January 2004 (figure 4).

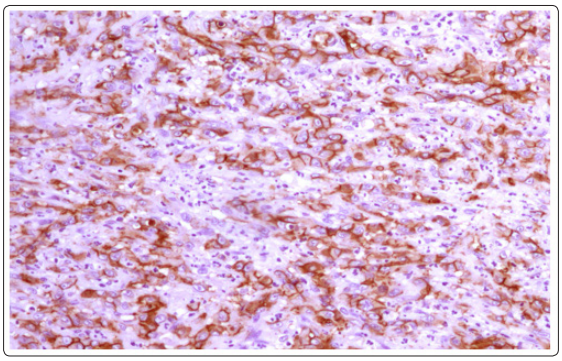

Figure 4: Tumour cells showed CD31 immunoreactivity

Forty days later, the CT and CT/PET scans showed a complete loco-regional response and no evidence of distant metastases. Clinically, the patient had apparent good general condition and symptoms controlled with no dysphagia and only minimal residual dysphonia. The patient underwent to a follow-up program involving clinical and radiological monitoring every 6 months.

After 4 years of negative follow-up, the CT-scan showed a focal, apparently extra-nodal lesion located in the right paratracheal area, suspected for recurrence. It was biopsied, the cytological exam revealed a laryngeal invasive squamous carcinoma. Tumor cells were positive for cytokeratin and p63, and negative for endothelial markers. On the 02nd of September 2008, the patient underwent laryngectomy with tracheostomy. No further radiotherapy was delivered. Seven months later, the patient experienced haemoptysis. In August 2009, the CT- scan showed a solid area near the tracheostomy extending from the cutaneous plane to the spinal profile. The fine needle biopsy documented microscopic recurrent squamous carcinoma at the tracheostomy site.

In September 2009 a second line chemotherapy scheme with Carboplatin, 5- Fluorouracil and Cetuximab was started, even though Cetuximab infusion was prematurely interrupted due to allergic reaction. After the 2nd cycle, patient general conditions got worse, the CT- scan documented multi-organ progressive disease and the chemotherapy was discontinued. The patient died 2 months later, seven years after the initial diagnosis of thyroid angiosarcoma. Autopsy was not performed.

Discussion

Thyroid angiosarcoma was firstly described in 1953, it's a very rare neoplasm representing less than 1% of all sarcomas, and shows a locally aggressive behavior and a high recurrence and metastatic rate. A sizeable majority has been described in the European Alpine regions and for this reason it has been speculated that iodine deficiency (and consequent long-standing goiter) might be a pathogenetic factor although confirmatory evidence is lacking. In contrast to other thyroid cancers, thyroid angiosarcoma is seen predominantly in aged (>60 years old) women, with a history of long-standing goiter followed by rapidly growing neck masses. Clinically, common presenting symptoms include sense of neck lump, shortness of breath, dysphagia, weight loss and local pain [7-10].

Fine needle aspiration cytology is not as accurate as in common thyroid tumors since the specimens yielded by this procedure are often haemorrhagic, and tumor cells are phenotypically difficult to distinguish from those of anaplastic carcinoma[11,12].

Histological examination often reveals degenerative changes, fresh and old stromal haemorrhage. In classic cases a freely anastomosing architecture may be noted featuring channels lined by atypical endothelial cells, focal tumor necrosis and spotty calcifications. The epithelioid variant is characterized by solid sheets of poorly differentiated polygonal cells with abundant, stainable cytoplasm. Rudimentary or abortive vascular differentiation featuring intra cytoplasmic vacuolations, either empty or containing red blood cells, may be recognized. Tumor cells have large vesicular nuclei with prominent nucleoli, and brisk mitotic activity is common.

Immunohistochemistry is a valuable tool in the evaluation of thyroid angiosarcoma being tumor cells positive for ERG, CD31, CD34, and the "time honoured" Factor VIII related antigen. As opposed to angiosarcoma of soft parts, epithelioid angiosarcoma of the thyroid may be positive for cytokeratin, however it is negative for thyroglobulin. Because of its rarity, no optimal management strategy has been established. A unanimously accepted surgical approach has not been proposed, and at present early total thyroidectomy with negative margins, when feasible, is the first choice of treatment and may to offer a chance for cure [10,13]. As far as adjuvant treatment is concerned no specific protocols or recommendations are available, and therapy is mostly adopted on an empirical basis by each referring Institution.

The value of radiation therapy is also disputed due to limited published series: surgical treatment followed by radiotherapy appears to improve patient's survival in several but not all published cases[14-17]. Table 1 enlists the main published experiences. American guideline for thyroid cancer recommends considering adjuvant external beam radiation therapy in patients older than 45 years- old with gross residual disease after surgery or radiotherapy with curative intent for unresectable, locally advanced, no-metastatic disease not responding to radioactive iodine treatment [18]. We chose to treat our patient with radiotherapy due to the well-known aggressiveness of angiosarcoma, hoping that a better local control could improve survival by prolonging the time to distant metastases. Also, the optimal timing (sequential or concomitant) for chemo-radiotherapy schedule is undefined. Chemotherapy regimen includes Taxanes, Epirubicin, Ifosfamide, Adriamycin, alone or in combination, unless the outcome of this approach is still uncertain [10]. Data about prognosis are non-homogeneous. Generally, patients with intra-thyroid tumors had longer survival compared to those with extra-capsular extension [1,19,20]. Poor prognostic factors include extra-capsular tumor spread and distant metastases8;19. However, long survivors especially from non-mountainous areas have been described [1,3,21].

Author	Year	country	Pts	sex	age	Neoadjuv treatment	Primary Treatment	Adjuvant treatment	Survival	CD31	CD34	Factor VIII RA	Vim	Weibel-Palade bodies	hTG	TTF1	FLI1	Ref
Chesky	1953	USA	1	F	67		Total thyroidectomy		1 y									
Chan	1986	China	1	F	73		Subtotal resection	Iiodine	6 m			+		+				
Tanda	1988	Italy	1	N/A	N/A		Total thyroidectomy	**RT**	10 m			+		+				
Lamovec	1994	Slovenia	2	N/A	N/A		N/A		n/a			+						
Maiorana	1996	Italy	7	N/A	N/A		Total thyroidectomy		Died (4): median 5 m; NED (3): 27m, 32m 66 m	+		+						
Proces	1998	Belgium	1	F	74		Subtotal resection		9 m			+	+					
Cutlan	2000	USA	1	M	61		Total thyroidectomy	**RT**	3y	+	+	+			-			
Astl	2000	Ungary	1	N/A	N/A	**RT**	Subtotal resection		N/A									
Lin	2001	Brazil	1	M	65		None		N/A	+		+	+					
Goh	2003	Singapore	2	M	89				5 m	+		+						
Ryska	2004	Czech Rep.	6	4F- 2 M	r54–81		N/A		DOD (2): 15 d / 3 m; NED (1): 21 m; DUC(1): 24 m; NA (2)	+			+	+	-			
Rhomberg	2004	Austria	12	8M -4F	r 55–81		Total thyroidectomy	**RT (2) CHT (6)**	Median: 14 m (range, 0.5–196 m)			+			-			
Yilmazlar	2005	Turkey	1	F	56		Total thyroidectomy	**CHT**	12 w		+	+						
Hassan	2005	Germany	1	F	73		Total thyroidectomy		13m	+	+	+						
Del Rio	2007	Italy	1	N/A	N/A		Total thyroidectomy		N/A	+	+	+						
Beer	2007	UK	1	N/A	N/A		None		2 w			+						
Fulciniti	2008	Italy	1	F	63		Total thyroidectomy		15 m	+	+				-			

Kalitova	2009	Czech Rep.	1	M	60		Total thyroidectomy		2 m	+	+	+					+	
Isa	2009	Malaysia	1	F	48		Subtotal thyroidectomy	**RT**	7 m	+					-			
Zouaidia	2010	Morocco	1	F	37		Subtotal thyroidectomy	**RT**	5 m	+	+	+			-			
Binesh	2011	Iran	1	F	21	**CHT**	RT		4 m									
Petronella	2012	Italy	1	M	71		Total thyroidectomy		3 m	+	+	+						
Kaur	2013	Baltimore	1	M	60		Total thyroidectomy		2 w	+	+	+			-			
Gouveia P	2013	Portugal	1	F	71		Total thyroidectomy		39 d									
Altinay	2014	Turkey	1	F	62		Total thyroidectomy		15 m	+			+	+				
Couto	2014	Portugal	1	F	61		Total thyroidectomy	**RT**	4 y	+	+				-			
Prather	2014	USA	1	M	60		Subtotal thyroidectomy		N/A	+								
Rotellini	2015	Italy	1	F	73		Surgical Biopsy		4m	+		+	+		-			
Bayir	2016	Turkey	1	M	74		Total thyroidectomy		7 d	+	+		+		+	-		
Collini	2016	Italy	6	3M-3F	r 53–68	**CHT**	Total thyroidectomy	**CHT (3) RTCHT (1)**	DOD (2): 36 m/ 9 m; NED (3): 82, 70, 59 m; NA (1)	+	-				-	-	+	
Yoon Moon	2016	Rep. Korea	1	F	48		Total thyroidectomy		2 y	+	+					-		
Wiedermann	2016	USA	1	F	80		Subtotal thyroidectomy	**RT**	N/A	+								
Lepe	2017	USA	1	N/A	N/A		RT		After treatment	+	+							
Navarria F	2019	Italy	1	F	25	**CHT**	Total thyroidectomy	**RT**	36 m				+			-		
Parisi G	2019	Italy	1	M	58		Total thyroidectomy	**RT**	5y and 4 m	+	+	+						

Abbreviations: M: male; F: female; RT: radiotherapy; CRT: chemoradiotherapy; CHT: chemotherapy; DOD: died of disease; DUC: died of unrelated causes; NED: no evidence of disease; ED: evidence of disease; N/A: not available; r: range, TTF: thyroid transcription factor; Vim: Vimentin ; hTGr: human thyroglobulin PR: partial response.

We have reported a case of thyroid angiosarcoma featuring a preponderant epithelioid morphology. Microscopically, the tumor showed distinctive microscopic features such as rudimentary endothelial differentiation, a focal "freely anastomosing vascular channel" pattern and immuno-positivity for endothelial markers. The combined absence of staining for epithelial markers further supported the microscopic interpretation of epithelioid angiosarcoma. Interestingly, our patient developed squamous carcinoma of the larynx about 4 years after thyroidectomy. In addition to obvious phenotypic evidence of epidermoid differentiation, the laryngeal neoplasm was positive for common epithelial markers and negative for an extended endothelial panel. The laryngeal neoplasm developed within the field of previous irradiation: since the patient was an alleged non-smoker it may be questioned whether local radiation might have a role in this tumor pathogenesis.

Conclusion

Due to the limited number of published cases, thyroid angiosarcoma is still a challenging tumor and leaves several open questions, especially on the therapeutic side. Optimal treatment remains controversial: despite a multimodal therapeutic approach may be successful, a consensus has not been reached yet and strategy treatment remains institution dependent. In our case, complete remission of tumor and the relatively long survival might indicate that total thyroidectomy plus radiation therapy might represent treatment reasonable approach. Compilation of further cases is however needed in order to validate this assumption.

Statements

The research has been conducted according to the accepted standards for ethic research practice and reporting. Informed consent was obtained from patient's next of kin for publication of this case report. All Authors declare no conflicts of interest.

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References

1. De Lellis, Ronald ADL, Ricardo VL, Philipp UH, Charis E (2004) Tumours of endocrine organs. In WHO Classification of Tumours. Geneva, Switzerland: WHO 113-114.
2. Sniezek JC, Holten M (2003) Rare tumors of the thyroid gland. Otolaryngol Clin N Am 36: 107-115.
3. Ryska A, Ludvikova M, Szepe P, Boor A (2004) Epithelioid haemangiosarcoma of thyroid gland. Report of six cases of non-alpine region. Histopathology 44: 40-46.

4. Gouveia P, Silva C, Magalhães F Santos C, Guerreiro E, et al. (2013) T Non-Alpine thyroid angiosarcoma International Journal of Surgery Case Reports 4: 524-527.
5. Hedinger E, Zur Lehre der Struma sarcomatosa (1909) I Die Blutgefs- sendothel iome der Struma. Frankfurt Z Pathol 3: 487- 540.
6. Limacher F (1983) Uber Blutgefssednotheliome der Struma mit einem Anhang ber Knochenmetastasen bei Struma maligna. Virchows [Arch Pathol Anal]; 151: 113-150. Quoted by: Egloff B. The hemangioendothelioma of the thyroid. Virchows Arch [Pathol Anal] 400: 119-142.
7. Chesky VE, Dreese WC, Hellwig CA (1953) Hemangioendothelioma of the thyroid; review of the literature and report of a case. J Clin Endocrinol Metab 13: 801-808.
8. Weiss SW, Goldblum JR (2008) Malignant vascular tumors. In Enzinger and Weiss's Soft Tissue Tumors 5th edition Edited by Weiss SW, Goldblum JR. Maryland Heights, MI, USA: Mosby 703-732.
9. Innari E, Succurro G, Tomaino F, Arturi (2013) Non alpine thyroid angiosarcoma in a patient with Hashimato thyroiditis, Case Rep. Oncol. Med. 2013: 901246.
10. Kaur A, Didolkar MS, Thomas A (2013) Angiosarcoma of the thyroid: a case report with review of the literature. Endocr Pathol 24: 156-161.
11. Fulciniti F, Di Mattia D, Patrizia B, Mastro AA, De Chiara A, et al. (2008) Fine needle aspiration of metastatic epitheloid angiosarcoma,Acta cytologica 52: 612-618.
12. Ain KB (2000) Unusual types of thyroid cancer, Rev. Endocr. Metab. Disord. 1: 225-231
13. Kalitova P, Plzak J, Kodet R, Astl J (2009) Angiosarcoma of the thyroid. Eur Arch Otorhinolaryngol 266: 903-905.
14. De Felice F, Moscatelli E, Orelli s, Bulzonetti N, Musio D, et al. (2018) Primary thyroid angiosarcoma: A systematic review Oral Oncology, 82: 48-52.
15. Isa NM, James DT, Saw TH, Pennisi R, Gough I (2009) Primary angiosarcoma of the thyroid gland with recurrence diagnosed by fine needle aspiration: a case report. Diagn Cytopathol. 37: 427-432.
16. Goh SG, Chuah KL, Goh HK, Chen YY (2003) Two cases of epithelioid angiosarcoma involving the thyroid and a brief review of non- Alpine epithelioid angiosarcoma of the thyroid. Arch Pathol Lab Med 127: E70-E73.
17. Astl J, Duskova J, Limanova Z, Povysil C, Kuchynkova Z (2000) Hemangiosarcoma of the Thyroid Gland. A case report. Neuro Endocrinol Lett 21: 213-216.
18. NCCN Clinical practice guidelines in Oncology- Thyroid Carcinoma Version. 3-2018- December 20, 2018. Https://www.nccn.org/professionals/physician_gls/pdf/thyroid
19. Papotti M, Arrondini M, Tavaglione V, Veltri A, Volante M (2008) Diagnostic controversies in vascular proliferations of the thyroid gland. Endocr Pathol 19:175-183.
20. Rhomberg W, Böhler FK, Eiter H, Fritzsche H, Breitfellner G (1998) Malignant hemangioendothelioma of the thyroid gland: new results on pathogenesis, therapy and prognosis. Wien Klin Wochenschr 110: 479-484.
21. Maiorana A, Collina G, Cesinaro AM, Fano RA, Eusebi V (1996) Angiomatoid carcinoma of the thyroid: clinicopathological analysis of seven cases from non-Alpine areas. Virchows Arch 429: 131-137.