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Anaplastic, Sarcomatoid Carcinoma of the Thyroid Originating from a Hürthle Cell Tumor

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The case of a 43-year old female with neck tumor is presented. Sections of the tumor revealed a poorly differentiated malignant neoplasm. A panel of immunohistochemical reactions was performed, and diagnosis of malignancy, most likely of a non-epithelial origin was given. Clinically, the tumor was characterized by a very high growth rate. An attempt at chemotherapy was made, but the patient died two months after the onset of the disease. At autopsy the tumor was extensively sampled. The histology revealed an anaplastic, sarcomatoid component, as well as a Hürthle cell carcinoma. The presented case is an excellent illustration of diagnostic difficulties that may be encountered in differential diagnosis of anaplastic, sarcomatoid thyroid carcinomas and true sarcomas.

Introduction

Sarcomas are very rare thyroid cancers (<1%), while the majority of tumors is of epithelial origin. Anaplastic thyroid carcinoma (ATC) is an infrequent histological type. The tumor is characterized by a very high aggressiveness, a rapid course and poor prognosis. It is well-known that in a great number of cases, ATC develops from well differentiated thyroid carcinoma (TC). Thyroid tumors that consist of oxyphilic cells are also uncommon. Here, similarly as in the case of typical follicular carcinomas, the criteria of malignancy include infiltration involving the entire width of the tumor capsule and vascular invasion. In the case of lesions that meet these criteria the prognosis is worse than in follicular carcinomas composed of conventional cells. The literature on the subject reports isolated cases of patients in whom such a tumor has undergone anaplastic transformation. The present communication describes a female patient in whom histological and immunohistochemical analysis of the biopsy strongly suggested a mesenchymal tumor, and the ultimate diagnosis was established only at autopsy.

A Case Description

A 43-year old woman was brought to the emergency service of the Otorhinolaryngology Department due to respiratory tract bleeding, dysphagia and increasing dyspnea. She reported the complaints to have begun three weeks previously and gradually aggravated. A preliminary examination revealed an exophytic, bleeding tumor visible in the lower pharynx and in the larynx. Fiberoscopy showed an exophytic tumor of the larynx, which was situated mainly subglotically. The lesion largely obstructed the tracheal lumen, involved the right vocal fold and displaced the left vocal fold downward. This picture suggested laryngeal infiltration by a thyroid tumor. Due to increasing dyspnea the patient was tracheostomized. While executing the section along the trachea, an extensive, easily bleeding tumor that hindered the assessment of the tracheal course was noted. Within the neck the patient presented with extensive infiltration, involving the thyroid region and resulting in bilateral lobe enlargement. Specimens for histology were collected from the region of the thyroid gland, larynx and pharynx. Laboratory tests demonstrated considerable leukocytosis with white blood cell count of 110,000/mm^3. In the course of the diagnostic management the patient gradually deteriorated. When the histological diagnosis was obtained, the woman was referred to the Oncology Department.

On admission, she was conscious, but at times falling asleep, with a tracheal and gastric tubes *in situ*. She was in the recumbent position due to markedly increased dyspnea and coughing when she attempted to change her body position. She presented with a hard edema around the tracheal tube; the swelling encircled the entire neck, bilaterally descended to the clavicular region, reaching superiorly to the mandibular level and ascending upward to the retroauricular region. The patient found it difficult to open her mouth.

In view of the rapid progression of the disease, doxorubicin and isophosphamide chemotherapy was attempted. The former was administered at the dose of 80mg, while the

total dose of isophosphamide (8,000mg) was divided and given over two days. On the second day following the introduction of chemotherapy she developed rest dyspnea and edema involving the cervical soft tissues. On the third day, the patient expired. The interval between the onset of clinical symptoms and death was slightly longer than two months.

Sections for histological examinations, as well as autopsy materials were fixed in 10% buffered formalin solution. The material was processed and embedded in paraffin using routine methods. From the paraffin blocks 4μm sections were prepared, which were stained with hematoxylin and eosin. Immunohistochemical reactions were done using routine methods with Dako Immunostainer (DAKO, Denmark). Antigen unmasking was performed by microwaving (700W over 5 minutes, followed by 600W over another 5 minutes) in citrate buffer (pH 6.0). Primary antibodies supplied by DAKO (Denmark) and Novocastra (United Kingdom) were used (Table 1). Secondary antibodies and other reagents from the ENVISION+System (monoclonal sera) and ENVISION (polyclonal sera) were manufactured by DAKO (Denmark).

Biopsy material from the thyroid tumor and tracheal infiltration (No 1488881 and 1489888) revealed a considerably necrotic tumor composed of elongated and irregular, highly atypical cells with abundant acidophilic cytoplasm (Fig. 1). On immunohistochemistry positive reactions for vimentin, desmin and myoglobin were seen, while reactions for cytokeratin, EMA and thyreoglobulin were negative. Basing on these findings, diagnosis of a non-epithelial malignant tumor, most likely of muscle origin, was stated.

The autopsy (No 122608) was performed 30 hours PM. External examination revealed a compact infiltration in the anterior part of the neck, with a 3cm skin ulceration. On dissection, in the anterior part of the neck, an extensive, partially necrotic, brownish-red infiltration was seen. The infiltration involved the soft tissues, larynx and the proximal tracheal and esophageal segments. Within the infiltration, small residual fragments of thyroid tissue were grossly seen.

The right pleural cavity contained approximately 250ml of clear, pinkish fluid. The pulmonary and parietal pleura were thin, smooth and shiny. The lungs, normal in size and shape, showed heterogeneous consistency. On dissection, pulmonary parenchyma was grayish, with blue-cherry-red foci. When compressed, the lungs let out fairly abundant, foamy, but focally non-foamy fluid. In the lower part of the left superior pulmonary lobe a solid, brownish tumor was noted, approximately 1cm in size.

Histologically, in the majority of the sections from the neck tumor a poorly differentiated malignant neoplasm was present. It was composed of slightly elongated and polymorphic cells that were similar to cells observed in histology of biopsy material. In other fields, highly elongated, spindle cells were present. In some sections larger cells with acidophilic cytoplasm were present, growing in distinctly follicular pattern. This picture was compatible with Hürthle cell tumor (Fig. 2). The lungs were edematous and slightly congested. Within some blood vessels, cancer cell emboli were seen. Sections of the tumor situated in the left lung showed the same histological structure as in the infiltration involving the neck, being consistent with diagnosis of metastasis. Immunohistochemistry showed some tumor cells, including the poorly differentiated component, to be positive for pan-cytokeratin and cytokeratin 18 (Figs. 3 and 4). The entire body of observations allowed for establishing the diagnosis of anaplastic, sarcomatoid carcinoma, developing from an oxyphilic tumor of the thyroid.

TABLE 1
Details of antibodies used

Specificity	Manufacturer	Type, clone	Concentration
p53	DAKO	DO-7	1:50
desmin	DAKO	D33	1:50
SMA	DAKO	1A4	1:50
CK	DAKO	MNF116	1:100
CK7	DAKO	OV-TL12/30	1:50
CK18	DAKO	DC 10	1:50
CK19	DAKO	RCK108	1:50
CK20	DAKO	Ks 20.8	1:50
EMA	DAKO	E29	1:100
myoglobin	DAKO	polyclonal, rabbit	1:500
CD34	DAKO	QBEnd10	1:25
CD10	Novocastra	56C6	1:50
CD20	DAKO	L26	1:50
CD3	DAKO	rabbit	1:100
CD43	DAKO	DF-T1	1:50
HMB-45	DAKO	MO684	1:50
vWF	DAKO	F8/86	1:25
LCA	DAKO	2B11+PD7/26	1:100
CD30	DAKO	BER-H2	1:40
vimentin	DAKO	V9	1:50
thyreoglobulin	DAKO	DAK-Tg6	1:50

Discussion

Carcinomas of the thyroid that originate from follicle cells account for a vast majority (95%) of thyroid tumors (95%). The most common forms of thyroid malignancy include papillary and follicular carcinomas, which are jointly termed "well differentiated thyroid carcinomas".

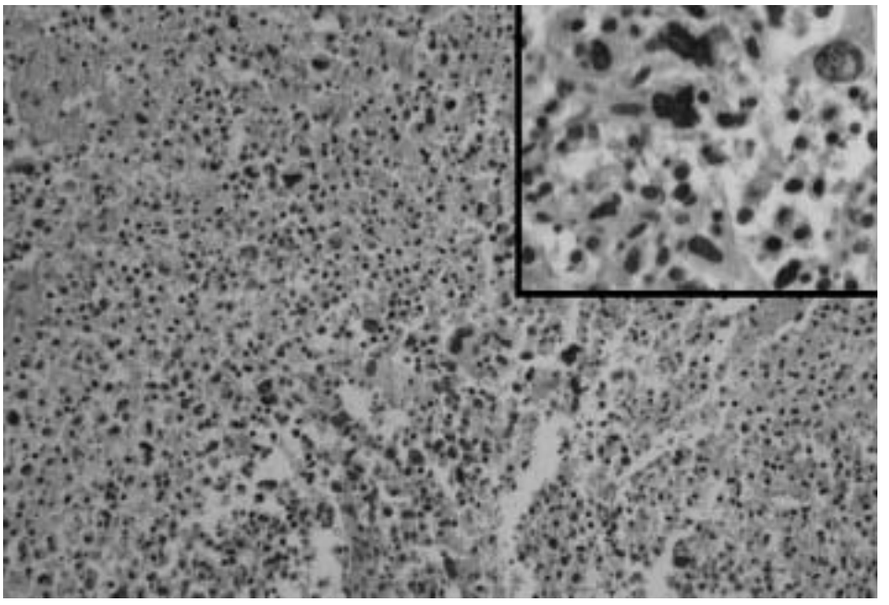

Fig 1. Highly anaplastic infiltrate seen in biopsy material. HE. Lens magn. 20x, insert 60x.

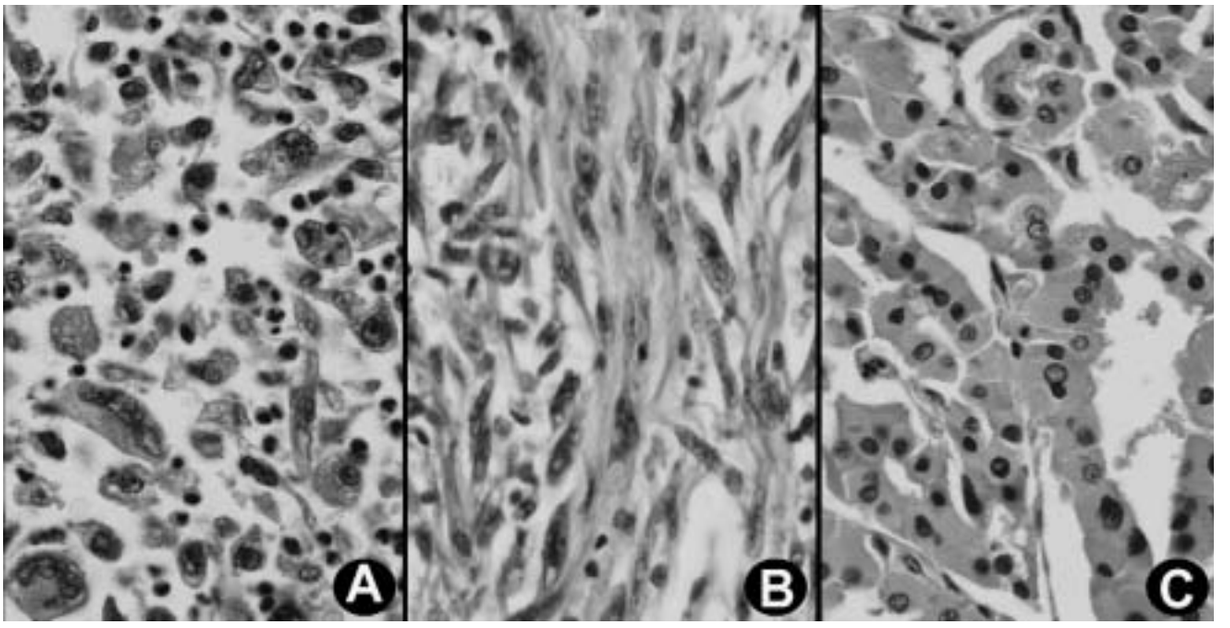

Fig. 2. Autopsy material. A pleomorphic area similar to the one seen in biopsy material (A), a spindle cell component with a high mitotic activity (B), a well-differentiated area composed of oxyphilic cells (C). Lens magn. 60x.

Hürthle cell carcinomas account for 1.2 - 10% of all thyroid tumors. They are composed of characteristic cells with eosinophilic, granular cytoplasm; ultrastructural studies reveal numerous swollen mitochondria. This form of thyroid cancer used to be subject of some controversy as to its prognostic value. Presently only tumors that infiltrate the capsule or demonstrate angioinvasion are regarded as carcinomas, while tumors that do not meet these criteria are classified as benign and diagnosed as oxyphilic (Hürthle) cells adenomas. Hürthle cell carcinomas are supposed to be - at least according to some authors - more aggressive than other well differentiated thyroid tumors.

Anaplastic thyroid carcinoma is a rare histological form. Microscopically these tumors are composed of spindle cells, in some cases also with giant cell and squamous components. Clinically, the lesion typically develops in the thyroid gland, showing nodullar hyperplasia; it may also originate from a well differentiated thyroid tumor. The course of ATC is very aggressive, chemotherapy is ineffective and the prognosis is usually very poor [1, 2, 7].

The mechanism of anaplastic transformation is unclear, but an important role is attributed to P53 as well as β-catenin genes mutations [5, 9]. In the case presented, immunohisto-

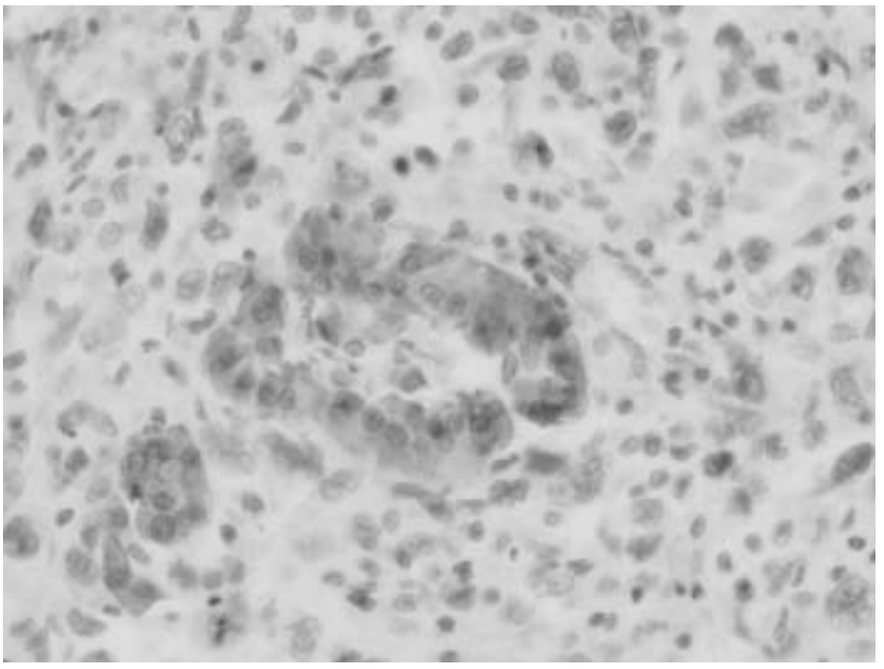

Fig. 3. Autopsy material. A strong reaction for CK18 in the well-differentiated component, while anaplastic areas show a weaker reaction in some but not all cells. Lens magn. 60x.

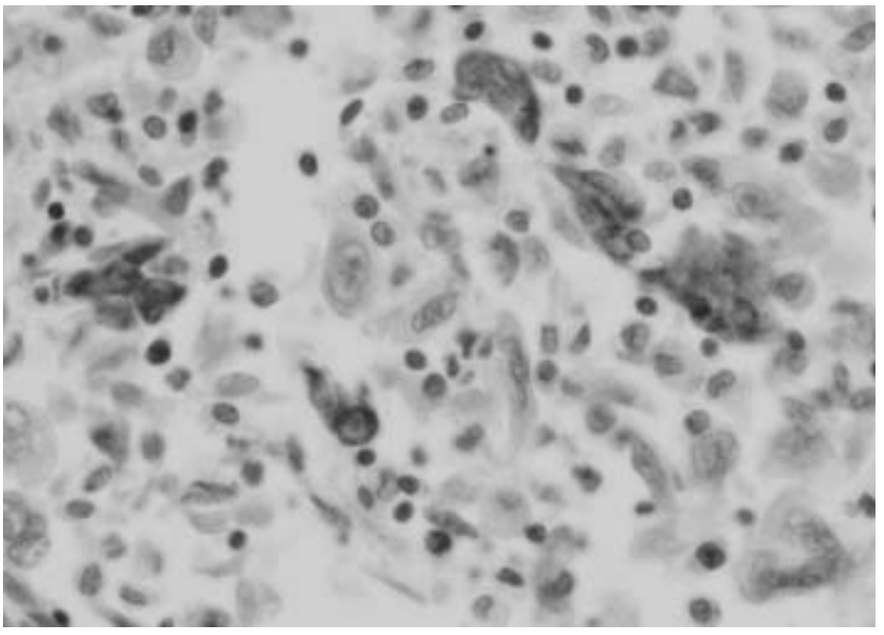

Fig. 4. Autopsy material. After a thorough search, some cells positive for pan-cytokeratin can be found. Lens magn. 60x .

chemistry failed to show p53 overexpression, but loss of heterozygosity at this locus by microsatellite markers could be demonstrated (data not shown). ATC developing from Hürthle cell tumors are sporadically described in the literature, although according to some authors the incidence of this malignancy may be considerably high [1, 6, 7]. Papotti et al. [8] described a series of 60 oxyphilic carcinomas among which they found not a single case of anaplastic transformation. On the other hand, the authors reported p53 overexpression to be associated with an unfavorable prognosis [9, 5]. Cytokines and growth factors produced by tumor cells may trigger hematological changes, as it happened in our patient [2].

The presented case provides an illustration of diagnostic difficulties that may occur in anaplastic thyroid carcinoma, also with extensive use of immunohistochemistry.

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