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Case Report

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Extremely rare primary undifferentiated pleomorphic thyroid sarcoma-Clinical case with a literary review

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Abstract

Anaplastic thyroid carcinoma (ATC) known as undifferentiated and dedifferentiated carcinoma, is a rare, highly aggressive neoplasm. We present an extremely fast growing undifferentiated pleomorphic sarcoma originating in the thyroid gland in an 80-year-old woman. Through this clinical case, we show the importance of the pathohistological characteristic and immunohistochemical analysis for diagnosis of these extremely malignant neoplasms. Due to the radiation- and chemoresistance of this malignant undifferentiated soft tissue neoplasm, early diagnosis for a small tumor volume without distant hematogenous metastases is required to perform maximum radical surgery. Locally advanced sarcomas with lung metastases are subject to symptomatic and palliative treatment and the prognosis is very unfavorable.

Keywords: Undifferentiated Pleomorphic Thyroid Sarcoma, Anaplastic Thyroid Carcinoma, Pathohistological Characteristic, Immunohistochemical Analysis, Locally Advanced Sarcomas.

Introduction

Anaplastic thyroid carcinoma (ATC) known as undifferentiated and dedifferentiated carcinoma, is a rare, highly aggressive neoplasm characterized by rapid growth that causes death soon after diagnosis [1,2]. ATC accounts for about 10% to 15% of all thyroid carcinomas in the United States [3]. Anaplastic type is quite rare, only 1%-2% [4]. Primary thyroid leiomyosarcoma (PTLMS) is a rare tumour and approximately only 30 cases have been reported previously [5-23]. Primary undifferentiated pleomorphic thyroid sarcoma (UPTS) is a subtype of primary thyroid sarcoma (reported frequency ranges from 0.01% to 1.5%) which is extremely rare with 20 cases reported in the English language literature, and only three cases reported in the past ten years [24,25]. We present an extremely quickly -growing pleomorphic sarcoma with the origin of the thyroid gland in an 80-year-old woman. Through this clinical case, we show the importance of the immunohistochemical analysis of the diagnosis and differential diagnosis of these malignant neoplasms.

Clinical Case

We present an 80-year-old woman. In July 2021, she noticed a rapid edema in the right cervical area, accompanied by pain and voice change, as well as difficulty swallowing. Local status/ October 2021-A dense formation is palpated in the right cervical area, which engages the right thyroid gland lobe and its Istmus and spreads to the anterior prelaryngeal region. *Mesopharyngoscopy*-Pale pink oropharyngeal mucosa, tongue moist, unprecedented. *Fibrolaryngoscopy*-A pronounced compression of the larynx from the neck formation to the right, as well as a narrow rhyme glotidis is visualized. The right laryngeal half is with limited mobility. Paralysis of the right vocal connection. CT of the neck soft tissue/October 2021-enlarged right forehead and thyroid gland from a dense tumor with a diameter of 114mm x 69mm. The cervical structures are pressed by the formation contralateral. On a small section the lobe base of the left thyroid gland is also infiltrated. The trachea has a preserved lumen. The smallest lumen settles in the larynx area that is edematous (Figure 1). *CT of the Upper* Mediastinum/October 2021-The tumor in the cervical right region descends behind the sternum and covers the anterior upper mediastinum mainly to the right, and subsequently to the left, pushes the trachea and hypopharynx and infiltrates the upper left lung lobe. Bilaterally in the lung parenchyma, diverse diffuse nodular soft tissue lesions are reported (Figure 2). Intraoperatively, an arched incision to the left of the middle line was made. It has reached a huge tumor, covering the trachea such as a cuff in the front, left and right, reaching the left jugolaris vein over the carotis artery. To reach the trachea, it went through the tumor and took a biopsy. Temporary tracheostoma was performed. *Histological result*- A high grade malignant neoplasm characterized by spindle-shaped, polygonal and epitheloid cells with diffuse pleomorphism in the absence of a specific line of differentiation. A morphological characteristic of undifferentiated pleomorphic sarcoma (Figure 3 and Figure 4). An immunohistochemical (IHC) analysis for verification of the tumor cells origin is required. IHC analysis reports: Vimentin strong positive in 100% of tumor cells; Ki 67 high mitotic activity up to 65%; smooth muscle actin (SMA) focal positive expression. Negative expression for TTF1, Desmin, AE1/ AE3 and S-100 protein (Figure 5).

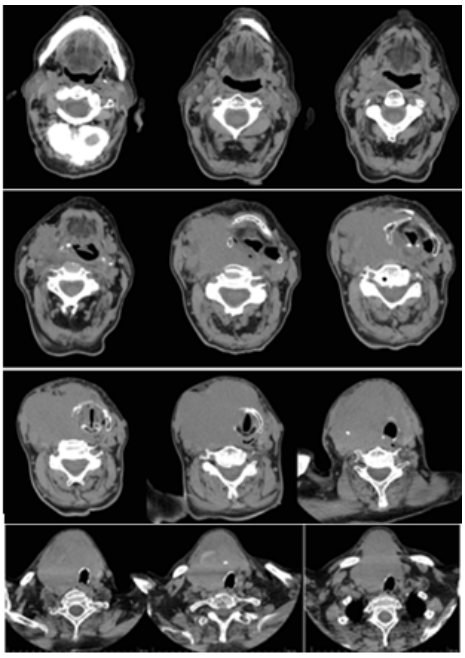

Figure 1: CT of the neck soft tissue/October 2021-enlarged right forehead and thyroid gland from a dense tumor with a diameter of 114 mm x 69 mm. The cervical structures are are contralateral compressed. The small section of the thyroid gland left lobe base is also infiltrated. The trachea has a preserved lumen. The smallest lumen settles in the larynx area that is edematous.

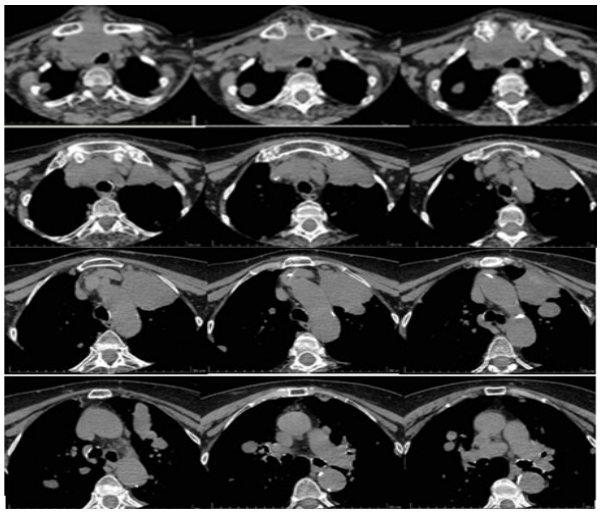

Figure 2: CT of the Upper Mediastinum/October 2021-The tumor in the cervical right region descends behind the sternum and covers the anterior upper mediastinum mainly to the right, and subsequently to the left, pushes the trachea and hypopharynx and infiltrates the upper left lung lobe. Bilaterally in the lung parenchyma, diverse diffuse nodular soft tissue lesions.

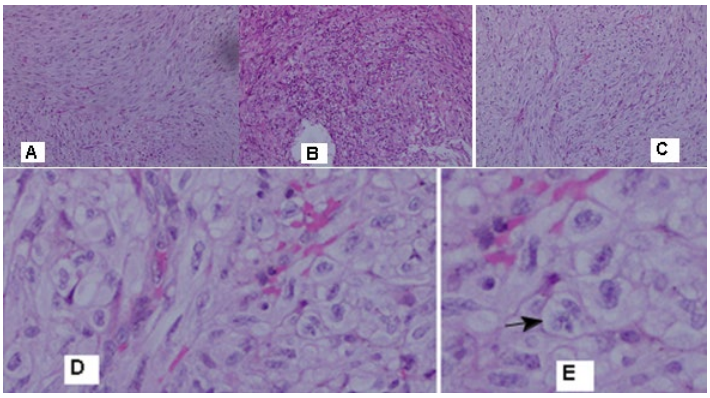

Figure 3: Pathohistological characteristic. A) Storiform pleomorphic appendance x 20; B) Atypical spindle-shaped and epithelioid cells with marked nuclear and cellular atypia, with vacuolized nuclear chromatin and nuclear polymorphism x 20; C) Pronounced cell and nuclear polymorphism x 20; D) Atypical spindle cells, arranged in the form of cords, resembling blood vessels and separate haemorrhage fields x 200; E) Giant histiocyte-like epithelioid cell with pale cytoplasm and atypical mitosis x 400 (with the black arrow shown asymmetry of the chromatin masses within the cell).

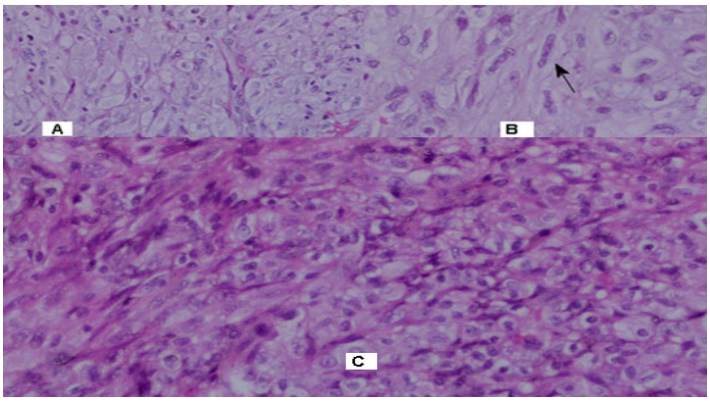

Figure 4: Pathohistological characteristic. A) Pronounced cell and nuclear polymorphism; B) spindle-shaped cells with cigar-shaped and blunt-ended atypical nuclei (shown with the black arrow); C) On the backgrund of the collagenezed stroma admixture of pleomorphic areas with sheets of polygonal, spindled and epithelioid cells with hyperchromatic irregular nuclei, abundant eosinophilic cytoplasm, marked nuclear pleomorphism, areas of necrosis, typical and atypical mitotic activity.

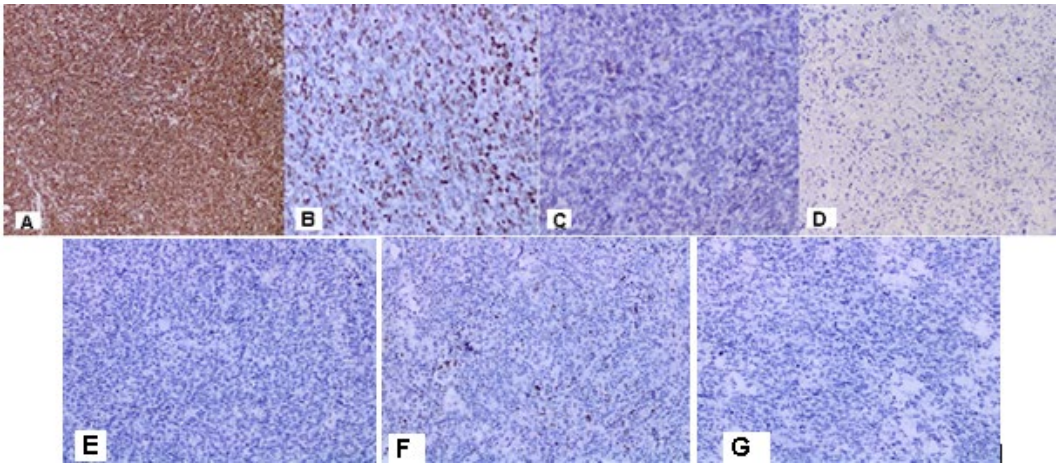

Figure 5: Immunohistochemical analysis. A) Vimentin-strong positive in 100% of tumor cells x 20; B) Ki 67 high mitotic Index/50 mitoses per 10 HPF x 20; C) Negative TTF1 expression x 20; D) Negative Desmin expression x 20; E) Negative AE1/AE3 expression x 20; F) Smooth muscle actin (SMA) focal positive expression x20; G) S-100 protein-negative expression x 20.

Following the broad IHC analysis and the reported positive expression for Vimentin, focal expression to SMA, the high mitotic index and the negative expression to AE1/AE3 are considered to be a highly malignant undifferentiated pleomorphic sarcoma of the thyroid gland. Due to the locally advanced malignant undifferentiated sarcoma, the presence of hematogenous pulmonary metastases, the advanced age and the presence of comorbidity, it is considered that the patient is subject to symptomatic treatment and palliative care. After three months of the tracheostoma, the patient died due to respiratory and heart failure.

Discussion

Sarcomas are classified inversely according to their level of differentiation, with well-differentiated tumors considered low-grade, moderately differentiated tumors as intermediate-grade, and poorly differentiated or undifferentiated tumors considered high-grade sarcomas [26]. The main subtypes of primary thyroid sarcoma (PTS) include angiosarcoma, hemangioendothelioma, leiomyosarcoma [5-23], fibrosarcoma, osteosarcoma, liposarcoma, and undifferentiated pleomorphic sarcoma (UPS-T) [27]. While PTS has no specific clinical signs or symptoms, it generally presents as a rapidly enlarging, firm, non-tender neck mass, which may be accompanied by acute onset of cough, dyspnea, orthopnea, and dysphagia due to compression of the trachea or esophagus, respectively [28]. In the clinical case we have presented, the above symptoms develop very quickly and require tracheostoma. In our clinical case similar to Shahrokh S. et al. [29], CT scan of the chest confirmed the presence of the thyroid nodules (Figure 1), and revealed a large anterior mediastinal mass and multiple bilateral pulmonary nodules (Figure 2). Due to the large tumor volume surrounding the trachea and infiltrating the anterior mediastinum, as well as CT data on bilateral lung metastases, this neoplasm is defined as unresectable.

According to WHO Classification of Tumours: Undifferentiated/ Anaplastic Thyroid Carcinomas are highly malignant tumours, that histologically appear wholly or partially composed of undifferentiated cells that exhibit immunohistochemical or ultra-structural features indicative of epithelial differentiation. Histologically they are composed of a mixture of spindle cells, pleomorphic giant cells and epithelial cells. There is considerable variation in both the percentage and distribution of these cellular elements from case to case[30]. The highly variable microscopic appearances of ATC are broadly categorized into three patterns, which can occur singly or in any combination: 1) The sarcomatoid form is malignant spindle cells with features commonly seen in high-grade pleomorphic sarcoma.; 2) The giant cell form is composed of highly pleomorphic malignant cells, some of which contain multiple nuclei; 3) The epithelial form manifests squamoid or squamous cohesive tumor nests with abundant eosinophilic cytoplasm; occasional keratinization can be present [31]. Undifferentiated high-grade Pleomorphic Sarcoma (UPS), formerly referred as malignant fibrous histiocytoma, is a high grade malignant neoplasm characterized by tumor cells with diffuse pleomorphism in the absence of a specific line of differentiation [32-35].

On microscopic pathochistological examination, PTS is classically composed of plump spindle cells arranged in a storiform pattern with high pleomorphism and giant cells [24,25,28]. In the rarely occurring UPS-T, HE stain revealed the tumor cells were spindle-shaped, round, or ovoid, and arranged in a whirlpool fashion with invasive growth, with high mitotic activity and areas of necrosis. It is consistent with a moderately differentiated thyroid sarcoma [4]. H&E stain of the patient's anterior mediastinal biopsy shows spindle cells with hyperchromatic irregular nuclei and inconspicuous nucleoli, along with indistinct cytoplasm set in a collagenized stroma, consistent with poorly differentiated neoplastic spindle cells, which was in favor of spindle cell neoplasm of the thyroid compatible with poorly differentiated thyroid sarcoma [29]. Pleomorphic areas contain plumper fibroblastic cells, rounded histiocyte-like cells arranged haphazardly with no particular orientation to vessels, and a large number of giant cells with multiple hyperchromatic irregular nuclei [36]. Most tumors

have a combination of storiform and pleomorphic areas, with preponderance on the latter, which also exhibit more accentuated pleomorphism and mitotic activity [34,37,38]. In the clinical case presented, it is observed admixture of pleomorphic and storiform areas with sheets of polygonal, spindled and epithelioid cells, abundant eosinophilic cytoplasm, marked nuclear pleomorphism, necrosis, epithelioid cells with typical and atypical mitotic activity, chains of atypical spindle cells, resembling blood vessels (Figure 3 and Figure 4).

In a typical undifferentiated cells with pathomorphological characteristics of undifferentiated, an immuno histochemical analysis is required to determine the exact pathohistological diagnosis. Immunohistochemically, undifferentiated thyroid carcinoma is generally negative for thyroglobulin and calcitonin. Pan-keratin and epithelial membrane antigen (EMA) are positive in about one-half and one-third of cases respectively [39]. Positive cytokeratin expression supports the epithelial nature of anaplastic thyroid carcinoma, but negative immunostaining for cytokeratin does not exclude the diagnosis [40]. Vimentin is positive in about 90% [36], and epithelial membrane antigen is positive in about 30% of cases [24,25,39,40]. Common thyroid-lineage markers such as TTF1 and thyroglobulin are usually absent, whereas PAX, also a thyroid-lineage marker, is retained in approximately half of all cases [25,39,40]. Although immunostaining is negative for muscle-specific actin, Factor VIII-related antigen, and desmin [36], these markers can differentiate ATC from some soft tissue sarcomas with which they can be confused [24,25,39]. USP must be differentiated from sarcomatoid carcinoma, fibrosarcoma, myxofibrosarcoma, pleomorphic forms of liposarcoma, leiomyosarcoma, rhabdomyosarcoma, osteosarcoma, and chondrosarcoma [34,35]. Following the broad IHC analysis and the reported positive expression for Vimentin, focal expression to SMA, the high mitotic index and the negative expression to AE1/AE3, thise neoplasm is taken as highly malignant undifferentiated pleomorphic sarcoma of the thyroid gland (Figure 5).

Because of the rarity of these tumors, there is no consensus on the best treatment approach [29]. According to TNM staging [41], all ATCs are stage IV. Stage IVA lesions are intrathyroidal, stage IVB involves gross extrathyroidal extension, and stage IVC disease includes distant metastasis. However, a tracheostomy may be necessary in cases of airway compromise. While complete excision is often impossible due to the local extension of the disease, the quality of resection is a significant prognostic factor for survival [42,43]. Due to the radiation- and chemoresistance of this malignant undifferentiated soft tissue neoplasm, early diagnosis for a small tumor volume without distant hematogenous metastases is required to perform maximum radical surgery. Eradication by complete surgical resection with total thyroidectomy, although often not feasible, followed or preceded by concurrent doxorubicin-based chemotherapy and hyperfractionated external beam radiation has been occasionally used and can rarely be associated with long-term survival [1]. Huber et al. reported improved outcomes and disease-free survival in patients with sarcomas of the head and neck larger than 4-cm who received adjuvant radiotherapy [44]. Studies suggest that high dose radiotherapy can also be of benefit for patients who have only had an R2 resection, have unresectable disease, or have limited metastatic disease [45]. Locally advanced sarcomas with lung metastases are subject to symptomatic and palliative treatment and the prognosis is very unfavorable.

Conclusion

We present extremely rarely diagnosed highly malignant thyroid pleomorphic sarcoma. A strict diagnosis requires careful pathohistological analysis and a wide immunohistochemical panel. Unresectable sarcomas are often diagnosed, as it is a locally advanced neoplasm with a high risk of hematogenous metastases. If possible for maximum radical surgery, adjuvant radiotherapy is required. In local advanced tumors with hematogenous metastases, only symptomatic and palliative treatment is possible.

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