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Case Report

Fine Needle Aspiration Cytology Diagnosis of Anaplastic Thyroid Carcinoma. Case Report of a Highly Aggressive Rare Tumor and Review of the Literature

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Abstract

Anaplastic thyroid carcinoma (ATC), is a rare, highly aggressive, and undifferentiated thyroid malignancy. Given the delayed diagnosis, ATC contributes to more than 30% of thyroid cancer associated deaths each year. Most ATC lesions are found within the neck region following metastasis to distant organs and lymph nodes. Diagnosis of anaplastic thyroid carcinoma is particularly challenging given the late presentation of compressive symptoms, histological variety, and rarity of the neoplasm. Early detection can be done with screening methods for high-risk patients with prior history of thyroid neoplasms. Even with a multimodal approach to therapy, ATC diagnosis yields a poor prognosis with less than six months of survival.

KEYWORDS: Anaplastic; Thyroid; Metastasis; Radiation; Prognosis

ABBREVIATION

ATC: Anaplastic thyroid carcinoma, **IHC**: Immunohistochemistry, **MRI**: Magnetic Resonance Imaging

INTRODUCTION

Anaplastic thyroid carcinoma (ATC), also known as undifferentiated carcinoma, is a rare, highly aggressive malignancy accounting for less than 5% of all thyroid gland neoplasms but contributing to greater than 30% of thyroid carcinoma deaths [1,2]. ATC can arise de novo or from pre-existing well-differentiated thyroid carcinoma requiring immunohistochemistry (IHC) support to determine the epithelial origin [4,13].

Classically, ATC presents as a neck lesion characterized by rapid growth with involvement of both lobes of the thyroid gland. Most common presenting symptoms are due to compression of local structures and can include dysphagia, vocal cord paralysis, stridor, dyspnea, and superior vena cava (SVC) syndrome [1]. Given that ATC is usually advanced at diagnosis, most patients have distant metastatic spread involving multiple organs and regional lymph nodes. Median survival is only six months to one year following diagnosis.

It is possible to find ATC nearby well-differentiated papillary or follicular thyroid carcinoma. Further histological analysis can show differentiation of multiple cell types including giant cell, sarcomatoid, and epithelial cell lines [4,12]. Increased risk factors for ATC include age greater than 50, female, and prior history of benign or malignant thyroid disease. The peak incidence of ATC diagnosis is reported to be between the ages of 60 – 70, with a mean age of 55 [1,5].

Fine Needle Aspiration (FNA) cytology, CT scans and Magnetic Resonance Imaging (MRI) are all useful in confirmation of ATC diagnosis [3]. The current standard of care for treatment of undifferentiated thyroid carcinoma utilizes a multimodal approach including combination of surgery, radiotherapy, and chemotherapy. Surgical intervention is warranted when curative resection can be done. Radiotherapy is used preoperatively to decrease the size of the tumor and combined with preoperative and postoperative treatment at high dosages to slow progression of disease [2]. Combination chemotherapy with taxanes, cisplatin, and angiogenesis inhibiting agents combined with surgery and radiotherapy have proven to briefly prolong survival [2,6]. Despite the aggressive therapy, poor prognosis follows the diagnosis of anaplastic thyroid carcinoma.

CASE PRESENTATION

A 61-year-old man presented with generalized weakness, fever and abdominal pain for three weeks. He also complained of presence of anterior neck swelling for several months, but

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recently rapidly enlarging. He also noticed changes in the quality of his voice, difficulty swallowing and breathing, with pain and tenderness around the lower neck. Patient reported history of controlled hypertension, hyperlipidemia, and localized colon adenocarcinoma treated with segmental resection three years prior to current presentation.

On physical exam, abdomen was distended, soft, and tender in the right upper quadrant with no rebound tenderness or guarding upon palpation. Further examination revealed a large thyroid mass measuring 4.2 cm involving both thyroid lobes and prominent cervical lymphadenopathy. Imaging studies confirmed infiltration of the thyroid mass into the surrounding tissue. CT scan of the chest and abdomen revealed multiple pulmonary, liver and bone masses, in addition to left adrenal nodule (**Figure-1A&B**). Imaging studies were highly suspicious of metastatic lesions. Of interest, blood work showed incidental hypereosinophilia and moderate neutrophilia.

Fine needle aspiration (FNA) of the thyroid mass was performed with adequate sample including sufficient material for cellblock preparation. Cytology sample displayed high cellularity with abundance of anaplastic pleomorphic large cells with epithelioid morphology showing bizarre nuclei and abundant intensely eosinophilic and slightly granular cytoplasm in a highly necrotic background and increased mitotic activity (**Figure-2C&F**). Focally, scattered cells with squamoid features were also identified. The cytomorphology was non-specific and suggested sarcomatous lesion versus an anaplastic malignant neoplasm. Immunohistochemistry (IHC) studies were essential to determine the line of cellular differentiation and were performed on cellblock. The tumor cells were positive for the following markers: cytokeratin AE1/ AE3 (**Figure-2B**), CK7, Vimentin (**Figure 2E**), TTF-1 (focally in squamoid cells- **Figure-2A**), Pax-8 (**Figure-2D**) and focal staining with p63. The tumor cells were negative for CK20, calcitonin, thyroglobulin, CDX2 and CD45. FNA of one cervical lymph node as well as one mass from the liver produced similar finding as that of the thyroid lesion and diagnosis of widely metastatic anaplastic thyroid carcinoma was rendered.

A multidisciplinary tumor board suggested a total thyroidectomy and initiation of radioactive iodine radiation treatment with chemotherapy. The patient was started first on experimental pazopanib with prednisone and rasburicase. However, following initiation of therapeutic regime, the patient's respiratory status deteriorated. The plan of care was changed to providing comfort measures; patient passed away two weeks after admission.

DISCUSSION

Anaplastic thyroid carcinomas are rare, highly aggressive, and undifferentiated carcinomas that account for less than five percent of all thyroid associated malignant neoplasms. ATC, arising from a multitude of oncogenic mutations, originate in the neck with diagnosis usually following distant metastasis. The most common clinical presentation depicts a painful, infiltrative, firm mass on the lower anterior neck. Upon further examination, invasion of the neoplasm is usually seen onto local cervical structures [3,13].

Diagnosis of ATC and determination of cell line differentiation is accomplished through radiography, immunohistochemistry and molecular studies. On CT, large isodense or hyperdense masses with calcification and necrosis can be seen in various organs indicating extensive metastasis. The best assessment method to determine extent of invasion is utilizing MRI imaging. Additionally, assessment with F-fluorodeoxyglucose position emission tomography fused with CT scan (FDG-PET) can show increased glucose transport expression showing increase in glucose uptake [13]. Tissue diagnosis can be accomplished by FNA perioperatively or during surgery or by surgical core biopsy. On cytologic examination, a biphasic population of tumor and uninvolved thyroid tissue can be visualized. The cytology specimen is usually highly cellular with scattered single cells and focal clusters of atypical and anaplastic cells in background of necrosis and rich inflammatory cells [12]. The differential diagnosis for ATC may include primary thyroid lymphoma, thyroid sarcoma, poorly differentiated thyroid carcinoma, squamous cell thyroid carcinoma, and medullary thyroid carcinoma.

Immunohistochemistry is beneficial in supporting the diagnosis of ATC and to rule out other poorly differentiated malignancies. On gross examination, a bulky mass with homogenous appearance can be seen infiltrating into adjacent soft tissue and organs [11]. As ATC displays spectrum of cell differentiation, microscopic examination can reveal the presence

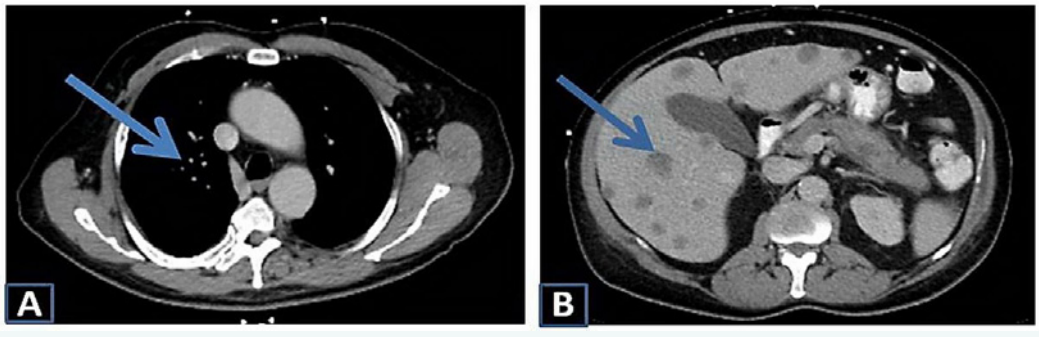

Figure 1 CT scan of the chest and abdomen showing multiple pulmonary (A) and liver (B) metastases (blue arrows).

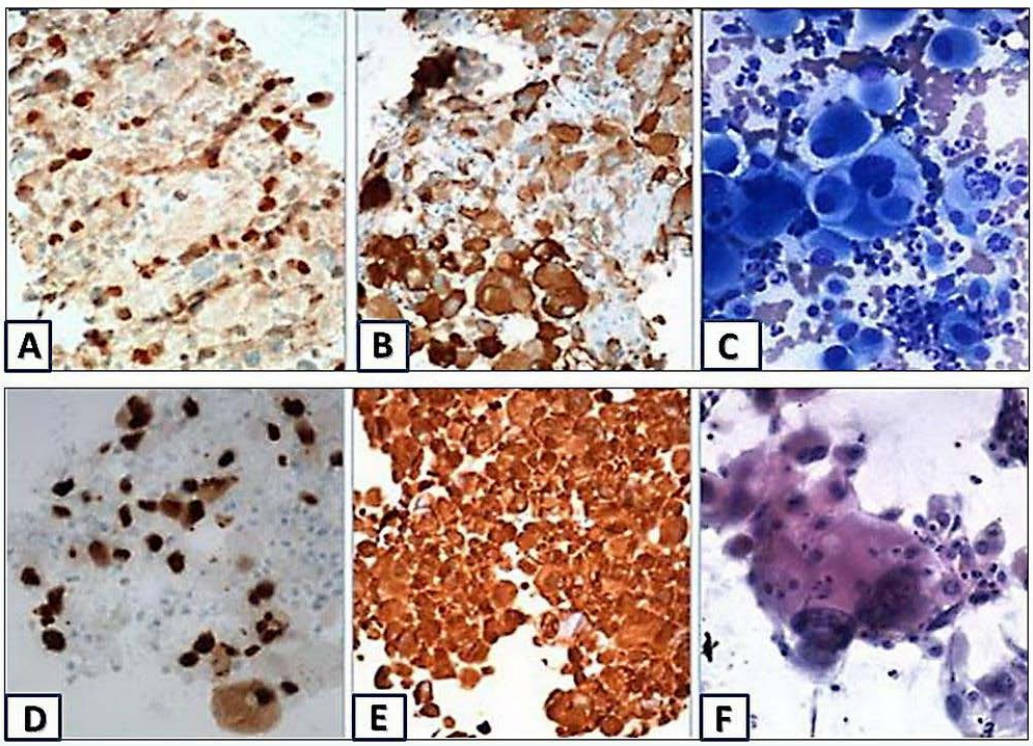

Figure 2 Cytomorphology and immunohistochemistry of the thyroid mass FNA
Tumor cells positive for TTF-1
Tumor cells positive for Cytokeratin AE1/ AE3
Anaplastic bizarre tumor cells (DQ Stain X60 magnification)
Tumor cells positive for Pax-8
Tumor cell positive for Vimentin
Anaplastic bizarre tumor cells (PAP Stain X60 magnification)
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of sarcomatoid, epithelial, or giant cell morphologic features. Specifically, the sarcomatoid form contains malignant spindle cells with high grade pleomorphic sarcomatous features. Giant cell variant reveals pleomorphic malignant cells containing multiple nuclei, and the epithelial form demonstrates malignant squamoid cells with prominent eosinophilic cytoplasm [4]. Positive cytokeratin in ATC supports the epithelial nature of origin but negative immunostaining is not sufficient to completely exclude ATC diagnosis [2,13].

Mutations noted in ATC, may include TP53, BRAF kinase (V600e), RAS, PIK3CA, and PTEN mutations [13]. TP53 gene inactivation plays a direct role in the progression of differentiated to undifferentiated ATC. Favorable prognostic indicators include age of onset, absence of distant metastasis, small unilateral tumors, absence of invasion, and initial diagnosis as an incidental finding before extensive metastasis.

A study by Marten et al. analyzed the role of the BRAK kinase mutation which led to activation of the MAPK pathway and uncontrolled cell proliferation [5,12]. Specifically, the BRAFV600E mutation, which substitutes glutamine for valine, leading to a 500-fold increase in MEK pathway activation. The case report presented a 51-year-old male evaluated for a two-week history of hoarseness of voice preceding ATC diagnosis. Genetic evaluation revealed a BRAF kinase mutation for which the patient was treated with vemurafenib, a BRAF kinase inhibitor usually used to manage advanced melanoma. However, the patient quickly deteriorated and died before combination therapy of MAPK inhibitors could be utilized [5]. Mitogen-activated protein kinase (MAPK) cascades are key signaling pathways involved in the regulation of normal cell proliferation, survival and differentiation. Raf activates the MAPK/ERK kinase (MEK)1/2 dual-specificity protein kinases, which then activate ERK1/2. The mutational activation of Raf in human cancers supports the important role of this pathway in human oncogenesis [18]

Given the reported observation of paraneoplastic phenomenon in thyroid cancers [17], further investigations are recommended to determine if the leukocytosis and eosinophilia observed in our patient is a prognostic indicator or a paraneoplastic feature of ATC. Camargos et al. published a case in which a 95-year-old woman had been treated for progressive dysphagia for eight years. When her condition deteriorated, blood tests revealed leukocytosis and eosinophilia in absence of thrombocytopenia. The patient died 11 days following diagnosis. On autopsy, an

upper mediastinal tumor was noted. Histopathology confirmed diagnosis of a neoplastic transformation of ectopic thyroid tissue [8]. Hyper eosinophilia paraneoplastic phenomenon is an exceedingly rare phenomenon. Camagros presented a rare case of leukemoid reaction and peripheral hyper eosinophilia as a paraneoplastic phenomenon of ATC [7,12]. Paraneoplastic phenomenon associated with various solid tumors has been reported in various tumors. Zalewska and colleagues presented a case of hyper eosinophilia following clear cell renal cell carcinoma diagnosis. Treatment with corticosteroids was the recommended course of action; however, only a transient decrease in eosinophil count was noted before the patient further deteriorated [12]. ATC should be differentiated from metastatic high-grade pleomorphic sarcoma to the thyroid gland as both can show similar histomorphologic features. Gao Y. et al. reported a case of metastatic leiomyosarcoma of the Thyroid Gland from a prior uterine leiomyosarcoma and demonstrated that immunohistochemistry and molecular testing can aid in definitive diagnosis [14].

The current standard of care of ATC includes surgery, radiotherapy, or chemotherapy, or a combination of the three. Recommended treatment is based on surgery when feasible or alongside chemoradiation following surgical intervention. Most ATC tumors are nonresectable due to late diagnosis and invasion of local structures. Debulking surgery is recommended, if possible, as the primary method of airway protection in effort to preserve the larynx. If preservation of local structures is unsuccessful, a tracheostomy may be necessary. Patients with metastatic ATC almost uniformly have short survival and no prospects for curative outcome [15]. For patients with advanced or unresectable disease, external bean irradiation or definitive radiation therapy in junction with chemotherapy is the recommended course of treatment. Common chemotherapeutic agents used include cisplatin and taxanes [1,3]. Recently, RAF inhibitors (non-specific serine / threonine protein kinase inhibitors) have also been used in treatment [1]. Adjuvant radiation therapy is recommended to be performed in all cases. In a recent report, it was suggested that EGFR, VEGFR and ALK alteration may be used for targeted therapy and some cases may express PD-L1 [16].

Anaplastic thyroid carcinoma is an undifferentiated cancer with dismal prognosis. Anaplastic thyroid carcinoma with widespread metastasis has a grave prognosis, and none of interventional strategies has shown to significantly prolong survival in these patients. Further investigation is recommended to understand the pathways of disease and the nuances in the multimodal therapeutic regime. The definitive diagnosis of ATC is made through tissue examination, imaging and immunohistochemical studies in addition to further molecular analysis. It is our hope that this report raises awareness of clinicians and pathologists of anaplastic thyroid carcinoma, and that continued investigation drives further development of efficacious diagnosis and safe treatments for improving patient outcomes.

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