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Case Report

Aggressive Thyroid Carcinoma Mimicking a Benign Histiocytic Proliferation-Utility of Tumor Markers by Immunohistochemical Analysis

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Abstract

Background: It is unusual for a malignant neoplasm to have morphologic resemblance to a benign disorder. We present a case of an unusual clinically aggressive thyroid carcinoma that morphologically mimicked a benign entity. **Clinical History**: A 58-year-old Vietnamese woman underwent a partial thyroidectomy followed by radioactive iodine 131 ablation for a "medullary thyroid cancer". Two months later, tissue samples failed to disclose a recurrence of the tumor. CT scan revealed a large thyroid mass with hemorrhage encroaching the trachea and bilateral pulmonary nodules consistent with metastasis. She underwent repeat neck exploration and hematoma evacuation. This surgical specimen had a benign appearing histiocytic proliferation with a high proliferative index (Ki-67 of 20%). A repeat review of the previous tissue sample showed a microscopic focus of thyroid follicles that merged imperceptibly into adjacent areas of foamy histiocytic proliferation. The final diagnosis was a poorly differentiated thyroid carcinoma. Although the patient was treated with chemotherapy concurrent with radiation, she rapidly deteriorated and succumbed to her illness. **Summary**: To our knowledge, this report represents a rare case of an aggressive poorly differentiated thyroid carcinoma variant mimicking a benign histiocytic proliferation. **Conclusion**: A malignant tumor mimicking a benign tissue has grave implications for patient care. Careful review of tissue samples and appropriate use of biomarkers to achieve accurate diagnosis is paramount to providing best oncologic care.

Keywords: Thyroid; Carcinoma; Histiocytic proliferation; Tumor marker; Immunohistochemistry

Introduction

The incidence of thyroid cancer has steadily increased over the past several decades [1,2]. Cancers of the thyroid gland are heterogeneous with indolent and aggressive subtypes. Well differentiated thyroid cancers have an overall 5-year survival of 95%, while patients with anaplastic thyroid cancers far much worse [3]. As such, the surgical and medical management varies widely depending on the histopathologic subtype. Although the stage of detection influences patient survival4, detection of thyroid cancer in early stages has been shown to significantly reduce mortality, with reported 5 year-survival rates approaching 100% if detected in early stages as compared to 59% if discovered in an advanced stage. Therefore, both accurate and timely tissue diagnosis is paramount for appropriate clinical management of thyroid cancer [4].

Fine-needle aspiration (FNA) is the most common initial modality used in the evaluation of a thyroid mass for cancer with reported sensitivity and specificity of 83% and 92%, respectively [5]. It is the most cost-effective method for tissue diagnosis [6]. However, it has been estimated that more than 30% of FNA results are indeterminate because of inadequate tissue sampling, limitations in cytology and the wide range of variability in interpretation amongst pathologists [7,8]. Although most thyroid growths are benign, these patients often require diagnostic thyroid surgery. To improve the diagnostic yield in patients with indeterminate results, techniques such as elastosonography, core needle biopsy and molecular biomarkers have emerged as adjunctive diagnostic technologies [9-11].

Clinical History

A 58-year-old Vietnamese woman, who was evaluated for neck swelling and hoarseness was diagnosed with medullary thyroid cancer after a partial thyroidectomy in Vietnam. The patient had no known past medical or surgical history, no family history of thyroid cancer and no known prior radiation exposure. The neck swelling persisted postoperatively and she received adjuvant radioactive iodine-131 treatment. Upon returning to the US two months after her surgery, she experienced rapidly enlarging neck swelling (Figure 1a and 1b) with airway obstruction requiring multiple immediate explorations with hematoma evacuations.

The initial histopathological analysis was a postoperative histocytic proliferation of uncertain significance, probably reactive. Immunohistochemical stains showed Ki67 of 5%, CD45 positivity in scattered lymphocytes, CD10 cytoplasmic positivity and CD38 positivity in foamy histocytic cells. However, the histiocytic cells were not immunoreactive for Calcitonin, CDX2, CEA-M, Chromogranin, CK19, Pankeratin, S100, Thyroglobulin and TTF-1. At this time, surgical specimen analysis failed to disclose evidence of a thyroid cancer. The histopathology of the tissue obtained in evacuations showed a poorly differentiated malignant neoplasm owing to the presence of neoplasm having an organoid pattern with fine fibrovascular stroma and numerous blood vessels in the intervening area. The cells have eccentrically placed irregular rounded to oval nuclei and eosinophilic cytoplasmic staining. The neoplasm had 10 mitosis per 10 hpf. The Ki67 has a high proliferation rate of 80%. The neoplasm was strongly positive for vimentin while PAX8 was weakly positive. Other immunohistochemical stains (Pankeratin, Chromogranin, Synaptophysin, CDX2, S100, CD68, Desmin, Calcitonin, CEA-M, NSE and Progesterone) were all negative. Alveolar soft part sarcoma was also considered but no TFE rearrangement seen in the tumor. As her condition worsens, she was transferred to our institution for a higher level of care. During this time, she was found to have numerous pulmonary metastases (Figure 1c). Tissue slides and blocks from her previous biopsies were obtained for a second review. The specimens showed diffuse histiocytic foamy cells in an organoid growth pattern representing a benign looking histiocytic proliferation (Figure 2a to 2c). Immunohistochemical stain, thyroglobulin, showed cytoplasmic positivity (Figure 2d), Ki-67 elicited a high proliferation index of 20% (Figure 2e), and p53with patchy nuclear positivity (Figure 2f). The remaining immunohistochemical tumor markers were negative (CD163, TTF-1, calcitonin, CEA, AE1/3, Chromogranin, Synaptophysin, CD56, S-100, Myo D, SOX10, GATA3, Inhibin). After a careful review of entire tumor morphology, a microscopic focus of thyroid follicles was present and it merged imperceptibly into the benign appearing adjacent foamy histiocytic proliferation (Figure 2d). All these features fit the Turin proposed criteria of a poorly differentiated thyroid carcinoma. Thereafter, the patient was started on paclitaxel concurrent with radiation; however, she continued to deteriorate rapidly and died from acute respiratory failure.

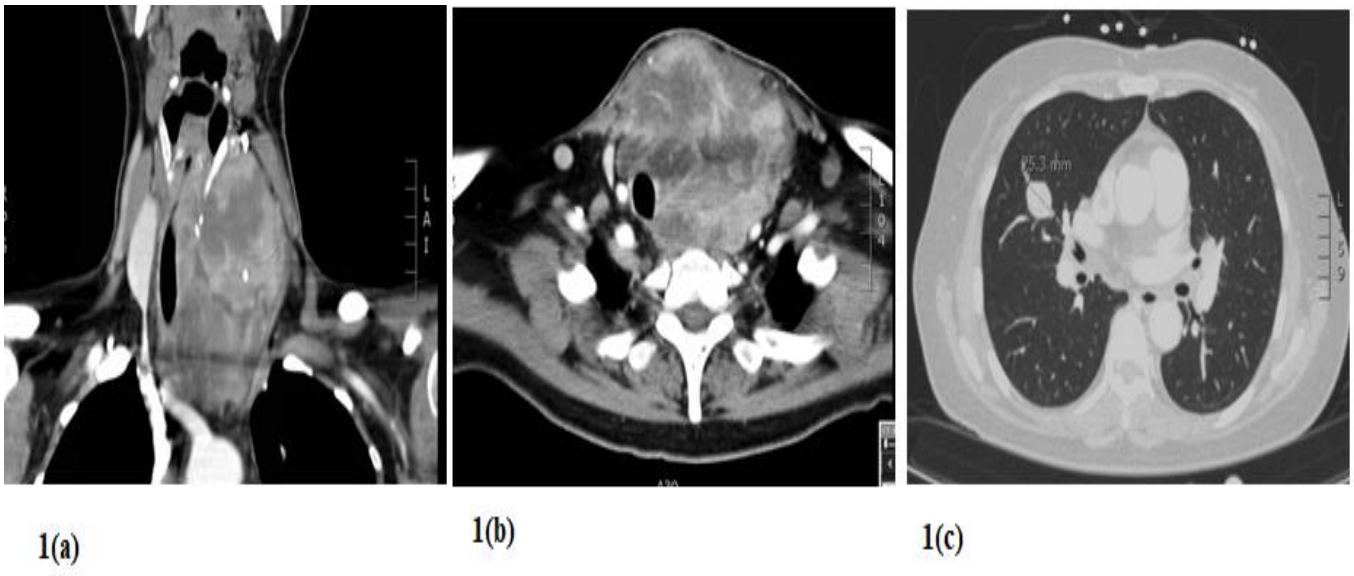

Figure 1: Neck CT scan showing a large thyroid mass present in the left side of the neck with hemorrhage encroaching the trachea and pushing it to the right side (A and B, arrows); contrast chest CT showing bilateral pulmonary nodules (C, arrows), consistent with lung metastasis.

Discussion

It is frequently challenging in the initial evaluation of FNA, core biopsy and excisional samples obtained from thyroid, because there is a potential for indeterminate or erroneous diagnoses as witnessed in our patient. It has been reported that in the initial cytological analysis of FNA of thyroid nodules, approximately 30% of aspirations are classified as indeterminate prompting an excisional surgical biopsy of specimens that are commonly benign. Furthermore, there is also a second-opinion diagnostic discordance ranging from 1.4 to 10.2% in reported series [19,20-22]. Conditions that may yield initial indeterminate diagnosis on conventional FNA samples of thyroid are solitary nodules, multinodular goiter [23,24], Hashimoto thyroiditis [25,26], cystic papillary carcinoma [27], and thyroid with calcification [28]. Thus, ultra-sound guided FNA procedure is superior to the conventional FNA to obtain diagnostic samples [29]. It also should be mentioned that the inherited errors in anatomic pathology together with quality improvement and assurance programs have been extensively discussed and reported in the literature [19-22,30,32-35].

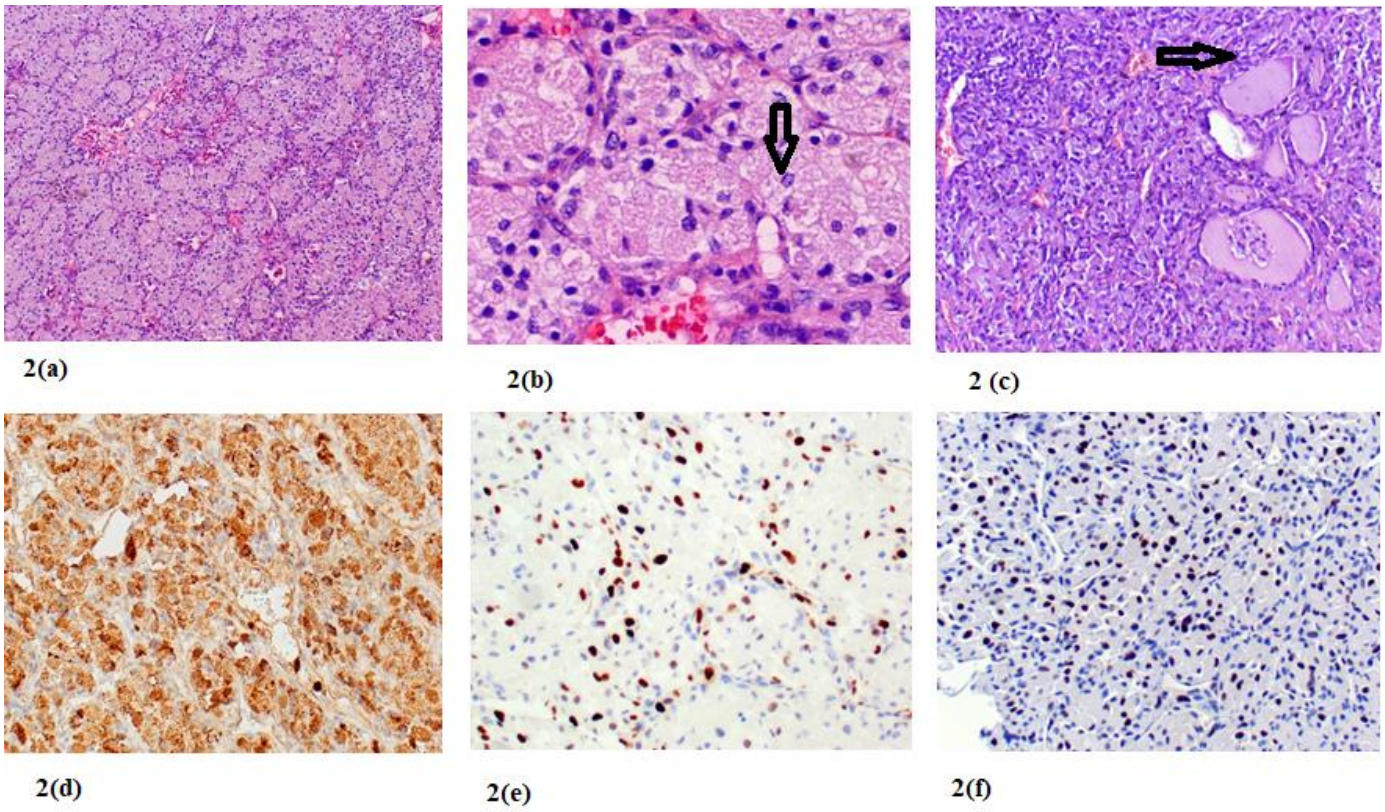

Figure 2: Low magnification of the tissue samples obtained from the neck mass showing a proliferation of benign appearing histiocytes in organoid pattern, intermingled with vascular channels (a); closer view showing those histiocytes with cytoplasmic vacoules (b, arrow); solid cellular areas of tumor composed of foamy cells with rare thyroid follicles remnant (c, arrow), indicating transformation of a poorly differentiated thyroid carcinoma. A panel of immunostains for tumor markers revealed cytoplasmic positivity for thyroglobulin (d); Ki-67 highlighted a tumor nuclear proliferation rate of 20% (e); p53 with patchy nuclear staining (f).

Aided by improved understanding of molecular mechanisms of thyroid carcinogenesis, numerous biomarkers have been developed in the evaluation of thyroid cancer [9-12]. Although histopathology provides most of the information used in thyroid cancer evaluation, including pTNM staging and morphological classification, biomarkers are being used more frequently as an adjunct to improve the diagnostic accuracy and prognostic capability of histopathology. Some specific tests being developed include those targeting nucleic acid mutations (CTTNB1, BRAF, RAS, PAX8/PPAR gamma, RET/PTC), microRNA profiles (miR-146b, 187, 221, 222, 197, 346, 138), genomic signatures and immunohistochemical protein biomarkers (HBME-1, Galectin-3, Cytokeratin19). There is significant research effort to develop these molecular tools for both diagnosis and treatment [10-18]. Although still in its infancy, molecular biomarker technology shows promise in guiding our physicians provide better oncologic care.

Because of the presence of benign appearing histiocytes in our initial surgical specimen, the diagnosis was missed resulting in a delay in appropriate treatment for this aggressive and lethal form of thyroid carcinoma. The error was ultimately recognized after a careful second review and use of molecular diagnostic adjuncts. A clue suggestive of malignancy in the reviewed sample was the elevated Ki-67 proliferative rate in the benign appearing histiocytes. A thorough review of the pathologic specimen also led to the identification of a small focus of malignant appearing tissue positive for thyroglobulin. Moreover, the need to repeat thyroglobulin stain on a different sample may assist in the interpretation of this particular neoplasm. Thus, it is critical to carefully review the entire specimen before ruling out a malignant disease.

Conclusion

To our knowledge, this report represents a rare case of aggressive thyroid carcinoma mimicking a benign histiocytic proliferation. To create a coordinated plan of care for patients afflicted with oncologic disorders, careful review of tissue samples and appropriate utility of biomarkers are important towards an accurate diagnosis.

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