

CASE REPORT

Thyroid regional metastasis from a giant cell malignant fibrous histiocytoma of the larynx in a patient with history of trichinellosis and tuberculosis

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Abstract

Sarcomas represent less than 1% of malignant laryngeal tumors and giant cell malignant fibrous histiocytoma is exceptionally rare. Diagnosis is histologically based and immunohistochemistry allows differentiation from other fibro-histiocytic neoplasms. We present the case of a 53-year-old male patient with positive medical history for trichinellosis and tuberculosis, and a laryngeal tumor invading the thyroid and causing respiratory distress by airway obstruction. Total laryngectomy and thyroidectomy were performed followed by thyroxine replacement therapy and radiotherapy. Histologically, the tumor consisted of spindle shaped cells with prominent mitoses, and abundant, osteoclast-like, multinucleated giant cells. Similar lesions were identified in the thyroid, adipose and muscular tissues. Parasitic elements were present in muscles. Tumoral cells showed positive immunostaining for Ki67 (40–50%) and vimentin and negative for AE1/AE3, CD31, S100 and myoglobin; the giant multinucleated cells were CD68-positive. Chronic infection might have had a pathogenic significance.

Keywords: giant cell malignant fibrous histiocytoma, larynx, thyroid, vimentin, CD68, trichinellosis, tuberculosis.

□ Introduction

Most of laryngeal malignancies originate from the laryngeal epithelium and affect the glottis. Glottic squamous cell carcinoma displays thyroid invasion in 23% of cases. Laryngeal tumors invading the thyroid gland also invade the cricothyroid membrane, anterior commissure, laryngeal ventricle and the thyroid cartilage, with an important impact on the patient's management [1].

Also, thyroid cancer may spread posteriorly, enhancing morbidity and mortality: it is estimated that overall, 15% of thyroid cancers exhibit extrathyroid spread [2], which warrants adjuvant radiotherapy and complicates airway management, especially in cases with anaplastic thyroid carcinoma, in which more than 70% of patients experience tumoral infiltration of the surrounding structures [3].

Age adjusted incidence rate of laryngeal cancer is 3.5 per 100 000 men and women per year, with an age adjusted death rate of 1.3 per 100 000 men and women per year (*U.S. National Cancer Institute*, <http://seer.cancer.gov/statfacts/html/laryn.html>).

Sarcomas represent less than 1% of malignant laryngeal tumors, are much more frequent in males, especially elderly, are most often situated in the vocal

cords, more definitely localized, and less likely to ulcerate and to infiltrate than squamous epithelial carcinoma. Accurate diagnosis depends on careful biopsy. Treatment consists of surgical excision followed by radiotherapy in cases with high grade lesions, positive surgical margins, tumor size greater than 5 cm or recurrent lesions; the effects of chemotherapy on laryngeal sarcomas has not been documented [4].

Survival at 5 years ranges from 50 to 77% [4, 5].

Malignant fibrous histiocytoma (MFH) is the most common soft tissue sarcoma in adults and consists of spindle shaped cells, histiocyte-like cells, polymorphic giant cells and inflammatory cells. There are several variants of MFH: myxoid, angiomyxoid, giant cell, inflammatory, common type (storiform pleomorphic) and skin atypical fibroxanthoma [6]. Approximately 15–20% of sarcomas occur within the neck and head [5]; most often MFH occurs in soft tissues of extremities and abdomen. Less than 50 cases with MFH of the larynx were reported [4, 7–9], two of them with giant cell variant [4, 9]. Less than 20 cases with primary thyroid MFH and several cases with metastatic thyroid MFH were also reported [10–13]. Here we report a case of giant cell MFH of the larynx with regional thyroid metastasis.

□ Patient, Methods and Results

We present the case of a 53-year-old male patient, referred to the Department of Endocrinology for goiter, weight loss (affirmatively 20 kg in the previous six months), fatigue, dyspnea lasting for one month, hoarseness and selective dysphagia, raising the clinical suspicion of compressive or infiltrative thyroid cancer. The patient was a smoker and an alcohol consumer and had a positive history for trichinellosis (20 years ago) and lung tuberculosis (10 years ago). Chest X-ray excluded active tuberculosis prior hospitalization.

Physical examination revealed underweight (body mass index 17 kg/m²), tachycardia, resting inspiratory dyspnea with stridor and a large, diffuse, painless goiter, with impalpable lower poles, firm texture, preserved movement during swallowing and absent regional lymph nodes.

Thyroid ultrasound revealed a 65 mL goiter with diffuse hypoechoic pattern and hyperchoic septae, resembling chronic thyroiditis, and an ill-defined hyperechoic region in the posterior part of the right lobe. No abnormalities were detected on abdominal ultrasound examination.

TSH was normal (2.26 mU/L) and also the routine laboratory screening except elevated ESR (35/63 mm), low blood glucose (75 mg/dL) and total cholesterol (138 mg/dL).

Laryngoscopy identified a violaceous, nonulcerated glottic tumor, extended subglottically and in the laryngeal vestibulum, with irregular-shaped surface; histologic examination of a tumoral fragment obtained by biopsy showed a proliferation of spindle shaped malignant cells invading the squamous epithelium.

The patients' condition aggravated, obstructive respiratory failure ensued, imposing emergency tracheotomy.

CT-scan was then performed, showing a 1.25/1.55/3.51 cm laryngeal mass infiltrating the right vocal cord and adjacent muscular and adipose tissues, with marked laryngeal narrowing (Figure 1), a large goiter extending to the cervicomediastinal junction, sequela lung tuberculosis, absence of distant lung, liver and spleen metastases and no regional lymph nodes greater than 1 cm.

Given the infiltrative features of the tumor, total laryngectomy and total thyroidectomy with lymph node dissection were performed under general anesthesia with endotracheal intubation, with pharyngeal suture, reposition of prelaryngeal muscular planes and skin sutures.



Figure 1 – CT-scan of the laryngeal MFH.

Specimens were fixed in 10% formalin, embedded in paraffin, sectioned, Hematoxylin-Eosin stained or processed by LSAB (HRP) (LSAB – Labeled Streptavidin Biotin; HRP – Horseradish Peroxidase) [14]. Monoclonal mouse antihuman antibodies (except for myoglobin-polyclonal) were used (DAKO Carpinteria CA) anti: cytokeratin (AE1/AE3 clone; citrate 5c; 1:50), vimentin (V9 clone; citrate 3c; 1:30), CD31 (JC 70A clone; Tris EDTA 5c; 1:20), CD68 (PG-M₁; citrate 7c; 1:100), Ki67 (MIB-1 clone; citrate 7c; 1:20) and also, without unmasking, S100 protein (1:500) and myoglobin (1:1000).

Histopathological examination revealed a malignant proliferation, consisting of spindle shaped cells, with prominent mitoses, abundant osteoclast-like multinucleated giant cells (Figure 2) and vascular tumoral emboli (Figure 3).

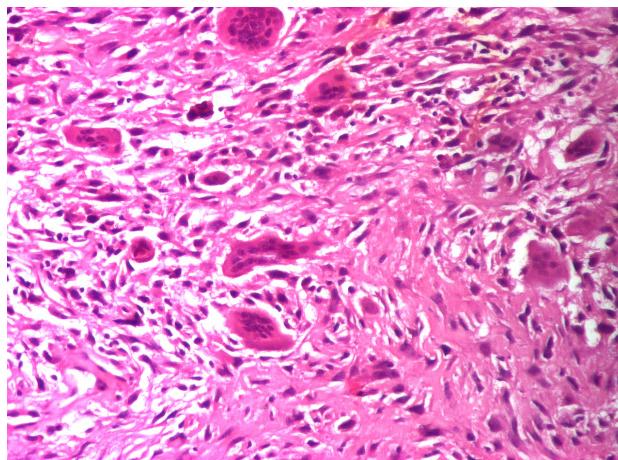


Figure 2 – Malignant proliferation consisting of spindle-shaped and multinucleated giant cells (HE stain, 100×).

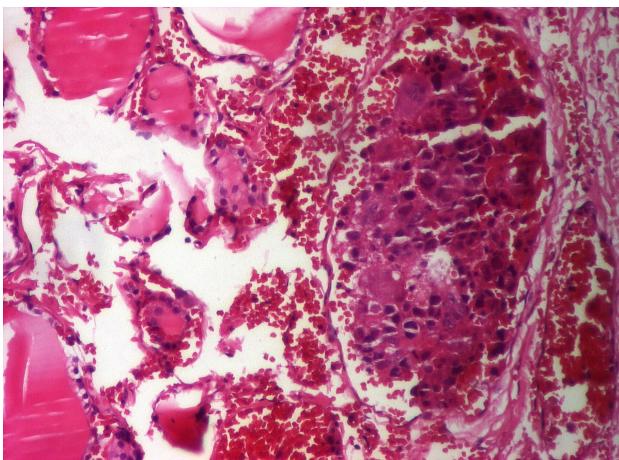


Figure 3 – Vascular emboli in tumoral vessels (HE stain, 100×).

Lesions with similar histologic pattern and inflammatory infiltrates were identified in the thyroid (Figure 4), adipose and skeletal muscular tissues (Figure 5). Parasitic elements (*Trichinella*) were identified in muscles (Figure 6). By immunohistochemistry, 40–50% of tumor cells were positive for Ki67 (Figure 7). Tumor cells were also vimentin-positive (Figure 8) and negative for AE1/AE3 (Figure 9), CD31, S100 and myoglobin. CD68 staining was present in the giant multinucleated cells and

histiocytes (Figure 10). Squamous epithelial cells were positive for AE1/AE3 (Figure 9), tumor vessels for CD31 (Figure 11), mesenchymal cells and nerve fibers for S100.

Histologic and immunohistochemical findings established the diagnosis of giant cell variant of malignant fibrous histiocytoma. After surgery, the patient was given L-Thyroxine replacement therapy and started radiotherapy.

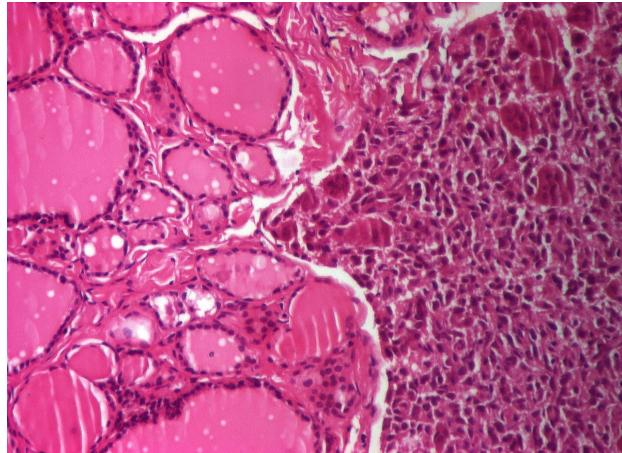


Figure 4 – Thyroid regional metastasis of laryngeal MPH (HE stain, 100×).

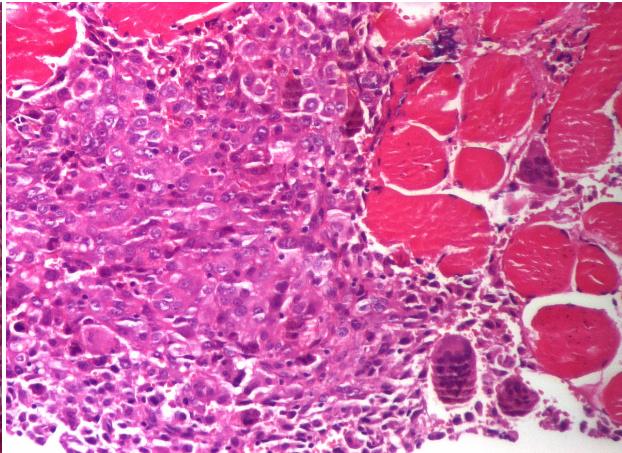


Figure 5 – Tumoral invasion in skeletal muscle (HE stain, 100×).

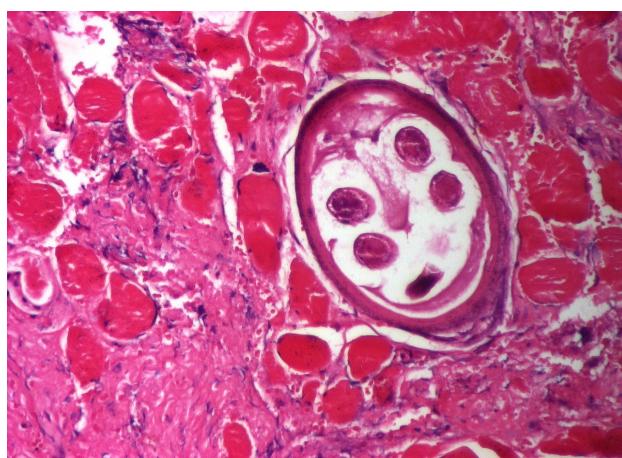


Figure 6 – *Trichinella spiralis* in muscular tissue (HE stain, 100×).

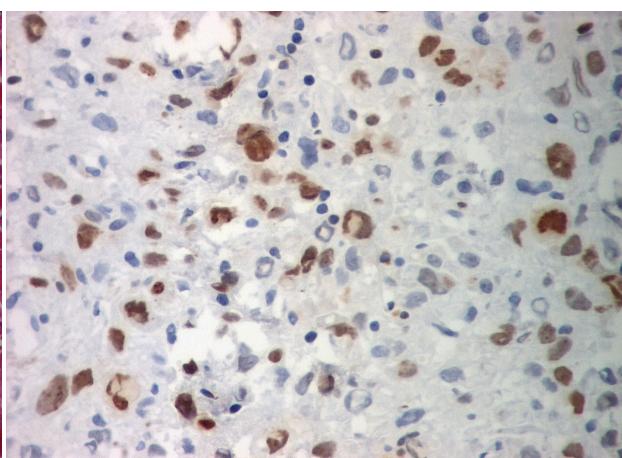


Figure 7 – Ki67-positivity in tumoral cells nuclei (IHC, 200×).

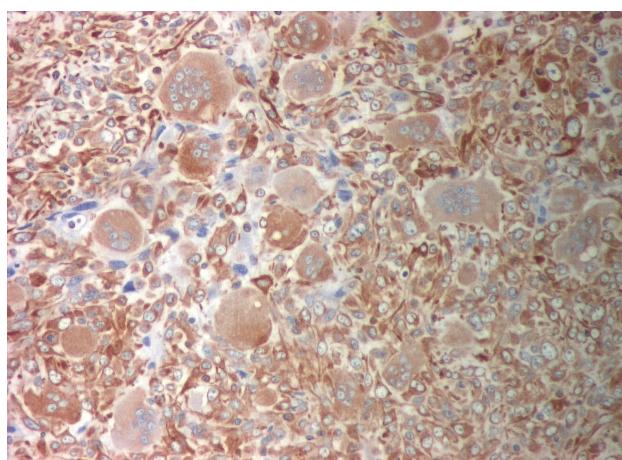


Figure 8 – Vimentin-positivity in tumoral cells (IHC, 100×).

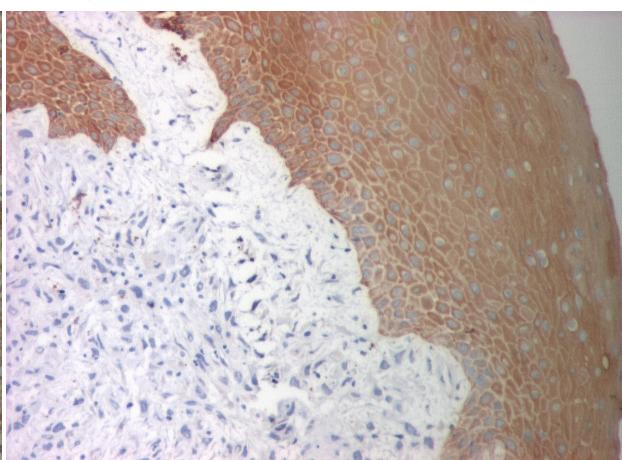


Figure 9 – AE1/AE3-negativity in tumoral cells; positive intern control in squamous epithelium (IHC, 100×).

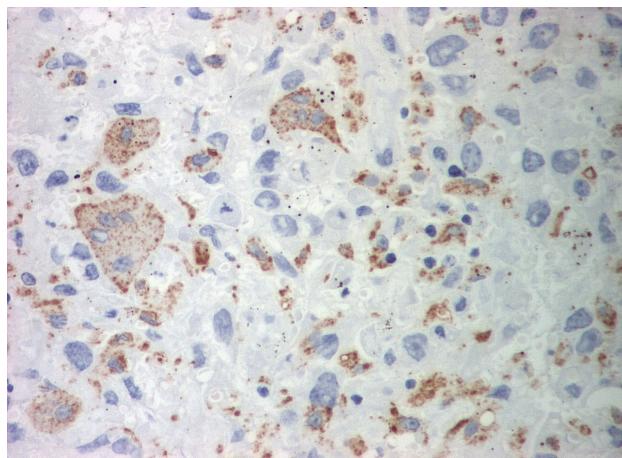


Figure 10 – CD68-positivity in histiocytes and multi-nucleated giant cells (IHC, 200×).

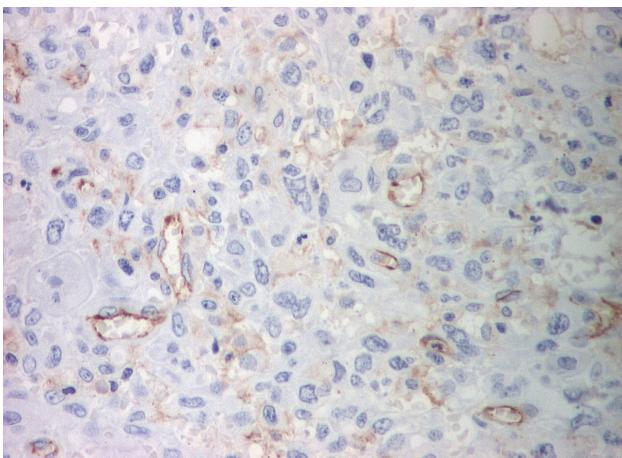


Figure 11 – CD31-positivity in tumoral vessels (IHC, 200×).

Discussion

Sarcomas are tumors of connective tissue comprising more than 100 distinct mesenchymal neoplasms with marked heterogeneity in structure and biological behavior. Mainly, sarcomas can be classified in soft tissue sarcomas and bone sarcomas. The most important prognostic variables are grade, size and location of the tumor. Surgical treatment alone is indicated in small, low-grade tumors with wide pathologically negative margins. Larger or higher-grade lesions must associate radiotherapy, which reduces the incidence of local recurrence but has no effect on overall survival. Chemotherapy may be used before or after surgery (doxorubicin, ifosfamide and gemcitabine alone or in combination with docetaxel) [15].

Soft tissue sarcomas may be benign, intermediate malignant or malignant and are classified according to their similarity to normal tissue; the current WHO classification include adipocytic, fibroblastic/myofibroblastic, smooth and skeletal muscle, pericytic and vascular, chondro-osseous tumors and tumors of uncertain differentiation (i.e. synovial sarcoma). Diagnosis is based on the study of Hematoxylin–Eosin sections, which represents the gold standard and immunohistochemical tests aimed to identify cell line differentiation or a typical antigen pattern [16].

MFH is now termed high-grade undifferentiated pleomorphic sarcoma [17]. No specific immunohistochemical marker exists for MFH, but immunohistochemistry can be used to differentiate MFH from other malignancies [18]. In the presented case, histological study confirmed giant cell MFH and immunohistochemistry confirmed the mesenchymal origin of the tumor (vimentin and CD68-positivity), allowed differentiation from a sarco-matoid carcinoma (AE1/AE3-negativity), malignant schwannoma and melanoma (S100-negativity), angiosarcoma (CD31-negativity), rhabdomyosarcoma (myoglobin-negativity); Ki67-positivity in 40–50% of tumor cells confirms malignancy and proves aggressiveness of the tumor.

It is considered that the development of sarcomas is unrelated to smoking and alcohol use (nevertheless, our patient was a smoker and an alcohol consumer)

and certain sarcomas are related to genetic syndromes (Li Fraumeni, neurofibromatosis) and irradiation [18].

Recently, major progresses were made concerning MFH pathogeny; it was shown that MFH is the only soft tissue sarcoma with a pattern of gene expression significantly associated to that of undifferentiated mesenchymal stem cells. This proves that human mesenchymal stem cells (hMSC) are the progenitors of MFH. Moreover, MFH cells overexpress DKK1, a secreted inhibitor of the Wnt developmental program, which stimulates proliferation of hMSC. WNT- β -catenin signaling mediates commitment of hMSC to differentiation and inhibition of WNT- β -catenin signaling results in MFH-transformation and morphology [19]. By the contrary, carcinogenesis (colorectal, breast, ovarian carcinomas and melanoma) is triggered by activating mutations in the WNT- β -catenin pathway. WNT-signaling mediates epithelial – mesenchymal transition, while WNT-pathway down-regulation mediates mesenchymal – epithelial transition [20]. In this context, the medical history of the patient (tuberculosis and trichinellosis) could be relevant for the occurrence of the tumor.

Several reports of trichinellosis and laryngeal cancer suggest that the chronic irritation of the larynx may have resulted in cancer [21–23]. Chronic trichinellosis elicits connective tissue mast cell hyperplasia with production of cytokines and chemokines required for pathogen clearance [24]. A reduced cell mediated immune response is induced by chronic tuberculosis; suppression of cell mediated immunity along with proangiogenic cytokines (IL-6) and reduced apoptosis by release of macrophage inflammatory protein (MIP-1) that suppresses p53-activity provide the ideal environment for occurrence of serial mutation required for the development of malignant disease [25].

Proliferation and differentiation of tissue progenitor cells or adult stem cells is the main prerequisite for tissue homeostasis maintenance, and tissue injury or repair stimulates stem cell recruitment. Persistent states of chronic inflammation, infection and injury promote genomic instability leading to DNA-damage, oncogene activation or impaired function of a tumor suppressor gene and further malignancy. After establishment of

cancer, the development of an inflammatory micro-environment promotes tumor cell proliferation, tumoral angiogenesis, invasion and metastasis [26]. Understanding the complex pathways involved in cancer-related inflammation will provide new therapeutic perspectives. It is estimated that head and neck MFH develop local recurrence in 20–42% of cases (more common seen in MFH with 19p⁺ cytogenetic alteration), regional lymph involvement in up to 15% of cases and distant metastases in 25–35% of cases, especially in the case of a high-grade tumor or larger than 5 cm. Distant metastases (lung, liver, bone) are rare in the absence of regional metastases. In the presented case, lymph node involvement was absent, and even if regional thyroid metastasis was documented, no distant metastases were detected. After surgical treatment (total laryngectomy and thyroidectomy) radiotherapy was indicated because of the high grade of the tumor and positive surgical margins detected on histologic examination.

Conclusions

Giant cell malignant fibrous histiocytoma of the larynx is a very rare tumor originating from mesenchymal stem cells. Diagnosis is based on the histologic appearance and immunohistochemistry allows differentiation from other tumors with similar features. No current guidelines for laryngeal MPH exists because of lack of evidence-based data. Treatment of this aggressive tumor consists of surgical removal and adjuvant radiotherapy but further understanding of malignancy related inflammation will reveal the molecular basis and will provide new-targeted therapeutic options.

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