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Our experience in the treatment of Malignant Fibrous Hystiocytoma of the larynx: clinical diagnosis, therapeutic approach and review of literature

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Abstract: Hereditary spherocytosis (HS) and Chronic myelocytic leukemia (CML) are both life threatening hemotologic diseases. They are rarely seen to occur simultaneously in one individual patient. Here we demonstrate a case of HS associated with CML in this study. The patient is a young female, diagnosed with HS in 2005, and was given partial embolization of the splenic artery. She got significant remission after the procedure. In 2008, she was found abnormal in blood routine test, after bone marrow routine, chromosome and fusion gene tests, she was diagnosed with CML (chronic phase). She did not receive regular treatment until 3 months prior, and is currently being treated with Dasatimib. She achieved hematological remission, but had no significant improvement in chromosome and fusion gene figures. Due to her severe condition of hemolysis, a splenectomy or an allogeneic hematopoietic stem cell transplantation is considered.

Keywords: Malignant Fibrous Hystiocytoma (MFH), CO^2 Laser Cordectomy, Vocal Cord Cancer, Glottic sarcoma

1 Introduction

Malignant Fibrous Histiocytoma, MFH, is a primitive, often pleomorphic, soft tissue sarcoma characterized by fibrous tissue with fibroblasts, histiocytes and myofibroblasts [1-5]. It was first described by O'Brein and Stout in 1964, as a 'fibrous histiocytoma or fibrous xanthoma.' It is assumed that in fibrous histiocytoma, cells behave as phagocytes but also form connective tissue fibers; whereas in pure histiocytoma no fibers are formed [5]. In 1983, Enzinger and Weiss, described storiform-pleomorphic, myxoid, giant cells, inflammatory and angiomatoid variants [6,7].

Storiform-pleomorphic phenotype is the most frequent; few cases of low differentiation MFH can be distinguished in high-grade pleomorphic sarcoma, pleomorphic sarcoma with giant cells and inflammatory pleomorphic sarcoma [8].

MFH is the most common subtype of soft tissue sarcoma in adults, described in bone, viscera and skin [9-12], it remains a rare malignancy in the head and neck region (3-13% of all malignant lesions), and it occurs even more rarely in the larynx, 10-15% of these cases [13-15].

As all sarcomas, the development of MFH is unrelated to smoking and alcohol consumption. Some sarcomas are

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related to genetic syndromes such as Li Fraumeni, neurofibromatosis, or rarely Cutis Laxa [4,16].

MFH can be correlated to hereditary mutations of oncosuppressor genes or environmental mutagens exposure as commonly reported in bowel tumors [17,18]; it is one of the most common radiation-associated sarcomas, accounting for almost 50% of all cases occurring in both bone and soft tissue [19,20].

43 cases of MFH of the larynx have been described in literature since 1972. Rolander et al. studied a review of case reports of MHF: 8 cases in supraglottic region (2 of these of epiglottis, 4 of aryepiglottic fold, 1 of Morgagni ventricle, 1 not specified); 19 glottis region (17 of vocal cords, 1 of anterior commissura, 1 not specified); 8 in subglottis region; 6 in not specified region; 1 in hemilarynx and 1 case of transglottic cancer (vocal cord and Morgagni ventricle) (Table 1).

Surgery with en-block resection of tumor is the first treatment choice: 60% of patients may survive over 5 years, and 40% over 10 years [14,15,19]. Radiotherapy is given to patients with risk of recurrence, in non-surgical patients or in cases with metastasis [20-24].

Adjuvant or neoadjuvant chemotherapy is suggested when patients have high risk of recurrence [25-27]. The prognosis is related to tumor differentiation, vascular invasion, size (over 5 cm), metastasis [25-28].

Endothelial Progenitor Cells (EPCs) a promising target of cell based therapy, just used in several benign and malignant diseases, should be a possible innovative non surgical approach [29-37].

We present one case of a cord-commissural MFH of larynx, the first treated in microlaryncoscopy with CO^2 laser.

2 Case report

C.L., 84 year-old male, smoker for 50 years, was admitted to the Department of Otorhinolaryngology of the Second University of Naples in March 2009. He had had hoarseness for 8 months and there had been familial cases of tumors, such as lung adenocarcinoma. During fiberoptic laryngoscopy, we discovered a red-violaceous nodular lesion of the left vocal cord and of the anterior commissure, with hypomobility of the left vocal chord (Figure 1); there was no palpable cervical lymphadenopathy. CT-scan of the neck and thorax was performed, showing a laryngeal mass infiltrating the left vocal cord and the anterior commissural; no cervical lymph nodes and no metastases were found. Transoral endoscopic cordectomy of the left vocal cord and of anterior commissural was performed in microlaryngoscopy with CO_2 (IVd) (Figure 2).

The surgical specimen was sent for histological examination.

At microscopic evaluation, a lesion, was observed, mostly formed of spindle-shaped malignant cells arranged in a fascicular/storiform pattern of growth, with several highly pleomorphic elements, in the corion. Moreover, a significant number of osteoclast-like giant-cells, with hypercrhomatic and slightly atypical nuclei, were found. A focal collagen deposition, consisting of bundles of fibrillar eosinophilic material, was associated.

At the immunohistochemical exam, the lesion showed a strong and diffuse positivity to vimentin and mild reactivity for CD68, more prominently in the giant cells counterpart. Finally, a diagnosis of malignant fibrous histiocytoma (MFH) was made (Figure 3).

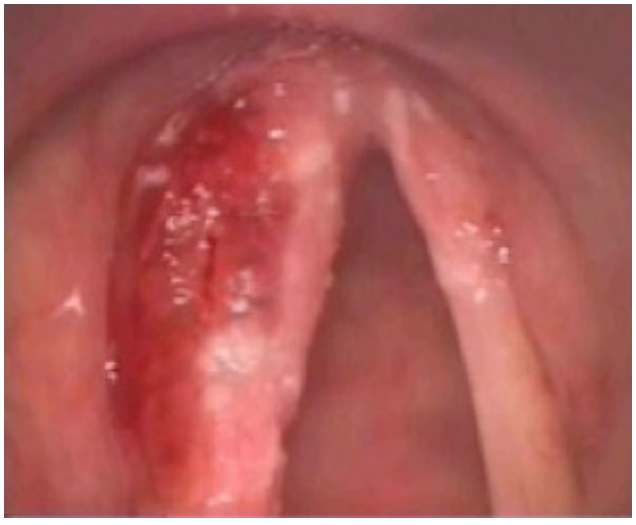

Figure 1: Fibrolaryngoscopy: red-violaceous nodular lesion of the left vocal cord and anterior commissure.

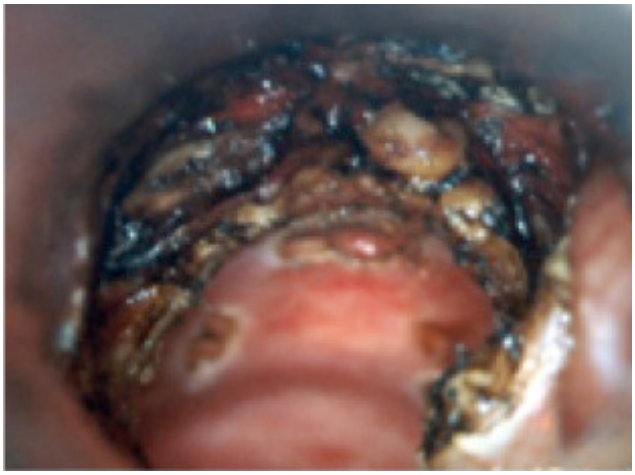

Figure 2: Microlaryngoscopic vision of the operative field after laser cordectomy.

Table 1: Clinical case review of MFH of the larynx.

Author	Year	Ages/Sex	Location	Treatment/Recurrence
Rolander et al.	1972	56/M	Epiglottis	Supraglottic laryngectomy, neck dissection/NER
Coyas et al.	1974	67/M	Vocal Cord	Tumor excision/Recurrence
Canalis et al.	1975	53/M	Vocal Cord	Piecemeal excision/Recurrence
Ribari et al.	1975	35/M	Subglottis	Tumor excision/Radiotherapy
Ferlito	1976	46/M	Larynx	Total Laryngectomy + Radiotherapy/Recurrence
Johnson and Poushtes	1977	67/F	Subglottis	Tumor excision/Recurrence
Ferlito	1978	58/M	Subglottis	Tumor excision/Recurrence
Ferlito	1979	68/M	Aryepiglottic fold	Total Laryngectomy /NER
Keenan et al.	1979	22/F	Subglottis	Tumor endoscopic excision/Recurrence
Setzen et al.	1979	ND	ND	ND
Setzen et al.	1979	ND	ND	ND
Ogura et al.	1980	22/F	Subglottis	Segmental cricotracheal resection/NER
Ogura et al.	1980	28/M	Subglottis	Partial cricotracheal resection/NER
Neblett and Coller	1891	22/F	Morgagni Ventricle	Partial Laryngectomy/NER
Bremer et al.	1982	45/M	ND	ND
Bremer et al.	1982	30/M	ND	ND
Yokoi et al.	1982	64/F	Vocal cord	Tumor excision /NER
Ferlito et al.	1983	67/M	Vocal cord	Total Laryngectomy + Radiotherapy/ Recurrence
Ferlito et al.	1983	51/M	Vocal cord	Total Laryngectomy /NER
Ferlito et al.	1983	63/M	Emilarynx	Laryngectomy and pharyngo esophagectomy /NER
Ferlito et al.	1983	8/F	Subglottis	ND
Radamass	1984	45/M	Vocal Cord	Total Laryngectomy/NER
Lobe and Katewkamp	1984	67/M	ND	Radiotherapy/NER
Volmer	1985	70/M	Vocal Cord	Tumor excision + Radiotherapy / NER
Volmer	1985	38/M	Vocal Cord	Tumor excision / NER
Godoy et al.	1986	26/F	Subglottis	Total Laryngectomy /NER
Barnes e Kanbour	1988	68/M	Vocal cord	Total Laryngectomy /NER
Masuda et al.	1989	80/M	Vocal cord	Tumor excision / NER
Saha et al.	1989	58/M	Epiglottide	Tracheotomy and Radiotherapy/ Recurrence
Majumder et al.	1989	45/M	Aryepiglottic fold Supraglottis	Total Laryngectomy + Radiotherapy/NER
Jordan and Soames	1989	54/M	Vocal cord	Tumor excision / Recurrence
Colev et al.	1989	57/M	Aryepiglottic fold	ND
Colev et al.	1989	64/M	Vocal cord	ND
Colev et al.	1989	75/M	Vocal cord	ND
Rosa et al.	1990	78/M	Vocal cord	Chordectomy/ Recurrence
Bernaldez et al.	1991	54/M	Vocal cord and Morgagni ventricle	Total Laryngectomy /NER
Weber et al.	1992	ND/M	Vocal cord	ND
Weber et al.	1992	ND/M	Plica ariepiglottica	ND
Harmoir et al.	1993	24/F	ND	ND
Kuwabara et al.	1993	46/M	Vocal cord	CO2 laser Tumor excision /NER
Pastore et al.	2001	32/M	Laryngeal Vestibule	Lateral Pharyngothiroidotomy, thyroid-hyoidpessia+radiotherapy/NER
Ortizbish et al.	2004	54/M	Vocal cord	Chordectomy with laryngofissure/ Recurrence
Ortizbish et al.	2004	67/M	Anterior Commissura	Tumor excision /NER
Anghelina et al.	2009	59/M	Vocal cord	Tumor excision /NER
Testa et al.	2015	84/M	Cord-commissural	CO2 laser Tumor excision /NER

At follow-up, laryngoscopy was performed every month for the first year after surgery and then every two months during the last three years. At the last follow-up examination, five year after surgery, the patient was asymptomatic and there was no recurrence of lesions.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

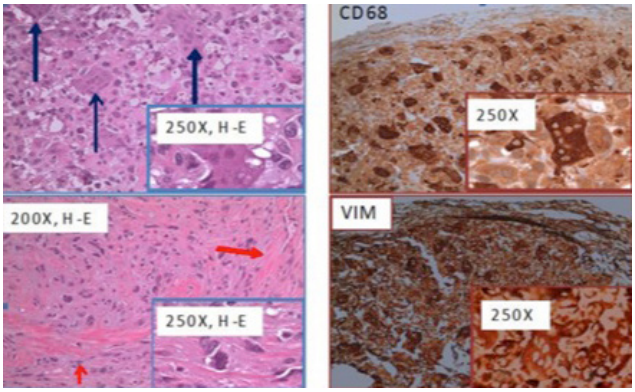

Figure 3: Microscopic evaluation showed a lesion mostly formed of spindle-shaped malignant cells arranged in a fascicular/storiform pattern of growth, with several highly pleomorphic elements, was observed in the corion. (green arrow). Moreover, a significant number of osteoclast-like giant-cells, with hyperchromatic and slightly atypical nuclei, were found (blue arrows). A focal collagen deposition, consisting of bundles of fibrillar eosinophilic material, was associated (red arrows). At the immunohistochemical exam, the lesion showed a strong and diffuse positivity to vimentin and a mild reactivity to CD68, more prominently in the giant cells counterpart. Finally, a diagnosis of malignant fibrous histiocytoma (MFH) was made.

3 Discussion

In 1964, O' Brein and Stout first defined MHF, in order to describe a histiocytic-like tumor with predominant fibroblasts [5]. MFH of the larynx is a rare disease, comprising approximately less than 2% of all head and neck tumors [19]. It is divided histologically into five variants: storiform-pleomorphic, myxoid, giant cells, inflammatory and angiomatous. Immunohistochemistry is needed to differentiate MFH from other malignant tumors such as sarcomatoid carcinoma (AE1/AE3-negativity), malignant shwannoma and melanoma (S100-negativity), angiosarcoma (CD3- negativity), rhabdomyosarcoma (myoglobin-negativity) [7].

The neoplastic cells of MFH are positive to vimentin and CD68 (histiocytic marker) and focally positive to S100 (neuroectodermic marker) and to smooth muscle actin (SMA) [7]. Age related incidence ranges from 4 to 84 (our patient) years; only one case occurring in a child (8 year-old female, 2,3% of all cases) [9], 8 cases (4 female and 4 male, 18,2% of all cases) [9] all between 20-30 years old. MFH is more common in male patients than in female (M:F, 4:1) [20]. Radiotherapy is given when patients have high risk of recurrence, in non-operated patients or in cases with metastasis; adjuvant or neoadjuvant chemotherapy is suggested when patients have high risk of recurrence [20-24]. The prognosis is related to tumor differentiation, vascular invasion, size (over 5 cm), resection margins, metastasis: 60% of the patients may survive over 5 years, and 40% of the patients may survive over 10 years [25-27].

Of the 43 cases of MFH of the larynx described since 1972 (Rolander et al.: 8 cases occurred in the supraglottic region (2 of these of epiglottis, 4 of aryepiglottic fold, 1 of Morgagni ventricle, 1 not specified); 19 in glottis region (17 of vocal cords, 1 of anterior commissura, 1 not specified); 8 in the subglottis region; 6 in unspecified regions; 1 in hemilarynx and 1 case of transglottic cancer (vocal cord and Morgagni ventricle) (Table 1). We have indicated treatments, recurrences and follow-ups in tab.1 [20]. Surgical intervention is the first choice of treatment and the majority of authors used demolitive surgical techniques: total, partial or supraglottic laryngectomy; traditional cordectomy, tumor excision, partial cricotracheal resection; in 1994 Kuwabara et al., described a glottic MFH (vocal cord) treated with CO^2 laser [22]. In our case CO^2 laser treatment wasn't associated to vocal cord lesion or paralysis [38].

In literature 8 Italian cases of MFH occurring in Italy were described from 1976 (Ferlito et al.) [23] to 2001 (Pastore et al.) [24], 7 male and 1 female, mean age 49.7 : 2 glottic cases, 2 supraglottic, 2 ipoglottic, 1 transglottic and 1 undetermined (Table 2) [20-22].

4 Conclusions

Our case represents the second case in literature of commissural MFH. Ortiz Bish et al. in 2004 described the first in 2004 [39], a 64 year old male who underwent traditional tumor excision and 6 months after surgery he did

Table 2: Italian cases of MFH of the larynx.

Author	Year	Ages/Sex	Location	Treatment/Recurrence	Subsequent Tratment
Ferlito	1976	46/M	NS	Total Laryngectomy/NER	Hypopharyngectomy+CT
Ferlito	1978	58/M	Hypoglottis	Tumor excision/Recurrence	Emilaringectomia e poi Laringectomia Totale
Ferlito	1979	68/M	Aryepiglottic fold	Total Laryngectomy/NER	
Ferlito et al.	1983	67/M	Vocal Cord	Total Laryngectomy + RT/Ricurrence	ND
Ferlito et al.	1983	51/M	Vocal Cord	Total Laryngectomy/NER	
Ferlito et al.	1983	63/M	Emilarynx	Laryngectomy and pharyngo esophagectomy /NER	-
Ferlito et al.	1983	8/F	Subglottis	ND	ND
Pastore et al.	2001	32/M	Laryngeal Vestibule	Lateral Pharyngothiroidotomy, thyroid-hyoidpessia+radiotherapy/NER	-
Testa et al.	2014	84/M	Cord-commissural	CO2 Laser/NER	

not present any recurrences [25-27]. We performed CO^2 laser tumor excision, the first time used in Italy for MFH of larynx.

Five years after surgery, without any adjuvant treatment, did not present any recurrence.

Malignant fibrous histiocytomas are a very rare mesenchymal neoplasm of the larynx. At present, no guidelines for laryngeal MFH exist because of lack of evidence-based data, the treatment of choice is surgical, in some cases associated with radiotherapy and chemotherapy. An innovative approach should be considered a cell based therapy using Endothelial Progenitor Cells (EPCs) [29-37]. EPCs pathogenic mechanisms involving in vascular and non vascular diseases includes several biomarkers and Ca^{2+} toolkit. [40-49].

We found 43 cases of MFH of the larynx, in literature the presented case is the second cord-commissural case described and the only commissural one treated with CO^2 laser surgery .

Conflict of interest statement: Authors state no conflict of interest.

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