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LARYNGOLOGY

Non-epithelial tumors of the larynx: case series of 12 years

Ozlem Saraydaroglu[1] · Selin Narter[1] · Mine Ozsen[2] · Hakan Coskun[3]

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Abstract

Purpose Laryngeal neoplasms are almost always epithelial in origin and squamous cell carcinoma is the most common tumor of the larynx. Non-epithelial tumors make a small subset of laryngeal neoplasms. We present the experience of a single institution to define clinical presentations and outcomes.

Materials and methods The pathology archives and clinical records of our center with the diagnosis of laryngeal tumors between the 2005 and 2018 were reviewed. Age, gender, symptoms, location of the tumor, histopathological diagnosis, treatment modality and disease status were discussed.

Results 657 patients were diagnosed with laryngeal tumor between 2005 and 2018 and 13 patients with non-epithelial tumors were identified. The majority of the patients were male. The age ranged between 13 and 93 years. The most common tumor localizations were vocal cords and subglottis. Seven patients were diagnosed with malignant tumors and six patients had benign tumors. Chondrosarcoma was the most common malignant mesenchymal tumor. Others were leiomyosarcoma, fibrosarcoma and liposarcoma. The most common benign non-epithelial tumors were schwannoma and hemangioma. Plexiform neurofibroma and granular cell tumor were the other benign tumors. Eleven patients underwent excisional biopsy. One patient underwent partial laryngectomy and one had total laryngectomy. Three cases presented with recurrent tumor. Among the recurrent cases, two were malignant tumors.

Conclusion Non-epithelial tumors of the larynx are rare and have a wide histological diversity. Immunohistochemical studies are of great importance in the diagnosis of these tumors. Primary mesenchymal tumors of the larynx should be kept in mind in differential diagnosis.

Keywords Head and neck · Larynx · Mesenchymal · Sarcoma

Introduction

Laryngeal neoplasms are almost always epithelial in origin and squamous cell carcinoma is the most common tumor of the larynx. These tumors develop from the squamous epithelium that lines the true vocal cords or from the metaplasia of the pseudostratified epithelium that are lining the areas outside the true vocal cords. Epithelial tumors might also develop from the minor salivary glands [1, 2]. Non-epithelial tumors make a small subset of laryngeal neoplasms and can arise from bone, cartilage, muscle, lipomatous, neuronal, connective tissue or blood and lymphatic vessels [2]. These tumors are rare and usually reported as case reports or small series.

Materials and methods

The pathology archives and clinical records of our institution with the diagnosis of laryngeal tumors between the 2005 and 2018 were reviewed and 13 patients were identified with non-epithelial laryngeal tumors. All the pathological materials of the cases were re-examined. Age, gender, symptoms, location of the tumor, histopathological diagnosis, treatment modality and disease status were discussed. The patients with the diagnosis of epithelial tumors were excluded.

✉ Ozlem Saraydaroglu
osaraydaroglu@uludag.edu.tr

[1] Department of Surgical Pathology, Faculty of Medicine, Uludag University, 16059 Gorukle, Bursa, Turkey

[2] Department of Surgical Pathology, Erzurum Regional Training and Research Hospital, 25240 Yakutiye, Erzurum, Turkey

[3] Department of Otorhinolaryngology, Faculty of Medicine, Uludag University, 16059 Gorukle, Bursa, Turkey

Results

657 patients were diagnosed with laryngeal tumor between 2005 and 2018 in our institution. When epithelial tumors were excluded, 13 patients with non-epithelial tumors were identified (Table 1).

The majority of the patients were male (11; 84.62%) and two cases were female. Twelve cases had tumors that presented in adulthood and one was a pediatric patient. The age ranged between 13 and 93 years (mean age 61.92 ± 18.91). The most frequent symptoms were dysphonia (five patients) and dysphagia (five patients). Other presenting symptoms were dyspnea and respiratory distress.

The most common tumor localizations were vocal cords (4; 30.77%) and subglottis (4; 30.77%). Vallecula, piriform sinus and aryepiglottic fold were among other tumor localizations. One patient had chronic obstructive pulmonary disease, one had chronic obstructive pulmonary disease and chronic lymphocytic leukemia and one patient was known to have neurofibromatosis type-1 (NF-1).

Seven patients were diagnosed with malignant tumors and six patients had benign tumors. Chondrosarcoma was the most common non-epithelial malignant tumor (three patients) and leiomyosarcoma followed it (two patients). Two of the cases of chondrosarcoma were grade 1 and one patient was diagnosed with grade 2 chondrosarcoma with a tumor showing hypercellularity and nuclear atypia (Fig. 1). Other malignant tumors were low-grade fibrosarcoma and well-differentiated liposarcoma. The most common benign non-epithelial tumors were schwannoma and hemangioma. Plexiform neurofibroma (Fig. 2) and granular cell tumor were the other benign tumors.

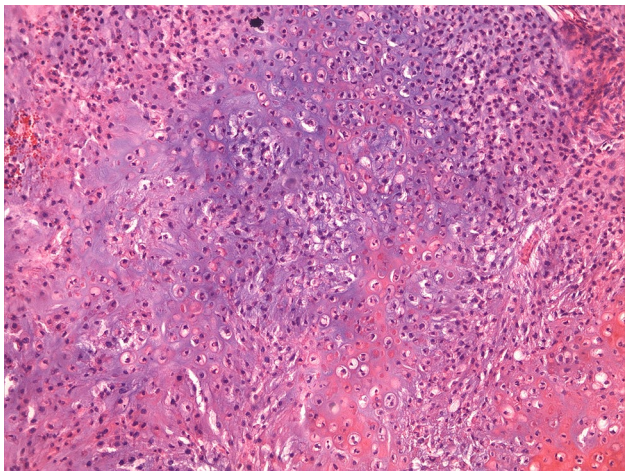

Fig. 1 Grade 2 chondrosarcoma characterized by hypercellularity and cells with hyperchromatic nucleus (H&E ×400)

Table 1 Patient demographics, treatment, pathological diagnosis and disease status of cases with non-epithelial tumors of the larynx

	Age/sex	Symptom	Tumor location	Pre-diagnosis	Treatment	Pathological diagnosis	Co-existing diseases	Status
1	70/M	Dysphagia	Vallecula	Malign tumor	Exc	Low-grade fibrosarcoma	–	NF
2	93/M	Dysphonia, dyspnea	Right subglottis	Malign tumor	Trach + Exc	Chondrosarcoma (grade 1)	–	NF
3	62/M	Dysphonia	Right vocal cord	Polyp	Exc	Schwannoma	–	NED
4	58/M	Dysphonia	Right vocal cord	Laryngocele	Exc	Granular cell tumor	–	NED
5	71/M	Respiratory distress	Subglottis-posterior cricoid	Malign tumor	Exc	Chondrosarcoma (grade 1)	COPD	NED
6	55/M	Dysphagia	Left piriform sinus	Malign tumor	Exc	Well-differentiated liposarcoma	–	Recurrence
7	58/M	Dysphagia	Left piriform sinus	Malign tumor	Exc	Hemangioma	–	NED
8	66/F	Dysphonia	Left vocal cord	Polyp	Exc	Leiomyosarcoma	–	NED
9	84/M	Respiratory distress	Right vocal cord	Malign tumor	Exc	Leiomyosarcoma	COPD + chronic lymphocytic leukemia	NF
10	13/M	Respiratory distress	Right aryepiglottic fold	Neurofibroma	PL	Plexiform neurofibroma	Neurofibromatosis type 1	Recurrence
11	48/M	Respiratory distress	Subglottis-trachea	Malign tumor	Exc	Schwannoma	–	NED
12	65/M	Dysphonia, dysphagia	Transglottic	Malign tumor	TL	Chondrosarcoma (grade 2)	–	Recurrence
13	62/F	Dysphagia	Subglottis	Malign tumor	Exc	Hemangioma	–	NED

M male, *F* female, *Exc* excision, *Trach* tracheotomy, *PL* partial laryngectomy, *TL* total laryngectomy, *COPD* chronic obstructive pulmonary disease, *NF* no follow-up, *NED* no evidence of disease

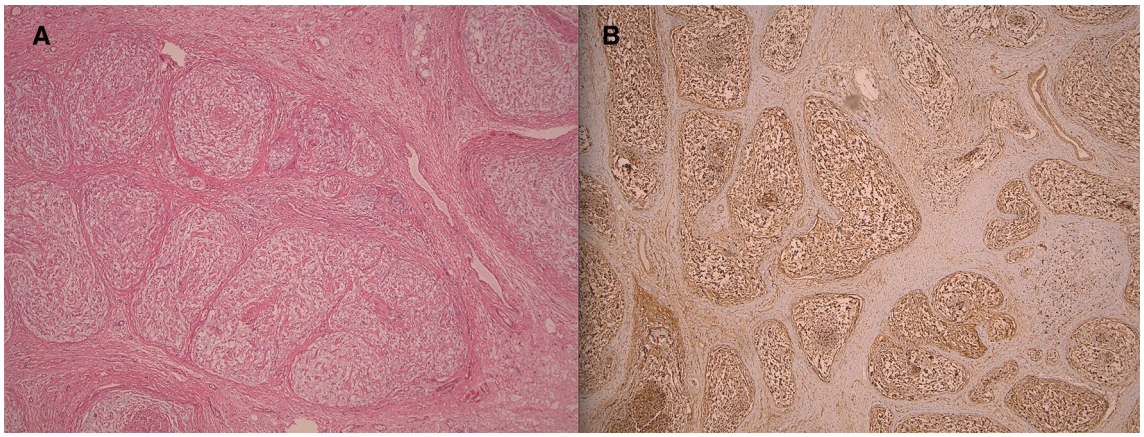

Fig. 2 **a** Spindle-shaped cells separated by collagen fibers and myxoid material confined within the epineurium of the involved nerve (H&E ×40). **b** Diffuse S-100 positivity of the tumor (DAB ×40)

Ten patients underwent endolaryngeal/open surgical excisional biopsy. One patient who was 93 years old and presented with dyspnea and dysphonia had emergency tracheotomy and excisional biopsy. One patient underwent partial laryngectomy and one had total laryngectomy.

Three cases presented with recurrent tumor. Among the recurrent cases, two were malignant tumors (chondrosarcoma grade 2 and well-differentiated liposarcoma) and one was the patient with NF-1 and had plexiform neurofibroma. Three cases were lost to follow-up. The other seven cases had no evidence of disease.

Discussion

Non-epithelial tumors of larynx are rare and constitute less than 1% of all primary laryngeal neoplasms [3, 4]. To date, a few case series have been reported from a small number of centers. In the literature, isolated case reports of laryngeal non-epithelial tumors are more frequently encountered. Malignant mesenchymal neoplasms of the larynx are more common than benign mesenchymal neoplasms [2]. In our series, 7 of 13 cases were malignant tumors (53.85%).

Chondrosarcomas are the most common mesenchymal tumor in the larynx [2, 4]. They constitute 0.007–2% of all laryngeal malignant neoplasms [5]. Chondrosarcomas are a member of soft tissue and bone sarcomas and are mesenchymal tumors that develop from transformed cells that produce cartilage matrix. They are usually seen in long bones, pelvis, and ribs but are rare in head and neck area [6]. Chondrosarcomas of the larynx are most frequently seen between 6th and 7th decades of life and have a male predominance. Our series includes 3 chondrosarcoma cases and they were 65-, 71- and 95-year-old male patients. Chondrosarcomas of the larynx mostly originate from cricoid cartilage; therefore, these tumors are commonly localized in the posterior lamina of cricoid cartilage [4, 7]. In our series, two of the cases arose from cricoid cartilage and were located in subglottis and one case had a right transglottic–paraglottic location. The final diagnosis is made by histopathological examination after surgical excision. Chondrosarcoma is histopathologically subdivided into three grades [4]. Our series includes two cases of grade 1 and one case of grade 2 chondrosarcomas in which pathological features were supported by radiological findings. Excisional biopsy was performed in two patients who had grade 1 chondrosarcoma and the patient with grade 2 chondrosarcoma underwent total laryngectomy. During the follow-up, recurrence was not observed in the cases with grade 1 chondrosarcoma. However, in the patient with grade 2 chondrosarcoma, tumor recurred after 5 months.

Our series includes two cases of leiomyosarcoma of the larynx. Leiomyosarcomas are rarely seen in head and neck region and they often involve paranasal sinuses, scalp and esophagus [8]. Laryngeal leiomyosarcomas are mostly seen in adults and there is a male predominance. They can occur at any part of the larynx, but supraglottic lesions are more frequently reported [9]. Our cases include one male and one female adult patient who had tumors on right and left vocal cord, respectively. The histopathological features and grading of smooth muscle tumors of the head and neck are similar to their soft tissue counterparts. Positive staining with smooth muscle markers are used in the diagnosis [10]. Our cases had positive immunohistochemical staining with smooth muscle actin (SMA), h-caldesmon, muscle-specific actin (MSA). Both cases were low-grade leiomyosarcomas and underwent excisional biopsy. One of the patients was lost to follow-up and the other is alive and well with no recurrence or metastasis.

Liposarcomas commonly occur in lower extremities and retroperitoneum. 5–9% of liposarcomas are seen in head and neck region and of those in the head and neck, 9% are located in the larynx [11]. Laryngeal liposarcomas are very rare and less than 40 cases have been reported so far. They are mostly seen in men and in the 4th–6th decades. The majority of laryngeal liposarcomas (75%) are supraglottic [12]. Our case is a 55-year-old male with a well-differentiated liposarcoma located in piriform sinus. Lipoblastic proliferation, pleomorphism and mitosis are taken into consideration for the histopathological evaluation. The differentiation of well-differentiated liposarcoma from lipoma is important and positive staining with MDM2 and CDK4 is suggestive of liposarcoma [13]. Liposarcomas have four histopathological subtypes: well-differentiated, myxoid/round cell, dedifferentiated and pleomorphic. Liposarcomas of the head and neck are usually low-grade tumors but they can behave locally aggressive and recur [12, 13]. Of the 37 laryngeal liposarcoma cases in the literature, 19 had recurred [12]. Our case had recurred 2 years after the first operation and 2 years after the second operation.

True fibrosarcomas located in the larynx are extremely rare and it must be supported by immunohistochemistry before the diagnosis is made. Ultrastructurally, fibrosarcomas consist of fibroblastic cells [14]. Fibrosarcoma is characterized by the fascicular pattern of highly cellular, spindle-shaped cells with oval nuclei. A pure fibrosarcoma is a marker negative tumor, except for Vimentin [15]. Differential diagnosis of fibrosarcoma must include laryngeal fibromatosis which might locally recur but does not metastasize. Wide local excision must be performed for primary and recurrent fibrosarcomas. If there is no clinical suspicion of metastasis, neck dissection is not necessary [14]. Our case of low-grade fibrosarcoma was a 70-year-old male patient who presented with dysphagia. The patient had a cystic mass located in vallecula and excisional biopsy was performed. Histopathological examination revealed a cellular tumor with spindle-shaped cells in a fascicular pattern. Tumor cells expressed vimentin positivity but lacked staining with cytokeratin, epithelial membrane antigen, SMA, desmin, myo-d1, CD34, CD68 and lysozyme.

In our series, among the seven cases of benign tumors, one case was a plexiform neurofibroma in a 13-year-old male patient with NF-1. Plexiform neurofibroma is rarely seen in larynx and often presents with obstructive airway symptoms. Most of the cases in the literature are pediatric patients with NF-1 syndrome. Plexiform neurofibromas are formed by the abnormal proliferation of ‘Schwann cell, neurons, fibroblastic cells and peripheral nerve cells. Plexiform neurofibromas are structurally similar to non-plexiform neurofibromas. They differ in their behavior as they widely spread around cranial nerves, the skin and the peripheral nerves of the gastro-intestinal system. Furthermore, they are unencapsulated, more invasive and hardly distinguished from surrounding tissue. Therefore, plexiform neurofibromas almost never be completely excised and recur after surgery [16, 17]. Characteristic histopathology and S-100 positivity is important for the diagnosis [18]. In our case, partial laryngectomy was performed but the tumor recurred after 6 years.

Schwannomas are benign peripheral nerve sheath tumors arising from Schwann cells [19]. Schwannomas of the head and neck are mostly seen in parapharyngeal region but rare in larynx. Laryngeal Schwannomas usually arise from the internal branch of superior laryngeal nerve. They are more common in women and present in the 4th or 5th decade of life [20]. Our series includes two Schwannoma cases, located in right vocal cord and subglottis. Both patients were male, and were 48 and 62 years old. Schwannomas are macroscopically well-defined, encapsulated, submucosal tumors. Histopathologically, cellular areas formed by palisading spindle cells (Anthony A) and poorly cellular, edematous areas (Anthony B) are typical. Tumor cells show positive reaction to S-100 protein. Surgical excision is the treatment of choice [19].

Laryngeal hemangiomas have adult and infantile forms. Unlike the infantile form, adult hemangiomas are very rare. Adult hemangiomas are more frequent in men and usually present with glottic or supraglottic masses [21]. Both of our cases are adults. One of the cases was a male patient and the other was female, they had tumors located in left piriform sinus and subglottis, respectively. Grossly, hemangiomas are red–purple exophytic submucosal masses. Hemangiomas have two subtypes: cavernous and capillary. Adult-form laryngeal hemangiomas are more often of cavernous type. Microlaryngoscopical excision is used for treatment [22]. One of our cases was cavernous and the other was capillary type, and were treated with endolaryngeal excision.

Granular cell tumors are benign neoplasms that are neuroectodermal in origin. These tumors are most frequently seen in head and neck region; however, less than 10% of the cases are reported in the larynx [23]. Macroscopically, they appear as pale, submucosal masses [24]. Histopathological examination reveals the proliferation of polygonal or elongated cells with small nucleus and eosinophilic granular cytoplasm. Mitosis is absent. Tumor cells show S-100 positivity and the lysosomes within the granular cells show periodic acid schiff staining [23, 25]. Squamous cell carcinoma should be considered in differential diagnosis of granular cell tumor. The absence of pleomorphism and mitosis in tumor cells and the detection of S-100 positivity is important in differentiating it from squamous cell carcinoma. The recurrence rates of granular cell tumor are low and local excision is the treatment of choice [26]. Our series includes one case of granular cell tumor which was located in right vocal cord and went to excision with the pre-diagnosis of laryngocele.

Conclusion

Epithelial neoplasms, especially squamous cell carcinoma represent the majority of laryngeal neoplasms. However, tumors of mesenchymal origin in the larynx are rare and have a wide histological diversity. In this study, we aimed to present mesenchymal tumors which are usually reported as case reports in the literature, with their clinical, histopathological features, treatment and prognosis. Immunohistochemical studies are of great importance in the diagnosis of these tumors. It should be kept in mind that primary non-epithelial tumors of the larynx exist and they should be considered in the differential diagnosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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