Granular cell tumors are rare and usually benign neoplasms that can occur in various parts of the body. We recently encountered three cases of granular cell tumor of the larynx; here, we present their clinicopathologic features, along with a review of reported Korean cases.

Granular cell tumors are rare and usually benign tumors that were first described by Abrikosoff in 1926 with the term myo-blastomas; these tumors are now accepted to be of neuronal origin. They can develop in any organ of the body, sometimes in multiple locations. The head and neck area is the most common region of granular cell tumor onset, accounting for approximately 30 to 50% of tumors. Laryngeal location accounts for 3 to 10% of tumors in adults, whereas it is extremely rare in children. Many small tumors of the upper breathing tract could be clinically considered in the differential diagnosis, including squamous cell carcinomas, papillomas, polyps, granulomas, cysts, neuromas, and neurofibromas. Here, we present the clinicopathologic findings of three new cases of laryngeal granular cell tumors, and suggest that smoking is a risk factor.

CASE REPORT

CASE 1

A 37-year-old male presented with hoarseness and foreign body sensation in his throat for 4 to 5 years. He had been a heavy smoker (2 packs per day) for 20 years. On endoscopic examination, a 3- to 4-mm-sized mass was present in the left true vocal cord (Fig. 1A).

Routine blood tests and chest radiography were unremarkable. The tumor was endoscopically resected using a carbon dioxide (CO\textsubscript{2}) laser. Histologically, the tumor was well circumscribed in the subepithelial area (Fig. 2A) and consisted of sheets of large rounded to polygonal cells with pale eosinophilic granular cytoplasm. The overlying epithelium was thin and unremarkable. Borders of tumor cells were characteristically indistinct, imparting a syncytial appearance. Nuclei were mildly hyperchromatic and pleomorphic. The intracytoplasmic granules were small and fine (Fig. 2B). Upon immunohistochemical study, the tumor cells were positive for both S-100 protein (Fig. 3A) and CD68 (Fig. 3B), but negative for desmin and p53.

Clinical and endoscopic examination has shown no evidence of recurrence in the 6 months following surgery.
CASE 2

A 63-year-old male visited the ENT clinic, complaining of voice change of 5-month duration. He had been a mild smoker (0.5 pack per day) for 40 years. On endoscopic examination, a 2-mm-sized mass was found in the right true vocal cord. Laboratory tests were unremarkable. Endoscopic removal of the tumor was performed with a carbon dioxide (CO\(_2\)) laser.

Histologically, the tumor was located in the subepithelial area and consisted of sheets of large polygonal or rounded cells with abundant, pale staining eosinophilic granular cytoplasm.

The patient has had no evidence of recurrence for 3 months after surgery.

CASE 3

A 45-year-old male came to the clinic with hoarseness and voice change for 7 months. He had been a heavy smoker (1.5 packs per day) for 30 years. A 4-mm-sized mass in the left arytenoid (Fig. 1B) was removed endoscopically. The histologic features of the tumor were those of a granular cell tumor. Tumor cells were positive for S-100 protein and CD68, but negative for p53 upon immunostaining. No evidence of recurrence was identified on endoscopic examination two months after surgery.

DISCUSSION

Granular cell tumors (GCT) were first described by Abrikossoff in 1926. He called them myoblastomas because he believed that the tumor was of skeletal muscle origin. However, the lesion more frequently arises in tissues other than muscle, and there is often a relationship between tumor cells and peripheral nerves. Based on microscopic and cytochemical staining techniques, Sobel and Marquet suggested a derivation from undifferentiated mesenchymal cells or Schwann cells. Currently, GCTs are regarded as a group of cytologically similar, but etiologically and clinically diverse tumors.

Half of all GCTs occur in the head and neck, with 33% of these occurring in the tongue. Tumors of the larynx are rare, accounting for only 3% to 10% of all reported cases of GCT. In Korea, seven individual GCT cases were previously reported. The ten Korean patients, including our cases, are nine...
males and one female, ages six to sixty-three (mean 37.1). The male preponderance and slightly older mean age differ from the epidemiology of laryngeal GCT reported in Western countries, where both sexes are equally affected at a mean age of 34 years. The etiology of laryngeal granular cell tumor is not established, and inflammatory, degenerative, regenerative and congenital etiologies have been proposed. Interestingly, all three of our patients were heavy smokers with over 20 pack years (mean: 35 pack years). Thus, we suspect that smoking may be a risk factor for GCTs of the larynx. We performed immunohistochemical staining for p53, one of the most commonly involved oncogenes in smoking-related head and neck cancers, but the results were negative. Among the seven previously reported cases in Korea, smoking history was revealed in only one case (18 pack years). Further investigation is therefore needed to explore the relationship between laryngeal GCT and smoking.

Clinically, the true vocal cords are the most common location for laryngeal GCT, but involvement of the arytenoids, anterior commissure, false vocal folds, subglottis and postcricoid has also been reported. The laryngeal symptoms depend on size and site of the lesion, and are most often dysphonia or chronic hoarseness. Rare symptoms include stridor, hemoptysis, dysphagia, otalgia, and dyspepsia, but these tumors may also be asymptomatic and discovered only during a routine physical examination. Grossly, they are firm, sessile, and small (less than 2 cm) lesions covered with intact mucosa. They are microscopically well-circumscribed, but not encapsulated, consisting of polyhedral cells with abundant pale-staining granular cytoplasm. Pseudoepitheliomatous hyperplasia of the overlying epithelium has been described in 50% to 65% of laryngeal GCT. Our cases did not show such findings, but this epithelial finding may lead to misdiagnosis as squamous cell carcinoma when a shallow biopsy is performed.

The procedure for laryngeal GCT removal also depends on the size and extension of the lesion. Local excision by microscopic laryngoscopy or endoscopy is performed for small tumors, whereas laryngofissure, partial laryngectomies, and irradiation are used for large tumors. Local excision results in the maintenance of normal structures, but the local tumor recurrence rate ranges from 2 to 8%. However, it is possible that some of these “recurrences” may actually be new primary lesions, because multiple lesions in various parts of the body occur in approximately 10% of patients.

Malignancy in granular cell tumor is very difficult to diagnose. The malignancy rate of laryngeal granular cell tumors has been reported to be 0.6%. Malignant tumors are typically larger (often over 4 cm), invasive, and grow rapidly. Metastases may occur in regional lymph nodes, lung, bones and other viscera. Metastasis to areas that are not ordinarily involved with multiple primary granular cell tumors is the only certain criterion for malignancy. In our three cases, there have been no recurrences; however, the follow-up periods only lasted 2 to 6 months. We strongly recommend long-term follow-up to detect recurrences and rare metastasis of laryngeal granular cell tumors, and to detect possible new primary head and neck cancers.

REFERENCES

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