Well-Differentiated Laryngeal/Hypopharyngeal Liposarcoma in the MDM2 Era Report of Three Cases and Literature Review

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Abstract Laryngeal/hypopharyngeal liposarcomas are very rare, fewer than 40 cases have been reported. These tumors are polypoid, with a male predisposition, and usually cause hoarseness and difficulty breathing. Their clinical course is characterized by multiple local recurrences. No distant metastasis has been reported, and dedifferentiation is extremely rare. In sum, the prognosis of these tumors is excellent; the 5-year survival rate is essentially 100 %. Pathologic diagnosis of these well-differentiated liposarcomas can be challenging. Many of them were initially diagnosed as benign lipoma, fibrovascular polyp, or “inflammatory polyp”. The correct diagnosis is usually made after multiple recurrences. On the other hand, the literature bears out that these incorrect diagnoses do not impact disease-specific survival. Here, we report three patients with laryngeal/hypopharyngeal well-differentiated liposarcomas; this is the first documentation of *MDM2* amplification in liposarcomas at this site.

Keywords Liposarcoma · Head and neck · Larynx · Pharynx

Introduction

As one of the most common sarcomas of the adult life, liposarcoma is rarely seen in larynx and hypopharynx, with only a few small case series and rare case reports in the

literature. Well-differentiated liposarcoma is by far the predominant subtype [1]. Previous reports showed that laryngeal/hypopharyngeal well-differentiated liposarcomas have the same histopathologic features as the soft tissue counterpart [2]. The diagnosis of soft tissue well-differentiated liposarcoma has been greatly facilitated by fluorescent in-situ hybridization (FISH) for *MDM2* gene [3]. *MDM2* amplification is considered both sensitive and specific for this neoplasm. Here, we report on three patients with laryngeal/hypopharyngeal liposarcoma, review clinical and pathologic features, and document *MDM2* amplification for the first time in tumors at this site.

Case Presentation

Case 1

This 34 year-old male presented with a 5-month history of progressive hoarseness and difficulty breathing. His past medical history was significant for having an “inflammatory fibroid polyp” of upper aerodigestive tract removed by simple excision 3 years prior. Physical examination at this presentation showed a 4 cm pedunculated polyp arising from the base of the left arytenoids. The polyp was removed via simple excision and a diagnosis of laryngeal “lipoma” was made. Thirty-two months after this procedure, a 20 cm polypoid mass developed at the same site, which again was removed by simple excision. At this time, a diagnosis of well-differentiated liposarcoma was rendered. It was noted that the tumor extended to the resection margin. The two prior tumors were reviewed and reclassified as well-differentiated liposarcoma. A fourth recurrence developed after 8 years (14 years after the index tumor) and a partial laryngopharyngectomy was performed. This tumor was diagnosed as well-differentiated liposarcoma.

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Case 2

This 70 year-old female presented with progressive dysphagia and difficulty breathing. Work-up showed two polypoid masses in the hypopharynx. The masses were removed by simple excision and diagnosed as benign lipomatous polyps. Two years later, she presented with dysphagia and a globus sensation. One polypoid mass was found by direct laryngoscopy and removed by simple excision. This was diagnosed as a lipoma of the right piriform sinus. A third recurrence developed after 11 years, causing dysphagia, hoarseness, sore throat and odynophagia. Again a polypoid mass was identified and removed by simple excision. A diagnosis of well-differentiated liposarcoma was rendered.

Case 3

This 56 year-old male presented with progressive difficulty breathing and swallowing. Workup showed a 4.5 cm hypopharyngeal mass arising from posterior arytenoids and the left piriform sinus. The mass completely occluded the postcricoid region and prolapsed into the glottic space. It was removed by simple excision. The postoperative course was uneventful at the 3 month's follow-up.

Histopathology

All resected tumors were described as polypoid, yellow, tan, and soft, ranging from 2 to 5 cm. The surface is smooth without ulceration or hemorrhage. The cut surface varies from soft yellow to white firm. No necrosis or hemorrhage was seen grossly.

Microscopically, the overlying squamous epithelium was unremarkable. The expansile tumors were composed of adipose tissue separated into variable sized lobules by bland fibrous septae (Fig. 1). Some tumors are composed of predominant fibrous tissue with only scattered small adipose lobules. Atypical spindle cells are usually readily visible at low power. These cells are found predominantly in the thin or thick fibrous septum within the adipose component, or adjacent to vessels. They have large pleomorphic nuclei with dark, smudgy chromatin. However, atypia can be subtle in some case and these cells are difficult to distinguish from atypical stromal cells in benign polyps (Fig. 2). Rare atypical lipocytes with hyperchromatic large nuclei were present within the adipose component (Fig. 3). Lipoblasts are found in one of these cases after careful search. Mitosis or necrosis is not found in any of these tumors.

There were no defined boundary between the tumor and normal tissue; all cases demonstrated atypical cells extend right up to overlying squamous epithelium. The tumors extend to the deep resection margin in the majority of cases.

Fig. 1 *Top* Polypoid well-differentiated liposarcoma in the laryngeal submucosa. *Bottom* Variable sized adipose lobules with cellular fibrous septae

In one case, skeletal muscle is present at the deep margin, which is infiltrated by bland fibrous tissue. As the tumor is composed also of bland fibroblastic cells, it is difficult to distinguish between infiltrating tumor cells and fibroblastic proliferation in response to adjacent mass (Fig. 4).

MDM2 Gene Status

MDM2 protein over-expression was examined by immunohistochemical stain using MDM2 antibody (Novacastra Laboratories, UK). Paraffin-embedded blocks were available for two patients. Immunohistochemical stain was performed on unstained slides. Both cases showed MDM2 over-expression. One of the cases showed diffuse strong positivity in more than 70 % of the tumor cells (Fig. 5), the other case showed strong positivity in about 30 % of the tumor cells.

MDM2 gene status was examined by FISH for all three patients. For the two patients with available paraffin blocks, FISH analysis was performed on unstained slides using the dual color MDM2/CEN12 probes (XL MDM2, Metasystems, Germany) to detect *MDM2* amplification. The probes were simultaneously hybridized, and tissue selection was

Fig. 2 **a** Well-differentiated liposarcoma extends up to intact squamous mucosa. **b** Interface between fibroblastic and lipomatous components. **c, e** Atypical fibroblasts with large, pleomorphic nuclei

and dark, smudgy chromatin. **d, f** Atypical lipocytes and rare lipoblasts within the adipose component

Fig. 3 Atypical fibroblasts infiltrate the adjacent skeletal muscle at the deep margin

correlated with a serial section stained with hematoxylin and eosin. Both cases showed *MDM2* amplification, with *MDM2*/CEN12 ratio of 8.7 and 3.4, respectively (Fig. 6). As paraffin block was no longer available from the third patient, FISH was performed on the destained H&E slide. Unfortunately, FISH assay in this patient resulted in no signals and poorly defined fluorescent stained cells. Thus the *MDM2* gene status remains unknown.

Discussion

Laryngeal / hypopharyngeal liposarcomas are very rare, fewer than 40 cases have been reported in the literature [4–6]. It predominantly involves male patients. Patients of

Fig. 4 MDM2 immunostaining result in one liposarcoma. Diffuse strong nuclear positivity is seen

Fig. 6 Regurgitated polypoid well-differentiated laryngeal liposarcoma in a Caucasian male. The tumor grossly is a well-circumscribed polypoid fibrous mass. Courtesy of Dr. Mark Reed, Jackson, Mississippi

all age groups are affected, with majority of patients in their 5th decade of life. Clinical presentations usually include progressive difficulty breathing and swallowing of

Fig. 5 MDM2/CEP12 FISH assay in two liposarcomas (a, b one case, c, d another case). The white arrows are examples of normal complement of signals (MDM2-red signals and CEP12-green

signals). Cells with yellow arrows are examples of increased FISH signals, corresponding to MDM2 gene amplification

several weeks up to several years. The mass can be viewed by laryngoscopy as a polypoid pedunculated mass. Long polyps may be sausage-like and regurgitable (Fig. 5). The clinical course is typically characterized by multiple recurrences, with intervals from several months, up to 26 years. No distant metastasis has been reported for this low-grade sarcoma.

Despite multiple recurrences, these tumors remain low-grade in the vast majority of cases. Here, the two patients with multiple recurrences showed no grade-progression. However, dedifferentiation does rarely occur in these tumors. Wenig et al. reported such a case in a 77 year old male. Three years after simple resection of a well-differentiated liposarcoma of the right pyriform sinus, the tumor recurred as a dedifferentiated liposarcoma. The patient was disease-free at 6 years after total laryngectomy [3]. A second report on a 62-year-old female documented dedifferentiation in the third recurrence [7]. To date, there is no reported case of distant metastasis from a laryngeal or hypopharyngeal liposarcoma. The overall prognosis is very good, with 5-year survival up to 100 %.

Given the long indolent clinical course of this disease, conservative local excision with preservation of laryngeal function is a reasonable treatment plan. Patients will require long term follow up for recurrences after conservative local excision [1]. Total laryngectomy may become necessary only after multiple recurrences. Some authors suggested that postoperative radiation is beneficial, especially for tumors with inadequate surgical excision [8]. However, due to the rarity of this tumor, only a few patients received low-dose radiation after simple resection of the tumor [9]. There was no systemic study comparing the outcomes of patients with or without radiotherapy. The efficacy of radiotherapy is still not clear for this tumor.

There are some similarities between laryngeal/hypopharyngeal liposarcoma and retroperitoneal well-differentiated liposarcomas. They are both characterized by an indolent clinical course with multiple local recurrences. For both lesions, a clear surgical margin is difficult to achieve. It is essentially impossible to obtain a clear margin for retroperitoneal liposarcoma; while for laryngeal/hypopharyngeal tumors a clear margin can be achieved by total laryngectomy, but with the sacrifice of laryngeal function. Many retroperitoneal liposarcomas eventually undergo dedifferentiation and distant metastasis. The dedifferentiation is considered a time-dependent and location-independent phenomenon when there is a high likelihood of clinically persistent disease [4]. The two reports of dedifferentiation in laryngeal/hypopharyngeal liposarcomas are in keeping with this theory. Fortunately, this is so rare, that local conservative excision remains a reasonable first line treatment plan.

Grossly, laryngeal/hypopharyngeal liposarcomas are white/tan lobulated polypoid mass. Most of the tumors are less than 5 cm in the greatest dimension. Cut surface is usually homogenous white yellow without necrosis or hemorrhage. Microscopically, the tumor is composed of lobules of adipose tissue separated by thick fibrous band. Fibrous component can be the predominant component while some cases only show scattered small clusters of lipocytes embedded in fibrous tissue. Atypical spindle cells with large nuclei, dark smudgy chromatin are seen in both the fibrous and adipose components. These cells can be difficult to find in subtle cases. The overlying epithelium is typically uninvolved and intact without ulceration. A significant portion of cases were diagnosed as lipoma, lipomatous tumor, or other benign entity, as two of the cases in this study. Similar to its soft tissue counterpart, lipoblast is not always present and its presence is not necessary for making the diagnosis.

The differential diagnosis includes benign polyps including lipoma, fibrovascular polyp and other benign entities. As soft tissue liposarcoma, differentiation from lipoma can be very difficult. Cytologic atypia of a well-differentiated liposarcoma can be subtle. In addition, polypoid benign masses at this location are subject to constant trauma. Secondary changes such as hemorrhage, calcification, fat necrosis and infarction are common. Metaplastic bone and cartilage may be seen in benign tumors [10]. According to literature, the vast majority of lipomatous tumors in the larynx and hypopharynx are benign. As a consequence, a significant number of the reported cases, as well as two of the cases in this study, were initially diagnosed as benign lipoma. The malignant nature of this tumor was revealed only after multiple recurrences.

Detecting *MDM2* amplification by FISH is a sensitive and specific method for distinguishing well-differentiated liposarcoma from benign lipoma. Although our results are not surprising, this is the first documentation of *MDM2* amplification in laryngeal/hypopharyngeal liposarcomas. This justifies abandoning former terminologies (e.g atypical lipomatous tumor, giant laryngeal atypical lipomatous tumor). *MDM2* amplification, plus the potential for multiple recurrences, provides the strong support that these tumors should be best classified as well-differentiated liposarcomas. On the other hand, lack of grade-progression or morbidity with recurrences support a conservative surgical approach. As its soft tissue counterpart, *MDM2* amplification can be very helpful in establishing the diagnosis in this anatomic location.

Compliance with Ethical Standards

Conflicts of interest None.

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