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Authors
Mahmood, Usama
Nguyen, John D
Chang, John
et al.

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Authors: Mahmood, Usama[1]
Nguyen, John D.[2]
Chang, John[3]
Gu, Mae[4]
Wong, Brian J. F.[3,5] *bjwong@uci.edu*

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Abstract: Although liposarcoma is the second most common soft-tissue sarcoma in adults, it is exceedingly rare in the head and neck. According to our MEDLINE search, only 11 cases of liposarcoma of the parotid gland have been reported since 1968. We report a new case of primary atypical lipomatous tumor/well-differentiated liposarcoma of the parotid gland in a 77-year-old man. Because only a very limited number of case reports and small series have been published on liposarcoma in the head and neck, we also provide a review of the literature on this uncommon disease entity. [ABSTRACT FROM AUTHOR]

Author Affiliations: [1]Department of Radiation Oncology, University of Maryland, Baltimore
[2]Department of Otolaryngology-Head and Neck Surgery, Keck School of Medicine, University of Southern California, Los Angeles
[3]Department of Otolaryngology-Head and Neck Surgery, School of Medicine, University of California Irvine
[4]Department of Pathology, School of Medicine, University of California Irvine
[5]Beckman Laser Institute, University of California Irvine, 1002 Health Sciences Rd., E, Irvine, CA 92612

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Introduction

Although liposarcoma is the second most common soft-tissue sarcoma in adults, it is exceedingly rare in the head and neck. According to our MEDLINE search, only 11 cases of liposarcoma of the parotid gland have been reported since 1968. We report a new case of primary atypical lipomatous tumor/well-differentiated liposarcoma of the parotid gland in a 77-year-old man. Because only a very limited number of case reports and small series have been published on liposarcoma in the head and neck, we also provide a review of the literature on this uncommon disease entity.

Liposarcoma is the second most common soft-tissue sarcoma in adults, but it is exceedingly rare in the head and neck.(n1) The more common head and neck sarcomas are malignant fibrous histiocytoma (29% of cases), undifferentiated sarcoma (16%), malignant peripheral nerve sheath tumor (16%), leiomyosarcoma (9%), fibrosarcoma (8%), and synovial sarcoma (7%); liposarcoma accounts for only 1 to 2% of soft-tissue tumors in this region.(n2)

According to our MEDLINE search, only approximately 200 cases of liposarcoma in the head and neck have been reported in the world literature since 1968, and only 11 of these tumors occurred in the parotid gland. We report a new case of primary atypical lipomatous tumor/well-differentiated liposarcoma of the parotid gland.

Case report

A 77-year-old white man presented to the Department of Otolaryngology-Head and Neck Surgery at the University of California Irvine Medical Center with an asymptomatic mass that had gradually enlarged over the area of the left parotid gland during the preceding 2 years. The patient denied a history of smoking, alcohol abuse, and radiation exposure. Physical examination revealed a rubbery, nontender, mobile mass 3.5 cm in diameter over the left mandibular angle. The overlying skin was normal. Facial nerve function was symmetrical bilaterally, and findings on the remaining head and neck examination were normal.

Magnetic resonance imaging (MRI) demonstrated a homogeneous, well-circumscribed mass just lateral to the left parotid gland; no fat plane was seen between the mass and the gland. On T1- and T2-weighted imaging, the mass demonstrated low and high signal intensity, respectively. T1-weighted imaging with gadolinium contrast showed homogeneous and bright enhancement (figure 1). There were no flow voids, although an incidental right parotid salivary cyst was noted. Findings on fine-needle aspiration analysis were nondiagnostic.

At surgery, a distinct tissue plane separated the mass from the superficial lobe of the parotid. A simple wide local excision was performed. The outer surface of the mass, which measured 3.5 x 3 x 2 cm, was smooth and pink (figure 2). Sectioning of the mass revealed a homogeneous gray-pink and myxoid cut surface. Findings on histologic examination with permanent sections were consistent with an atypical lipomatous tumor/well-differentiated liposarcoma with myxoid and sclerosing features (figure 3).

The patient's postoperative course was uneventful. Thereafter, he was lost to follow-up.

Discussion

Epidemiology. Liposarcomas account for 10 to 15% of all adult sarcomas,(n1) and they affect nearly twice as many men as women (65 to 35%).(n3, n4) Overall, their incidence is highest among 40- to 60-year-olds,

although the myxoid variant occurs in a slightly younger age group: 30- through 50-year-olds.(n3, n5, n6) These tumors are rare in infants and young children.

Most cases occur in patients with no known risk factors. Liposarcoma attributable to radiation is infrequent.(n5) The demographic characteristics of head and neck liposarcomas, including age and sex distributions, are similar to those of liposarcomas overall.

Pathology/histology. Liposarcomas arise from primitive mesenchymal cells.(n7) They do not arise from mature fat cells; indeed, they are quite uncommon in the subcutaneous fat and submucosa or subserosa of the intestinal tract, which are the most common sites of lipomas. Instead, liposarcomas often arise in deeper soft-tissue spaces, especially in intermuscular fascial planes or large connective spaces such as along vessels and nerves.(n4) As a result, liposarcomas are frequently oval-shaped secondary to compression by surrounding muscle tissue.(n8) Predictably, lipomas and lipomatoses are not believed to increase the risk of liposarcoma.(n5, n7, n9)

The constitutive cells in adipose tissue are prolipoblasts, lipoblasts, preadipocytes, and adipocytes. These four cell lines give rise to the four major histologic categories of liposarcoma: (1) round-cell liposarcomas (from lipoblasts), (2) myxoid liposarcomas (from preadipocytes), (3) atypical lipomatous tumors/well-differentiated liposarcomas (from adipocytes), and (4) pleomorphic liposarcomas (from all four cell types).(n7) Most studies have found the myxoid variety is the most common in the head and neck, representing approximately 50% of cases; following in descending order are the atypical lipomatous tumors/well-differentiated liposarcomas, the round-cell liposarcomas, and the pleomorphic liposarcomas.(n5, n9, n10) Five to 10% of cases involve mixed tumors.(n5)

The behavior of liposarcomas depends on the cell type and the degree of cell differentiation. The grade of malignancy is believed to increase as the pleomorphism, cellularity, and number of abnormal mitoses increase and the relative intracytoplasmic fat globule content and differentiation decrease.(n7) As is the case at other sites, the pleomorphic and round-cell variants of liposarcoma in the head and neck are notable for a higher local recurrence rate, a higher incidence of metastasis, and a lower 5-year survival rate than are the well-differentiated and myxoid subtypes.(n1-n3)

In 1979, Evans et al proposed that tumors in superficial tissues that are histologically consistent with well-differentiated liposarcomas be referred to as atypical lipomas. (n11) This proposal was based on the fact that compared with deep-seated lesions, superficial lesions tend to recur locally and rarely metastasize, and therefore they are associated with lower mortality. Both superficial and deep tumors are characterized by the presence of specific karyotypic changes. These include findings such as a supernumerary ring and giant chromosomes, in which sequences from the 12q14-15 chromosome region are amplified and, as described more recently, amplification of chromosome 1 sequences.(n12)

Grossly, most liposarcomas range in size from 5 to 10 cm, although some tumors have grown to massive proportions.(n5) Compared with lipomas, liposarcomas are firmer, less compressible, and more often fixed to surrounding tissue.(n8) Liposarcomas are typically well circumscribed or pseudoencapsulated, and they demonstrate a lobulated pattern.(n13) Lobules often become separated from the main tumor mass and give rise to satellite nodules.(n14) Their cross-sectional appearance is determined by the relative presence or absence of mucinous substance, lipids, and fibrosis.(n14) A high lipid content confers a more firm consistency and imparts a pale yellow to bright orange hue. Fibrotic tumors, on the other hand, have a gray-white appearance. Necrosis, hemorrhage, and cysts are more commonly associated with less-well-differentiated liposarcomas.(n5)

Sarcomas as a group account for only 1% of all head and neck neoplasms.(n15) Naturally, the differential diagnosis of liposarcoma includes a number of soft-tissue tumors of the head and neck, including malignant fibrous histiocytoma, embryonal rhabdomyosarcoma, malignant peripheral nerve sheath tumor, and

leiomyosarcoma.(n2, n8, n16) A major diagnostic challenge is to distinguish lipoblasts, which are characteristic of liposarcomas, from vacuolated cells, which are present in a number of mesenchymal and epithelial neoplasms. In general, vacuolated cells contain rounded vacuoles with irregular borders; in contrast, liposarcoma cells feature scalloped and indented nuclei. Moreover, liposarcoma cells can be confused with cells that have large amounts of mucin or glycogen. Staining for the presence of intracellular lipids will aid in the diagnosis of liposarcoma, as will ruling out the presence of other intracellular materials such as mucin or glycogen.(n5) Finally, one must realize that the peripheral portions of malignant tumors that have invaded adipose tissue or that have undergone vacuolar degeneration may mimic the histologic appearance of a liposarcoma.

Clinical presentation. The two most common sites affected by liposarcoma are the retroperitoneum and the extremities; head and neck cases constitute only 5.6% of all liposarcomas.(n3) In the head and neck region, most cases involve the neck, followed by the face and scalp.(n2, n5) In a review of 76 cases of head and neck liposarcoma, Golledge et al found involvement of the neck in 28%, the head (scalp and face) in 26%, the larynx in 20%, the pharynx in 18%, and the mouth in 8%.(n2) In the head alone, McCulloch et al reported the following distribution: the face in 43%, the dura in 20%, the orbit in 20%, the ear/mastoid in 7%, the mandible in 7%, and the parotid area in 3%.(n3) The most common intraoral sites are the buccal mucosa and the floor of the mouth.(n7, n9, n13) Within the larynx, the supraglottis is the most common site (78% of all laryngeal liposarcomas).(n17, n18) More specifically, the pre-epiglottic space is the most likely site within the larynx to give rise to liposarcoma because this area is an interfascial connective tissue space that houses cells with totipotential mesenchymal cells. Within the pharynx, the most common site is the nasopharynx (56% of all pharyngeal liposarcomas).(n2)

In the body, liposarcomas typically manifest as solid, slowly growing, ill-defined masses that usually become quite large before patients seek medical attention. Patients with head and neck tumors typically present with similar findings (i.e., a solid, painless mass) and symptoms that have manifested only as a response to compression of adjacent structures. Zheng and Wang reported a series of 10 patients with liposarcoma in the oral and maxillofacial area in which the tumors typically began as unremarkable, slowly growing, painless masses; the interval between tumor onset and a patient's clinical presentation ranged from 2 months to 2 years.(n9) Fanburg-Smith et al reported a much longer interval-a mean of 3.6 years-in their series of 18 cases of oral and salivary gland liposarcoma.(n13)

Patients typically seek medical treatment in response to the development of pain or an accelerated growth of the mass. Tenderness, firmness, and poorly delineated masses are often characteristic of more advanced cases. Regression to a more aggressive variant (dedifferentiation) may manifest as accelerated growth. Moreover, given the functionality of structures within the head and neck, involvement of specific anatomic sites often results in the onset of characteristic symptoms. For example, liposarcoma of the larynx or pharynx may produce dysphagia, globus pharyngeus, voice changes, respiratory infections, dyspnea, or airway obstruction.(n19) In a report of 10 cases of hypopharyngeal and laryngeal liposarcoma, Wenig et al found that the two most common presenting complaints were airway obstruction (50% of cases) and dysphagia (30%).(n20) In the oral cavity, liposarcomas often imitate benign tumors. Liposarcomas in the parotid area also grow very slowly.(n16) Later on, tumor growth accelerates and tenderness develops.(n9, n21, n22) Painless enlargement progressing to bony destruction and resorption characterizes liposarcoma of the mandible.(n9) Plain-film x-rays may demonstrate the bony destruction as radiolucent lesions.

Radiographic findings. Computed tomography (CT) has been recommended as the primary tool for the initial radiographic evaluation of lipomatous soft-tissue masses.(n10) One goal of imaging is to distinguish liposarcoma from lipoma. Kransdorf et al identified a number of radiographic features that are capable of making this distinction.(n23) The most useful of these features are the presence of nodular and/or globular areas of nonadipose tissue within the tumor mass, thickened septa within the lesion, a total amount of adipose tissue less

than 75% of the tumor mass, and associated nonadipose tissue masses; all of these findings are characteristic of liposarcomas. Moreover, lipomas show homogeneous fatty attenuation on CT.

On MRI, lipomas demonstrate homogeneous signal intensity identical to fat in all pulse sequences.(n23) In contrast, liposarcomas are more heterogeneous as a result of the juxtaposition of both adipose and nonadipose tissue. The nonadipose tissue may represent entrapped muscle fibers or tumor invasion of surrounding muscle tissue.(n24)

MRI with gadolinium enhancement may be the most useful form of imaging to distinguish liposarcoma from lipoma.(n23) Liposarcomas demonstrate signal enhancement on T1-weighted sequences with gadolinium administration. This is in contrast to lipomas, which generally do not enhance. The enhancement found in liposarcomas is attributable to the presence of thickened septa, which is believed to represent more vascular nonadipose tissue; lipomas are characterized by thin septa.(n23)

The MRI features of liposarcomas are useful in the planning of surgical procedures, particularly in the selection of biopsy sites. In fact, Menown et al recommended that MRI be used for preoperative staging and follow-up studies.(n10) The histologic diagnosis of liposarcoma over lipoma is often based on the presence of sparse atypical cells or lipoblasts, which are most prominent in the nonadipose tissue areas of the tumor. Thus, prebiopsy gadolinium-enhanced MRI of lipomatous masses will identify nonadipose components, thereby increasing the yield of biopsy for liposarcoma.(n23, n24)

Treatment. When possible, the primary therapy for liposarcomas in the head and neck should be wide or radical surgical excision. Tumor-free margins should be obtained if possible.(n7, n22) Zheng and Wang resected tumors with margins of 1.5 to 2 cm.(n9) Similarly, Larson et al recommend a tumor-free margin of 2 cm.(n14)

Total parotidectomy with facial nerve preservation has been used to treat liposarcomas overlying the parotid area. Subtotal mandibulectomy may be used for the treatment of liposarcoma of the mandible.(n9) For liposarcomas of the larynx, a variety of procedures has been employed, including total laryngectomy, hemilaryngectomy, supraglottic laryngectomy, hypopharyngectomy, and transoral epiglottectomy.(n25) Routine neck dissections are generally unnecessary because nodal disease is rare.(n1)

An important consideration in the head and neck is the proximity of vital neurovascular structures and the ensuing morbidity that can be a consequence of wide excision. For superficial tumors, such as atypical lipomatous tumors, the postoperative morbidity of wide excision should be weighed against the possible need for later re-excision since the tumor typically recurs only locally if at all.

Because of the inherent limits of surgical resection in the treatment of liposarcoma in the head and neck, much interest has been focused on the use of postoperative radiotherapy. Liposarcomas have been reported to be radiosensitive.(n7) Adjuvant radiotherapy may be beneficial in delaying tumor growth and preventing recurrences. Furthermore, adjunctive radiotherapy may reduce tumor size and thus facilitate resection.(n2) As far back as 1954, Pack and Pierson demonstrated a higher rate of 5-year survival with radiotherapy combined with surgery than with surgery alone-88 and 67%, respectively.(n26) While other studies have been unable to replicate those results, Eeles et al were able to lower the local recurrence rate of head and neck sarcomas from 60 to 40% with radiotherapy.(n27) It is interesting that postoperative radiation is especially effective in patients with the myxoid variant of liposarcoma.(n5) However, radiotherapy should not be used alone for the treatment of liposarcoma.(n5) Golledge et al reported that none of 3 patients who were treated with radiotherapy alone in their series survived to 5 years.(n2) Kindblom et al best described liposarcomas as radiosensitive, not radiocurable. (n28)

No study has provided conclusive evidence to support the use of chemotherapy in the routine treatment of all liposarcomas, although there have been reports that chemotherapy has been useful in the treatment of the myxoid variant of liposarcoma. For example, Patel et al reported a 44% response rate with the use of doxorubicin and dacarbazine-based chemotherapy for the treatment of myxoid liposarcoma.(n6)

Recurrence. By and large, surgical accessibility along with tumor subtype, size, and location determine the risk of recurrence.

Surgical accessibility. The most important determinant of recurrence risk may be surgical accessibility. For head and neck liposarcomas, complete excision is associated with only a 17% recurrence rate, compared with an 80% recurrence rate following partial or incomplete excision.(n3) Enucleation of the tumor should be avoided because it is associated with a higher recurrence rate. Despite appearing well circumscribed, satellite nodules may be present and missed at the time of surgical excision.(n2, n3, n5, n7, n9) Examination of multiple frozen sections is recommended to ensure the completeness of an excision. For obvious reasons, clinical follow-up monitoring for recurrences is a necessity.(n8)

Tumor subtype. Besides surgical accessibility, histology correlates best with recurrence in head and neck liposarcomas. In a group of 31 such cases, the recurrence rate among patients with well-differentiated and myxoid liposarcomas was only 26%, compared with 75% in patients with the pleomorphic and round-cell subtypes.(n3) In their series of 10 patients with oral and maxillofacial liposarcomas, Zheng and Wang found that the local recurrence rate in patients with the pleomorphic and round-cell variants was 50%, compared with only 22% in patients with well-differentiated and myxoid liposarcomas.(n9) Stewart et al reported similar results, as local recurrence rates associated with pleomorphic and round-cell subtypes were greater than those associated with well-differentiated and myxoid tumors-80 and 50%, respectively.(n1) Of note, McCulloch et al reported that the pleomorphic and round-cell subtypes made up 50% of all incompletely excised liposarcomas and only 17% of completely excised tumors.(n3) This may partly explain the higher recurrence rates among patients with the pleomorphic and round-cell variants. Of note, other series have found that well-differentiated and myxoid subtypes are associated with a greater number of recurrences, which may be explained by lower rates of distant metastasis and, therefore, the longer survival of these patients.(n5, n29)

Tumor size. As one might expect, larger tumors have been associated with higher rates of recurrence. For instance, in their series of 18 oral and salivary gland liposarcomas, Fanburg-Smith et al found that the only tumors that recurred locally were those larger than 5 cm in their maximum dimension.(n13)

Tumor location. Some authors have suggested that differences in head and neck liposarcoma recurrence rates may be at least partially associated with the site of the primary tumor. Golledge et al examined 50 cases of head and neck liposarcoma and found that local recurrence rates were roughly in the 20 to 30% range: 33% for pharyngeal primaries, 30% for laryngeal primaries, 23% for head primaries, and 21% for neck primaries.(n2) The one notable exception was liposarcoma of the mouth, in which there were no recurrences among 4 patients. Fanburg-Smith et al also found a relatively low rate of recurrence in their 18 cases of liposarcoma in the oral cavity and salivary gland area.(n13)

Metastasis. As is the case with the risk of recurrence, tumor histology dictates to a large extent the risk of metastasis. The pleomorphic and round-cell varieties are notably more aggressive than the well-differentiated and myxoid forms. In the series of 50 patients by Golledge et al, 50% of pleomorphic tumors and 60% of round-cell tumors had metastasized at 5 years of follow-up, but no metastases occurred among 31 patients with well-differentiated or myxoid tumors.(n2) The interval between primary disease and metastasis may be measured as a matter of months for patients with poorly differentiated liposarcomas and as a matter of years for those with myxoid liposarcomas.(n8, n17) As mentioned earlier, well-differentiated liposarcomas can be further

differentiated into the less aggressive, superficially located atypical lipomatous tumors or into the more aggressive, deep variety.(n11)

Lymph node metastasis is uncommon except in advanced disease. In their review, McCulloch et al studied 77 head and neck liposarcomas and found only 1 case of nodal metastasis.(n3) Similarly, in the series by Zheng and Wang, neither of the 2 patients who had undergone neck dissection had any nodal disease.(n9) Accordingly, surgical treatment does not necessitate regional lymph node dissection except in cases of obvious lymph node involvement.(n1, n2, n30)

Primary tumor histology of head and neck liposarcoma also appears to influence metastatic target preference.(n1, n9, n10) The most common distant metastatic target is the lung. Head and neck myxoid liposarcomas have a predilection for the serosa of the pleura, pericardium, diaphragm, and occasionally the viscera.(n6) Poorly differentiated tumors metastasize to the lung, viscera, and bone.

Data on the risk of metastasis according to the site of the primary tumor within the head and neck are extremely limited in the literature. The data that are available suggest that the risk of metastasis may be low for liposarcomas that involve the larynx and hypopharynx. In the series by Menown et al, no distant metastases were found among 10 patients with liposarcoma of either the larynx or hypopharynx during a follow-up period that extended out to 40 years.(n10)

Finally, evidence suggests that liposarcomas of the oral and salivary gland area follow an indolent course. In the series of 18 cases of oral and salivary gland region liposarcoma reported by Fanburg-Smith et al, there were no instances of metastasis.(n13)

Prognosis. For all liposarcomas, 5-year survival rates range from 59 to 64% and 10-year rates from 45 to 50%.(n5) Survival is linked in large part to tumor histology. Pleomorphic and round-cell tumors are associated with worse 5-year survival rates (21 and 18%, respectively) than are well-differentiated and myxoid liposarcomas (85 and 77%).(n3)

Similar observations have been made in the head and neck. In Zheng and Wang's series, all patients with pleomorphic or round-cell liposarcomas had died by 4 years of follow-up, while the combined mortality rate for patients with well-differentiated or myxoid liposarcomas was only 25%.(n9) Golledge et al reported similar results; of the 50 patients with head and neck liposarcoma, no patient with well-differentiated liposarcoma had died at a mean follow-up of 5 years.(n2) In contrast, there was a 27% mortality rate among patients with myxoid tumors. Patients with pleomorphic and round-cell tumors fared even worse, with mortality rates of 47 and 80%, respectively, at a mean follow-up of 2 and 3 years, respectively.

With regard to tumor site, Golledge et al reported that the prognosis was best for patients whose liposarcomas involved the larynx (5-year survival: 89%).(n2) Facial and scalp liposarcomas were also associated with a favorable prognosis (5-year survival: 83%). Survival was poorer in patients with intraoral and pharyngeal tumors (50 and 59%, respectively). The prognosis was particularly poor for patients with tumors of the floor of the mouth or the buccal vestibule; 2 of 4 patients with such tumors died within 2 years, despite the fact that 1 tumor was well differentiated and the other was myxoid. Zheng and Wang also reported 4 deaths in their series of 10 patients; 2 of those deaths occurred in patients who had oral cavity liposarcomas.(n9) However, the literature is not consistent in this regard. At least two reports suggest that oral cavity liposarcomas are associated with a better prognosis, noting that this site is generally associated with lower-grade liposarcoma subtypes, smaller tumor size, and lower rates of metastasis.(n13, n22)

In conclusion, liposarcomas are rare tumors of the head and neck that often present as asymptomatic masses. Our case typified the usual presentation of a liposarcoma in the head and neck. No definitive recommendations

exist for the management of this tumor in the head and neck, but the consensus in the literature is that treatment should consist of wide local excision with the selective use of postoperative radiotherapy. The unique anatomy of the head and neck region requires that the benefits of tumor-free margins be weighed against the morbidity of wide excision.

Figure 1. Coronal T1-weighted MRI with gadolinium contrast shows the homogeneous enhancement of the parotid mass

Figure 2. The excised specimen measures 3.5 x 3 x 2 cm

Figure 3. Findings on histologic analysis are consistent with an atypical lipomatous tumor/well-differentiated liposarcoma with myxoid and sclerosing features (H&E, original magnifi cation x20)

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By Usama Mahmood, MD, From Department of Radiation Oncology, University of Maryland, Baltimore; John D. Nguyen, MD, Department of Otolaryngology-Head and Neck Surgery, Keck School of Medicine, University of Southern California, Los Angeles; John Chang, MD, Department of Otolaryngology-Head and Neck Surgery, School of Medicine, University of California Irvine.; Mae Gu, MD, PhD, Department of Pathology, School of
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Medicine, University of California Irvine and Brian J. F. Wong, MD, PhD, Department of Otolaryngology-Head and Neck Surgery, School of Medicine, University of California Irvine.

Brian Wong, MD, Beckman Laser Institute, University of California Irvine, 1002 Health Sciences Rd., E, Irvine, CA 92612. E-mail: bjwong@uci.edu)
