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Low-grade myofibrosarcoma of the maxillary sinus – case report. Study of 2 cases and literature review

Low grade myofibrosarcoma of the maxilla sinus

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Abstract

BACKGROUND

Low-grade myofibroblastic sarcoma (LGMS) is an extremely rare tumor characterized by the malignant proliferation of myofibroblasts. LGMS most commonly develops in adults, predominantly in males, in the head and neck region, oral cavity, especially on the tongue, mandible, and larynx. This article presents a low-grade myofibroblastic sarcoma localized to the maxillary sinus and provides an overview of the available literature.

CASE SUMMARY

Two patients with low-grade myofibroblastic sarcomas located in the maxillary sinus underwent surgery at the Department of Head and Neck Surgery.

CASE 1

A 46-year-old patient was admitted to the clinic with suspected LGMS recurrence in the right maxillary sinus (rT4aN0M0), with symptoms of pain in the suborbital area, watering of the right eye, thick discharge from the right nostril, and augmented facial asymmetry. After open biopsy-confirmed LGMS, the patient underwent expanded maxillectomy of the right side with immediate palate reconstruction using a microvascular skin flap removed surgically from the middle arm. The patient qualified for adjuvant radiotherapy for the postoperative bed, with an additional margin. Currently, the patient is under 1,5 years of observation with no evidence of disease.

CASE 2

A 45-year-old man was admitted to our clinic with facial asymmetry, strabismus, exophthalmos, and visual impairment in the right eye. Six months earlier, the patient had undergone partial jaw resection at another hospital for fibromatosis. A contrast-enhanced computed tomography (CT) scan revealed a tumor mass in the postoperative log after an earlier procedure. An open biopsy confirmed low-grade fibrosarcoma

(rT4aN0M0). The patient qualified for an extended total right maxillectomy with orbital excision and right hemimandibulectomy with immediate microvascular reconstruction using an anterolateral thigh flap. The patient subsequently underwent adjuvant radiotherapy to the postoperative area. After nine months, recurrence occurred in the right mandibular arch below the irradiated area. The lesion infiltrated the base of the skull, which warranted the withdrawal of radiotherapy and salvage surgery. The patient qualified for palliative chemotherapy with a regimen of doxorubicin + dacarbazine + cyclophosphamide and palliative radiotherapy for bone metastases. The patient died 26 months after surgical treatment.

The cases have been assessed and compared with cases in the literature.

CONCLUSION

No specific diagnostic criteria or treatment strategies have been developed for LGMS. The treatment used for LGMS is the same as that used for sinonasal cancer radical tumor excision; adjuvant radiotherapy or chemoradiotherapy should also be considered.

They have low malignant potential but are highly invasive, tend to recur, and metastasize to distant sites, and should undergo regular follow-up examinations to detect recurrence or metastasis at an early stage. Patients should be treated and observed at the highest referral centers.

Key Words: Head and neck cancer; Paranasal sinuses; Maxillary sinus; sarcoma; Low-grade myofibroblastic sarcoma; Case report

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Core Tip: Low-grade myofibroblastic sarcomas are tumors of low malignant potential; however, they are highly invasive and a high tendency to recur and metastasize to distant sites. Since only 55 cases of LGMS have been described, it is impossible to establish guidelines. As there are no specific diagnostic criteria, it is necessary to consider the occurrence of myofibroblastic sarcoma more often than reported in the literature.

INTRODUCTION

Low-grade myofibroblastic sarcoma (LGMS) is characterized by malignant proliferation of myofibroblasts. LGMS is extremely rare and most commonly presents on the tongue in the head and neck region. According to the literature, LGMS may also be present in the trunk and pelvis. Sarcomas are histologically atypical with infiltrating myoepithelial cells and morphological, immunochemical, and ultrastructural features of myofibroblast origin.

Myofibroblasts, also called modified fibroblasts, are myoepithelial cells or stellate cells of mesenchymal origin, discovered in 1971 during the healing of granulation tissue [1]. These cells have contractile properties and are present between fibroblasts, and smooth muscle cells present in almost every tissue [2]. In adults, myofibroblasts have also been discovered in the periodontium and around the somniferous tubules in the testicle [3].

Myofibroblasts have an irregular, hyperchromatic, enlarged nucleus with moderate atypia in amphophilic cytoplasm [4]. They are also characterized by the presence of α-smooth muscle actin, Vimentin and extra domain A of the fibronectin domain, however, do not contain Desmin and Myosin in smooth muscle cells, differentiating them from other cells. These cells play a crucial role in physiological and pathological processes such as fibrotic diseases (lungs, kidney, intestine, and liver) and the etiopathogenesis of

bronchial asthma. Myofibroblasts are particularly important during wound healing [5]. It is suspected that the transformation of fibroblasts to myofibroblasts occurs under the influence of Transforming Growth Factor-B and extra domain A of fibronectin or the mesenchymal transformation of fibrocytes from bone marrow [1,6].

LGMS most frequently occurs in men and is extremely rare in children. It is highly malignant and characterized by metastasis to distant sites. To the best of our knowledge only 5 cases of maxillary sinus LGMS are available [2,7,8]. Patients rarely report symptoms, mainly complaint is painless edema. Radiologically, LGMS can present a destructive, growth pattern.

CASE PRESENTATION

Chief complaints

Case 1

A 46-year-old male previously treated at another hospital was admitted to the outpatient clinic of the Maria Sklodowska-Curie National Research Institute of the Oncology Department of Head and Neck Oncology. The patient presented with right-sided pain.

Suborbital area, watering of the right eye, thick discharge from the right nostril with augmented facial asymmetry.

Case 2

A 45-year-old male was admitted to Maria Sklodowska-Curie National Research Institute of Oncology presenting with strabismus, exophthalmos, and visual impairment.

History of present illness

Case 1

The patient had previously undergone surgery at another hospital for Low-Grade Myofibroblastic Sarcoma. The patient underwent paramedic resection of the maxilla using a lateral rhinotomy. The patient was reoperated because of the surgical margins. Histopathological examination confirmed radical resection and the patient qualified for observation. Thirty months after the surgery, clinical examination confirmed an advanced tumor infiltrating the right nasal cavity, hard palate, and soft palate.

Case 2

6 months earlier; the patient underwent partial resection of the maxilla because of fibromatosis.

History of past illness

Case 1

Generally healthy, did not report chronic diseases, allergies, or medications taken regularly. At the age of 4 years, there was an electric burn on the index finger of the left hand and subsequent amputation.

Case 2

Overall healthy. He does not take medications chronically. Allergy to penicillin.

Personal and family history

Case 1

Professional driver by profession. Irrelevant family history – no family history of malignancy.

Case 2

No family history of malignancy

MATERIALS AND METHODS

Two cases of LGMS of the right maxillary sinus were surgically treated at the Department of Head and Neck Oncology of the Maria Sklodowska-Curie National Research Institute of Oncology. Postoperative specimens were stretched, marked, and fixed in 10% buffered formalin and paraffin. After 48 h of fixation, specimens were cut and embedded in paraffin blocks. The skin fragments were stained with hematoxylin and eosin and cut after dewaxing the paraffin blocks.

An immunohistochemical examination was performed: Smooth Muscle Actin (SMA); cytokeratin AE1 and AE3 (CKAE1/3), Mucin 4 (MUC4); Cluster of Differentiation 34 (CD34); Desmine; SRY-Box Transcription Factor 10 (SOX10); S100; Ki-67 5%; hHf35(-); Epithelial Membrane Antigen (EMA); Caldesmon; H3K27me, Anaplastic Lymphoma Kinase (ALK), Receptor Tyrosine Kinase 1 (ROS1); HMB45, Melan-A; Miogenina; Myogenic Differentiation 1 (MyoD1) according to the instructions provided by the manufacturer. Staining results were assessed using a light microscope.

Clinical and control information was provided directly from patients, doctors, and medical documentation.

For the literature review, the PubMed/Medline electronic databases were searched for up until October 2022, including specific terms.

Imaging examinations

Case 1

Computed tomography (CT) (Figure 1) and magnetic resonance imaging (MRI) (Figure 2) of the head and neck region revealed extensive soft tissue masses in the right maxillary sinus, nasal cavity, nasopharynx, ethmoid cells, and frontal sinus. Infiltration and partial osteolysis were observed in the bone structures on the right side, including the sinus walls, hard palate, medial and suborbital bones, and pterygoid plates.

Case 2

CT, with contrast scan (Figure 3), revealed a tumor mass in the postoperative lobe after the first surgery.

Tumor infiltration was observed in the pterygopalatine and right temporal fossa. Infiltration also involved the lateral pterygoid and masseter muscle, the lateral wall of the nasal cavity and the oral cavity.

Soft tissue mass protruding from the tumor into the posterior orbit through the superior orbital fossa.

Tumor progression and rapid recurrence after primary surgery. The histopathological examination results were verified at the Maria Sklodowska-Curie National Research Institute of Oncology (MSCNRIO). After additional examinations and multispecialty consultation, the primary diagnosis was changed from fibromatosis to inflammatory myofibroblastic tumor.

Laboratory examinations

Case 1

Laboratory tests - without deviations.

Case 2

Laboratory tests without any significant deviations

Physical examination

Case 1

Facial asymmetry-highlighting of the right cheek.

Eyeball movement was preserved, and the patient denied diplopia or any other deviation from the norm. On intraoral examination, an exophytic tumor of the hard

palate reached the midline. Lymphadenopathy was not present during the physical examination.

Case 2

Facial asymmetry, swelling of the right cheek. Scars on the right cheek from previous surgery. Strabismus and exophthalmos of the right eye, significant visual impairment - preserved response to light.

In intraoral examination a palpable tumor on the palate on the right side was observed.

Palpable cervical bulb on the right in group 2.

FINAL DIAGNOSIS

Case 1

Histological examination confirmed the recurrence of low-grade myofibroblastic sarcoma (rpT4aN0M0) (8^{th} Edition, American Joint Committee on Cancer) of the right maxilla, 8 cm in size. Neoplasms with spindle-cell proliferation and moderate cellular atypia.

Mitotic activity was low (4 mitoses per 10 **High Power Field** HPF), without atypical mitosis. The collagenous stroma was partially myxoid and contained an increased number of thick-walled capillaries; no necrosis was observed. Bone destruction is also observed.

Immunohistochemistry staining performed: Smooth Muscle Actin (+, in parts of cell population), reaction type "tram truck", cytokeratin AE1 and AE3 (CK AE1/3) (-/+, insufficient focal reaction), Mucin 4 (MUC4) (-), Cluster of Differentiation 34 (CD34) (-), Desmin (-), Sex Determining Region Y-Box 10 (Sox10) (-), S100 protein (-), Ki-67 protein (5%), hHf35 (-), Epithelial Membrane Antigen (EMA) (-/+), Caldesmon (-/+, trace), trimethylation of lysine 27 on histone H3 (H3K27me3) (+, expression prohibited), Anaplastic Lymphoma Kinase (ALK) (-), Receptor Tyrosine Kinase 1 (ROS1) (-), Human

Melanoma Black-45 (HMB45) (-), Melan-A (-), Miogenina (-), Myogenic Differentiation 1 (MyoD1) (-).

Case 2

Histopathological examination confirmed low-grade myofibroblastic sarcoma. The tumor was poorly demarcated, cream-gray in color, macroscopically without necrosis, and 8 cm in diameter with endophytic growth. (rpT4aN0M0) (8th Edition, American Joint Committee on Cancer).

Microscopic examination revealed proliferation of spindle cells with moderate cellularity and focal moderate cellular atypia; mitotic activity was low (four mitoses per 10 - **High Power Field** HPF) without atypical mitosis. The collagen stroma was partially edematous without necrosis. Natural invasion has also been observed.

IHC staining performed: Smooth Muscle Actin (SMA) (+), Desmin (-), Cluster of Differentiation 34 (CD34) (-), Epithelial Membrane Antigen (EMA) (-), cytokeratin AE1 and AE3 (CKAE1/3) (-), Caldesmon (-), Mucin 1 (MUC1) (-), S100 protein (-), Anaplastic Lymphoma Kinase 1 (ALK1) (-), Signal Transducer and Activator of Transcription 6 (STAT6) (+/-), B-creatinin (-).

TREATMENT

Case 1

Based on the physical, histopathological, and radiological examinations, the patient qualified for an expanded maxillectomy of the right side with immediate palate reconstruction using a microvascular skin flap removed surgically from the middle arm. An intraoperative photograph was captured (Figure 4) after buccal flap creation. The right lymph nodes were selectively resected for vascular anastomosis. Because infiltration was present within the tissues, exenteration was performed on the right side with a partial right-sided sphenoethmoidectomy (Figure 5). Figure 6 shows the post-

resection lodges. Fastened preparation of blocks. During the procedure, leakage of cerebrospinal fluid from the olfactory filament area and right sphenoid sinus was observed. Duraplasty was performed using the latae of the tensor fascia, a mucoperiosteal flap, and a topical fibrin sealant patch. The patient did not experience any complications peri- or postoperatively.

The patient was qualified for adjuvant radiotherapy IMRT + CBCT for the postoperative treatment, with additional margins. The patient received a fractional dose of 200 centiGray (cGy) for a total dose of 6600 centiGray (cGy).

Case 2

Open biopsy confirmed recurrence of low-grade myofibrosarcoma. Based on clinical, histopathological, and radiological results, the patient qualified for expanded complete right-sided maxillectomy and right-sided hemimandibulectomy with immediate microvessel reconstruction using an *anterolateral thigh flap* (ALT flap) and selective resection of the lymph nodes on the right side. Because of infiltration of the orbital tissues, right-sided exenteration was performed.

The patient qualified for adjuvant radiation therapy (IMRT) of the postsurgical bed with a fraction dosage of 200 centiGray (cGy) to a total dose of 6600 cGy.

OUTCOME AND FOLLOW-UP

Case 1

Currently, the patient is under observation with no evidence of disease.

Case 2

After nine months of observation, recurrence appeared in the right mandibular arch below the irradiated area. CT confirmed the progression in both the irradiated and the previously irradiated areas. The lesion is located at the base of the skull.

There were increasing postoperative risks, which justified refrainment from radiotherapy and salvage surgery.

The patient was qualified for palliative chemotherapy with doxorubicin + dacarbazine + cyclophosphamide regimen. Due to pathological L1 and L5 fractures, metastases to L1 and L2, and metastasis to the right hip bone, the patient was eligible for Radiation Therapy (fractions of 3 Gray (Gy) to a total dose of 36 Gy) and second-line chemotherapy (gemcitabine + docetaxel). The patient died 26 months after surgical treatment.

A comparison of the immunohistochemical studies of Cases 1 and 2 is shown in Table 1.

DISCUSSION

Low-grade myofibroblastic sarcoma (LGMS)

LGMS is a recently discovered and extremely rare malignant tumor. The first such case was diagnosed in the 1998s. In 2002, the World Health Organization (WHO) made the LGMS a separate unit in the pathology and genetics of soft tissue and bone tumors [9]. Clinically, it manifests as a slow-growing and infiltrating tumor. LGMS is a low-grade malignant tumor with a high tendency for recurrence and distant metastases, even after several years [10,11].

LGMS most commonly develops in adults, predominantly in males, and in the head and neck.

The tumor most often appears in the oral cavity, especially in the tongue, mandible, and larynx [6].

Other localizations include the limbs, abdominal cavity, and pelvis, and long bones [12]. LGMS of the maxillary sinus is extremely rare, and only five cases have been described so far. Here, we present two more cases (Table 2) [2,7,8,13]. In cases of soft tissue sarcomas

of the head and neck, magnetic resonance imaging (MRI) with contrast and/or computed tomography (CT) with contrast should be performed (NCCN Guidelines version 2. 2022) [14].

Radiologic imaging typically shows a well-limited tumor with visible margins of destructive growth [6,10].

Histology

Histologically, the tumor is composed of spindle and stellate cells collected in clusters of different lengths, with a focal herringbone, spiral, or no pattern [13]. Cancerous cells are composed of a mild to moderate amount of pale eosinophilic cytoplasm and a spindle nucleus, which can be spiral or circular, and vesicles with cavities.

In most cases, focal atypia of the nucleus is observed; however, this is usually benign with enlarged hyperchromatic nuclei. Additionally, larger atypical cells can be sometimes observed [11].

Microscopic image 7 shows spindle cell infiltration, hypocellularity with mild atypia, and stromal collagen. Hypercellular proliferation and bundles of spindle cells are observed with H&E staining (Figure 8). Figure 9 shows focal expression of smooth muscle actin and figure 10 – no expression of anaplastic lymphoma kinase.

Immunophenotype

Neoplastic cells in low-grade myofibroblastic sarcoma have a variable immunophenotype:

Actin positive(+)/Desmin negative(-), Actin negative(-)/Desmin positive(+), and Actin positive(+)/Desmin(+) positive. In addition, tumor cells may stain positively for fibronectin,

Focal expression of clusters of differentiation 34 (CD34) and 99 (CD99) has been reported, while S100 protein, epithelial markers, laminin, and h-caldesmon are negative(-) [2,15].

Differential diagnosis

The differential diagnosis of LGMS includes both malignant and benign tumors such as nodular fasciitis, myofibroblastic tumors, fibromatosis, myofibroma, myopericytoma, monophasic synovial sarcoma, malignant peripheral nerve sheath tumors, spindle cell rhabdomyosarcoma, fibrosarcoma, leiomyosarcoma, and melanoma [5,6,16].

Procedure

The golden standard procedure in cases of sarcoma infiltrating bones is radical excision of the tumor [12, 17]. In cases of positive margins, the radicalization procedure should be primarily considered. When radicalization is impossible, soft tissue margins are narrow and large. If tumors infiltrate the blood vessels or nerves, radiotherapy or chemoradiotherapy should be considered [12, 18, 19]. The LGMS head and neck recurrence rate is 25-40% and is the highest when the tumor is in the nasal cavity or paranasal sinuses. A higher frequency of recurrence was observed in the patients who underwent adjuvant RT. This is probably a result of the qualification of patients with unfavorable prognostic factors.

The most important prognostic factor was the resection state. Positive margins, regional lymph node involvement, and age > 60 years [12].

The clinical cases presented above were characterized by characteristics specific to the described type of sarcoma, which enabled the identification of certain groups of tumors. As shown in Table 2, males are mostly affected (57%), which is also indicated in previous literature.

The average age of the patients is 41 years old ± 17.2 (females 45 ± 25.8, males 38 ± 10.6). The most common symptoms are nasal congestion, rhinorrhea, edema, and pain. Exophthalmos was present in two patients; however, visual impairment was present in 1 patient.

LGMSs are tumors of low malignancy; however, they are highly invasive, with a high tendency for recurrence and a high risk of distant metastases [6].

Several factors may contribute to this paradox of LGMS. Tumors with a low grade of malignancy may have a lower mitotic index, but this does not necessarily reflect their invasive potential or likelihood of metastasis.

It is suspected that these tumors may show infiltrative growth patterns, making complete surgical removal difficult, residual microscopic disease left after surgery can lead to recurrence.

Even within a specific histological subtype, in tumor can be significant heterogeneity in terms of biological behavior. Some cells may have more aggressive features.

Tumor behavior is also influenced by genetic and molecular characteristics. Some low-grade tumors may contain genetic changes or mutations that contribute to their ability to recur or metastasize.

CONCLUSION

LGMSs are tumors of low malignant potential; however, they are highly invasive and a high tendency to recur and metastasize to distant sites.

A standard treatment strategy has not been developed yet for patients with LGMS. Because of its low frequency of occurrence, it is impossible to establish guidelines. Therefore, the treatment used for LGMS is the same as the ones used for sino-nasal carcinoma (SNC).

It is important that patients with LGMS be closely monitored by a multidisciplinary healthcare team to determine the most appropriate treatment plan and follow-up. Regular follow-up examinations are crucial to detect recurrence or metastasis at an early stage.

Considering the lack of precise diagnostic criteria, LGMS occur more often than the literature indicates and may include various clinicopathological forms.

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