Case Report
Primary orbital dedifferentiated liposarcoma with leiomyosarcomatous and low-grade osteosarcomatous differentiation

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Abstract: Liposarcoma originating in the orbit is extremely rare. Herein, we report a dedifferentiated liposarcoma arising from the orbit of a Chinese woman. This patient underwent tumor resection at the age of 56 years and recurred 50 months after the initial resection. Histologically, the initial lesion exhibited features of well-differentiated liposarcoma with focal areas of well-differentiated ossified component. The recurrent tumor predominantly consisted of spindle cell sarcoma, low-grade ossified component, and a small amount of well-differentiated liposarcoma. Immunohistochemically, the spindle cell sarcomatous component of the recurrent lesion exhibited strong positivity for desmin, smooth muscle actin, and H-caldesmon. Both the original and recurrent lesions showed strong positivity for p16, MDM2, and CDK4. Fluorescence in situ hybridization revealed MDM2 gene amplification in all of the tumor components. To the best of our knowledge, this is the first published example of orbital dedifferentiated liposarcoma exhibiting leiomyosarcomatous and low-grade osteosarcomatous differentiation.

Keywords: Dedifferentiated liposarcoma, orbit, leiomyosarcoma, paraosteal osteosarcoma, osteosarcoma

Introduction
Liposarcoma represents one of the most common soft tissue sarcomas [1, 2]. However, this entity is considered to be one of the rarest tumors of the orbit [3]. A search of the English literature indicated that, thus far, only 54 previous cases of primary orbital liposarcoma have been reported. Among the 44 known subtypes, there were 22 myxoid liposarcomas, 17 well-differentiated liposarcomas, and 5 dedifferentiated liposarcomas [4-8]. Importantly, the majority of these reported liposarcomas have not been confirmed by genetics. About 5-10% of dedifferentiated liposarcomas can develop heterologous differentiation, such as rhabdomyosarcomatous, osteo/chondrosarcomatous, leiomyosarcomatous, and angiosarcomatous elements [1, 9]. To the best of our knowledge, the current case represents the first reported orbital dedifferentiated liposarcoma with both leiomyosarcomatous and low-grade osteosarcomatous components. Additionally, this is the only orbital dedifferentiated liposarcoma confirmed by detection of 12q14-15 amplification.

Materials and methods

Case history
In 2008, a 56-year-old woman was referred to a peripheral hospital with a 6-year history of increasing painless right proptosis. She underwent tumor resection in February 2008, and a histological diagnosis of “lipoma” was rendered. In April 2012, 50 months after the first operation, she was admitted to our hospital with a 1-year history of right upper lid swelling and right proptosis with slight pain. On ocular examination, there was proptosis of the right eye with marked restriction of ocular movement. A hard, irregular and ill-defined 2-cm mass was palpable in the upper part of the right orbit causing downward displacement of the globe. The intraocular pressure and fundus examination was normal. The left eye was normal. The patient suffered from hypertension and diabetes for one year. Computed tomography revealed an ill-defined soft tissue mass containing a heavily calcified area located near the lacrimal gland extending to the orbital apex.
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(Figure 1). The tumors showed no connection to the skeletal system. An anterior orbitotomy was performed, and a 4.0 cm×2.0 cm×2.0 cm irregular hard nodular mass was identified, infiltrating the superior oblique muscle. Both the intraoperative impression and a postoperative computed tomography scan confirmed that gross total tumor resection had been achieved. Postoperatively, there was a marked reduction of proptosis. The patient did not accept any adjuvant therapy despite a recommendation. At the most recent follow-up, 49 months after the surgery, she was in good status without recurrence or metastasis.

Immunohistochemical analysis

Immunohistochemical stain was performed on 4-µm thick formalin-fixed paraffin-embedded tissue sections, using the EnVision Plus detection system (DAKO, Carpinteria, CA) with controls. Standard immunohistochemical studies were performed using the following antibodies: MDM2 (clone SMP14, ready-to-use; ZSGB-Bio), CDK4 (clone EP180, 1:100; ZSGB-Bio), p16 (clone 16P04/JC2, ready-to-use; ZSGB-Bio), desmin (clone D33, 1:100; Dako, Carpinteria, CA), smooth muscle actin (clone 1A4, 1:100; Dako, Carpinteria, CA), H-caldesmon (clone h-CD, 1:100; Dako, Carpinteria, CA), CD34 (clone QBEnd 10, 1:100; Dako, Carpinteria, CA), p63 (clone 4A4, 1:400; Biocare, Concord, CA), cytokeratin (clone AE1/AE3, 1:200; Dako, Carpinteria, CA), epithelial membrane antigen (clone E29, 1:100; Dako, Carpinteria, CA), S-100 protein (clone 4C49, 1:100; MxB), ki-67 (clone MIB-1, 1:100; Dako, Carpinteria, CA), HMB45 (clone HMB-45, 1:50; Dako, Carpinteria, CA).

Fluorescence in situ hybridization

Formalin-fixed paraffin-embedded tissue representative of the neoplastic components was used for fluorescence in situ hybridization analysis to identify amplification of MDM2 located on chromosome band 12q15. We used a commercially available Vysis LSI MDM2 Dual Color Probe (Abbott Molecular, Des Plaines, IL, USA) for MDM2 on chromosome 12q15. The fluorescence in situ hybridization assay was performed on 4-µm-thick sections according to an established laboratory protocol, as described previously [10]. Tumor samples were scored by two investigators in 100 cells in a blind fashion. Amplification was defined as MDM2 signals/CEP12 ratio ≥3.

Results

Pathologic findings

Gross examination revealed a fragmented specimen with bone tissue measuring 3.5...
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Histological analysis revealed that the lesion was mainly composed of interlacing bundles and fascicles of spindle cells. The spindle tumor cells exhibited blunt-ended nuclei, abundant eosinophilic cytoplasm, and scattered juxtanuclear vacuoles (Figure 2A). Moderate nuclear atypia was present in the neoplasm. The mitotic activity was up to 5/10 high-power fields. Necrosis could not be detected through the whole tumor. A small amount of lipogenic area was observed in juxtaposition to the spindle cell tumor (Figure 2B), and this tumor component infiltrated into the skeletal muscles. Both atypical, hyperchromatic stromal cells and lipoblasts were found in the lipogenic component (Figure 2C), which is typical of well-differentiated liposarcoma. The interface between the two zones was abrupt. Notably, the ossified component was identified in some areas. This area was composed of mature appearing bone surrounded by a hypocellular fibroblastic stroma with bland cytologic atypia (Figure 2D).

Immunohistochemical findings

Immunohistochemically, the spindle cell sarcomatous component exhibited strong positivity for desmin (Figure 3A), smooth muscle actin (Figure 3B), and H-caldesmon but was negative for p63, S-100 protein, CD34, HMB45, epithelial membrane antigen, and cytokeratin. The MIB-1 index was 15% of the spindle cell neoplastic cells. All of the three components (spin-
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dle cell sarcoma, well-differentiated liposarcoma, and ossified component) were strongly positive for p16, MDM2, and CDK4.

Molecular findings

Fluorescence in situ hybridization revealed MDM2 gene amplification in the spindle cell, lipogenic, and ossified components (Figure 3C).

Diagnosis

Based on the aforementioned findings, the final diagnosis was dedifferentiated liposarcoma with leiomyosarcomatous and low-grade osteosarcomatous component. A detailed examination did not reveal any evidence of a tumor in other sites.

Subsequently, the sections diagnosed as “lipoma” from the first operation were re-examined. The initial one was composed of partly mature adipocytic proliferation showing a marked variation in cell size. In some areas, atypical cells with hyperchromatic nuclei could be observed, especially in the fibrous septa. Notably, a focus of low-grade osteosarcomatous component were observed in some areas (Figure 3D). The above morphologic findings were similar to that of the lipogenic and ossified component of the recurrent tumor. However, the leiomyosarcomatous component was not observed in the tumor. Most importantly, MDM2 amplification was identified in the tumor by fluorescence in situ hybridization analysis. Therefore, the diagnosis of the original tumor should have been well-differentiated liposarcoma with low-grade osteosarcomatous component instead of lipoma.

Discussion

The orbit is an extremely rare location for liposarcomas, particularly for the dedifferentiated

Figure 3. The spindle cell component of the recurrent tumor showing positivity for desmin (A) and smooth muscle actin (B) (immunostaining, 400×). C. FISH showing a high level of amplification of the MDM2 locus in the majority of the neoplastic cells (MDM2, red signals; CEP12, green signals). D. The initial tumor exhibiting features of well-differentiated liposarcoma and focal areas of well-differentiated ossified component (H&E, 100×).
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liposarcoma [3], although this type of neoplasm is well-known to occur in the retroperitoneum and deep soft tissues of the extremities [1, 2]. To the best of our knowledge, thus far, only 5 cases of orbital dedifferentiated liposarcoma have been documented in the English language literature worldwide [4-8]. Herein, we present an orbital dedifferentiated liposarcoma occurring in a Chinese woman. Of the total of 6 cases in the literature, including the case in this context, the age of the patients ranged from 23 to 56 years (median 54.5 years, average 45.5 years). There were 5 females and 1 male (ratio: 5:1), showing a predilection for women.

The dedifferentiated component of the reported primary orbital dedifferentiated liposarcomas was described as spindle cell in 2 cases, fibrosarcoma in 1 case, rhabdomyosarcoma in 1 case, and unknown in 1 case [4-8]. The current case revealed both divergent leiomyosarcomatous and low-grade heterologous components. To our knowledge, this feature has not been documented in this location before.

The differential diagnosis of primary orbital dedifferentiated liposarcoma is broad and might be very challenging due to its rarity, especially in small biopsy samples. The differential diagnosis of the recurrent tumor should include non-adipocytic and adipocytic sarcomas, such as leiomyosarcoma, parosteal osteosarcoma, malignant mesenchymoma, and metastatic liposarcoma. The initial tumor of the first operation should be distinguished from lipoma, herniated orbit fat, parosteal osteosarcoma, and benign bone lesions.

Dedifferentiated liposarcoma with extensive leiomyosarcomatous differentiation could be easily confused with leiomyosarcoma on morphologic grounds only, particularly when the well-differentiated liposarcoma component is obscure or not identified. However, the distinction between dedifferentiated liposarcoma and leiomyosarcoma is important because dedifferentiated liposarcoma seems to have a significantly lower metastatic potential compared with conventional leiomyosarcoma [11]. For example, the present patient had been in a good status without evidence of recurrence or metastasis 49 months after the second total resection. Careful inspection identified typical well-differentiated liposarcoma component, which played an important role in establishing the diagnosis. In addition, the current case also exhibited a heterologous ossified component, which is more suggestive of dedifferentiated liposarcoma instead of conventional leiomyosarcoma. More importantly, leiomyosarcoma can be excluded due to the presence of both the high-level amplification of the MDM2 locus and the diffuse nuclear positivity for MDM2, CDK4 and p16.

A small minority of dedifferentiated liposarcoma can exhibit heterologous osteogenic differentiation, and most frequently resemble conventional high-grade osteosarcoma [1, 2]. However, the present case displayed only low-grade osteosarcomatous component both in the initial and recurrent lesions. Awareness of this peculiar component is very important because it may be confused with benign lesions, such as heterotopic ossification or myositis ossificans. For instance, the original tumor of this case was misinterpreted as lipoma with metaplastic bone because of under-recognition of both well-differentiated liposarcoma and neoplastic ossified components. However, both this case and a series by Yoshida et al [12] revealed the presence of MDM2 gene amplification and immunoreactivity for MDM2, CDK4 and p16 in the relatively mature bone component, suggestive of its malignant natures and an integral part of the well-differentiated liposarcoma/dedifferentiated liposarcoma instead of benign process. In contrast, 12q14-15 amplification has not been described in any of the benign bone-forming lesions.

Skeletal parosteal osteosarcoma can exhibit dedifferentiation, resembling high-grade sarcomas. Furthermore, most parosteal osteosarcoma are also manifested by constant MDM2 gene amplification and overexpression [13], which simulate dedifferentiated liposarcoma. Thus, skeletal parosteal osteosarcoma of the orbital bone should also be considered in the differential diagnosis. However, parosteal osteosarcoma usually present as a mass attached to the cortex of the underlying bone. In the present case, both imaging studies and operative findings did not find any relation to the orbital skeletal system. Additionally, careful histological inspection identified typical areas of a malignant adipocytic component, which rules out the possibility of dedifferentiated parosteal osteosarcoma.
Owing to the coexistence of leiomyosarcomatous and osteogenic components in this case, malignant mesenchymoma should also be enrolled into the differential diagnosis. However, the presence of the well-differentiated liposarcoma component and identification of MDM2 amplification could be invaluable to secure the diagnosis of dedifferentiated liposarcoma. It is noteworthy to mention that some so-called malignant mesenchymoma can be classified more specifically. In fact, according to the previous series, malignant mesenchymoma should be discarded because the majority of these tumors can be reclassified as dedifferentiated liposarcoma or other tumors [11].

Subconjunctival herniated orbital fat is a rare clinical condition and usually occurs as a bilateral or unilateral intraorbital mass. Herniated orbital fat usually contains floret-type giant cells and Lochkern cells and can simulate an adipocytic neoplasm, especially well-differentiated liposarcoma [14]. In contrast to well-differentiated liposarcoma, enlarged, hyperchromatic cells cannot be identified in these lesions. More importantly, the detection of MDM2 gene amplification can be invaluable in distinguishing well-differentiated liposarcoma from herniated orbital fat.

The orbit is an extraordinarily rare location for dedifferentiated liposarcoma. Therefore, the possibility of a secondary liposarcoma should always be excluded. In the present case, both imaging studies and physical examinations ruled out the possibility of metastatic lesion.

In conclusion, dedifferentiated liposarcoma exhibiting leiomyosarcomatous and low-grade osteosarcomatous differentiation is an exceedingly rare neoplasm in the orbit, and therefore, it should be rigorously distinguished from other types of spindle cell neoplasm, especially when a well-differentiated liposarcoma component is obscure. Low-grade osteosarcomatous differentiation should be recognized as part of well-differentiated liposarcoma/dedifferentiated liposarcoma rather than a benign reactive change, which is useful for arriving at the diagnosis of this tumor type.

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Disclosure of conflict of interest

None.

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