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Case Report

A case of dedifferentiated liposarcoma with well-differentiated liposarcomatous, inflammatory myofibroblastic tumor-like, and low- and high-grade osteosarcomatous components: common *MDM2* amplification supporting divergent morphological change of well-differentiated liposarcoma

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Abstract: Myofibroblastic dedifferentiation of well-differentiated liposarcoma (WDL) has rarely been documented, and WDL-associated low-grade osteosarcoma (OS) is extremely rare. Here we present a case of a 51-year-old man with three adjacent retroperitoneal masses corresponding to WDL, inflammatory myofibroblastic tumor (IMT)-like, and low- and high-grade OS components. Regarding the IMT-like and low-grade OS components adjacent to the WDL component, it was ambiguous whether they represented WDL dedifferentiation or were primary tumors. In our case, all of the abovementioned components exhibited *MDM2* amplification. Even though *MDM2* amplification could be observed in primary IMT and primary low-grade OS, this finding strongly supported that those components constituted the spectrum of a single tumor along with their spatial relationship.

Keywords: Dedifferentiated liposarcoma, fluorescence in situ hybridization, high-grade osteosarcoma, inflammatory myofibroblastic tumor-like, low-grade osteosarcoma, *MDM2*

Introduction

Several studies have documented myofibroblastic differentiation in dedifferentiated liposarcoma (DDL). Henricks et al. reported low-grade dedifferentiated liposarcomas with areas resembling fibromatosis, a kind of a myofibroblastic lesion [1]. Hasegawa et al. described a case of myofibrosarcomatous DDL [2]. Much more recently, Lucas et al. suggested that myofibroblastic and inflammatory myofibroblastic tumor (IMT)-like dedifferentiation seem to be relatively common but was an under-recognized finding in DDL [3]. They also clearly illustrated IMT-like components in six cases of DDL (14% of the total cohort) [3].

With respect to the low-grade osteosarcoma (OS) component associated with well-differentiated liposarcoma (WDL), there has only been one well studied report by Yoshida et al. [4]. Regarding low-grade OS component, they suggested that the morphological features of low-grade OS component, its transformation to high-grade OS component in some cases, and the immunoreactivity of MDM2 and/or CDK4 in atypical osteoblasts could rule out the possibility of metaplastic bone formation looking like low-grade OS; low-grade OS component was considered to be truly neoplastic [4]. However, they did not conclude that low-grade OS component represents a dedifferentiated component arising from the WDL. Although MDM2 and/or CDK4 immunoreactivity is well known in WDL/DDL [5]. It is seen in low-grade OS as well [6]. Both WDL/DDL and low-grade OS share a common genetic alteration that is characterized by the amplification of 12q13-15 involving *MDM2* and *CDK4* [7-9]. In addition, there have been

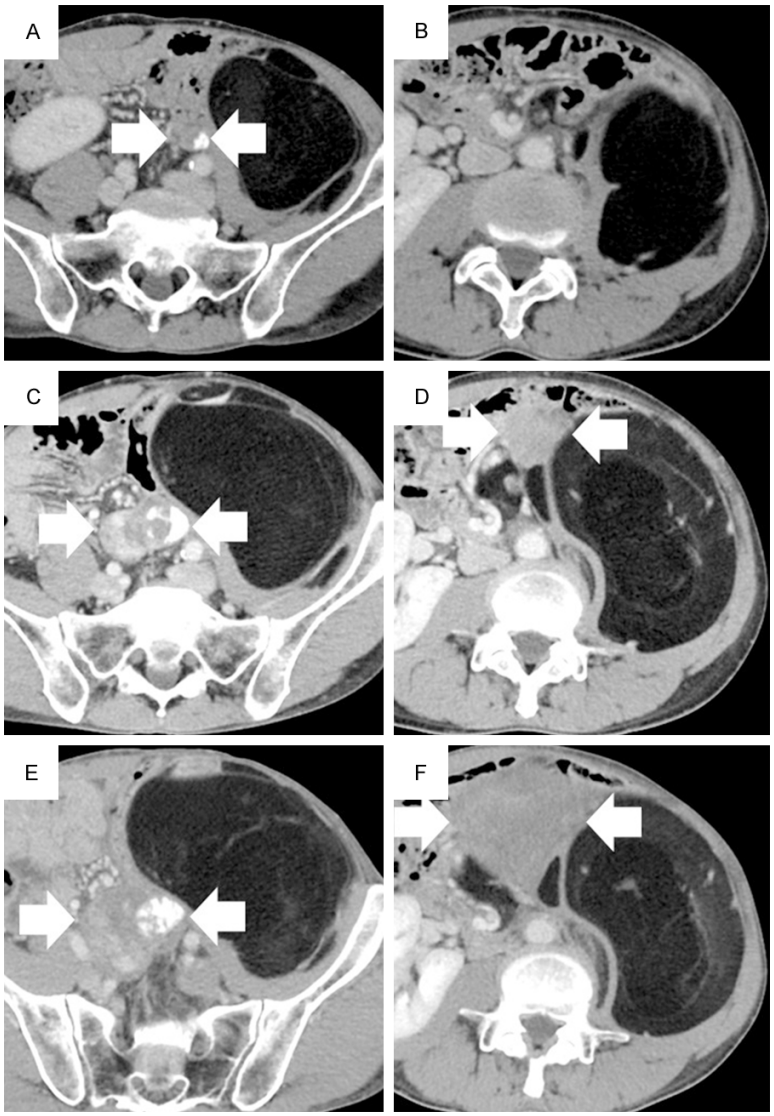

Figure 1. Computed tomography findings. A. A well-circumscribed fat density mass was found in the left retroperitoneum to which a soft tissue density mass with calcification (arrows) was adjacent. B. At the ventral part of the fat density mass, no soft tissue density mass was visible at this time. C. The fat density mass and the mass containing calcification (arrows) were enlarged. D. At the ventral part of the fat density mass, a soft tissue density mass (arrows) was visible. E. The size of the fat density mass increased slightly. In contrast, the mass containing the calcification (arrows) remarkably increased; the calcification itself did not increase so much. F. The mass present at the ventral part of the fat density mass (arrows) was remarkably enlarged.

several reported cases of extraskeletal low-grade OS [10-14].

Here we present a case having three retroperitoneal masses representing a WDL mass in contact with IMT-like and low-grade and high-grade OS masses. Tumor cells in each of these masses were analyzed by fluorescence in situ hybridization (FISH) targeting *MDM2* (12q15) to see if they are genetically related.

Clinical summary

A 51-year-old man presented with a retroperitoneal mass on a routine check-up. He had no other chief complaint and physical and laboratory examinations revealed no abnormalities. On contrast-enhanced computed tomography (CT), a well-circumscribed fat density mass measuring 12 × 8 × 7 cm was found in the left retroperitoneum (**Figure 1A**). Adjacent to this mass, a soft tissue density mass with calcification measuring 1 × 1 × 0.5 cm was identified (**Figure 1A**). A retroperitoneal WDL with DDL component differentiating to OS was suspected. At the patient's request, surgery was not immediately performed. No soft tissue density mass was noted at the ventral part of the fat density mass at that time (**Figure 1B**). Six months later, the fat density mass enlarged to 17 × 12 × 8 cm and the mass containing calcification also enlarged to 3 × 2 × 1.5 cm (**Figure 1C**). At the ventral part of the fat density mass, there appeared a soft tissue density mass measuring 3 × 2 × 2 cm (**Figure 1D**) that was also suspected to be a DDL component. After 6 months, the size of the fat density mass slightly increased to 18 × 12 × 10 cm; on the other hand, the mass containing calcification remarkably increased to 5 × 4 × 4 cm, while the calcification itself did not increase so much (**Figure 1E**). The mass present at the ventral part of the fat density mass also enlarged remarkably to 7 × 6 × 5 cm (**Figure 1F**). No metastases were identified. With the patient's consent, surgical resection was performed. The three abovementioned masses were resected separately.

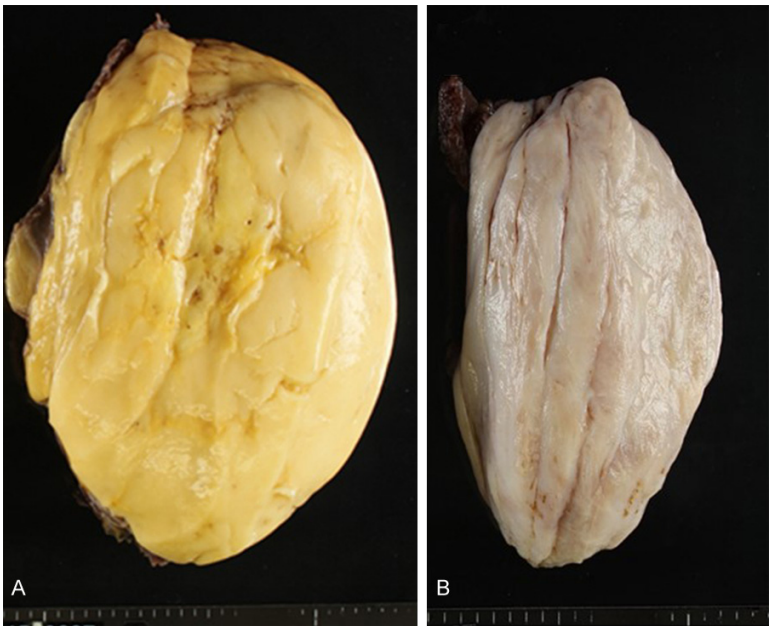

Figure 2. Macroscopic findings. A. A yellowish tumor that was soft and almost homogeneous in color with some thin band-like fibrous areas was observed. B. A whitish tumor that was elastic, hard, and relatively homogenous on the cut surface was observed.

Pathological findings

Gross examination of the three surgically resected masses revealed a yellowish tumor, whitish tumor, and hard tumor. The yellowish tumor was soft and almost homogeneous in color with some thin band-like fibrous areas (**Figure 2A**). The whitish tumor was elastic, hard, and relatively homogenous on the cut surface (**Figure 2B**). The cut surface of the hard tumor was not photographed.

Microscopically, there were four histological types in the three tumoral masses. The yellowish tumor corresponded to the WDL component and was lipoma-like with prominent spindle- to stellate-shaped atypical cells in a patchy fibrous area. These cells had nuclei of variable shapes showing hyperchromasia; adipocytes comprising a WDL component were of various sizes (**Figure 3A**). The whitish tumor exhibited IMT-like morphology. The tumor cells were spindle-shaped and showed relatively uniform oval nuclei with distinct nucleoli. No nuclear hyperchromasia was present. Prominent lymphocyte and plasma cell infiltrations were observed with scattered lymph follicles (**Figure 3B**). The hard tumor consisted of low- and high-grade OS components that occupied 20% and 80% of its mass, respectively. The transition between them was gradual. It is probable that the calcification observed on CT primarily represented the low-grade OS component. In the low-grade OS component, tumor cells with mild nuclear atypia were not dense, while well-formed woven bone was present (**Figure 3C**). In high-grade OS component, tumor cells having pleomorphic nuclei were dense, while poorly formed lace-like bone or osteoid was present (**Figure 3D**); areas not exhibiting osteoid formation were also observed. We postulated that the remarkable enlargement of the mass containing the calcification observed on CT was attributable to the rapid proliferation of the high-grade OS component.

Immunohistochemistry (IHC) revealed that the tumor cells in all of the components were diffusely positive for MDM2 (**Figure 4A-D**) and CDK4 (**Figure 4E-H**). The IMT-like component was diffusely positive for α-smooth muscle actin (**Figure 4I**) and focally positive for desmin in approximately 15% of the tumor cells (**Figure 4J**). The IMT-like component tested negative for ALK.

The fluorescent in situ hybridization (FISH) analysis was performed using a Spectrum Orange-labeled *MDM2* probe and a Spectrum Green-labeled centromere probe of chromosome 12 (Vysis MDM2/CEP 12 FISH Probe Kit; Abbott Molecular, Chicago, IL). *MDM2* amplification (the ratio of *MDM2*/CEP ≥ 2) [15] was observed in all four components, but the amplification level did not differ significantly among the four components (**Figure 5A-D**).

We considered the four components as representing a spectrum of one tumor; they were encompassed by DDL. However, there may be differing opinions that three separate tumors existed, represented by WDL, IMT, and OS. In particular, the correlation between the WDL component and the low- and high-grade OS components could become a matter of debate.

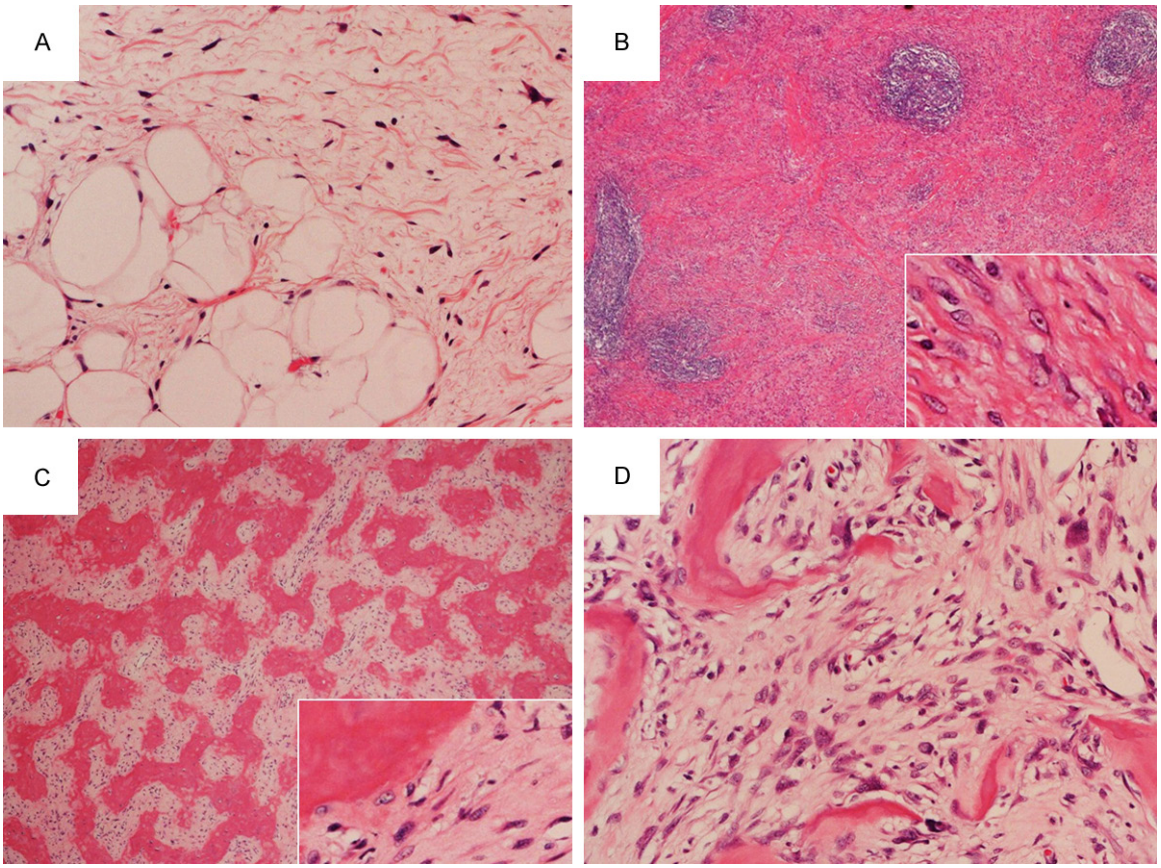

Figure 3. Microscopic findings. A. The yellowish tumor was lipoma-like with prominent spindle- to stellate-shaped atypical cells in a patchy fibrous area. These cells had nuclei of various shapes showing hyperchromasia; the adipocytes varied in size. B. The whitish tumor was composed of spindle-shaped tumor cells with relatively uniform oval nuclei and distinct nucleoli. Nuclear hyperchromasia was not present. Inflammatory cell infiltration, such as lymphocytes and plasma cells, was prominent and lymph follicles were focally formed. Inset: A high-power view showing the tumor cell characteristics. C. In the portion of the tumor containing the hard part, tumor cells with mild nuclear atypia were not dense and well-formed woven bone was present. Inset: A high-power view exhibiting tumor cell characteristics. D. In another portion of the tumor containing the hard part, the tumor cells with pleomorphic nuclei were dense and poorly-formed lace-like bone or osteoid was present.

Discussion

Dedifferentiation of WDL to IMT-like morphology is reportedly relatively common though previously under-recognized [3], and we regarded the IMT-like component as a dedifferentiated component. However, whether the IMT-like component in this case is truly a dedifferentiated component should be carefully examined. Although IMTs are more common in children and young adults, they also occur in older adults, often within the abdomen and retroperitoneum [16]. Thus, age and anatomic location overlap with those of dedifferentiated liposarcoma [3]. Three major histological patterns are seen in IMTs: myxoid, cellular, and hypocellular fibrous patterns [17]. According to these patterns, this case showed an IMT-like component with a cellular pattern; thus, the IMT-like component was morphologically indistinguishable from IMT. Regarding the IHC and FISH results, MDM2 expression and *MDM2* amplification are well known for WDL/DDL [5, 9]. However, Yamamoto et al. found MDM2 expression in 27% of IMT cases as well as *MDM2* amplification in some IMT cases [18]. Thus, MDM2 expression and *MDM2* amplification alone might not be a strong evidence distinguishing DDL with an IMT-like component from IMT. As a basic observation, the IMT-like component developed at the portion adjacent to the WDL component on CT; thus, the IMT-like component appeared to arise from the WDL component. Combining these observations, it is reasonable

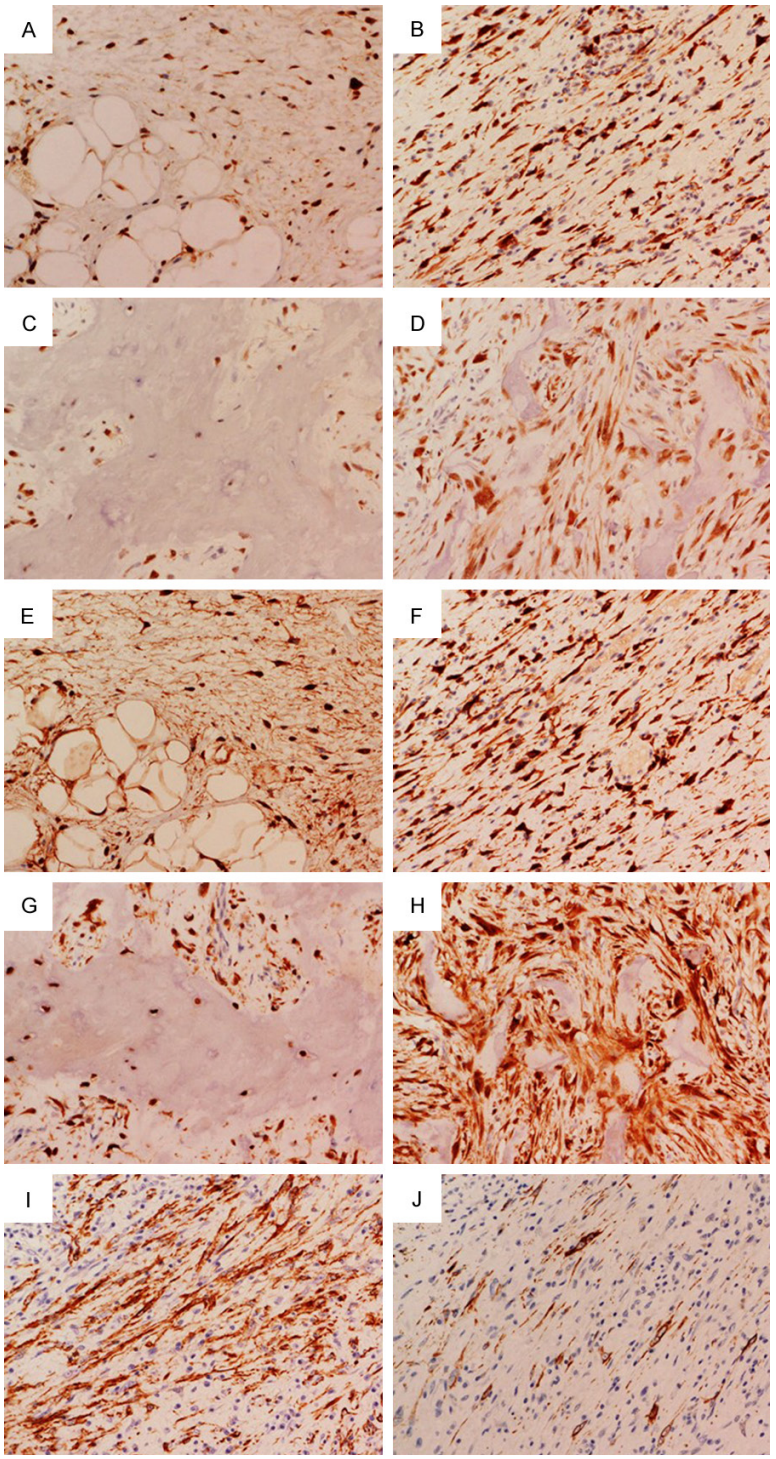

Figure 4. Immunohistochemical findings. (A-D) Diffuse MDM2 staining was common in the well-differentiated liposarcoma (A), inflammatory myofibroblastic tumor-like (B), low-grade osteosarcoma (C), and high-grade osteosarcoma (D) components. (E-H) Diffuse CDK4 staining was common in the well-differentiated liposarcoma (E), inflammatory myofibroblastic tumor-like (F), low-grade osteosarcoma (G), and high-grade osteosarcoma (H) components. (I) In the inflammatory myofibroblastic tumor-like component, the tumor cells were diffusely positive for α-smooth muscle actin. (J) In the inflammatory myofibroblastic tumor-like component, the tumor cells were focally positive for desmin.

to consider the IMT-like component as representing a DDL component.

With respect to muscle marker positivity in the IMT-like component, it has recently been revealed that retroperitoneal liposarcoma can be divided into different risk categories according to muscle marker expression [19]. Myogenic differentiation determined by muscle marker expression was chiefly observed in DDL (48% of 92 cases), although it was occasionally seen in WDL (15.3% of 52 cases) as well [19]. The presence of myogenic differentiation in retroperitoneal liposarcoma was independently associated with a higher risk of distant metastasis and tumor-specific death; Local recurrence was not significantly influenced by the presence of myogenic differentiation [19]. Although myogenic differentiation on the basis of α-SMA and desmin was observed in our case, possibly indicating an elevated risk of distant metastasis and tumor-specific death, the high-grade OS component seemed to more strongly affect the patient's prognosis.

The high-grade OS component expressed MDM2 and CDK4 in this case. There are two possible way to explain their expression. First, the high-grade OS component was a dedifferentiated component of DDL; thus, MDM2 and CDK4 were expressed as was usually observed in DDL [5]. Second, the low-grade OS component represented extraskeletal low-grade OS [10-14] and the high-grade OS component appeared as result of pro-

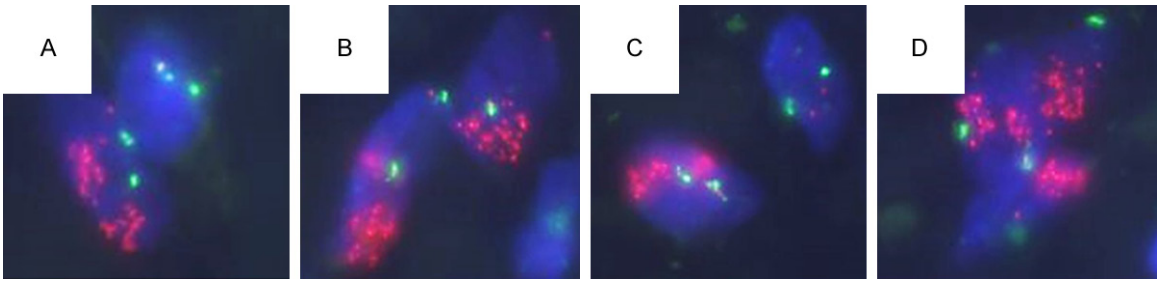

Figure 5. Fluorescence in situ hybridization findings. The visible orange signals corresponded to *MDM2*, while the green signals represented the centromere of chromosome 12. Amplification of *MDM2* was visible in the well-differentiated liposarcoma (A), inflammatory myofibroblastic tumor-like (B), low-grade osteosarcoma (C), and high-grade osteosarcoma (D) components.

gression from extraskeletal low-grade OS. As was observed in our case, Yoshida et al. found that high-grade OS component emerged in juxtaposition to the low-grade OS component in three (33%) of the nine cases in which the WDL component was also present in proximity to the OS component; they did not conclude whether the OS represented extraskeletal OS or a dedifferentiated component of DDL [4]. In another report, Yoshida et al. showed that MDM2 and CDK4 expression rarely occurred in primary, recurrent, and metastatic high-grade OS, and that most cases of high-grade OS expressing MDM2 and CDK4 were considered to be transformed from precursor low-grade OS expressing them as well [20]. Thus, there exist a possibility that low-grade and high-grade OS components observed in our case were independent of WDL component, which meant they constituted a spectrum of an extraskeltal OS. However, as was observed in the IMT-like component, the OS component developed in contact with the WDL component on CT. Thus, it is probable that the OS component was a dedifferentiated component of DDL, along with *MDM2* amplification in OS component. Of note, there exists one documented case of liposarcoma showing OS and IMT-like components as DDL components [3].

In conclusion, WDL, IMT-like, low-grade OS, and high-grade OS components were observed in this case. IMT-like and low- and high-grade OS components formed masses seemingly developing from the mass of WDL component. All four of those components exhibited amplification of *MDM2*. Since *MDM2* amplification could be observed in primary IMT and primary low-grade OS, this finding alone did not mean that those four components constituted the spectrum of a single tumor. In addition to *MDM2* amplification, spatial relationship among the four components also suggested that they were within a spectrum starting from the WDL component; the other three components were derived from the WDL component through dedifferentiation.

Disclosure of conflict of interest

None.

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