Dedifferentiated liposarcoma with abrupt transition of low-grade and high-grade dedifferentiation: A rare case report

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Abstract
Dedifferentiated liposarcoma is a unique subtype of liposarcoma, which has obvious histological heterogeneity. In affected patients, the condition typically manifests as the dedifferentiation of high-grade histological morphology, but it may also manifest as the dedifferentiation of low-grade histological morphology. In some cases, unique histological or immunophenotypic characteristics are observed. We describe, herein, a rare case of dedifferentiated liposarcoma, in which the high-grade and low-grade dedifferentiated components coexisted with a relatively sharp transition in pathology.

Keywords
dedifferentiation, liposarcoma, neoplasm, histopathology, magnetic resonance imaging

Introduction
Liposarcoma is the single most common soft tissue sarcoma, accounting for 20–35% of soft tissue sarcomas.1,2 Although atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS) and dedifferentiated liposarcoma (DDLPS) have similar genetic characteristics, WDLPS and DDLPS represent two ends of the histologic and behavioral spectrum for a single disease entity.2,3 Histopathologically, DDLPS may show a markedly heterogeneous morphology. In most patients, the condition manifests as the dedifferentiation of high-grade histological morphology, similar to undifferentiated pleomorphic sarcoma or high-grade myxofibrosarcoma. In some cases, the condition may manifest as the dedifferentiation of low-grade histological morphology or mixed high-grade and low-grade histological morphology.4-6 Low-grade DDLPS may be similar in histology to low-grade myxofibroblastic sarcoma, fibromatosis, inflammatory myofibroblastic tumor, gastrointestinal stromal tumor (GIST), or solitary fibrous tumor.4,5,7 Distinguishing the various histological types of liposarcoma is not always easy, even for an experienced pathologist, especially when only a few samples are available.

In this article, we retrospectively analyze the pathological and imaging findings of a rare case of DDLPS with mixed high-grade and low-grade dedifferentiated histological features with multiple focal regions of a sudden transition. We also review the relevant literature.

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Case report

The patient was a 69-year-old woman, who was admitted to the emergency department of our hospital with severe abdominal pain lasting 1 h in February 2020. The patient accidentally discovered a mass in the left middle abdomen 4 months prior. The patient had begun to have abdominal cramps repeatedly over the preceding 3 months. The abdominal pain was intermittent, and it relieved spontaneously after discharging a large amount of watery stool. On physical examination, a very large soft mass could be palpated in the left abdomen. Laboratory findings were considered as normal, and tumor markers (carcinoembryonic antigen and CA19-9) were within normal limits.

Magnetic resonance imaging (MRI) examination showed an 8 cm × 13.3 cm × 20.9 cm mass in the left retroperitoneal cavity. The MRI signal intensity for most of the mass was hyperintense on T1-weighted images and T2-weighted images (Figure 1(a)), with drop-out on MRI fat-suppressed sequence images (Figure 1(b)). A solid nodule was seen in the lesion with a heterogeneous signal. During laparotomy, the well-circumscribed, lobulated mass, which was located in the left retroperitoneum and about 25 cm × 20 cm × 22 cm in size, underwent complete excision. The upper part of the tumor was very hard and adhered to the mesocolon of the descending colon; a large amount of brown-yellow fat-like tissue was seen in the lower part of the tumor. Grossly, the size of the grayish-yellow fatty mass was about 9 cm × 8 cm × 7 cm, and a round nodule with a complete capsule was seen adjacent to the fatty mass, which was about 11 cm × 9.5 cm × 7 cm in size. A grayish-yellow necrotic area (about 8 × 6 × 5 cm) was seen in the nodule’s center, surrounded by a crescent-shaped grayish-white and grayish-brown tumor. There was a clear boundary between brown tumor foci near the capsule and other gray-white or fish flesh-colored tumor foci (Figure 2).

Microscopically, the grayish-yellow lipoid nodule was WDLPS (Figure 3(a)), and the solid nodule was DDLPS. DDLPS showed two different histological types and grades. Most of the solid nodule were high-grade pleomorphic undifferentiated sarcomas with extensive tumor necrosis, and the tumor cells had obvious atypia and active mitotic images (about 50/50 high-power microscopic field; HPF) (Figure 3(b)). The low-grade DDLPS were located...
near the capsule of the solid nodule; histologically, they were inflammatory myofibroblastic tumor-like (Figure 3(c)) and fibromatosis-like features. Most of the tumor cells were spindle-shaped and had slight atypia, with pleomorphic tumor cells occasionally seen (Figure 3(e)). The average mitotic images were about 3/50 HPF, and no tumor necrosis was identified. The low-grade DDLPS with multiple foci can be seen, which suddenly transits to the high-grade DDLPS (Figure 3(d) and (f)). Immunohistochemical staining showed that p16, MDM2, and CDK4 were diffusely expressed in WDLPS and DDLPS (including high-grade dedifferentiation and low-grade dedifferentiation), and smooth muscle actin and CD34 were locally expressed in the low-grade DDLPS. Both components were negative for DOG1, c-KIT, desmin, and S100 protein. Ki67 is about 60% in high-grade DDLPS and 8% in low-grade DDLPS. Fluorescence in situ hybridization (FISH) analysis showed the presence of MDM2 gene amplification. These findings supported a diagnosis of DDLPS.

The patient recovered well and was discharged from the hospital on the seventh day after surgery. Follow-up was performed regularly, and there was no sign of local recurrence or distant metastasis during a 15-month follow-up.

Figure 3. Histologic analysis of dedifferentiated liposarcoma specimens. (a) Typical well-differentiated liposarcoma of the adipocytic/lipoma-like type (hematoxylin–eosin stain; ×100). (b) High-grade dedifferentiated liposarcoma demonstrates high cellularity, pleomorphism, and marked cellular atypia (hematoxylin–eosin stain; ×100). (c) and (d) Transition from low-grade dedifferentiation with inflammatory myofibroblastic tumor-like features to high-grade dedifferentiation with undifferentiated pleomorphic sarcoma features (hematoxylin–eosin stain; c ×40). The boundary (white arrows) between them is clear (hematoxylin–eosin stain; d ×20). (e) and (f) Transition from low-grade dedifferentiation with fibromatosis-like features to high-grade dedifferentiation with undifferentiated pleomorphic sarcoma features (hematoxylin–eosin stain; e×40). The boundary (white arrows) between them is clear (hematoxylin–eosin stain; f ×20).

Figure 4. Fluorescence in situ hybridization of the MDM2 gene. FISH analysis confirmed MDM2 gene amplification (clustering of red signals) in the nuclei of atypical cells. FISH: fluorescence in situ hybridization.
Discussion

According to the World Health Organization (WHO) classification standards, the definition of DDLPS is a bone and soft tissue tumor or ALT/WDLPS that has dedifferentiated into a different degree of sarcoma at the same time or before/after the development of ALT/WDLPS. Dedifferentiated areas usually consist of undifferentiated pleomorphic sarcoma or spindle cell sarcoma, with high to moderate cellularity and pleomorphism. Traditionally, DDLPS are all considered high-grade sarcomas, and no further histological grading is required. Recently published clinicopathological analyses have confirmed that DDLPS can be further divided into low-grade (equivalent to Grade 2) and high-grade DDLPS (equivalent to Grade 3) according to the French National Federation of The Centers for the Fight Against Cancer (FNCLCC) grading system. Grade 2 DDLPS occupied about 10% of all DDLPS and had a better prognosis and overall survival rate than Grade 3 DDLPS. In contrast to ALT/WDLPS, which has a relatively clear histological subtype, DDLPS represents a morphologically heterogeneous group. In the case described above, DDLPS was characterized by the coexistence of high- and low-grade dedifferentiated components. This manifestation is rare in clinical practice. We summarize the associated pathological features and MRI findings to deepen the awareness of this rare type of DDLPS.

DDLPS presents most commonly in middle-aged and older adults and affects both genders equally. The condition is extremely rare in children and adolescents. The retroperitoneum is the site most frequently affected, followed by the limb and spermatic cord/paratesticular area. Rarely affected sites include the chest cavity, mediastinum, and head and neck (such as the larynx or esophagus). Due to the large space for tumor growth in the posterior peritoneal area, ALT/WDLPS in this area can grow for a long time without causing symptoms. There is therefore a high risk (about 28%) that dedifferentiation will be observed at the time of diagnosis.4,7

The histology of DDLPS usually includes ALT/WDLPS components that have transformed into non-fatty tumor components, and the two components are usually clearly demarcated under the microscope. The most common histological type of ALT/WDLPS in DDLPS is lipomatous and sclerotic. As seen in our case report, the retroperitoneal mass was huge and contained many WDLPS components, and the dedifferentiated components were characterized by the coexistence of low-grade and high-grade dedifferentiated components.

High-grade dedifferentiation can coexist with low-grade dedifferentiation, but this is rare. The pathological manifestations of this case belong to this category. In this case, the histological morphological characteristics of low-grade dedifferentiation in the specimen showed bidirectionally, and some areas showed inflammatory myofibroblastic tumor-like characteristics changes, while some areas showed fibromatosis-like characteristics changes, and the coexistence of these two histomorphology reflected the variability and relative instability of the histological phenotype of low-grade dedifferentiation when they are formed. The low-grade dedifferentiation components accounted for only 10% of the dedifferentiated tumor and were located in the periphery of the high-grade dedifferentiation components, and the two dedifferentiated portions suddenly transition with a clear boundary. We speculated that low-grade dedifferentiation may be a precursor to high-grade dedifferentiation, the conversion starts from the periphery in DDLPS, and this deduction has also been described in another article.4 Besides, the dedifferentiation components can also show other histological morphological characteristics, such as concentric circle-like changes and even mixed distribution.11

As mentioned above, DDLPS can show a wide spectrum of histological morphology. In addition to the common histological features similar to other types of soft tissue sarcomas described above, many structural characteristics that are difficult to describe in morphology can also be seen. If DDLPS occurs outside the retroperitoneum, it can simulate the more common soft tissue tumor in this site, thus confusing the differential diagnosis, particularly for the low-grade DDLPS. For example, the low-grade DDLPS occurring in the gastrointestinal tract may simulate the more common GIST or inflammatory fibrous polyp,12 and the low-grade DDLPS arising in the paratesticular locations may be similar to the cellular angiofibroma, etc. This also reminds us to be vigilant and carefully understand our daily work.

Besides, in the differential diagnosis of fatty tumors other than ALT/WDLPS, immunohistochemical staining that is positive for p16, MDM2, and CDK4 has high sensitivity and specificity for the diagnosis of DDLPS. In this case, well-differentiated liposarcoma components and dedifferentiated liposarcoma components (including high-grade dedifferentiation and low-grade dedifferentiation) all diffusely express P16, MDM2, and CDK4. However, in the differential diagnosis of DDLPS and non–fat-derived tumors, the specificity of the above three markers is insufficient.

At this time, the use of FISH to detect the amplification of the MDM2 gene is highly specific and sensitive for the diagnosis of DDLPS, especially when diagnosed with small biopsy specimens. The use of FISH is even more specific and sensitive in small biopsy specimens without typical WDLPS components or low-level dedifferentiation and rare types of DDLPS. Amplification of the MDM2 gene is generally considered as the gold standard for the diagnosis of ALT/WDLPS and DDLPS.

The diagnosis of DDLPS requires the existence of two components in the tumor: lipogenic WDLPS and cellular nonlipogenic sarcoma. MRI can easily be used to identify fat-derived components in tumors through the use of fat-suppressed T2 images or short tau inversion recovery imaging.14 These approaches allow for the identification of
WDLPS components in DDLPS, which is more helpful for diagnosis; however, in some cases, the WDLPS composition may go unnoticed. Because DDLPS is the conversion of WDLPS components to non-fat-derived tumor components, DDLPS lesions may lack signs of lipid characteristics on MRI.

Conclusion
For the diagnosis of liposarcoma, whether based on MRI or pathology, we should pay attention to typical fat components. MRI has some limitations when used for the preoperative diagnosis of liposarcoma in samples lacking fatty components or for the diagnosis of liposarcoma. The differential diagnosis for DDLPS is wide, and there are many diagnostic traps. Extensive sampling of the mass is recommended to avoid missing any component. Sampling should be performed in both non-fatty and fatty tissues. To avoid the misdiagnosis of DDLPS, it is sometimes necessary to perform immunohistochemistry (such as MDM2 gene amplification). The transition between high- and low-grade differentiation components of DDLPS characterized in this case report is an important aspect of rare pathological manifestations of DDLPS.

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Ethical approval
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Informed consent
Written informed consent was obtained from the patient for anonymized patient information to be published in this article.

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