Int Surg 2016;**101**:217–221
DOI: 10.9738/INTSURG-D-14-00282.1

Case Report

Dedifferentiated Liposarcoma of Retroperitoneum With Extensive Osteosarcomatous Component

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Dedifferentiated liposarcoma (DDLS) is a rare subtype of liposarcoma composed of 2 components: a well-differentiated liposarcoma (WDLS) and a nonlipogenic sarcoma (dedifferentiation component), represented in >90% of cases by a high grade undifferentiated pleomorphic sarcoma, in the form of both small microscopic foci and/or grossly recognizable nodular masses. The paper reports a rare case of a retroperitoneal DDLS, in which approximately half of a tumor mass is composed of a high-grade osteosarcoma. A 68-year-old Caucasian woman affected by abdominal discomfort. Clinical examination showed a large, hard and fixed abdominal mass. Computed tomography scan revealed a huge retroperitoneal mass composed of 2 distinct components: the upper part showed a hypodense tissue, while the lower part showed a higher density and coarse calcifications. Patient underwent to a challenging surgical resection of the mass that, at histological examination, resulted to be a DDLS, in which a WDLS coexisted with an osteosarcoma. Presurgical diagnosis of DDLS is difficult due to the great morphologic variability of the dedifferentiated component, ranging from low to high-grade nonlipogenic sarcoma. The present case contributes to widen the morphological spectrum of DDLS, emphasizing the possibility that a retroperitoneal mass with a

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dual tissue component, one of which containing extensive areas with coarse calcifications, is highly suspected to be a DDLS with an osteosarcomatous component. This pre-operative finding should alert the surgeon because it has a significant impact on prognosis, increasing the risk of local recurrence and of death by disease in a few months after diagnosis.

Key words: Retroperitoneal tumors – Dedifferentiated liposarcoma – Osteosarcomatous dedifferentiation

Dedifferentiated liposarcoma (DDLS) is a peculiar subtype of liposarcoma commonly arising from the retroperitoneum or limbs of adults. Histologically it shows abrupt transition from a well-differentiated liposarcoma (WDLS) to a high grade, or less frequently low-grade, nonlipogenic sarcoma.

In literature it was already known that the nonlipogenic component of a DDLS usually consists of undifferentiated high-grade pleomorphic sarcoma. Notably only about 5 to 10% of DDLS may additionally exhibit heterologous components, such as osteosarcomatous/chondrosarcomatous, usually in the form of small foci. Instead only a few cases were reported in which the heterologous components, especially rhabdomyosarcomatous one, are so extensive to result into large, macroscopically-evident mass.

We herein report the radiologic, surgical, and pathologic features of a rare case of DDLS of retroperitoneum, in which approximately half of tumor mass was composed of a high-grade osteosarcoma.

Case Report

A 68-year-old woman was admitted to our hospital with complaints of abdominal discomfort, but with no recent change in bowel habits. She also referred pain at her left limb, especially at the level of the thigh. Her laboratory data were normal, including the values of tumor markers (CEA, CA–125, CA–19.9).

Clinical examination showed a large, firm in consistency, and fixed abdominal mass (diameter of about 15–20 cm), which presented indistinct margins and occupied the entire left part of the abdomen; the left thigh appeared slightly edematous.

Radiography and an ultrasound examination of the abdomen were performed, and both confirmed a huge mass with exuberant calcifications.

Computed tomography (CT) scan revealed a huge retroperitoneal tumor mass that occupied the entire left abdomen, extended inferiorly to the left iliac fossa (cranial-caudal diameter of about 17 cm) and reached anteriorly the rectus abdominis muscle. The left kidney was displaced superiorly and the renal vessels were stretched but noninfiltrated. Interestingly, the mass was composed of 2 distinct components: (1) the upper part (full arrow in Fig. 1A), that appeared homogeneous, with well circumscribed margins, and composed of hypodense tissue; (2) the lower part (empty arrow in Fig. 1A), with ill-defined margins, a higher density, an evident enhancement after the intravenous administration of contrast medium, and some extensive areas with coarse calcifications. There were neither signs of local invasion nor nodal/distant metastases.

The patient underwent surgical resection and the retroperitoneal mass was completely removed as two distinct masses: (1) the first mass (full arrow in Fig. 1B), was resected together with the left adrenal gland and the left kidney, that were widely connected with the tumor without a cleavage plane; (2) the second mass (empty arrow in Fig. 1B), was resected together with an infiltrated portion of the left psoas muscle.

Gross examination of the first mass revealed a solid, oval-shaped tumor with smooth surface, which at cut section showed the typical appearance of a lipomatous tumor (Fig. 2A). Histologically, it exhibited the characteristic features of a well-differentiated liposarcoma, lipoma-like variant, being composed of mature adipose tissue intersected by thick fibrous septa, which contained atypical stromal cells (Fig. 2B).

Gross examination of the second mass showed a fleshy, round-shaped mass, reddish to brown in color, which was difficult to be sectioned for the presence of extensive calcifications and at cut section presented extensive hemorrhagic areas (Fig. 2C). At histologic examination it was composed of small- to medium-sized round undifferen-

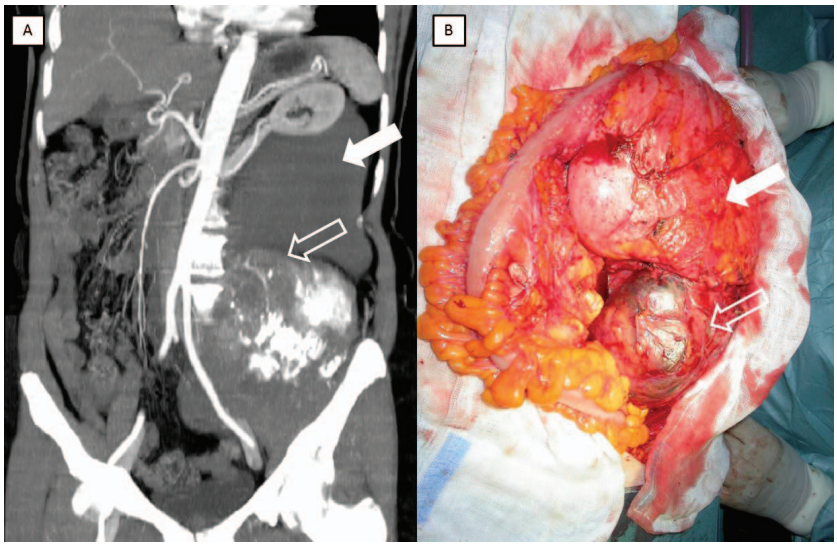

Fig. 1 CT post-contrastographic coronal reconstruction image (A) and surgical specimen (B).

tiated malignant cells producing brightly eosinophilic osteoid matrix, with or without calcifications, consistent with the diagnosis of "high-grade osteosarcoma" (Fig. 2D). As this tumor was an integral part of the lipomatous mass, it was considered as the dedifferentiated component of the well-differentiated liposarcoma and the final diagnosis of "dedifferentiated liposarcoma with extensive osteosarcomatous component" was rendered.

The patient was subsequently treated with radiotherapy. After 6 months, patient experienced a local recurrence in the pelvis, near the iliac vessels, with consequent progressive swelling of the left thigh and then of the entire left lower limb. The additional radiation treatment had no results and the patient died of neoplastic cachexia about 1 year after surgery.

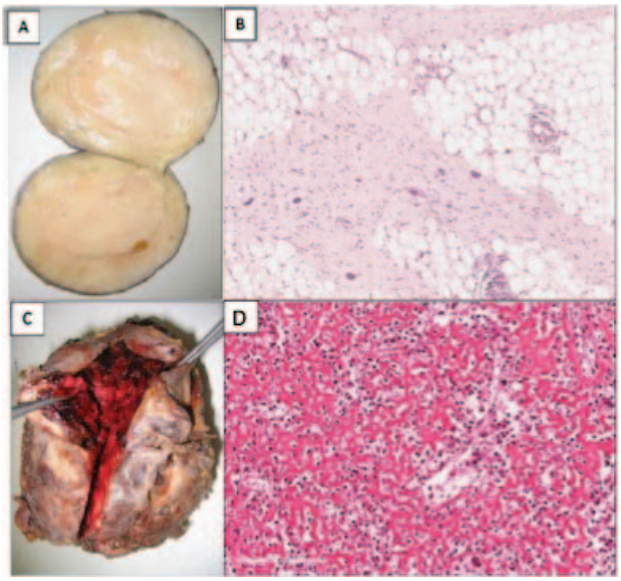

Fig. 2 Pathologic assessment of both lipogenic (A and B) and nonlipogenic (C and D) components of the mass.

Discussion

Although liposarcoma is the second histotype among all sarcomas (after fibro-histiocytic tumors), it remains a rare disease with an incidence of 2 to 3 out of 100,000 new cases per year.[1]

According to the most recent World Health Organization (WHO) classification, DDLS is one of the 5 subtypes of liposarcoma[2] and it is composed of 2 distinct components: a WDLS and a nonlipogenic sarcoma. In 90% of cases the dedifferentiated component is represented by a high-grade undifferentiated pleomorphic sarcoma, while only rarely a rhabdomyosarcomatous, leiomyosarcomatous[3] or an osteosarcomatous component can be encountered. Notably, in our case a retroperitoneal WDLS contained an unusual, large (about half of the entire tumor volume) high-grade osteosarcoma as dedifferentiated component.

The first case of WDLS with a concurrent osteosarcoma was reported by Evans in 1979.[4] Toshiyasu *et al*, in a study conducted in 2009, described 2 similar cases, which were added to a list of other 7 cases previously reported in the literature.[5] Subsequently, in 2013, Fujii *et al* reported their own case and, by reviewing the literature on the topic, they found 4 additional cases of DDLS with osteosarcomatous components, for a total of 14

cases.[6] To the best of our knowledge, no other cases of DDLS with osteosarcomatous component have been reported so far in the English literature, and so our case is the 16th case.

In the past, similar tumors were labelled with the generic term of "malignant mesenchymoma"[7] and they were regarded to arise from mesenchymal cells differentiated along several cell lines, including the osteosarcomatous line.[8] Actually, the most accepted hypothesis is that the dedifferentiation is due to the acquisition of additional mutations in oncogenes implicated in liposarcomagenesis within a preexistent WDLS.[9] The dedifferentiation occurs more frequently in the retroperitoneum, as a time-dependent event, related to the fact that diagnosis of retroperitoneal WDLS is usually achieved more lately than in superficial soft tissues.[10] In our case only a delayed diagnosis was obtained because, despite a retroperitoneal mass of enormous size (about 17 cm), the symptomatology was very poor and only mild signs of compression on the adjacent intestinal and vascular structures were the onset. Imaging was crucial in orienting our preoperative diagnosis. In particular we exploited the capacity of CT in showing the particular dual internal structure of the mass, thanks to the close correspondence between the tissue composition and the CT density.[11] Percent of fat, focal nodular/water density, ground glass opacities, and hypervascularity are important radiologic criteria to distinguish between WDLS and DDLS.[12] In our case a fatty part of the mass was clearly discernible by a nonfatty, hypervascularized and calcified part, which was highly suspected to be the dedifferentiated component of a DDLS.

Hong *et al*, reviewing the CT and MR images of 15 patients with histologically proven DDLS, identified 4 morphologic patterns based on the more or less abrupt transition to the dedifferentiated part: nonfatty component within predominant fatty mass (type I), focal fatty component within large nonfatty mass (type II) and two masses with predominantly nonfatty component (type IV) were the most found typologies (respectively 33%, 40%, and 20%). Remarkably the occurrence of a well-defined lipomatous mass juxtaposed to another nonlipomatous mass (type III), as seen in our case, is described in only 1 of the 15 patients; moreover, the only case of DDLS with osteosarcoma of this study showed a morphology of type I, but not type III.[13]

In our DDLS on CT images the most relevant elements in the context of the osteosarcomatous component were diffuse and coarse calcifications. However it is remarkable that calcifications and ossified areas not always indicate the concomitance of an osteosarcoma and only the histologic demonstration of malignant elements, which produce osteoid matrix, can prove the existence of an osteosarcomatous differentiation.[14] DDLS is characterized by more malignant behavior and worse overall survival than WDLS. As demonstrated by Tateishi *et al*, in addition to the diagnostic role, calcifications and ossification have a significant impact on prognosis, increasing the risk of local recurrence and of death by disease in a few months after diagnosis; no other parameters, including age, sex, size, imaging (localization, margins, local invasiveness, presence of septa or capsule), the extension of the dedifferentiated component and its histological subtype, have been significantly correlated to survival.[15]

In our case the overall good health of the patient encouraged performing a challenging radical surgery, which included the excision of adjacent organs, such as left kidney and adrenal gland, because it appeared as the only chance of obtaining a R0 resection. This approach was justified by the fact that the ideal treatment of all subtypes of retroperitoneal liposarcomas remains a wide surgical resection with tumor-free margins and efficacy of chemotherapy and radiotherapy is still controversial.[16] However Keung *et al*, in a large study (cohort of 119 patients) on primary retroperitoneal DDLS surgically removed, recently showed that the outcome is very poor because, although a macroscopically complete surgical resection (R0/R1) can often be achieved, despite large tumor size and proximity to vital organs, histologic examination only rarely confirms tumor-free margins. For this reason DDLS develop local recurrence or progression in about 84% of cases and related-disease death in about 53% of cases.[17] Our patient presented a pelvic recurrence at 6 months after surgery and died from tumor cachexia after 12 months of diagnosis. So our experience confirmed unfortunately the high malignancy of DDLS.

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