Giant dedifferentiated liposarcoma of the neck with osteosarcoma and chondrosarcoma components: A case report

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Received September 27, 2024; Accepted January 7, 2025

DOI: 10.3892/mco.2025.2824

Abstract. Dedifferentiated liposarcoma (DDLPS) is a subtype of LPS characterized by two distinct levels of differentiation and morphological structures, comprising areas of well-differentiated LPS and dedifferentiated, non-lipogenic, highly malignant components. DDLPS most frequently occurs in the retroperitoneum and the soft tissues of the pelvis and limbs, and is rare in the head and neck region, accounting for only 1% of head and neck sarcomas. The present study describes the case of a 72-year-old male with a 30-year history of left upper limb numbness and heaviness. During physical examination, a tumor measuring ~13x22 cm was discovered in the left posterior region of the head and neck. The mass was hard in texture and had limited mobility. A biopsy of the lesion revealed a mesenchymal tumor rich in adipose components with ossification, containing heterologous elements primarily indicative of osteosarcoma, highly suggestive of DDLPS. A radical excision of the tumor was subsequently performed. The surgical specimen exhibits cross-sections with a gray-white to gray-yellow solid consistency, featuring gray-white, semi-transparent areas resembling cartilage. Immunohistochemical staining was positive for murine double minute 2 (MDM2), cyclin-dependent kinase 4 (CDK4), P16, P53, Vimentin and Ki-67, and negative for cytokeratin pan, S-100, CD34 and smooth muscle actin. Fluorescence *in situ* hybridization results indicated amplification of the MDM2 and CDK4 genes. In the present study, a case of a large DDLPS in the neck with components of osteosarcoma and chondrosarcoma was reported. There was no recurrence during the follow-up period. The pathological characteristics, diagnosis and current treatment methods for DDLPS were also described. Although cases of DDLPS have been reported, the number of cases described at this site remains limited to date, and it is currently not possible to accurately predict the treatment efficacy and prognosis.

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Key words: dedifferentiated, liposarcoma, osteosarcoma, chondrosarcoma

Introduction

Liposarcoma (LPS) represents the most prevalent type of soft tissue sarcoma, comprising ~20% of all soft tissue sarcomas (1). In 2020, the World Health Organization classified these tumors as atypical lipomatous tumors (ALT)/well-differentiated LPS (WDL), dedifferentiated LPS (DDLPS), myxoid LPS, pleomorphic LPS and myxoid pleomorphic LPS (2). DDLPS, a rare subtype of LPS, predominantly manifests in the interstitial limbs between the posterior peritoneum and the pelvic soft tissues. It is exceedingly uncommon in the head and neck region, where it accounts for only 1% of all sarcomas in this area (3). The histological features of DDLPS are characterized by the transformation of mature adipocytes into cells exhibiting marked atypia. This transformation typically results in the formation of regions with two distinct components: WDL and dedifferentiated non-adipose high-grade malignant components (4).

The present study reported a case of DDLPS with a history spanning 30 years, characterized by multiple recurrent episodes and culminating in the development of a substantial DDLPS in the neck, exhibiting components of osteosarcoma and chondrosarcoma. This case is intended to heighten awareness among clinicians and radiologists, offering critical insights for diagnosing and treating patients with DDLPS.

Case report

A 72-year-old male patient had initially presented with a pebble-sized, painless lump in the left neck ~30 years previously, which lacked ulceration. The lump gradually enlarged to the size of an adult's fist over five years. Following surgical excision at a local hospital, the patient experienced temporary improvement. However, five years post-surgery, a mass of a

similar size re-emerged in the same location, necessitating further surgical intervention at the same hospital. At two years subsequent to the second surgery, the mass recurred and pathological analysis confirmed it as a lipoma. In April 2023, the patient sought care at The 940th Hospital of Joint Logistic Support Force of Chinese People's Liberation Army (Gansu, China), reporting numbness and heaviness in the left upper limb, significantly impacting the patient's daily activities. Palpatory examination of the size, texture and mobility of the mass revealed a 13x22 cm mass in the left posterior region of the head and neck, characterized by a hard texture and limited mobility.

X-ray imaging revealed a large, dense mass in the subcutaneous soft tissue of the left posterior neck. This mass displayed inhomogeneous density, exerting pressure on adjacent bronchial tubes and causing lumen narrowing (Fig. 1A and B). Computed tomography (CT) scans demonstrated a substantial lobulated mass with mixed densities in the left neck, shoulder and back, measuring ~13x11x22 cm. The borders of this mass were poorly defined, containing multiple flakes, extensive flaky calcifications and hypodense areas resembling fat, with indistinct demarcation from surrounding tissues (Fig. 1C and D). Magnetic resonance imaging (MRI) showed a large soft tissue mass characterized by signal inhomogeneity. The primary body of the lesion presented with low signals on both T1-weighted MRI (T1WI) and T2WI, as well as in the fat suppression sequences. In addition, multiple patchy high-signal areas were observed on both T1WI and T2WI within the lesion, with the posterior part displaying rounded high-signal shadows on T1WI, low on T2WI, and high on fat suppression sequences; overall, the lesion exhibited heterogeneous signal characteristics (Fig. 1E-G).

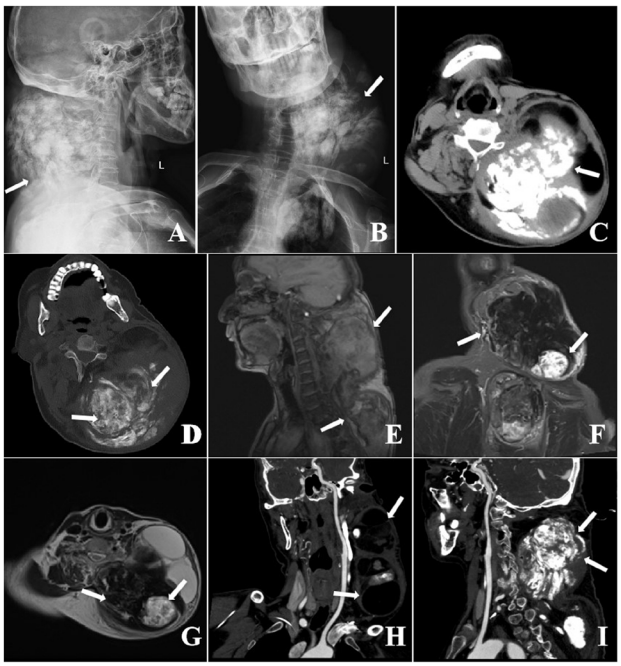

Figure 1. Imaging findings: (A) X-ray orthopantomograph and (B) X-ray lateral view. The shadow of a large soft tissue mass is seen subcutaneously in the left posterior aspect of the neck. (C and D) Preoperative CT findings: Massive lobulated mixed-density soft tissue mass shadow seen in the left side of the neck. (C) Soft tissue window and (D) bone window. (E-G) MRI findings. (E) T1-weighted MRI in the sagittal position, (F) T2-weighted in the coronal position, (G) T2-weighted MRI in the axial position. (H and I) CT findings after chemotherapy: Reduction in tumour size seen after chemotherapy. (H) Coronal and (I) sagittal positions.

Preoperative ultrasound-guided aspiration biopsy of the left neck mass was performed. Histological staining was performed using hematoxylin and eosin (H&E), with a standard protocol including the application of GM hematoxylin (Abcam) for 4 min and pure eosin (Abcam) for 2 min at room temperature. H&E staining revealed a fat-rich mesenchymal tumor with ossification and visible heterologous components, predominantly chondrosarcoma, highly suggestive of DDLPS (Fig. 2). For further analysis, immunohistochemistry (IHC) was carried out. The paraffin-embedded sections of the tumour were cut to a thickness of 4 μm and placed onto slides. Sections were immersed in citrate buffer (Gibco; Thermo Fisher Scientific, Inc.) and heated in a water bath for 25 min at 95-100˚C for antigen retrieval. Prior to staining of the sections, endogenous peroxidase activity was blocked using 3% H_2O_2 with incubation for 10 min at 37˚C. The sections were then incubated with specific primary antibodies for 2 h at 37˚C, and subsequently, anti-rabbit IgG (cat. no. RAB-0102; 1:500; Maixin Biotechnologies) was applied to the sections and incubated for 10 min at 37˚C. Visualization was performed using a diaminobenzidine chromogen (Abcam) as a substrate (incubation for 3-5 min at room temperature). Sections were counterstained with hematoxylin (Abcam). A final drop of neutral resin was added for sealing with a coverslip and slides were observed under a light microscope. The IHC staining results using antibodies from Maixin Biotechnologies were as follows: i) Murine double minute 2 [MDM2, (+); cat. no. MAB-0744; pre-diluted 5 μg/ml]; ii) cyclin-dependent kinase 4 [CDK4, (+); cat. no. RMA-0741; pre-diluted 5 μg/ml]; iii) P16, (+); cat. no. MAB-0673; pre-diluted 10 μg/ml; iv) P53, (wild-type); cat. no. MAB-0674; pre-diluted 5 μg/ml; v) cytokeratin pan, (-); cat. no. RAB-0050; pre-diluted 10 μg/ml; vi) vimentin, (+); cat. no. Kit-0019; pre-diluted 10 μg/ml; vii) S-100, (-); cat. no. RAB-0150; pre-diluted 30 μg/ml; viii) CD34, (-, microvessel +); cat. no. Kit-0004; pre-diluted 10 μg/ml; ix) smooth muscle actin, (-); cat. no. Kit-0006; pre-diluted 10 μg/ml; x) Ki-67, (index: 70%); cat. no. MAB-0672; pre-diluted 20 μg/ml.

The patient exhibited a prolonged disease course, characterized by a high propensity for recurrence. Prior to admission, the patient had undergone three surgical interventions. Considering both the clinical findings and auxiliary examination results, the diagnosis was strongly suggestive of a DDLPS in the soft tissue of the neck (2). At the time of presentation at our hospital, the mass was substantial in size and associated with numbness and heaviness in the upper limbs. After departmental discussions, it was decided to administer two cycles of chemotherapy drugs (isocyclophosphamide 12.5 mg + epirubicin 120 mg) through a peripherally inserted central catheter with the aim of reducing the tumor size. The multidisciplinary team formulating the treatment plan comprised an attending physician, the deputy chief of spine surgery, the chief of medical oncology and the chief of pain medicine. Subsequent imaging with CT post-chemotherapy revealed a decrease in tumor size relative to the baseline measurements (Fig. 1H and I). Before surgically

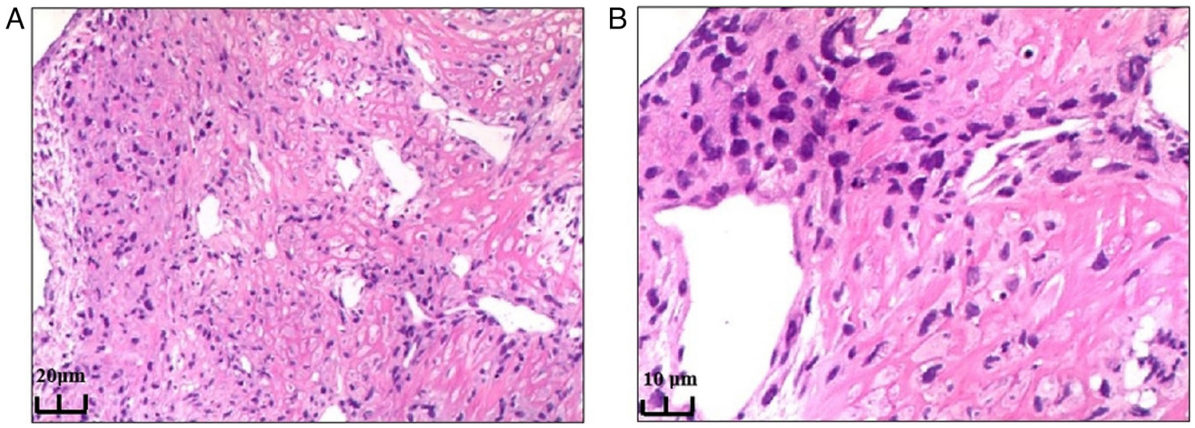

Figure 2. Preoperative pathological biopsy of a left neck mass: (A) Tumours of mesenchymal origin rich in fatty components with ossification, in which dedifferentiated components are seen, are mainly chondrosarcomas (H&E staining; magnification, x10). (B) (H&E staining; magnification, x20).

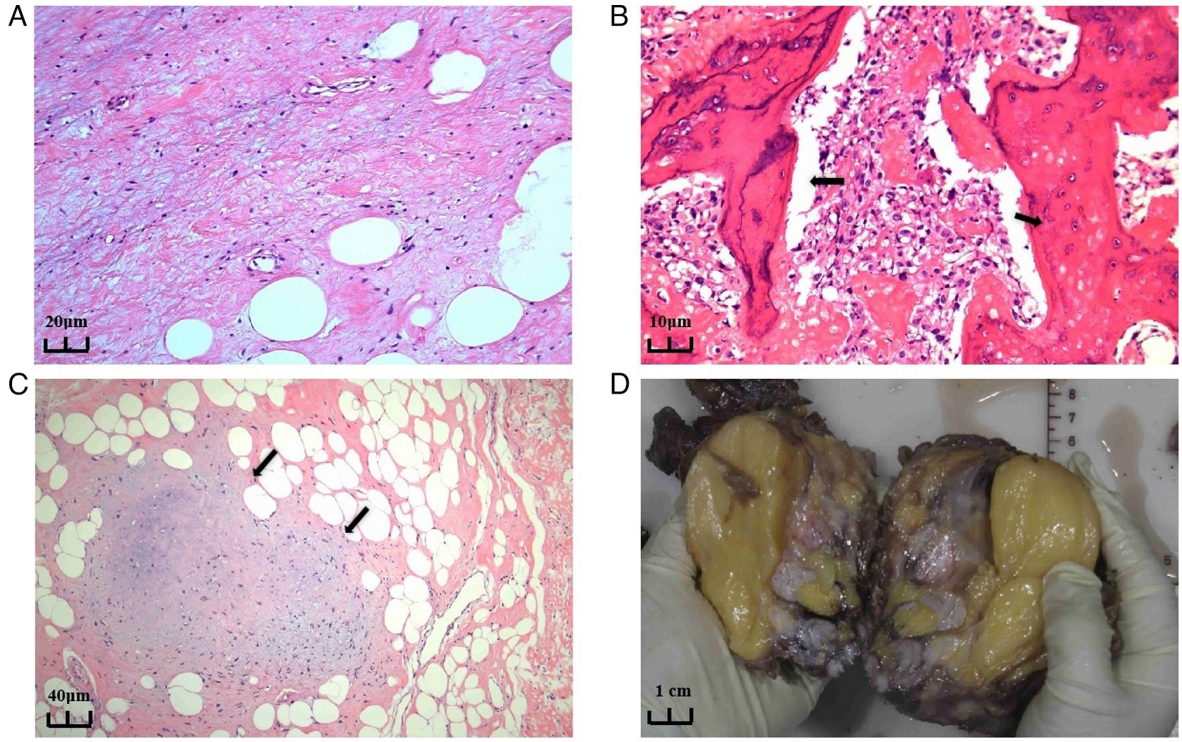

Figure 3. Pathologic findings. (A) Part of the well-differentiated liposarcoma shows mature adipocytes and abundant fibrous tissue. There are more collagen fibers in the surrounding area and the diversity of cell nuclei is relatively low, indicating a lower degree of heterogeneity (H&E staining; magnification, x20). (B) A large number of spindle-shaped cells and pleomorphic tumor cells are present, with a significantly increased cell density. The stroma shows sclerosis accompanied by infiltration of inflammatory cells (as indicated by the arrows). Nuclear atypia of the tumor cells is evident, displaying typical features of dedifferentiated liposarcoma. Cell proliferation is active, exhibiting malignant characteristics, along with osteosarcoma and tumor-related osteogenesis (H&E staining; magnification, x40). (C) The combination of adipocytes and fibrous tissue still exhibits highly differentiated characteristics in its organizational structure. However, in certain areas, the arrangement of cells shows abnormalities, suggesting the presence of potential dedifferentiation. This indicates a transitional zone between high differentiation and dedifferentiation, hinting at possible malignant changes (H&E staining; magnification, x10). (D) Gross appearance of cross-sectional view of the resected neck mass.

removing the tumor, a carotid angiography and thyroid artery embolization were performed. The purpose was to reduce the tumor's blood supply and surgical bleeding, clarify the surgical field, shorten the operation time and improve the tumor resection rate. As the tumor was too large, complete removal in a single piece was difficult. Therefore, a bone knife was used to divide the tumor into several large sections before removing the entire mass. Finally, the tumor was completely removed and sent to the Department of Pathology.

The resected neck mass consisted of several pieces of unshaped tissue, grayish-yellow to grayish-brown in color, with a total size of 30x25x6 cm. The postoperative pathological results were as follows: DDLPS, with differentiated components being ALT/WDL, and dedifferentiated components being osteosarcoma and chondrosarcoma (Fig. 3A-C).

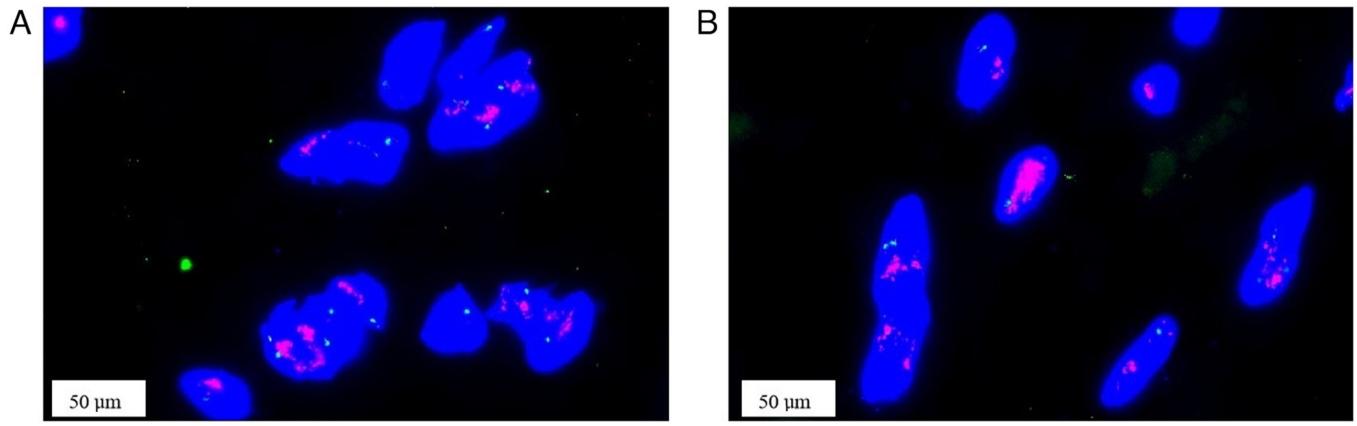

Figure 4. Results of the FISH. (A) MDM2-amplified cells, osteosarcoma, chondrosarcoma and liposarcoma components (the probe for the MDM2 locus is labeled in spectrum red and the copy number control probe for the centromeric region of chromosome 12 is labeled in spectrum green). (B) CDK4-amplified cells, osteosarcoma, chondrosarcoma and liposarcoma components (similarly, the probe for CDK4 is labeled in spectrum red and the probe for the centromeric region of chromosome 12 is labeled in spectrum green) (scale bar, 50 μm). CDK, cyclin-dependent kinase; MDM2, murine double minute 2.

The excised tissue's cut surface was grayish-yellow, solid and hard; portions of the tissue exhibited bone that was visibly gray and translucent, resembling cartilage. Adipose tissue adhered to certain areas of the unplasticized tissue, which was enveloped by periosteum; these sections were grayish-yellow, solid and soft. Certain local sections appeared gray and solid with a medium texture (Fig. 3D). The main reason for the moderate texture of the mass in our patient was considered to be its nature in between hard and soft. Fluorescence *in situ* hybridization (FISH) analysis showed amplification of the MDM2 and CDK4 genes (Fig. 4). For FISH, 2.5 μm paraffin-embedded sections were baked at 65˚C for 2 h. Sections were deparaffinized with xylene and washed with 100% ethanol. After pre-treatment in boiling water for 20 min, the sections were incubated in a 0.5 mg/ml trypsin solution (Gibco; Thermo Fisher Scientific, Inc.) at 37˚C for 7 min. The probe mixture (probe/hybridization buffer/purified H_2O=1:7:2; Beijing GP Medical Technologies Co., Ltd.) was then added to the slides. The slides were then incubated at 83˚C for 5 min to denature them and then hybridized with the probe at 42˚C overnight. After hybridization, the slides were counterstained with 10 μl of DAPI reagent and mounted with coverslips. Finally, the fluorescent signals were observed by fluorescence microscopy.

Pathology combined with clinical and molecular findings led to the diagnosis of DDLPS with a differentiated component of ALT/WDL and a dedifferentiated component of osteosarcoma and chondrosarcoma. At 10 days after surgery, the patient was discharged normally, and after discharge, celecoxib was given orally for pain relief for two weeks. The patient was followed for up to one year after the operation. During this period, phone follow-ups indicated that the patient had recovered well with no recurrence of the local mass. The patient was repeatedly advised to visit either our hospital or a local hospital for postoperative checkups. However, residing in a remote mountainous area of China and facing financial and geographical constraints, the patient did not undergo professional checkups. Consequently, telephone inquiries were performed to monitor the patient's condition. Follow-up assessments primarily focused on the healing of surgical incisions, recurrence of local lumps, numbness in the upper limbs, alleviation of severe symptoms, as well as the patient's mental status, diet and bowel movements. The timing of these assessments coincided with that of the post-operative review noted in the patient's discharge certificate (1, 3, 6 months and 1 year after the operation).

Discussion

ALT/WDL exhibits few or no mitotic figures and generally lacks prominent fibrous or sarcomatous features macroscopically. Microscopically, fat vacuoles of varying sizes and lipoblasts are typically observed and the stroma contains irregular, hyperchromatic and pleomorphic atypical spindle cells (5). ALT/WDL is considered a different stage of the same tumor type, characterized by slow growth, with numerous patients having had it for several years or even decades by the time of diagnosis (6). DDLPS usually arises from ALT/WDL, presenting as a sudden, gradual or mixed transition from ALT/WDL to non-lipogenic sarcoma; in this zone, cellular atypia gradually increases, fibrous septa become thicker and stromal cells proliferate, ultimately developing into high-grade sarcomatous components (7). This means that within the same tumor, both well-differentiated lipogenic components and dedifferentiated non-lipogenic malignant components are present (8,9).

DDLPS is more commonly observed in middle-aged and older individuals, with rare occurrences in children and adolescents (10). DDLPS may result from the transformation of these lower-grade tumors into higher-grade sarcomas, typically accompanied by rapid symptom deterioration and a sharp increase in tumor growth. A history of illness lasting up to 30 years is often associated with the presence of WDL. However, certain studies suggested that ALT/WDL can transform into DDLPS, a relatively rare process, often accompanied by changes in specific biomarkers (11). The amplification of the MDM2 and CDK4 genes is commonly associated with DDLPS, while it is not evident in most ALT/WDL cases (12).

In DDLPS, the dedifferentiated component and the ALT component coexist within the same tumor and the boundary

between the two may be clear, ambiguous or even exhibit mixed growth (13). In certain cases, there is a distinct histological boundary between the ALT component and the dedifferentiated high-grade sarcoma component, and under the microscope, there is a clear transition from mature, less atypical adipose tissue to highly undifferentiated sarcoma tissue (7).

'Dedifferentiation' refers to the progression of low-grade sarcomas to high-grade sarcomas, including low-grade osteosarcomas, chondrosarcomas and fibrosarcomas (14). In certain cases, the dedifferentiated and transformed component may be a homologous pleomorphic LPS (15). Dedifferentiation can occur in any part of the body, with an estimated frequency of ~10% (16). In ~5-10% of cases, DDLPS may exhibit heterologous differentiation, including rhabdomyosarcomas, leiomyosarcomas, osteosarcomas and chondrosarcomas (17). Dedifferentiation is time-dependent, with an increased likelihood of occurrence as time progresses, with an average time to dedifferentiation of 7-8 years (18). DDLPS is highly invasive, with a strong tendency for distant lung metastasis and local recurrence (4). The local recurrence rate is 41%, the metastasis rate is 17% and the disease-related mortality rate is 28% (19). In the present case, the dedifferentiated components of osteosarcoma and chondrosarcoma were observed in the tumor, which was partially replaced by fibrotic tissue, leading to erosive damage to the surrounding bone and resulting in local metastases, as shown on preoperative imaging.

In terms of symptoms, DDLPS typically presents as a syndrome caused by the compression of surrounding tissues. However, LPS in the retroperitoneal region of the pelvis may grow for extended periods without causing any symptoms (20). In the present study, the tumor was located in the patient's neck, resulting in numbness and a sensation of heaviness in the distal left upper extremity, symptoms that are not specific to DDLPS diagnosis. Therefore, other diagnostic methods are necessary to identify the tumor. Ultrasound findings of DDLPS are typically heterogeneous, solid and hypoechoic, and LPS should be suspected when the tumor exhibits structural heterogeneity and relatively low vascular echoes. In addition to ultrasonography, CT and MRI offer greater precision in differentiating between adipose and other soft tissue components (21). MRI provides information on the exact location of the tumor but does not allow for definitive pathological staging. Imaging can determine the extent of the tumor and its infiltration of surrounding organs, but a final diagnosis requires pathological examination.

Preoperative diagnosis of DDLPS is challenging. Davis *et al* (22) reported that one-third of patients with head and neck LPS are misdiagnosed upon initial pathology, and diagnostic errors can lead to delayed or inadequate treatment. Immunohistochemistry, FISH, quantitative PCR and comparative genomic hybridization are commonly used to identify MDM2 amplification in lipomatous tumors, requiring a highly experienced pathologist for accurate diagnosis (23). A characteristic feature of DDLPS is the amplification of the chromosomal region 12q13-15, which encodes potential oncogenes, including MDM2 and CDK4, with MDM2 being the most prominent. This feature is highly informative for diagnosing DDLPS (24). MDM2 is an oncogene that promotes the degradation of the tumor suppressor protein p53, which is considered the key gene in DDLPS tumorigenesis. MDM2 is widely amplified and expressed in nearly all DDLPS cases (25). The amplification and overexpression of the 12q13-15 region correspond to elevated levels of MDM2 and CDK4 proteins, and MDM2, CDK4 and p16 are present in both the WDL and DDLPS components. While MDM2 and p16 exhibit high sensitivity, they lack specificity and can be found in various high-grade sarcomas (25). Therefore, the concurrent use of MDM2, CDK4 and p16 is often required to improve diagnostic specificity in DDLPS. Immunohistochemical staining for MDM2 and CDK4 is therefore highly useful in diagnosing DDLPS (4). FISH is a molecular cytogenetics technique. It utilizes fluorescently labeled specific nucleic acid probes to hybridize with target DNA or RNA sequences in cells or tissues, allowing for the detection of the presence, location and quantity of the target sequences using fluorescence microscopy (26). A study shown that FISH is more sensitive in detecting MDM2 amplification and can be incorporated into diagnostic protocols for refractory lipomas (27). The present case is consistent with positive expression of MDM2, CDK4 and p16.

The primary treatment for DDLPS involves extensive surgical resection, radiation therapy and adjuvant chemotherapy. Certain studies have indicated that systemic radiotherapy combined with surgical treatment reduces the recurrence of DDLPS (3). However, even with multidisciplinary approaches, DDLPS often recurs rapidly at the local site and can metastasize to the lungs, bones or liver, leading to disease progression that becomes difficult to manage (28). Furthermore, certain studies suggest that potentially targeted molecular therapies, such as tyrosine kinase inhibitors, MDM2 antagonists, CDK4 inhibitors, peroxisome proliferator-activated receptor-γ agonists and nelfinavir, may have therapeutic effects on DDLPS (11,29). Early diagnosis of the present case was difficult. Although early surgical intervention was performed, the disease kept recurring, later leading to repeated exacerbations, which seriously affected the patient's quality of life and physical and mental well-being.

The current study presented a case of giant DDLPS of the neck with osteosarcoma and chondrosarcoma components and reported on its diagnosis, pathology, imaging manifestations and course of treatment in the hope of gaining the attention of clinicians and radiologists. In patients with DDLPS, early and accurate diagnosis can significantly improve prognosis and quality of life. In addition, the complete resection of the tumor during surgery combined with the use of radiotherapy may be reasons for the lack of recurrence after surgery in this patient. However, the prognosis of patients with DDLPS is poor and new treatment strategies are needed in the future to improve the prognosis and treatment.

Acknowledgements

Not applicable.

Funding

This study was funded by the High-Level Talent Cultivation Project at the 940th Hospital of Joint Logistics Support Force (grant no. 2024-G3-5), the Lanzhou Science and Technology Project (grant nos. 2023-2-11 and 2023-ZD-170) and the

Gansu University of Traditional Chinese Medicine Mentorship Project (grant no. 2023YXKY015).

Authors' contributions

JZ obtained the data and wrote the manuscript. RG and KY acquired the data and provided clinical advice. FT, PL, JL, XW and JW evaluated the images. YQ and SZ made significant contributions to the acquisition, analysis and interpretation of the histopathology data. JZ and SZ confirm the authenticity of all the raw data.All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the No. 940 Hospital of the People's Liberation Army Joint Logistics Support Force (approval no.2023KYLL242).

Patient consent for publication

Written informed consent has been obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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