Image Quiz for Surgeons

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Dedifferentiated Liposarcoma of Sigmoid Mesocolon - A Case Report

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Rezumat

Liposarcom dediferențiat mezocolon sigmoidian – caz clinic

Liposarcomul dediferențiat este un tip particular de liposarcom ce conține o componentă bine diferențiată suprapusă cu arii de sarcom non-lipogenetic cu grad înalt de diferențiere despre care s-a crezut că apare după o evoluție de câțiva ani dintr-un liposarcom bine diferențiat. Liposarcomul dediferențiat se dezvoltă cel mai frecvent în spațiul retroperitoneal, în timp localizarea intraperitoneală este extrem de rară, doar șapte cazuri au fost raportate în literatura medicală. Mai mulți anatomopatologi recunosc că un număr mai mare de sarcoame intrabdominale slab diferențiate ar fi de fapt liposarcoame dediferențiate. Prezentăm cazul unui pacient în vârstă de 73 de ani cunoscut cu multiple antecedente personale patologice cardiovasculare, accident vascular cerebral sechelar și o formațiune voluminoasă intrabdominală în evoluție de trei ani de zile. Acesta s-a prezentat în serviciul nostru acuzând dureri abdominale nesistematizate și tulburări de tranzit intestinal. Cu toate că aspectele clinice și imagistice erau sugestive pentru prezența unui GIST, examenul anatomopatologic a relevat diagnosticul de liposarcom dediferențiat.

Cuvinte cheie: liposarcom dediferențiat, mezocolon sigmoidian, formațiune tumorală abdominală

Abstract

Dedifferentiated liposarcoma is a liposarcoma that contains a well-differentiated liposarcoma component juxtaposed to areas of high-grade non-lipogenic sarcoma and was believed to occur from well-differentiated liposarcoma after several years. Dedifferentiated liposarcoma most commonly occurs in the retroperitoneum, while an intraperitoneal location is extremely rare, only seven cases have been reported in literature. Many pathologists recognize that a large number of intra-abdominal poorly differentiated sarcomas are dedifferentiated liposarcomas. We present the case of a 73 years old patient known with multiple cardiovascular comorbidities, stroke sequelae and a large abdominal mass evolving for 3 years. He was referred to our clinic for abdominal pain and bowel disorders. Instead of all clinical and imagistic aspects suggested a gastrointestinal stromal tumour, the histological exam revealed the diagnosis of a dedifferentiated liposarcoma.

Key words: dedifferentiated liposarcoma, sigmoid mesocolon, abdominal mass

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Introduction

Liposarcoma is the most common malignant soft tissue tumor with a mesenchymal origin. It typically occurs in the lower extremities, accounting for 56% of all liposarcomas. The retroperitoneum is the next most frequent location with 15% to 20% of liposarcomas. Also liposarcomas arising from the mesentery are extremely rare. There are five histological types of liposarcomas with different degree of malignancy: well-differentiated liposarcoma, myxoid liposarcoma, dedifferentiated liposarcoma, round cell liposarcoma and pleomorfic liposarcoma according to World Health Organization (1). Liposarcomas represent 10-14% of all soft tissue sarcomas and dedifferentiated type is less than 1% of all malignant tumors (2). Both well-differentiated and dedifferentiated liposarcomas equally affects both sexes with a peak incidence in the 6^{th}-7^{th} decade of life (3). The prevalence of dedifferentiated liposarcoma in Europe is 1-9/1000000 (4). Dedifferentiated liposarcoma is a very aggressive subtype of liposarcoma. It has been shown that it progresses from well-differentiated liposarcoma and often occurs in the retroperitoneum. The global incidence is approximately 1/ 330, 000 persons/year. The etiology of this tumor is unknown (5). The symptoms are nonspecific: abdominal pain, bowel disorders, weight loss, anemia and in some cases palpable tumor mass. There are difficulties in diagnosis and treatment of this type of neoplasm. Actually a large number of intra-abdominal poorly differentiated sarcomas are dedifferentiated liposarcomas, according to the pathologists. Complete surgical excision is considered the gold standard and the curative R0 resection is the main treatment for primary and recurrent liposarcomas (6). We report a case with imagistic investigations and intraoperative macroscopic aspect suggestive for a gastrointestinal stromal tumor of the sigmoid colon but the immunohistochemistry confirmed the dedifferentiated liposarcoma with focal rhabdoid differentiation. To the best of our knowledge this is the second reported case with this localisation and the same histologic type.

Case report

A 73 years old patient known with hypertension, atrial fibrillation, benign prostatic hyperplasia, stroke and repaired bilateral inguinal hernia in the past medical history was admitted to the department of General Surgery of the St Mary Clinical Hospital on the 16th of December, 2015 complaining of abdominal pain and bowel disorders. The patient was on regular medication with oral anticoagulants for atrial fibrillation. Physical examination revealed a large hypogastric mass with approximate diameter of 15x20 cm, well delimited, mobile, painless on palpation, with moderately elastic consistency and a high volume of the left leg with subcutaneous oedema. The laboratory results showed the following abnormalities: iron-deficiency anaemia, lymphopenia, neutrophilia and inflammatory syndrome. The chest x-ray showed no evidence of evolutive pleuro-pulmonary lesions. A Doppler echography was performed that excluded a deep vein thrombosis of the left leg. The barium enema revealed a dolichosigmoid located inferior to the splenic flexure of the colon and a lacunar image on the ascendant sigmoid loop, probably caused by an extrinsic compression (Fig. 1). Abdominal CT showed the presence of a voluminous expansive pelvic tumour, with maximum axial diameters measuring 15/10,5 cm, well defined tumour, with no homogeneous structure. The origin of the tumour was not found (Fig. 1, 2, 3). Pre anaesthetic assessment included: subcutaneous LMWH (low molecular weight heparin) administration and mechanical bowel preparation. The laparotomy (the 23rd of December, 2015) was performed under general anaesthesia. It was found a 20 cm large abdominal mass lesion with elastic fat density and yellowish coloured in the lower right abdominal cavity, displacing the small bowel and transverse colon ventrally, without invasion of the surrounding tissues. The origin of the tumour was found in the sigmoid mesocolon with invasion in the sigmoid wall. The macroscopically aspect suggested a gastrointestinal stromal tumour and a complete extra mucous removal of the tumour without bowel resection was considered the appropriate surgical management and the wall of the colon was repaired with monolayer continuous suture. After surgical removal of the tumour, the second detailed exploration of the abdominal cavity found no other intra-abdominal abnormalities. There were no postoperative complications. The postoperative pains and the resumption of bowel function required common analgesics and prokinetic medication. The patient was submitted to the Intensive Care Unit for cardiac monitoring after one episode of paroxistic atrial fibrillation (heart rate over 150 bpm). He was discharged in the 12th postoperative day after 20 days hospital stay, in good medical condition, with the recommendations for oncological evaluation and continuing the treatment with oral anticoagulants(no histological report

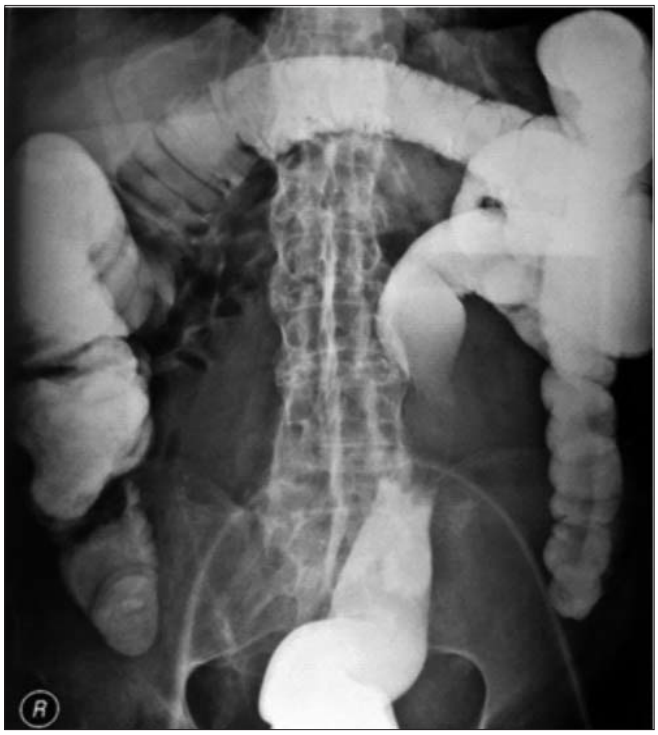

Figure 1. *Barium Enema - lacunar image*

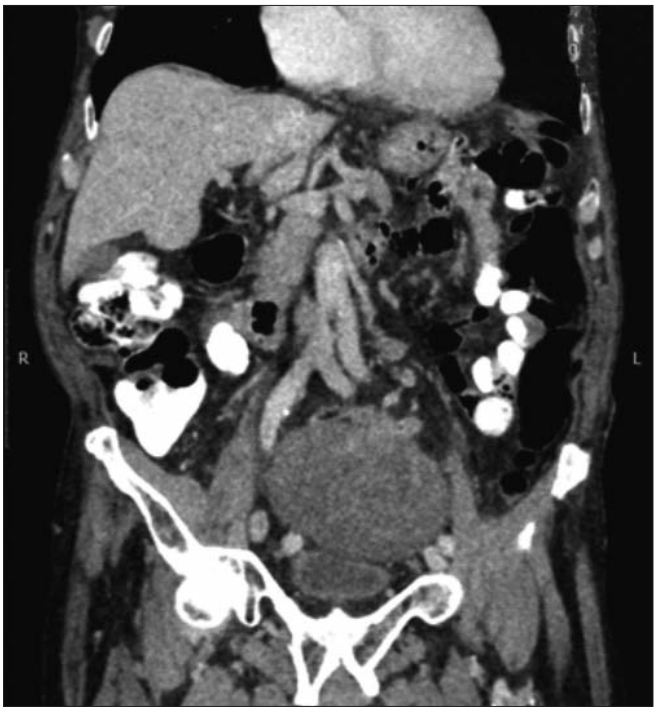

Figure 2. *Abdominal CT - Coronal view*

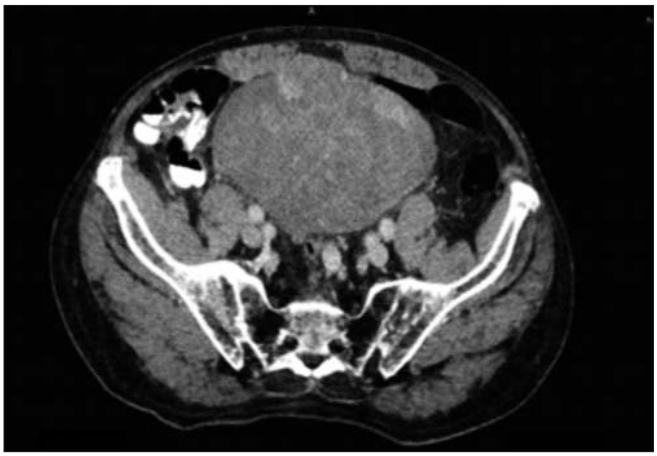

Figure 3. *Abdominal CT - Axial view*

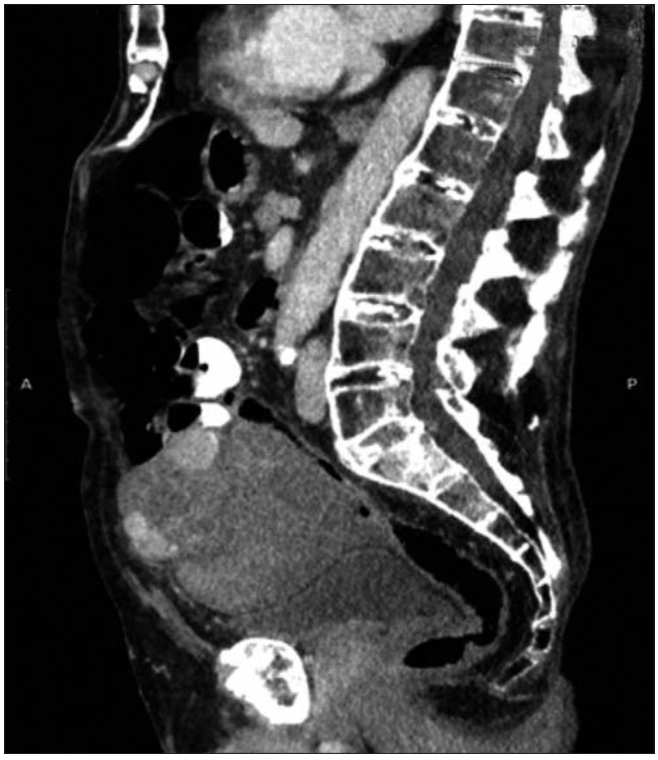

Figure 4. *Abdominal CT - Sagital view*

available on the discharge date). The pathology report was inconclusive showing malignant tumor proliferation composed of fusiform cells with increased pleomorphism, with multiple nuclei, disposed in a fasciculate pattern, with necrosis area; intratumoral blood vessels with branched aspect and focal presence of cells with intracytoplasmic lypoblastic/pseudolypoblastic vacuoles. The result of immunohistochemistry tests showed positive "S 100" in frequent tumor cells, "CD117" negative, "CD34" negative in tumor cells, positive in vessels, "Ck19" negative, "ACT" negative in tumor cells, positive in vessels, "Desm" positive in dispersed tumour cells, "Ki67" positive in almost 40-50% of tumor cells. The histological report and the immunohistochemistry tests suggested a dedifferentiated liposarcoma with focal rhabdoid differentiation. The patient was assessed by oncologist and the adjuvant treatment was not recommended for the patient. The patient is still alive, free from recurrence 6 months after surgery and is due for oncological and surgical follow up.

Discussions

Dedifferentiated liposarcoma is a distinctive clinic pathological entity. The term "tumour dedifferentiation" as established in 1971 by Dahlin and Beabout, characterizes "the morphological progression of a low-grade tumour to a less differentiated neoplasm with a more aggressive behaviour"(7) . Dedifferentiated liposarcoma is traditionally known to be "a non-lipogenic high-grade sarcoma arising from a well-differentiated liposarcoma that confers metastatic potential" .The term dedifferentiated liposarcoma was first introduced by Evans in 1979, describing a liposarcoma that contains a well-differentiated liposarcoma component juxtaposed to areas of high-grade non-lipogenic sarcoma and was believed to occur from well-differentiated liposarcoma after several years (8). The retroperitoneum is the most common location, despite of somatic soft tissue location by at least 5/1 (9,10,11). More than 90% of dedifferentiated liposarcoma arises de novo (synchronous), while $<10\%$ occurs in recurrences (metachronous). Histologically, most cases of dedifferentiated liposarcoma show areas of high-grade poorly differentiated sarcoma resembling high-grade myxofibrosarcoma, fibro sarcoma, malignant solitary fibrous tumour, or pleomorphic sarcoma NOS. Recent studies have reported that most sarcomas diagnosed as poorly differentiated sarcomas, arising in the retroperitoneum are, in fact, dedifferentiated liposarcomas.

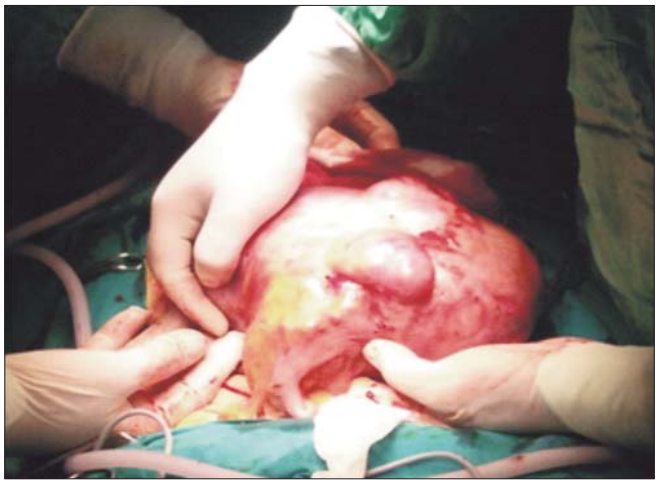

Figure 5. *Intraoperative picture*

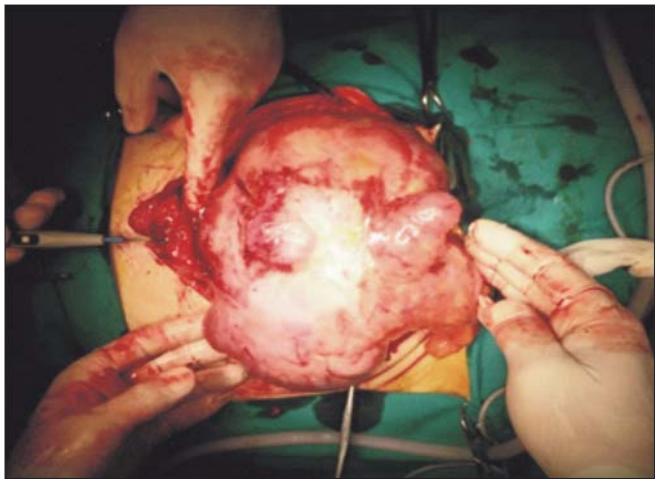

Figure 6. *Intraoperative picture*

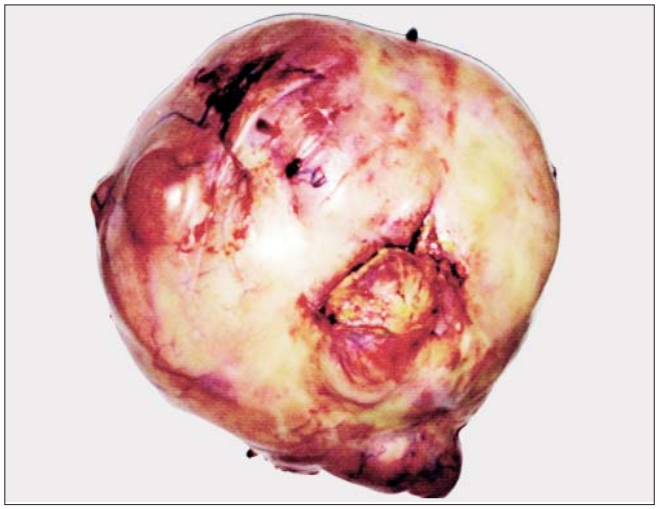

Figure 7. *Tumorectomy specimen*

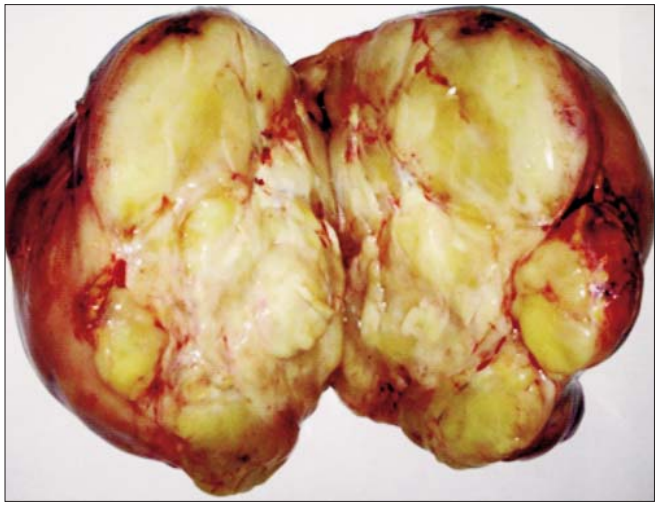

Figure 8. *Tumorectomy specimen 20 cm large tumoral mass with elastic fat density and yellowish coloured*

MDM2 proto-oncogene (E3 ubiquitin-protein ligase) amplification can be the base of the diagnosis. The presence of supernumerary ring and/or giant rod chromosomes that contains amplified segments from the 12q13-15 region (9,10,11,12) characterize the dedifferentiated liposarcoma. Several oncogenes residing in this region have been identified , including MDM2, CDK4, HMGA2, TSPAN31 (SAS), YEATS4, miR-26a-2, CPM, OS1, OS9, CHOP (DDIT3), and GLI1 (12). The metastatic rate in dedifferentiation is 15–20%; however, it depends on uncontrolled local recurrences, rather than metastatic spread. Therefore, it is of clinical importance to distinguish a dedifferentiated liposarcoma from a de novo high-grade pleomorphic sarcoma of some other type (13). The concept of dedifferentiation in liposarcoma has undergone an evolution in the last several years and the traditional views have been modified by the concept of low-grade dedifferentiation in dedifferentiated liposarcoma (13). Nowadays, there is some suggestion that the lower grade progression has a better prognosis than the high-grade undifferentiated type of dedifferentiated

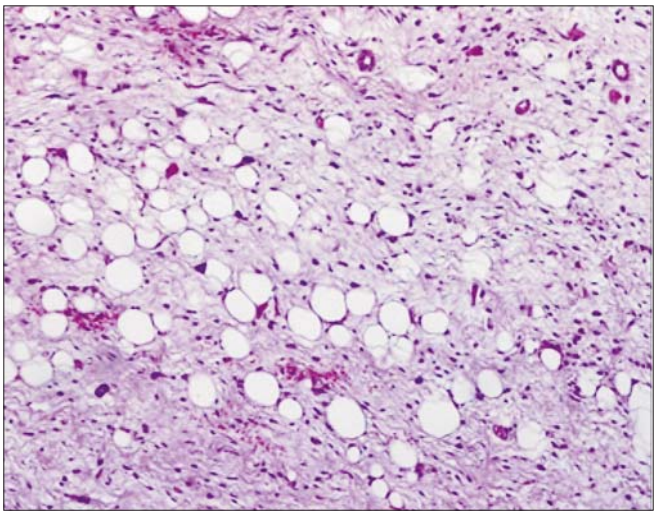

Figure 9. *HE 20X Dedifferentiated liposarcoma component*

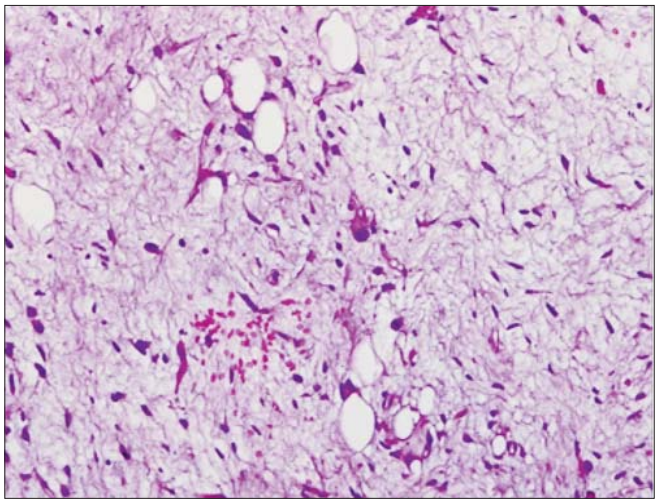

Figure 10. *HE 10X Dedifferentiated liposarcoma component with atypical cells and myxoid stroma*

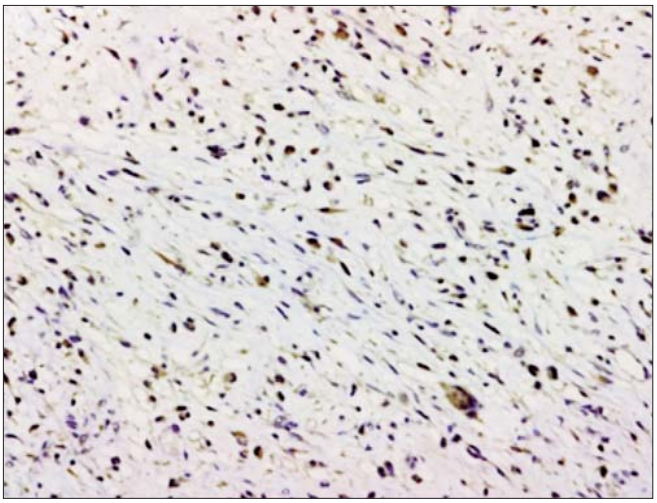

Figure 11. *S100 200X positive in frequent tumoral cells*

liposarcoma. The mechanisms responsible for progression from well-differentiated liposarcoma to dedifferentiated liposarcoma are incompletely understood. MDM2 and CDK4 amplifications are present in both well-differentiated and dedifferentiated liposarcoma, so the presence of these amplifications as such are not triggers for dedifferentiation in liposarcomas, but dedifferentiated liposarcomas show more complex chromosomal aberrations than do well-differentiated liposarcomas (14). In this case considering that the tumour's macroscopic intraoperatory aspect suggested a GIST, it has been decided that a complete removal of the tumor with clear resection margins should be performed; afterwards the patient did not received an adjuvant treatment considering the histological results and the medical condition of the patient. The patient's follow up should be performed at 6 months and at 1 year. The tumoral type can be preoperative suggested by the radiological and imaging location of the tumour. If the macroscopic and imagistic diagnosis of dedifferentiated liposarcoma is difficult the histopathological diagnosis is more challenging and consists in : pleomorphic liposarcoma, lipomatous hemangiopericytoma, non-lipogenic sarcoma, gastrointestinal stromal tumor. The differences are the cytologically aspect, tumour localisation and the presence of MDM2, CDK4, CD117, DOG1 and CD34. According to the espression of the oncogenes, the presence of the MDM2 in differentiated liposarcoma is 95%, in myxofibrosarcoma 42%, in leiomyosarcoma 6%, and in malignant peripheral nerve sheath tumor is 64%. The presence of CDK4 in differentiated liposarcoma is 92%, in myxofibrosarcoma 17%, in leiomyosarcoma 1%, and in malignant peripheral nerve sheath tumour is 12% (15). Complications of dedifferentiated liposarcomas may include the following: large tumours may put pressure on the femoral veins and lead to a deep venous thrombosis, retroperitoneal location of large tumours can cause abdominal pain, weight loss, frequent urination, and kidney injury due to compression of the kidney, metastasis of the tumour to other body regions. In some cases, recurrence of the tumour after surgery may occur, if the tumour is not completely removed. In

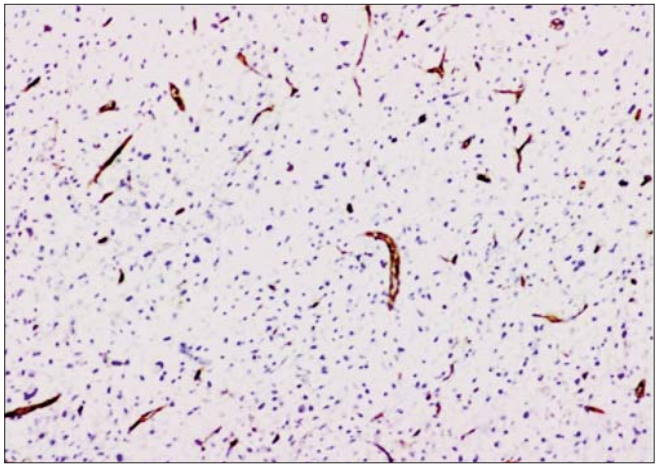

Figure 12. *CD 34 200X positive in capillary blood vessels, negative in tumoral cells*

some cases, the dedifferentiated liposarcoma may return as a well-differentiated liposarcoma, for unknown reasons (16,17, 18,19). The prognosis of dedifferentiated liposarcoma is good with detection in the early stages and surgical excision of the tumour with clear limits. The site of the tumour influences the outcome. Completely excised tumours have better prognosis than those that cannot be completely removed. Statistically, about 20% of the tumours metastasize and some tumours are known to recur. Typically, the 5 years survival rate is 65%. If the tumour is present in the retroperitoneal region, the mortality rate is high, because a complete excision of the tumour is difficult in many cases. There are no data about the prognosis of palliative resection of dedifferentiated liposarcoma (17, 19). In this case, we give the patient an uncertain prognosis because of the histology of the tumour, his age and multiple comorbidities; for the same reasons, the oncologist did not recommended adjuvant treatment. Preoperative radiation helps to avoid damage to radiation sensitive structures and organs, which usually fill in the resection bed after removal of these large tumours.

The treatment compliance is usually better and related toxicity less in the preoperative setting. Adjuvant radiation therapy may constitute a valuable treatment option in order to improve local control, specifically with involved margins or high-grade tumours, local recurrence remaining common and constitutes the most frequent cause of death (20). In the palliative management of advanced or metastatic soft tissue sarcoma, chemotherapy has an important role. Active agents include the anthracyclines (doxorubicin and epirubicin) and the alkylating agent ifosfamide (21). In patients with resistant disease, gemcitabine, docetaxel, trabectedin, and pazopanib were established as effective second or third line options over the last decade (22). The response of liposarcoma to chemotherapy differs according to histological subtype and grade. Dedifferentiated liposarcoma is not very responsive to chemotherapy, so new molecular targets will be identified to extend the possibilities of adjuvant therapies. The reported results of recent clinical trials for new systemic therapies in advanced liposarcoma are overall encouraging. The majority of these recent therapies are based on the understanding of disease biology inherent to a given sarcoma histology, in many cases targeting a specific, aberrant genetic, or molecular pathway and the treatment efficacy is heavily dependent on subtype. Dedifferentiated liposarcoma is relatively resistant to systemic chemotherapy, MDM2 and CDK4 targeted therapy may be a very promising treatment, especially for advanced or unresectable well-differentiated and dedifferentiated liposarcoma. A class of imidazoline compounds, termed nutlins, has been identified as potent and selective small-molecule MDM2 inhibitors (23, 24).

Conclusions

Dedifferentiated liposarcoma is an aggressive variant of liposarcoma. It occurs most commonly in the retroperitoneum and rarely in other anatomic locations. The symptoms are nonspecific: abdominal pain, bowel disorders, weight loss, anaemia and in some cases palpable tumour mass. There are difficulties of clinical and imaging diagnosis and management of this type of neoplasm and the curative R0 resection remains the main treatment for primary and recurrent abdominal dedifferentiated liposarcomas. Long-term detailed follow up is necessary. The prognosis of dedifferentiated liposarcoma patients depends on the moment of diagnosis, surgical removal of the tumour with clear margins, the site of the tumour, the presence of other comorbidities. The 5 years survival is 65%. In case of a well defined, voluminous tumour suggesting a gastrointestinal stromal tumour, there must be considered the diagnosis of liposarcoma. Immunohistochemistry is mandatory for a safe diagnosis. The particularity of the case is represented by the intraperitoneal location of a rare tumour which often occurs retroperitoneal. This special clinical and imagistic topography suggested the presence of a gastrointestinal stromal tumour. Finally, the diagnosis was an immunohistochemical surprise.

Conflict of interest

The authors declares that there is no conflict of interest regarding the publication of this article.

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Authors contributions:

1 - general surgeons, 2 - medical students, 3 - pathologist. All authors have read and approved the final manuscripts.

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