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REVIEW ARTICLE

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Liposarcoma — spectrum of disease

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ABSTRACT

Liposarcomas are the most common soft tissue sarcomas in adults. Diagnosis and treatment of liposarcoma should always be planned and conducted in centres experienced in the treatment of these heterogeneous malignancies with different prognosis and sensitivity to the treatment used. In the following paper, we present a summary of current knowledge about liposarcomas considering the differences between subtypes and new directions in treatment.

Key words: soft tissue sarcoma, liposarcoma, multimodality therapy.

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Introduction

Liposarcomas (LPS) account for 20% of all sarcomas and are the most common malignancies of soft tissues [1]. They usually occur in 5th–7th decade of life, with equal frequency in both sexes.

The World Health Organisation (WHO) distinguishes four subtypes of LPS:

— atypical lipomatous tumour/well-differentiated liposarcoma (ALT/WDLS);
— dedifferentiated liposarcoma (DDLPS);
— myxoid liposarcoma (MLS);
— pleomorphic liposarcoma (PLS).

The mixed LPS subtype has been removed from the latest WHO sarcoma classification from 2013, together with the development of methods for molecular diagnostics and assignment of ambiguous morphologically cases to one of four clearly defined subtypes of LPS [2].

The sarcoma subtypes mentioned above, which have a common feature of more or less expressed fatty differentiation, are in fact different types of tumours, showing extremely different molecular changes and clinical course. The degree of histological malignancy (reflected in the extent of differentiation) remains the most important prognostic factor for the clinical course of the disease and prognosis. In patients with low-grade MLS and well-differentiated liposarcomas, the five-year survival rate reaches 90%. In the case of high-grade variants, such as high-grade MLS, PLS, and DDLPS, the percentage of five-year survival is 60%, 30–50%, and 75%, respectively [3]. Among the various LPS subtypes, also different is the sensitivity to radiotherapy and systemic treatment.

Characteristics of liposarcoma subtypes

Atypical lipomatous tumour/well-differentiated liposarcoma

Well-differentiated liposarcomas (ALT/WDLS) constitute 40–45% of LPS and thus form the largest group of these tumours [4].

According to the WHO classification (2013 edition), the following subtypes are distinguished [2]:

— lipoma-like: histologically dominated by mature adipose tissue with the presence of septa of connective tissue, visible in magnetic resonance imaging (MR)

[5] and — sometimes only single, dispersed — atypical cells, including lipoblasts;
— sclerosing: characterised mainly by the growth of fibrous tissue and with a relatively small fat component of the tumour; in this subtype a higher rate of recurrence after resection is observed;
— inflammatory, in which chronic inflammatory infiltration is primarily visible;
— spindle cell: which is usually characterised by a monomorphic population of spindle cells and often the present myxoid component. Another molecular basis of this subtype is an argument for separating it as a separate disease entity [6, 7].

As is clear from the above description, it is a histologically very diverse group of tumours in which both the fatty component and atypical cells, in particular lipoblasts, can be significantly reduced. In oligo biopsy materials, these elements, which are important from a diagnostic point of view, may be absent, which is the source of two typical diagnostic errors:
— diagnosis of lipoma instead of WDLS, subtype "lipoma-like" due to lack of atypical cells in the oligobiopsy [8];
— diagnosis of another disease entity, in particular: idiopathic retroperitoneal fibrosis (Ormond's disease) [9] instead of the fibrotic WDLPS variant and inflammatory myofibroblastic tumour [9] instead of the WDLPS inflammatory variant due to the lack of a tumour fat component.

It is easy to avoid the above diagnostic errors; for this purpose one should compare the microscopic image with the MR image (i.e. the presence of a fat tumour with baffles) [5] and perform immunohistochemical staining of MDM2 or fluorescence in situ hybridisation (FISH).

The molecular basis of ALT/WDLPS, with the exception of the spindle cell subtype, which is characterised by the loss of RB expression and mutation of the RB gene [10, 11], is amplification of the region 12q13-15 [12], in which the *MDM2*, *CDK4*, and *HMGA2* genes are present [13], and the resulting over-expression of MDM2, CDK4, and HGMA2 proteins in atypical cells [14].

The most important prognostic factor in ALT/WDLPS is the anatomical location of the tumour and the associated risk of local recurrences. The mortality of patients with tumours located in somatic soft tissues (limbs) is close to 0%, even with marginal resection of the lesion (i.e. enucleation) — for this reason tumours in this localisation are referred to as ALT [15, 16].

Mortality due to centrally located/visceral tumours (most often retroperitoneal space and inguinal canal, pelvis, less frequently mediastinum) reaches 40–80% and is the result of high risk of recurrence after even multi-organ resection. Due to this fact, tumours in these locations are referred to as WDLPS.

Dedifferentiated liposarcoma

Dedifferentiated liposarcoma is a tumour showing presence of highly differentiated fat component (ALT/WDLPS) and additionally sarcoma fields mostly non-adipocytic, high-grade, most often the morphology of undifferentiated pleomorphic sarcoma and myxofibrosarcoma or with heterologous differentiation towards rhabdo- and leiomyosarcoma, osteosarcoma, angiosarcoma [2, 17]. Dedifferentiation towards PLS occurs comparatively rarely [18].

About 90% of DDLPS cases develop *de novo*, 10% is the result of ALT/WDLPS progression.

The dedifferentiated component should occupy a diameter of at least 1 cm and exhibit mitotic activity of at least 5/10 HPF (0.2 mm^2) [19].

DDLPS defined in this way shows a statistically significantly increased frequency of local recurrences and shorter survival periods compared to ALT/WDLPS and have — in contrast to ALT/WDLPS — the potential for metastasis at the level of 15–20% of cases.

All ALT/WDLPS with non-adipocytic (fibrous or myxoid) fields with increased (sometimes to a high degree) cellularity but with mitotic activity below 5/10 mm^2, previously called "low-grade dedifferentiated liposarcoma", do not differ statistically significantly in relation to the frequency of local recurrences and survival time from ALT/WDLPS, and no distant metastases have been noted in these cases; for this reason, they should be referred to as ALT/WDLPS cellular variants (cellular ALT/WDLPS) [19].

Patients with DDLPS in centrally located/visceral locations, whose sarcoma recurrence was classical or cellular ALT/WDLPS, have a statistically longer survival time than in the opposite clinical situation (i.e. when ALT/WDLPS recurred as DDLPS compared to recurrent ALT/WDLPS) [19].

When the diagnosis of DDLPS is confirmed, the prognostic factors include grade of histological malignancy according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) criteria and muscle differentiation of the tumour, including the presence of a smooth or rhabdo cellular component, which worsens the prognosis [20, 21]. On the other hand, the size of the dedifferentiated component does not affect the diagnosis [22].

From the above diagnostic criteria for DDLPS, as well as the presence of ALT/WDLPS fibrotic and myxoid variants, the determination of each radiologically-assessed adipocytic tumour with solid (non-fatty) fields as DDLPS is an excessive simplification because not all adipocytic tumours with such a radiological presentation will be histologically de-differentiated, even with the assumption of taking biopsy material from the fat-free part of the tumour.

Biopsy of the de-differentiated part of the adipocytic tumour without clinical information of the fatty nature of changes in the imaging examination may contribute to diagnostic errors in this group of tumours. The percentage of five-year survival in patients diagnosed with DDLPS is 44%, compared with 93% in those diagnosed with pure WDLPS [3].

For any undifferentiated/pleomorphic spindle cell sarcoma located in retroperitoneal space, pelvic and inguinal canal/spermatic cord, even without a pronounced fat component in the MR examination, MDM2 protein expression and/or *MDM2* gene amplification status by FISH should be determined. The molecular basis of DDLPS, occurring most often in the above-mentioned locations, is analogous to ALT/WDLPS — amplification of the region 12q13-15 [23].

Myxoid liposarcoma

Myxoid liposarcoma is the second most frequent subtype of LPS, accounting for about 30–35% of these tumours [24]. It is located mainly in the soft tissues of the lower limb (usually the proximal thigh), with the peak of incidence in the 4th–5th decade of life. It may occur sporadically in children and the elderly.

A characteristic feature of this sarcoma is predilection for metastases on serosal surfaces (including retroperitoneal space), bones (which may be the most common place for MLS metastasis), and soft tissues, usually without lung involvement [25].

The microscopic nature of the tumour with numerous, branching blood vessels, relatively low cellularity, low cytological atypia of oozy cells, and the presence of lipoblasts is a very characteristic low-grade MLS microscopic image.

Age of patients over 45 years, the presence of necrosis fields and the histological degree of tumour malignancy — these are important prognostic factors [26]. High-grade MLS cases (formerly round cell liposarcoma) are characterised by the presence of fields with increased cellularity/round cell (> 5%) [27]. The risk of distant metastasis depends on the extent of the rich cell/round cell component (RCL, round cell liposarcoma) in the tumour (23% with RCL < 5% *vs.* 35% with RCL 5–25% *vs.* 58% in RCL > 25% tumour incidence) [22, 26].

Due to the lack of specific MLS immunohistochemical markers (the S100 reaction is not specific and is not always positive in MLS) and the need to differentiate the tumour, especially with sarcomas such as ALT/WDLPS and extra-skeletal myxoid chondrosarcoma and with benign tumours such as spindle cell lipoma, FISH molecular analysis and polymerase chain reaction (PCR) are used in histopathological diagnostics. Myxoid liposarcoma is characterised by rearrangement of the *DDIT3* gene (*CHOP*). In 98% of cases the partner of this translocation is the *FUS* gene (*TLS*): t (12; 16) and in 2% the *EWSR1* gene: t (12.22) [24].

The use of the abovementioned molecular tests is of particular importance in the diagnosis of high-grade MLS with high-grade malignancy, in which the tumour takes the form of a round cell sarcoma without any or with minimal fatty differentiation, and for differentiation of MLS with the myxoid form of ALT/WDLPS or DDLPS.

Pleomorphic liposarcoma

Pleomorphic liposarcoma is a high-grade pleomorphic sarcoma with adipocytic differentiation in the form of lipoblasts [28]. This tumour accounts for 5% of all LPS, although its frequency may be underestimated due to the cases of PLS with few, barely identifiable lipoblasts [2]. The average age of patients at the time of diagnosis is 53 years (range 14–84 years). Frequent locations of the tumour are thigh soft tissues (34%) and pelvis (15%) [29].

Two-thirds of the cases show a phenotype of pleomorphic/spindle-sarcoma of the UPS type (undifferentiated pleomorphic sarcoma) with the presence of lipoblasts. The remaining one-third of cases are characterised by epithelioid cell morphology (epithelioid variant of PLS) [30, 31]. There is a very rare morphology similar to myxofibrosarcoma (MFS-like) and a histological picture dominated almost exclusively by highly atypical lipoblasts [22].

Pleomorphic liposarcoma, except in rare intradermal form [32], is a very aggressive sarcoma. The risk of metastases — regardless of morphology — is 30–50%, and mortality reaches 50% of cases [33]. The most common sites of metastasis are the lung (82%) and liver (18%).

Like other pleomorphic sarcomas, PLS is characterised by complex chromosomal abnormalities, without a specific molecular marker [29], in particular without amplification of the *MDM2* gene, which distinguishes it from DDLPS despite the morphological similarity of these tumours [34].

Diagnostic imaging

The picture of LPS in imaging studies is often very characteristic, especially in the retroperitoneal space, where the well-differentiated part of the tumour is easily identified and often accompanied by a dedifferentiated component. The imaging by computed tomography (CT) of that part of the tumour has a density of fat, usually by Hounsfield units (HU). The dedifferentiated component has a more variable but higher density by HU. In the case of relapse, the lesions are often multifocal, with limited possibility of radical resection. In the retroperitoneal

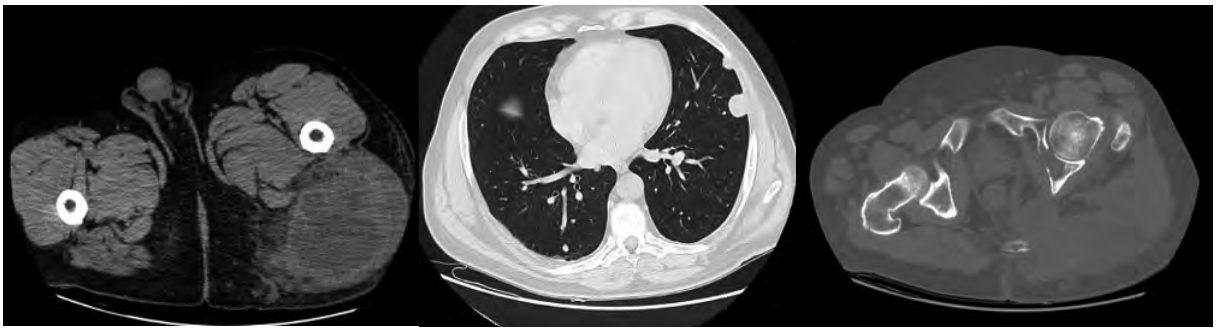

Figure 1. CT images of a patient with extensive myxoid liposarcoma (MLS) of a buttock metastatic to the lungs and bones

Table 1. Clinical characteristics of liposarcoma (LPS)

Subtype	Risk of local recurrence	Risk of metastatic disease	Sensitivity to chemotherapy	Sensitivity to radiotherapy
Well-differentiated	Low	Low	Low	Moderate
Dedifferentiated	High	Low	Low	Moderate
Myxoid:				
Low grade	Low	Low	High	High
High grade (round cell)	Intermediate	High	High	High!
Pleomorphic	Intermediate	High	High	Intermediate

space, the lesions are large, often with a well-differentiated component that can develop over the years. Dedifferentiated component of the tumour is responsible for the symptomatic progression of the disease, associated with infiltration and displacement of neighbouring organs. Pleomorphic liposarcoma has a relatively high risk of metastasis to many locations, including the lung, soft tissue, bone, and liver. As mentioned above, in the MLS it is frequently found atypical for metastatic sarcoma locations, such as bone or soft tissue (Fig. 1) [35].

Treatment

The basis of treatment and the only method that gives a chance to cure a patient with LPS, regardless of the subtype, is surgery. Individual subtypes, however, differ in sensitivity to radiotherapy and chemotherapy, and indications for adjuvant therapy and treatment regimens in the event of metastatic disease will be different. The location of the primary tumour determines the approach to treating the patient. Table 1 presents a summary of clinical characteristics of LPS subtypes.

Treatment of locally advanced tumours

The strategy of local treatment of LPS in limb localisation is the same as for all soft tissue sarcomas. The basis of surgical treatment is radical tumour excision. Recommendations in the field of reaching a few-centimetre margin of tumour-unchanged tissues in practice are difficult to implement. The margin obtained is narrow in the case of adjacent resistant anatomical structures (e.g. muscle fascia, periosteum, and perineurium), but may be extensive in other soft tissues (e.g. muscles, especially in the longitudinal axis of the limb) [36].

The primary goal of surgery in LPS localised in retroperitoneal space (in this localisation there are mainly WDLPS and DDLPS) should be total resection of all tumour sites. R2 resections (in the macroscopic margin of tumour tissue) are associated with significantly worse results than resections of R0 or R1, and in the majority of cases patients with residual disease have the same poor results as patients who have not undergone any surgery [37]. There are still discussions about the extent of surgery of sarcomas located in the retroperitoneal space. The results of a retrospective analysis were published comparing patients treated with excision of the primary tumour together with the surrounding adipose tissue and fascia (e.g. kidney capsule) with results obtained in patients treated by "extended resection", i.e. removal of the tumour with surrounding organs, where these organs provided an additional centimetre of margin (e.g. colon, pancreas, and spleen). In the case of extended resection, lower percentages of local recurrence of the disease were noted, and after a long period of observation results sug-

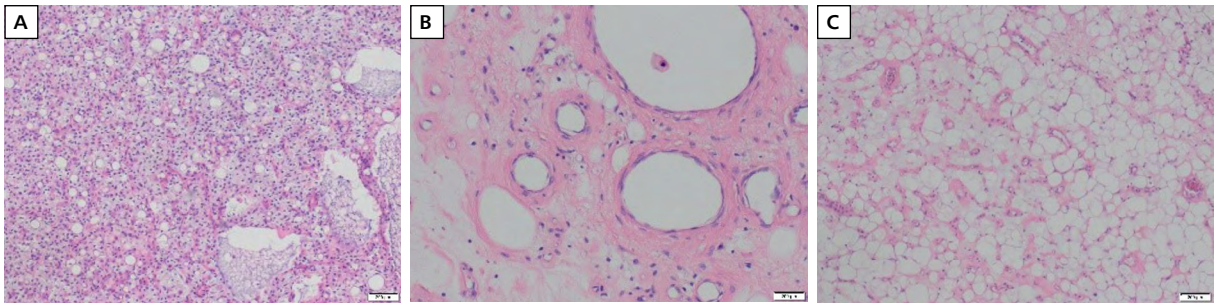

Figure 2. Histopathological picture of myxoid liposarcoma (MLS): **A.** Before treatment — image of plexus blood vessels, rich cell; **B.** Response to irradiation — fibrosis and thickening of the vessel wall; **C.** Response to radiotherapy — induction of adipogenesis

gested improvement in overall survival (most failures of treatment of patients with retroperitoneal DDLPS are a result of local recurrence) [38].

The use of neoadjuvant chemotherapy is not a standard in all patients. This treatment can be considered in individual patients when adverse prognostic factors occur (large, fast-growing, high-grade tumours), although the data on the efficacy of peri-operative systemic treatment in LPS are limited. The results of a very important study were published comparing the effectiveness of chemotherapy adapted to the histological subtype in comparison with the standard scheme of anthracycline and ifosfamide. Only in the group of MLS patients treated with trabectedin was it shown that the "matched" approach is no worse than the standard scheme [39]. Therefore, if a patient with the diagnosis of LPS is qualified for systemic pre-operative treatment, the scheme of choice should be the doxorubicin and ifosfamide regimen.

The use of adjuvant radiotherapy (prior or post-operative) is indicated in large tumours (> 5 cm), high-grade, and deep-seated [40]. Myxoid liposarcoma is a subtype with particular sensitivity to radiotherapy compared to other soft tissue sarcomas (Fig. 2) [41], and this property may have value both in the treatment of locally advanced tumours (currently a lot of research is ongoing to optimise the dose of radiation therapy in the perioperative treatment in this particular subtype) as well as in the case of metastatic disease (e.g. irradiation of symptomatic lesions in the spine).

The role of radiotherapy in the treatment of retroperitoneal sarcomas is debatable. The efficacy of neo-adjuvant radiotherapy was evaluated in two prospective studies in which 72 patients participated, of whom only 40% were diagnosed with LPS, and 25% were treated due to recurrence of the disease. Of the 54 patients who received radiotherapy followed by radical tumour resection, the five-year survival without local recurrence was 60% compared to non-irradiated historical controls, with a five-year relapse-free experience of 30–60% [42]. The role of pre-operative radiotherapy in the treatment of primary retroperitoneal sarcomas is currently being evaluated in a large prospective phase III trial, the final results of which have not yet been presented (STRASS study).

Palliative treatment (inoperable/metastatic tumours)

Because soft tissue sarcomas are a very heterogeneous group of tumours, often in clinical trials the effectiveness of systemic treatment is assessed among many very different subtypes of sarcomas with very different course and prognosis, as well as different sensitivity to systemic treatment. An important role is therefore played by very careful monitoring of subgroup analyses of patients included in clinical trials, as well as retrospective analyses focusing on specific subtypes of sarcomas.

An analysis was published presenting different sensitivity to chemotherapy among individual LPS subtypes. Jones et al. [43] evaluated the results of treatment in 88 patients receiving chemotherapy for recurrent or metastatic LPS. They found that patients with a diagnosis of MLS had a significantly higher response rate compared to all other LPS subtypes, at 48% (95% confidence interval 28–69) and 18% (95% CI 8–31), respectively. Fourteen per cent of patients received adjuvant treatment, usually with doxorubicin and ifosfamide.

Despite the higher percentage of responses for lower grade malignancies, the prolongation of time to progression for high-grade (round cell) tumours compared to MLS with lower malignancy was 16 months compared to four months. This indicates the activity of chemotherapy in MLS regardless of the degree of histological malignancy. It is worth noting that the response rate for patients diagnosed with WDLPS was 0% [43].

The particular sensitivity of MLS to chemotherapy was also confirmed in other published retrospective analyses (percentage of objective responses to treatment > 40%) [44].

Trabectedin is a relatively new drug available to patients with diagnosis of LPS. The drug was registered in Europe based on the results of a phase II

randomised clinical trial. Patients were assigned to one of two arms: in the first one the drug was given at 1.5 mg/m^2 for 24 hours every three weeks, in the other arm at 0.58 mg/m^2 for three hours once a week for three out of four weeks. Before entering the study, the patients had to have documented progression of the disease while taking doxorubicin and ifosfamide. The 24-hour infusion regimen showed a significantly longer mean time to progression (3.7 *vs.* 2.3 months) and progression-free survival (3.3 *vs.* 2.3 months) compared to a three-hour infusion. There was no significant difference in overall survival between the two arms of the study, but there was a strong trend in favour of the 24-hour infusion (13.9 *vs.* 11.8 months) [45].

Trabectedin has been approved in the United States based on a phase III randomised trial. Only patients with diagnosed LPS (all subtypes) and leiomyosarcomas were included. PFS showed improvement compared to treatment with dacarbazine (which is a drug with low efficiency, when used in monotherapy in patients with the diagnosis of soft tissue sarcoma). The most significant improvement in PFS was reported in patients with MLS (median PFS 5.6 months in the trabectedin arm *vs.* 1.5 months with dacarbazine) [46].

Results of two retrospective studies on the efficacy of trabectedin only among patients with MLS were published. In the first group 32 patients were analysed, who were treated with the drug after failure of previous therapy. The percentage of objective responses was 50%; two patients had complete response (CR), and 14 had a partial response (PR) for treatment. Stabilisation of the disease (SD) was reported in another 14 patients. In 90% of patients, disease control (CR + PR + SD) was achieved. The median PFS for the whole group was 17 months. Six months after the start of therapy, 90% of subjects were free of disease progression. Some patients after the use of this treatment were qualified for resection of residual lesions, which was not possible before starting the therapy. The median duration of treatment was 10 months, and 24 subjects (75%) received more than eight courses of treatment [47].

In a further study conducted in a group of 51 patients from several centres, the results were quite similar: two CR and 24 PR were found; in total 51% of patients had an objective response to treatment. The median PFS was 14 months, and the proportion of patients free of progression after six months of starting treatment was 88%. Interestingly, 17 of 23 patients responding to therapy had changes in the density of the lesions in CT or reduced contrast uptake in the MR study, which was preceded by a reduction in tumour size [48].

The newest registered drug for patients diagnosed with LPS is eribulin — a new microtubule inhibitor that has been approved by the US Food and Drug Administration (FDA) in 2016 based on the results of a large phase III study comparing the efficacy of eribulin and dacarbazine. Treatment with eribulin resulted in improved overall survival and PFS. Overall survival improved significantly in patients treated with eribulin compared to patients receiving dacarbazine (median 13.5 months *vs.* 11.5 months, p = 0.0169).

Summary

Diagnosis and treatment of LPS should always be planned and conducted in centres experienced in the treatment of these rare malignancies with heterogeneous prognosis and different sensitivity to the treatment used.

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