Liposarcoma: Dedifferentiated or mixed-type?

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ABSTRACT

Histopathological subtype of liposarcoma is one of the factors to assess biological behaviour of the tumour. It can be challenging for histopathologists if it is composed of more than one histological subtype or non-lipogenic dedifferentiated components. Two cases of liposarcoma with combined lipogenic and various non-lipogenic components were reported. Both cases were male patients in their fifties with deep seated soft tissue tumour in thigh. The first case was dedifferentiated liposarcoma; 30% of tumour showed features of atypical lipomatous tumour, and 70% of tumour showed dedifferentiated fibrosarcoma like pattern and malignant fibrous histiocytoma like pattern with abrupt transition in between. The second case was mixed-typed liposarcoma with combination of typical myxoid liposarcoma and dedifferentiated liposarcoma. Thorough sampling is necessary for identification of specific histological subtypes and its combination in liposarcoma. Ancillary immunohistochemistry, cytogenetic and molecular studies may be needed in difficult cases for histological subtyping which can guide the development of new therapeutic approach of targeted therapy.

Keywords: Liposarcoma, dedifferentiated liposarcoma, myxoid liposarcoma, mixed-typed liposarcoma

INTRODUCTION

Liposarcoma (LPS) is one of the most common malignant mesenchymal tumour and account for approximately 20% of soft tissue sarcoma. 1 According to the World Health Organisation (WHO) classification, liposarcomas has five histological subtypes which include atypical lipomatous tumour/ well-differentiated liposarcoma (ALT/WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid/round cell liposarcoma (MLPS/RLPS), pleomorphic liposarcoma (PLPS) and mixed-typed liposarcoma. 2 Based on the similarity of molecular and cytogenetic abnormalities, it can be grouped into three types; ALT (WDLPS)/DDLPS, MLPS/RLPS and PLPS. 2, 3 MLPS is the most common subtype. 2 However, some literature reported that ALT/WDLPS with or without dedifferentiation (DDLPS) is the commonest accounting for 45% of all LPS. 4
behaviour. Decision to make histological subtyping of LPS is sometimes challenging for histopathologists if it is composed of more than one histological subtype. We reported two cases of liposarcoma with various non-lipogenic dedifferentiated histopathologies.

CASE REPORTS

CASE 1: A 57-year-old Malay man presented with a left thigh swelling of nearly 10 years. It was painless and slow growing until a few months before admission when it rapidly increased in size within three months and became painful. On examination, there was a huge mass in the medial aspect of the left thigh (30 x 20 x 11cm) with soft to cystic consistency. Imaging was suggestive of a high grade sarcoma. A trucut biopsy revealed spindle cell lipoma but the pathologist advised repeat sampling. The mass was widely excised. It was a huge soft tissue tumor mass measuring 30 x 27 x 20cm in diameter and weighing 7.5 kg. Serial cut sections showed fairly circumscribed, capsulated, and gray to yellowish, multilobular appearance with myxoid areas, haemorrhages and necrosis. Entrapped skeletal muscles were seen within the tumor mass.

Histological examination (Figures 1a and b) revealed most of the sections were composed of nodules divided by fibrous septa. Skeletal muscle fibers were entrapped in the septa and some are atrophic. Some of the nodules were composed of lipogenic cells with variable pleomorphism from mild pleomorphic cells to vacuolated lipoblasts. Some were composed of loosely arranged round to oval shape cells with mild pleomorphism, and easily seen mitoses in the background of myxoid stroma. Rich capillary networks were seen within the myxoid stroma. In the vicinity to myxoid area with lipogenic cells, cellular areas were composed of pleomorphic spindle cells.

Figs. 1: a) Lipogenic area composed of pleomorphic lipogenic cells (H&E, x20), b) Transition of lipogenic area into non-lipogenic area composed of spindle shaped cells (H&E, x20), c) Lipogenic foci and non-lipogenic foci intermingle each other giving rise to mosaic pattern. (H&E, x20), and d) Nodule composed of spindle shaped cells with enhanced cellularity at the periphery (H&E, x10).
shaped cells. These spindle cells were arranged into interlacing fascicles which gave rise to the pattern of fibrosarcoma. Some foci show abrupt transition of lipogenic to non-lipogenic spindle shaped cells with hypercellularity. Some cellular areas were forming nodules, and enhanced cellularity was seen at the periphery of nodules in which spindle cells were more pleomorphic. In areas, alternative lipogenic and non-lipogenic cells were arranged into a mosaic pattern intermingling each other. In non-lipogenic areas, some showed fibroblastic area like fibrosarcoma pattern, and some showed malignant fibrous histiocytoma (MFH) like pattern with multinucleate giant cells and floret cells. Some nodules were composed of paucicellular pleomorphic non-lipogenic cells in the background of myxoid stroma, giving rise to the features of myxofibrosarcoma. All the surgical margins were free of tumour. Immunohistochemical staining showed only positive for vimentin. Cytokeratin (CK) AE1&3, SMA, S100, desmin, CD34, CD99 were negative. The histological features were consistent with DDLPS.

**CASE 2:** A 50-year-old Arab man presented with a painless left thigh mass of three year. It had rapidly increased in size within the last year. A trucut biopsy that was done three years previously was reported as intramuscular lipoma. On examination, there was a huge mass at the lateral aspect of the left thigh measuring 28 x 28 x 12cm diameter, firm in consistency with ill defined border. A magnetic resonance imaging (MRI) was consistent with liposarcoma without bony invasion. A repeat revealed myxoid liposarcoma. The patient proceeded to excision of the tumour.

The excised specimen consisted of a huge soft tissue tumour weighing 9 kg and measuring 28 x 29 x 15cm. The overlying skin was ulcerated. Serial cut sections showed well encapsulated tumour enclosing lobulated fatty tissue without gross infiltration.
into the skeletal muscle. Most of the areas were myxoid appearance with jelly like materials. Areas of necrosis, haemorrhage and cystic degeneration were seen.

Histological examination (Figures 2a & b) revealed most of the sections were myxoid appearance with some cystic like spaces. Both univacuolated and multivacuolated lipoblasts were seen in the myxoid background. Cystic spaces and myxoid stroma enclosing lipogenic cells resembled pulmonary oedema pattern. In some areas, stroma was more cellular with pleomorphic spindle-shaped cells without any lipogenic cells. These spindle-shaped cells were arranged into storiform interlacing pattern. In one foci of non-lipogenic area, tumour cells were very plump and epitheloid looking with abundant eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli. Foci of metastatic cartilage and bone formation were also seen. Immunohistochemical profile of non-lipogenic spindle cell area showed only vimentin positivity with negative for S100, SMA, desmin, CD99 and HMB45. Non-lipogenic epitheloid cell area was strongly positive for vimentin and focally positive for CK AE1&3 and EMA. Based on histological findings, mixed-typed LPS with combination of MLPS and DDLPS was reported.

**DISCUSSION**

Although histopathological diagnosis of LPS is based on finding of lipoblast(s), histopathological subtyping is also important to assess biological behaviour. The behaviour ranges from non-metastasising neoplasms (e.g ALT/WDLPS) to high-grade sarcomas with full metastatic potential (e.g PLPS). Tumour location, size and histological subtype are the most important prognostic indicator. Retroperitoneal and intra-abdominal locations with tumour larger than 5 cm are of worse prognosis. ALT/WDLPS does not recur after complete wide excision. DDLPS, despite its high grade morphology, is less aggressive clinically than other types of high grade sarcoma. MLPS and PLS have tendency to metastasize distantly. Both of our cases were located in the thigh which is a common site of most soft tissue sarcoma, and both are larger size tumour of more than 5 cm in diameter.

Among the five histological subtypes, DDLPS was first described in 1979 by Evans. It is defined as ALT/ WDLPS juxtaposed to areas of high-grade non-lipogenic sarcoma, usually resembling either fibrosarcoma or malignant fibrous histiocytoma (MFH). The transition between lipogenic and non-lipogenic area is abrupt, either in the primary or in a recurrence, from ALT/WDLPS to non-lipogenic sarcoma of variable histological grade. Most cases of DDLPS showed abrupt transition with few gradual transitions, and occasional tumours showed mosaic pattern. Dedifferentiation is the process in which differentiated cell revert back to a less differentiated stage within its own lineage.

In our first case, 70% of all tumours composed of non-lipogenic DDLPS which include fibrosarcoma pattern, MFH pattern and myxofibrosarcoma pattern. Only about 30% of tumour nodules were composed of lipogenic component which showed features of ALT, lipoblasts and small foci of MLPS/RLPS with prominent capillary networks. DDLPS with prominent myxoid stroma resembling other sarcoma such as MLPS and myxofibrosarcoma were reported.
lipogenic dedifferentiated pattern, and also mosaic pattern in this case. These features were consistent for DDLPS. Foci of ALT/WDLPS in this case were very scant, and it was mixed with MLPS/RLPS pattern and LPS of not otherwise specified pattern. We assumed that the 10 years history of tumour mass might be the period for transformation of the ALT/WDLPS into higher grade liposarcoma. Most of the dedifferentiated foci in the first case were high grade. That features were similar to findings of some previous literatures.\(^8,^{11}\)

Mixed-type LPS is a very rare type and it shows features of combined MLPS/RLPS and ALT (WDLPS)/DDLPS or of MLPS/RLPS and PLPS.\(^2\) Most of the cases were reported predominantly in retroperitoneal or intra-abdominal locations.\(^2,^{12}\) Mediastinum and deep soft tissue of extremities are rare sites. It is important for the prognosis to decide whether it is combined MLPS and DDLPS (mixed-typed), or myxoid degeneration of DDLPS, and/or dedifferentiation with myxofibrosarcoma pattern.\(^2\)

In the second case, more than 70% of the tumour was composed of MLPS pattern characterized by loose myxoid stroma enclosing uni- and multi-vacuolated lipoblasts. Cystic spaces with paucicellularity giving rise to pulmonary oedema pattern were seen. From lipogenic myxoid pattern, stroma gradually transformed into more cellular myxoid which resembled round cell LPS. Then it transformed into the area composed of non-lipogenic, spindle-shaped cells displaying interlacing storiform pattern and small foci of plump epitheloid cells. These epitheloid cells were positive for cytokeratin AE1&3 and EMA immunohistochemically. Epithelial variant of non-lipogenic cells are commonly seen in PLPS.\(^2,^{5}\) To the best of our knowledge, this is the first case of combined MLPS with dedifferentiated epithelial cells. MLPS with dedifferentiated non-lipogenic foci were previously described as dedifferentiated MLPS.\(^{13}\) Actually those dedifferentiated MLPS represents mixed-type liposarcoma showing a combination of MLPS/RLPS and DDLPS.\(^2\)

Nowadays, more useful immunohistochemical stains which are not available in our center can be used for ALT/WDLPS, such as MDM2 and CDK4.\(^3,^{14}\) In recent years, ancillary cytogenetic and molecular studies of MLPS, detection of translocations of CHOP and FUS genes has been introduced.\(^{15}\)

In conclusion, thorough sampling is necessary for identification of specific histological subtypes and its combination in LPS. Ancillary immunohistochemistry, cytogenetic and molecular studies are useful tools for the cases which are difficult for histological subtyping, and are helpful to develop new therapeutic approaches of targeted therapy.

REFERENCES
\(^4:\) Stancey E Mills. Editor. In Chapter 5. Disorders of Soft Tissue. Sternberg’s Diagnostic Surgical Pa-