CASE REPORT

Multicystic dedifferentiated retroperitoneal liposarcoma: tumour cyst fluid analysis and implications for management

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SUMMARY

Liposarcomas are soft tissue sarcomas of adipocyte origin. We describe a case of a dedifferentiated retroperitoneal liposarcoma with an unusual presentation on recurrence as a large, multicystic tumour. The patient was a 72-year-old woman who had undergone multiple treatments including two prior resections. For her most recent locoregional disease recurrence, the patient was offered surgical debulking for symptom palliation. At this operation, performed after two cycles of chemotherapy, the tumour cyst fluid was analysed and found to have a predominance of immune cells with no identifiable malignant cells. This case and the results of our tumour cyst fluid analysis raise several interesting considerations for the management of this unique situation in a rare disease.

BACKGROUND

Soft tissue sarcomas represent less than 1% of all adult solid tumours.^{1–2} Over 50 subtypes of soft tissue sarcoma are recognised by the WHO, each with unique genetic/cytogenetic features, clinical behaviour and response to therapy. Liposarcomas are soft tissue sarcomas of adipocyte origin and can be further divided into three categories: (1) well-differentiated/dedifferentiated (WD/DD) (2) myxoid/round cell and (3) pleomorphic.^{3–4} We describe a case of a DD retroperitoneal liposarcoma with an unusual presentation at the time of locoregional recurrence, as a large, multicystic tumour. This case and the results of our tumour cyst fluid analysis raise several interesting considerations for the management of this unique situation in a rare disease.

CASE PRESENTATION

The patient was a 72-year-old woman who had initially presented with left lower quadrant and groin pain at a local emergency room in December of 2009. Her initial diagnostic work up was negative, but ultimately, an abdominal ultrasound performed on 8 November 2010 revealed a lobulated complex cystic mass adjacent to the inferior pole of the left kidney. The patient then underwent CT of the chest, abdomen and pelvis, which demonstrated an 8.7 cm left retroperitoneal mass involving the psoas muscle. There was no evidence of distant metastasis. An image-guided biopsy was performed and the pathology was interpreted as a high-grade sarcoma.

The patient was evaluated by a surgical oncologist, and after discussion at a multidisciplinary sarcoma conference, the decision was made to begin with neoadjuvant treatment. The patient initially received three cycles of gemcitabine and taxotere, but then developed pulmonary oedema, and was switched to adriamycin/dacarbazine. After six cycles of systemic chemotherapy, repeat imaging showed slight disease progression and she went on to receive a total of 50 Gy of radiation therapy to her tumour. On 6 August 2011, the patient underwent resection of the retroperitoneal sarcoma, en bloc with a left nephrectomy, partial adrenalectomy and resection of the left diaphragm with repair. Pathology was consistent with an 11 cm multicystic DD liposarcoma.

Approximately 1 year later, the patient developed radiological evidence for locoregional disease recurrence at the left hemidiaphragm. This was the only site of disease and, therefore, on 6 November 2012, the patient underwent robotically-assisted thoracoscopic resection of the tumour. Pathology was consistent with a 2.5 cm non-cystic DD liposarcoma.

The following year, the patient again developed locoregional recurrence, but this time was found to have an extensive, 20 cm predominantly multicystic mass occupying the entire pelvis and the majority of the abdominal cavity (figure 1). Image-guided biopsy demonstrated that this was compatible with DD liposarcoma. As the patient was symptomatic from her tumour, she was offered surgical debulking. While waiting for her surgery to be scheduled, the patient was given two cycles of single-agent gemcitabine; she demonstrated no appreciable change clinically, but did not undergo repeat imaging.

Surgical debulking was performed on 8 June 2013. On entry into the peritoneal cavity, the tumour was immediately decompressed with aspiration of approximately 2 L of tumour cyst fluid. The solid components of the tumour were removed in piecemeal fashion. Removal of the tumour required resection of a short segment of small bowel and the left ovary. Pathology for the tumour fragments confirmed DD liposarcoma. Postoperatively, the patient developed refractory pleural effusion, which required video-assisted thoracoscopic talc sclerotherapy. She ultimately recovered and was discharged home.

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Figure 1 CT scan of multicystic dedifferentiated retroperitoneal liposarcoma; (A) axial view and (B) coronal view.

INVESTIGATIONS

Tumour cyst fluid analysis

Cytology revealed only acute inflammation and reactive changes with no malignant cells identified.

A portion of the tumour cyst fluid was also analysed for immune cell phenotype by flow cytometry (figure 2, summarised in table 1). Nearly all (97.2%) of the live cells in the tumour cyst fluid were CD45 positive haematopoietic, immune

cells (figure 2B). CD3 positive T cells represented 9.4% of the total live cells. Most of the T cells were CD4 positive (66.7%), but there was also a substantial CD8 positive population (27.7%) (figure 2C, right). Only 0.95% of the total live cells were CD56 positive natural killer cells (figure 2C). No CD20 positive B cells were observed (figure 2D). Of note, 1.8% of the total live cells were negative for CD3/CD19/CD16, but expressed HLA-DR (major histocompatibility complex, MHC class II), suggesting an antigen-presenting cell phenotype (eg, dendritic cells, macrophages) (figure 2E).

The vast majority of cells (55.5%) found in the tumour cyst fluid were negative for CD3/CD19/CD16 and HLA-DR (figure 2F). Among these double negative cells, 4.9% expressed both CD11b and CD33, suggesting a myeloid-derived suppressor cell phenotype. A larger population of double negative cells (76.9%) was CD11b positive, but CD33 negative. These cells exhibited more of a granulocytic phenotype (CD14 negative), with high internal granularity (side scatter (SSC)) and size (forward scatter (FSC)) (data not shown).

OUTCOME AND FOLLOW-UP

The debulking operation provided significant symptom palliation, but the patient was left with residual disease in the pelvis (figure 3A). For her residual disease, she continued to be treated

Figure 2 Flow cytometry data from tumour cyst fluid. See text for full description; (A) live cells, (B) haematopoietic, immune cells, (C) T cells, including CD4 and CD8 subpopulations, and natural killer (NK) cells, (D) B cells, (E) antigen presenting cells and (F) Double negative immune cells, including myeloid-derived suppressor cells (MDSCs).

Table 1 Summary of tumour cyst fluid analysis

Phenotype	Cell type	Live cells, %	Parent population, %
HLA-DR+, CD3/CD19/CD16–	Antigen presenting cells (dendritic cells/macrophages)	1.84	
CD45+	Haematopoietic/immune cells	97.20	
CD45+CD3+	T cells	9.4	80.7
CD4+	Helper T cells	5.95	66.7
CD8+	Cytotoxic T cells	2.47	27.7
CD45+CD3–CD56+	NK cells	0.95	8.1
CD45+CD20+	B cells	0.00	
HLA-DR–, CD3/CD19/CD16–		55.5	
CD11b+CD33+	MDSCs	2.72	4.9
CD11b+CD33–	Granulocytes and others	42.30	76.9

MDSCs, myeloid-derived suppressor cells; NK, natural killer cells.

with single-agent gemcitabine. The tumour enlarged but the walls of the cysts became thinner (figure 3B). After a further 2 months, the tumour began to shrink and reached maximum regression after almost a year of chemotherapy (figure 3C). Unfortunately, after 14 months of systemic treatment and 18 months after her debulking surgery, the patient relapsed with a new, solid, enhancing lesion (figure 3D). Despite this, she remained symptom free with good performance status.

DISCUSSION

WD/DD liposarcomas are closely related malignancies of adipocyte origin that share similar cytogenetic features (chromosomal 12q13–15 amplification); DD is a high grade tumour and requires five or more mitoses per 10 high power fields to establish a definitive diagnosis.^{3–4} On gross examination, both tumours are mostly fat content (almost entirely for WD); however, DD tumours typically have a more solid and/or vascularised component. To our knowledge, only one other case of a multicystic WD/DD retroperitoneal liposarcoma has been described previously.⁵ Our current case highlights several interesting considerations regarding management of this unique situation in a rare tumour.

Figure 3 Serial CT scans after palliative debulking surgery. (A) Initial postoperative scan with residual disease in the pelvis; (B) change in tumour size and cyst wall thickness after single agent gemcitabine; (C) maximum regression of disease on single agent gemcitabine and (D) new, solid, enhancing lesion (green arrow).

To assess tumour response to treatment (eg, systemic chemotherapy), standardised criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST), have been established that measure the change in tumour size by the sum of greatest diameter measurements.⁶ This method of response assessment may not be appropriate for cystic or multicystic tumours for which a substantial part of the tumour bulk is fluid. In our patient, the predominant presence of immune cells without malignant cells would seem to suggest positive response to treatment despite any radiological change in tumour size. In addition, after surgical debulking, while on systemic treatment, the patient's residual tumour cyst wall thickness changed despite an overall increase in tumour size (figure 3A vs B). Other methods from radiological assessment of tumour response, such as positron emission tomography fluorodeoxyglucose avidity for the non-cystic, solid components of tumour, may have also been useful.

For most cases of retroperitoneal liposarcoma, surgery remains the mainstay of treatment and complete resection is the goal.⁷ In patients with recurrent disease, complete resection may become very challenging. Surgical debulking may be of benefit, especially for palliation in patients with symptomatic disease.^{8–9} In our patient, surgical debulking not only provided symptomatic palliation, but also made it possible for her to tolerate systemic treatment with gemcitabine, a chemotherapeutic agent with documented activity against soft tissue sarcoma.¹⁰ Given the lack of malignant cells in the tumour cyst fluid, in retrospect, non-surgical options for symptom palliation, such as percutaneous aspiration or drainage, may also have been appropriate.

From a disease biology standpoint, the tumour cyst fluid analysis suggested that tumour lysis had occurred, either naturally or through treatment, and, importantly, an immune response was taking place within the tumour microenvironment. The vast majority of immune cells identified appeared to be innate cells, including granulocytes. The role of granulocytes in cancer remains controversial, with conflicting evidence to suggest a role for these cells in promoting tumour growth¹¹ as well as in mounting an anti-tumour response.^{12–14} Owing to the limited sample that was available, we were unable to stain for other granulocyte markers and further study is needed to characterise these cells. A small population of cells exhibited an MDSC phenotype. These cells likely promote tumour growth,^{15–16} however, these cells could also be precursors of functional antigen presenting cells, capable of ultimately mounting an adaptive antitumour immune response, once appropriately differentiated and activated.^{17–21}

Interestingly, we did find evidence for a synchronously occurring adaptive immune response within this patient's tumour microenvironment (figure 2). A small population of HLA-DR positive cells (antigen presenting cells) was identified in the tumour cyst fluid. In addition, T cells and specifically cytotoxic CD8 T cells were also found. In a separate analysis, production of interferon- γ was observed by ELISA performed on the supernatants from in vitro plated tumour cyst fluid immune cells (data not shown).

From a therapeutic standpoint, these immunological findings raise the possibility that in cystic/multicystic liposarcoma, the existing adaptive immune response may benefit from augmentation through immunotherapeutic strategies, such as immune adjuvants (toll-like receptors, TLR agonists) or immune checkpoint blockade. Lymphocytes, including T cells, have also been reported in one other case of a cystic liposarcoma of the pleura.²² In fact, for conventional (non-cystic) liposarcoma, 'lymphocyte-rich' variants have been described previously by others^{23–24} and recently, by our own group.^{25–26}

Learning points

- ▶ Standardised criteria to assess tumour response to treatment, such as Response Evaluation Criteria in Solid Tumors (RECIST), may not be appropriate for multicystic tumours.
- ▶ Non-surgical options for symptom palliation, such as percutaneous aspiration or drainage, may also be appropriate.
- ▶ Treatment of multicystic liposarcoma may benefit from augmentation through immunotherapeutic modalities.

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Competing interests None declared.

Patient consent Obtained.

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