Rare aggressive behavior of *MDM2*-amplified retroperitoneal dedifferentiated liposarcoma, with brain, lung and subcutaneous metastases

Imen Ben Salha, Shane Zaidi, Jonathan Noujaim, Aisha B. Miah, Cyril Fisher, Robin L. Jones, Khin Thway

Sarcoma Unit, Royal Marsden Hospital, London, UK

Abstract

Dedifferentiated liposarcoma (DDL) is a histologically pleomorphic sarcoma, traditionally defined as well-differentiated liposarcoma with abrupt transition to high grade, non-lipogenic sarcoma. It can occur as part of recurrent well-differentiated liposarcoma, or may arise *de novo*. DDL most frequently occurs within the retroperitoneum, and while it is prone to local recurrence, it usually has a lower rate of metastasis than other pleomorphic sarcomas. We describe a case of retroperitoneal dedifferentiated liposarcoma in a 63-year-old male, who showed *MDM2* amplification with fluorescence *in situ* hybridization, which displayed unusually aggressive behavior, with brain, lung and subcutaneous soft tissue metastases. As previous reports of metastatic liposarcoma have largely grouped DDL in with other (genetically and clinically distinct) liposarcoma subtypes, we highlight and discuss the rare occurrence of brain metastasis in *MDM2*-amplified retroperitoneal liposarcoma.

Introduction

Dedifferentiated liposarcoma (DDL) is traditionally defined as well-differentiated liposarcoma (WDL) with abrupt transition to high grade, non-lipogenic sarcoma, either in primary or recurrent tumor. Most DDL (80-90%) occur *de novo*. Secondary dedifferentiation occurs in approximately 10% of cases and seems to be associated with multiple recurrences of well-differentiated liposarcoma.[1-3] Dedifferentiated liposarcoma has a lower tendency to local recurrence and metastasis, compared with both other liposarcoma subtypes (myxoid liposarcoma and pleomorphic liposarcoma), which are genetically and clinically distinct.[4] Retroperitoneal DDL is a biologically heterogeneous neoplasm, which presents considerable treatment challenges due to its deep location and size at the time of diagnosis. While it has a tendency to recur following surgical excision, often repeatedly, metastasis of DDL outside the abdominal cavity is very rare.[1] We describe a case of DDL that metastasized to the soft tissues, lung and brain. This pattern of metastatic disease, and in particular brain metastasis of DDL is exceptionally rare, and expands the documented behavioral spectrum of this heterogeneous neoplasm.

Case Report

A 63-year-old male presented with a history of progressive abdominal distension and abdominal pain. Computed tomography (CT) scan showed a 28×20 cm fatty mass expanding the right retroperitoneum, extending from the subhepatic space into the right pelvis, and displacing the kidney superiorly. Inferiorly there was a 12×11 cm solid, focally calcified component and a 5 cm solid nodule invading mesenteric fat and containing soft tissue stranding, as well as several smaller peripheral solid soft tissue nodules. There was no evidence of disease elsewhere in the chest, abdomen or pelvis. The radiological impression was of a large right-sided retroperitoneal well-differentiated liposarcoma with multiple dedifferentiated components. At laparotomy, the retroperitoneal mass was completely resected with *en bloc* resection including a right nephrectomy. Microscopic margins were negative.

Two years following primary tumor resection, follow-up imaging detected multifocal recurrence in the retroperitoneum and in the lungs, complicated with thrombus within the inferior vena cava and left femoral vein. The patient underwent sequential chemotherapy (prolonged infusional ifosfamide) and high-dose palliative radiotherapy to the retroperitoneal and tumor bed masses.[5] One year later, he presented with multiple cutaneous lesions, a left submandibular tumor deposit and an incidental metastatic right cerebellar hemisphere brain deposit (Figure 1). The patient underwent palliative radiotherapy to the whole brain and submandibular region. Three months later, he developed rapidly progressive neck and back cutaneous lesions; CT showed the presence of widespread progressive disease including a new right ventricular mass and progressing brain and submandibular metastases. He was not eligible for a clinical trial due to his poor performance status and opted for best supportive care.

Histopathology

Macroscopically, the primarily excised retroperitoneal tumor was a 7.8 kg, 30×25×15 cm circumscribed lobulated mass lined by peritoneum on one surface and by a focally disrupted thin fibrous capsule on the opposite surface. The cut surface was yellow to pale white and firm, with approximately 20% necrosis. At one edge there was a 6×1.5×0.5 cm unremarkable adrenal gland. The kidney was encased by tumor. Histologically, the tumor was a partially circumscribed malignant neoplasm with two components. One component consisted of sheets of variably sized adipocytes with scattered lipoblasts and fibrous septa with pleomorphic spindle cells, which showed atypical, enlarged hyperchromatic nuclei. Focal fat necrosis and infarction were present. The second component comprised solid aggregates of pleomorphic spindle cells in patternless distributions. There was marked atypia, prominent necrosis and a mitotic index greater than 20/10 high-power fields (HPF), including atypical forms. In places, the tumor contained multiple osteoclasts associated with epithelioid spindle cells with variably sized ovoid nuclei, coarse chromatin and prominent nucleoli, with abundant amphophilic cytoplasm and inconspicuous cell borders (Figure 2A). Focally within these areas there was dense eosinophilic stroma, containing cells with mildly to moderately atypical nuclei, with calcification and ossification (Figure 2B), in keeping with osteosarcomatous differentiation. In places, the pleomorphic component infiltrated the well-differentiated component in a pattern of co-mingling. The tumor infiltrated the renal capsule and focally extended beyond it within the renal parenchyma predominantly in a pushing growth pattern. Immunohistochemically, the tumor was diffusely positive

Correspondence: Khin Thway, Sarcoma Unit, The Royal Marsden NHS Foundation Trust, 203 Fulham Road, London SW3 6JJ, United Kingdom.
Tel.: +44.207.808.2631 - Fax: +44.207.808.2578.
E-mail: khin.thway@rmh.nhs.uk

Key words: Dedifferentiated liposarcoma; sarcoma; *pathology; genetics;* MDM2 amplification.

Acknowledgments: We acknowledge support from the NIHR RM/ICR Biomedical Research Centre.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflicts of interest.

Received for publication: 31 October 2015.
Revision received: 6 February 2016.
Accepted for publication: 25 February 2016.

This work is licensed under a Creative Commons Attribution NonCommercial 4.0 License (CC BY-NC 4.0).

©Copyright I.B. Salha et al., 2016
Licensee PAGEPress, Italy
Rare Tumors 2016; 8:6282
doi:10.4081/rt.2016.6282

Non commercial use only

for CDK4 (Figure 2C) and p16. There was focal positivity for desmin in the pleomorphic sarcomatous component, while myogenin was negative. Amplification of the *MDM2* gene at 12q15 was demonstrated by fluorescence *in situ* hybridization (FISH).

The features were consistent with well-differentiated and dedifferentiated liposarcoma with osteosarcomatous differentiation, grade 3 according to the French Federation of Cancer Centres Sarcoma Group grading system. The tumor did not infiltrate the adrenal gland or the ureter, although focally the tumor capsule was disrupted, with tumor present at the free surface.

A subsequent core biopsy of the patient's subcutaneous back nodule, which developed three years following the primary resection, showed tumor composed of highly atypical spindle cells with multinucleate giant cells, a mitotic index of more than 20 mitoses/10 HPF and early infiltration of skeletal muscle (Figure 2D). No tumoral osteoid was present. FISH again showed amplification of the *MDM2* gene at 12q15, consistent with the subcutaneous metastasis representing dedifferentiated liposarcoma.

Discussion

Retroperitoneal sarcomas are a heterogeneous group of neoplasms, mainly comprising two sarcoma subtypes: well-differentiated/dedifferentiated liposarcomas and leiomyosarcoma. Dedifferentiated liposarcoma occurs most commonly within the retroperitoneum, and accounts for the majority of spindle cell or pleomorphic sarcomas at this site,[6] and molecular techniques have shown that a large proportion of DDL were previously misdiagnosed as undifferentiated pleomorphic sarcoma (previously malignant fibrous histiocytoma).[7]

Immunohistochemistry for CDK4, MDM2 and p16 are useful diagnostic adjuncts, helping to distinguish WDL and DDL from other adipocytic neoplasms in their differential diagnosis; these markers have been shown to be expressed in 70% of WDL/DDL with almost 95% expressing at least two markers.[8,9] WDL and DDL characteristically contain supernumerary ring and/or giant chromosomes; these contain amplicons from the 12q13-15 region which houses proto-oncogenes including cyclin-dependent kinase 4 (*CDK4*), murine double minute type 2 (*MDM2*) and high-mobility AT-hook 2 (*HMGA2*). *MDM2* is the most frequently amplified gene, present in almost 100% of WDL and DDL, and *CDK4* is amplified in over 90%. Amplification of *MDM2, CDK4* and *HMGA2* can be detected by molecular techniques including FISH and reverse transcription-polymerase chain reaction. *MDM2* amplification by FISH is a hallmark for these tumors and is now the gold standard in the diagnosis of WDL/DDL,[10,11] although is not a specific test, as up to 40% of other soft tissue sarcomas can harbor *MDM2* amplification.[12] However, *MDM2* amplification is not associated with the other liposarcoma subtypes (myxoid and pleomorphic liposarcomas).[10]

In our case, *MDM2* amplification was demonstrated in both the primary retroperitoneal tumor and the subsequent subcutaneous metastasis. The median survival for DDL patients with metastatic disease has been reported in the region of 28 months, compared

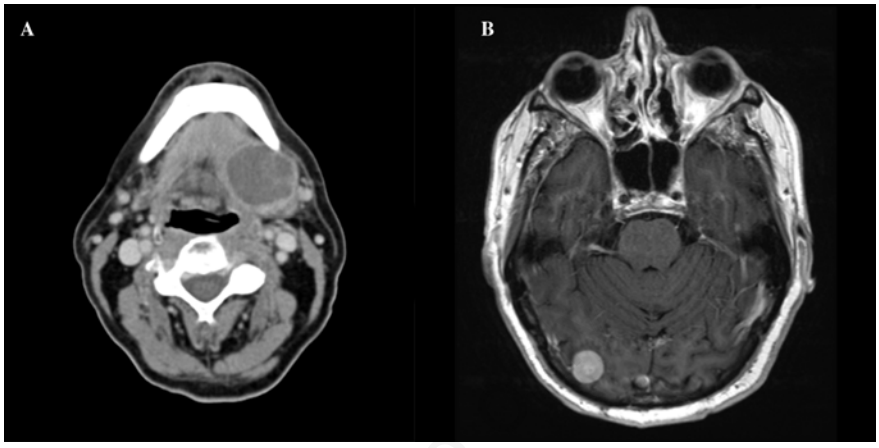


Figure 1. A) A partially necrotic metastatic lesion is present in the left submandibular region, distorting the submandibular muscles and the tongue. B) There is an enhancing right occipital nodule in keeping with a brain metastasis. No peritumoral edema was identified.

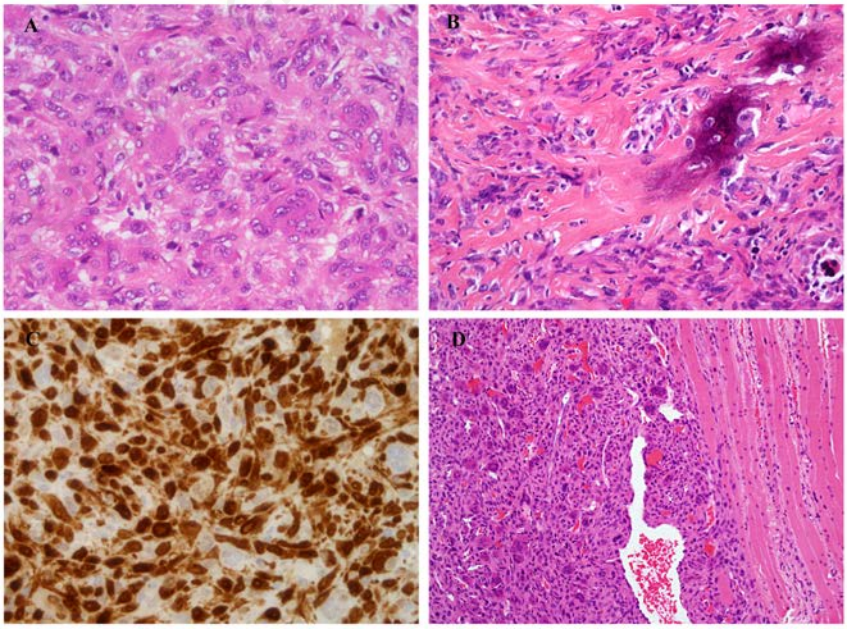


Figure 2. A) Dedifferentiated liposarcoma. The excision specimen from the retroperitoneal mass shows cellular tumor, composed of sheets of atypical spindle cells with hyperchromatic nuclei and moderate amounts of amphophilic cytoplasm. Prominent osteoclast-like giant cells are dispersed within the neoplasm (Hematoxylin and eosin). B) Ill-defined foci of moderately cellular tumoral osteoid are present within the primary tumor, and contain mildly atypical osteocytes, and this is in keeping with heterologous osteosarcomatous differentiation. Mineralization is also seen. C) Immunohistochemically, the neoplasm shows diffuse, strong nuclear expression of CDK4, consistent with the diagnosis of dedifferentiated liposarcoma. D) The biopsy from the subcutaneous mass shows similar tumor, composed of atypical spindle cells with interspersed giant cells, although tumoral osteoid is not evident in the biopsy sample.

to 38 months for patients without metastases.[13] Locoregional recurrence of WDL/DDL represents the main cause of mortality and disease burden, with 40-80% of patients developing recurrence after surgery.[14] Metastasis of DDL is rare; the literature mainly comprises isolated case reports and a few case series, with reported rates of metastatic DDL of about 1-18%.[1,15,16] A recent study by Tirumani and colleagues reported an incidence of metastatic disease in a series of patients with DDL of 29.76%.[13] The authors suggested that this high incidence of metastatic disease could be attributable to referral bias at their tertiary cancer center, and potential detection bias related to more frequent thoracic screening. Sites of metastasis included lung in 33 (22.3%), subcutaneous or intramuscular soft tissue in 23 (15.5%), lymph nodes in 15 (10.1%), liver in 11 (7.4%), bone in 7 (4.7%), mediastinum in 4 (2.7%), adrenals in 3 (2.0%), and brain, thyroid and tongue metastasis each in one patient (0.7%).

The development of brain metastasis in DDL is an exceedingly rare finding. In a retrospective study of brain metastasis in patients with sarcoma, Shweikeh and colleagues described nine published reports of liposarcoma metastasis to the brain between 1988 and 2010. However, these reports did not specify the liposarcoma subtype.[17] In a cohort of 3829 sarcoma patients treated at Memorial Sloan Kettering between 1982 and 1999, 40 soft tissue sarcoma patients developed brain metastasis, of whom 12.5% (5 patients) had liposarcoma. Similarly, this study did not specify the liposarcoma subtype, and consequently did not reflect the exact prevalence of brain metastases in DDL.

There are few published studies evaluating potential predictive factors of metastasis in DDL. In a study of retroperitoneal sarcomas, Toulmonde and colleagues confirmed the impact of histologic grade on survival of DDL.[18] Tirumani and colleagues also found a statistically higher incidence of metastases in high grade DDL,[13] but in contrast a prior study of 155 patients by Henricks and colleagues reported no relationship between histologic grade and the risk of metastases.[1] Tirumani and colleagues also observed that the presence of local recurrence correlated with a statistically increased risk of distant metastasis, while earlier studies noted the presence of distant metastases in the absence of recurrence. The size of the primary tumor, number of surgical resections, involved surgical margins or administration of chemoradiation had no influence on the development of metastatic disease.[13,16]

Although there are no established predictive factors of DDL metastasis, in our patient we note specific characteristics of the primary tumor which differ from those seen in most retroperitoneal DDL, which we speculate may have contributed to its unusually aggressive behavior: i) it was a grade 3 sarcoma, in contrast to most retroperitoneal DDL which in our experience have relatively fewer mitoses and smaller amounts of necrosis than other pleomorphic sarcomas and tend to be more frequently grade 2 neoplasms; ii) there was focal osteosarcomatous differentiation in the primary tumor but not in the core biopsy of the subcutaneous metastasis, raising the question as to whether there might be a link between a heterologous high-grade sarcomatous component and the risk of metastasis. A recent study has shown that retroperitoneal liposarcomas with myogenic differentiation (particularly those with a rhabdomyoblastic component) have a significantly worse outcome;[19] iii) the tumor showed histologic infiltration of the kidney capsule and renal parenchyma, in contrast to most retroperitoneal WDL/DDL which tend to encase but not infiltrate the parenchyma of retroperitoneal organs. Early infiltration of skeletal muscle was also noted in the core biopsy of the subcutaneous metastasis, highlighting the unusually infiltrative behavior of this neoplasm.

Conclusions

In conclusion, we reported a case of *MDM2*-amplified retroperitoneal dedifferentiated liposarcoma with lung, subcutaneous and brain metastases. Metastasis of DDL outside the abdominal cavity is rare, and brain metastasis is exceptional. Because prior series of metastatic liposarcomas have typically not subclassified neoplasms into precise subtypes, we highlight the importance of documentation of this rare phenomenon, including the potential reasons for its unusual behavior. Further large studies of stringently diagnosed DDL are required to better understand their biologic behavior and to determine the factors related to metastases for this heterogeneous liposarcoma subtype.

References

1. Henricks WH, Chu YC, Goldblum JR, Weiss SW. Dedifferentiated liposarcoma: a clinicopathological analysis of 155 cases with a proposal for an expanded definition of dedifferentiation. Am J Surg Pathol 1997;21:271-81.
2. Lucas DR, Nascimento AG, Sanjay BK, Rock MG. Well-differentiated liposarcoma. The Mayo Clinic experience with 58 cases. Am J Clin Pathol 1994;102:677-83.
3. Nascimento AG. Dedifferentiated liposarcoma. Semin Diagn Pathol 2001;18:263-6.
4. McCormick D, Mentzel T, Beham A, Fletcher CD. Dedifferentiated liposarcoma. Clinicopathologic analysis of 32 cases suggesting a better prognostic subgroup among pleomorphic sarcomas. Am J Surg Pathol 1994;18:1213-23.
5. Martin-Liberal J, Alam S, Constantinidou A, et al. Clinical activity and tolerability of a 14-day infusional ifosfamide schedule in soft-tissue sarcoma. Sarcoma 2013;2013:868973.
6. Dalal KM, Kattan MW, Antonescu CR, et al. Subtype specific prognostic nomogram for patients with primary liposarcoma of the retroperitoneum, extremity, or trunk. Ann Surg 2006;244:381-91.
7. Coindre JM, Mariani O, Chibon F, et al. Most malignant fibrous histiocytomas developed in the retroperitoneum are dedifferentiated liposarcomas: a review of 25 cases initially diagnosed as malignant fibrous histiocytoma. Mod Pathol 2003;16:256-62.
8. Thway K, Flora R, Shah C, et al. Diagnostic utility of p16, CDK4, and MDM2 as an immunohistochemical panel in distinguishing well-differentiated and dedifferentiated liposarcomas from other adipocytic tumors. Am J Surg Pathol 2012;36:462-9.
9. Binh MB, Sastre-Garau X, Guillou L, et al. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. Am J Surg Pathol 2005;29:1340-7.
10. Thway K, Wang J, Swansbury J, et al. Fluorescence in situ hybridization for MDM2 amplification as a routine ancillary diagnostic tool for suspected well-differentiated and dedifferentiated liposarcomas: experience at a tertiary center. Sarcoma 2015;2015:812089.
11. Ware PL, Snow AN, Gvalani M, et al. MDM2 copy numbers in well-differentiated and dedifferentiated liposarcoma: characterizing progression to high-grade tumors. Am J Clin Pathol 2014;141:334-41.
12. Weaver J, Downs-Kelly E, Goldblum JR, et al. Fluorescence in situ hybridization for MDM2 gene amplification as a diagnostic tool in lipomatous neoplasms. Mod Pathol 2008;21:943-9.
13. Tirumani SH, Tirumani H, Jagannathan JP, et al. Metastasis in dedifferentiated liposarcoma: Predictors and outcome in 148 patients. Eur J Surg Oncol 2015;41:899-904.
14. Keung EZ, Hornick JL, Bertagnolli MM, et al. Predictors of outcomes in patients with primary retroperitoneal dedifferentiated liposarcoma undergoing surgery. J Am Coll

Non-commercial use only

Surg 2014;218:206-17.
15. Huang HY, Brennan MF, Singer S, Antonescu CR. Distant metastasis in retroperitoneal dedifferentiated liposarcoma is rare and rapidly fatal: a clinicopathological study with emphasis on the low-grade myxofibrosarcoma-like pattern as an early sign of dedifferentiation. Mod Pathol 2005;18:976-84.
16. Ghadimi MP, Al-Zaid T, Madewell J, et al. Diagnosis, management, and outcome of patients with dedifferentiated liposarcoma systemic metastasis. Ann Surg Oncol 2011;18:3762-70.
17. Shweikeh F, Bukavina L, Saeed K, et al. Brain metastasis in bone and soft tissue cancers: a review of incidence, interventions, and outcomes. Sarcoma 2014;2014:475175.
18. Toulmonde M, Bonvalot S, Meeus P, et al. Retroperitoneal sarcomas: patterns of care at diagnosis, prognostic factors and focus on main histological subtypes: a multicenter analysis of the French Sarcoma Group. Ann Oncol 2014;25:735-42.
19. Gronchi A, Collini P, Miceli R, et al. Myogenic differentiation and histologic grading are major prognostic determinants in retroperitoneal liposarcoma. Am J Surg Pathol 2015;39:383-93.

Non commercial use only