Medical student electives

Recurrent retroperitoneal liposarcoma in a patient with neurofibromatosis type I

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Summary

Introduction Liposarcoma complicating neurofibromatosis is very rare. Only a few cases have been described until now. We present a case of recurrent dedifferentiated retroperitoneal liposarcoma in a patient with neurofibromatosis type I (NF-1).

Case presentation A 47-year-old Caucasian woman with NF-1 presented to the hospital initially complaining of left lumbar pain irradiating to the anterior thigh and knee. Physical examination showed atrophy of the lower extremities bilaterally and decreased motor strength on the left lower extremity. Radiological studies demonstrated an enhancing lesion in the left paraspinal region, suggesting malignancy. The patient underwent local resection of tumour with safety margins. Pathological examination was consistent with dedifferentiated liposarcoma (DDLs) with positivity for MDM2 and CDK4 markers. No evidence of metastasis was noted on the radiological studies. The final diagnosis was DDLs, high-grade (G3), pT2bN0M0, stage III. After 6 weeks post-tumour resection, the patient experienced recurrence of malignancy. Chemotherapy with cisplatin and doxorubicin was initiated in the patient.

Conclusions Liposarcoma in the context of neurofibromatosis is very rare. To the best of our knowledge, only six cases have been reported until now in the literature. We are presenting this case to underline the possibility of recurrence in the case of retroperitoneal DDLs despite local tumour resection. Also, although the role of chemotherapy is controversial we decided to start treatment with cisplatin and doxorubicin given the success of chemotherapy in similar case presentations.

BACKGROUND

Soft tissue sarcomas (STS) represent less than 1% of all human neoplasms; however, despite their rarity, these tumours have substantial morbidity and mortality.^{1 2}

Liposarcoma is one of the most common STS and has a number of different subtypes: well-differentiated/dedifferentiated, mixoid/round cell and pleomorphic.²⁻⁶ Retroperitoneal liposarcomas (RLSs) are most commonly well differentiated/dedifferentiated and have a worse prognosis than liposarcoma of the extremities.^{2 4 5} Risk of recurrence is high for patients with dedifferentiated histology or retroperitoneal location.⁷ Moreover, dedifferentiated RLSs have a higher incidence of distant metastasis and a decreased 5-year overall survival.^{2 7}

Neurofibromatosis type I (NF-1), also known as von Recklinghausen disease, is a common genetic disorder that affects 1 in 3000 people. NF-1 is characterised by multiple cutaneous, subcutaneous or plexiform neurofibromas, café-au-lait spots, freckling in axillary or inguinal areas, soft papillomas, Lisch nodules, optic pathway gliomas, bone abnormalities such as pseudarthrosis, sphenoid bone dysplasia, cortical thinning and a first-degree relative as a risk factor.⁸⁻¹⁰

Approximately 50% of the cases are inherited in an autosomal-dominant manner, and the remaining half of the cases are due to new mutations (sporadic).^{8 10} Deletion of the NF-1 gene located on the long arm of chromosome 17 (q11.2), a tumour suppressor gene that codes for the protein neurofibromin, is responsible for the increased risk

of cancer in patients with NF-1.^{3 9 10} Lifetime risk of developing malignancies such as malignant peripheral nerve sheath tumours (MPNST) and STS is increased in NF-1.¹¹ The combination of liposarcoma complicating NF-1 is very rare.^{3 11-13} Until now, few cases have been reported in the literature. We present a case of recurrent RLS (dedifferentiated type) in a patient with NF-1.

CASE PRESENTATION

A 47-year-old Caucasian woman, with a history of NF-1 diagnosed in 1970, status-post-multiple tumour resections, presented initially with severe left flank pain and left anterior thigh and knee pain. The patient's history was positive for chronic neuropathic pain; she underwent placement of spinal cord stimulator in 2009. The patient's surgical history revealed resection of neurofibromas around the left knee and left ankle as well as resection of a lower cervical neurofibroma in 2002. Her family history was unremarkable for either cancer or neurofibromatosis. The physical examination was positive for generalised soft, skin-coloured cutaneous neurofibromas, multiple café-au-lait spots on thighs, sacral region and neck; freckles on axillary and inguinal regions and multiple scars on the left ankle, left knee, left flank and thoracic spine (figure 1). Her neurological examination was remarkable for decreased motor strength in the left lower extremity, and atrophy of muscles of lower extremities bilaterally. Also, a palpable mass was felt on the left lumbar region.

Figure 1 Generalised cutaneous neurofibromas. A scar on the left flank is noted corresponding to resection of liposarcoma.

Non-contrast and contrast-enhanced CT of the abdomen and pelvis demonstrated a 12 cm diameter left paraspinal mass that extended from L1 to iliac crest. This mass appeared to protrude from L1 to L2 intervertebral foramina and was causing elevation and rotation of the left kidney as well as atrophy of the psoas muscle (figures 2 and 3).

The patient underwent local radical tumour resection with safety margins. The entire tumour was separated from the nerves; some of the nerves were sectioned in order to isolate the tumour.

Pathological evaluation of the tumour revealed a dense proliferation of medium to large hyperchromatic spindle cells with frequent mitoses and multiple areas of geographic necrosis with little intervening stroma (figure 4A,B). The tumour had almost no morphological changes, suggesting a specific lineage, with the exception of focal areas with increased cytoplasmic vacuolisation that were suggestive of lipocytic differentiation (figure 4C). Immunohistochemical studies showed the tumour to be negative for neural markers (S-100 protein, glial fibrillary acidic protein (GFAP)) and muscle markers (desmin and smooth muscle actin). The tumour had a proliferative index of 60% as measured by the Ki-67 immunostain. The tumour showed strong nuclear positivity for the immunostains MDM2

and CDK4 (figure 4D), consistent with the amplification of these genes in the long arm of chromosome 12, which, when considered in light of the high-grade histological features, led to the diagnosis of DDLS.

The screening for metastasis included CT of the chest, abdomen and pelvis, brain and bone scintigraphy. No evidence of metastasis was found, and the tumour was categorised as DDLS high grade (G3), pT2bN0M0. This correlated with stage III, according to the staging system of the American Joint Committee on Cancer.

The patient was discharged and sent out for physical therapy and pain management and was being followed as an outpatient. However, 6 weeks after resection, the patient presented again with excruciating pain in the left lumbar region and left flank irradiating to the left anterior thigh and knee with associated paresthesia on the left anterior thigh and knee; she also complained of a 20 lb weight loss in a 3-week period. The patient's history did not reveal any preceding trauma. On physical examination, NF1 signs were found as well as reduced motor strength in the left lower extremity and decreased sensation to light touch on the left anterior thigh and knee. Radiological examination included contrast-enhanced CT of the chest, abdomen and pelvis. Contrast-enhanced CT of the abdomen and pelvis showed an 11 × 5 cm² enhancing mass, ill-defined, in the left psoas muscle which appeared to protrude from the left neural foramen at L1–L2, consistent with malignancy (figure 5). Several enhancing masses representing neurofibromata were noted on the left lateral abdominal wall. No metastatic lesions were visualised in this study.

Owing to the recurrence of malignant tumour, the patient was started on chemotherapy with cisplatin 100 mg/m² and doxorubicin 75 mg/m². Cardiac and liver function tests were monitored before starting chemotherapy. The patient is being followed up and screened at the cancer centre.

DISCUSSION

NF-1 represents a major risk factor for the development of malignancy, particularly MPNST and STS.^{3 9 11} The mechanism responsible for the underlying tumours is attributed to the loss of function of the NF-1 gene, a tumour suppressor gene located in the chromosome 17.^{8–10} This gene

Figure 2 Non-contrast (left) and contrast (right) axial CT scan of the lumbar spine demonstrates a heterogeneously enhancing left paraspinal mass measuring approximately 12 cm in diameter.

Figure 3 Coronal view of CT scan of the lumbar spine, showing left paraspinal mass with heterogeneous enhancement that appears to extend from L1 to L2 nerve roots (left figure). This large retroperitoneal mass was elevating and rotating the left kidney (right figure).

codes for the protein neurofibromin, a GTPase-activating protein, which downregulates the p21-ras proto-oncogene responsible for cellular proliferation and growth. Hence, loss of heterozygosity of the NF-1 gene predisposes individuals with NF-1 to develop a wide range of tumours such as the classic neurofibromas, gliomas, pilocytic astrocytomas, gastrointestinal stromal tumours, leukaemia, MPNST and STS.¹⁰ However, loss of neurofibromin function is not sufficient to result in malignancy. Korf⁹ and De Clue *et al*¹⁴ suggested that activation of epidermal growth factor receptor contributed to the malignant transformation of

MPNST. Also, an experimental study in mice showed that mutations in both NF-1 and p53 genes render them susceptible to develop sarcomas.¹⁵

STS are rare tumours, and 2.8% of them have been associated with genetic diseases. A study carried out in France showed that 2.1% of sarcomas are linked to NF-1.¹⁻³ However, liposarcoma complicating NF-1 is rare, and until now only six cases have been reported in the literature.¹¹⁻¹³ Liposarcomas associated with NF-1 have been described in the omentum, skull, upper extremity and lower extremity.^{3 11-13}

Figure 4 (A) Low-power view, demonstrating geographic necrosis in a dense spindle cell tumour with no apparent areas of adipocytic differentiation. (B) High-power view, demonstrating pleomorphic, hyperchromatic spindle cells with increased mitotic figures. (C) Intermediate power view of an area with rare cytoplasmic vacuolisation, suggesting adipocytic differentiation. (D) Intermediate power view, demonstrating strong nuclear expression for CDK4.

Figure 5 Axial (on left) and coronal (on right) views of CT abdomen and pelvis, demonstrating an ill-defined mass measuring approximately $11 \times 5 \text{ cm}^2$ consistent with the recurrence of left retroperitoneal tumour.

The possibility of liposarcoma arising from neurofibroma relies on the fact that the neurilemmal cell is multipotential and can undergo metaplasia to fat.³

Liposarcoma is the second most common STS and has different subtypes: well-differentiated/dedifferentiated; mixoid/round cell and pleomorphic.^{4–7} RLSs account for 0.1% of all malignancies and the majority of them tend to be well differentiated and dedifferentiated.^{2–4–5–16} Liposarcomas arising from the retroperitoneum usually acquire large dimensions before manifest symptoms appear.^{2–5–7} It has been shown that RLS have a higher rate of local recurrence (43%) compared to liposarcomas arising from the trunk or extremities (10–16%).^{2–7} The histological type also plays an important role in prognosis.^{4–16} Dedifferentiated RLS have a high incidence of local recurrence (83%), distant metastasis (30%) and a decreased 5-year overall survival (20%) than those with well-differentiated subtype, according to the MSKCC series.⁷ Similar results were found at the University of Texas MD Anderson Cancer Center.²

Our case was consistent with dedifferentiated RLS. The patient presented initially with a large retroperitoneal mass weighing 922 g, which is consistent with the fact that these tumours in general tend not to produce symptomatology until they are quite large.

Given the unfavourable anatomic location of RLS, surgery is challenging since critical structures can interfere with resectability. Although surgical resection and radiotherapy are the standard therapy for local control, chemotherapy has also been used for more extensive disease.^{4–5–7} Also, chemotherapy sensitivity varies across the different subtypes of RLS. Mixoid liposarcoma has a better response to chemotherapy (48%) compared to DDLS (11%).⁶

The decision was to do surgery in our patient since it is the standard therapy in the case of RLS. Preoperative radiation has the advantage of reducing tumour size, but 25% of patients who received radiotherapy preoperatively have wound-healing complications.¹⁷ Hence, radiotherapy was held in the patient and local tumour resection with safety margins was performed. Since the patient experienced recurrence of tumour, which according to the literature is common in retroperitoneal DDLS,^{2–4–7–16–18} a decision was

made to start chemotherapy with cisplatin and doxorubicin. Chemotherapy with cisplatin and ifosfamide showed a favourable response in the case of RLS according to Yokoi *et al.*¹⁹ Meta-analysis of 14 randomised trials of adjuvant therapy for STS demonstrated that doxorubicin-based chemotherapy improves overall survival and time to local and distant recurrence. Also, cisplatin has showed efficacious results in the treatment of STS.²⁰

Nonetheless, Smith *et al.*² report that patients with dedifferentiated subtype had a 5-year survival of 36.5% despite an aggressive surgical approach combined with high-dose systemic chemotherapy. Hence, there is a need for novel molecular therapies to address the treatment of DDLS.

DDLSs are characterised by amplified segments on chromosome 12 (q13–15);^{5–18} several oncogenes have been identified in this region such as MDM2, CDK4, HMGA2 and TSPAN31. MDM2 encodes a negative regulator of the tumour suppressor gene p53 and also acts as ubiquitin ligase targeting p53 for proteosomal degradation. Hence, MDM-2 antagonists leave p53 free to exert its antitumorous properties as well as to induce cell death.^{5–16} An important MDM2 antagonist on phase I trial for liposarcoma is RO5045337. Also, CDK4 is amplified in DDLS and helps in the transition from G1 to S in the cell cycle, thereby stimulating cell proliferation. CDK4 antagonists such as PD0332991, R547 and P1446A05 are also being tested in phase I and II trials.⁵

Immunostain in the patient's resected tumour showed strong positivity for MDM2 and CDK4 markers. If the patient does not respond to chemotherapy, a novel molecular treatment could be considered as targeted therapy.

Although liposarcoma complicating neurofibromatosis is rare, we present this case of dedifferentiated RLS to stress the high probability of this type of tumour to recur in spite of surgical resection. We are currently using high-dose chemotherapy with cisplatin and doxorubicin since it has been shown to be the most hopeful regimen for STS in many studies. The pathological examination of the tumour, as well as the positivity for MDM2 and CDK4, suggests that targeted molecular therapy could be beneficial in this particular case.

Learning points

- ▶ Liposarcoma complicating neurofibromatosis is very rare. Only a few cases have been reported until now.
- ▶ Neurofibromatosis represents a risk factor for the development of soft tissue sarcomas (liposarcoma) due to mutations in the neurofibromatosis type I (NF-1) gene. It is thought that the neurilemmal cell can undergo metaplasia to fat, resulting in the development of liposarcoma in patients with NF-1.
- ▶ Dedifferentiated retroperitoneal liposarcomas (RLSs) have a high rate of recurrence.
- ▶ Surgical management is the standard treatment for dedifferentiated RLS; chemotherapy with cisplatin and doxorubicin have also been shown to be helpful.
- ▶ Novel targeted molecular therapy can be considered if standard therapy fails.

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Competing interests None.

Patient consent Obtained.

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