

Case Report

Open Access

Malignant Retroperitoneal Tumor of the Peripheral Nerve Sheath Associated with Neurofibromatosis Type 1

Beatriz Cros Montalbán*, Pilar Palacios Gasos, Rocío Ferrer Sotelo, José Fernando Trebollé, Mónica Valero Sabater, Carlos Yanez Benítez, Elena Gonzalvo González, Juan Luis Blas Laina
Hospital Royo Villanova, Zaragoza, Spain

Article Info

Article Notes

Received: February 08, 2020
Accepted: May 21, 2020

*Correspondence:

Beatriz Cros Montalbán, Hospital Royo Villanova, Zaragoza, Spain. Email: bcrosmontalban@gmail.com

©2020 Montalbán BC. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License.

Key Words:

Malignant peripheral nerve sheath tumor
Type 1 neurofibromatosis

Abstract

The malignant peripheral nerve sheath tumor (MPNST) is a spindle cell sarcoma, which accounts for 5-10% of soft tissue sarcomas. We present the case of a 39-year-old woman with a history of Neurofibromatosis type 1, who in the study for abdominal pain was diagnosed on abdominopelvic CT with a large retroperitoneal adenopathic conglomerate without distant extension. By laparoscopy, complete exeresis of the lesion was performed, with nil complications in the postoperative period. In the histological sections, a nodular lesion of 4 cm in diameter was identified, with neoplastic proliferation showing diverse growth patterns, low mitotic index and positive immunohistochemistry for S-100 and Vimentin, confirming the diagnosis. MPNSTs are aggressive behavioral sarcomas with a high recurrence rate. They present distant metastases, even in early clinical stages. The treatment of choice is complete resection with free margins, because of the high rate of recurrence and limited therapeutic response to radiotherapy and chemotherapy.

Introduction

Malignant peripheral nerve sheath tumor (MPNST) is a spindle cell sarcoma which accounts for 5-10% of soft tissue sarcomas^{1,2}. The principal risk factor for MPNST is a diagnosis of Neurofibromatosis Type 1 (NF-1). Retroperitoneal MPNSTs are extremely rare tumors. The lifetime risk of MPNST in NF1 is 8-13% as compared to 0.001% in the general population^{3,4}. NF1 syndrome is characterized by the loss of the tumor suppressor gene, neurofibromin, and clinically the patient presents with multiple plexiform neurofibromas all over the body, which may transform to MPNST³⁻⁵. MPNSTs are aggressive life-threatening sarcomas that have a high probability of recurring or metastasizing³. They are often inoperable and do not respond well to current chemotherapy or radiation therapy⁴. For those reasons, tumor biology and complete surgical excision are two significant factors for consideration in the management of these tumors.

Case presentation

A 39-year-old woman with a history of NF-1 with multiple cutaneous neurofibromas all over her body with classical café au lait skin spots over her back and abdomen and major depression. She was diagnosed in childhood with an optic glioma affecting her right eye that required enucleation in adolescence with the placement of prosthesis. Furthermore, when she was 35 years underwent surgery to remove a neurofibroma of the left scalene nerve located in the C6 root. She had no family history of neurofibromatosis. The patient was examined with regard to abdominal pain for a period

of 2 months with no other associated symptoms. On examination, her overall status and vital signs were under normal conditions. Nevertheless, the physical assessment showed epigastric pain upon palpation. An abdominal ultrasound was performed, aiming a rounded and cystic lesion in the epigastric. It was diagnosed by abdominopelvic CT (Figure 1) of a voluminous retroperitoneal adenopathic conglomerate suggestive of lymphoproliferative process and numerous cutaneous neurofibromas with no other findings. An extended clinical and radiological evaluation was performed at the head, neck, and thoracic level with no distal metastatic disease identifiable and no pathological image at a distance (brain MRI and thoracic CT). In addition, no significant alterations were observed in the blood tests. After obtaining anaesthetic fitness, the patient was

posted for retroperitoneal tumor excision under general anaesthesia. Prophylactic treatment with intravenous amoxicillin/clavulanic acid and antithrombotic prophylaxis (subcutaneous sodium bemiparin 3500 UI (according to protocol)) were given prior to surgery. The patient was operated by laparoscopy, in a programmed way, performing complete exeresis of the lesion (Figure 2) located between the superior mesenteric artery, the splenic artery and the left renal vein, (infrapancreatic) settled on a conglomerate of neurofibromas removed along with the lesion (Figure 3). Less than 100 ml of blood was lost during the 90 minutes of surgery. The postoperative period was free of incidents with antithrombotic prophylaxis (subcutaneous sodium bemiparin 3500 UI (according to protocol) every 24 hours), and the patient could be discharged after 48 hours of admission. In the histological sections, a nodular lesion of 4 cm in diameter was identified, with neoplastic proliferation showing different growth patterns, low mitotic index, and positive immunohistochemistry for S-100 and Vimentin

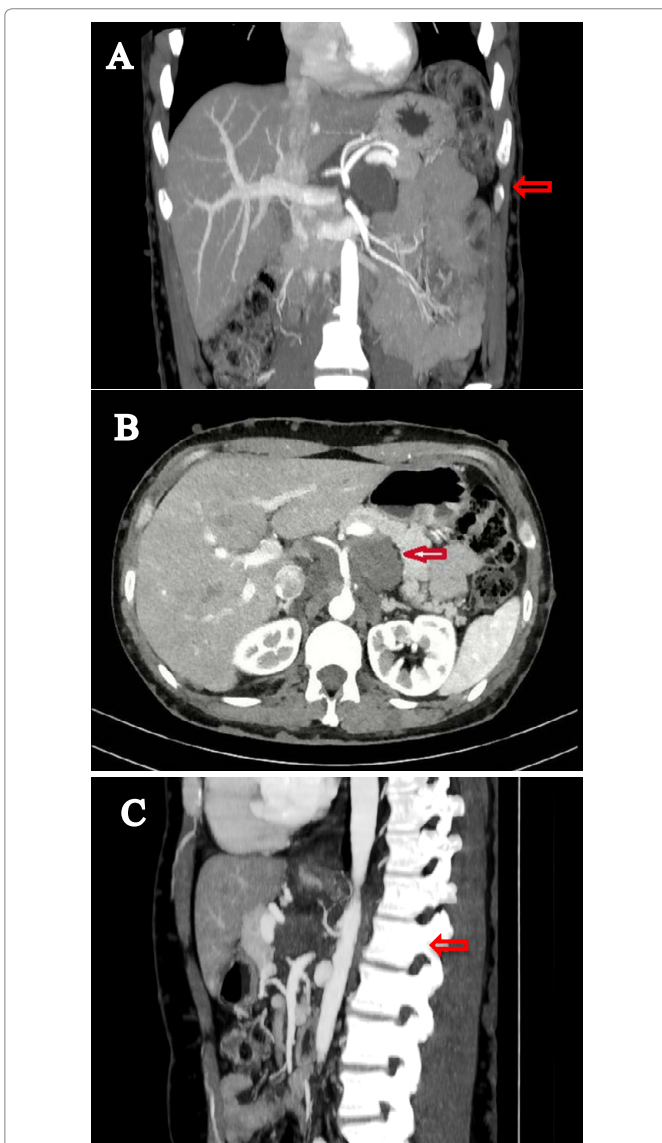


Figure 1: (A-C) Coronal, transverse and sagittal planes of abdominal CT showing numerous cutaneous neurofibromas and large, retroperitoneal mass, whose upper limit is the splenic artery and the lower limit is the superior mesenteric artery, contacting the left renal vein, without infiltration or distant extension.

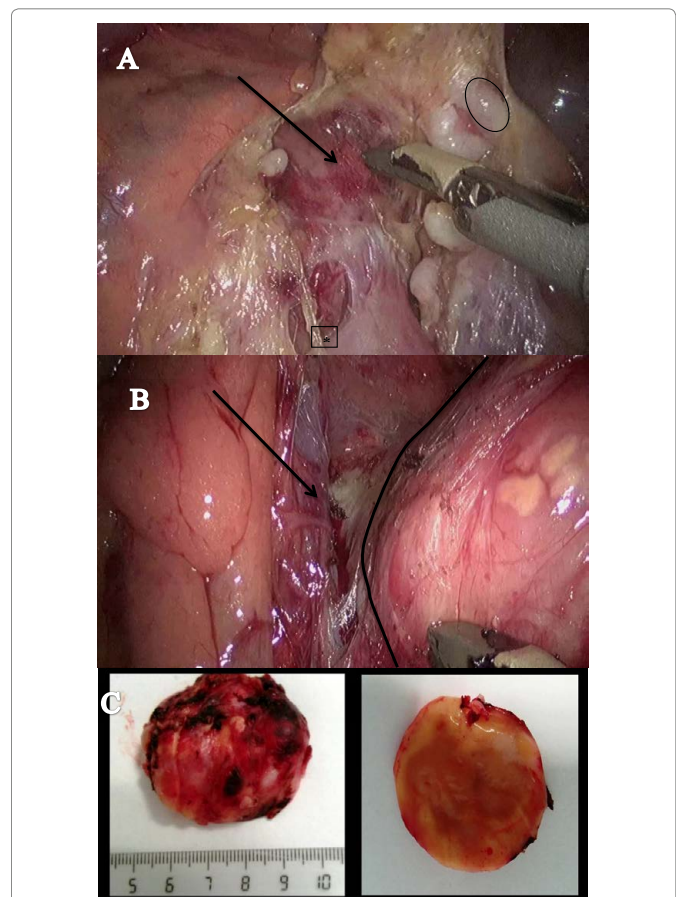


Figure 2: Shows an intra-op photo of the laparoscopic approach. A. Having previously mobilized cranially the transverse colon it is possible to observe the MPNSTs (arrow) appear to arise within preexisting plexiform neurofibromas (circle) in close proximity to the ligament of Treitz*. B. MPNST (curved line delimiting lesion) located adjacent to the superior mesenteric artery (arrow). C. Tumour piece (4.5x4 cm): Pseudo-encapsulated, with a fleshy consistency. No focal points of necrosis or haemorrhage.

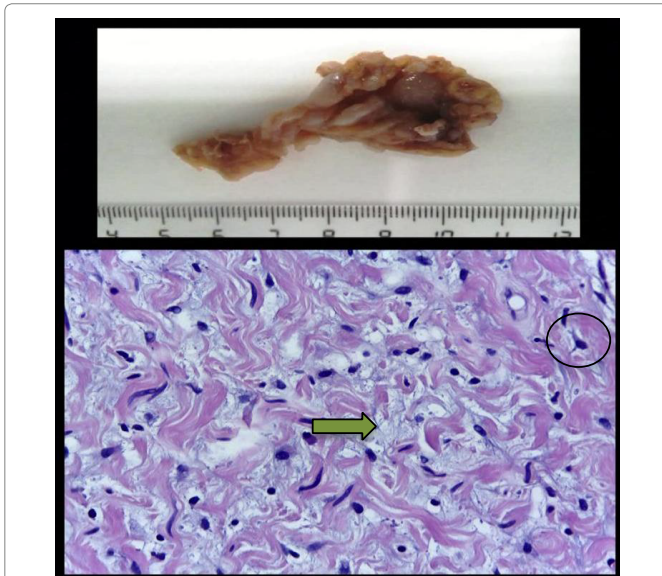


Figure 3: Benign neurofibromas: Non-encapsulated, gelatinous and elastic consistency. Microscope: Irregular spindle cell fascicles (circle) on a mixed or collagenous background (arrow).

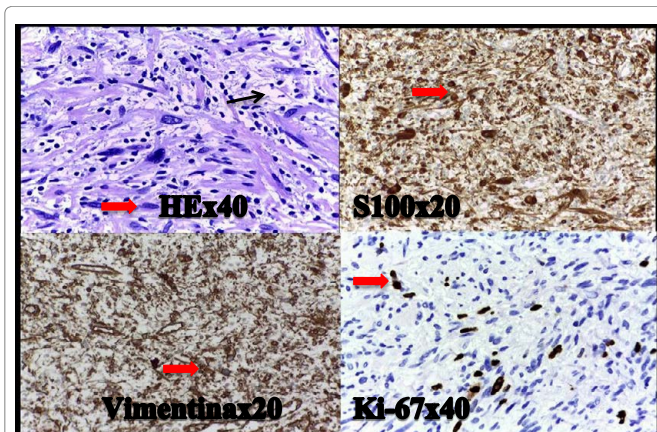


Figure 4: Tumour piece: Microscope: More uniform and tight fascicles. H&E x40: Shows how the tumor cells are arranged haphazardly in a fibromyxoid stroma (thin arrow), with elongated wavy nuclei and eosinophilic cytoplasm (arrow). S100x20 and Vimentinx20 immunostaining show strong nuclear and cytoplasmic positivity in a high percentage of the tumor cells (arrows). With the Ki 67 technique, nuclear positivity of up to 30% is observed (arrow) (mitotic index up to 5 mitoses per 10 high magnification fields). With immunohistochemical techniques the cells show positivity for S100 and Vimentin + thus confirming the diagnosis and ruling out melanoma (HMB45-, Melan A-) and other types of sarcoma of muscular origin (Actina-, Desmina-) or epithelial (EMA-, CK AE1:AE3-).

(Figure 4). (Pathology report: Malignant peripheral nerve sheath tumor (WHO Classification of Tumours of Soft Tissue and Bone 2013). Necrosis tumoral, lymphovascular invasion, and focal haemorrhages were not identified. Mitotic index: Up to 5 mitoses per 10 high-magnification fields. Neurofibromas (satellite nodes) without sign of malignancy. Histologic grade: Peripheral Nerve Sheath

Tumor's gradation is not recommended based on WHO Classification of Tumours of Soft Tissue and Bone 2013 criteria, however as per mitotic activity for this particular case (in the range of 0–5/high-magnification fields), it is stated as low grade. Free surgical margins. Stage pT1(the tumor was smaller than 5 cm)N0(0/3)M0)). Discussed in the Sarcoma Committee, despite the complete surgical resection and achievement of tumor free margins, given the high-risk retroperitoneal tumor in patient with NF-1, it was decided to complement the treatment with sequential chemotherapy and radiotherapy. The patient completed four cycles of chemotherapy with adriamycin and ifosfamide. A thoraco-abdominal CT was performed without signs of progression and treatment with radiotherapy was initiated for two months (28 sessions, doses per fraction 180 cGy, total doses 50.4 Gy) After finishing treatment in June 2018 the patient is being monitored with radiological follow-screening, first every three months in 2018, and subsequently every six months using low dose thoraco-abdominal CT. At the time of manuscript submission, the patient is asymptomatic of disease without locoregional or distant recurrence.

Discussion

Malignant peripheral nerve sheath tumor (MPNST) is a rare variety of soft tissue sarcoma of neural origin^{1,2}. MPNSTs are the most frequent malignant neoplasms associated with NF1 occurring in approximately 10% of affected patients, and they tend to occur at a younger age in people with NF1, usually in third or fourth decade, in comparison to the general population, mostly in seventh decade⁵. As in our case, most NF1-associated MPNSTs appear to arise within preexisting plexiform neurofibromas, and in majority of cases, the associated nerve is hard to identify^{1,5,6}. Its most common locations are the trunk, pelvis, and lower limbs, and they are linked to main lumbar or sacral plexus, with the retroperitoneum being a rare location for a primary MPNST to develop³⁻⁵. They tend to cause pain and weakness in the affected area and may also cause a growing lump or mass^{1,5}. The median life expectancy of patients with NF1 is approximately eight years lower than in the general population. Malignancy (especially malignant peripheral nerve sheath tumors) and vasculopathy are the most important causes of early death in these patients⁷. The diagnosis of MPNST can be a significant challenge on imaging alone, and biopsy is the gold standard, as in our case. Some studies have suggested that the MRI is the method of choice for demonstrating the size and extent of plexiform neurofibromas and for monitoring their growth over time: Tumors > 5 cm, invasion of fat planes heterogeneity, ill-defined margins and surrounding edema are highly suggestive of MPNST⁸⁻¹¹. CT is fully used in the evaluation of retroperitoneal masses, but the CT features of retroperitoneal plexiform neurofibromas have been

described in only a few case reports. Some studies comparing the CT findings of these benign retroperitoneal tumors, with those trademarks that indicate a concurrent malignant tumor as well as signs suggestive of malignant transformation¹². Examination by PET or PET/CT is useful in distinguishing benign and malignant peripheral nerve sheath tumors⁵. Because of the high risk of malignancy, NF1 patients must be followed carefully. Histologically, MPNSTs are composed of spindle cells arranged in intersecting fascicles^{3,6}. Compared with benign neurofibromas, MPNSTs usually demonstrate a marked increase in tumor cellularity, pleomorphism, and mitotic activity and show a more organized cellular growth pattern, with less extracellular matrix material³. There is no pathognomonic molecular or immunohistochemical study for MPNST. S-100 protein has been identified in about 50-90% of MPNST by immunohistochemistry, usually with a focal pattern. Therefore, it is the most often used marker to document the differentiation of peripheral nerve sheath, but it is also present in synovial sarcomas, fusiform melanomas, and schwannomas⁵. Radical and complete surgical excision is the best and only curative method of treatment available for MPNST. Small lesions should be widely resected, and the tumors ≥ 10 cm should be removed as widely as possible to prevent centripetal dissemination⁶. ¹⁸FDG PET or low dose CT might be a useful screening method for this group of "at-risk" patients. Adjuvant chemotherapy or radiotherapy is sometimes used as well and appears to have benefitted some patients with NF1 (only in a minority)¹³. Overall, MPNST is known to have a high recurrence rate, high metastatic potential, and poor prognosis with 5-year survival ranging between 15% and 50%³. Poor prognostic factors are large tumor size at presentation (>5 cm), tumor grade, truncal location, surgical margin status, local recurrence, and heterologous rhabdomyoblastic differentiation^{3,5}. If the tumor size is more than 5cm, neoadjuvant radiotherapy is advocated to shrink the size of the tumour and reduce local recurrence^{3,14}. Postoperative radiation requires higher doses of radiation. It must be taken into account the risk-benefit profile of adjuvant radiation in patients with NF1 because of radiation-induced sarcomas³. Common sarcoma treatment regimens with radiation and chemotherapy have been adapted for MPNST (doxorubicin, ifosfamide, and etoposide)^{3,4,6}. Chemotherapy is implicated for use in high grade and metastatic disease, but some studies suggest that chemotherapy may yet have a role in the multimodality treatment of selected MPNST patients with nonmetastatic disease³, as in our case, with favourable results, remaining the patient disease-free in the first three years after surgery. Additionally, many studies are ongoing, looking at genetic and molecular pathways that can be targeted by new treatments³⁻⁶.

Conclusions

Close follow-up is essential from childhood in patients

with NF1 because of the malignant potential of this disease. MPNST can become a disastrous complication of NF1 because of its aggressive nature and limitations in early diagnosis and management. For this reason, it should be managed by multidisciplinary teams with extensive knowledge in the diagnosis and treatment of this disease. We consider this case interesting as it reveals that early suspicion of MPNST in a patient with NF1 and prompt surgical treatment were key to its complete removal by laparoscopy with free margins given its retroperitoneal location and at the confluence of large vessels.

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Consent

Written informed consent was obtained from the patient's legal representative for publication of this case report and accompanying images.

Conflict of interest

The authors declare no conflicts of interest of any nature.

References

1. Evans DG, Baser ME, McLaughran J, et al. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. *J Med Genet.*2002;39:311-4.
2. Hagel C, Zils U, Peiper M, et al. Histopathology and clinical outcome of NF1-associated vs. sporadic malignant peripheral nerve sheath tumors. *J Neurooncol.*2007;82:187-92.
3. Farid M, Demicco EG, Garcia R, et al. Malignant peripheral nerve sheath tumors. *Oncologist* 2014;19:193-201.
4. Guo J, Chaney KE, Choi K, et al. Polo-like kinase 1 as therapeutic target for malignant peripheral nerve sheath tumors (MPNST) and schwannomas. *Am J Cancer Res.*2020;10(3):856-869.
5. Friedman JM. Neurofibromatosis 1. 1998 Oct 2 [Updated 2019 Jun 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Bookshelf URL: <https://www.ncbi.nlm.nih.gov/books/>
6. Ferner RE, Gutmann DH. International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis. *Cancer Res.*2002;62:1573-1577.
7. Evans DG, O'Hara C, Wilding A, et al. Mortality in neurofibromatosis 1: in North West England: an assessment of actuarial survival in a region of the UK since 1989. *Eur J Hum Genet.*2011;19:1187-91. PubMed PMID:21694737
8. Pilavaki M, Chourmouzi D, Kixiridou A, et al. Imaging of peripheral nerve sheath tumors with pathologic correlation: pictorial review. *Eur J Radiol.*2004;52(3):229-239.
9. Friedrich RE, Kluwe L, Funsterer C, et al. Malignant peripheral nerve sheath tumors (MPNST) in neurofibromatosis type 1 (NF1): diagnostic findings on magnetic resonance images an mutation analysis of the NF1. *Gene.* 2005;25(3A(May-June)):1699-1702.
10. Hirbe AC, Gutmann DH. Neurofibromatosis type 1: a multidisciplinary approach to care. *Lancet Neurol.*2014;13:834-43. Pubmed PMID:25030515.

11. Nguyen R, Dombi E, Widemann BC, et al. Growth dynamics of plexiform neurofibromas: a retrospective cohort study of 201 patients with neurofibromatosis 1. *Orphanet J Rare Dis.*2012;7:75. PubMed PMID:23035791
12. Bass JC, Korobkin M, Francis IR, et al. Retroperitoneal Plexiform Neurofibromas: CT Findings. *AJR.*1994;163:617-620.
13. Valentin T, Le Cesne A, Ray-Coquard I, et al. Management and prognosis of malignant peripheral nerve sheath tumors: the experience of the French Sarcoma Group (GSF-GETO). *Eur J Cancer.*2016;56:77-84. PubMed PMID: 26824706.
14. Dunn GP, Spiliopoulos K, Plotkin SR. Role of resection of malignant peripheral nerve sheath tumors in patients with neurofibromatosis type 1. *J Neurosurg.*2013;118:142-148.