Retroperitoneal malignant triton tumor in an adolescent with Neurofibromatosis type 1

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Abstract

Malignant triton tumor (MTT) is a very infrequent variant of the malignant peripheral nerve sheath tumor (MPNST) with rhabdomyoblastic differentiation. Up to 70% of cases are diagnosed in patients with neurofibromatosis type 1 (NF1). It is a highly aggressive pathology with early relapses occurring in up to 50% of patients. Despite multimodal treatment the prognosis is poor, with long term survival rates not exceeding 15%. We present the case of an adolescent male with known NF1 diagnosed with an aggressive retroperitoneal MTT and disseminated pulmonary disease.

Introduction:

Malignant triton tumor (MTT) is a very rare variant of the malignant peripheral nerve sheath tumor (MPNST), with rhabdomyoblastic differentiation, which primarily affects young adult patients (1-3). Up to 70% of cases are diagnosed in patients with neurofibromatosis type 1 (NF1), although sporadic and radiotherapy related cases have been also described (1-6). Clinical course is highly aggressive, with relapses occurring in up to 50% of patients. The prognosis is very poor and, with multimodal treatment, reported 5-year survival rates do not exceed 15% (1-3).

We present the case of an adolescent male with known NF1 diagnosed with an aggressive retroperitoneal MTT and disseminated pulmonary disease.

Results:

An 18-year-old male diagnosed with NF1 (de novo mutation) presented with a 4-month history of abdominal pain and paresthesias in his right lower limb, associating loss of strength and sensory in the last month along with urinary obstruction. Physical examination showed abdominal distension with a palpable mass in addition to numerous subcutaneous neurofibromas, café-au-lait spots, Lisch nodules and axillary ephelides. Abdominal magnetic resonance imaging (MRI) revealed a large retroperitoneal mass with intense heterogeneous contrast enhancement and diffusion restriction as well as innumerable neurofibromas derived from intercostal nerves and lumbosacral plexus (Fig. 1). The suspected diagnosis was a MPNST within a previous neurofibroma. The patient underwent partial surgical resection of the large mass with infiltrated margins. The surgical specimen showed a neoplastic proliferation of spindle cells with marked pleomorphism, frequent mitosis and atypias, forming small fascicles with predominance of perivascular growth. Immunohistochemical staining demonstrated focal positivity for S100, myogenin and desmin, with a proliferative index (Ki 67) of approximately 50%, compatible with high-grade MPNST with rhabdomyoblastic differentiation (Fig. 2). After surgery the patient experience a great improvement of abdominal and lower limb pain as well as urinary obstruction resolution. PET-CT performed three weeks after surgery showed signs of local progression with soft tissue mass enlargement and high FDG uptake (SUV 26.7) together with multiple bilateral pulmonary nodules suggestive of metastasis. Bilateral bone marrow biopsy ruled out tumor infiltration.

The patient started chemotherapy treatment according to European Paediatric Soft Tissue Sarcoma Study Group protocol for rhabdomyosarcoma (EpSSG RMS 2005), based on vincristine (1.5 mg / m^2 / day, days +1, +8 and +15), ifosfamide (3000 mg / m^2 / day, days +1 and +2), actinomycin (1.5 mg / m^2 / day, day +1), and doxorubicin (30 mg / m^2 / day, days +1 and +2) in a 21-day interval. The aim of this systemic treatment was to achieve the control of metastatic disease to further consider surgical second-look followed by local radiotherapy. Unfortunately, symptoms progressed after the first cycle and the patient ultimately died of disease progression.

A whole exome sequencing analysis (WES) was performed on surgical material, identifying two genetic gains (duplication/amplification) affecting chromosomal region 7q31.2 of *MET* gene and 8q24.21 of*MYC* gene. Mutational disruption of *SUZ12*c.1214C>G and *TP53* c.681delT were also revealed. No gene fusions were detected. This analysis was only available after the patient passed away and therefore could not be used for therapeutic purposes.

Discussion:

Malignant peripheral nerve sheath tumors account for about 5-10% of soft tissue sarcomas and are derived from either peripheral nerve Schwann cells or pre-existing neurofibromas. Among the different histological variants, 10% of MPNST show foci of skeletal muscle differentiation (1-3). This subtype of MPNST with rhabdomyoblastic differentiation was first described in a patient with NF1 by Masson and Martin in 1932 (7). The term MTT was suggested in 1973 by Woodruff referring to the ability of the Triton salamander to regenerate supernumerary limbs containing muscle, bone and neural components after the implantation of the cut end of the sciatic nerve into the soft tissue of its back (8). Since then, less than 200 cases of MTT have been reported to date, many of them in patients with NF1 who have a 10% life time risk of malignant transformation from plexiform neurofibromas.

Although most MTT cases are diagnosed in patients under 35 years of age, few cases have been reported in children and adolescents (9-19). Main series have shown no gender predilection and, although widely distributed, the head, neck and trunk have been described as the most common locations. Those MTT associated with NF1 constitute over 50-70% of cases and display a young age, male predominance, and frequent head and neck involvement. Nevertheless, sporadic cases tend to affect female patients at older age and are frequently located on the trunk (1-3, 10, 13, 19, 20). Up to 8% of reported cases have been related to previous radiation (4-6). Other unusual locations such as intracranial fossa, spinal cord, mediastinum, uterus or epididymis have been described in the literature (17, 21-29). Our patient presented with a huge retroperitoneal mass, which is an uncommon finding with less than 20 similar cases reported to date (30-35).

The histogenesis of these composite tumors has not been clearly defined. They may reflect the capability of the nerve sheath cells to induce mesenchymal differentiation or may be explained by the potential of the neural crest to differentiate into both Schwann and muscular tumoral cells. Woodruff proposed three criteria to establish the diagnosis of MTT, including tumor origin in peripheral nerves of patients with known NF1, predominance of Schwann cell growth pattern and the presence of rhabdomyoblastic differentiation in the absence of extension or metastasis of a rhabdomyosarcoma (8). Further on, Daimaru suggested the omission of the first criteria to include sporadic cases (36). It is currently assumed that histological diagnosis must be supported by immunohistochemical findings. S-100 and Leu-7 proteins positivity reflect nerve sheath differentiation, whereas the positivity of actin, desmin, myogenin, MyoD1 and vimentin confirm rhabdomyoblastic differentiation (1).

The WES analyses performed in our patient revealed both *SUZ12*c.1214C>G and *TP53* c.681delT mutations, both variants not previously described. *SUZ12* inactivating mutations have been related with *NF1* and *CDKN2A* loss of function in the progression of neurofibromas to MPNST, and somatic mutations in *TP53* have been also demonstrated in most MPNST/MTT samples (37). Gains affecting *MET* have been related with the development of MPNST from plexiform neurofibromas and might involve *RAS*deregulation contributing to therapy resistance (38). Our patient also presented with a *MYC* amplification, usual across many cancer types including MPNST by regulating proliferation, cell cycle and tumor vascularization (39).

As illustrated by the present case, the natural history of MTT is much more aggressive than MPNST. The percentage of patients with metastatic disease at diagnosis reaches 30-50% with pulmonary involvement being the most frequent location, whereas lymph node involvement has not been reported (1-3).

The therapeutic strategy for MTT is primarily based on wide surgical resection (R0). Although the role of radiotherapy is not well established, it should be considered after inadequate surgical excision or high risk of local recurrence due to large tumor size or high histological grade. Chemotherapy regimens may be reserved for disseminated or unresectable disease, second-line treatment or palliation (1-3, 13, 32). Despite a multidisciplinary approach the prognosis of MTT is very poor, with 5-year overall survival rates not exceeding 15%. Early local and distance metastasis occur in up to 50% of patients, especially in cases with large tumors, incomplete surgery, location in the trunk or retroperitoneum and associated NF1 (1-3, 10, 13, 20, 26, 32).

In conclusion, MTT is a very rare form of MPNST, typically associated with NF1, with an aggressive behaviour. No standard treatment has yet been accepted, although surgical resection followed by radiation therapy have demostyrated to be essential to achieve long term survival. The poor prognosis of this entity requires collaborative efforts to obtain biological information and develop new targeted therapeutic strategies in the future.

Conflicts of interest: none to declare.

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Legends:

Fig 1.

Coronal (A) T2-weighted MRI of the abdomen show a huge retroperitoneal mass with partially well delineated margins and markedly heterogenous intensity signal, causing upper displacement of the right kidney and enlarging of neual foramina. Multiple subcutaneous, paraspinal and pelvic plexiform neurofibromas with the characteristic target sign are shown. Axial MRI demostrate a mostly homogeneous isointense retroperitoneal mass in T1- weighted image (B) with peripheral inhomogenous contrast enhancement after gadolinum intravenous administration (C) and heterogenous diffusion restriction in diffusion- weighted MRI (D) and ADC map (E).

Fig. 2.

Spindle cell neoplasm showing alternating celular and less celular areas (tapestry pattern) and geographical necrosis. HE, 4X (A). Focal positivity for S100 protein, showing up Schwann cell differentiation. S100 IHC, 10X (B). Focal positivity for myogening, evidencing skeletal muscle differentiation. Myogenin IHC, 10X (C).