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Case Report

Malignant peripheral nerve sheath tumor of the bladder
A case report

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Summary

Malignant peripheral nerve sheath tumor (MPNST) is an uncommon malignant tumor often associated with Neurofibromatosis type 1 (NF1). Although different soft tissue mesenchymal tumors may arise in the bladder, MPNST is a very rare occurrence. Here, we present a case of MPNST of the bladder in a 50 year old patient with NF1 with involvement of the entire wall of the organ leading to a functional exclusion. The principal differential diagnoses and a short review of the literature are presented.

Key words

Malignant peripheral nerve sheath tumor • Bladder

Introduction

Urothelial cell carcinoma is the most frequent malignant tumor of the bladder and may show various divergent differentions, most frequently squamous cell carcinoma or adenocarcinoma differentiations. Sarcomatoid features are also a possible finding, particularly in muscle infiltrating urothelial cell carcinoma. Hence, when dealing with a malignant mesenchymal-like tumor of the bladder a sarcomatoid carcinoma must be ruled out [1], and this is a frequent diagnostic experience in the daily practice of microscopical examination of the chips of transurethral resection of the bladder (TURB).

Nevertheless, besides rhabdomiosarcoma, which is the most common malignant bladder tumor in infancy [2], primary bona fide sarcomas of the bladder in adult are a rare but real occurrence and have been described in the literature, although only in small series or isolated case reports [3]. They are mainly represented by leyomiosarcoma [4] and angiosarcoma [5]. MPNST is the among the rarest sarcomas arising in the urinary bladder and only a few cases have been documented, predominantly in middle aged patients, with complaints of hematuria [6 7]. Some of those cases arose in the setting of neurofibromatosis type 1 (NF1), probably originating from neurofibromas of autonomic nerve plexuses of the bladder wall [8 9].

In this paper, we describe a case of MPNST of the bladder in a patient affected by NF1, with the involvement of the entire organ. The differential diagnoses of the case are presented.

Case report

A 50-year-old man without history of cigarette smoking and affected by NF1, with a previous diagnosis of skin neurofibroma, was admitted to the Urology Division of Sant'Anna Hospital of Como for numerous episodes of urinary retention and sepsis. After radiological investigations, a prostate trans-uretral resection (TURP) was performed with a histologic diagnosis of fibroleyomiomatous hyperplasia. Nevertheless, urinary function did not improve; therefore, laboratory tests and further radiological investigations were performed. CT scan showed a full thickness neoplastic growth of the bladder with a diffuse involvement and irregular polipoid

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thickening of the wall and involvement of the entire organ, without a distinctive mass (Fig. 1). Since bladder function was compromised by the tumor, the patient underwent a cistoprostatectomy.

On gross examination, the bladder wall was diffusely thickened, and showed hard consistency with grey to white tissue on cut surface, with subtotal vanishing of the normal detrusor muscle, although without the finding of appreciable nodules in muscolaris propria and/or mucosal lesions; hence a broad sampling was performed.

At histological examination we observed normal and intact urothelium that was lining a diffuse spindle cell proliferation with bland aspect in the more superficial layers of the wall, with comma-shaped nuclei and collagenous extracellular matrix (Fig. 2); more deeply in the wall a denser cellular proliferation, particularly around vessels, with prominent cytological atypia, mitoses, and infiltrative pattern of growth were present (Fig. 3). The tumor was in close contact with peripheral nerves.

Considering the possible differential diagnoses, the absence of a residual urothelial carcinoma in situ together with the absence of cytokeratin immunoreactivity of the tumor, excluded a mixoid variant of sarcomatoid carcinoma. Moreover, the diffuse involvement of the organ without polipoid masses, the absence of inflammation and the presence of prominent atypia were not compatible with a myofibroblastic inflammatory tumor. Likewise, atypia and infiltrative pattern of growth were not compatible with a large neurofibroma or with other benign entities. Moreover, absence of fascicles and cytological features were not suggestive of a leyomiosarcoma; finally, the lack of lipoblasts and a proper vascular network ruled out a liposarcoma.

We performed a wide panel of immunohistochemical stainings that showed tumor immunoreactivity for S100, p16, neurofilaments, CD56 and negative

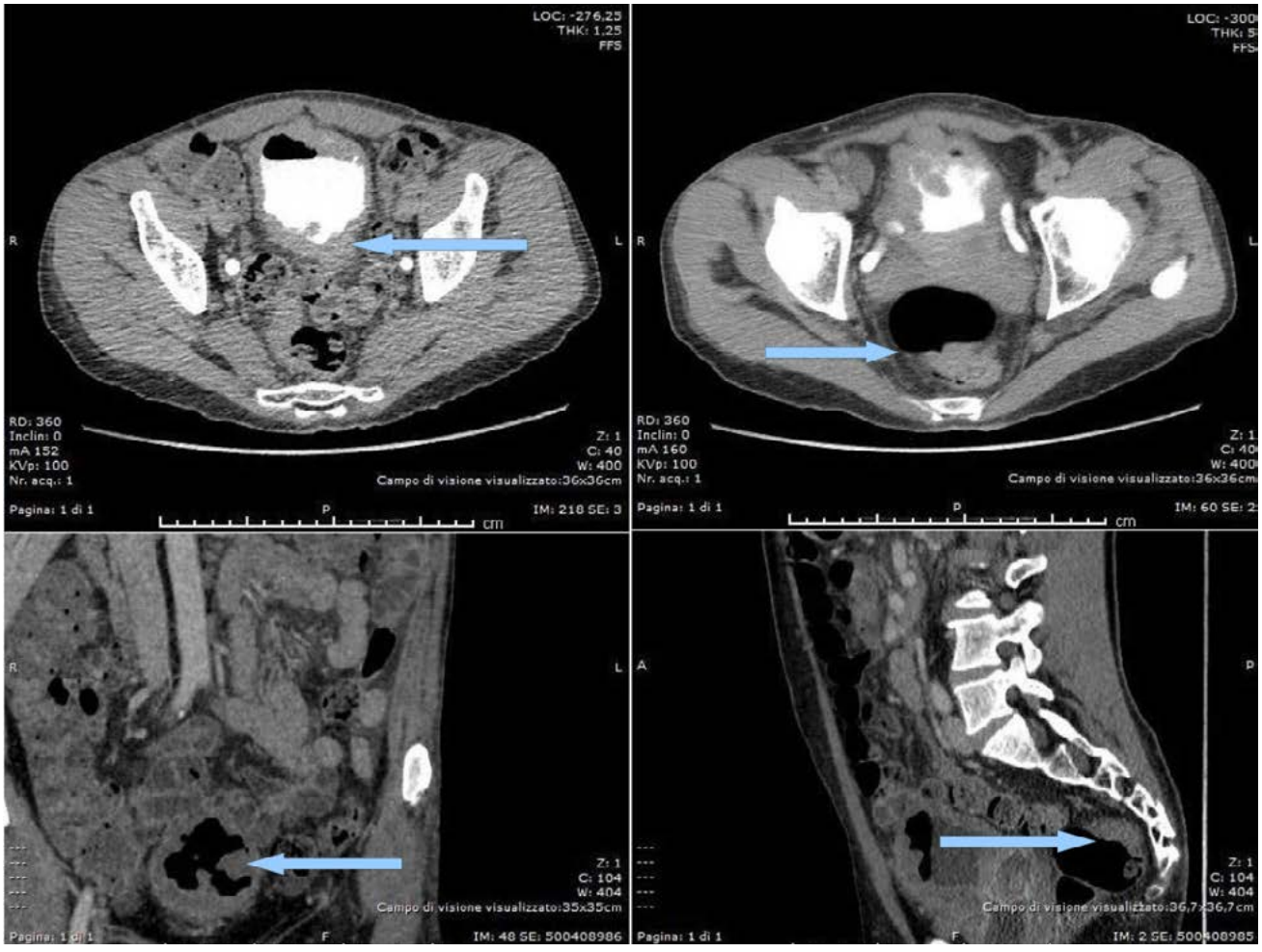

Fig. 1. CT scan diffuse involvement of the bladder with uneven thickening of the entire wall.

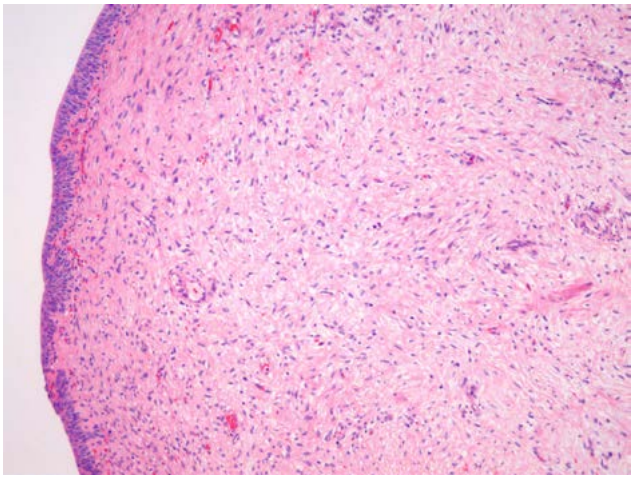

Fig. 2. Mesenchymal hypocellular proliferation of the subepithelial more superficial fascicles of the tumor (H&E 10x PF).

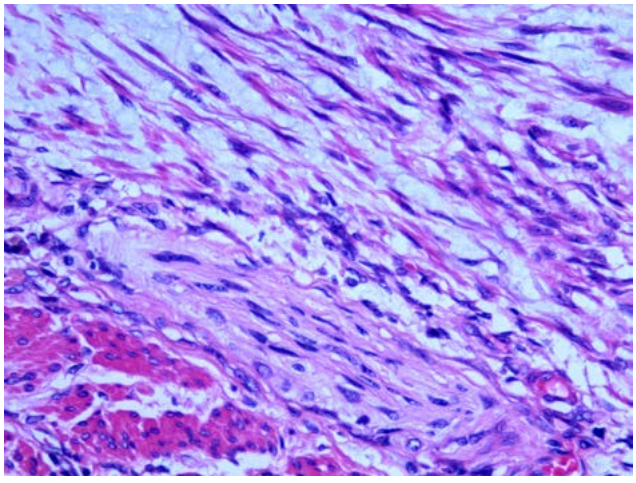

Fig. 3. Hypercellular proliferation of MPNST (H&E 40x PF) with involvement of muscolaris propria bundles and nuclear atypia.

staining for cytokeratin pool, EMA, MDM2, p63, ALK, CD117, DOG1, myogenin, desmin and actin smooth muscle.

On the basis of the morphological and immunohistochemical features of the tumor, as well as on the basis of the presence of an association with NF1, we reached a diagnosis of malignant peripheral nerve sheath tumour.

Interestingly, during a surgical bowel recanalization performed after a few months, numerous small nodules were found, histologically identified as multiple gastrointestinal stromal tumor (GIST).

Discussion

Malignant peripheral nerve sheath tumours mainly affect adults with a roughly equal sex distribution and tend to occur at a younger age in patients with NF1 [10 11], with a peak incidence in the fourth decade. NF1, called also von Recklinghausen disease from the first clinical description, is an autosomal dominant disorder characterized by cafè au lait spots, axillary and inguinal freckels, Lisch nodule of the iris, two or more neurofibromas including plexifom neurofibroma, distinctive bone lesions such as sphenoid dysplasia and coexistence with a variety of neoplasms such as optic gliomas, higher grade astrocytic neoplasms and pheochromocytomas.

NF1 is a common genetic disease with a high rate of penetrance and affects approximately 1 in 3500 newborns. At the basis of this disease are germ line mutations (i.e. deletions, insertions, stop mutations and splicing mutations) causing inactivation of the NF1 tumor suppressor gene located on 17q11.2. Interestingly, the large size of the NF1 gene, the different mutations and the complexity of the disease are at the base of the extremely variable expressivity of the disease [10 11].

A very important problem in patients with NF1 disease is posed by malignant neoplastic occurrences. The exact incidence is not determinated but the lifetime risk of developing MPNST in NF1 patients is 5 to 10-13% [10 11 13], while it is 0.001% in the general population; moreover, individuals with NF1 microdelection have 16-26% risk [12] of malignant transformation. MPNST in NF1 mainly arise in the extremities, followed by the trunk and the head/neck area. Patients with MPNST associated with NF1 have a poorer outcome than sporadic cases and this neoplasm is the main cause of death in patients with NF1 [13].

The occurrence of MPNST arising in the bladder is extremely rare with only a few cases reported in the literature [6-9], and never with such an entire organ involvement. Two of them arose from a malignant transformation of previous neurofibroma in the setting of NF1 [8 9], and two cases occurred sporadically [6 7], in one case [7] presenting at the microscope in an epithelioid variant. In these former cases, MPNST have been observed arising from the trigone and from the lateral or posterior walls of the bladder, with multiple nodules with surface ulceration and areas of necrosis. The tumor sometimes infiltrated focally the entire thickness of the bladder wall, with involvement of perivesical soft tissues or pelvic peritoneum, or may exhibit metastases [7].

In our patient there were urological symptoms due to a mass effect and we had no information about previous lesions or deep-seated plexiform neurofibroma. How-

ever, in our case the presence of von Recklinghausen disease helped us to frame the lesion in the correct clinical context and the findings of mitosis and atypia as well as the phenotype supported us in achieving the diagnosis of MPNST. Moreover, the multiple gastrointestinal stromal tumors (GIST), identified during a surgical bowel recanalization performed after a few months, represent described gastrointestinal manifestations of NF1 [14].

The differential diagnosis between neurofibroma and low grade MPNST is difficult [15] because these lesions represent a histological continuum without clear histological demarcation. Indeed, in the literature no clear cut-off for mitotic index or atypia indicating malignancy is reported, although a poorer prognosis is associated with large tumors (with size varying from 5 to 7 cm in different studies), association with NF1, a mitotic index of greater than 6/10x high-power fields and incomplete resection [10].

Effective targeted molecular treatments are still lacking, hence surgical resection remain the main treatment, also in young patients [10 16]. The recurrence rate is up to 40%, frequently with subsequent hematogenous metastasis. Five-year survival has varied in series from 26 to 60%, and 10-year survival is approximately 45% [10]. At 18 months after surgery our patient had no signs of recurrence.

CONFLICT OF INTEREST STATEMENT

None declared.

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