Von Recklinghausen's Disease Associated with Malignant Peripheral Nerve Sheath Tumor Presenting with Constipation and Urinary Retention: A Case Report and Review of the Literature

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Abstract. *A malignant peripheral nerve sheath tumor (MPNST) is a rare neoplasm arising from peripheral nerve sheaths. We herein report the first case of MPNST originating from the left gluteal muscle region, diffusely extending into the adjacent small pelvis and perineum. The patient was a 25-year-old man who presented with symptoms of progressive constipation and urinary retention associated with weight loss. The patient had a family history of neurofibromatosis type 1. Physical examination showed numerous cafe-au-lait spots and sessile cutaneous neurofibromas. A computed tomography scan revealed a giant tumor which displaced the bladder and segments of the intestine. The histopathological diagnosis was MPNST. The mass was considered inoperable and palliative colostomy was performed. The patient declined chemotherapy and radiation therapy and died 2 months later.*

Neurofibromatosis type 1 (NF-1) is diagnosed clinically based on the presence of two of the following seven criteria developed by a panel of experts in 1987 (1, 2): at least five café-au-lait spots greater than 5 mm (six greater than 15 mm if prepubertal); two or more neurofibromas of any type or one plexiform; multiple large freckles in the axillary or inguinal regions; sphenoid wing dysplasia; bilateral optic nerve gliomas; multiple iris nodules (Lisch spots); a first-degree relative with the above criteria.

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Gastrointestinal (GI) involvement of neurofibromatosis occurs in 10-25% of cases (3). Benign and malignant neoplasms may arise in the abdomen in both pediatric and adult patients with NF-1. The abdominal tumors in NF-1 can be divided into five basic categories: neurogenic, neuroendocrine, embryonal, nonneurogenic GI mesenchymal and miscellaneous (4). GI neurofibromas can rarely occur as sporadic lesions in the stomach and jejunum, and only exceptionally in the mesentery (5). Intestinal neurofibromas may arise at any level of the alimentary tract, with the small intestine being the most common site of involvement; they usually originate from the intramuscular plexus of Auerbach (6, 7) and are generally submucosal but may extend to the serosa (3). Plexiform neurofibromatosis of the mesentery or retroperitoneal space may lead to arterial compression or nerve injury. Common clinical manifestations of GI involvement include abdominal pain, constipation, anemia, melena and a palpable abdominal mass. Reported serious complications include intestinal or biliary obstruction, bowel ischemia, perforation and intussusceptions (3).

We herein describe a malignant peripheral nerve sheath tumor (MPNST) which displaced the intestine and the bladder and produced symptoms of constipation and urinary retention in an NF-1 patient.

Case Report

A 25-year-old white man presented at our Department complaining of progressive constipation (not controlled with early intake of laxatives) and weight loss (~10 kg) during the previous 3 months. Fifteen days before admission, he also experienced urinary retention requiring bladder emptying catheterization. His medical history included asymptomatic NF-1 without hospitalizations, or surgery, or any medication in the past; the patient's father also had asymptomatic NF-1.

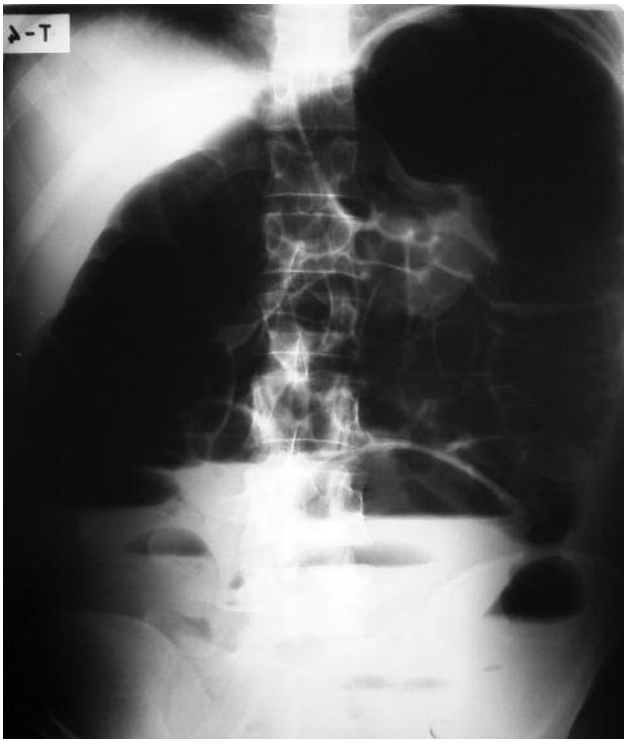

Figure 1. *Multiple air-fluid levels in small and large bowel, suggesting ileus development.*

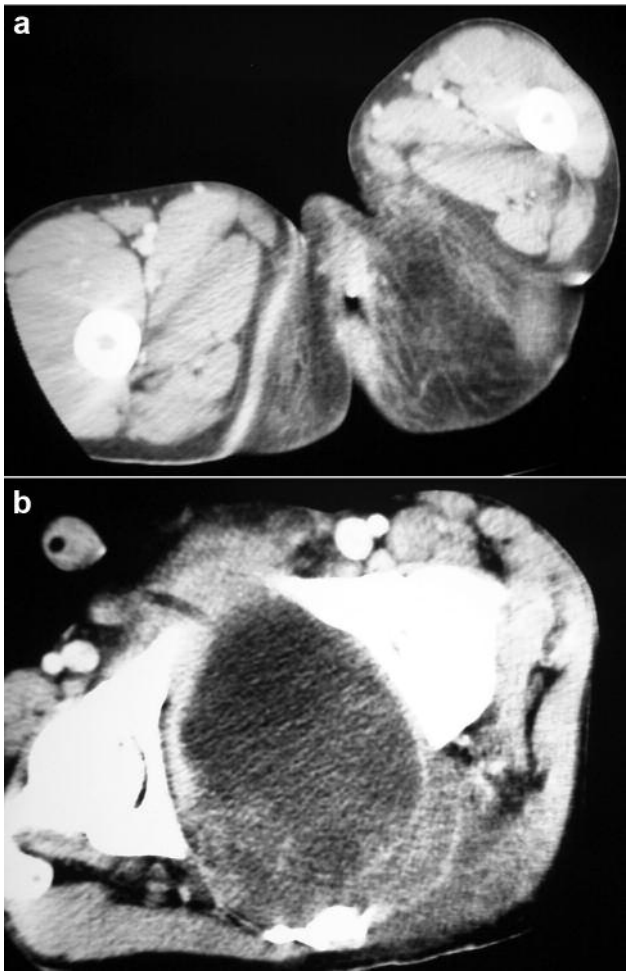

Figure 2. *a, CT image showing the solid mass originating from the left gluteal muscle region and extending into the adjacent small pelvis and perineum. b, CT image showing the solid mass of low attenuation in the small pelvis displacing segments of intestine to the right.*

On admission, the patient was pale, malnourished, anxious and febrile (38°C). Clinical examination revealed numerous cafe-au-lait spots and sessile cutaneous neurofibromas throughout the body (mainly on the trunk). His abdomen was distended but not tender, with normal bowel sounds. Palpable lymphadenopathy and hepatosplenomegaly were absent. Careful clinical examination revealed a 4 cm firm and tender-on-palpation mass in the left buttock. Digital rectal examination was negative for blood or mass but gave the impression of possible external compression of the luminal wall.

The routine laboratory tests revealed: normochromic normocytic anemia (hematocrit 34% , hemoglobin 11.5g/dl), leukocytosis (WBC=17,600/mm^3; normal value <10,000/mm^3), and increased erythrocyte sedimentation rate (80 mm/h; normal value <20 mm/h) and C-reactive protein (97 mg/l; normal value <5 mg/l). The biochemical blood analyses, coagulation tests, thyroid function tests, serum calcitonin and urinalysis were normal. Plain abdominal radiography showed opacity due to fecal retention. Upper GI endoscopy and colonoscopy did not reveal any abnormalities.

During hospitalization, the size of the mass increased rapidly, extending to the suprapubic region and became painful, necessitating the use of analgesics. The constipation also became severe and ultimately an incomplete ileus developed (Figure 1). Computed tomography (CT) revealed a giant mass involving the left gluteal muscle region (Figure 2a) and diffusely extending into the adjacent small pelvis and perineum; the mass displaced the bladder and segments of the intestine (Figure 2b). Liver, spleen, pancreas and kidneys showed no abnormalities.

Upon these findings, open biopsy of the lesion was undertaken. Microscopic examination showed a very dense population of atypical spindle cells with wavy, hyperchromatic nuclei and high mitotic activity (Figure 3a). Alternating hypercellular/hypocellular regions were noted. The results of immunohistochemical staining showed positivity for S-100 protein, CD-34 and Ki-67 (Figure 3b). Negativity was observed for the following: vimentin, desmin, EMA, SMA, MIC-2, c-KIT, Leu-7 and cytokeratins. The microscopic and immunohistochemical findings supported the final diagnosis of MPNST. The mass was considered

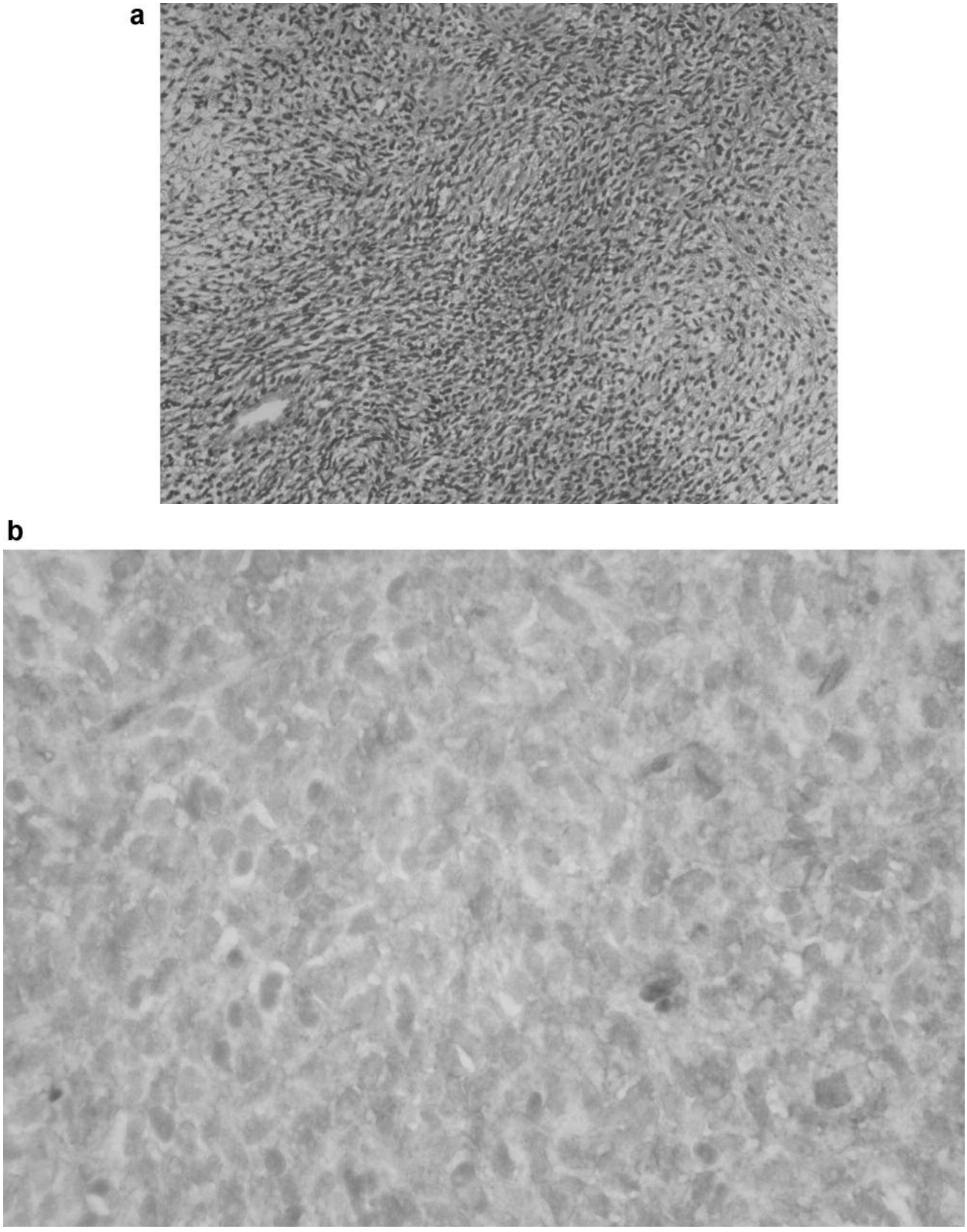

Figure 3. *a, Neoplastic spindle cells with wavy-shaped dark nuclei (AE ×100). b, Positivity of neoplastic cells for S-100 (PAP ×400).*

inoperable and palliative colostomy was performed. The patient declined chemotherapy and radiation therapy and died 2 months later.

Discussion

To our knowledge, this is the first MPNST case presented with short-term symptoms of constipation and urinary retention. One more case regarding a 32-year-old patient with giant ancient pelvic schwannoma who also presented with urinary retention and chronic constipation was reported in the literature (8).

NF-1 is one of the most fascinating and common autosomal dominant disorders, affecting one in 3,000 individuals (9). It is a multisystem complex disease, with patients having myriad of manifestations, including an increased prevalence of both benign and malignant neoplasms throughout the body (10, 11).

Reports detailing probable cases of neurofibromatosis have appeared since the 16th century. The disease bears the name of Friedrich von Recklinghausen (1833-1910), a German pathologist, who was not the first to report the disease but was the first to recognize that the characteristic peripheral neurofibromas arise from nervous tissue (12).

Specifically, NF-1 is a single gene disorder inherited with variable penetrance; the penetrance for NF-1 nears 100% during adulthood (13). In our patient and his father, NF-1 was identified in early childhood, as usually occurs in the majority of cases. Using genetic linkage studies, the *NF-1* gene has been localized on chromosome 17q 11.2. The gene spans over 350 kb of genomic DNA and encodes a protein, neurofibromin (11), a guanosine triphosphate (GTP)ase that works to control cellular proliferation through complex interactions with *ras* oncogenes (14); it modulates signal transduction through the ras pathway. Neurofibromin appears to have a tumor suppressive role and is involved in growth regulation (15). Mutations of the *NF-1* gene lead to abnormal tumor suppression (10); the resulting hyperplasias, hamartomas and neoplasms (benign and malignant) occur in a variety of tissues and organs owing to abnormal tumor suppression (4).

Estimates of the rate of malignancy associated with NF-1 are quite variable but more recent figures range from 3.6% to 4.6% (16). Apart from neurofibromas, other tumors such as pheochromocytoma (with or without type 2B multiple endocrine neoplasia), duodenal and ampullary carcinoid tumors, pancreatic adenocarcinoma, malignant schwannoma, GI stromal tumors (GISTs) and sarcomas occur more commonly in NF-1 patients. Life expectancy is usually shortened by 10 to 15 years. In adults, the most common causes of death are MPNSTs, soft tissue sarcomas, vasculopathy, acute hydrocephalus, and complications from hypertension (16).

The majority of MPNSTs are high-grade sarcomas with a high likelihood of local recurrence and distant metastasis (17). About half occur in patients with NF-1. As in our case, when MPNST develops in patients with NF-1, the neoplasm is diagnosed when the patients are younger (mean, 26 years) and has a poorer prognosis than MPNSTs in patients without NF-1 (18). Moreover, neoplasms arising in central locations, such as the paraspinal region of the retroperitoneum, are associated with lower 5-year survival rates, higher recurrence rates and higher frequency of metastasis compared with neoplasms at other body sites (19, 20).

MPNSTs, like other sarcomas, present as solitary (sometimes multiple) enlarged masses noted over several months before definite diagnosis. They arise in association with major nerve trunks such as the brachial plexus, sacral plexus and the sciatic nerve, producing a striking constellation of sensory and motor symptoms, including projected pain (more prevalent in patients with NF-1), paresthesias and weakness in the corresponding anatomical sites of proximal upper and lower extremities, and trunk. Occasionally these sarcomas may grow to an enormous size, causing compression and infiltration of the surrounding tissues. As in our case, MPNST arising in an extremity most frequently manifests as a painful tumor (21). In contrast, those tumors that arise in the abdomen and retroperitoneum are frequently clinically silent (18).

Imaging techniques used for the evaluation of patients with MPNSTs include CT, magnetic resonance imaging (MRI) and FDG-PET (^{18}F-fluorodeoxyglucose positron-emission tomography). They are useful in early detection of malignant changes in plexiform neurofibromas (22, 23) contributing to staging, therapy planning and subsequent follow-up (24). Importantly, MPNST tends to be heterogeneous in CT attenuation and MRI signal intensity because necrosis is frequently present within the mass (25). Although asymmetry in size or in CT attenuation suggests malignant degeneration of the larger mass, it has been shown that these criteria are not reliable indicators of malignancy (26, 27). The borders of the mass are frequently irregular and infiltrative. MPNST might invade adjacent organs or destroy adjacent vertebrae or pelvic bones (26). MPNST cannot be accurately differentiated from nerve sheath benign tumors solely on the basis of cross-sectional imaging criteria because characteristics such as tumor heterogeneity, irregular or infiltrative borders, and bone erosion might also be observed in benign nerve sheath tumors (26). In some studies, gallium 67 (^{67}Ga) citrate scintigraphy has been shown to help in the differentiation between malignant and benign nerve sheath tumors: the majority of malignant tumors show ^{67}Ga-citrate uptake and benign tumors do not (26, 28). However, ^{67}Ga-citrate scintigraphy is helpful only for those malignant tumors that show uptake because the prevalence of MPNSTs that are ^{67}Ga-citrate-negative and the sensitivity of ^{67}Ga-citrate scintigraphy for malignancy are undetermined. In our case, CT scan showed a tumor of

enormous size occupying most of the small pelvis. Further aforementioned imaging evaluation was unnecessary as the results of the biopsy specimens confirmed the final diagnosis of MPNST.

At histological analysis, MPNST is characteristically a high-grade tumor with a high mitotic rate (1, 17), as also observed in our case. In rare cases, the MPNST may be called a malignant triton tumor because it has histological evidence of rhabdomyosarcomatous differentiation. It is important to note that the histological diagnosis of MPNST is difficult and elusive due to a lack of standardized diagnostic criteria. Most are easily diagnosed as malignant tumors and the major challenge resides in distinguishing them from other sarcomas such as fibrosarcoma, monophasic synovial sarcoma and leiomyosarcoma. The term MPNST is preferred for most spindle cell sarcomas arising from peripheral nerves and neurofibromas, or those demonstrating Schwann cell differentiation on histological examination. Confirming diagnostic features include (1): (a) alternating hypocellular/hypercellular regions also observed in our patient; (b) appearance of thin, wavy, comma- or bullet-shaped nuclei, particularly in hypocellular areas, also noticed in our patient; (c) presence of nuclear palisading (which may also be prominent in a leiomyosarcoma); (d) presence of nerve-like whorls or tactoid bodies resembling Wagner-Meissner corpuscles; (e) prominent thick-walled vasculature; and (f) presence of heterologous elements.

There are a number of useful antigens in identifying nerve sheath differentiation. These include S-100 protein, Leu-7 and myelin basic protein. S-100 protein is the most widely used antigen for neural differentiation and can be identified in 50% to 90% of MPNSTs. Leu-7 and myelin basic protein are found in about 50% and 40% of MPNSTs respectively. Immunostaining for cytokeratin and S-100 protein also aids in the differential diagnosis; only the latter should be positive in a MPNST (29, 30). In our patient, apart from S-100 protein, immunostaining was also positive for CD-34 and Ki-67 which are known to be involved in oncogenesis.

Although it might be expected that sarcomas arising in NF-1 would exhibit deletions of the *NF-1* locus, this has not proven to be the case. Both Menon *et al*. (31) and Reynolds *et al*. (32) documented various abnormalities on chromosome 17 outside the region of the *NF-1* gene, possibly involving the p53 gene. Recent findings support a model of a co-inactivation of TP53 and Rb pathways in 75% of MPNSTs, with functional consequences on cell growth control and apoptosis (33). P53 reactivity appears to be a marker for high tumor grade. P16 (34, 35), p27 (35), TGF-beta 1 (transforming growth factor beta 1) (36), EGF-R (epidermal growth factor receptor) (37) and HGF-alpha (hepatocyte growth factor alpha) (36, 37) may be involved in the malignant transformation of neurofibroma to MPNST. The exact mechanism of malignant transformation or tumor progression is not fully understood, but it may involve a multistep process in which genes apart from the *NF-1* gene also participate. Aside from the foregoing genetic predilection to develop MPNSTs, little is known concerning the pathogenesis of these tumors in humans. About 10% of cases occur as a result of therapeutic or occupational irradiation after a latent period of over 15 years.

The most effective treatment appears to be early diagnosis and wide surgical excision but early diagnosis is hampered by frequent occurrence within preexisting large tumors making new growth or change difficult to detect (38, 39). Complete tumor removal is the mainstay of treatment and the most significant prognostic factor of MPNST. Adjuvant radiotherapy should be used to assist surgical excision in local control. The role of adjuvant chemotherapy remains controversial (40); chemotherapy seems to have little effect on MPNSTs (41, 42). In our case, the tumor was inoperable due to its size and extensive infiltration of the small pelvis, possibly in the setting of a preexisting neurofibroma. Moreover, our patient declined chemotherapy and/or radiotherapy.

Regarding the differences in the clinical course of sporadic and NF-1-associated MPNST, early studies showed contradictory results. Recent data suggest that NF-1 patients have a significantly shorter survival time than patients with sporadic MPNST. Moreover, the time interval to local recurrence and metastatic spread is also significantly shorter in NF-1 patients. These differences between NF-1-associated and sporadic MPNST with regard to the clinical course might reflect some essential differences in biology and pathogenesis of the two tumor groups (43). The overall 5-year survival rate in the experience of Wanebo *et al*. (44) was 43.7% with factors such as age of patient, size, location of tumor and margins influencing the outcome. Longer survival has been correlated with improved imaging techniques leading to early diagnosis and aggressive treatment with complete surgical excision combined with neoadjuvant treatment modalities (chemotherapy and radiation), small tumor size (<5 cm) and presence of a low-grade component. The most common metastatic site of this tumor is the lung, followed by bone, pleura and retroperitoneum. One should also be aware of the propensity for tumor spreading for considerable distances along the nerve sheath. There are reports of tumors entering the subarachnoid space of the spinal cord *via* this route.

In conclusion, we report a MPNST case presenting with both constipation and urinary retention associated with poor prognosis. Sudden enlargement and/or pain of a preexisting mass in this setting should indicate the need for immediate biopsy to exclude the possibility of malignant transformation of a neurofibroma.

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