Sirolimus Improves Pain in NF1 Patients With Severe Plexiform Neurofibromas

abstract

Plexiform neurofibromas (PNs) are common and potentially debilitating complications of neurofibromatosis 1 (NF1). These benign nerve-sheath tumors are associated with significant pain and morbidity because they compress vital structures. The mammalian target of rapamycin (mTOR) pathway is a major mediator involved in tumor growth in NF1. We present 3 cases of patients with NF1, aged 8, 16, and 17 years, followed for inoperable and symptomatic PNs; patients received sirolimus for life-threatening and painful neurofibromas after multidisciplinary consultation. Epidemiologic, clinical, and radiologic data were retrospectively collected. The volume of PNs did not differ between baseline and 12-month follow-up and pain was alleviated, with withdrawal of analgesics in 2 cases at 6 months, and significantly decreased for the third case. Sirolimus for inoperable symptomatic PNs in patients with NF1 permitted stabilization of mass and produced unpredictable and important alleviation of pain in all cases with good tolerance. This treatment was proposed in extreme cases, in absence of therapeutic alternatives, after multidisciplinary consensus. The mTOR pathway may be both a major mediator of NF1 tumor growth and regulator of nociceptor sensitivity. mTOR inhibitors clinically used as anticancer and immunosuppressant drugs could be a potential treatment of chronic pain. *Pediatrics* 2014;133:e1792–e1797

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KEY WORDS

neurofibromatosis type 1, plexiform neurofibromas, therapeutics, pain management, sirolimus

ABBREVIATIONS

5-FDG-PET/CT—5-fluorodeoxyglucose-positron emission tomography-computed tomography
mTOR—mammalian target of rapamycin
mTORC1—mTOR complex 1
NF1—neurofibromatosis 1
NRS—Numerical Rating Scale
PNs—plexiform neurofibromas

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Neurofibromatosis 1 (NF1) is one of the most common autosomal dominant disorders, with an incidence of 1 in 2500 to 3000 births.[1] The NF1 gene encodes for a tumor suppressor protein, neurofibromin. This protein can downregulate cell growth by inhibiting the Ras proto-oncogene.[2,3] Mutation of this gene in NF1 is associated with increased risk of developing tumors.[4] Over the past 10 years, significant advances have been made in understanding NF1 molecular mechanisms underlying specific disease complications. New pharmacological approaches have been developed to target signaling pathways, such as Ras, angiogenesis, growth factors, mast cell proliferation, and mammalian target of rapamycin (mTOR), all involved in NF1.[5–7] mTOR is a serine/threonine kinase that is frequently hyperactivated in cancer, which promotes tumor progression.[8] Recent studies showed that neurofibromin Ras-mediated regulation of growth operates through the mTOR pathway.[9,10] The identification of mTOR as a major mediator of NF1 tumor growth has led to clinical trials of mTOR inhibitors, such as sirolimus.[11,12]

Patients with NF1 are at increased risk of developing tumors of the central and peripheral nervous system, including plexiform neurofibromas (PNs).[13] These benign nerve-sheath tumors are associated with significant morbidity, mortality, and decreased quality of life because of disfigurement, compression of vital structures, and often-unremitting pain. Surgery is the only standard treatment. However, given the location, infiltrative nature, high vascularity, and size of PNs, complete resection is often not feasible. In this report, we present 3 cases of young patients with NF1 who received sirolimus for life-threatening PN as compassionate use.

CASE REPORTS

All 3 patients met the diagnostic criteria for NF1 established at the National Institutes of Health Consensus Development Conference.[4] PNs could not be surgically removed because of their location and proximity to vital body structures. Because of lack of other treatment options, patients were treated with sirolimus to shrink growth of PNs, after a multidisciplinary staff reviewed their cases. Data were retrospectively collected and analyzed. Evaluation of the response to sirolimus therapy was based retrospectively on a 1-year morphologic study of PN with 3-dimensional MRI analysis by using field strength of 1.5 T, T1- and T2-weighted, and on reduction in pain level. Patients 1 and 2 were evaluated each month during the first 3 months and then every 3 months by a dermatologist and a pain specialist by using a numerical rating scale (NRS) from 0 (no pain) to 10 (the worst pain imaginable). Patient 3 was evaluated each month by an oncologist and pain was assessed by using the faces rating scale.

PATIENT 1

A 17-year-old adolescent boy with sporadic NF1 was followed for an extensive PN. The lesion measured 20 × 13 cm on MRI in July 2009 and extended from the true pelvis to porta renis to anterior sacral foramina (Fig 1). This inoperable internal neurofibroma caused painful compression on the gastrointestinal tract and induced bowel obstructive symptoms. The maximal pain intensity was scored 9 of 10 on an NRS. The severity of symptoms required oral morphine treatment and emergency consultations for intravenous morphine to manage acute pain crisis. A 5-fluorodeoxyglucose-positron emission tomography–computed tomography (5-FDG-PET/CT) scan revealed no signs of malignant transformation (maximum standard uptake value 3.2). According to the severity of clinical symptoms, sirolimus was initiated in April 2010 at an initial dosage of 1 mg per day after discussion by health care providers. The dosage was increased to 3 mg per day at 3 months and 4 mg per day at 6 months. Sirolimus was well tolerated by clinical and biological profiles. At 6 months, pain was decreased in intensity and frequency and morphine was gradually stopped without withdrawal symptoms. Two short painful episodes were reportedly relieved by prompt morphine; sirolimus had been temporarily discontinued because of subcutaneous NF surgery. At 1 year, there was no more abdominal pain and no need for analgesic treatments (NRS 0/10). MRI revealed no difference from baseline in volume of PN and 5-FDG-PET/CT images were unchanged.

Three years after starting sirolimus, the volume of the PN was stable and the patient remained pain-free.

PATIENT 2

A 16-year-old adolescent boy with familial NF1 was followed for painful and diffuse subcutaneous and internal neurofibromas. MRI revealed a large PN involving the brachial plexus (4 × 14 cm). In addition, a retroperitoneal mass (7 cm) and pelvic mass with diffuse extension into the sciatic nerves (11 cm) were identified (Fig 2). 5-FDG-PET/CT revealed no signs of malignant transformation. The patient experienced intense neuropathic pain of the 4 limbs (average pain score 8/10 on the NRS), which was uncontrolled by maximal tolerated doses of pregabalin, amitriptyline, and tramadol. The patient had been hospitalized a few months earlier with coma because of excess drug consumption. Surgery was not advised because of the extensive nature of internal lesions. After discussion, sirolimus as compassionate use was started at 1 mg per day in December 2010. A dosage of 2 mg per day was not well tolerated because of drowsiness. The dosage was finally maintained at 1 mg per day. At 6 months, the patient had no more pain,

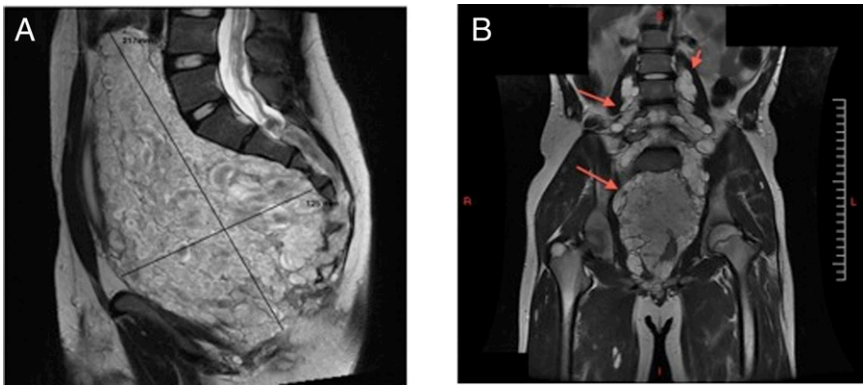

FIGURE 1
Baseline MRI of patient 1 with plexiform neurofibromas. Sagittal T2-weighted (A) and coronal T2-weighted (B) MRIs with fat saturation of a voluminous plexiform neurofibroma in the pelvis (arrows).

which led to decreasing pregabalin and amitriptyline. All analgesics were stopped at 1 year, without any relapse in pain. The average pain was scored 3 of 10 on the NRS. MRI revealed no difference from baseline in volume of PNs. 5-FDG-PET/CT revealed mild hypermetabolism (maximum standard uptake value 3) without signs of malignant transformation.

At 2.5 years, patient 2 had stable volume of PN and the near disappearance of pain.

PATIENT 3

An 8-year-old girl with a sporadic NF1 had extensive PNs of the right thigh (107 × 88 × 86 mm) and pelvis (199 × 173 × 79 mm). These lesions compressed adjacent organs, particularly the rectum, bladder, and right sciatic nerve infiltration and were responsible for excruciating neuropathic pain. The pain specialist prescribed several oral analgesics, which failed to relieve the pain, including gabapentine at 30 mg/kg per day, codeine at 0.75 mg/kg per day, diazepam at 1 mg 3 times daily, amitriptyline at 8 mg once daily, and carbamazepine at 20 mg/kg per day. Pain scored an average of 4 of 10 on the faces rating scale, with peaks of pain described as being 10 of 10 in intensity. Because of the pain, she used a wheelchair. Surgical management was considered not possible. After multidisciplinary evaluation, the patient received imatinib, 260 mg/m^2, in 2009 for 6 months. This treatment was not helpful for control of tumor growth or pain. To preserve renal function, bilateral ureterostomy with cystectomy and panhysterectomy was performed in January 2010. After multidisciplinary discussion, sirolimus was given orally in April 2010, at a beginning daily dosage of 0.25 mg/m^2 body surface area, 0.2 mg per day, as established for patients with tuberous sclerosis with angiomyolipomas[14] and then gradually increased to achieve a maximum tolerated dose of 2 mg per day in December 2011. At 6 months, pain had completely disappeared, which allowed for stopping amitriptyline and carbamazepine. At 1 year, no relapse of pain was observed. MRI revealed stable volume of the internal PN as compared with baseline. Sirolimus was well tolerated on clinical profile. Slightly increased triglyceride levels were observed. While stable on sirolimus for 36 months, transformation of the PN to a malignant peripheral nerve sheath tumor occurred in May 2013.

DISCUSSION

The National Institutes of Health NF1 diagnostic criteria were used to confirm the diagnosis in our 3 cases.[4,15] No genotype-phenotype correlations have been demonstrated for NF1 except in cases of large NF1 gene deletions.[16] Performing genetic testing to confirm the NF1 diagnosis was not done in our patients because this was not the standard of care at our institution at the time this retrospective study was performed. In addition, for the same reason, genomic data were not available for the plexiform neurofibroma tumor specimens before the initiation of sirolimus. PNs, although benign nerve-sheath tumors, can be debilitating complications of NF1. Sirolimus was initiated as compassionate use for inoperable and painful PNs with significant risk of morbidity. At 1 year, although we could have expected an enlargement of mass, the volume of PNs had not changed. Furthermore, pain had decreased substantially in all 3 cases, which led to decreasing and finally stopping all analgesics. Stable volume of PN was observed at 2.5 years and the near disappearance of pain. The analgesic effect of sirolimus in patients with NF1 has never been reported and may be directly explained by inhibition of the mTOR pathway.[17,18]

Sirolimus inhibits mTOR activity by phosphorylation of proteins involved in cell growth control and angiogenesis. Previous studies demonstrated an activation of the mTOR pathway in NF1, which could be inhibited with sirolimus.[9–11,19] As well, sirolimus reduced proliferation associated with loss of neurofibromin expression in human malignant peripheral nerve sheath tumor cells.[12] However, the lifetime risk of developing malignant transformation in presence of PN is 20 times higher than in individuals without internal PN,[13] and at year 3, patient 3 developed a malignant peripheral nerve sheath tumor that was not prevented by the use of sirolimus.

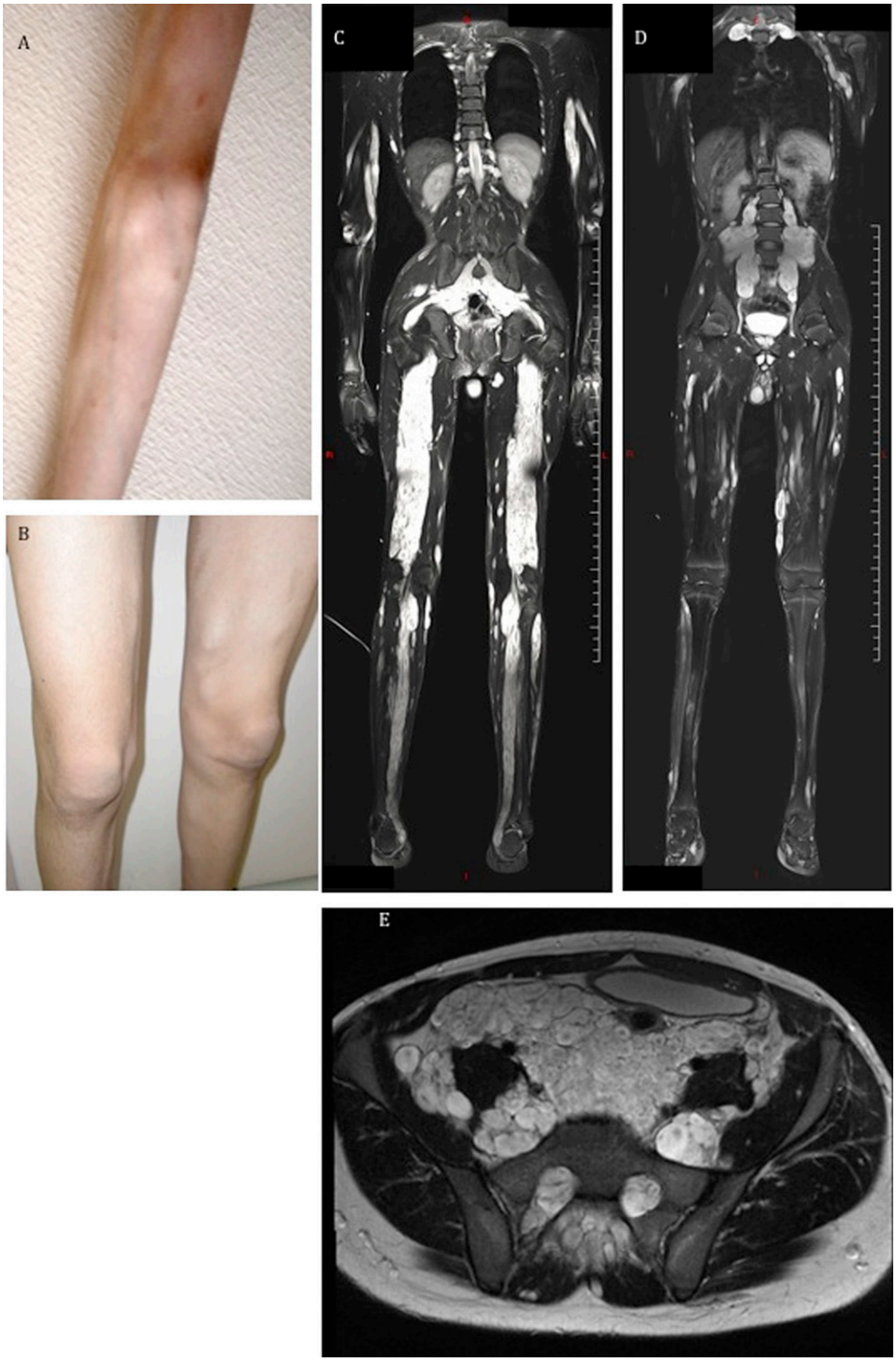

FIGURE 2
Baseline images of patient 2 with plexiform neurofibromas. A, B, Subcutaneous neurofibromas and café-au-lait spots on legs. C, D, E, T2-weighted coronal and axial whole-body MRIs of plexiform neurofibromas in both legs along the sciatic nerves and in the brachial plexus.

mTOR seems to be involved in pain processing. The mTOR complex 1 (mTORC1) is implicated in regulating local protein synthesis in dendrites and axons and in modulating plasticity and memory processes.[20,21] Furthermore, mTOR is expressed and constitutively phosphorylated in myelinated A-fibers in the peripheral nerve, and afferent nociceptors are thought to be regulated by the mTORC1 signaling pathway.[21,22] Recently, inhibition of mTOR activity by

intraplantar injection of rapamycin in mice blocked hypersensitivity induced by local injection of capsaicin, as well as neuropathic pain induced by spinal nerve ligation.[17,22] In addition, in a mouse model of neuropathic pain, systemic administration of the mTORC1 inhibitor temsirolimus acutely and chronically inhibited the mTORC1 pathway in sensory axons and the spinal dorsal horn.[23] These results highlight the importance of the mTORC1 pathway as a regulator of nociceptor sensitivity[24,25] and its potential indication for therapeutic intervention in chronic neuropathic pain.[23]

CONCLUSIONS

Severe PNs in NF1 are a major cause of morbidity due to intractable pain. PNs carry a high risk of malignant transformation and can be life-threatening. Our clinical observation emphasizes an unexpected effect of sirolimus on pain, which contributes to improve quality of life. The mTOR pathway may be both a major mediator of NF1 tumor growth and regulator of nociceptor sensitivity. The role of the mTORC1 pathway as a regulator of nociceptor sensitivity could be discussed. mTOR inhibitors clinically used as anticancer and immunosuppressant drugs may be a potential treatment of severe NF1.

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