Trametinib Induces Neurofibroma Shrinkage and Enables Surgery

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Abstract

Plexiform neurofibromas are congenital peripheral nerve sheath tumors characteristic of neurofibromatosis type 1 (NF1)—a frequent neurocutaneous disorder caused by mutations of the NF1 tumor suppressor gene. Since plexiform neurofibromas are a major cause of the burden of disease and may also progress to malignancy, many efforts have been undertaken to find a cure for these tumors. However, neither surgery nor medication has so far produced a breakthrough therapeutic success. Recently, a clinical phase I study reported significant shrinkage of plexiform neurofibromas following treatment with the MEK inhibitor selumetinib. Here, we report an 11-year-old NF1 patient with a large plexiform neurofibroma of the neck that had led to a sharp-angled kinking of the cervical spine and subsequent myelopathy. Although surgical stabilization of the cervical vertebral column was urgently recommended, the vertebral column was inaccessible due to extensive tumor growth. In this situation, treatment with the MEK inhibitor trametinib was initiated which resulted in a 22% reduction in tumor volume after 6 months of therapy and finally enabled surgery. These data show that MEK inhibitors may not lead to complete disappearance of NF1-associated plexiform neurofibromas but can be an essential step in a multimodal therapeutic approach for these tumors. The course of our patient suggests that MEK inhibitors are likely to play a significant role in providing a cure for one of the most devastating manifestations of NF1.

Keywords
- plexiform neurofibroma
- neurofibromatosis type 1
- MEK inhibitor
- trametinib
- tuberous sclerosis
- everolimus

Introduction

Neurofibromatosis type 1 (NF1) is a frequent neurocutaneous disorder caused by mutations of the *NF1* tumor suppressor gene on 17q22.1 and shows a highly variable phenotypic expression. The hallmark of the disease are benign tumors of the peripheral nervous system, termed neurofibromas,[1] which are caused by NF1 loss in Schwann cells.[2] Depending on the developmental stage in which a *NF1* mutation in Schwann cells occurs, different types of neurofibromas can evolve.[3] Plexiform neurofibromas are congenital tumors,[3] may lead to diffuse overgrowth of the affected body region,[1] and carry a 15% lifetime risk to progress to malignancy.[4]

Surgical approaches often fail in completely removing plexiform neurofibromas or even significantly reducing the tumor size. Since neurofibroma formation is the consequence of *NF1*-induced hyperactivation of the proto-oncogene Ras[1] and effective Ras inhibitors are not yet available, many efforts have been undertaken to tackle the signaling cascade downstream of Ras-GTP. Studies with conditional

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Nf1 knockout mice have demonstrated that pharmacological inhibition of the downstream Ras effector MEK results in a significant growth reduction of neurofibromas.[5] Based on these findings, a phase I clinical trial using the MEK inhibitor selumetinib was conducted which corroborated the preclinical results and showed significant decrease of neurofibroma volume in all treated patients.[6]

We here present an 11-year-old girl with NF1 and a huge nonresectable plexiform neurofibroma of the neck that had led to an extreme deformity of the cervical vertebral column. Although surgery was urgently recommended to prevent further kinking of the cervical spine and spinal paralysis, the vertebral column was inaccessible due to the extensive tumor masses. Treatment with the MEK inhibitor trametinib over a period of 6 months led to a 22% reduction in tumor volume and finally enabled surgery.

Case Report

The 11-year-old girl was diagnosed with NF1 in early childhood based on the presence of multiple café-au-lait spots, axillary freckling, and slight developmental delay. This clinical diagnosis was confirmed by identification of a truncating mutation in exon 42 of the *NF1* gene which had previously been described as pathogenic.[7] Due to a visible but at that time rather discrete swelling of the right side of the neck, magnetic resonance imaging (MRI) was performed and showed numerous neurofibroma nodules of all cervical spinal roots extending into the distal peripheral nerve branches. Additionally, an intraspinal neurofibroma on the level of the fourth cervical body was detected. Regular clinical and MRI follow-up revealed a slow but constant growth of the intraspinal neurofibroma so that finally a laminectomy and successful tumor excision were performed to prevent further damage of the cervical spine.

While the immediate postoperative course was uneventful, the girl presented 2 years later with a visible increase in the cervical soft tissue swelling and an extreme kyphotic deformity of the cervical vertebral column that had led to a sharp kinking of the cervical spine. MRI workup demonstrated massive growth of the cervical neurofibromas which now extended to both sides of the neck and had displaced much of the surrounding soft tissue as well as the carotid and vertebral arteries. Within the tumor masses, one large nodule with a diameter of more than 4 cm was standing out. Fluorodeoxyglucose-positron emission tomography of this suspicious nodule showed a standardized uptake value of 4.9 suggestive of malignant transformation.[8] The tumor nodule was completely removed by surgery. Histopathological examination did not reveal any signs of malignancy and established the diagnosis of a plexiform neurofibroma World Health Organization grade 1.

In the following months, increasing spasticity of the right leg was observed with compromised motor function and instable gait. These symptoms could be attributed to the sharp-angled kinking of the cervical spine which had already resulted in a cervical myelopathy as depicted on spinal MRI scans (►**Fig. 1**). Therefore, surgical stabilization of the cervical vertebral column was urgently recommended to prevent paraplegia. However, the vertebral column appeared inaccessible for surgery due to the extensive growth of the surrounding neurofibroma masses.

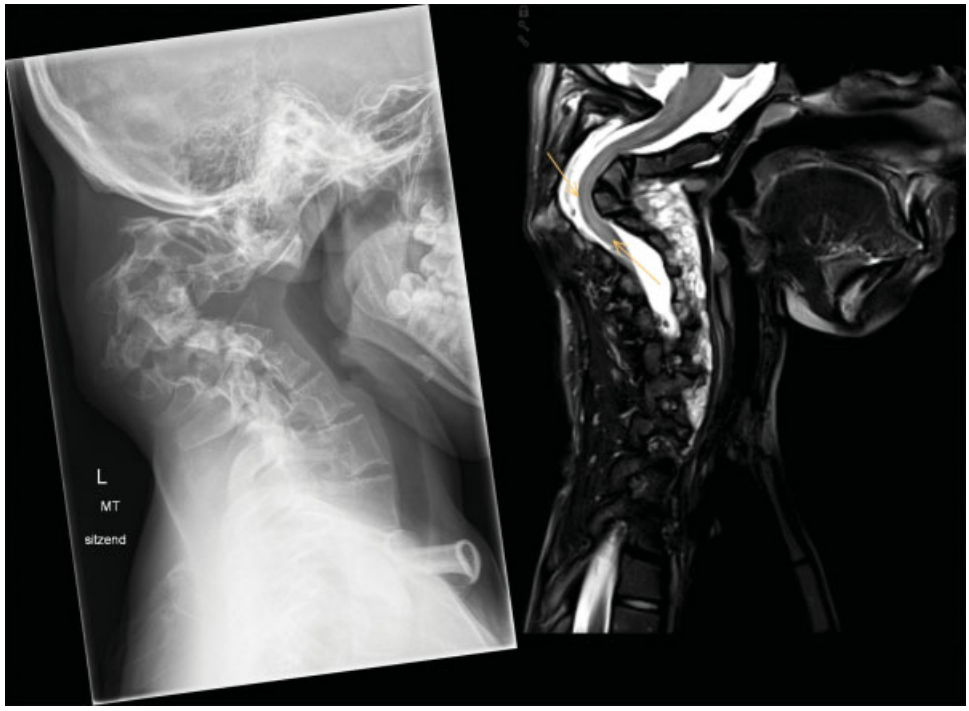

Fig. 1 Lateral X-ray of the cervical vertebral column and skull base (left panel) shows a sharp-angled kyphoscoliotic kinking of the cervical spine. Corresponding sagittal T2 magnetic resonance imaging demonstrates a myelopathic lesion (right panel, arrow) which resulted in progressive myelopathy with spasticity of the right leg and disturbed gait.

In this situation, oral therapy with the MEK inhibitor trametinib was initiated after informed consent was obtained. Based on the findings by McCowage et al,[9] we started with a single dose of 0.5 mg per day (0.015 mg/kg) which was increased up to 0.5 mg twice daily (0.03 mg/kg) after the first week of therapy. Common toxicities reported in trametinib treatment in adults include rash, fatigue, fever, diarrhea, pneumonitis, uveitis, retinopathy, liver function abnormalities, and left ventricular ejection fraction dysfunction.[10] Therefore, monitoring of our patient consisted of monthly clinical and laboratory evaluation (including full and differential blood count, electrolytes, creatinine, urea, uric acid, bilirubin, alanine-aminotransferase, aspartate-aminotransferase, g-glutamyl transferase, lactate dehydrogenase, lipase, alkaline phosphatase, coagulation parameters, and thyroid stimulating hormone) as well as ophthalmological and cardiac examination. Chest X-ray was planned in case of clinical symptoms suggestive of pneumonitis but was not necessary during the course of trametinib therapy. Apart from occasional epistaxis and facial rash, no side effects were observed.

Prior to trametinib therapy, exact dimensions of the neurofibroma were defined by volumetric MRI which was repeated after 3 and 6 months of therapy. While the 3-month control did not show any change, the 6-month control demonstrated a 22% tumor volume decrease from baseline regarded as partial response[11] (►**Fig. 2**).

Upon clinical examination, the swelling of the neck appeared less pronounced and the girl herself had noticed an increased mobility of her neck and shoulder.

Due to tumor shrinkage, the vertebral column now appeared accessible for surgery. Following 8 weeks of halo traction, the cervical vertebral column was stabilized with a combined anterior and posterior approach and instrumentation to prevent further kinking.

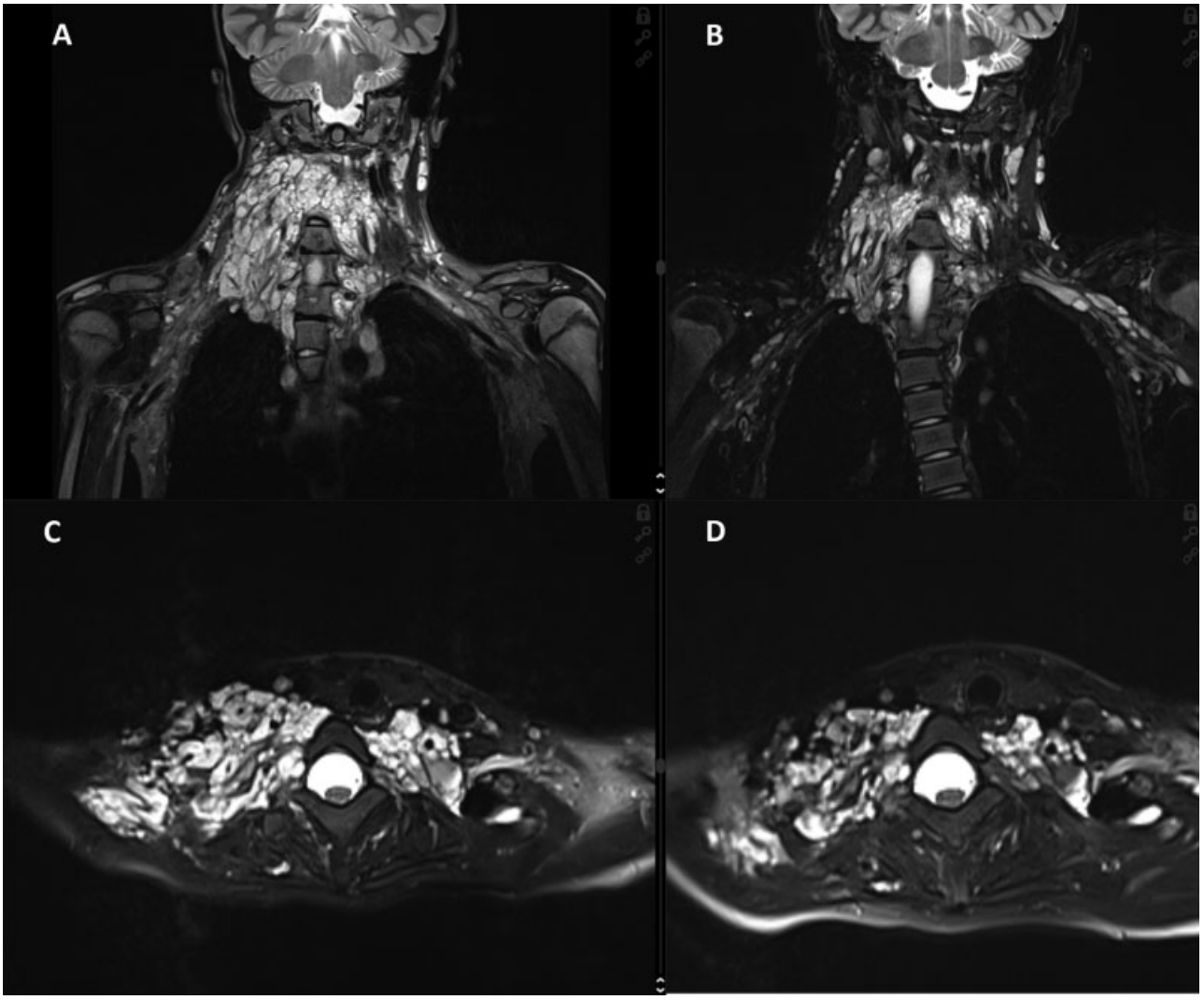

Fig. 2 Magnetic resonance imaging follow-up of the cervical plexiform neurofibroma. Coronal T2 inversion recovery sequences (3 mm, TR 7930 ms, TE 41 ms, TI 240 ms) and axial T2 turbo spin echo sequences with spectral fat saturation (3 mm, TR 9370 ms, TE 89 ms) were obtained with a 3 T Magnetom Spektra (Siemens, Erlangen/Germany) before (**A**, **C**) and after 6 months of trametinib treatment (**B**, **D**). For volumetric analysis tumor margins were manually outlined and the tumor area calculated on each axial T2 image. Area measurements were summed and multiplicated by slice thickness to obtain the total tumor volume. All measurements were done by the same neuroradiologist. While no changes were observed after 3 months of trametinib treatment (data not shown), measurement after 6 months of treatment revealed a 22% reduction in tumor volume. TE, echo time; TI, inversion time; TR, repetition time.

Discussion

Preclinical and clinical studies have shown that the MEK inhibitor selumetinib can decrease the size of NF1-associated plexiform neurofibromas.[5,6] Since results of an ongoing phase II clinical trial are still pending, selumetinib is not yet available as medication for NF1 patients.[12] In contrast, the MEK inhibitor trametinib is routinely used for the treatment of malignant melanoma in adults and has also been tested in a small number of NF1 patients with plexiform neurofibromas[9,13] and astrocytomas.[14]

For the treatment of neurofibromas, McCowage et al[9] have previously evaluated safety and pharmacokinetics of trametinib at a daily dosage of 0.0125 mg/kg, 0.025 mg/kg, and 0.04 mg/kg, respectively. Dose-limiting toxicity occurred more frequently under the 0.04 mg/kg regimen so that a recommended dose of 0.025 mg/kg per day for children above the age of 6 years was established.[9] Based on these findings and considering that trametinib is only available in 0.5 and 2.0 mg tablets, treatment was started in our patient with the above-mentioned dosage of 0.03 mg/kg per day. This resulted in significant tumor shrinkage after 6 months of therapy as defined by Dombi et al[11] and finally enabled further surgical treatment.

To date, it is unclear if MEK inhibitor treatment can be terminated after a certain period of time or if this will result in tumor regrowth. Dombi et al reported slow tumor regrowth following dose reduction in selumetinib due to toxic side effects.[6]

This indicates a dose-dependent effect of MEK inhibition and suggests that neurofibromas might regrow after cessation of therapy.[6] Another issue is the beginning of MEK inhibitor treatment. In our patient, surgical correction of the spinal deformity was not feasible due to progressive neurofibroma growth. In this situation, MEK inhibitor treatment appeared to be an option to enable surgery. It is worth asking if an earlier beginning of MEK inhibitor treatment might have prevented neurofibroma growth and subsequent neurological symptoms.

Similar issues are currently on debate in the context of tuberous sclerosis complex (TSC), a neurocutaneous disorder caused by hyperactivation of the mTOR signal transduction pathway. Mechanistic target of rapamycin (mTOR) hyperactivation can efficiently be downregulated by the mTOR inhibitor everolimus which has been approved as causal therapy for several TSC-associated disease manifestations such as subependymal giant cell astrocytomas (SEGA), renal angioleiomyomas, or refractory epilepsy.[15] Everolimus treatment is usually initiated when SEGA or renal tumors exceed a certain size and then halts further tumor growth. Recently, it has been discussed if early everolimus treatment could prevent the development of tumors and other TS-associated complications at all.[15] Similarly, in NF1 MEK inhibition might be a therapeutic option for several disease manifestations beyond plexiform neurofibromas [6,9,12,13] and astrocytomas[14] where it has successfully been tested.

While much more data are necessary to answer this question, the course of our patient as well as clinical data published elsewhere demonstrate that MEK inhibitors are likely to play an essential role in a multimodal therapeutic approach for NF1-associated plexiform neurofibromas.

Conflict of Interest
None declared.

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