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CLINICAL CASE

# MEK inhibitors in maintenance of a postoperative patient with vasculopathy due to neurofibromatosis type I

## *Inhibidores MEK en mantenimiento de un paciente posoperado, con vasculopatía por neurofibromatosis tipo I*

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## Abstract

*Vasculopathy in the context of neurofibromatosis type I is challenging, and its management requires a multidisciplinary approach. We describe the case of a 24-year-old girl with NFI and vascular complications who was successfully managed with MEK inhibitors, obtaining clinical stabilization. After left occipital artery embolization prior to surgical resection of an occipital neurofibrom, a left internal carotid artery pseudoaneurysm was detected, requiring open repair that failed, leading to direct ligation due to profuse bleeding. In the immediate postoperative period, during a coughing spell, rupture of the left subclavian artery occurred, which was successfully treated by implanting a 7 × 10 mm Viabahan®. Trametinib (0.5 mg/24 h) was administered, replaced by selumetinib (45 mg every 12 h), both therapies in compassionate use. Selumetinib was effective in stabilizing the development of vascular complications, achieving good control over symptomatology of the patient. Three months after starting treatment with MEK inhibitors, no new events have occurred.*

***Keywords:*** *Neurofibromatosis. Trametinib. Selumetinib. Vasculopathy. Pseudoaneurysm.*

## Resumen

*La neurofibromatosis tipo I (NFI) es un trastorno que conduce a una sobreactivación de la vía RAS, asociando anomalías vasculares de mediano y gran vaso, espectro denominado vasculopatía de la NFI. Presentamos el caso de una paciente de 24 años con NFI que tras el intento fallido de reparación de un pseudoaneurisma de la arteria carótida interna, requirió ligadura por sangrado profuso. Durante un acceso de tos, presentó ruptura espontánea de la arteria subclavia izquierda, tratada con éxito implantando un Viabahn® de 7 x 10 mm. En el postoperatorio se inicia trametinib (0.5 mg/24 h), reemplazándose por selumetinib 45 mg cada 12 h por dos meses. Tras el alta hospitalaria, el selumetinib fue eficaz para estabilizar el desarrollo de complicaciones vasculares. A tres meses de iniciado el tratamiento farmacológico, no ha presentado nuevas complicaciones.*

***Palabras clave:*** *Neurofibromatosis. Trametinib. Selumetinib. Vasculopatía. Pseudoaneurisma.*

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## Introduction

Neurofibromatosis type I (NFI), or von Recklinghausen disease, is an autosomal dominant disorder affecting 0.03% of the general population[1]. It is caused by the mutation of the NF1 gene, a tumor suppressor gene that encodes for the neurofibromin protein that inactivates the RAS-mitogen-activated protein kinase (MAPK) pathway, which regulates cell proliferation and differentiation. This dysfunctional neurofibromin leads to an overactivation of the RAS pathway.

Clinical manifestations affect the nervous system, skin, and bones. Vascular abnormalities are a well-recognized manifestation, occurring with a prevalence of 0.4% to 6.4% according to large clinical series[1-3] and the term NF-I vasculopathy has been coined in the medical literature to describe aneurysms and pseudoaneurysms, stenosis, and arteriovenous malformations occurring in these patients[2]. The prevalence is underestimated because imaging studies are performed exclusively in symptomatic patients, and screening studies of vascular lesions in these patients are not routinely established. Neurofibromin expression has been demonstrated in the vascular endothelial and smooth muscle cells, suggesting that deficiency in neurofibromin in NF-I may cause proliferation within the vessel wall, a process analogous to that which produces multiple cutaneous neurofibromas. However, it remains unclear why these clinical features take place, but they usually happen in multiple locations and are detected in imaging-complementary tests during the follow-up. The renal artery is the most frequent site of involvement, with abdominal aortic coarctation, internal carotid artery aneurysms and pseudoaneurysms, and cervical vertebral arteriovenous malformations being other common manifestations[3].

## Methods

We present the case of a 24-year-old girl with no previous pathology who was diagnosed with NFI at 12 years old. After the resection of several plexiform neurofibromas (PN) in the paravertebral and occipital regions and a low-grade ventricular glioma, she progressively developed a neurofibroma in the left cervical region and on the left shoulder that was surgically treated (Fig. 1). Previously to this procedure, embolization with polyvinyl alcohol particles of the left occipital artery was performed through the left common carotid artery in order to minimize intraprocedural bleeding.

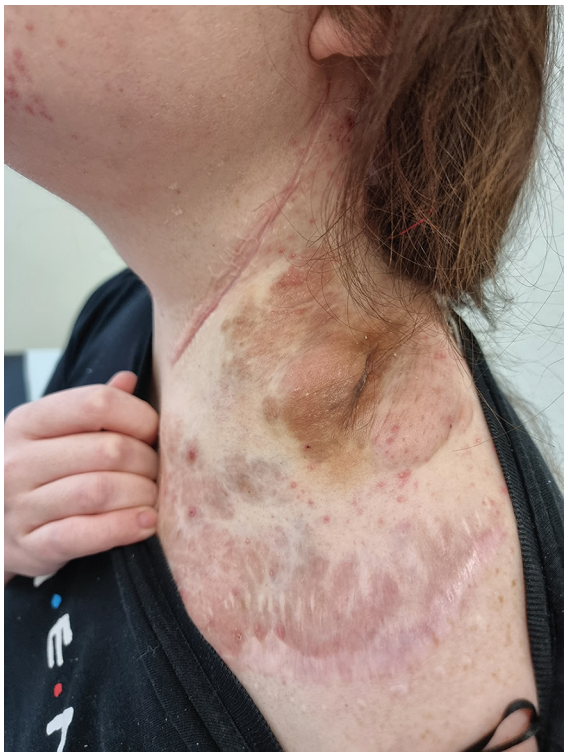

**Figure 1.** Neurofibroma in the left cervical region and on the left shoulder area.

## Results

Six months after left occipital artery embolization, she refers to pain and swelling in the left cervical region as well as a throat-forehead body feeling, detecting in the MRI an 11 × 19 mm pseudoaneurysm in the left common carotid artery, right in the access of the previous embolization. The case is presented in a multidisciplinary clinical session, deciding open approach due to the anatomical features of the lession, location, and patient age.

During the intervention, although we performed a gentle, atraumatic, and soft dissection of the tissue and artery wall, extremely friability of the vessels and surrounding tissue was observed, with multiple episodes of bleeding that led to the ligation of the left internal carotid artery to control bleeding and stabilize the patient (Fig. 2). During dissection, neurofibroma samples were collected (Fig. 3).

After two days of close surveillance, no neurological complications or focalities were observed, and the patient was discharged.

Seven days later, she came to the emergency room with important swelling in the left cervical region after

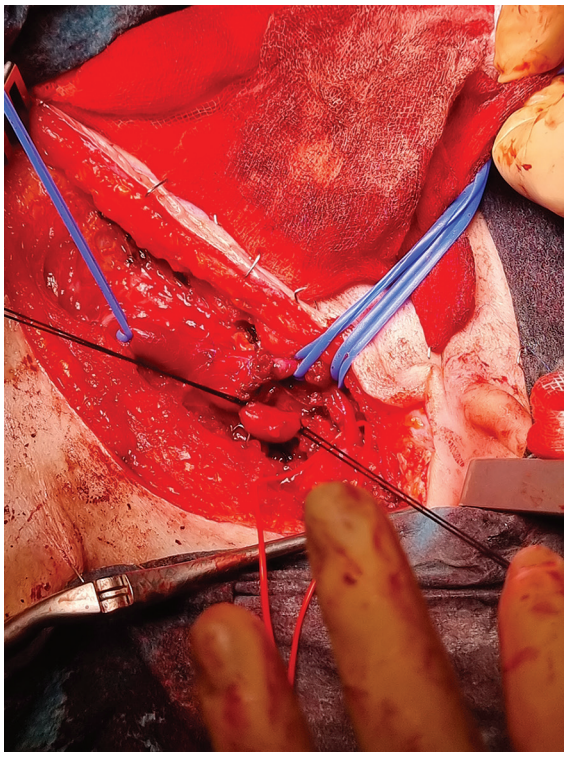

**Figure 2.** Ligation of left internal carotid artery due to multiple episodes of profuse bleeding. Besides gentle, atraumatic, and soft dissection of the tissue and artery wall, extreme friability of the vessels and surrounding tissue was observed.

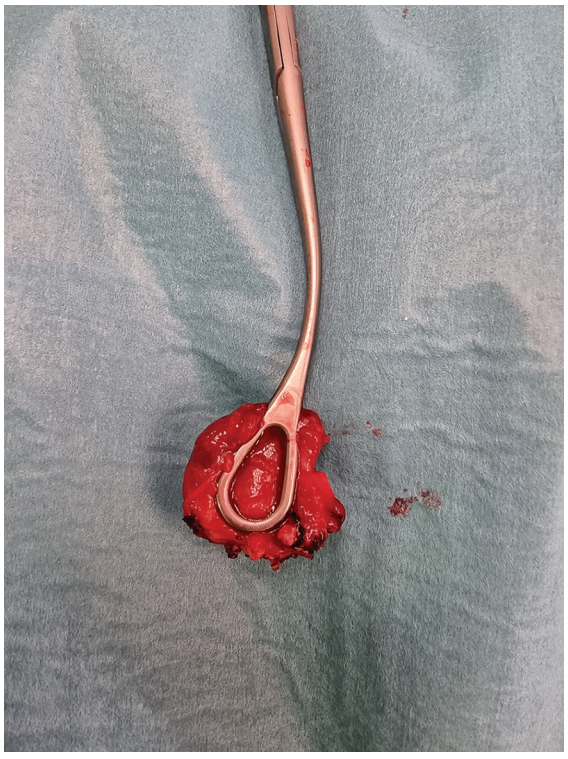

**Figure 3.** Neurofibroma sample collected during internal carotid artery dissection.

a coughing spell and mild difficulty swallowing and breathing. Due to the emergency, the patient was monitored, an airway was ensured, and a CT scan was developed. The observing acute contained rupture of the left subclavian artery right at the origin of the vertebral artery that conditioned displacement of the airway.

The patient was taken to the operation room, where an angiography was performed, observing a giant pseudoaneurysm in the origin of the left vertebral artery as well as two others distal to this segment (Fig. 4A). A 7 × 10 mm Viahban® was placed occludding the vertebral artery without further captioning of contrast inside the pseudoaneurysm in angiography (Fig. 4B).

After the procedure, the patient was taken to the intensive care unit, where she remained for 14 days due to a medical complication (nosocomial pneumonia). A tracheostomy was performed due to complicated extubation due to airway compromise. After resolution, decanulation was possible, and the patient was discharged.

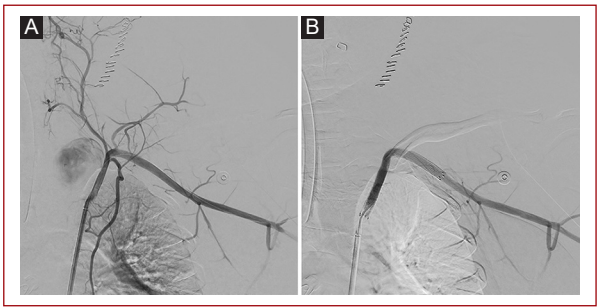


**Figure 4. A:** angiography: giant pseudoaneurysm in the origin of left vertebral artery. **B:** placement of a 7 × 10 mm Viahban®, ocludding vertebral artery and without further caption of contrast inside de pseudoaneurysm in the control angiography.

## Discussion

Lesions of the arterial wall are important manifestations of NFI, causing high rates of morbidity and potential mortality, as we could see with our patient. The pathogenesis remains poorly defined. It is not clear if vascular lesions occur either by the proliferation of nerves within the vessel walls or from compression or

invasion by neural tumors[2], a fact that does not correlate with the clinical findings we observed in the OR. Vascular histology was first classified by Reubi et al.[4] into intimal, aneurysmal, or fusocellular forms. A common finding between the types is spindle cell proliferation. Another frequent finding is fibromuscular dysplasia with intimal thickening. Oderich et al. suggest that arterial stenoses or aneurysms in these patients occur through a dynamic process of cellular proliferation, degeneration, healing, smooth muscle loss, and fibrosis[5]. They also described a different pattern in type, location, and histology of aneurysm distribution among young and older patients. While carotid-vertebral, renal, and mesenteric locations with fibromuscular dysplasia were common in young patients, degenerative atheroesclerotic aortic aneurysms were common in the oldest ones.

Spontaneous contained ruptured vertebral and internal carotid artery aneurysms and spontaneous subclavian artery rupture have been previously described[6-8] and are challenging situations that can lead to high morbidity and mortality. Vascular disease has been recognized as the second cause of death in the context of NFI, especially among patients under 40 years old[9].

Management of this spectrum of the disease is complex, requiring multiple vascular surgical procedures, sometimes without optimal outcomes.

Lately, with the development of inhibitors of the MEK pathway like trametinib and selumetinib, management of vascular complications could change, maybe being a powerful tool to improve the life quality of these patients, increase life expectancy, and help to control new events.

Trametinib is a third-generation, orally available, highly selective allosteric ATP noncompetitive inhibitor of the two isoforms of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2[10]. It has been previously used and approved by the FDA for BRAF V600E/K melanoma when its efficacy in reducing progression and increasing survival was proved[11]. Based on these previous findings, and this well-known mechanism as an inhibitor of endothelial cell growth and vascularity in some tumors, such as pediatric low-grade glioma[12], and according to our previous surgical experience and extremely discouraging prognosis of NF type I, we considered using trametinib, which has no current FDA approval for this specific indication, in order to control vascular complications. The initial dose was 0.5 mg every 24 h.

We observed during the first intervention, open repair of an internal carotid artery pseudoaneurysm, that vessels in NFI are aberrant, extremely fragile, and friable, making the surgical approach highly demanding and challenging and sometimes leading to dramatic outcomes such as ligation of the artery. According to this situation, our experience in arterial, venous, and lymphatic malformations, and the new era of genetic testing that provide us with targeted medical therapies, we find extremely useful the use of this MEK inhibitor in a "compassionate use" way.

Recently, Selumetinib (AZD6244, ARRY-142886) was approved in the United States to treat children over 2 years of age with NF1 and symptomatic, inoperable PN[13]. The approval of Selumetinib is expected to revolutionize the management of children with NF1, particularly those with inoperable tumors. A phase 2 trial of selumetinib in children with symptomatic, inoperable PN showed that it produced durable tumor shrinkage and clinical benefit[14]. Hwang et al. presented in 2022 a systematic review that evaluated the efficacy and safety of Selumetinib in children with NF1. Five studies involving 126 patients were included, evaluating the objective response rate (ORR), defined as the proportion of PN lesions that have a partial or complete response to selumetinib, and the disease control rate (DCR), defined as the proportion of PN lesions that have a partial or complete response or stable disease. They concluded that this MEK inhibitor is an effective and safe treatment for pediatric patients with inoperable, symptomatic PN[15], observing a pooled ORR of 73.8% and a pooled DCR of 92.5% and having a tolerable side-effect profile and safety level.

Based on the latest evidence, after 2 months of treatment, we decided to replace trametinib with selumetinib, 45 mg every 12 h, with good control of the symptoms in the first 2 months of follow-up and no evidence of new vascular lesions in the control CT scan (Fig. 5A and B). Mild side effects were observed 5 weeks after the start of trametinib (abdominal discomfort and acneiform eruption). MEK inhibitor trametinib frequently induces acneiform eruptions that are reversible and have a good response to oral and topical antibiotics and steroids[16] (Fig. 6). In this case, the patient was treated with oral doxycycline (100 mg every 24 h) for 14 days and topical betamethasone and gentamicin twice a day for 7 days and once a day for 2 weeks, with significant improvement.

## Conclusion

Although further larger-scale randomized controlled studies are needed to confirm the long-term outcomes of patients treated with these drugs, we consider, given their relatively high safety profile, that inhibitors of the

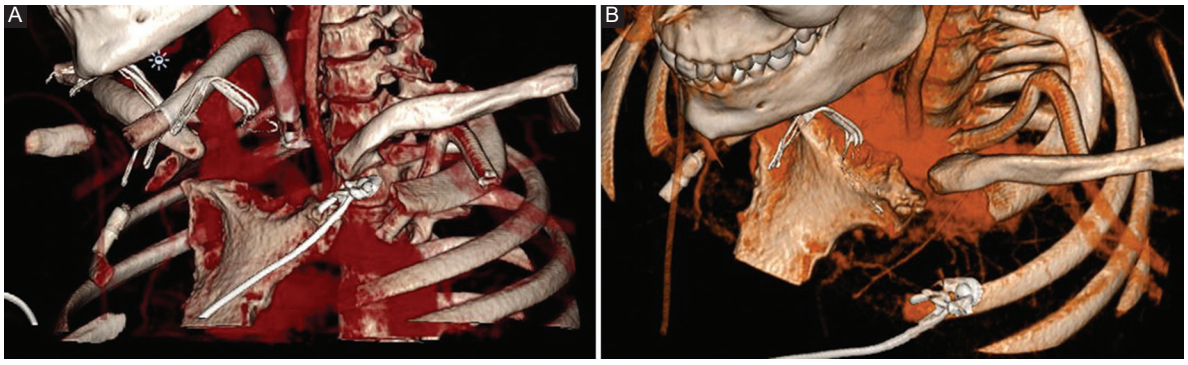


**Figure 5. A and B:** 3D Reconstruction of control computed tomography scan 2 months after spontaneous left subclavian artery rupture. Correct placement of the stent with no new vascular events.

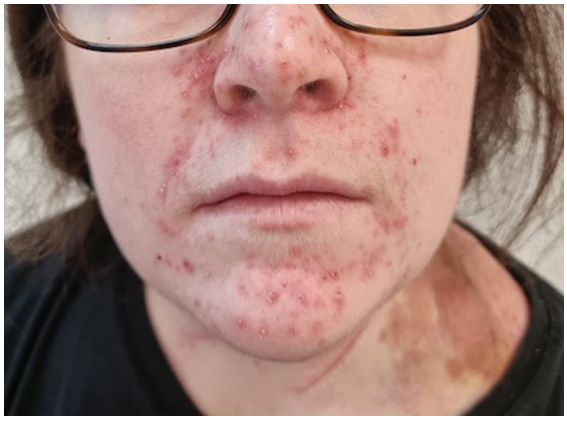

**Figure 6.** Acneiform eruption after 5 weeks of treatment with trametinib. This is a common mild side effect that is reversible and has a good response to oral and topical antibiotics and steroids.

MEK pathway could be a promising option in the maintenance treatment of patients with NFI vasculopathy and its complications, such as arterial spontaneous rupture. We advocate for a proper multidisciplinary approach and highlight the value of using genetic testing and targeted therapies in the approach to the vascular spectrum of NFI, the way we routinely do with vascular anomalies.

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## Conflicts of interests

The authors declare no conflicts of interest.

## Ethical disclosures

**Protection of people and animals.** The authors declare that no experiments were carried out on humans or animals for this research.

**Data confidentiality.** The authors declare that they have followed the protocols of their work center regarding the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

## References

1. Lin AE, Birch P, Korf BR, Tenconi R, Niimura M, Poyhonen M, et al. Cardiovascular malformations and other cardiovascular abnormalities in neurofibromatosis Type I. Am J Med Genet. 2000;95:108-17.
2. Friedman JM, Arbiser J, Epstein JA, Gutman DH, Huot SJ, Lin AE, et al. Cardiovascular disease in neurofibromatosis 1: report of the NF1 cardiovascular task force. Genet Med. 2002;4:105-11.
3. Hamilton SJ, Friedman JM. Insights into the pathogenesis of neurofibromatosis 1 vasculopathy. Clin Genet. 2000;58:341-4.
4. Reubi F. Les vaisseaux et les glandes endocrines dans la neurofibroma-tose: le syndrome sympathicotonique dans le maladie de Reckling-hausen. Schweiz Z Pathol Bacteriol. 1944;7:168-236.
5. Oderich GS, Sullivan TM, Bower TC, Gloviczki P, Miller DV, Babovic-Vuksanovic D, et al. Vascular abnormalities in patients with neurofibromatosis syndrome Type I: clinical spectrum, management, and results. J Vasc Surg. 2007;46:475-84.
6. Miyazaki T, Ohta F, Daisu M, Hoshii Y. Extracranial vertebral artery aneurysm ruptured into the thoracic cavity with neurofibromatosis Type 1: case report. Neurosurgery. 2004;54:1517-20.

7. Smith BL, Munschauer CE, Diamond N, Rivera F. Ruptured internal carotid aneurysm resulting from neurofibromatosis: treatment with intraluminal stent graft. J Vasc Surg. 2000;32:824-8.
8. Yoshida K, Tobe S. Dissection and rupture of the left subclavian artery presenting as hemothorax in a patient with von Recklinghausen's disease. Jpn J Thorac Cardiovasc Surg. 2005;53:117-9.
9. Rasmussen SA, Yang Q, Friedman JM. Mortality in neurofibromatosis 1: an analysis using U.S. death certificates. Am J Hum Genet. 2001;68:1110-8.
10. Lugowska I, Koseła-Paterczyk H, Kozak K, Rutkowski P. Trametinib: a MEK inhibitor for management of metastatic melanoma. Onco Targets Ther. 2015;8:2251-9.
11. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012;367:1694-703.
12. Arnold A, Yuan M, Price A, Harris L, Eberhart CG, Raabe EH. Synergistic activity of mTORC1/2 kinase and MEK inhibitors suppresses pediatric low-grade glioma tumorigenicity and vascularity. Neuro Oncol. 2020;22(4):563-574.
13. Markham A, Keam SJ. Selumetinib: first approval. Drugs. 2020;80:931-7.
14. Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb P, Fisher MJ, et al. Selumetinib in children with inoperable plexiform neurofibromas. N Engl J Med. 2020;382:1430-42.
15. Hwang J, Yoon HM, Lee BH, Kim PH, Kim KW. Efficacy and safety of selumetinib in pediatric patients with neurofibromatosis Type 1: a systematic review and meta-analysis. Neurology. 2022;98:e938-46.
16. Anforth R, Liu M, Nguyen B, Uribe P, Kefford R, Clements A, et al. Acneiform eruptions: a common cutaneous toxicity of the MEK inhibitor trametinib. Australas J Dermatol. 2014;55:250-4.