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Clínica Universitária de Cirurgia II

Case Report: Neurofibromatosis type 1, a new therapeutic approach

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ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disease with an unpredictable phenotypic expression which affects 1 in every 2500/3000 births. Plexiform neurofibromas (PN) occur in up to 50% of the patients and represent a very severe form of this disease involving, in many cases, great morbidity and a poor quality of life. Surgery has been the only available therapeutic measure to deal with these tumors. Selumetinib is a MEK 1 and 2 inhibitor that recently showed great results treating children with plexiform neurofibromas. In this case report is described the case of an eleven-year-old boy with NF1, presenting a lumbosacral plexiform neurofibroma with pelvic and lower limbs extension. Refractory chronic pain, gait impairment and urinary incontinence were the causes of great morbidity in this patient.
He was submitted to a surgery, a PEG-interferon alfa-2b treatment and an imatinib treatment. During this period no response was registered and a new left cervical neurofibroma has developed. Later, he started selumetinib and, in six months, significant clinical improvement and major functional gains were verified. However, while the other tumors have shrunk, disease progression has occurred in the left cervical plexiform neurofibroma leading to the need of excision.
This case demonstrates a severe and complex case of a patient with NF1 who clinically improved with selumetinib treatment. Additionally, it leads to the reflection that there may exist features in tumors that dictate the response to specific treatments.
Key words: Neurofibromatosis type 1, Plexiform neurofibromas, Selumetinib, Genetic features

RESUMO

A Neurofibromatose tipo 1 é uma doença genética autossómica dominante com uma expressão fenotípica imprevisível que afeta 1 em cada 2500/3000 nascimentos. Os neurofibromas plexiformes afetam 50% destes doentes e representam uma forma severa desta doença envolvendo, em muitos casos, grande morbilidade e má qualidade de vida. A cirurgia tem sido a única medida terapêutica disponível para lidar com estes tumores.
O sulemetinib é um inibidor da MEK 1 e 2 que recentemente mostrou grandes resultados no tratamento de criança com neurofibromas plexiformes. Neste artigo é descrito o caso de um rapaz de 11 anos com NF1 que apresentava um neurofibroma plexiforme lombo-sagrado com extensão pélvica e para os membros inferiores. Dor crónica refratária, dificuldades na marcha e incontinência urinária eram as principais causas de morbilidade deste doente.
Foi submetido a uma cirurgia, a um tratamento com PEG-interferão alfa-2b e a um tratamento com imatinib. Durante este período, não foi registada qualquer resposta e um novo neurofibroma cervical esquerdo desenvolveu-se. Mais tarde, o doente iniciou sulemetinib e, após seis meses, havia uma melhoria clínica e grandes ganhos funcionais. No entanto, enquanto os outros tumores diminuíram de tamanho, foi registada progressão da doença num neurofibroma plexiforme cervical esquerdo, levando à necessidade de excisão do mesmo.
Este caso demonstra um caso grave e complexo de um doente com NF1 que melhorou clinicamente com sulemetinib. Adicionalmente, leva à reflexão sobre a existência de características nos tumores que ditam a sua resposta a tratamentos específicos.
Palavras-chave: Neurofibromatose tipo 1; Neurofibromas plexiformes; Selumetinib; Características Genéticas

O Trabalho final exprime a opinião do autor e não da FML

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Introduction

Neurofibromatosis type 1 is an autosomal dominant genetic disorder affecting 1 every 2500/3000 births [1]. It is caused by mutations on the *NF1* gene. Although many mutations have been described, a well-defined genotype-phenotype correlation has not been established [2].

NF1 diagnosis is established through the presence of at least two of the seven criteria: six or more café-au-lait spots, with at least 0.5 cm in children; two or more neurofibromas on or under the skin, or one plexiform neurofibroma; axillary or inguinal ephelides; optic pathway glioma; two or more Lisch nodules; bone changes such as bowing of the long bones or sphenoid wing dysplasia; a close relative with a confirmed diagnosis of NF1 [3].

Neurofibromas are benign tumors that represent the major cause of morbidity in these patients and can be divided into four types: superficial cutaneous neurofibromas - soft and buttonous; subcutaneous neurofibromas - in the dermis adjacent to subcutaneous nerves; nodular plexiform neurofibromas - form an extensive network in the subcutaneous tissue; diffuse plexiform neurofibromas - compromise all layers of the skin and can penetrate deep into the muscles, bones and sometimes involve the viscera [4]. Plexiform neurofibromas are present in about 50% of the patients and most of the time are a major cause of morbidity in this population [5]. Surgery is indicated in symptomatic PN, however many of them are considered inoperable or return to grow after partial tumorectomy [6].

The NF1 gene mutation present in these patients is responsible for the production of neurofibromin. This protein is involved in the negative regulation of cell division inhibiting RAS signalling. Because it is not functional, it allows the abnormal formation of tumors that characterizes neurofibromatosis [2]. Some studies attempted to use this knowledge and interfere with RAS signalling, using pegylated interferon alfa 2b [7] and imatinib [8].

Selumetinib is a new selective inhibitor of MEK 1 and 2, reducing RAS chain activity. After being used in other solid tumors in adults, it was tested in phase 1 and 2 clinical trials in children with neurofibromatosis type 1, showing a high response rate. According to *Eva Dombi et al* [9] children with plexiform neurofibromas would benefit from prolonged treatment with selumetinib in a maximum dose of 25 mg per m^2 every 12 hours. In this trial, 71% of the children had a reduction of more than 20% in the volume of their neurofibromas and no progression of the disease was registered in any of them. This promising treatment is already being used across several countries worldwide and shows potential to become an established alternative to surgery [9,10].

There is no consensual approach to clinical monitoring of NF1 patients regarding plexiform neurofibromas. Routine whole body MRI in asymptomatic children allows the identification of asymptomatic lesions and PN burden assessment in patients with known lesions. With a 10% probability of malignant evolution during lifetime, the routinely use of FDG-PET in these tumors is also controversial and, according to the main orientations, should only be used when lesions with suspicious features are found, even knowing that some plexiform neurofibromas evolve into malignant tumors without other symptoms [4,11,12].

Case Presentation

An eleven-year-old black male patient was admitted due to a 4-year history of progressive swelling of his lower limbs with gait impairment and urogenital symptoms of incontinence and dysuria. Physical examination was remarkable for multiple *café-au-lait* spots, axillary ephelides and extensive lower limbs masses with soft consistency. Proximal and distal grade 3 paresis was observed. Gait was possible only with assistance. The Lansky performance score was 60. The patient denied recent change of lesions' size or consistency, neither new pain nor neurologic symptoms occurred.

The whole body MRI revealed multiple plexiform neurofibromas, extending form lumbosacral plexus to both lower limbs. The c.5944-5A>G NF1 gene mutation was documented as well. The diagnosis of inoperable plexiform neurofibromas in a NF1 patient was established.

Pain control was the priority of treatment and diverse analgesics were applied: paracetamol, metamizole, pregabalin, amitriptyline and later oxycodone. As a palliative measure the excision of the neurofibromas of the right leg and foot was performed. An operative piece with 1126 g and 45 cm of greater axis had been removed.

After surgery PEG-interferon alfa-2b was initiated and complied for 40 weeks until drug withdrawal from the market. At the end of the treatment the MRI control exam was performed and showed no morphological or volumetric improvements. Due to inefficacy of previous treatment, the need of a new approach was considered and a therapy with Imatinib was started. After 14 months of treatment with imatinib it was suspended as a new cervical mass developed and was confirmed on MRI to be a new plexiform neurofibroma.

Later, as he met inclusion criteria of having a non-resectable plexiform neurofibroma and a significant morbidity associated with chronic pain and great deformity, the patient was enrolled into a clinical trial with selumetinib. After exclusion of cardiac abnormalities, the treatment could

be started. The patient was followed every 15 days on consultation with height, weight, blood pressure monitoring and blood laboratory tests performed by the neuro-paediatrician. Moreover, a regular evaluation by a surgeon to assess eventual tumor progression made part of the protocol.

The patient soon started to feel a subjective decrease of all neurofibromas' volume, except the cervical one. The urinary incontinence disappeared after less than a month of treatment. The analgesia with metamizole, amitriptyline and oxycodone was stopped, maintaining only pregabalin and paracetamol. The gait impairment didn't improve and the Lansky performance score was 70 at that time.

During the treatment, one severe adverse event occurred, which was an asymptomatic and isolated creatine phosphokinase elevation up to 1604 U/L [CTCAE grade 3], which decreased spontaneously to 211 U/L on the following evaluation.

Despite the performance status improvement, the follow-up PET-FDG, performed after 6 months of treatment revealed an increased metabolic activity in the supraclavicular plexiform neurofibroma with a maximum SUV of 3.7, increasing from 2.5. A biopsy was made following neurofibroma excision. Although cervical tumor progression occurred during the treatment with selumetinib it was not taken as reason to stop the therapy since reduction of other bulky tumors was observed, together with significant clinical improvement and major functional gains.

Discussion

Plexiform neurofibromas occur in about 50 % of the patients with Neurofibromatosis type 1 [5] and this case represents one of them. The patient had multiple nodular plexiform neurofibromas in the pelvic region with extension to the lower limbs and one in the cervical region. These lesions impaired patient´s autonomous gait and were responsible for a low quality of life.

Due to bulky tumor masses, which the patient presented, only a palliative partial tumorectomy was possible. Pharmacological treatments with agents that interfere with the RAS pathway were being tested by that time and PEG-interferon alfa-2b and Imatinib were tried in our patient. Both agents showed to be inefficient, especially imatinib, while there was a disease progression during the treatment.

Selumetinib is proven to have great outcomes in children with plexiform neurofibromas [9, 10]. Our patient, with two failed therapeutic approaches and a significant physical impairment, seemed

to be a perfect case to include in the treatment trial with this new agent. He was the second child treated with selumetinib in Portugal under the IPO of Lisbon protocol.

After the first 6 months of treatment, our patient felt a subjective decrease of the neurofibromas' volume. Additionally, the urinary incontinence that accompanied him over the time disappeared and significant pain relieve was noted, allowing analgesic therapy reduction. However, the gait impairment didn't improve substantially and the patient continued to need an assistance. The cervical neurofibroma showed no reduction of its dimensions.

Regarding the adverse effects of the treatment, the most commonly reported in clinical trials were: acneiform rash, gastrointestinal symptoms and asymptomatic creatine phosphokinase [CK] elevation [9, 10]. Our patient suffered from an isolated elevation of CK up to 1604 U/L, corresponding to a CTCAE grade 3. Fortunately, this value was temporary and decreased on the next evaluations, without the need to withdraw from the trial. Sporadic episodes of vomits, nausea and abdominal pain (CTCAE level 1) were also registered during the treatment.

Considering a favourable treatment response, it was a surprise to find an increased metabolic activity of the cervical plexiform neurofibroma on a follow-up FDG-PET. A maximum SUV increased from 2,5 to 3,7. Disease's progression under selumetinib treatment has not been reported in the previous trials, making it unexpected in a patient who apparently responded well to treatment and had functional improvement [9, 10].

The fact that the others plexiform neurofibromas were responding to the selumetinib treatment with exception of the cervical one, may suggest that some genetical differences between these lesions could exist, even though they are present in the same patient and no differences were found between the anatomo-pathological reports of both tumors (Fig. 3). It would be interesting to characterize all tumors genetically with aim to verify eventual differences. Some specific genetical features may be responsible for the resistance to selumetinib observed in the case of the cervical tumor. Unfortunately, genetic studies were not available.

The present case also shows that although selumetinib therapy has positive outcomes in terms of plexiform neurofibromas, it may not prevent their eventual malignant transformation. Possibly, some genetical features play a major role in this phenomenon. We also assume that other gene mutations can be responsible for resistance to selumetinib treatment and only further investigation by monitoring bigger samples of patients, would achieve reliable conclusions.

Conclusions

The presented case shows a new perspective on the way patients with plexiform neurofibromas should be treated and indicates an alternative to the consecutive surgeries to which patients are so many times submitted with all the risks associated. Additionally, by describing the evolution of a plexiform neurofibroma under the treatment with selumetinib, this case suggests that not all plexiform neurofibromas should be treated with selumetinib and possibly, a genetical characterization of each tumor would help to identify the ones that would be more likely to respond to this treatment.

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Images

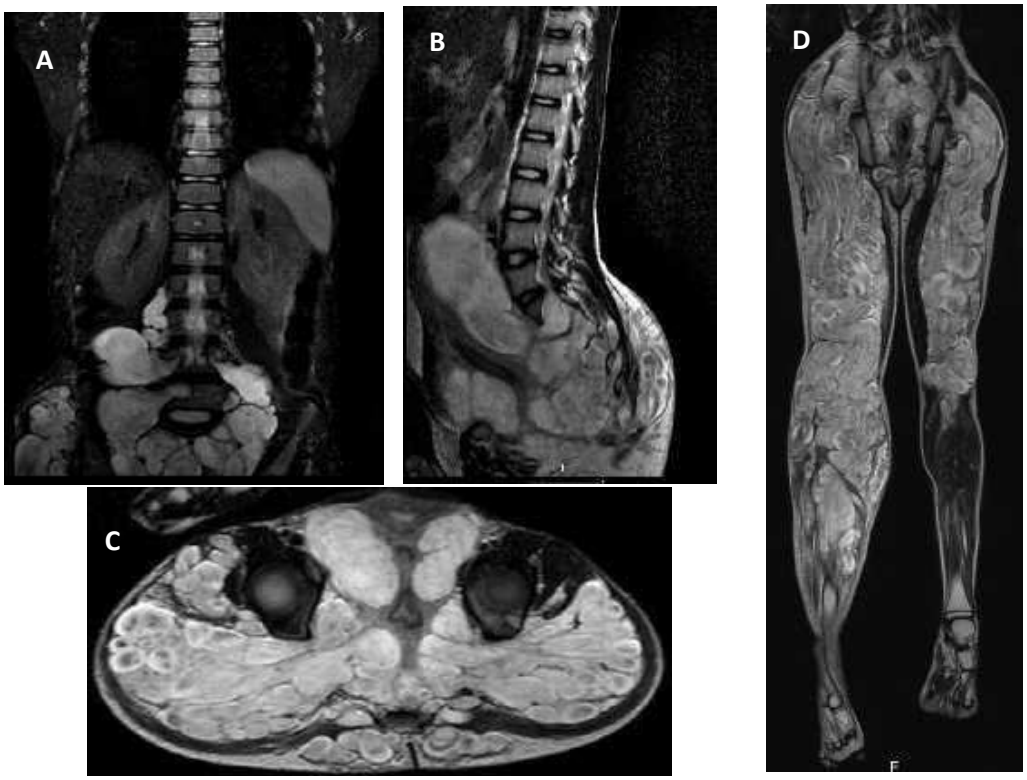

Fig. 1. Patient´s MRI showing lumbosacral plexiform neurofibromas. **A.** Coronal view. **B.** Sagittal view. **C.** Inguinal level. **D.** Lower limbs extension

Fig. 2. Photography. Patient two months after starting selumetinib

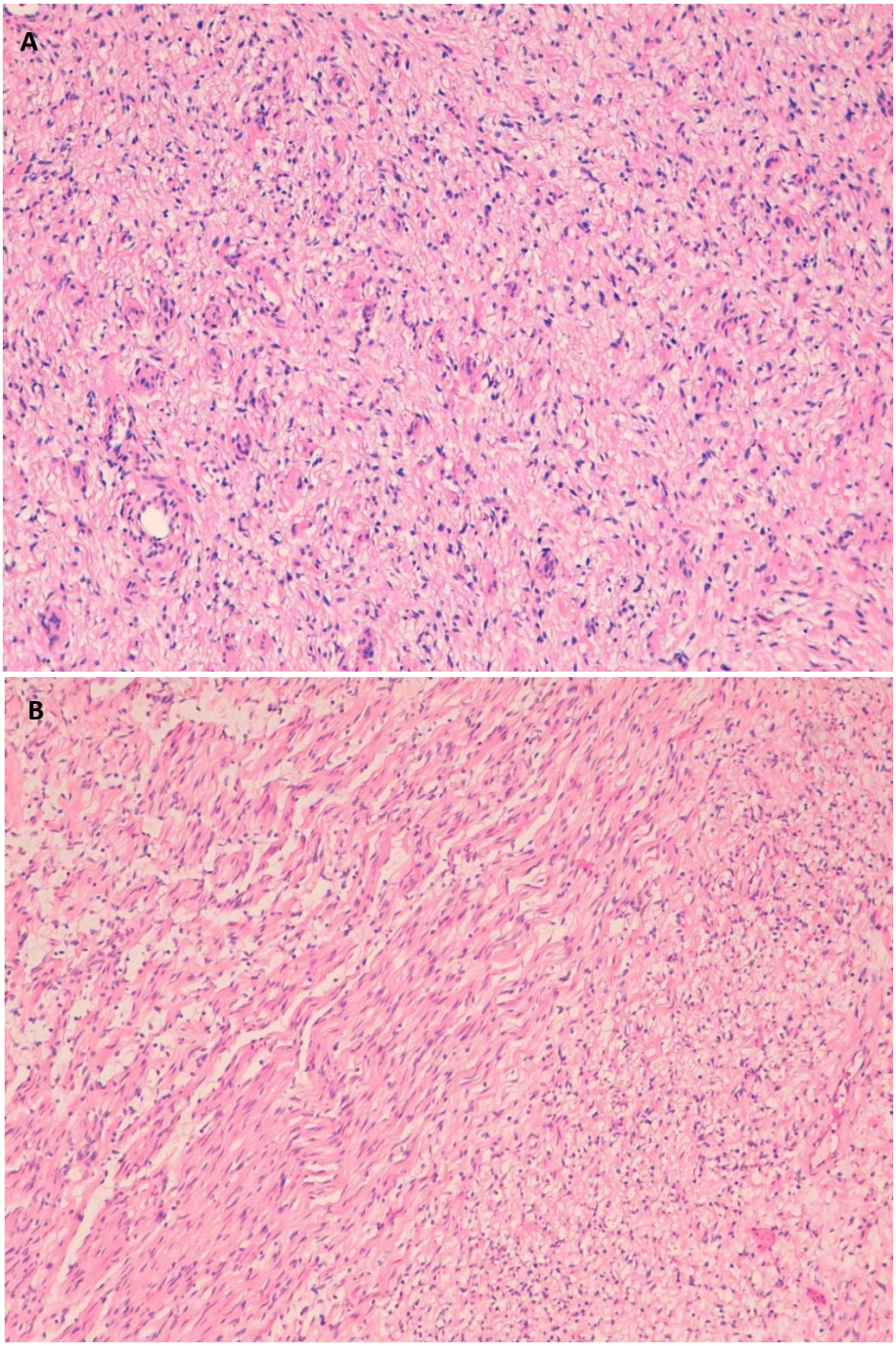

Fig. 3. Fusocellular mesenchymal neoplasm, moderately cellular, composed of bundles of spindle cells, with badly defined cytoplasm and elongate nuclei, with few cytological atypia and without evidence of mitotic activity, dispersed in a collagen stroma. **A.** section from the cervical neurofibroma [X200] **B.** section from the lumbosacral plexiform neurofibroma [X100]. Note that no morphological differences were found between the two plexiform