Diffuse Neurofibroma In Neurofibromatosis Type 1: Case Series

Neurofibroma Difuso en Neurofibromatosis Tipo 1: Serie de Casos

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Resumen

Los neurofibromas difusos son tumores benignos poco definidos de la vaina nerviosa periférica con un patrón de crecimiento invasivo. No se asocian comúnmente con la neurofibromatosis ni otras enfermedades neurocutáneas. Este manuscrito tiene como objetivo documentar la aparición de neurofibromas difusos en pacientes con NF1, a la vez que proporciona una revisión exhaustiva de este tipo de tumor. Presentamos tres casos que destacan las características clínicas, radiológicas e histológicas de los neurofibromas difusos en pacientes con una historia extensa de NF1. Estos tumores poco frecuentes tienen una baja prevalencia, pero cuentan con características patológicas, radiológicas e inmunohistoquímicas definidas y características para su diagnóstico. El tratamiento es desafiante debido a la falta de estandarización en las terapias y debe analizarse caso por caso. Los neurofibromas difusos deben ser incluidos en el diagnóstico diferencial de pacientes con NF1 y cualquier lesión cutánea asociada. Se requieren más estudios para estandarizar un enfoque integral en estos pacientes.

Palabras clave: neurofibroma difuso, paraneurofibroma, neurofibromatosis tipo 1, NF1, serie de casos.

Abstract

Diffuse neurofibromas are poorly defined, benign tumors of the peripheral nerve sheath with an invasive growth pattern. They are not commonly associated with neurofibromatosis or other neurocutaneous disorders. This manuscript aims to document the occurrence of diffuse neurofibromas in patients with NF1, while providing a comprehensive review of this type of tumor. We present three cases highlighting diffuse neurofibromas' clinical, radiological, or histological characteristics of diffuse neurofibromas in patients with a long-standing history of NF1. These rare tumors have a low prevalence but have defined and characteristic pathologic, imaging, and immunohistochemistry features for diagnosis. Treatment is challenging due to the lack of standardization in therapies and should be analyzed on a case-by-case basis. Diffuse neurofibromas should be included in the differential diagnosis in patients with NF1 and any associated cutaneous lesions. Further studies are needed to standardize an integral approach in these patients.

Keywords: diffuse neurofibroma, paraneurofibroma, neurofibromatosis type 1, NF1, case series.

Rev. Ecuat. Neurol. Vol. 34, N° 1, 2025

Introduction

Diffuse neurofibromas are ill-defined benign peripheral nerve sheath tumors (PNSTs) with an infiltrative growth pattern. Although diffuse neurofibromas are typically isolated growths and not frequently associated with neurocutaneous syndromes, the three patients presented here had a long-standing history of neurofibromatosis type 1 (NF1). They developed symptoms like pain, restricted movement, and swelling with mass effects, which were attributed to diffuse neurofibromas. We also discuss these tumors' clinical features, imaging, and histopathologic findings.

Case series

Case 1

A 43-year-old female with a history of NF1 presented with an asymptomatic, progressively enlarging plaque-like lesion in the left gluteal region. Over the years, she developed multiple cutaneous neurofibromas treated with electrodesiccation and two debulking surgeries for a right hip and gluteal neurofibroma. Pelvic MRI (Fig. 1A, 1B, 1C) revealed an infiltrative soft tissue mass in the subcutaneous space, extending into the superficial fascia of the paraspinal musculature, consistent with

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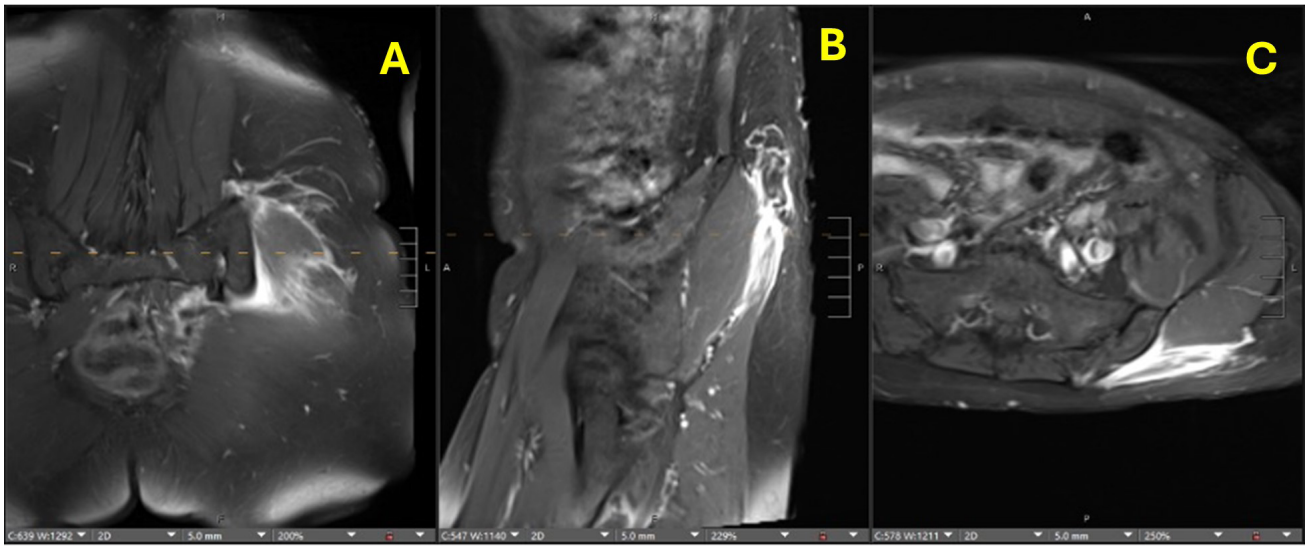

Fig 1. Pelvic magnetic resonance imaging. (A) Axial T1-weighted with contrast demonstrating hyperintense left gluteal diffuse neurofibroma. (B). Parasagittal T1-weighted with contrast that shows hyperintense posterior subcutaneous diffuse neurofibroma (C). Axial T1-weighted with contrast that demonstrates hyperintense posterior subcutaneous diffuse neurofibroma.

diffuse neurofibroma. The patient sought treatment for cosmetic reasons.

Case 2

A 27-year-old male with NF1 presented with increased right leg circumference. His medical history included pulmo-pleural blastoma, right hip and gluteal neurofibrosarcoma, lower back large cutaneous and plexiform neurofibromas, and left post-chiasmatic optic nerve glioma. Pelvic MRI (Fig. 2A, 2B, 3A, 3B, 3C, 3D) revealed an enhancing lesion in the subcutaneous tissue and gluteus maximus muscle. Surgical resection in January 2024 confirmed diffuse cutaneous neurofibroma, characterized by variable SOX10 expression and CD43-positive dendritic fibroblasts. Post-surgical growth prompted consideration of Selumetinib as treatment.

Case 3

A 32-year-old man presented to the clinic for progressive left hip pain and new onset numbness in the left leg. The patient has a history of untreated NF1, diagnosed when he was eight years old, and a history of severe sco-

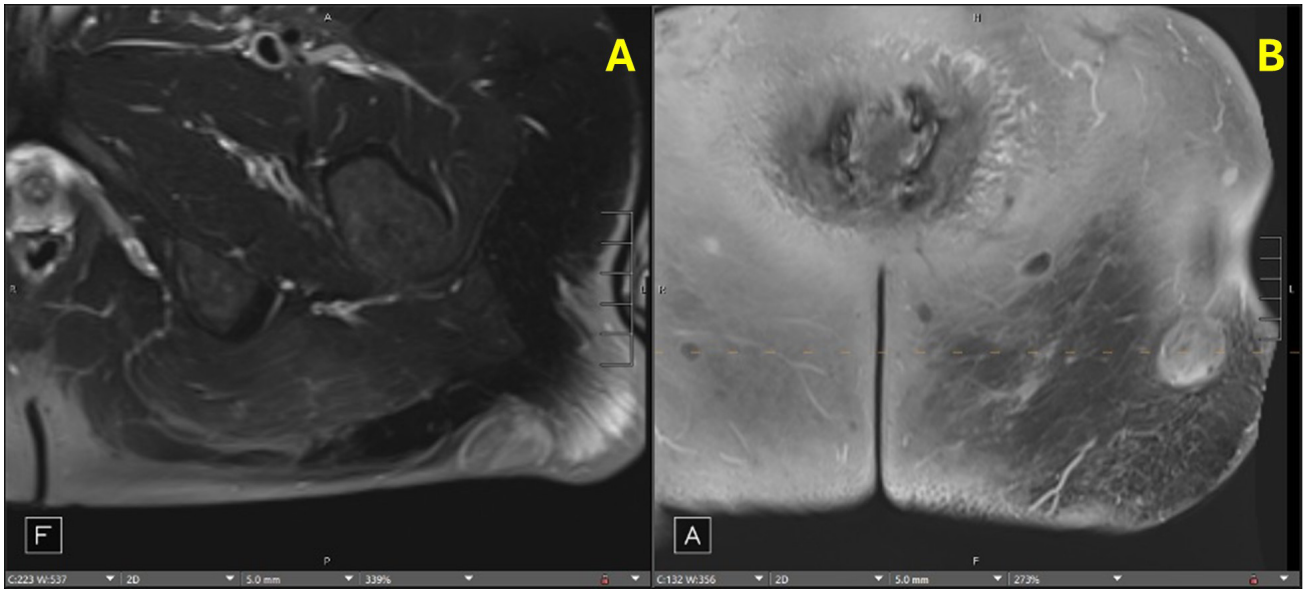

Fig 2 (A, B). Axial T1-weighted magnetic resonance imaging with contrast of the left lower extremity, which demonstrates a hyperintense lesion in the left lower limb compatible with a diffuse neurofibroma.

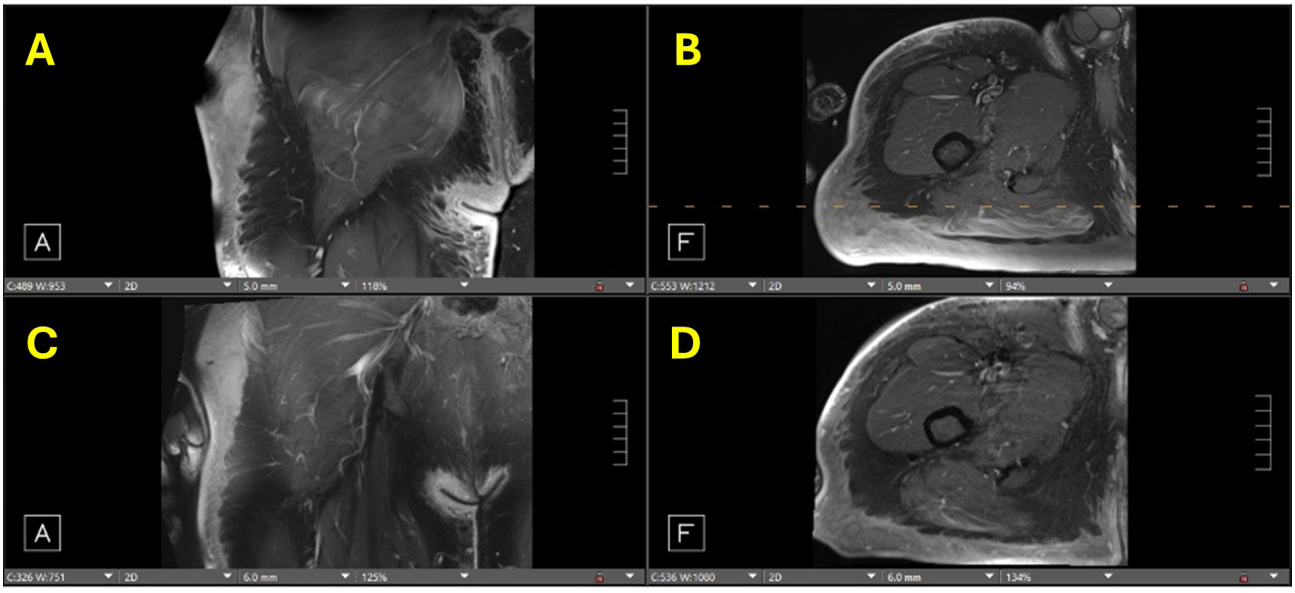

Fig 3. T1-weighted magnetic resonance imaging with contrast of the right femur. (A) Top left: coronal view (2024). (B) Top right: axial view (2024). (C) Bottom left: coronal view (2019). (D) Bottom right: axial view (2019).

liosis with dural ectasia. The patient did not follow regular appointments with any physician. Instead, he had been visiting a chiropractor for ten years and used medical cannabis for pain control. An MRI of the whole body was ordered, which demonstrated the lumbar levoscoliosis and marked progression of lumbar dural ectasia with aneurysmal dilatation of right-sided nerve root sleeves (Fig. 4A, 4B). Compared to the 2008 MRI, the aneurysmal dilation now causes severe mass effects upon adjacent structures. Marked myositis of the right iliopsoas and right lower paraspinal muscles were also present, with severe right upper thigh subcutaneous edema, which increased concern for the progression of a diffuse neurofibroma.

Commentary

Neurofibromas are histologically benign (WHO grade 1) soft tissue tumors arising from peripheral nerve sheaths.[1] They can occur sporadically or in association with neurofibromatosis type 1 (NF1). While neurofibromas are usually benign, approximately 10-15% have the potential to become malignant.[2] Neurofibromas are categorized as localized, diffuse, or plexiform. Diffuse neurofibroma

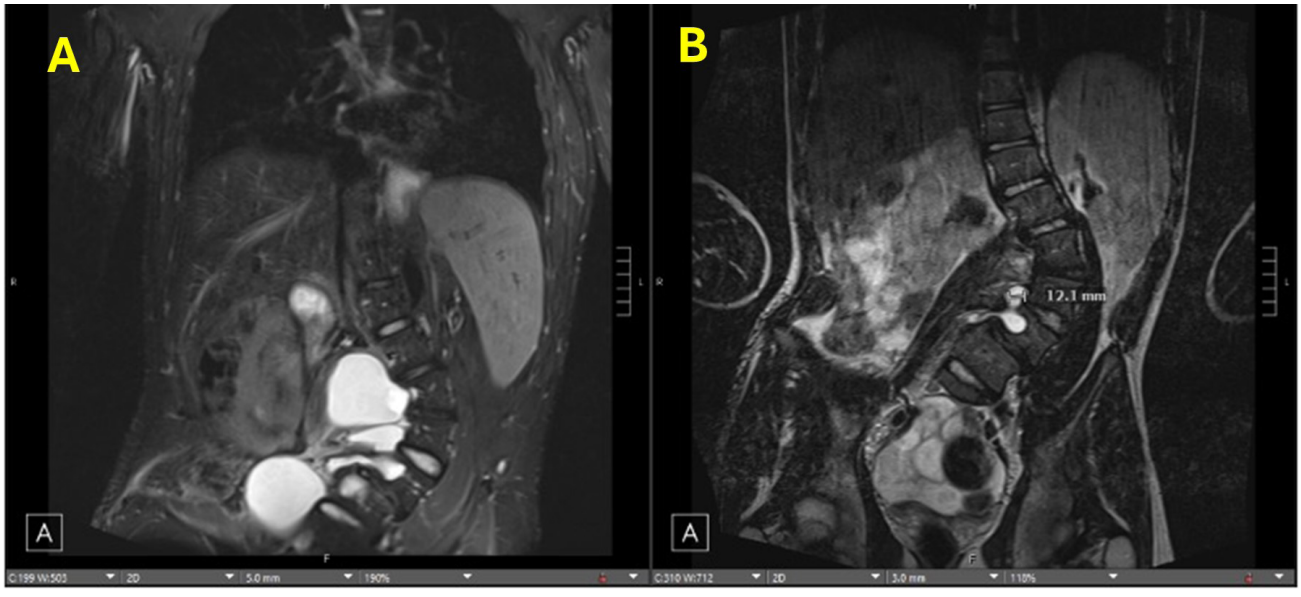

Fig 4. Thorac-abdominal magnetic resonance imaging. (A) 2024 coronal T1-weighted MRI with contrast that depicts lumbar levoscoliosis and marked progression of lumbar dural ectasia causing a severe mass effect to adjacent structures, compared to the (B) coronal T1-weighted contrast MRI of 2008.

present diagnostic challenges due to their varied clinical, radiological, and histological characteristics.[3,4] This case series examines three NF1 patients with diffuse neurofibromas, highlighting the importance of understanding this uncommon presentation in NF1 management.

Characteristics

Diffuse neurofibroma, or paraneurofibroma, typically affects children and young adults with no gender predilection and is commonly located in the head and neck region, trunk, and extremities.[5] It is a slow-growing, ill-defined mass with skin thickening and induration, infiltrating subcutaneous tissue without destroying skin appendages. Symptoms may include swelling, pain, and functional impairment.[3,6,7] This deep infiltration is evident in case 1, where the mass extends through the subcutaneous tissue to the superficial paraspinal fascia.

NF1 gene heterogeneity loss occurs in 20-50% of cases. NF1 deficiency activates Ras, subsequently activating AKT/mTOR and Raf/MEK/ERK pathways, offering potential therapeutic targets. Nonfunctional neurofibromin influences tumor growth along nerves. Further research on specific genes and neurofibromin's role in diffuse neurofibromas is needed.[8]

Associations

Even though diffuse neurofibromas are rare, 10% of these tumors are found in patients with neurofibromatosis type 1. This tumor should be regarded as a mosaic manifestation of NF1. Therefore, patients who initially present with diffuse neurofibromas should be evaluated for any other NF1 stigmata.[9] In rare instances, diffuse neurofibroma is seen in other syndromes that share some similarities with NF1, such as neurofibromatosis type 2, schwannomatosis, Carney complex, and Tuberous sclerosis complex.[10]

Diagnosis

These tumors have a distinctive radiographic appearance. Some literature suggests that the diagnosis could be based on imaging findings alone.

Imaging

MRI with contrast best characterizes diffuse neurofibromas. Key findings include isointense or mildly hyperintense signals on T1-weighted MR images, and markedly hyperintense signals are found in T2-weighted images. Moreover, a prominent internal vascularity enhances homogeneously with contrast.[5,11,12] The most common growth patterns are plaque-like and infiltrative. Diffuse neurofibromas have extensive infiltration of the skin and subcutaneous tissue, enveloping vessels and tendons without local destruction.[5,12] Possible bone erosion and intracranial extension, when found, are characteristic of paraneurofibromas.[13]

Hence, Hassell et al. proposed that the combination of plaque-like growth, prominent internal vascularity, and marked enhancement were highly indicative of diffuse neurofibroma.[5] Nonetheless, definitive diagnosis may be necessary to differentiate from subcutaneous hemangioma, and cutaneous lymphoma.[11]

Current neuro-oncology practice prioritizes using non-invasive image-based recognition techniques, such as CT and MRI, for the screening and diagnosis of PNST. The metabolic activity of these malignancies, as quantified by PET scans, does not consistently exhibit a reliable correlation with the histopathological grade of the tumor.[14]

Histology

The definitive diagnosis of diffuse neurofibroma is made after histological confirmation. Gross pathology demonstrates an ill-defined mass with a tan-white cut section,[9] while microscopic pathologic findings include elongated spindle cells with round or fusiform nuclei and eosinophilic cytoplasm within a loose matrix of thin fibrillar collagen. Pseudomeissnerian-body-like structures are characteristic but not always present and an ectatic blood vessel may be seen.

Immunochemistry

Neurofibromas consist of Schwann cells, CD34+ fibroblasts, mast cells, macrophages, and nerve fibers. They show immunoreactivity to S-100 protein and diffuse expression of SOX-10. There is variable expression of epithelial membrane antigen (EMA) and CD34+ from fibroblast cells.[6,15] The SOX10 immunostaining is a specific marker used to identify peripheral nerve tumors and differentiate neurofibromas and schwannomas from fibrosarcoma, leiomyosarcoma, and synovial sarcoma.[16,17] CD34+ immunostaining in spindled fibroblasts creates a characteristic fingerprint pattern and helps differentiate neurofibroma from early desmoplastic melanoma when CD34+ reactivity exceeds 60%.[18]

Treatment

Treatment options for diffuse neurofibromas include surgery, radiation, and chemotherapy, though their effectiveness is debated due to potential risks.[19] Currently, there is no approved treatment for NF1 in adults, and no trials specific to diffuse neurofibromas.[20] The surgical and pharmacological treatments aim to reduce the growth of neurofibromas, mitigate the symptoms, or avoid complications due to compression of adjacent structures or their potential to become malignant. Gabapentin can be used to treat neuropathic pain and pruritic sensations.

For monitoring purposes during treatment, the consensus guidelines of Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) state that volumetric analysis of MRI should be used to assess tumor response in NF1-related plexiform neurofibromas in clinical trials.[21,22]

Selumetinib, a MEK inhibitor, was approved in 2020 for pediatric NF1 patients with inoperable plexiform neurofibromas. Clinical trials showed tumor volume reduction and decreased pain intensity. Common side effects include gastrointestinal symptoms, an asymptomatic increase of serum creatine phosphokinase, acneiform rash, and paronychia. Other less common but severe adverse drug reactions included retinal detachment, reduced left ventricular ejection fraction, and cardiomyopathy in patients under treatment for many years.[23,24]

Other drugs under investigation include Mirdametinib, a MEK inhibitor, showing tumor volume reduction in some patients.[25] Cabozantinib, a tyrosine kinase inhibitor that targets cMET and the vascular endothelial growth factor receptor 2 (VEGFR2), demonstrated partial response or stable disease in a phase two trial.[26] Imatinib mesylate, a protein kinase inhibitor, caused disease regression in some patients with plexiform neurofibromas.[27] Pegylated interferon alfa-2b showed limited efficacy due to tumor progression and malignant transformation in some patients.[28] On the other hand, tipifarnib, sirolimus, and pirfenidone did not demonstrate clinical efficacy.[29]

Surgical excision, laser removal, and electrodesiccation may be considered for superficial neurofibromas but are controversial for diffuse types due to the difficulty in defining their shape and size. Additional therapies like physical therapy, orthopedic devices, and language and respiratory therapy may be necessary depending on the affected structures.[19]

Prognosis

The prognosis of diffuse neurofibroma varies depending on whether it is an isolated finding or a manifestation of a neurocutaneous syndrome. These tumors can significantly impact the quality of life due to pain, organ compression, and disfigurement. NF1 patients with diffuse neurofibromas may have a reduced life expectancy of 8-15 years.[30] Regular monitoring is crucial due to the potential for malignant transformation, even though it is low (approximately 3%).[5] While surgical excision is challenging due to the tumor's diffuse nature, recent FDA approval of Selumetinib for pediatric NF1 patients with plexiform neurofibromas offers hope.

Conclusion

Our cases highlight the importance of recognizing diffuse neurofibromas within the spectrum of benign tumors in neurofibromatosis type 1 patients. Despite their typically slow-growing and benign nature, they can cause significant local disfigurement and potentially induce pain and compression of nearby structures and organs. Their infiltrative nature often complicates surgical excision or radiation treatment. Emerging pharmacologic therapies, such as MEK inhibitors like Selumetinib, may offer promising treatment options for adult patients with diffuse neurofibromas, potentially improving outcomes and quality of life.

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