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CLINICAL CASE

Neurofibromas in Type I Neurofibromatosis. Description of a clinical case and literature review

Neurofibromas en la Neurofibromatosis tipo I. Descripción de caso clínico y revisión de la literatura

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What do we know about the subject matter of this study?

Neurofibromatosis is an uncommon condition in the general population. Neurofibromas are the most frequent benign tumors of this syndrome, they have a wide variety of clinical presentations, and some have potential risk of malignancy. Health professionals need to be aware of these lesions in order to contribute to an opportune diagnosis.

What does this study contribute to what is already known?

The clinical case presented allows us to describe the clinical variability of neurofibromas during adolescence, highlighting the clinical and ultrasound findings that allow their diagnosis.

Abstract

Neurofibromatosis type 1 (NF1) is the most frequent genodermatosis. Its cutaneous findings are key for early diagnosis, as they usually appear at early age. Café-au-lait macules are the most known cutaneous findings. Neurofibromas are the most frequent cutaneous tumors in patients with NF1, showing multiple clinical manifestations. They are classified as superficial and deep lesions, and superficial neurofibromas are subdivided in cutaneous or subcutaneous. Some neurofibromas may be present since birth; however, most appear during adolescence. Neurofibromas constitute 2 out of 7 of the NIH criteria of Neurofibromatosis type 1. Most of them are benign, do not require treatment and their recognition allows an early diagnosis of the disease. **Objective:** To describe and classify neurofibromas associated with NF1 through a clinical case. **Clinical Case:** 18-year-old male diagnosed

Keywords:
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since childhood with NF1 presents with multiple oval nodules on his face, occipital area, and wrist, multiple blue-red macules on his back and an asymptomatic pink plaque in his thigh. Ultrasound of the nodules was suggestive of neurofibromas and a skin biopsy of the lesions in the back and thigh were consistent with cutaneous neurofibromas. **Conclusion:** This case illustrates the varied clinical manifestations of neurofibromas in adolescence. Recognition of neurofibromas by the pediatrician, pediatric neurologist and/or dermatologist is crucial for the early diagnosis of NF1.

Introduction

Neurofibromatosis type I (NF-1) is the most common neurocutaneous syndrome, affecting 1 in 3000 live newborns worldwide[1]. It is caused by germline NF1 gene mutations (on chromosome 17q11.2) with autosomal dominant transmission, complete penetrance, and variable phenotypic expression[2,3]. Approximately 42-50% of patients have spontaneous mutations[4,5].

More than 3000 genomic variants of the NF1 gene have been described[5]. This gene encodes the cytoplasmic protein Neurofibromin, which suppresses the prooncogenic RAS pathway. This protein is expressed in all cells but mainly in neurons and Schwann cells, and can cause ophthalmologic, endocrinologic, musculoskeletal, dermatologic, central and peripheral nervous system, learning disorders, and autoimmune and tumor manifestations[3].

Since it is considered within the group of RASopathies, it is a condition that presents a higher risk of developing benign and malignant neoplasms, with an estimated 59.6% lifetime risk of developing cancer in patients with NF-1[6]. The most described NF-1-associated malignancies are pheochromocytoma, sarcomas -especially malignant peripheral nerve sheath tumor-, melanoma, breast cancer (especially under 50 years of age), leukemia, and gastrointestinal tumors[5].

The most frequent clinical manifestations of NF-1 are cutaneous, therefore, recognizing them is fundamental for suspicion and early diagnosis, which continues to be mainly clinical, based on the 1988 NIH diagnostic criteria[7].

Among the cutaneous clinical manifestations of NF-1, neurofibromas (NF) are the most frequent tumors, reported in up to 78-99% of adults[5,8]. These tumors can appear in the neonatal period and increase in number with age, especially during puberty and pregnancy, in part due to the presence of progesterone receptors[3,5]. Thus, cutaneous NFs are observed in 10% of children under 10 years of age and in up to 99% of adults[8,9]. They are defined as benign tumors derived from the neural sheath of peripheral nerves.[3] It is hypothesized that Schwann cells would initiate tumor development due to the inactivation of the NF1 gene[10], and then other cells such as mast cells, fibroblasts, perineurial cells, endothelial cells, and extracellular matrix with collagen or more myxoid would be recruited[3].

Cutaneous NFs are located mainly on the trunk and increase with age; a recent study showed that their number is significantly higher in patients with family members with NF-1[11]. They are usually asymptomatic, although 20% of patients have pruritus associated with rapid growth[12]. Despite being benign, they can generate significant morbidity due to pain, disfigurement, local compression, and alteration of nerve function, large vessels, and airway[5], significantly affecting the quality of life of these patients[13].

The best-known form of NF is the typical superficial cutaneous NF, with globular or pedunculated forms. However, multiple types of cutaneous NF have been described in the literature. Thus, there are different clinical, imaging, and histopathologic classifications to characterize NF[1,3,8], From the clinical-echographic perspective, the classification of García-Martínez and Hernández-Martín et al. seems the most practical (Table 1)[1,3,14]. Given the high incidence of NF in this disease, the objective of this report is to describe and classify NF-1-associated neurofibromas through a clinical case.

Clinical Case

18-year-old male patient with a clinical diagnosis of Neurofibromatosis type 1 since the first year of life. Among his medical history, he has complete education, his parents are not consanguineous, and has no family history of *café-au-lait* spots. Regarding neurological features, during childhood, he developed fine and gross psychomotor developmental delay, predominantly expressive language disorder, with phonological and semantic alteration of language, which was managed with speech therapy in a language school, in addition to kinesiotherapy and occupational therapy. During adolescence, he was diagnosed with Attention-Deficit/Hyperactivity Disorder, which was managed with methylphenidate, maintaining regular school performance, and presented normal pubertal development.

Regarding ophthalmological aspects, he developed

Table 1. Clinical and ecographic classification of Neurofibromas in type I Neurofibromatosis. Adapted from García-Martínez et al[1] and Hernandez-Martín et al[3] clasification

Superficial Neurofibromas (seen or palpable)		Deep neurofibromas (diagnosed only by imaging)
Cutaneous or dermal	**Subcutaneous**	Subfascial Neurofibroma
Clasic Cutaneous or Dermal	Subcutaneous nodular neurofibroma	Spinal neurofibromatosis
Blue-red macules	Diffuse subcutaneous neurofibroma	Deep (or Internal/visceral) neurofibroma
Pseudoatrophic Neurofibroma		orbital or cranio-orbitotemporal neurofibromatosis

Lisch nodules at the age of 4, euryblepharon, and astigmatism. He was annually monitored by Ophthalmology and Neuropediatrics. His last brain MRI was performed 6 months before the dermatologic consultation, without pathological findings and the spine MRI showed L5-S1 discopathy and perifacet enhancement in T11-T12 and T12-L1. At the age of 16, a genetic study was performed which showed deletion of exons 5-47 of the NF1 gene.

At the age of 18, he consulted the Dermatology Service of the *Centro de Referencia en Salud Peñalolén Cordillera Oriente* due to a new lesion on the left thigh during the last year, asymptomatic. He also reported new asymptomatic nodules on the right wrist, right supraciliary area, and scalp, that have been present for a few months.

Physical examination revealed normal blood pressure, macrocephaly (HC: 60 cm), multiple generalized *café-au-lait* spots, axillary freckles (Figure 1), and 0.5 cm-oval well-defined subcutaneous mobile nodules in the right supraciliary area, scalp, and right wrist; and a 25 mm soft plaque, somewhat pink, with loss of skin appendages on the left lateral thigh (Figure 2). Finally, in the lumbar area and chest, there were multiple small red-bluish macules, less than 5 mm each, some of them slightly depressed (Figure 3).

A skin biopsy of bluish macules on the chest and thigh plaque was performed (Figure 4), and both were compatible with NF. Ultrasonography of supraciliary and scalp nodules was performed, which confirmed subcutaneous nodular NF.

Using the clinical classification of García-Martínez et al[1], the patient was diagnosed with superficial subcutaneous nodular NF in the right supraciliary area, scalp, and right wrist, pseudo-atrophic superficial cutaneous NF in the left lateral thigh, and bluish-red superficial cutaneous NF in the lumbar area and chest.

Discussion

There are multiple classifications for NF, which are confusing as they include both clinical and histological criteria[3]. From a clinical-echographic perspective, the classification of García-Martínez and Hernández-Martín et al.[1,3,14] seems easier to use and replicate. In this classification, NFs are classified into superficial and deep NF according to their clinical characteristics, patient age, and ultrasound characteristics, and congenital NF are classified in a separate special category. Superficial NFs are those that are visible or palpable on examination while deep NFs are those that can only be distinguished by imaging (ultrasound, MRI, among others) (Table 1), but can be palpated or seen as they grow. Congenital NF can be superficial or deep, they are present from birth and can change during their evolution. Only superficial congenital NFs are evaluable by physical examination, so we will only address them in this discussion (table 2).

Within superficial NFs, there are cutaneous and subcutaneous. Superficial cutaneous NFs are defined as benign tumors that grow from dermal peripheral

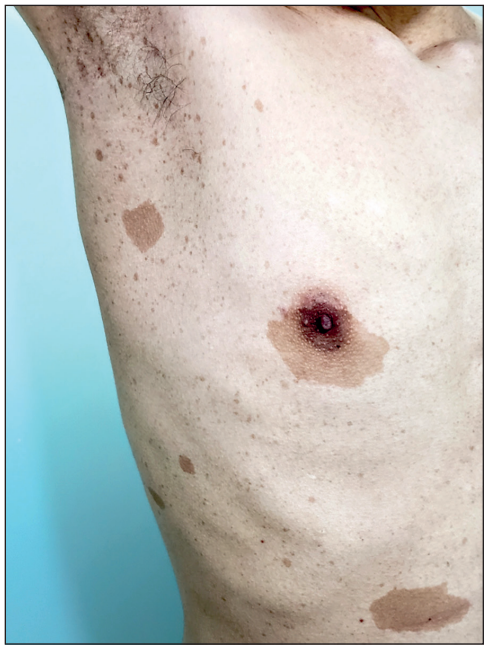

Figure 1. Multiple café-au-lait spots of more than 15 mm each and freckles in the armpits (Crowe's sign).

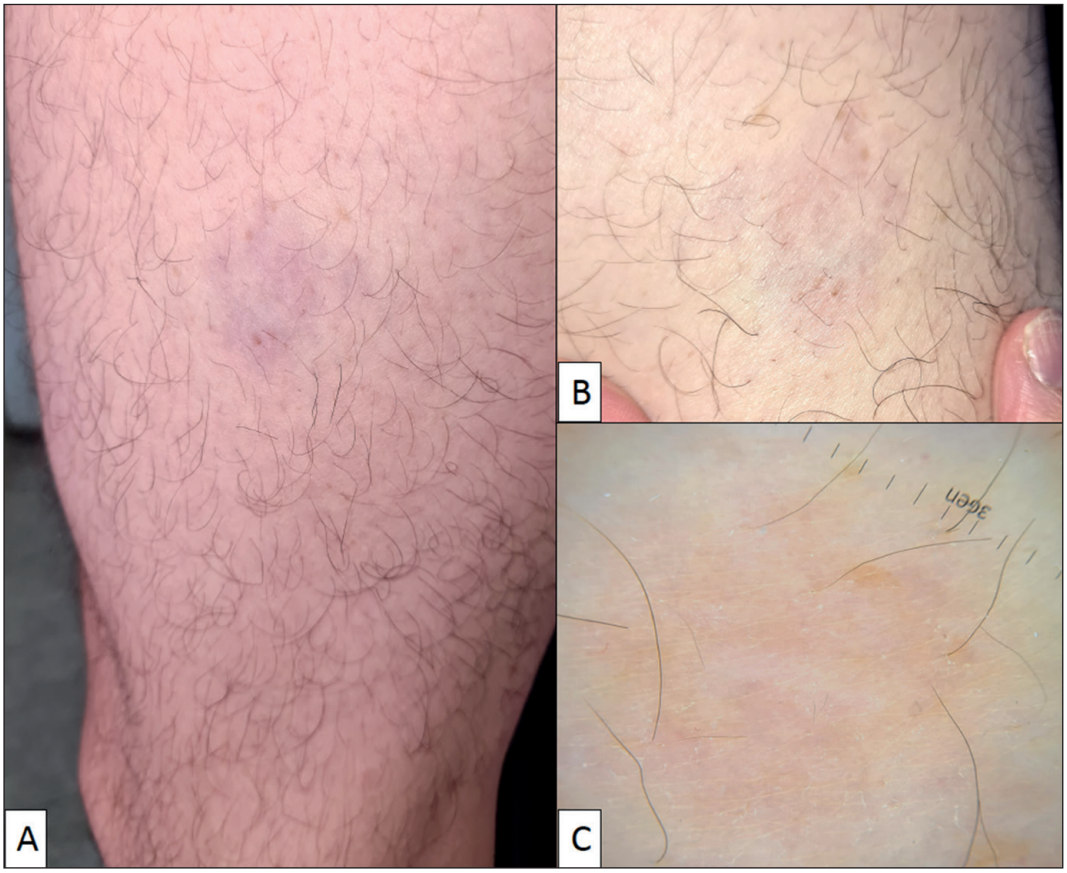

Figure 2. A. Pinkish depressed plaque with a 25-mm largest diameter in the left thigh; **B.** with atrophic skin and loss of hair follicles. **C.** Dermatoscopy shows a pink spot with no follicular openings, compatible with pseudoatrophic NF.

nerves. They are mainly located on the trunk and increase with age.

Typical superficial cutaneous NFs (including flat, pedunculated, and sessile globular NFs)[1] are the most common NF and may appear as early as 8 years of age and increase with age, especially at puberty and pregnancy[3]. They present as globular or pedunculated skin-colored tumors, elastic in consistency, soft, sessile, or pedunculated, and depressible on palpation. They are usually asymptomatic but may itch when they grow rapidly. On ultrasound, they appear as irregular or triangular nodules in the dermis, hypoechoic, without vascularization[1].

Other less frequent special subtypes of superficial cutaneous NF are:

- Pseudo-atrophic cutaneous NF: it presents as a depressed, thin, soft, pink, or hypopigmented plaque, usually appearing on the trunk (Figure 2)[3,14,15]. On ultrasound, it appears as a scattered, poorly defined, iso- or hypoechoic lesion located in the dermis or at the dermo-hypodermal level, which generates posterior shadowing and presents vascularization[1]. Histologically, they may show decreased collagen in the reticular dermis and increased perivascular neural tissue[16].
- Bluish-red macules or bluish-red NF (Figure 3) are small somewhat depressed bluish-red macules predominantly on the chest and back.[3,14] On ultrasound, they appear as dermal or dermo-hypodermal oval lesions, with irregular borders, hypoechoic but with hyperechoic dots inside, without vascularization[1].

Both types of NFs appear to have a similar chronology to typical superficial cutaneous NFs, being detected mainly in adolescence[15].

Another group of superficial NFs is subcutaneous NFs, which can be nodular or diffuse. Our patient had nodular subcutaneous NF (Figure 4) on the wrist, scalp, and supraciliary area. These are characterized by their firm consistency and a cord-like pattern as they follow peripheral nerves, and therefore may simulate adenopathy[3,16]. In these cases, ultrasound is useful as they typically present as well-defined, homogeneous iso- or hyperechoic subcutaneous nodules. Diffuse superficial subcutaneous NFs present as diffuse palpable plaques of elastic consistency that may or may not present with hypertrichosis and/or hyperpigmentation[1,3].

Five percent of superficial NF can present since birth in a very subtle form, appearing as congenital

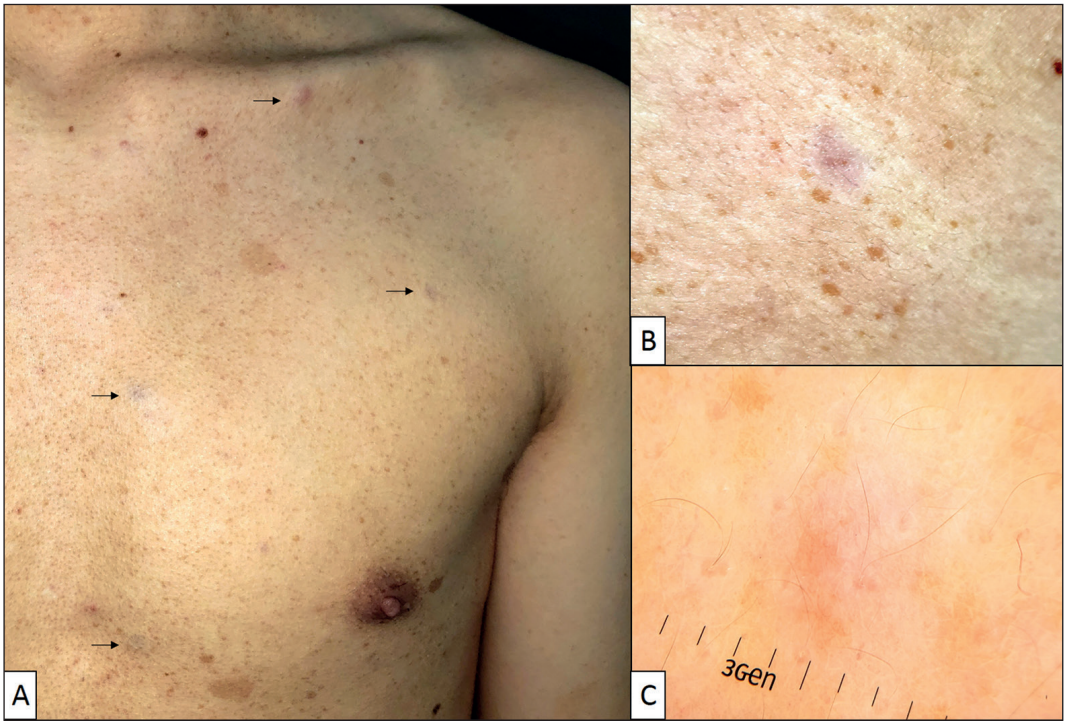

Figure 3. A. Multiple 5-mm red-violet, depressed macules (arrows). **B.** Depressed bluish-red macule with atrophic skin. **C.** Pink macula without loss of adnexa, compatible with bluish-red NF.

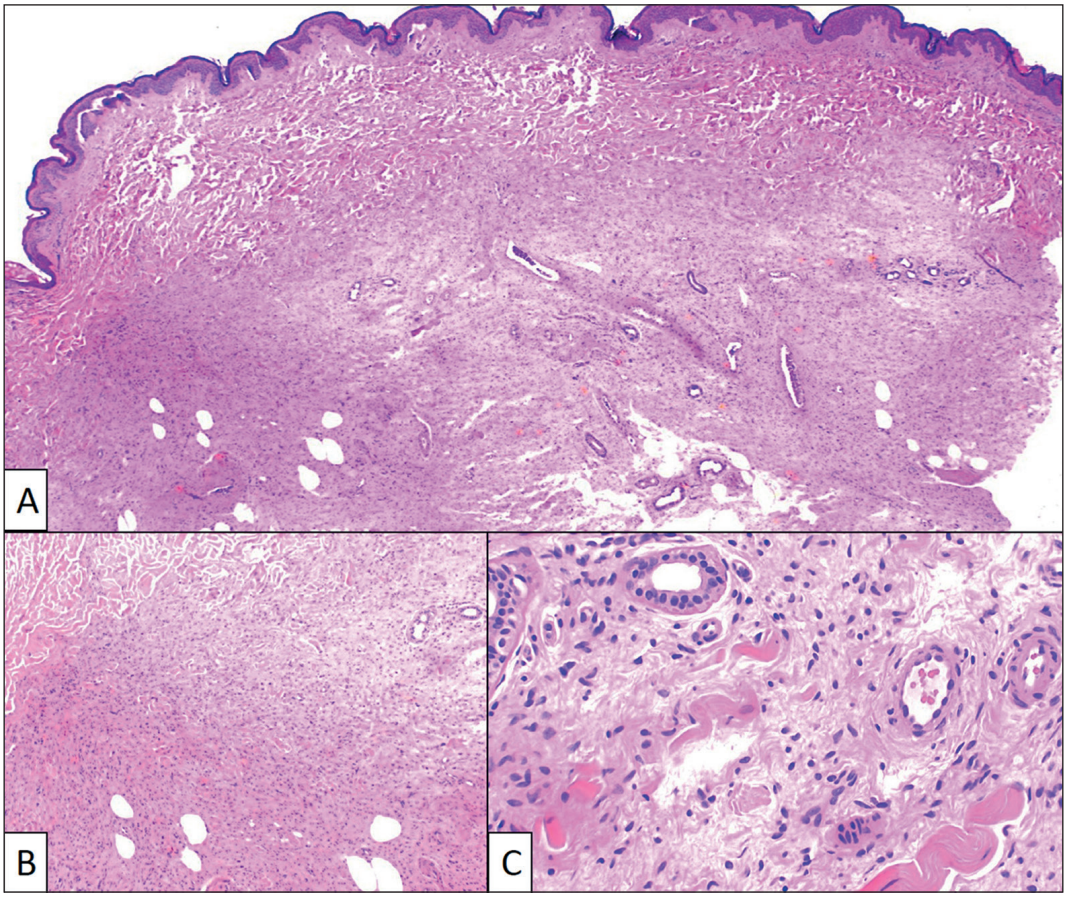

Figure 4. Biopsy of atrophic plaque in the thigh. **A.** Skin with preserved epidermis. Deep reticular dermis and hypodermis with fusocellular, hypocellular proliferation. (H-E; 2x); **B.** Partially defined border with overlying dermis. The entrapment of collagen bundles and annexes (4x H-E). **C.** Cells with elongated, wavy nuclei, without atypia, in lax myxoid stroma, with some mast cells, consistent with neurofibroma. (20x;H-E)

Table 2. Clinic and sonographic classification of congenital neurofibromas in Type I. Neurofibromatosis. Adapted from García-Martínez et al[1] and Hernández-Martín et al[3].

Congenital Neurofibromas
Congenital Cutaneous Neurofibroma
Congenital Plexiform Neurofibroma
Congenital diffuse and plexiform Neurofibroma

hyperpigmentation or hypertrichosis[3]. Early detection is essential for the pediatrician since its recognition would allow early diagnosis of NF1 (table 2). Superficial congenital NF presents as atypical or giant *café-au-lait* spots, with irregular or scalloped edges (coast of Maine) or as a tuft of hairs. They eventually become palpable and may feel like an elastic "bag of worms" with subcutaneous nodules, with or without hypertrichosis and/or hyperpigmentation[3,17].

The histologic nature (cutaneous, diffuse, or plexiform) of these congenital NFs cannot be demonstrated until the nerve fascicles proliferate. A biopsy of these congenital lesions at different ages showed that superficial congenital NFs present histological features of diffuse NF if the biopsy is performed before the age of 2 years or in macular areas, but that at older ages or if the sample is collected from a palpable area, it is likely to detect features of plexiform NF, whose diagnosis is histopathological and constitutes a diagnostic criterion for NF1[18].

The main differential diagnoses of superficial congenital NF are smooth muscle hamartoma, extensive *café-au-lait* spots, Becker's nevus, and congenital nevi[3]. In these cases, high-resolution ultrasound may help since superficial congenital NFs present as poorly defined masses that border the superficial dermis (Grenz zone), have irregular edges with projections, and heterogeneous echogenicity with hypo- or hyperechoic areas and hyperechoic dots, associated with nerve branches.[1] In addition, the presence of a honeycomb pattern on ultrasound, where hypoechoic tracts of neurofibromatous tissue are mixed with hyperechoic stromal bands, could suggest the histopathologic diagnosis of a plexiform NF[1].

Deep NFs (internal or visceral) are those that are not evident clinically but only by imaging. They are tumors that originate in peripheral nerves or nerve trunks, hence their name intraneural. It is estimated that 10% of children with NF-1 present deep NF. Some authors have described an increased risk of deep NF in NF-1 patients with two or more subcutaneous NFs[19]. They are usually congenital but take time to grow and become symptomatic, so their diagnosis is delayed. They usually grow in adolescence, are larger in women[3], can have nodular or diffuse morphology, and occur in any location[17,19]. Deep NFs are an important cause of morbidity, generating pain, compression, and/or disfigurement.

There are two subtypes of NF-1 characterized by deep NFs: spinal neurofibroma with bilateral deep NFs in spinal roots with or without other signs of NF-1 and orbital neurofibroma where a deep NF occupies the entire ocular orbit, invades orbital muscles, generates exophthalmos, temporal deformity, sphenoid dysplasia, and temporal lobe herniation[3].

Deep internal NF evaluated with ultrasound present at subfascial level as a lobular, poorly defined mass of homogeneous hypoechogenic consistency[1]. Deep NFs, especially those with plexiform histology, have a high risk of malignancy described between 8-13%[17,20], which occurs in adulthood during the third to the fourth decade, being the main cause of death from the disease, with a 5-year survival rate between 20-50%[20]. Some symptoms and signs suggestive of malignancy are constant pain, induration, and rapid growth, especially in adults since in children and adolescents plexiform NFs can grow[20].

Regarding histopathological characteristics, NFs are benign, well-demarcated, unencapsulated, dermal, or subcutaneous tumors composed of spindle-shaped Schwann cells with scant clear cytoplasm, a characteristic wavy nucleus, and a fibrillary, collagenous, and/or myxoid matrix. Inflammatory cells, especially mast cells, may also be present (Figure 5)[22]. Also, NF-1 lesions are highly vascularized[22,23].

Diffuse NF is characterized as neurofibroma tissue but with an infiltrative growth pattern, a more collagenous stroma, and Meissner's corpuscles differentiation. Plexiform NF is a mass of nerve fibers in a tortuous "bag of worms" arrangement within a matrix of fibroblasts and Schwann cells. They present a diffuse growth that replaces a nerve, usually involving multiple nerve fascicles[22].

Plexiform NF can be suspected by imaging and is usually seen as a complex mass generated by a network of thickened nerves. A complete imaging study in adult patients with NF1 showed that 50% of them have plexiform NFs[21]. Plexiform NFs present the highest risk of complications such as spinal cord compression, airway obstruction, orbital changes, and malignant transformation.

Malignant peripheral nerve sheath tumor, formerly called neurofibrosarcoma, is the main malignant tumor in patients with NF1. It originates from previous NFs, especially deep and plexiform ones. Warning signs of development of this neoplasm are rapid growth of a pre-existing plexiform NF, change to a hard consistency of an NF, or sudden and cons-

tant local pain. Ultrasound, MRI, and PET-CT scans could differentiate a malignant peripheral nerve sheath tumor from an NF. On ultrasound, these are characterized by presenting as heterogeneous hyperechoic masses with a pseudocapsule and anarchic vascularization[1]. Regarding histopathological characteristics, it presents as a pleomorphic spindle cell tumor, with significant nuclear atypia, high mitotic index, and areas of necrosis, which can develop within an NF. Characteristically, they lose the S100 and SOX 10 expression, characteristic of NFs[22].

The management of NFs is clinical observation but mainly surgical. In complex plexiform NFs, new treatment studies have begun with biological therapy, mainly with MEK inhibitors, but mTOR inhibitors and receptor tyrosine kinase, among others, have also been tested, with good response[24]. In the case of malignant peripheral nerve sheath tumor, the treatment of choice is surgery. When surgery is not possible, chemotherapy offers less than 20% survival at 5 years[25].

In conclusion, NFs are the most common tumors in patients with NF-1, have multiple forms of presentation, constitute 2 of the 7 diagnostic criteria for NF-1, and can present since birth. Our case illustrates the diversity of clinical presentation of NF in the context of NF-1, to contribute to early recognition by pediatricians, neurologists, and dermatologists.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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