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CLINICAL CASE

Pigmented neurofibroma with hypertrichosis

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Abstract

Background: *Pigmented (or melanocytic) neurofibroma (PN) constitutes only 1% of cases and is considered a rare variant of neurofibroma containing melanin-producing cells. In addition, the association of PN with hypertrichosis is infrequent.* **Case report:** *We describe the case of an 8-year-old male with a neurofibromatosis type 1 (NF1) diagnosis, who presented a light brown hyperpigmented plaque, smooth and well-demarcated, and hypertrichosis on the left thigh. The skin biopsy showed characteristics of neurofibroma; however, in the deep portion of the lesion, melanin deposits positive for S100, Melan-A, and HMB45 were observed, thus establishing the diagnosis of pigmented neurofibroma.* **Conclusions:** *Although PN is a rare subtype of neurofibroma, it is considered a chronically progressive benign tumor containing melanin-producing cells. These lesions can appear alone or in association with neurofibromatosis. Since this is a tumor that can be confused with other skin lesions, biopsy analysis is essential to differentiate it from other pigmented skin tumors, such as melanocytic schwannoma, dermatofibrosarcoma protuberans, neurocristic hamartoma, or neuronevus. Surveillance is part of the treatment, and surgical resection is sometimes performed.*

Keywords: *Neurofibroma. Pigmented neurofibroma. Melanotic neurofibroma. Hypertrichosis. Latino. Case report.*

Neurofibroma pigmentado con hipertricosis

Resumen

Introducción: *El neurofibroma pigmentado (NP) o melanocítico constituye solamente el 1% de los casos y se considera como una variante rara del neurofibroma que contiene células productoras de melanina. Además, la asociación de NP con hipertricosis es muy rara.* **Caso clínico:** *Se describe el caso de un paciente de sexo masculino de 8 años 2 meses de edad con diagnóstico de neurofibromatosis tipo 1 (NF1), quien presentaba en la cara anterior del muslo izquierdo una placa hiperpigmentada de color café claro, bien delimitada y de consistencia suave, e hipertricosis. La biopsia de piel presentó cambios característicos de neurofibroma; sin embargo, en la porción profunda de la lesión se observaron depósitos de melanina positivos para S100, Melan-A y HMB45, con lo que se estableció el diagnóstico de neurofibroma pigmentado.* **Conclusiones:** *Aunque el NP es un subtipo raro del neurofibroma, se considera que es un tumor benigno de evolución crónica de células productoras de melanina. Estas lesiones aparecen en solitario o asociadas con neurofibromatosis. Dado que es un tumor que puede confundirse con otras lesiones cutáneas, es fundamental el análisis de la*

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biopsia para diferenciarlo de otros tumores cutáneos pigmentados, como el schwanoma melanocítico, dermatofibrosarcoma protuberans, hamartoma neurocrístico o neuronevus. La vigilancia es parte del tratamiento y, en ocasiones, se lleva a cabo la resección quirúrgica.

Palabras clave: *Neurofibroma. Neurofibroma pigmentado. Neurofibroma melanocítico. Hipertricosis. Latino. Reporte de caso.*

Introduction

Neurofibromas are benign peripheral nerve sheath tumors[1]. Pigmented neurofibroma (PN), also called melanocytic neurofibroma, is a rare subtype of neurofibroma that contains melanin-producing cells and constitutes only 1% of neurofibroma cases[2]. As other pigmented tumors share the same neuroectodermal origin, the clinical and pathologic diagnosis of these tumors is challenging. The occurrence of hypertrichosis in neurofibromas (including PN) is very rare[3]. Here, we present the case of PN associated with hypertrichosis in a schoolchild.

Clinical case

We describe the case of an 8-year-2-month-old male patient, native and resident of Oaxaca, Mexico, the only child of non-consanguineous parents. Family history: a father with NF1, normal perinatal data, uncomplicated pregnancy. Birth weight was 3130 g, height 49 cm, and head circumference 35 cm. Currently, the patient presents complete neurodevelopment for his age.

The patient has congenital pseudarthrosis of the left tibia and fibula, requiring osteotomy of the left tibia. In addition, he has right multicystic renal dysplasia, hydronephrosis, secondary arterial hypertension, and neurogenic bladder. Since the patient is a carrier of NF1, he is under multidisciplinary medical follow-up in a tertiary hospital in Mexico City.

At one year of age, his current condition began when he presented a localized dermatosis on the left lower extremity affecting the anterior aspect of the thigh and ipsilateral knee, consisting of a light brown hyperpigmented spot, well-demarcated and smooth in consistency. The lesion was asymptomatic, with slow and progressive growth after the patient's development. An increase in the volume of the area and the appearance of hair follicles (data compatible with hypertrichosis) on the spot's surface were observed at the age of 3 years (Figure 1). Due to the progression of the lesion (increase in volume, number, and diameter of hair follicles), we decided to perform a skin biopsy.

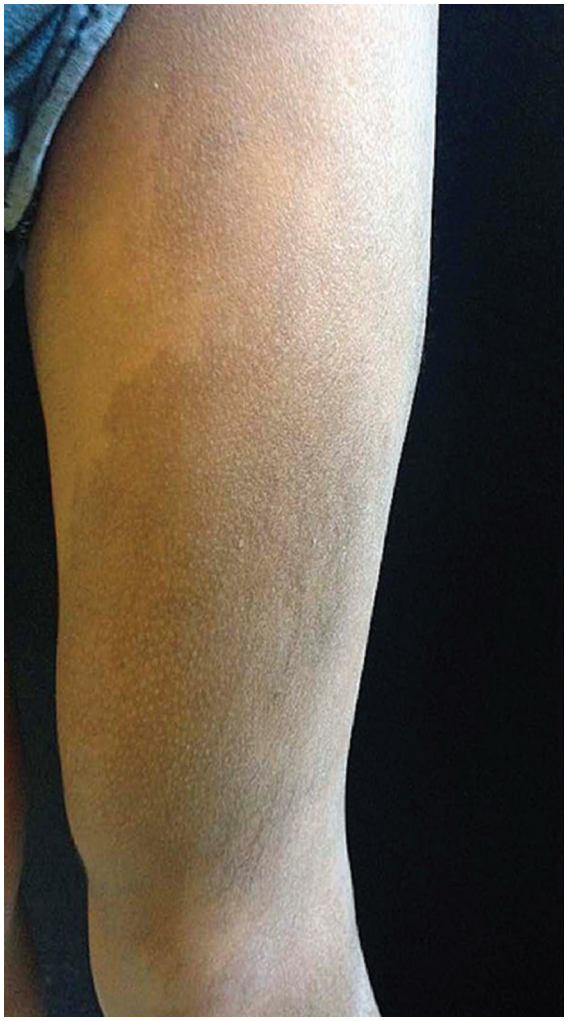

Figure 1. Neoformation with the appearance of a light brown hyperpigmented plaque and well demarcated with hypertrichosis (16 × 9 cm).

Skin biopsy showed an epidermis with stratum corneum in a basket network and flattening of the interpapillary processes. The superficial to mid-reticular dermis showed a proliferation of spindle cells with "italic" S-shaped nuclei intermingled with mast cells and concentrically arranged in a myxoid stroma (Figure 2). In the deep portion of the lesion, melanin deposits were found interspersed between the spindle cells, which stood out with the Fontana-Masson stain (Figure 3A).

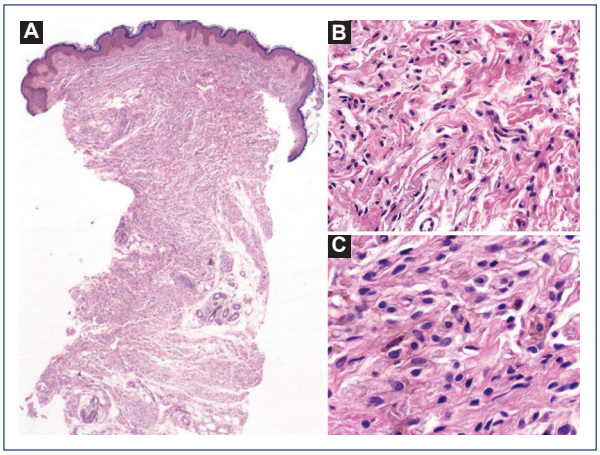

Figure 2. A: skin biopsy showing a diffuse spindle cell proliferation affecting the superficial, middle, and deep dermis, as well as adipose tissue. **B:** superficial portion of the lesion showing spindle cells with "italic" S-shaped nuclei intermixed with mast cells and arranged in a whirling pattern in a lax stroma. **C:** in the deep portion, more bulky ovoid cells with brown pigment deposits in their cytoplasm are identified.

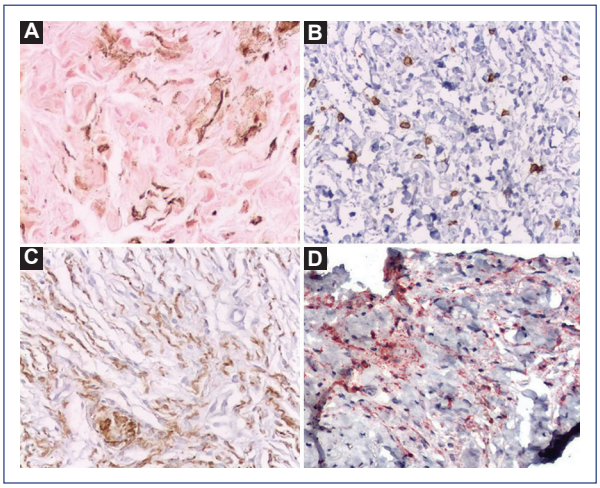

Figure 3. A: Fontana Masson stain positive for melanin in the cytoplasm of ovoid cells in deep dermis and in macrophages. **B:** CD117 labeling for plasma cells, which intercalate between the dendritic cells of the neurofibroma. **C:** S100 protein positive (brown) in Schwann cells of neurofibroma. **D:** Melan-A (in red) positive in melanin-producing spindle cells.

Immunohistochemistry showed CD117-positive mast cells (Figure 3B) and S100-positive spindle cells (Figure 3C). Immunohistochemical markers Melan-A and HMB45 showed some interspersed melanocytes, mainly in the deep portions of the lesion (Figure 3D). Intercalated structures were observed between spindle cells with immunolabeling for neurofilaments (Figure 4). On this basis, the anatomopathological diagnosis of PN was established. The patient continued with his multidisciplinary medical follow-up. Regarding the management of PN, it was decided to monitor the lesion every six months.

Discussion

PN is a cutaneous tumor that affects more females and predominates during the second and third decades of life, although some reports show an age range of 2 to 71 years[3,4]. These tumors can occur in isolation or be associated with NF1.

PN has been described more frequently in dark-skinned populations: in two series, 86% of patients were from Africa, Asia, or Latin America[3,5,6]. The most frequent topography of this pathology is the scalp[3,5]; other locations are the neck, hands, buttocks, thighs, and legs[6]. Morphologically, the lesions are tumors with no visible pigment in most cases. Occasionally, the lesions are accompanied by hyperpigmented spots with shades ranging from gray to brown and different pigment intensities. In a case series, Fetsch et al. observed that only 16% of the tumors investigated showed macroscopically detectable areas of pigmentation. The lesions had a rubbery consistency with poorly defined borders[2]. Moreover, a size range from 1 to 50 cm in diameter has been described[7]; some tumors appear as a single lesion, although two lesions have been identified in the same patient[6].

Furthermore, an association between hypertrichosis and neurofibroma is rare, especially in PN[2,3,8]. This lesion's mechanism for excessive hair growth has not been well established. Some authors consider that localized hypertrichosis may occur due to abnormal signals for follicular papilla elongation, including growth factors (epidermal bone growth factor, vascular endothelial growth factor, platelet-derived growth factor, and bone morphogenic protein) and a prolonged anagen phase of the hair cycle[3]. Other authors have established the possibility that localized acquired hypertrichosis may occur in areas of friction, trauma, or inflammation, suggesting that local factors may influence these growth mediators and determine the increase in the anagen phase[3].

Only five cases of PN associated with hypertrichosis have been published[2,3,8]. These tumors are usually accompanied by hyperpigmented spots with hypertrichosis on their surface and are lesions > 10 cm. In addition, the lesions appear early in life and progress gradually. Finally,

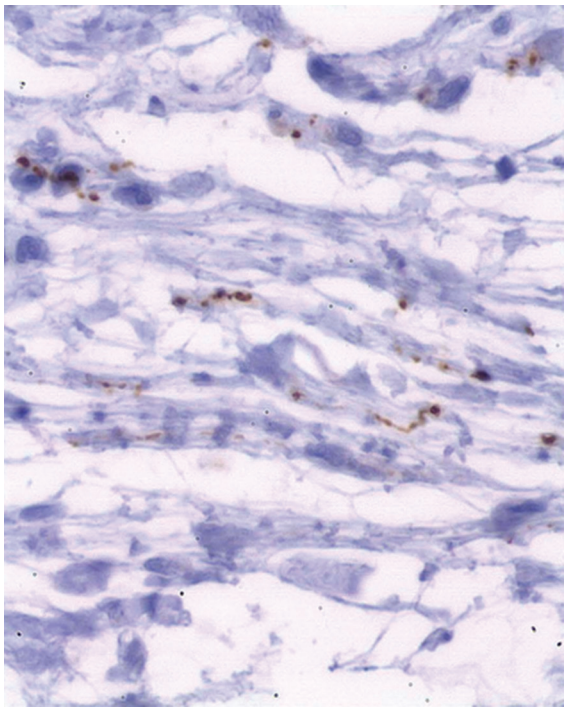

Figure 4. Positive immunolabeling for neurofilaments (in brown) characteristic of neurofibroma. The presence of these structures is essential for differential diagnosis with other pigmented neural tumors.

most PNs are part of the clinical spectrum of NF1, with neither sex nor age group predominance.

PN is an exophytic neoformation involving the dermis and subcutaneous cellular tissue, composed of fascicles of spindle or epithelioid cells distributed throughout the tumor, immersed in a stroma with collagen and matrix. Microscopically, PNs present the features of neurofibromas. Most cases show features of diffuse neurofibroma; others resemble the plexiform type, and in other cases, characteristics of both[4,6]. Occasionally, the spindle cells may be arranged in a storiform pattern[7]. Most lesions may contain abnormal nerve segments with disorganized Schwann cells and Wagner-Meissner corpuscles[6]. Other findings include increased mast cells and the occasional presence of randomly distributed multinucleated giant cells in the stroma[6].

PN is the only subtype of neurofibroma that contains melanin-producing cells that tend to be located in the deep dermis and subcutaneous cellular tissue; according to Motoi et al., this pattern may be a valuable tool to differentiate PN from other pigmented lesions[5]. The presence of melanin-producing cells may be due to the origin of melanocytes and Schwann cells, which is from neural crest cells[5,9]. To date, it has been debated whether the pigmented cells in this tumor are displaced melanocytes or Schwann cells with aberrant melanogenesis[6]. Detecting microphthalmia transcription factor (MITF) in the nuclei of PN tumor cells further supports the phenotypic relationship between melanocytes and melanin-producing Schwann cells, as this transcription factor is essential for melanocyte development and survival[10,11].

Melanin within phagocytes can be identified in different areas of the dermis and subcutaneous cellular tissue when stained with Fontana-Masson and Warthin Starry[12]. On immunolabeling, the tumor expresses S100 protein and melanin markers[4-6]: Melan-A, MITF (critical regulatory factor of melanogenesis), and HMB45. At times, these tumors are positive for tyrosinase and C-Met (involved in regulating melanogenesis)[5]. The characteristic immunohistochemistry of PN suggests that it is a single tumor showing differentiation towards mature melanin production (with mature melanocytes) but with apparently impaired synthesis capacity[5,6].

Fetsch et al. proposed some pathological diagnostic criteria for PN in their review: 1) mild histologic appearance to diffuse neurofibroma or a neurofibroma with combined histologic features of plexiform and diffuse; 2) immunolabeling to S-100 protein, HMB-45 antigen, and CD34[2,6].

PN can be confused with pigmented and hypertrophic tumors or masses. The primary differential diagnoses of this tumor are melanocytic schwannoma[13], pigmented dermatofibrosarcoma protuberans (Bednar's tumor)[14,15], cellular blue nevus[16,17], giant congenital melanocytic nevus with neuroid features[18,19], and cutaneous neurocristic hamartoma[20-23] (Table 1). To prevent doubts during diagnosis due to the clinical expression of PN, it is always advisable to take a biopsy of the lesion, whose anatomopathological characteristics may define the final diagnosis.

No standardized treatment for PN has been established. In some situations, partial resection of the tumor is necessary due to extra weight, limitations in daily activities, and cosmetic improvement. Surveillance is suggested, as some cases of PN present recurrence. No malignant transformation has been shown in any of these tumors, and follow-up data are insufficient to comment specifically on this issue[4,7]. Finally, there is no treatment to prevent the appearance of PN.

Most of the time, PN appears in individuals with a confirmed diagnosis of neurofibromatosis; therefore, patients already have a multidisciplinary medical follow-up of their genodermatosis and only need clinical observation of the PN. Surveillance or surgical management will be chosen depending on the tumor's evolution. When a PN appears spontaneously, other cutaneous

Table 1. Differential diagnoses to be considered in pigmented neurofibroma

Characteristics	Pigmented neurofibroma	Melanocytic schwannoma[13]	Dermatofibrosarcoma protuberans pigmentosum (Bednar's Tumor)[14,15]	Blue cellular nevus[16,17]	Cutaneous neurocristic hamartoma[18,19]	Giant congenital melanocytic nevus with neuroid features[20-23]
Origin	Peripheral nerve sheath: neuro-mesenchymal tissue; perineural, Schwann and melanin-producing cells	Peripheral nerve sheath consisting of Schwann cells	Fibrohistiocytic with dendritic cells	Dendritic melanocytic	Neuro-mesenchyme with fibrogenic, melanogenic and neurosustentacular differentiation	Melanoblasts: nevus cells and Shwann cells
Location	Hairy skin, neck and lower extremities	Axial region, nerve roots of the spinal cord, central and autonomic nervous system	Trunk, inguinal region and lower extremities	Buttocks in sacrococcygeal region, hairy skin, face and extremities	Head (in hairy skin) and trunk (thorax and back)	Trunk in bathing suit area and extremities.
Clinical manifestations	Hyperpigmented, poorly defined tumors of rubbery consistency	Solid mass with well-demarcated brown and/or black borders	Multinodular pigmented tumor firm to touch/Sclerotic or atrophic plaque	Dark blue neoformation with smooth dome-shaped surface	Focal alopecia Solitary neoformation of nodular appearance	Brown plaque with flat or mammillary surface, well-demarcated borders, hypertrichosis
Accompanying symptoms	Asymptomatic	Radicular pain, dysesthesias and progressive sensory-motor involvement.	Asymptomatic	Small painless lesions, large ones painful and ulcerating	Asymptomatic	Asymptomatic occasional pruritus
Cell phenotype	Spindle or epithelioid cells	Elongated cells some with epideloid appearance	Mesenchymal spindle cells	Pigmented dendritic melanocytes mixed with epitheloid cells	Nevomelanocytes, schwann cells, pigmented dendritic cells, spindle cells and fibroblasts	Neuroid and Schwan elements
Other histological data	Wagner-Meissner bodies, Schwann cells and mast cells	Psammoma bodies (40-50%) Laminated calcifications Mature adipocytes	Pigmented dendritic cells Verocay bodies	Cell islets may form digitate projections or bulbous expansion (dumbbell pattern)	Tactoid bodies Decrease in hair follicles	Elongated or thin melanocytes (type C) with fibrillar collagen structures resembling Meissner's corpuscles or Verocay's bodies
S-100	Positive	Positive	Negative	Positive	Positive	Positive
HMB45 and/or Melan-A	Positive	Positive	Negative	Positive	Positive	Positive
Other immunomarkers	MIFT, CD34	Vimentin, Leu7	CD34+, SMA, CD117, vimentin	SOX10, MART-1	CD34 and NSE	
Associations	Neurofibromatosis 1	Carney complex Recurrence, malignancy (10%) and metastasis capacity	Intermediate malignancy, high risk of recurrence		Possible transformation to malignant melanoma	Spina bifida, neurocutaneous melanosis and potential for malignant transformation

signs of NF1 (more than six café-au-lait spots, axillary or inguinal ephelides, and more neurofibromas)[24] should be sought. Patients should be referred to ophthalmology, neurology, orthopedics, cardiology, gastroenterology specialties, and genetics to determine whether their tumor is associated with NF1 or is found in isolation (solitary PN); this latter presentation is significantly rarer.

Currently, no preventive treatment is available to prevent the formation of these lesions; however, documenting them early on favors their close surveillance and timely therapeutic decision.

PN is a rare subtype of neurofibroma considered a benign tumor of unknown origin and chronic evolution that presents melanin-producing cells. Clinically, most patients show tumors without visible pigment, but some have hyperpigmentation, hypertrichosis, or both. These lesions appear solitary or associated with NF1. Histologically, their type is diffuse, although some have features of both types (diffuse and plexiform) and are accompanied by melanin-producing cells. As this tumor can be confused with other skin lesions, it is essential to take a biopsy. The histological, ultrastructural, and immunohistochemical findings will allow skin lesion diagnosis and differentiation from other pigmented skin tumors. In case of a new lesion, a multidisciplinary evaluation (Ophthalmology, Neurology, Genetics) should exclude neurofibromatosis. It is necessary to provide genetic counseling to the family upon genodermatosis confirmation. Treatment of PN consists of surveillance and, occasionally, surgical resection.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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