Cutaneous neurofibromas

Current clinical and pathologic issues

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Abstract

Objective
To present the current terminology and natural history of neurofibromatosis 1 (NF1) cutaneous neurofibromas (cNF).

Methods
NF1 experts from various research and clinical backgrounds reviewed the terms currently in use for cNF as well as the clinical, histlogic, and radiographic features of these tumors using published and unpublished data.

Results
Neurofibromas develop within nerves, soft tissue, and skin. The primary distinction between cNF and other neurofibromas is that cNF are limited to the skin whereas other neurofibromas may involve the skin, but are not limited to the skin. There are important cellular, molecular, histologic, and clinical features of cNF. Each of these factors is discussed in consideration of a clinicopathologic framework for cNF.

Conclusion
The development of effective therapies for cNF requires formulation of diagnostic criteria that encompass the clinical and histologic features of these tumors. However, there are several areas of overlap between cNF and other neurofibromas that make distinctions between cutaneous and other neurofibromas more difficult, requiring careful deliberation with input across the multiple disciplines that encounter these tumors and ultimately, prospective validation. The ultimate goal of this work is to facilitate accurate diagnosis and meaningful therapeutics for cNF.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by The Neurofibromatosis Therapeutic Acceleration Program at Johns Hopkins.

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Glossary

cNF = cutaneous neurofibromas; NF1 = neurofibromatosis type 1; NOS = not otherwise specified; OCT = optical coherence tomography; pNF = plexiform neurofibromas; QoL = quality of life; US = ultrasound.

There are many clinical features associated with the neurogenetic condition neurofibromatosis type 1 (NF1). However, the feature that affects the majority of NF1 patients is the development of cutaneous neurofibromas (cNF).\(^1\) Neurofibromas are defined as histologically benign (WHO grade I) tumors composed of multiple cell types including Schwann cells, fibroblasts, immune cells (such as mast cells and macrophages), and other elements of nerve.\(^2\) Regardless of their location, all neurofibromas share certain histologic and cellular characteristics.

The most common and prominent location of neurofibromas is the skin (skin is defined in this article as including epidermis and dermis). Discrete lesions are often referred to as dermal or cutaneous neurofibromas. cNF are benign and, unlike plexiform neurofibromas (pNF), are not known to have any malignant potential.\(^3\)

Although not life-threatening, cNF have a major effect upon quality of life (QoL) for most patients with NF1 due to their prevalence and disfigurement.\(^4\)\(^-\)\(^12\) Furthermore, the number of cNF increases with age after adolescence and throughout a patient’s lifespan. Despite the high prevalence of cNF in people with NF1 and their documented influence on QoL, current treatment is limited to surgical removal or physical destruction.

There have been several efforts to define the various forms of neurofibromas, resulting in a number of classification systems proposed by neurologists, clinical geneticists, dermatologists, pathologists, and basic researchers (table 1).\(^3\)\(^,\)\(^13\)\(^-\)\(^16\) Some of these schemes are incompatible with one another, which may impede, rather than enhance, the transfer of knowledge from basic and translational science to clinical care. An agreed-upon classification system would facilitate research addressing critical questions such as the comparisons between human disease and Nf1 mouse models of cNF, whether there are specific responses to treatments based on potential subtypes of cNF, or if cNF might respond similarly or differently to therapies than other neurofibromas (potentially allowing cNF to serve as a surrogate for pNF). This article reviews the terms in current use for cNF and outlines the critical factors contributing to the definition of cNF, with the ultimate goal of creating a draft framework for a classification system to be validated in future prospective studies.

Methods

This work is the result of 2 multidisciplinary meetings, one sponsored by the Neurofibromatosis Therapeutics Acceleration Program in 2016, and another by The European Neurofibromatosis Group in 2008. Across these 2 meetings, international experts from within and outside the NF field (with expertise in dermatology, genetics, neurology, neuro-oncology, dermatopathology, neuropathology, regenerative medicine, and plastic surgery) reviewed different aspects of cNF, including clinical features, biology, effects on QoL, and existing proposed classification schemes of neurofibromas (table 1).

A literature search using the terms NF1, cNF, plexiform neurofibroma, dermal neurofibroma, classification, pain, itching, and QoL was completed. Although cNF may be sporadic in some instances, this review is focused on the cNF arising in the context of NF1. The investigators met to review these areas, including critical elements of each proposed classification system, with the intent of using this information as a framework for the longer-term goal of developing a single unified, data-driven classification system for cNF incorporating core features of cNF including pattern of growth (localized or diffuse) and anatomical location (skin, subcutaneous tissue, or deep nerve).

Results

Cutaneous neurofibromas: Clinical definitions or descriptors

This article is focused on cNF, which are benign and arise in and are limited to the skin. They are localized but not encapsulated and do not show clear association to myelinated nerves. They present clinically as a well-defined cutaneous lesion, most often as a nodule or plaque.\(^1\) cNF is the preferred term over dermal neurofibroma, as the term cNF distinguishes between discrete neurofibromas of the skin and neurofibromas that arise in deeper tissues but invade into the dermis. The term cNF does not encompass deep, large, or diffusely infiltrating tumors that involve the dermis.\(^5\) However, the skin may also be secondarily involved by extension of a deep or plexiform neurofibroma, either by involvement of cutaneous nerves (i.e., plexiform growth pattern) or by diffuse infiltration of the subcutaneous and cutaneous tissue (i.e., diffuse growth pattern). The importance of distinguishing true cNF from extension of deep neurofibromas into the skin is particularly important when atypical changes are present. The presence of cytologic atypia or proliferation in a cNF represents reactive or degenerative changes and is not worrisome, while similar changes in a plexiform neurofibroma that may involve the skin can be a manifestation of malignant transformation.\(^17\)

Natural history of cNF

cNF most commonly become clinically apparent after puberty.\(^3\) However, there is a wide range of clinical presentation
with select genotype–phenotype correlations. In the small subset of people with NF1 microdeletions, cNF are more likely to be apparent earlier in childhood. In contrast, in people with NF1 deletion in p.Met992del, or a missense mutation affecting p.Arg1809, there are few to no cNF throughout life. Additional details around the biology of genotype–phenotype correlations are discussed by Brosseau et al. in this series. In the majority of people with NF1, the number of cNF increases with age such that there are more tumors present in older patients. There are no known predictive factors to determine the eventual number or types of cNF that will appear on an individual with NF1 (other than the small subsets with specific types of mutation listed above). Furthermore, there is dramatic variability in cNF burden between patients, and even within families harboring the same NF1 mutation. Retrospective studies suggest that women experience an increase in the size and numbers of cNF during pregnancy. Finally, it has been suggested that people with NF1 have low serum vitamin D concentrations, especially those with many cNF. However, it is not clear if these factors are causative or correlative.

Table 1 Clinicopathologic classification of neurofibromas

<table>
<thead>
<tr>
<th>Proposed classification</th>
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<tr>
<td>Cutaneous neurofibromas</td>
<td>Jouhilahti et al.</td>
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<td>Subcutaneous neurofibromas</td>
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<td>Intraneural neurofibromas</td>
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<td>Plexiform neurofibromas</td>
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<td>Localized cutaneous neurofibromas</td>
<td>Carroll and Ratner</td>
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<td>Diffuse cutaneous neurofibromas</td>
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<td>Localized intraneural neurofibromas</td>
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<td>Plexiform neurofibromas</td>
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<td>Massive soft tissue</td>
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<td>Localized neurofibromas</td>
<td>Rosenberg</td>
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<td>Plexiform neurofibromas</td>
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<td>Diffuse neurofibromas</td>
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<td>Pigmented neurofibromas</td>
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<td>Dermal neurofibromas</td>
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<td>Nodular neurofibromas</td>
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<td>Plexiform neurofibromas</td>
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<td>Discrete cutaneous neurofibromas of the dermis and epidermis (endoneurial neurofibroma)</td>
<td>Friedman and Riccardi</td>
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<td>Discrete subcutaneous neurofibromas that lie deeper in the skin (perineurial neurofibroma)</td>
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<tr>
<td>Nodular plexiform neurofibromas (perineurial neurofibroma)</td>
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<td>Diffuse plexiform neurofibromas (epineurial neurofibroma)</td>
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<td>Cutaneous neurofibromas</td>
<td>Goldblum et al.</td>
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<td>Subcutaneous neurofibromas</td>
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<td>Diffuse neurofibromas</td>
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<td>Localized cutaneous neurofibromas</td>
<td>Stemmer-Rachamimov, Wolkenstein, and Ortonne (unpublished, 2008)</td>
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<td>Localized subcutaneous neurofibromas</td>
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<td>Diffuse cutaneous and subcutaneous neurofibromas</td>
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<td>Localized intraneural neurofibromas</td>
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Clinical features and effect on QoL
Patients and clinicians report multiple different appearances of cNF, ranging from barely visible flat nodules with subtle discoloration to large and pedunculated masses (figure 1). It remains unknown if this variability in appearance is an expression of the various stages of the evolution of a single tumor, or represents different subtypes of cNF. One proposed classification system assigns 1 of 5 subcategories to describe the clinical appearance of cNF:28 nascent, flat, sessile, globular, or pedunculated (figure 2). The nascent/latent cNF (figure 2A) is not apparent by inspection or palpation of the skin, but can be appreciated by proper imaging techniques, such as high-resolution ultrasound (US) and optical coherence tomography (OCT) imaging, which are discussed by Cannon et al.29 in this series. The flat cNF (figure 2B) is visible at the skin surface, and is distinguished primarily by its slightly raised surface. The surface may appear thinner and somewhat pale compared to adjacent uninvolved skin, or there may be some increased pigmentation and peripheral coarse hairs (bristles). Flat cNF tend to range in size from 0.5 to 12 millimeters. The sessile cNF (figure 2C) is raised compared to the adjacent skin and there is usually an apparent apex. The height of the apex may be as high as 8–10 mm. The surface and texture are essentially the same as that of the flat lesion. There may be erythema or hyperpigmentation, as well as bristle hirsutism. These lesions typically have a maximal diameter of roughly 1.0 to 10–12 mm. Imaging (US or OCT) may reveal more extensive cNF elements below the surface of the skin. The globular cNF (figure 2D) has a base at the surface of the skin that may be 20–30 mm in diameter, with a comparable height and a globular shape. Moving the raised portion of globular neurofibromas (i.e., above the surrounding uninvolved skin surface) can help a clinical examiner...
to identify a deeper part of the lesion. The pedunculated cNF (figure 2E) has a stalk that joins the portions above and below the skin surface. The stalk is usually several millimeters long and 1–3 mm in diameter. The diameter of the superficial portion is usually between 5 and 25 millimeters.

Roughly 20% of people with NF1 report pruritus. Chronic pruritus can be an independent factor for altered QoL as it causes sleep disruption as well as the emotional experience of chronic pain. Among those with pruritus, 52.5% complained of pruritus localized to one or more cNF. The pathophysiology of pruritus in NF1 is not well-understood. It is hypothesized that mast cells and components released from their degranulation are a major cause of pruritus, as mast cells are well-known to be present in the cNF microenvironment and may contribute to tumor initiation, progression, and angiogenesis. However, it is also possible that pruritus is a manifestation of a neuropathy affecting the small nerve tributaries in the skin, which are integral to the development of these tumors. Indeed, anecdotally, people with NF1 report improvement in pruritus after therapy with antineuropathic agents such as gabapentin or mast cell stabilizing agents such as ketotifen, indicating that both mechanisms may be active.

Although cNF are not life-threatening, the majority of patients report cNF-associated disfigurement as their major problem related to NF1. Combined responses from several surveys show that between 97% and 100% of adults with NF1 who participated reported skin lesions and >60% reported moderate to severe visibility of these lesions. In all of these studies, the visibility of disease was independently associated with adverse emotional state, physical symptoms, and poor function assessed with skin-disease-specific QoL and general health measures. The effect of disfigurement on QoL has been evaluated through the use of dermatologic scales such as Skindex. Using this tool as well as measures of overall disease-associated QoL (i.e., Short Form–36), the burden of disfigurement on QoL in patients with NF1 has been highlighted across multiple studies.

Histology of cNF
Histologically, all neurofibromas are mixed tumors consisting of cells of diverse lineages. cNF are composed of neoplastic Schwann cells and non-neoplastic elements including mast cells and fibroblasts. There are also often other cells including nerve sheath elements (i.e., perineurial cells) and cells from various skin adnexae (e.g., hair follicles, eccrine sweat glands, sebaceous glands). On occasion, adipocytes may be seques
tered in or intrinsic to the lesion. Correspondingly, the use of traditional histologic stains, as well as immunohistochemistry with a variety of biomarkers and electron microscopy, has shown the involvement of S100+ Schwann cells, EMA+ perineurial cells, mast cells, lymphocytes, CD34+ fibroblasts, as well as skin disease-specific QoL...
as axonal elements\textsuperscript{41,42} (figures 3 and 4). Pigmented cNF may be associated with melanocytic cells (or the neoplastic Schwann cells that may become melanotic).\textsuperscript{43} Other notable features seen on occasion include the formation of Meissner-like corpuscles.\textsuperscript{44} It is presumed that the Schwann cells are neoplastic (\textit{NF1}\textsuperscript{−/−}) and that the other cells are either present initially or recruited into the lesion, but are not neoplastic (\textit{NF1}\textsuperscript{+/−}). However, the definitive cell of origin for human cNF has yet to be defined but has been postulated to be a progenitor cell called a skin-derived precursor cell. Preclinical models suggest that these cells are distinct from the cells that give rise to pNF.\textsuperscript{45} There are additional data indicating that multipotent neurofibroma-derived precursor cells, perhaps arising from stem cells around hair roots closely associated with cNF, are the causative cells.\textsuperscript{3} Together, these data suggest that cNF and other forms of neurofibromas may arise from different precursor cells even though they have similar cellular compositions.

The diverse cellular components of neurofibromas are embedded in an abundant collagenous and often myxoid extracellular matrix. Histologically, cNF cannot be differentiated from neurofibromas elsewhere in the body as the features and cell composition are present in the various forms of neurofibromas. Hence, to accurately identify a lesion as cNF, the surgical specimen must include a margin of uninvolved skin.

\textbf{Figure 4} Histopathologic features of cutaneous neurofibromas (cNF)

\textit{cNF in which various cell types are evidenced using immunostainings. (A, B) Hematoxylin & eosin at 25 and 200 magnification show a cNF presenting as a self-limiting tumor in the skin with no peripheral capsule and in which numerous spindle cells are seen. (C–G) Immunostainings developed with DAB with antibodies to CD117 (C, ×200), S100 protein (D ×25 and E ×100), and CD34 (F ×25 and G ×100). These stains demonstrate numerous mast cells showing strong membrane expression of CD117 (C), Schwann cells displaying heterogeneous cytoplasmic and nuclear expression of S100 protein (D, E), and CD34+ fibroblasts (F, G).}
Cutaneous neurofibromas as a subset of all neurofibromas: Plan to address the challenges in creating a modern classification system

In addition to classifications already published in articles or textbooks, other unpublished classification systems have been proposed. Two unpublished systems were presented at the European NF meeting (2008) by Ortonne et al. and Stemmer-Rachamimov et al., in which a comprehensive synthesis of clinical and pathologic features was attempted (table 1 and figure 5). These schemes propose defining neurofibromas by their clinical appearance and histologic features: growth pattern (diffuse/infiltrating or localized), relationship to nerve (intraneural or extraneural, without any perineurial capsule), and anatomic location (cutaneous, cutaneous/subcutaneous, deep). The resulting categories proposed were cutaneous NF (discrete) and larger NF involving skin and subcutaneous tissue (diffuse, with or without atypia) (table 2). This scheme for cNF (table 2 and figure 5) aims to differentiate classic cNF from deep neurofibromas that may involve skin and subcutaneous tissues. As above, it is important to appreciate that an underlying plexiform NF extending into the skin (plexiform intraneural, diffuse associated with plexiform) has different risk profiles than cNF purely limited to the skin. This histologic distinction cannot be made if the sample provided does not reveal the underlying plexiform lesion and shows only the extraneural diffusely infiltrating portion of the tumor in skin. In such instances, histologic distinction from a true cNF is impossible and the term NF involving skin and subcutaneous tissue; diffuse, not otherwise specified (NOS) is most appropriate. Although molecular information is lacking, there is an opportunity to apply common terminology to classify neurofibromas clinically and pathologically in a systematic fashion. Based on the current state of the field, a modern classification system for cNF will be built on the defined clinical and...
pathologic features (Table 2) with a plan to incorporate molecular and imaging data as they become available. An ongoing study is evaluating the accuracy of this system with a blinded review by dermatopathologists and neuropathologists. The long-term goal is to have an integrated molecular, clinical, and pathologic classification that best reflects the biology of cNF.

As a first step, the term cNF should be reserved for the discrete neurofibroma limited to the skin, which develop into and mainly involve the dermis, never show a plexiform architecture, and never transform into a malignant peripheral nerve sheath tumor. Further research is needed to determine if there are subtypes of cNF. The term diffuse neurofibroma is advisable for neurofibromas that involve the skin and subcutaneous tissues without clear margins. These tumors may have a diffuse, plexiform, or both patterns. Inherent in these terms is an ambiguity between neurofibromas that are clinically localized but have no perineural capsule and so could be histologically diffuse and those that are clinically more diffuse. In the case of partial biopsies or superficial excisions, one may miss a deeper plexiform organization or the involvement of a definable nerve trunk, and so the category for diffuse, NOS was introduced. It is important to note that the approach for resection and clinical description of the lesion is particularly important for these tumors. The term plexiform is applied to intraneural neurofibromas. These initial definitions will be applied to prospective validation studies across dermatopathologists and neuropathologists to formalize the pathologic definitions of cNF.

Discussion

cNF are common and a major clinical burden for people with NF1, prominently affecting QoL and emotional well-being as well as physical comfort. Currently, the only way of treating cNF is removal by procedural methods such as electrodesiccation, CO₂ laser, or surgery. Developing effective medical therapies for existing cNF and prevention of cNF are priorities for the majority of adults with NF1. Development of a reliable and widely accepted nosology based on clinical, genetic, and radiologic features of cNF is a crucial step in investigating these tumors to better understand their development and start to uncover opportunities for tumor-specific therapies that will allow reduction in the clinical symptoms and burdens of cNF for people with NF1. The work presented here creates a framework for prospective validation studies to more accurately define cNF. Ultimately, this will facilitate score diagnosis of these lesions and the efficient development of therapeutics.

Author contributions


Study funding

This publication was supported by an agreement from The Johns Hopkins University School of Medicine and the Neurofibromatosis Therapeutic Acceleration Program (NTAP). Its contents are solely the responsibilities of the authors and do not necessarily represent the official views of The Johns Hopkins University School of Medicine.

Disclosure

N. Ortonne reports no disclosures relevant to the manuscript. P. Wolkenstein receives fees from Pierre Fabre Dermatologie. J. Blakeley reports no disclosures relevant to the manuscript. B. Korf reports consulting fees from Novartis. S. Plotkin reports ownership in NFlection and consulting fees from Novartis. V. Riccardi, D. Miller, S. Huson, J. Peltonen, A. Rosenberg, S. Carroll, S. Verma, V. Mautner, M. Upadhyaya, and A. Stemmer-Rachamimov report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.
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Cutaneous neurofibromas: Current clinical and pathologic issues
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Neurology 2018;91;S5-S13
DOI 10.1212/WNL.0000000000005792

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