

SOLITARY NEUROFIBROMA FEATURING PROMINENT WAGNER-MEISSNER BODIES AND FLORET-LIKE MULTINUCLEATED GIANT CELLS: A CASE REPORT

Tihomir Dikov^{*}, Vesela Ivanova^{*}, Milen Karaivanov^{**}, Ivelina Yordanova^{***}

^{*}*Department of General and Clinical Pathology, Medical Faculty,
Medical University – Sofia, Bulgaria*

^{**}*Department of General and Clinical Pathology, Medical Faculty,
Medical University – Pleven, Bulgaria*

^{***}*Department of Experimental and Clinical Pharmacology, Dermatology and Venerology, Medical
Faculty, Medical University – Pleven, Bulgaria*

Corresponding author:

Vesela Ivanova, MD, PhD

Department of General and Clinical Pathology,

Medical University - Sofia

Zdrave Str. 2, 1431, Sofia, Bulgaria

e-mail: veselaivanovamd@gmail.com

ABSTRACT

Solitary neurofibromas can present as discrete localized masses - most commonly as a cutaneous neurofibroma, clearly unrelated to neurofibromatosis genetically-driven syndromes. Their cellular composition is known to be quite invariable but at times diagnostically challenging lesions occur.

A female patient, aged 63, presented with a solitary cutaneous lesion in her lower-back that reportedly was of 9 year duration, slow-growing, painless mass. Surgical excision with tumor-free borders was performed. On gross examination unremarkable skin was covering a well-delineated but unencapsulated, soft, pale gray-yellowish mass measuring max 4 cm, occupying the dermis and subcutaneous fat.

Histology revealed spindle-to-ovoid cells, embedded in a mixture of collagenised matrix (van Gieson positive) and moderate amount of mature fat tissue. Some of the cells displayed a marked degree of nuclear pleomorphism; unevenly dispersed were floret-like multinucleated giant cells. Careful examination failed in finding any mitotic figures. In addition, numerous eosinophilic rounded structures were present, single or in small clusters. These were composed of elongated cells stacked in a lamellar arrangement, similar to the tactile corpuscle-like Wagner-Meissner bodies. Immunophenotypic studies, employing S-100, CD34, GFAP, NSE, CD68, and Ki-67 revealed differential expression within cellular components.

Despite initial impression of highly-malignant and unusual lesion, complete diagnostic work-up and clinical correlation uncovered a simple, diffuse type of solitary neurofibroma. The presence of specialized tactile-receptor like structures and floret-like multinucleated giant cells is peculiar, but its emergence and significance are still enigmatic.

Key words: *solitary diffuse neurofibroma, Wagner-Meissner bodies, floret-like multinucleated giant cells, immunohistochemistry.*

INTRODUCTION

Neurofibroma is the designation for a group of common, closely related benign nerve sheath tumors that according to present evidence have a similar molecular pathogenesis. These tumors typically present either as a localized lesion or as part of a generalized syndrome of neurofibromatosis generally known as neurofibromatosis type-1 (NF1) or von Recklinghausen disease. NF1 is a common human autosomal dominant disease, affecting 1 in 3500 individuals worldwide (4). It is caused by a mutation in the *NF1* gene located on chromosome 17q11.2 that encodes the protein neurofibromin. Patients with NF1 may develop tumors at any site in the body, including skin, internal nerve trunks, and viscera. It seems likely that loss-of-function alterations in the *NF1* gene play a role in both NF1 associated and sporadic neurofibromas. It was identified a

population of stem/progenitor cells residing in the dermis termed skinderived precursors that, through loss of *NF1* gene, could origin dermal neurofibromas. Furthermore, it seems that the loss of *NF1* gene in skin-derived precursors is required, but not sufficient, to induce tumors, suggesting an essential role for the tumor microenvironment, including neurons and hormones, in neurofibroma development (5).

Neurofibromas are composed of a dual population of Schwann cells and fibroblasts, and entrapped axons are often present in intraneural lesions. Neurofibromas occur in people of all ages, but they are most commonly diagnosed in young adults. They can present in superficial or deep soft tissues, and each subtype can present in a wide variety of anatomic locations. The most common form is solitary cutaneous neurofibroma. A review of the histopathological features in 114 neurofibromas demonstrated 10 variants: classic, cellular, myxoid, hyalinized, epithelioid, plexiform, diffuse, pigmented, granular cell, and pacinian (7). Subsequently, new variants were incorporated, as dendritic cell neurofibroma with pseudorosettes, lipomatous, and hybrid tumors (8).

CASE PRESENTATION

A female patient, aged 63, presented with a solitary cutaneous lesion in her lower-back. She reported 9 years observation of this slow-growing, painless mass; no prior and/or family history for tumors. The patient's general physical examination was otherwise unremarkable. Blood and urinalysis were within normal limits. Surgical excision with tumor-free borders was performed. On gross examination, an oval piece of skin was covering a well-delineated but unencapsulated tumor formation with no evidence for attachment to the overlying epidermis (Fig. 1 A). Cut surface exposed a soft, pale gray-yellowish mass, measuring max 4 cm, occupying the dermis and subcutaneous fat.

Routine histology revealed spindle-to-ovoid cells, embedded in a mixture of collagenised matrix (van Gieson positive) and moderate amount of mature fat tissue. Some of the cells displayed a marked degree of nuclear pleomorphism; unevenly dispersed were floret-like multinucleated giant cells (FMGCs), (Fig. 1 B). Careful examination failed in finding any mitotic figures. In addition, numerous eosinophilic rounded structures were present, single or in small clusters. These were composed of elongated cells stacked in a lamellar arrangement, similar to the tactile corpuscle-like Wagner-Meissner bodies (Fig. 1 C, D).

Ancillary immunohistochemical (IHC) investigation with a panel of antibodies was performed (all provided by DAKO), adhering to the manufacturer's instructions. S-100 protein showed strong and diffuse positivity in tumor cells, both cytoplasmic and nuclear (Fig. 1 E). Similar expression was noted for NSE, whereas GFAP was attenuated but clearly positive in Wagner-Meissner-like bodies (Fig. 1 F). CD34-positivity was limited to the intrinsic vasculature. Occasional tumor-infiltrating macrophages were decorated by CD68. Not surprisingly, Ki-67 labeled only a few scattered cells, comprising less than 1% in tumor cells.

Based on the clinical, histological and IHC features of the neoplastic lesion, a diagnosis of solitary diffuse neurofibroma was favoured. The patient was followed-up for 2 years, at this point patient is free of disease recurrence or progression.

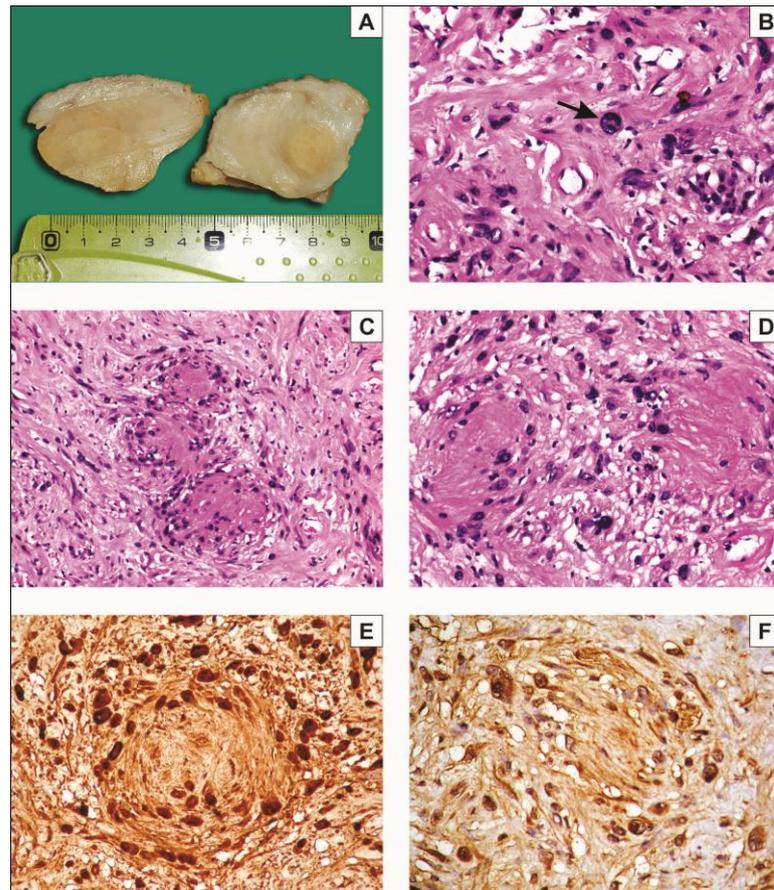


Fig. 1. **A** – Gross specimen. **B, C, D** - Hematoxylin&Eosin staining revealed floret-like multinucleated giant cells (arrow) and Wagner-Meissner bodies-like structures. **E:** S-100 protein and **F** – GFAP immunopositivity of Wagner-Meissner bodies-like structures.

DISCUSSION

Diffuse neurofibroma is a less common variant of neurofibroma. Grossly, the lesion varies from plaque-like to large contiguous mass that can reach disfiguring proportions (8). On sectioning, it is textureless, gray-white, and varies from soft, slightly mucoid to firm and rubbery. The excised tumor from locations such as the eyelids is often relatively small, but in the trunk and extremity, the lesion often measures 5 cm or more, and can reach massive proportions in NF1 patients. The borders are indistinct, and the subcutis is primarily involved. Histologically, diffuse neurofibroma resembles cutaneous neurofibroma, but it has prominent, diffuse fat infiltration.

The Wagner-Meissner corpuscles are the touch receptors of the skin. They are located in dermal papillae, especially on the palmar and plantar surface. Whorled structures resembling tactile corpuscles may occasionally be seen in otherwise typical neurofibromas, especially in diffuse histological type. They are characteristic, but are not always present (10). This particular type is often associated with NF1. However, in our case NF1 was ruled out based on clinical, imaging studies and family history.

Multinucleated floret-like giant cells can be present in around 23% of the neurofibromas (6). They are easily distinguished by the presence of multiple nuclei arranged randomly or in a wreath-like configuration and abundant eosinophilic cytoplasm. The presence of FMGCs in sporadic neurofibroma, usually reported as a rare finding, adds to the growing list of soft tissue tumours with FMGCs, which include pleomorphic lipoma, giant cell collagenoma and giant cell fibroblastoma (1, 9, 3). FMGCs have also been described in giant-cell-rich variant of solitary fibrous tumour also known as giant cell angiofibroma (2). Based on a clinicopathologic study of 94 cases, Margo et al.

concluded that was no significant correlation between of FMGCs (presence or absence) and NF1, gender and age (6). FMGCs in this investigation were more frequently found in cutaneous versus deep-soft tissue neurofibromas. Among superficial neurofibromas, only diffuse type contained FMGCs. The histogenesis of FMGCs in neurofibroma is still to be established. It could be postulated that FMGCs occasionally encountered in neurofibromas may merely represent a reactive change of either dermal and endoneurial fibroblasts or dendritic cells in response to unknown stimuli. Immunohistochemical analysis, revealing exclusively vimentin and CD34 expression, would support the fibroblastic or dendritic nature of FMGCs. In our case, no positivity for CD34 in FMGCs was seen while S-100 protein was found expressed, this could possibly be explained as degenerative morphological changes occurring in cells with Schwann origin.

Although the occasional presence of numerous FMGCs in a neurofibroma may represent an alarming feature, these cells should not be misinterpreted as atypical tumor cells characterizing the atypical neurofibroma or malignant peripheral nerve sheath tumor. Unlike FMGCs, however, atypical tumor cells have hyperchromatic and irregular nuclei and may also exhibit prominent intranuclear pseudoinclusions. The presence of numerous atypical tumor cells uniformly distributed in a neurofibroma, in association with an increased cellularity and mitotic figures, is a reliable indicator of malignant transformation. The absence of significant proliferative activity as measured by IHC markers (Ki-67) would help in ruling out malignancy.

IN SUMMARY, we present a rare case of diffuse type solitary neurofibroma in a female patient not associated with NF1. Histologically, the lesion featured prominent Wagner-Meissner-like differentiation and presence of floret-like multinucleated giant cells. We emphasize that S-100 protein and/or GFAP expression combined with analysis of immunohistochemical proliferative activity is helpful and leading to accurate identification of the lesion. Awareness of the spectrum of cytologic changes within this entity is critical to prevent overdiagnosis of malignancy.

REFERENCES:

1. Azzopardi, J.G., J. Iocco, R. Salm, 1983. Pleomorphic lipoma: a tumour simulating liposarcoma, *Histopathology*, 7: 511-523.
2. Dei Tos, A.P., S. Seregard, E. Calonje, J.K. Chan, C.D. Fletcher, 1995. Giant cell angiofibroma. A distinctive orbital tumour in adults, *Am J Surg Pathol*, 19: 1286-1293.
3. Fletcher, C.D., 1988. Giant cell fibroblastoma of soft tissue: a clinicopathological and immunohistochemical stud, *Histopathology*, 13: 499-508.
4. Jett, K., J.M. Friedman, 2010. Clinical and genetic aspects of neurofibromatosis 1, *Genet Med* 12 (1): 1-11.
5. Le, L.Q., T. Shipman, D.K. Burns, L.F. Parada, 2009. Cell of origin and microenvironment contribution for NF1-associated dermal neurofibromas, *Cell Stem Cell*, 4 (5): 453-463.
6. Magro, G., P. Amico, G.M. Vecchio, 2010. Multinucleated floret-like giant cells in sporadic and NF1-associated neurofibromas: a clinicopathologic study of 94 cases, *Virchows Arch*, 456: 71-76.
7. Megahed, M., 1994. Histopathological variants of neurofibroma. A study of 114 lesions, *Am J Dermatopathol*, 16 (5): 486-495.
8. Rodríguez-Peralto, J.L., E. Riveiro-Falkenbach, R. Carrillo, 2013. Benign cutaneous neural tumors, *Seminars in Diagnostic Pathology*, 30: 45-57.
9. Rudolph, P., C. Schubert, D. Harms, R. Parwaresch, 1998. Giant cell collagenoma: a benign dermal tumour with distinctive multinucleate cells, *Am J Surg Pathol*, 22: 557-563.
10. Van Zuuren, E.J., A.N. Posma, 2003. Diffuse neurofibroma on the lower back, *J Am Acad Dermatol*, 48: 938-940.