

## BRIEF ARTICLE

## Cutaneous Angioneurofibroma: A Vascularized Histopathologic Variant of Neurofibroma

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### ABSTRACT

Angioneurofibroma is a rare histopathological variant of cutaneous neurofibroma, characterized by a more densely vascularized stroma when compared to classic neurofibroma. Here we describe a case of this entity, which presented as a tender penile plaque in a young man, and discuss the clinicopathologic differential. The unique histologic findings in this case supports the recognition of angioneurofibroma as a distinct subtype of neurofibroma, and dermatologists should be aware of this rare variant.

### INTRODUCTION

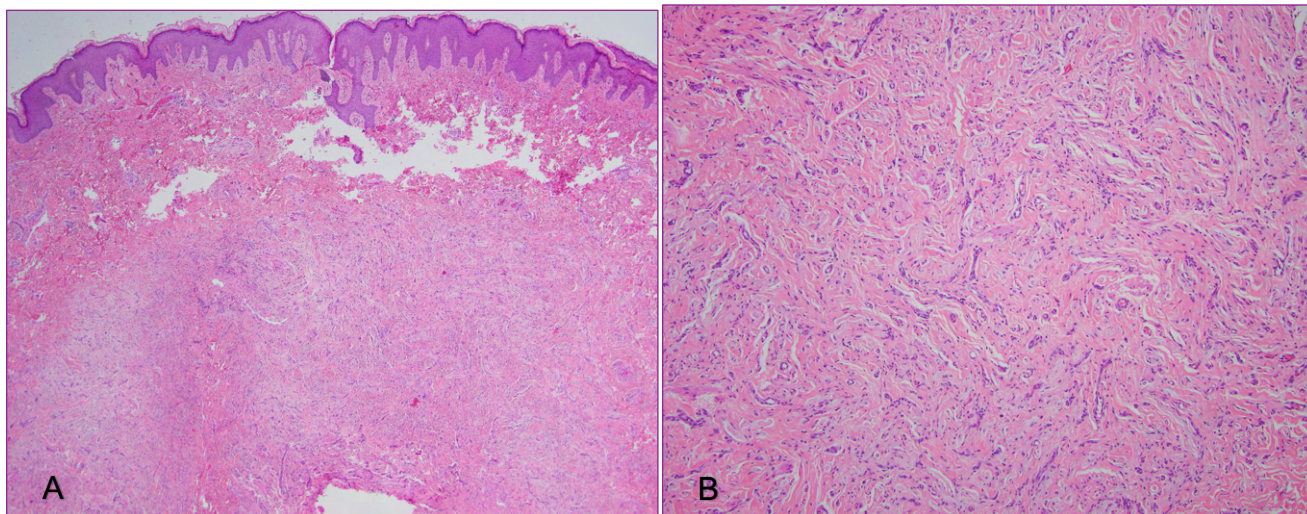
Angioneurofibroma is a rare and recently described histopathological variant of cutaneous neurofibroma, characterized by a markedly higher stromal vascular density, with reported averages of 51 blood vessels per 10 high-power fields vs. 23 vessels per 10 high-power fields in classic neurofibroma.<sup>1</sup> Like classic neurofibromas, angioneurofibromas are unencapsulated dermal tumors composed of loosely arranged spindle cells with wavy nuclei and scant cytoplasm.<sup>2</sup> They are often positive for S-100 protein, with an intact overlying epidermis separated from the lesion by a dermal grenz zone.<sup>3</sup> Clinically, lesions have a similar appearance to classic neurofibromas and may appear as skin-colored papules or small subcutaneous nodules. Here we present a case of this rare variant and discuss the histologic differential.

### CASE REPORT

A 27-year-old man presented with a tender 1.2 cm skin-colored plaque on the foreskin of the penis. The patient was otherwise healthy with no history of skin cancer or other pertinent medical history. Excisional biopsy was performed to further characterize the nature of the lesion.

The biopsy revealed a well-circumscribed nodule formed by a dermal proliferation of spindle cells with wavy and syncytially arranged cytoplasm with a prominent vascular component composed of numerous small, thin-walled vessels (134 vessels per 10 high-power fields) beneath an unremarkable epidermis. (**Figure 1**). Occasional mast cells were identified. Atypia was not identified. The spindle cells were positive for S-100 and focally positive for neurofilament protein, while CD31 and SMA were positive in the vascular component (**Figure 2**). The morphological and

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**Figure 1.** A. Well-circumscribed nodule in the dermis (H&E, 4x). B. Spindled cells with wavy and syncytially arranged cytoplasm and a high vascular density of thin-walled vessels surrounding the lesion (H&E, 10x).

immunohistochemical profile together supported a diagnosis of angioneurofibroma. The patient returned for follow-up and suture removal 2 weeks following biopsy and reported no complications.

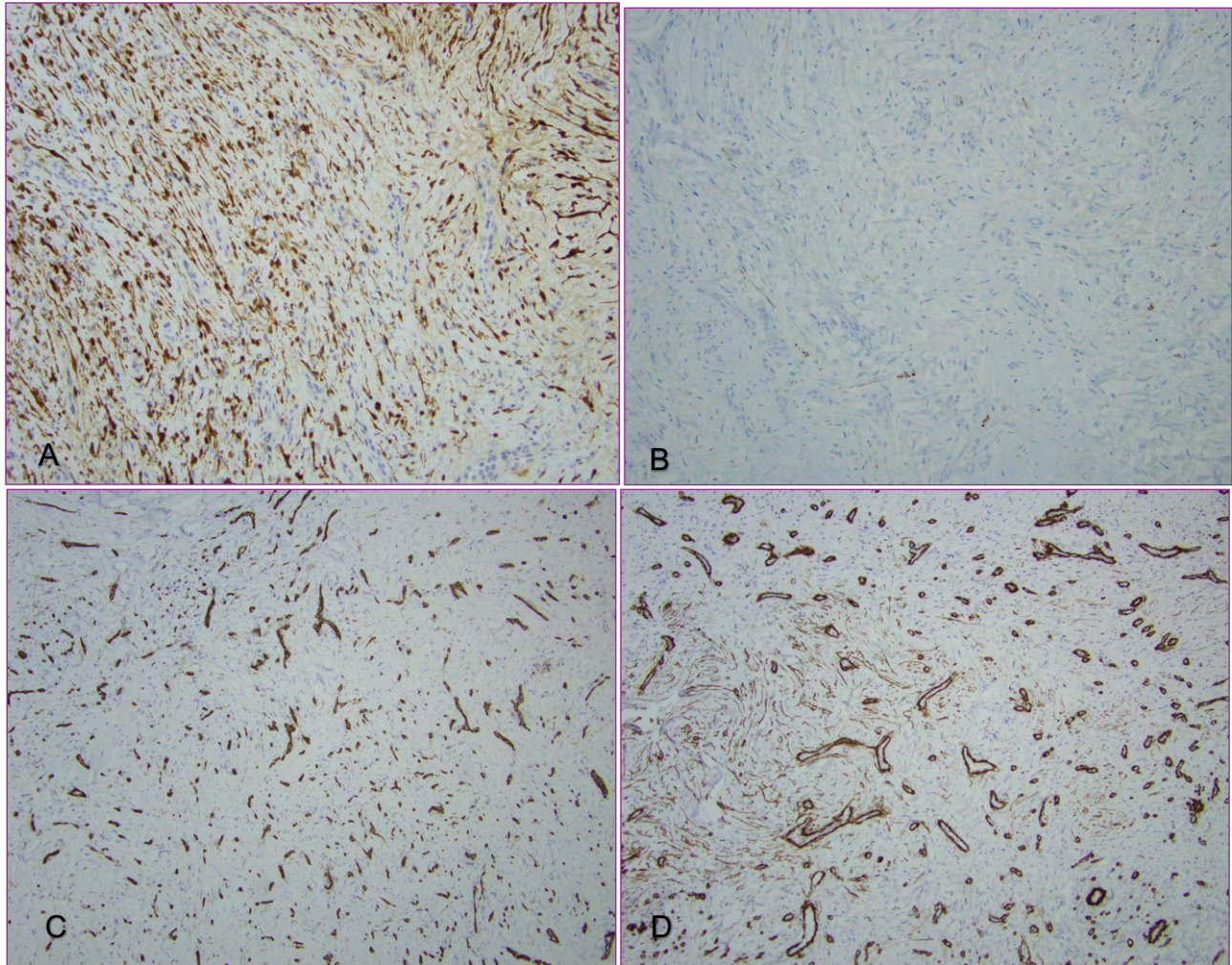
## DISCUSSION

Angioneurofibromas are rare benign tumors, and prior to further characterization in a case series of 6 lesions published by Saxer-Sekulic et al in 2014, there were few descriptions of these lesions in the literature.<sup>1,4-6</sup> The first report by Fleming et al in 1924 described a tumor arising in the cerebellopontine angle of a patient with neurofibromatosis, but likely represented a vestibular schwannoma, otherwise called an acoustic neuroma.<sup>5</sup> Two other cases, described by Tepavicharova and Ymele et al, both showed large pedunculated vulvar tumors with a histopathological diagnosis of angioneurofibroma.<sup>4,6</sup> However, little histopathologic information was reported in these cases, and it is possible these lesions

represented fibroepithelial stromal polyps of the vulva.

Other recognized variants include cellular, myxoid, hyalinized, diffuse, and plexiform neurofibromas, among others. Cellular, myxoid, and hyalinized neurofibromas are similar to classic neurofibroma but contain a prominent cellular component, an extensive deposition of stromal mucin, or thick collagen bundles, respectively.<sup>2</sup> Diffuse neurofibroma is characterized by an ill-defined lesion with an infiltrative growth pattern in a uniformly collagenous matrix, often with differentiation towards a Meissner's corpuscle.<sup>2</sup> Plexiform neurofibroma, typically pathognomonic for NF-1, consists of tortuous masses of hypertrophied nerve fibers, a feature which was not present in our case.<sup>2</sup>

The differential diagnosis of angioneurofibromas also includes superficial angiomyxomas, aggressive (deep) angiomyxomas, nerve sheath myxomas (myxoid neurothekeomas), angiofibromas, fibroepithelial stromal polyps, and



**Figure 2.** A. Expression of S-100 in spindle cells (20x). B. Focal expression of neurofilament (20x). C. Expression of CD31 in the vascular component (20x). D. Expression of SMA in the vascular component (20x).

myxofibrosarcomas. Many of these entities present clinically in a similar fashion as skin colored, fleshy papules or nodules and may only be differentiated by histologic evaluation. Superficial angiomyxomas have a similar clinical presentation to angioneurofibromas as solitary, asymptomatic nodules or polypoid lesions.<sup>7</sup> Histologically, the lesions are present in the superficial dermis and are composed of multiple, poorly circumscribed myxoid lobules containing numerous small blood vessels with admixed stellate or spindled cells.<sup>7</sup> However, unlike angioneurofibromas, the tumor cells are negative for S-100 and

neurofilament protein and positive for vimentin with focal actin and CD34 positivity.<sup>7</sup>

Aggressive angiomyxomas have related similarities to angioneurofibromas, including cytologically bland tumor cells with spindled, ovoid, or stellate appearances and numerous blood vessels against a myxoid background.<sup>8</sup> However, these tumors frequently infiltrate local soft tissue with characteristic entrapment of muscle, nerve, and adipose tissue.<sup>8</sup> The tumor cells are also negative for S-100, positive for vimentin and desmin, and characteristically positive for estrogen receptor and progesterone receptor.<sup>8</sup> Nerve

sheath myxomas contain scattered epithelioid to spindle-shaped cells often arranged in cords or nests but can sometimes demonstrate a syncytial pattern resembling myxoid neurofibromas. Similar to neurofibromas, mast cells and multinucleate giant cells may be present, and the tumor cells are often positive for S-100 protein, SOX-10, and low-affinity nerve growth factor receptor. However, clinically these lesions arise most often on the extremities<sup>7</sup>. Histologically, they are negative for neurofilament and have a distinct multilobular architecture, which is absent in myxoid neurofibromas, and do not contain the vascular predominance as seen in the present case.<sup>7</sup>

Angiofibromas are well-circumscribed but unencapsulated tumors composed of short, bland, Factor XIIIa+ and occasionally CD34+ spindle-shaped cells and, similar to angioneurofibromas, frequently contain thick-walled, medium-sized hyalinized blood vessels. However, these lesions are negative for S-100 protein.<sup>7,9</sup> In men, angiofibromas correspond clinically to pearly penile papules on the corona or frenulum. Fibroepithelial stromal polyps, which clinically present as polypoid or pedunculated vulvovaginal lesions in women of reproductive age, also share the histologic feature of thick-walled blood vessels within a variably cellular, loose connective tissue stroma. However, these tumors are positive for desmin, vimentin, and estrogen and progesterone receptors. Lastly, myxofibrosarcomas, particularly of the low-grade histologic variant, may resemble angioneurofibromas. These are malignant fibroblastic tumors with a myxoid background and characteristic curvilinear thin-walled blood vessels. However, most lesions arise in the subcutis, and the spindle cell proliferation is negative for S-100 and shows some degree of cytologic atypia, pleomorphism,

and rare mitoses which are absent in angioneurofibroma.<sup>7</sup>

Management of angioneurofibroma often involves surgical excision of solitary lesions. Given the highly vascular nature of this tumor, prior literature has suggested a potential role for angiogenesis inhibitors as medical therapy, though further studies are needed to characterize the utility of these treatment modalities.<sup>1</sup>

In conclusion, this report presents a case of cutaneous neurofibroma with prominent vascular density and reviews the histologic differential, further supporting the recognition of angioneurofibroma as its own histopathological subtype. Clinicians should be aware of this rare but distinct variant of neurofibroma.

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