Multiple cutaneous linear neuromas

Julien Lanoue, BA, Rajendra Singh, MD, Chen Chen, MD, and Robert Phelps, MD
New York, New York

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Multiple cutaneous neuromas are an uncommon finding that has been reported to occur idiopathically and in association with multiple endocrine neoplasia (MEN) 2B and phosphatase and tensin homolog (PTEN) tumor-hamartoma syndrome (PTHS).[1-5] Multiple cutaneous neuromas with linear configurations are an even rarer phenomenon that, to our knowledge, has only been described in 3 prior case reports.[1,6,7] Here, we report a unique case of diffuse cutaneous neuromas of linear configurations and distribution without findings of other associated genodermatoses.

Abbreviations used:

MEN:	multiple endocrine neoplasia
PEN:	palisaded and encapsulated neuroma
PTEN:	phosphatase and tensin homolog
PTHS:	PTEN tumor-hamartoma syndrome

CASE REPORT

At the age of 48 years, our patient developed 3 small, lightly pigmented macules on the lower aspect of her back, each measuring approximately 0.5 cm in length. Over the next 5 years, the lesions began to darken and increase in number, spreading laterally to the flanks and vertically to the mid aspect of her back (Fig 1, *A* and *B*). These lesions were largely linear in individual configuration and in their collective distribution, running parallel to dermatomes and spreading out perpendicularly from the spinal cord. At age 53 years, the patient developed similar lesions on the inferior aspect of her forearms that also appeared to run along cutaneous nerve distributions (Fig 1, *C*). The head, legs, and mucosa were spared from involvement.

The patient currently has over 70 individual lesions ranging from 0.5 to 3.0 cm in length. These lesions are generally flat, but some exhibit minimal elevation, particularly on the forearms. The lesions on the patient's trunk are generally asymptomatic but can become sensitive and pruritic with physical contact whereas the lesions on her forearms can cause sharp pains that radiate up the arms when pressure is applied.

Complete physical examination of the patient was unremarkable with no marfanoid body habitus or palpable enlargement of the thyroid. The patient's medical history was significant for hypertension and a prior dermatofibrosarcoma protuberans that was successfully removed from her right flank via a wide excisional resection with clear margins. She denied a family history of similar cutaneous lesions, endocrine abnormalities, or cancer of any type.

Punch biopsy specimens of lesions from the forearm and flank revealed numerous neural-like proliferations, occasionally bundled together, running tortuously throughout the mid dermis (Fig 2). These growths were sharply demarcated from the surrounding connective tissue and exhibited no associated inflammation or fibrosis. The bulk of these growths was composed of spindle-shaped cells with wavy, basophilic nuclei and poorly delineated eosinophilic cytoplasm (Fig 3, *A*). This tissue was confirmed to be of neural origin with positive Bodian, protein gene product 9.5, and S-100 staining (Fig 3, *B* and *C*). A variably thick layer of perineurium, as confirmed by epithelial membrane antigen staining, was seen surrounding each nerve bundle.

During the ensuing workup, the patient was found to have a 2-mm thyroid cyst and a benign 4-mm thyroid nodule. Results of complete thyroid, parathyroid, calcitonin, and urine metanephrine studies were within normal limits. Routine laboratory results

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Correspondence to: Robert Phelps, MD, Icahn School of Medicine at Mount Sinai, Annenberg Bldg Room 308, 1468 Madison Ave, New York, NY 10029. E-mail: robert.phelps@mountsinai.org.
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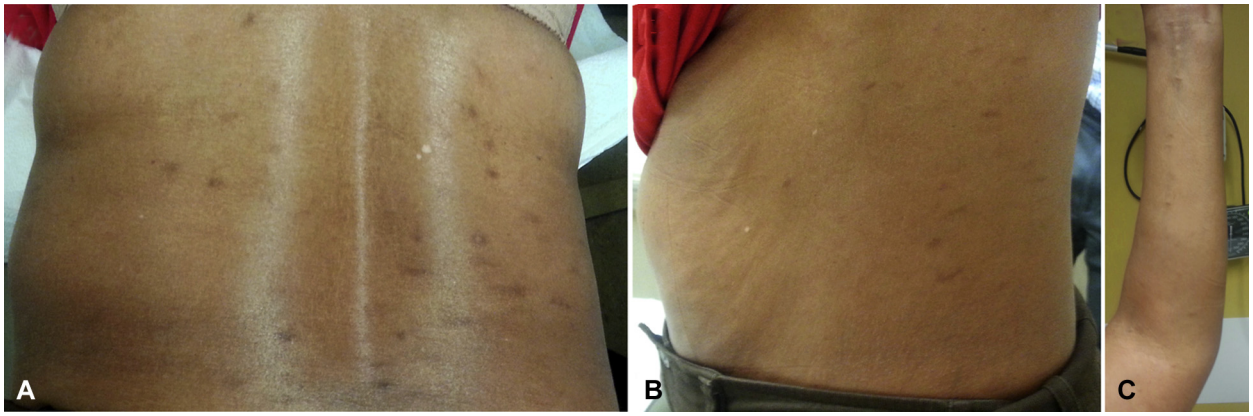

Fig 1. A, Numerous hyperpigmented lesions with linear and ovoid configurations appear to spread out perpendicularly from the spinal cord in linear distributions. **B**, These lesions wrap around the flanks but spare the front of the abdomen. **C**, Papular lesions can be seen along the forearm in a linear distribution.

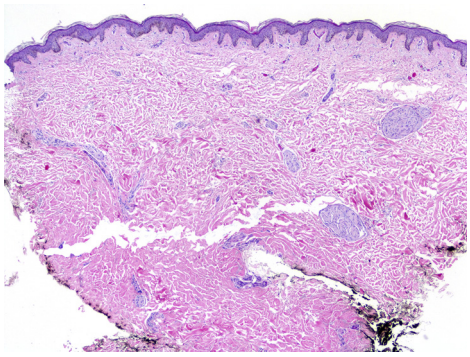

Fig 2. Numerous neural proliferations, occasionally bundled together, run tortuously throughout the mid dermis.

were normal. Positron emission tomography, computed tomography, magnetic resonance imaging, and formal ophthalmologic examination revealed no significant findings. Bidirectional sequence analysis of exons 10, 11, 13, 14, 15, and 16 of the RET proto-oncogene, which identifies 98% of individuals with MEN 2A and over 99% of individuals with MEN 2B, revealed no mutations.[8]

DISCUSSION

Palisaded and encapsulated neuroma (PEN) typically presents in adults as a solitary, asymptomatic skin-colored papule on the face, but may occur anywhere on the body.[9] Histologically, PENs appear as compact arrangements of well-circumscribed hypertrophic nerve bundles in the papillary dermis with variable encapsulation by perineural cells. Intersecting fascicles of spindled cells separated by clefts are a characteristic feature.[9] There have been reports of multiple idiopathic PENs with up to a handful of lesions and no additional abnormalities, including 1 case that described several PEN in a linear distribution.[3,9,10] In contrast to our patient, however, the individual's lesions in the latter report were papular in configuration, nonpigmented, and limited to the acral skin.

Multiple cutaneous neuromas have also been reported in association with PTHS and MEN 2B. The PTHS, which include Cowden and Bannayan-Riley-Ruvalcaba syndrome, are characterized by numerous hamartoma growths of ectodermal, mesodermal, and endodermal tissues. Mucosal neuromas are reported in addition to cutaneous neuromas in PTHS, but neither are part of the formal diagnostic criteria.[2] Although MEN 2B is most classically associated with mucosal neuromas as they occur in virtually all afflicted patients, cutaneous neuromas are occasionally seen.[1,7,11] In regards to histologic presentation, the mucosal and cutaneous neuromas seen in both MEN and PTHS are nearly identical.[2] These neuromas look similar to that of PENs but tend to show more scattered individual nerve fibers and fascicles as compared with the larger well-delineated mass of intersecting fascicles seen in PENs.[2,9]

Of the 3 cases of multiple cutaneous neuromas with linear configurations reported in the literature, 2 were cited in individuals with features of MEN 2B whereas the remaining case reported no additional systemic pathology (Table I). The neuromas in our patient share characteristics with all 3 previously reported cases but are also unique in their combination of features. The lesions in our patient are largely macular and pigmented such as those seen in the 1987 case,[6] but they are more similar in individual configuration to those seen in the 1973 case[7] and 2007 case.[1] The broad distribution of lesions and lack of additional systemic findings or mucosal lesions are most similar to the 1973 case.[7] The histology seen in

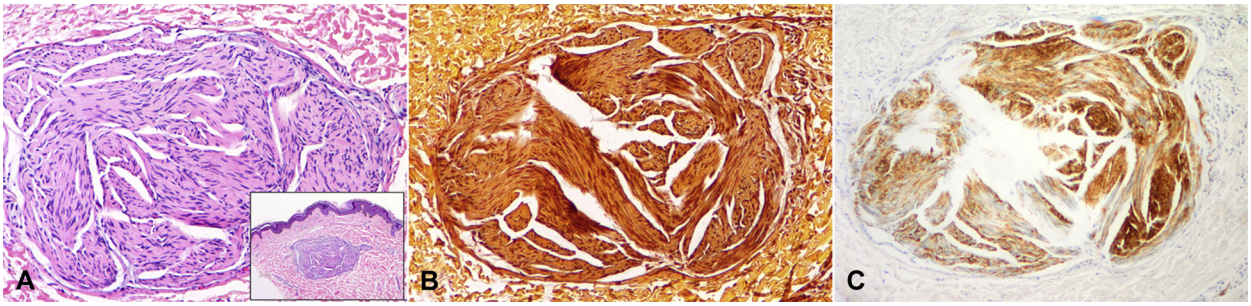

Fig 3. **A**, On hematoxylin-eosin stain, the borders of this nerve bundle are sharply demarcated from the surrounding connective tissue with no associated inflammation or fibrosis. A thin layer of epithelium can be seen encapsulating the intersecting fascicles of nerve fibers. Within the bundle, proliferations of spindle-shaped cells with wavy, basophilic nuclei and poorly delineated eosinophilic cytoplasm are seen. *Inset* shows a large nerve bundle in the mid dermis with overlying mild basal layer hyperpigmentation. **B**, Silver-impregnated Bodain stain highlights myelinated nerve axons and neurofibrils in the neuroma. **C**, S-100 demonstrates interspersed cells of neural-crest origin, likely Schwann cells. (**A-C**, Original magnifications: A, B, and C, ×20; A inset, ×4.)

Table I. Prior reports of multiple cutaneous neuromas with linear configurations

Report	Age, y/gender	Cutaneous findings	Other systemic findings	Genetic analysis
Baykal et al[1] (2007)	45/Female	Flesh-colored papular lesions, some of which exhibited a linear configuration, distributed throughout the trunk, shoulders, neck, and arms; macular amyloidosis on the back; no mucosal lesions	Medullary thyroid cancer	RET exon 13 mutation
Guillet et al[6] (1987)	60/Female	Multiple, large, flat, pigmented bands wrapped around the trunk; exaggerated tongue papillae	Marfanoid habitus, hypertrophy of corneal nerves, and abnormal electromyography	Not reported
Holm et al[7] (1973)	70/Male	Flesh-colored papules on the trunk and proximal upper extremities distributed in a manner that appeared to follow thoracic nerve distributions; no mucosal lesions	Slightly enlarged but functionally normal thyroid gland	Not reported

our patient closely resembles that seen in all 3 prior reports.

Although the original authors of the prior reports described histology identical to that of the multiple mucosal neuromas of MEN 2B, others have since described the neuromas as PENs.[3,10] While we agree that the histology is more consistent with a PEN given the intersecting fascicles, poorly delineated nerve fibers, and partial encapsulation, the clinical presentation is not compatible. Given the overall clinical and histologic similarities of our patient's presentation to prior reports that exhibited features and mutations highly suggestive of MEN 2B, we conclude our case likely represents a forme fruste of MEN 2B that will require continued monitoring for endocrine changes. Although genetic sequencing failed to reveal any common RET mutations, we cannot rule out the possibility of genetic mosaicism, intron mutations, rare mutations on untested exons, or mutations in downstream targets of RET signaling as potential causes for our patient's unique presentation.

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