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Histologic Variants of Periungual Fibromas in Tuberous Sclerosis Complex

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To the editor: Periungual fibroma (PF) is a cutaneous manifestation of tuberous sclerosis complex (TSC). Although a benign tumor, it can bleed, cause pain, and distort the nail. Non-traumatic PFs are among the major diagnostic criteria of tuberous sclerosis complex (TSC).¹ The lesions usually develop post-puberty, are more common on toenails than on fingernails, and occur more frequently in women than in men.^{2,3}

We conducted a retrospective review of 32 PFs from 18 TSC patients seen at the NIH between 2000–2008. The clinical features of these cases are summarized in Table 1. All but one patient were females since they were enrolled in studies of lymphangioleiomyomatosis, a pulmonary disease in TSC patients that occurs almost exclusively in women.³ The average age of the patients included in this study was 49.8±7.7 years old. All but two of the PFs were obtained from the toes and the remaining were from the fingers. The duration of the lesions ranged from 2 to 40 years.

Grossly, most PFs are pink to red, firm, conical papules emerging from under the proximal nail fold (Figure 1A, 1C and 1E). A longitudinal nail groove extends from under the tumor to the free edge of the nail.⁴ The lesions usually measure 1–5 mm from the base to the tip. Histologically, they are non-encapsulated and are comprised of stellate shaped fibroblasts admixed with vertically oriented dense collagen and blood vessels. The lesions can be highly vascular, predominantly fibrotic, or show a mixed pattern. The epidermal changes are characterized by compact hyperkeratosis, acanthosis, thickened granular layer and irregular rete ridges (Figures 1B, 1D, and 1F). Parakeratosis is not observed.

The histological appearance of TSC PFs varied depending on the relative proportions of vascular proliferation and stromal fibrosis. The angiomatous subtype, observed in 5 samples, is characterized by numerous dilated vascular spaces, lined by plumped endothelial cells. The vascular lumens were large compared to that in normal skin. In between the vascular spaces are proliferation of stellate fibroblasts admixed with variable amounts of dense dermal collagen (Figure 1B). The fibrotic subtype, observed in 19 samples, featured predominantly vertically oriented thick collagen bundles in the dermis admixed with thick-

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walled small blood vessels (Fig. 1D). Elastic tissue (EVG) staining showed significantly decreased amounts of dermal elastic fibers, compared to the non-lesional skins obtained from the same patients (figure not shown). A third histologic subtype, observed in 8 samples, showed histological features intermediate between angiomatous and fibrotic subtypes and therefore was categorized as mixed subtype (Fig. 1F). Some of these changes were consistent with the observations of Nickle and Reed⁵, and of Kint and Barran⁶.

Lesions categorized histologically as angiomatous subtype generally appeared more red, while the fibrotic subtype tended to be more white and firm; there was no obvious correlation of subtype with tumor location. Although the angiomatous and fibrotic subtypes can be distinguished histologically, they may represent a spectrum of changes of these tumors from angiomatous to fibrotic subtype over time. The proposed histologic sub-typing of periungual fibromas may provide helpful insights into the pathogenesis of these lesions.

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Abbreviations

TSC	tuberous sclerosis complex
PF	periungual fibroma

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Figure 1. Variants of periungual fibroma, showing paired gross and microscopic images.

Angiomatous

A) A clove-shaped, red nodule emerges beneath the proximal nail fold of the great toe. B)

There is proliferation of blood vessels with dilated vascular lumens and stellate shaped fibroblasts in the stroma. **Fibrotic.** C) A pink, firm papule on the right 5th toe. D) There is

prominent fibrosis with vertically oriented dense collagen bundles admixed with thick-walled small blood vessels in the stroma. **Mixed.** E) A pink to red papule on the left 5th toe.

F) The stroma shows moderate fibrosis and variable degree of vascular proliferation.

Table 1

Clinical and histological features of periungual fibromas in TSC

Patient	Subtype	Location	Patient	Subtype	Location
#1	Angiomatous	Left 4 th finger and right great toe	#8	Angiomatous	Right 3 rd toe
	Fibrous	Right third toe and right 4 th toe	#9	Fibrous	Right 4 th and 5 th toe
#2	Fibrous	Right small toe, 4 th toe, 5 th toe and left 5 th toe	#10	Mixed	Right 5 th toe
			#11	Mixed	Left 3 rd toe
	Mixed	Right 2 nd finger	#12	Fibrous	Left 2 nd toe
#3	Fibrous	Left small toe	#13	Fibrous	Left 5 th toe
#4	Angiomatous	Right great toe	#14	Fibrous	Left 3 rd toe and right 5 th toe
	Mixed	Right 5 th toe	#15	Mixed	Right 2 nd and 3 rd toe
#5	Fibrous	Left 4 th toe	#16	Mixed	Left 5 th toe
#6	Angiomatous	Left 3 rd toe	#17	Fibrous	Left 3 rd toe
	Fibrous	Right 4 th toe		Mixed	Left 5 th toe
#7	Fibrous	Right 4 th and 5 th toe	#18	Fibrous	Right 5 th toe