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LETTER TO THE EDITOR

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Squamous cell carcinoma–like ungual fibroma as early diagnostic indicators of tuberous sclerosis complex in an elderly patient

Dear Editor,

Tuberous sclerosis complex (TSC) is a highly heterogeneous clinical entity with variable presentation and severity of disease. The most frequent cutaneous findings include periungual and subungual fibromas (Koenen tumors), multiple facial angiofibromas, hypopigmented macules, and shagreen patches.[1]

A 64-year-old woman presented at our university hospital complaining of a skin tumor on her right toe. She did not find any other abnormalities prior to noticing the skin tumor. She had had mild and transient epilepsy in her childhood, but this had resolved naturally. The patient revealed skin-colored rubbery nodules and papules on all her toes and several fingers (Figure 1A,B). She had a pedunculated and squamous cell carcinoma–like skin tumor on her right 5th digit (Figure 1C). We suspected these nodules and papules to be Koenen tumors and performed further cutaneous examination. A physical examination revealed many skin-colored papules on her face (facial angiofibromas) and a shagreen patch with hypomelanotic macules on her back and lumbar area (Figure 1D,E). Histological analysis of the squamous cell carcinoma–like skin tumor on her right 5th digit revealed acanthosis with a thickened horny layer and a stroma that contained capillaries surrounded by collagen fibers, which appeared to be induced by fibroblasts. The tumor was diagnosed as hamartomatous fibroma but not skin cancer. Her mental and developmental indicators were normal, and she had no family history of TSC. There was no evidence of lymphangioleiomyomatosis, angiomyolipoma, or subependymal giant cell astrocytoma based on brain, lung, and abdominal computed tomography and other TSC-related clinical evaluations. Ophthalmological results were normal. She was treated with topical rapamycin but no improvement was noticed.

DNA was extracted from peripheral blood leukocytes and a squamous cell carcinoma–like skin tumor by the standard method. We identified a frameshift mutation in *TSC1* exon 15 from both the blood and skin tumor samples based on genotypic analysis of *TSC1* and *TSC2* genes including the CHIPS method and Sanger sequencing (Figure 1F).[2] We further performed deep sequencing analysis by next-generation sequencing and found no second-hit mutations in the skin tumor sample.

Our elderly patient was diagnosed based on cutaneous signs and symptoms, and we found a *TSC1* frameshift mutation. Some authors have suggested that TSC patients with *TSC1* mutations are less common and demonstrate a milder phenotype compared with those with *TSC2* mutations.[1,3] Skin manifestations have been regarded as a secondary complication following neurologic manifestations, occurring in up to 80% of patients. Periungual and subungual fibromas occur commonly in late-onset patients with TSC.[4,5] We suggest that these cutaneous manifestations, such as squamous cell carcinoma–like periungual and subungual fibromas, could serve as markers for making earlier diagnosis in late-onset patients with *TSC1* gene mutations. Therefore, we propose that dermatological examination could be useful for earlier diagnosis in elderly and clinically mild TSC patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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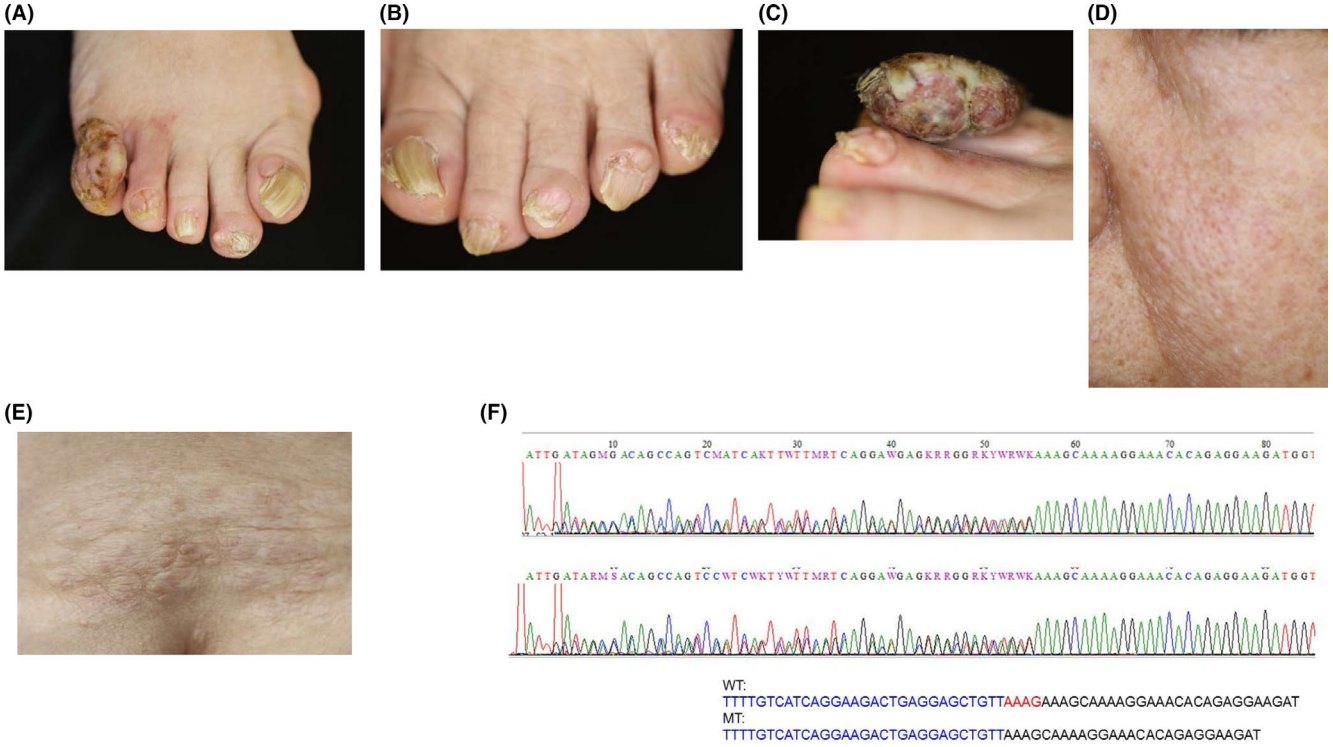

FIGURE 1 A and B, Periungual and subungual fibromas, known as Koenen tumors, were found on all toes (A: right, B: left). C, Her right 5th digit had a pedunculated and granulomatous skin tumor. D, She had skin-colored papules along the nasolabial folds and cheeks, known as facial angiofibromas. E, Shagreen patch with hypomelanotic macules presented over the back and lumbar area. F, TSC1 exon 15 direct DNA Sanger sequencing (upper: blood; lower: tumor)

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