in 28.1%, and grade 3 skin-related adverse events were reported in 1.8% of pirfenidone-treated patients [4].

The exact mechanism of pirfenidone-induced phototoxicity remains unknown. In an *in vivo* study [5], orally administered pirfenidone at a dose of 160 mg/kg was phototoxic in rats, whereas phototoxic skin responses were negligible at lower doses (30 mg/kg). After oral administration of pirfenidone, the distribution of the drug was higher in UV-exposed tissues (such as the skin and eyes) than the lungs. These findings suggest that a high dose of pirfenidone might cause phototoxic responses through the generation of reactive oxygen species in the skin, and strategic application of appropriate drug delivery systems might be efficacious in reducing the phototoxic risk. Several studies have reported that an inhalable powder formulation of pirfenidone reduced its phototoxic risk.

Some cases of pirfenidone-induced photoallergic reaction have also been reported [6, 7]. Unlike the photoallergic reaction, phototoxic reaction does not necessitate sensitization, thus the symptoms start immediately or within a few hours after UV exposure, and the cutaneous lesions are limited to light-exposed areas. Histologically, phototoxic reactions show vacuolated and apoptotic keratinocytes, as in our case. Despite the high reported rate of cutaneous adverse events associated with pirfenidone, pirfenidone-induced phototoxic reactions have only rarely been reported. Clinicians should be aware of the phototoxic effects of oral pirfenidone, and patients taking pirfenidone should be advised to avoid sunlight and to use photoprotective clothing and sunscreen. ■

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Leg ulcers associated with cutaneous vascular degeneration in a patient receiving pazopanib chemotherapy

Pazopanib is an oral multi-targeted tyrosine kinase inhibitor (TKI) used for the treatment of advanced renal cell carcinoma (RCC) and soft tissue sarcoma. Cutaneous adverse effects of pazopanib are very rare. We herein report a patient with advanced RCC who developed, during chemotherapy with pazopanib, multiple ulcers on both lower legs associated with cutaneous vascular degeneration.

A 66-year-old man was diagnosed with metastatic RCC (of clear cell type) and underwent left nephrectomy. Thereafter, chemotherapy with sorafenib, in combination with interferon-α, was initiated to treat bone, lung, and brain metastases. He also received radiation to the femur and the brain. However, chemotherapy was discontinued after 29 days due to hand-foot syndrome induced by the sorafenib and a skin ulcer on the left thigh caused by the subcutaneous injection of interferon-α. He was administered pazopanib at 800 mg/day. Eight weeks after the initiation of pazopanib, he developed, on both his lower legs, multiple small skin ulcers of less than 20 mm in diameter, erythema, and oedema (*figure 1A*). A biopsy specimen from the ulcer of the right leg showed in the dermis diffuse lymphocytic infiltration and eosinophilic vascular degeneration, characterized

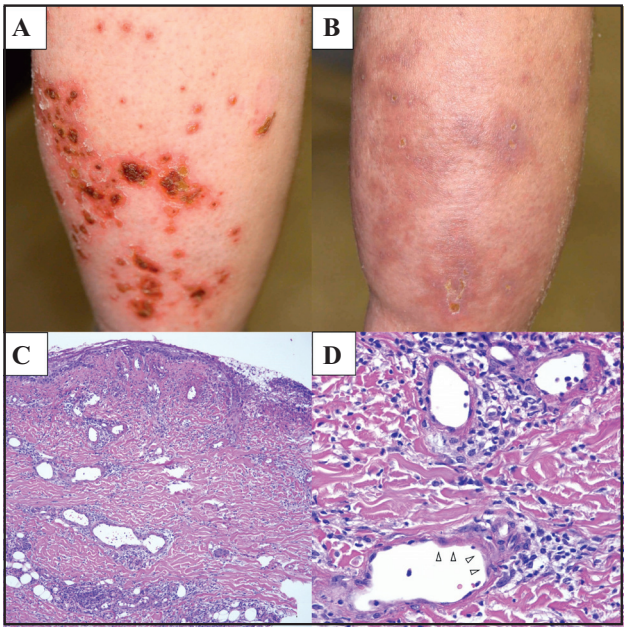

Figure 1. Clinical and histopathological features of the ulcers. **A**) Multiple skin ulcers with crusts on the flexor side of the lower legs. **B**) The ulcers improved two weeks after pazopanib discontinuation. **C**) Histopathological features of a skin biopsy specimen from an ulcer on the right leg. An open ulcer and dilated blood vessels with inflammatory cell infiltration; degeneration of the vessel wall is observed. **D**) Oedematous change and pyknosis of endothelial cells on the vessel walls (white arrowhead), but no apparent infiltration of inflammatory cells. Hematoxylin-eosin staining; original magnification: ×100 (**C**) and ×200 (**D**).

by loss or degeneration of endothelial cells and thickening of the vessel walls. Although lymphocytic infiltration was observed around the degenerated vessels, no active vasculitis was seen (*figure 1C, D*). The ulcers enlarged despite topical application of a steroid ointment for one week. Thus, oral pazopanib was discontinued, and the ulcers significantly improved and epithelized within two weeks, with slight scarring and pigmentation (*figure 1B*). We presumed this case to be a cutaneous adverse drug reaction due to pazopanib. No skin ulcer recurrence has been observed in the one-year follow-up period.

TKIs are among the most successful drugs for treating metastatic RCC [1]. They are regarded as anti-angiogenic agents, and function primarily by inhibiting tumour angiogenesis and tumour cell survival signalling [1]. Pazopanib targets multiple tyrosine kinases, including VEGFR-1, -2 and -3 [2]. Serious cutaneous adverse effects of TKIs tend to occur during the initial two months of treatment, particularly in males and older patients [3]. Major adverse effects of pazopanib include hypertension, diarrhoea, hair colour changes, nausea, anorexia, and vomiting, whereas cutaneous manifestations are rare [3]. Hand-foot syndrome is frequently seen in patients treated with sorafenib and sunitinib, but less commonly with pazopanib [4]. Regarding the skin ulcers associated with pazopanib, there are only two similar published case reports [5, 6]. Both cases presented with multiple ulcers on the lower legs, as in our patient. To the best of our knowledge, detailed histopathological features of vascular degeneration have never been described in patients treated with pazopanib. In the present case, the vascular degeneration lacked apparent active vasculitis, suggesting that the vascular change was primarily due to the anti-angiogenic effect of pazopanib, rather than to vasculitis. Further cases should be accumulated to elucidate more precisely the mechanisms of pazopanib-associated skin ulcers. ■

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Fibroblastic connective tissue nevus: the role of histopathological and molecular techniques in differential diagnosis

Fibroblastic connective tissue nevus (FCTN) is a rare benign cutaneous mesenchymal lesion of fibroblastic/myofibroblastic origin, first described by Feraudy and Fletcher [1], and almost simultaneously by Saussine *et al*. as "cellular connective tissue nevus" [2]. This lesion typically occurs on the trunk, head, and neck of children. Histopathologically, it is a poorly-circumscribed, unencapsulated lesion, composed of fibroblastic/myofibroblastic spindle cells in the reticular dermis and subcutis, with overlying epidermal papillomatosis. The neoplastic cells are positive or negative for CD34 as well as alpha-smooth muscle actin (α-SMA) [1]. Cytological atypia and pleomorphism are rare. The cells characteristically proliferate in short-intersecting fascicles in a disorderly manner and entrap skin appendages. We report a case of FCTN lacking collagen type1 α1 (*COL1A1*)/platelet-derived growth factor B-chain (*PDGFB*) fusion transcripts, as observed by reverse transcription polymerase chain reaction (RT-PCR) and discuss the relevance of this finding in the differential diagnosis of FCTN.

A nine-year-old girl was referred to us with a two-year history of a slightly brown nodule on the left side of the back, measuring 9×6 mm (*figure 1A*). Excisional biopsy was performed for diagnosis and treatment. Histopathologically, the epidermis showed papillomatosis. The tumour was poorly circumscribed and composed of spindle cells in the reticular dermis and subcutaneous tissue (*figure 1B-E*). The spindle cells were arranged in a disorderly manner without notable nuclear pleomorphism or mitotic figures (*figure 1C, D*). Adnexal structures of the skin were entrapped but not destroyed. In the subcutis, fascicles of spindle cells traversed the adipose tissue (*figure 1E*). Immunohistochemically, the spindle cells were positive for CD34 (*figure 1F*), but negative for S100 protein, CD99, and Bcl-2.

The differential diagnoses considered for this lesion, made of CD34+/S100 protein-spindle cells, included plaque-like CD34-positive dermal fibroma, lipofibromatosis, and dermatofibrosarcoma protuberans (DFSP). Plaque-like CD34-positive dermal fibroma presents as a band-like fibroblastic proliferation in the upper two thirds of the dermis and rarely extends into the subcutis [3]. Lipofibromatosis occurs primarily in deep soft tissue of the extremities and contains adipose tissue as an integral component [4]. These two conditions were therefore ruled out. DFSP is typically composed of spindle cells arranged in a storiform pattern, but the pattern can sometimes be inconspicuous without epidermal papillomatosis. Although FCTN generally shows weak and focal CD34 positivity, some cases show strong and diffuse positivity, as in DFSP. Nevertheless, the lack of *COL1A1-PDGFB* fusion