Letters to the Editor

Title

Squamous cell carcinoma arising in a chronic leg ulcer in Klippel-Trenaunay syndrome after the Charles procedure: A case with 40 years of follow-up

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Running title: SCC in KTS after Charles procedure

Dear Editor,

Klippel-Trenaunay syndrome (KTS) is a congenital limb overgrowth disorder characterized by slow-flow vascular malformations. We report here a case of KTS with 40 years of follow-up in which squamous cell carcinoma (SCC) developed in a chronic leg ulcer after the Charles procedure.

A 1-year-old boy was originally referred to our hospital for evaluation of congenital port wine stains on the lateral side of an edematous right lower limb. At age 5, he underwent the Charles procedure for the lower leg edema. Thereafter, he has had recurrent leg ulcers and cellulitis in the affected limb (Fig. 1a,b,c). From age of 20 onward, he has undergone several sessions of sclerotherapy and debulking surgery for treatment of the affected painful thigh. At age 37, he developed a leg ulcer on the medial malleolus of the affected limb, which enlarged under conservative treatment (Fig. 1d). Within 1 year, a 4.5 × 3.5 cm ulcer with hyperkeratosis was noted (Fig. 1e). The histopathological diagnosis from the biopsy specimen was SCC, rather than pseudocarcinomatous hyperplasia, based on the results of immunohistochemical staining for p53 (Fig. 1f) and Ki-67. Following wide excision, the wound defect was covered with a split-thickness skin graft after histopathological confirmation. There has been no recurrence of the tumor in the 2 years of follow-up to date (Fig. 1g,h,i).

Skin ulceration is considered an uncommon complication in patients with KTS, with prevalence reported at 7.6%.[1] There have been only three reports of the development of skin cancer in KTS in association with a skin ulcer on an affected lower limb.[2-4] These were two cases of basal cell carcinoma, one in a 38-year-old woman with a small knee ulcer of 7 years' duration[2] and the other in a 61-year-old woman with a large foot ulcer of 3 years' duration,[4] and one case of SCC in a 48-year-old woman with a large ankle ulcer of 10 years' duration. Although an association between KTS and skin cancer is difficult to prove, chronic

skin ulcers that are refractory to treatment may indicate an underlying skin cancer in patients with KTS.[3, 4] In patients with chronic skin ulcers, it is essential to distinguish between SCC and pseudocarcinomatous hyperplasia, a benign condition characterized by a reactive proliferation of the epithelium.

In general, appropriate conservative treatment with graduated compression garments is beneficial for patients with KTS.[1] Inappropriate surgical treatment may damage the already impaired venous and lymphatic circulation with further worsening of venous insufficiency and limb swelling. The Charles procedure is the most extensive debulking surgery utilized in lower limb primary lymphedema, involving radical excision of the affected skin in its entirety and the subcutaneous tissues down to the deep fascia, then coverage using split skin grafts salvaged from the specimen. The potential long-term complications of this procedure include recurrent cellulitis, skin ulceration, and poor cosmetic results such as verrucous hypertrophy.[5] To our knowledge, this is the first report of a patient with KTS who had undergone the Charles procedure and developed SCC in a chronic leg ulcer.

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Conflict of Interest

None declared.

References

1 Gloviczki P, Stanson AW, Stickler GB *et al.* Klippel-Trenaunay syndrome: the risks and benefits of vascular interventions. *Surgery* 1991; **110**: 469-479.

2 Salman SM, Phillips T, Rogers GS. Klippel-Trenaunay syndrome and cutaneous carcinomas. *J Dermatol Surg Oncol* 1993; **19**: 582-584.

3 De Simone C, Giampetruzzi AR, Guerriero C, De Masi M, Amerio P, Cina G. Squamous cell carcinoma arising in a venous ulcer as a complication of the Klippel-Trenaunay syndrome. *Clin Exp Dermatol* 2002; **27**: 209-211.

4 Langner D, Heining B, Schonlebe J *et al.* Foot ulcers in Klippel-Trenaunay syndrome: two case reports and one metatypical basal cell carcinoma. *J Biol Regul Homeost Agents* 2015; **29**: 27-30.

5 Miller TA. Charles procedure for lymphedema: a warning. *Am J Surg* 1980; **139**: 290-292.

Figure

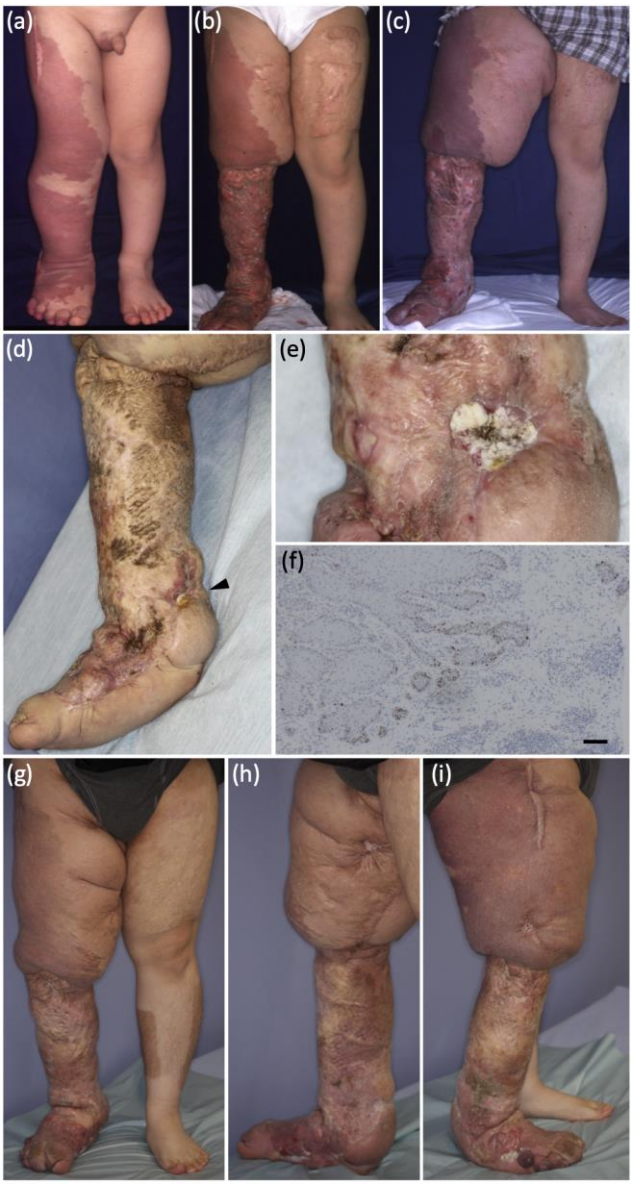

Figure 1. A male patient with Klippel-Trenaunay syndrome **(a)** at age 5 years, **(b)** at age 11 years after the Charles procedure, and **(c)** at age 20 years before sclerotherapy and debulking surgery of the affected thigh. **(d)** A leg ulcer on the medial malleolus of the affected limb at age 37 years. **(e)** The enlarged ulcer (4.5 × 3.5 cm) with hyperkeratosis at age 38 years. **(f)** Immunohistochemical staining for p53 in the biopsy specimen of the ulcer is strongly positive in the atypical nuclei of the epithelium, which led to the diagnosis of squamous cell carcinoma. Bar, 100 μm. At age 40 years, **(g)** front view of the lower limbs and **(h)** medial and **(i)** lateral aspects of the affected limb without tumor recurrence.