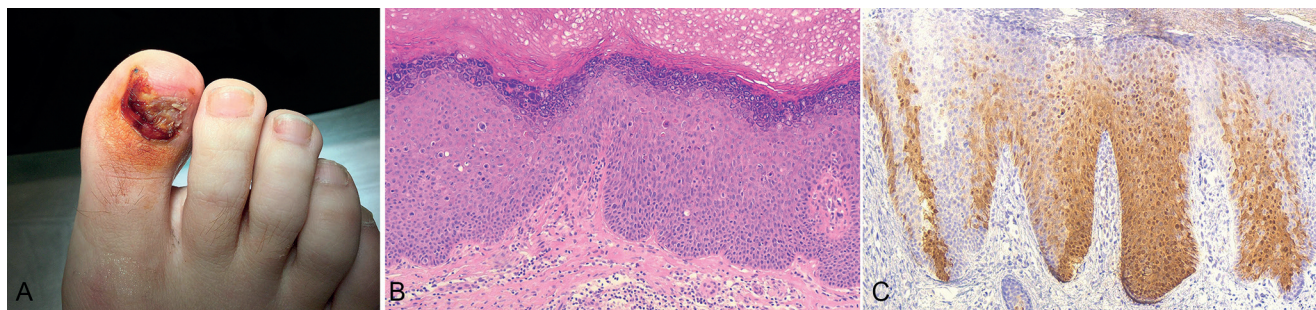


Appendix S1

### SUPPLEMENTARY CASE REPORT

**Patient 2.** A 31-year-old Caucasian woman presented with complete destruction of the nail apparatus of the right hallux. (SFig. 1A). The patient had noticed the lesion 2 years previously, beginning at the lateral and proximal nail fold. At that time, a diagnosis of onychomycosis had been made, and treatment with oral terbinafine had been initiated, without clinical improvement. The patient had a history of plantar warts on the same foot that had been surgically removed. She was HIV-negative and denied

trauma and exposure to radiation. Further examination of the skin and mucous membranes was unremarkable. Her general medical history was unremarkable including a lack of HPV-associated anogenital disease, but the patient was a heavy cigarette smoker, which constitutes a risk factor for persistent HPV-infection and HPV-induced disease. A lesional skin biopsy revealed typical histological features of SCC *in situ* (SFig. 1B), and p16<sup>INK4a</sup>-immunostaining was strongly positive (SFig. 1C). HPV-analyses showed infection with HPV16 and a high lesional HPV16 load (15,250 HPV16 DNA copies per beta-globin gene copy). The lesion was surgically removed, with a margin of 5 mm, followed by wound healing by secondary intention.



**SFig. 1. Patient 2.** (A) Clinical findings at first presentation in our department. Complete destruction of the nail apparatus of the right hallux with serosanguineous discharge. (B) Histopathological findings of a representative lesional biopsy. Atypical keratinocytes, koilocytes and numerous mitoses are present in the epidermis, consistent with squamous cell carcinoma *in situ* (original magnification 200×). (C) Immunohistochemical staining with p16<sup>INK4a</sup>. Strong nuclear and cytoplasmic p16<sup>INK4a</sup>-expression is present in the epithelium (original magnification 200×).