

# Squamous Cell Carcinoma of the Nail Bed: Is Finger Predominance Another Clue to Etiology? A Report of 5 Cases

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*Although squamous cell carcinoma (SCC) is commonly found on sun-exposed skin, the occurrence of this malignancy in the nail bed is rare. We report 5 cases of SCC of the nail bed and suggest that the disproportionate number of neoplasms of this type on the second, third, and fourth fingers, combined with the known relationship of SCC and human papillomavirus (HPV), is evidence that most SCC of the nail bed result from contact with HPV. Moreover, we suggest that patients who present with new, verrucous lesions of the nail bed and have a history of cervical dysplasia, cervical carcinoma, or condyloma acuminata undergo diagnostic biopsy as opposed to traditional destructive therapy for a lesion presumed benign.*

**S**quamous cell carcinoma (SCC) frequently develops on skin that has been exposed to sun, but the occurrence of this malignancy in the nail bed is uncommon. We report 5 cases of SCC of the nail bed and suggest that the disproportionate number of neoplasms of this type on the index, middle, and ring fingers, combined with the known relationship of SCC and human papillomavirus (HPV), is evidence that most SCC of the nail bed result from contact with HPV. In our opinion, patients with verrucous lesions of the nail bed, especially those with a history of cervical dysplasia, cervical carcinoma, or condyloma acuminata, should be evaluated for the possibility of SCC and undergo diagnostic biopsy before the destruction of any lesion presumed benign.



**FIGURE 1.** A longitudinal depression of the nail plate on the radial side of the right third finger (patient 1).



**FIGURE 2.** High-power magnification of the affected digit in Figure 1. Subtle darkening of the depressed nail plate and focal erosion of the proximal nail plate to the underlying nail bed are visible (patient 1).

## Case Reports

**Patient 1**—A 71-year-old right-handed woman presented with the chief complaint of an irregular growth of the nail on her right middle finger. She was unsure of the duration of her disease and was in no discomfort. There was no history of trauma. She

admitted to prior treatment with an unspecified oral antifungal medication but had not experienced improvement.

Examination of the right third finger revealed a longitudinal depression of the nail plate on the radial side (Figures 1 and 2). Subtle darkening of the depressed area was evident. The area was nontender, and focal erosion of the proximal nail plate to the underlying nail bed was noted. No regional adenopathy was identified. A biopsy of the proximal nail bed revealed poorly differentiated SCC with verrucous features. No solar alteration of the subepithelial connective tissue was seen. Immunoperoxidase (IP) stains for HPV demonstrated background staining as a consequence of extensive necrosis of neoplastic cells and were inconclusive. Radiologic studies of the bone were negative for invasive disease.

In surgery, the entire nail plate, nail bed, and nail matrix were excised to the level of the underlying distal phalanx. Histologic examination by frozen section showed the margins of the excised tissue to be tumor free. An abdominal pedicle flap was created and attached to the distal portion of the right middle finger defect (Figure 3). The patient tolerated the procedure well. At 16 days, the abdominal pedicle flap was divided and closed, and the distal portion of the graft on the finger was repaired (Figure 4). At the 6-month follow-up examination, healing was complete and no evidence of recurrence was noted.

*Patient 2*—A 47-year-old right-handed woman presented with the chief complaint of a nail abnormality on her right middle finger. Although asymptomatic, she was troubled by the appearance of the nail and the failure of the condition to respond to the oral itraconazole therapy prescribed by her primary care physician. There was no history of trauma or verrucae at the site.

Examination of the right third finger revealed mild longitudinal elevation of the radial side of the nail plate. A longitudinally oriented, firm, nontender, subungual mass extending to the lateral nail fold was evident (Figure 5). Initial radiographic studies of the digit were negative for pathologic changes. No regional adenopathy was noted. A biopsy revealed a proliferation of strikingly atypical keratinocytes in irregular aggregations that extended into the subepithelial connective tissue at the base of the specimen. No solar alteration was noted. The findings were diagnostic of SCC. Special stains for L1 capsid protein of HPV were positive throughout the neoplasm. A bone scan showed increased radioisotope accumulation in the distal phalanx, a finding indicative of the neoplasm's invasion of the underlying bone.



**FIGURE 3.** An abdominal pedicle flap, which was created to repair the defect after excision of SCC of the nail plate, nail bed, and nail matrix to the level of the underlying distal phalanx (patient 1).

An amputation of the right middle finger at the distal interphalangeal joint was performed. Histologic examination by frozen section showed the proximal portions of the amputated digit to be tumor free. The defect was repaired with volar flap reconstruction and, at 1 month, no complications from surgery were evident.

*Patient 3*—A 52-year-old right-handed woman presented with a 9-month history of tenderness and abnormal growth of her right fourth fingernail. Over the preceding 6 months, she had been treated with griseofulvin for onychomycosis of the fingers and toes. The other nails improved, but the one on her right ring finger remained tender and unchanged in appearance. The patient denied any trauma to the finger or nail, but she acknowledged a history of warts on her fingers.

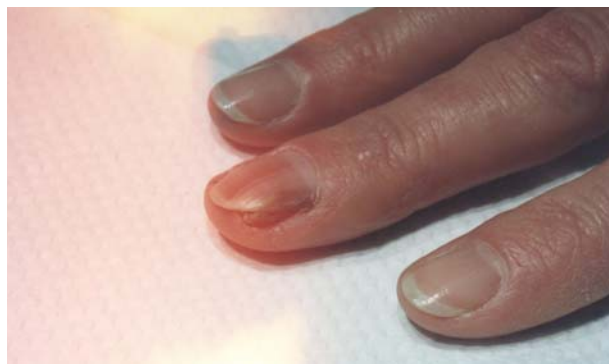
Examination of the right fourth finger revealed a tender, firm, hyperkeratotic papule with a bent, misshapen fingernail of normal thickness that was separated distally from the nail bed. There was no axillary lymphadenopathy. A punch biopsy revealed moderately differentiated SCC with no evidence of solar elastosis. Special stains for HPV were attempted, but only a small amount of tissue was available for study, and the results were inconclusive.

The patient underwent 3 stages of Mohs' surgery for removal of the neoplasm. The operative defect measured 13×14×5 mm and extended to the periosteum, but the nail matrix was spared. The defect was allowed to heal by secondary intention. There was no evidence of recurrence after 2 years, and although nail regrowth was normal, the nail plate did not reattach to the nail bed.

*Patient 4*—An 89-year-old right-handed man presented with a nonhealing lesion on his right fourth finger. He believed the lesion began to form 6 months earlier when he injured the nail bed while trimming



**FIGURE 4.** At 16 days, the abdominal pedicle flap was divided and closed, and the distal portion of the graft on the finger was repaired (patient 1).



**FIGURE 5.** A longitudinally oriented, firm, nontender, subungual mass of the radial side of the nail plate on the right third finger overtaking the lateral nail fold (patient 2).

the nail. He presented to our Department of Dermatology after receiving care from his family physician, whose regimen of oral antibiotics, soaks, and topical nystatin/triamcinolone cream failed to cause improvement.

Examination revealed that the lateral portion of the nail plate was absent. A beefy, red nodule resembling granulated tissue was evident. There was erythema and swelling of the lateral and proximal nail folds, and the area was tender to palpation. No adenopathy was identified. A biopsy revealed SCC of the nail bed with superficial dermal invasion, and IP stains for L1 capsid protein of HPV were positive.

The patient was referred to a hand surgeon for surgical treatment, but declined partial amputation and was not a candidate for a cross-finger flap because of considerable risk of postprocedure joint stiffness. The lesion was treated by a radiation oncologist with 6160 rad of electron beam therapy over 6 weeks. At 1 year, the affected finger was well healed, the nail plate was completely regrown, and there were no complications.

*Patient 5*—A 72-year-old right-handed man presented with complaints of a painful growth on the nail bed of his left middle finger. He stated that the lesion had been present for 3 to 4 weeks. The patient had been taking cimetidine for a stomach ailment for a number of years. No treatment had been initiated for the nail disorder, and the patient was concerned because it had failed to heal.

Examination of the affected digit revealed a hyperkeratotic nodule of the nail bed with peripheral erythema. The lesion was tender to palpation. Regional adenopathy was not identified. A curettage biopsy revealed SCC with superficial dermal invasion, and IP stains for HPV were positive.

A surgical procedure to completely excise the remainder of the lesion was recommended, but the

patient declined. Six treatments with Grenz radiation totaling 6000 rad were administered to the nail bed, were well tolerated, and produced no complications. The area healed with no evidence of recurrence after 7 months.

### Comment

Although acral SCC is the most common primary neoplasm of the hand, its overall incidence relative to other cutaneous neoplasms is low.<sup>1</sup> The exact etiology of this neoplasm is unknown, but possible agents include chronic solar radiation, x-irradiation, chronic inflammation, and HPV. Ultraviolet radiation is the most common oncogenic stimulus for the development of SCC on glabrous skin. Ultraviolet A penetrates the nail plate, but ultraviolet B is blocked by nail plate keratin; therefore, ultraviolet exposure probably plays a minor role in the development of subungual SCC.

The fact that many patients have extensive solar alteration of the skin on the dorsa of the hands but few develop subungual SCC strongly suggests that another factor is involved in the development of these lesions. A number of studies have been conducted to evaluate the possible role of HPV in causing subungual SCC.<sup>2-5</sup> HPV, especially types 16 and 18, are known carcinogens, and these viruses have been strongly implicated as the cause of noncutaneous SCC of the uterine cervix,<sup>6-8</sup> cutaneous SCC in renal allograft patients,<sup>9</sup> SCC of the anogenital area, and SCC that develops in patients with epidermodysplasia verruciformis.<sup>10-12</sup>

Although most cases of extragenital SCC are not associated with HPV,<sup>13-15</sup> studies have demonstrated that more than 60% of SCC of the nail bed contain HPV 16 DNA.<sup>3-5</sup> Several reports found patients with periungual verrucae who had the same HPV strains as those found in the HPV-induced lesions of the geni-

Table 1.

**Location of Digits With SCC of the Nail Bed**

Author	Case No.	Finger	Hand Dominance
Moy et al <sup>3</sup>	1a	L2	NA
	1b	L3	NA
	2	R4	NA
	3	R2	NA
	4	L3	NA
	5	L4	NA
	6	L3	NA
	7	R2	NA
	8	L4	NA
9	R1	NA	
Ashinoff et al <sup>4</sup>	1	L3	NA
	2	L2	NA
	3	R3	NA
	4	R4	NA
	5	R1	NA
	6	R3	NA
	7	R1	NA
	8	R5	NA
	9	L2	NA
	10	L4	NA
	11	R3	NA
	12	L3	NA
This study	1	R3	Right
	2	R3	Right
	3	R4	Right
	4	R4	Right
	5	L3	Right

NA indicates not available.

tal tract.<sup>16-18</sup> A recent report by Forslund et al<sup>18</sup> described 2 cases in which each patient's DNA sequences from HPV of Bowen's disease of the fingers were compared with the patient's DNA sequences from archival samples of genital dysplasia. The HPV 16 DNA sequences found in the finger lesions and in genital tissue were identical in each case.<sup>18</sup> It was concluded that autoinoculation of HPV was a plausible explanation for the development of Bowen's disease of the fingers in these patients.<sup>18</sup> Thus, the evidence that most subungual SCC are caused by HPV is strong. In 3 of our cases that were acceptable for evaluation, immunohistochemical staining for HPV was positive, which further corroborates this theory.

To date, no studies have evaluated which specific finger or fingers are most likely to be affected by subungual SCC. To assess whether there was predilection for the involvement of a specific digit, we evaluated historical information from studies by Moy et al<sup>3</sup> and Ashinoff et al<sup>4</sup> and examined the informa-

tion from our 5 patients. These data are summarized in Table 1. Although no particular digit is affected more often than others, the index, middle, and ring fingers were involved in 23 of 27 (85.2%) cases reviewed. Neoplasms affecting the second and third fingers alone accounted for 16 of 27 (59.3%) cases reviewed. Information regarding hand dominance was available from only 5 patients, and the neoplasm occurred on the dominant hand in 4 of those cases. The number of cases in which hand dominance is known is too small to produce significant conclusions. However, in the context of the predominantly affected fingers, we are led to speculate that these digits are more commonly affected because they are the ones that patients use most often to pick, poke, or probe. This supports the concept that HPV can be traumatically implanted and may produce a neoplasm.

Because primary SCC of the nail bed can easily mimic benign lesions such as verrucae, a high index

of clinical suspicion for malignancy in nail bed lesions is recommended. These neoplasms may masquerade as infections such as onychomycosis, or a concomitant infection may obscure them.<sup>19</sup> Often, these lesions are more destructive than SCC of glabrous skin because they may involve bone and can metastasize.<sup>20</sup> Perhaps traditional destructive methods of treatment for solitary presumed-benign lesions of the nail bed should be reconsidered in favor of procedures from which a diagnosis can be histologically confirmed. However, the presence of verrucous lesions of the nail bed occurring simultaneously on multiple digits should not be construed as a criterion for the exclusion of malignancy because several cases of multiple SCC of the nail bed have been reported.<sup>21-23</sup> Additionally, inquiries regarding a history of cervical dysplasia, condyloma acuminata, genital tract cancer, and the resemblance of Portnoy's condition should be made during the patient's initial evaluation.<sup>24</sup> A subungual lesion found in an individual who has a history of an HPV-associated neoplasm might be more likely to represent subungual SCC.

Periungual HPV infections occur frequently in children and are most commonly caused by HPV types 1, 2, and 4.<sup>25,26</sup> The assumption that periungual verrucae are not at the same risk for SCC as lesions of the nail bed is based solely on the HPV subtype and its known association with SCC of the nail bed.<sup>2-6,16-18</sup> A recent study that was supported by the predominance of HPV types 1, 2, 3, and 4 in genital warts in children proposed that hand to genital contact causes many cases of pediatric genital warts.<sup>26</sup> It is equally plausible that, irrespective of age, genital to hand contact also may play a role in the formation of genital warts. Controlled studies would be necessary to evaluate this fully. However, histologic evaluations of solitary nail bed lesions in children should be considered, especially when a presumed benign lesion has been unresponsive to therapy.

Subungual SCC is generally treated by surgical excision. Two of our patients responded well to this procedure and histologic verification of removal by frozen section. Mohs' surgery, which was utilized in the third case, is another method by which complete removal of the neoplasm can be achieved with a high degree of success.<sup>27-29</sup> Because this technique allows for histologic verification of removal at the time of surgery, it is considered the treatment of choice by many. However, because the surgical defects produced by excision and Mohs' surgery may be severe and the skin is difficult to close, complicated methods of closure are usually required. An abdominal pedicle flap was utilized in one of our patients because of the exposed bone and the ability of an island flap to maintain good blood supply.<sup>30</sup> Volar flap reconstruction, used to

repair the postamputation defect in the second patient, is a common method of stump repair, especially when the thumb is amputated.<sup>31</sup> Properly applied, this technique provides for good repair of the amputation defect while enabling length to be maintained.<sup>31</sup>

Radiation therapy was utilized in 2 of our patients and remains a viable treatment option for selected cutaneous neoplasms. It is an especially good choice when the patient is unable to tolerate surgery or is unwilling to undergo an involved or potentially disfiguring procedure. Radiation surgery also may be used as adjunctive therapy for lesions with high rates of local recurrence after primary excision.<sup>32</sup>

### Conclusion

SCC is an uncommon neoplasm that has been linked to HPV infection. In our opinion, the frequency with which SCC occurs on the index, middle, and ring fingers supports the theory that this neoplasm is the result of traumatic implantation of the virus. A diagnosis may be delayed because SCC may simulate other less serious processes; this puts patients at risk for dangerous sequelae such as bone involvement and subsequent metastasis. A high index of suspicion is required, and appropriate diagnostic techniques, including biopsy, should be undertaken in any lesion that could involve SCC.

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