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Digital squamous cell carcinoma associated with possibly carcinogenic human papillomavirus type 73 (HPV73): a case report

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Abstract

We present a case report of a 64-year-old female patient with a 5-year history of a digital papule that clinically mimicked a common wart but was histologically diagnosed as digital squamous cell carcinoma (DSCC), a rare malignant cutaneous entity etiologically associated with high-risk human papillomaviruses (HR HPVs). This DSCC was positive for HPV73, which is currently classified under possible human carcinogens and has already been identified in DSCCs. Treatment with electrocoagulation and subsequent total excision with safety margins was successful, and no recurrence was detected during 6 years of follow-up. Analogously to cervical and other anogenital carcinomas, we assume that the incidence of DSCC will significantly decrease in the near future due to the widespread use of effective prophylactic HPV vaccines, which cover the majority of HR HPV types also associated with DSCC. However, HPV73 and other possibly carcinogenic and HR HPV types (as classified per the International Agency for Research on Cancer), which are not included in current prophylactic measures, will cause some portion of HPV-associated neoplasms, but this portion will be very minor.

Keywords: digital papule, digital squamous cell carcinoma, human papillomavirus, common wart, HPV73, carcinogens

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Introduction

In recent decades, more than 200 different human papillomavirus (HPV) types have been identified, with the clinically most important being *Alpha*-HPVs, which cause the great majority of HPV-associated benign and malignant lesions of mucosae and the skin (1). According to the classification of the International Agency for Research on Cancer (IARC), HPVs are classified depending on the risk of causing cervical and other anogenital cancers to become high-risk (HR), probably carcinogenic, possibly carcinogenic, not classifiable, and low-risk (LR) HPV types (2). The following 12 HPVs are currently recognized as HR carcinogenic agents: HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, and HPV59. They are involved in the development of the majority of cervical and anal carcinomas and a substantial portion of penile, vulvar, vaginal, and oropharyngeal cancers (3). On the other hand, LR HPV types cause benign mucosal lesions, such as anogenital warts and laryngeal papillomas, which are mainly associated with HPV6 and HPV11 (4), and ubiquitous cutaneous warts, which are most frequently etiologically associated with HPV1, HPV2, HPV27, and HPV57 (5–7). However, the clinical presentation of cutaneous warts is variable and they can be misdiagnosed as calluses, fibromas, seborrheic keratoses, molluscum contagiosum, condylomas, and even squamous cell carcinoma (SCC) or melanoma (8, 9). Therefore, histopathological examination is considered a gold standard for reliable diagnosis of warty skin lesions (10).

Case presentation

A 64-year-old woman presented with a 5-year history of a slightly erythematous and keratotic papule on the fifth finger of her dominant right hand (Fig. 1). The lesion was painful and aesthetically disturbing, and it persisted after two cryotherapy sessions with liquid nitrogen, which was performed due to an assumed common wart. The patient's history was significant for arterial hypertension, dyslipidemia, dyspepsia, allergic asthma, and pollen allergy. Her medications comprised fexofenadine, perindopril, atorvastatin, omeprazole, inhaled formoterol, and beclomethasone.

The patient was invited to participate in a recent study of common warts (7) and her written consent was obtained. In line with the study protocol, a 3 mm punch biopsy of the lesion was performed with subsequent total electrocoagulation. Microscopic examination revealed acanthotic epidermis, covered with thick parakeratotic scale (Fig. 2) and atypical epithelial changes comprising nuclear hyperchromatism, multinucleation of keratinocytes, cytoplasmic

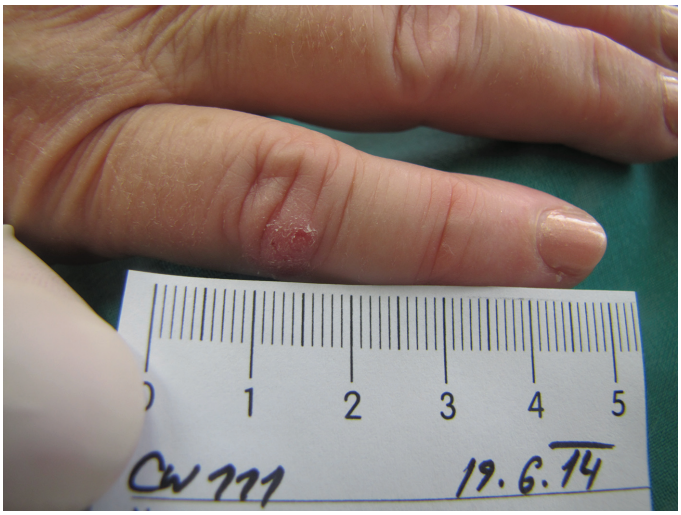

Figure 1 | Erythematous papule with a roughened surface on the dorsal side of the fifth finger, measuring 6 mm in diameter.

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perinuclear vacuolation, rare dyskeratotic cells, increased mitotic activity, and atypical mitoses (Fig. 3). The histopathological features were consistent with a bowenoid type of intraepithelial SCC. Subsequently, a fresh tissue sample was tested using two broad spectrum in-house PCRs targeting altogether 54 LR and HR *Alpha*-HPVs (HPV2, HPV3, HPV6, HPV7, HPV10, HPV11, HPV13, HPV16, HPV18, HPV26, HPV27, HPV28, HPV29, HPV30, HPV31, HPV32, HPV33, HPV34, HPV35, HPV39, HPV40, HPV42, HPV43, HPV44, HPV45, HPV51, HPV52, HPV53, HPV54, HPV55, HPV57, HPV56, HPV58, HPV59, HPV61, HPV66, HPV68, HPV70, HPV71, HPV72, HPV73, HPV74, HPV77, HPV81, HPV82, HPVsub82, HPV83, HPV84, HPV89, HPV90, HPV91, HPV94, HPV117, and HPV125) in combination with Sanger sequencing of the PCR products, as described previously (11). HPV73 was identified as the only HPV type present in the tissue sample. The patient was referred to a plastic surgeon for total excision with a safety margin. Histopathological examination of the excised tissue revealed no residual malignant keratinocytes and only small foreign body granulomas with scarring tissue (due to primary treatment with electrocoagulation). No recurrence of digital SCC (DSCC) was detected during 6 years of follow-up.

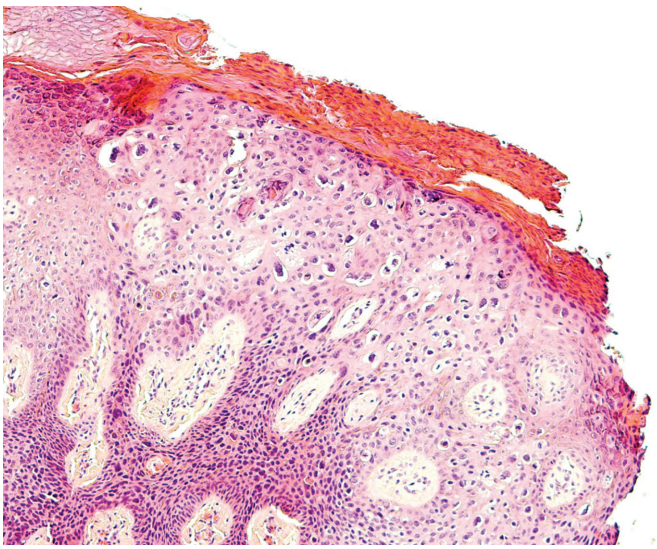

Figure 2 | Intraepithelial squamous cell carcinoma of the bowenoid type with acanthotic epidermis, covered with a thick parakeratotic scale (H&E staining, 100×).

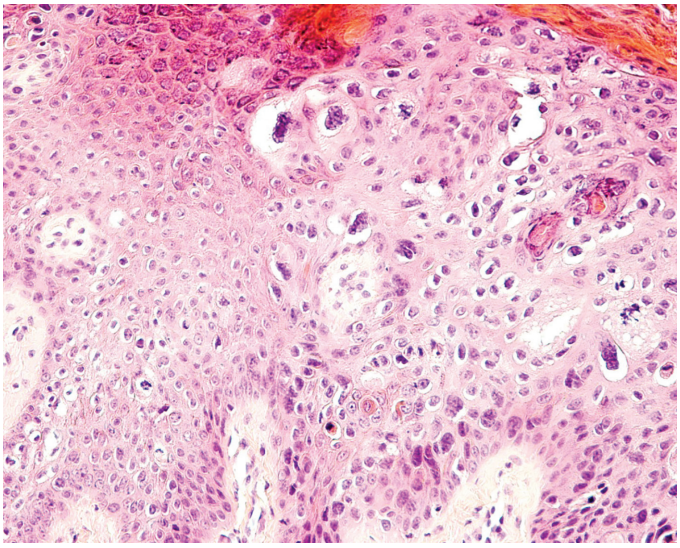

Figure 3 | Koilocytotic changes with hyperchromatic and multinucleated nuclei, dyskeratotic cells, and atypical mitoses (H&E staining, 200×).

Discussion

In the patient presented, a digital papule with a roughened surface was first clinically diagnosed as a common wart (12), a LR HPV-associated lesion that occurs in approximately 3.5% of adults (13) and is usually of long duration due to lack of effective treatment or prophylactic measures (14). However, differential diagnosis of a digital papule is extensive and encompasses both benign and malignant lesions. A benign digital papule usually represents a common wart and less frequently an acquired digital fibroma, periungual fibroma, neurofibroma, ganglion, epidermal inclusion cyst, pyogenic granuloma, glomus tumor, large-cell tumor of the synovia, or poroma, whereas a malignant digital papule comprises SCC, basal cell carcinoma (BCC), keratoacanthoma, melanoma, porocarcinoma, epithelioid sarcoma, and metastasis (15).

Remarkably, histopathological examination of the patient's digital papule revealed intraepithelial SCC with signs of koilocytosis, which represents a pathognomonic feature of HPV infection (16). Additional molecular diagnostics targeting broad-spectrum *Alpha*-PVs ascertained a relatively uncommon and possibly carcinogenic HPV type, HPV73 (2), and the diagnosis of DSCC was established. Due to the largely unknown carcinogenic potential of HPVs from four other genera in immunocompetent patients, we decided not to extend the spectrum of HPVs tested in this sample.

In contrast to more frequent and well-studied HPV-associated mucosal SCCs, HPV-associated cutaneous SCCs are relatively rare and can present in 1) patients with *epidermodysplasia verruciformis*, a rare autosomal recessive genodermatosis with an increased susceptibility to specific HPV types, mostly *Beta*-PVs, and a predisposition to numerous wart-like lesions and SCCs (17), 2) immunocompromised patients, especially organ transplant recipients and HIV-infected individuals (usually associated with *Beta*-PVs) (18–20), and in 3) immunocompetent patients, whose SCCs are predominantly associated with HR *Alpha*-PVs, which are frequently found on the fingers and are thus designated DSCC (22).

DSCC is diagnostically challenging because it is a relatively rare entity with approximately 200 cases reported in the literature (23) and because it mimics more common benign skin lesions, possibly resulting in a delay in diagnosis up to 5 years (24), as seen in the patient presented. Clinically, it usually manifests as a verrucous papule or plaque, particularly on the peri- and subungual skin, and it can also cause nail changes such as onycholysis, onychodystrophy, and longitudinal melanonychia (24).

Riddle et al. analyzed 120 DSCCs and found that they usually present as a solitary lesion on the right dominant hand with average duration of 5.3 years in immunocompetent patients with an average age of 58.2 years (range 22 to 89 years) (22), similar to our case. However, a preponderance of male gender was reported (22, 24). In the patient presented, surgical excision of DSCC was carried out in addition to previous electrocoagulation due to an inability to reliably determine the level of invasion in the biopsy tissue and because of the high prevalence of recurrences of DSCCs, which is estimated at 26% and 43% after Mohs micrographic surgery and wide surgical excision, respectively (22, 24). Amputation and adjuvant topical immunomodulatory therapy with imiquimod were reported as additional treatment options (24). Despite frequent recurrences of DSCCs, which are probably associated with the presence of HPVs in the surrounding skin, the rate of metastasis is relatively low (2 to 3%) (24). Thus, the long-term prognosis of DSCC is generally favorable. However, due to the increased risk of

developing another SCC on the fingers or the anogenital mucosa (16), from where the HPVs are most probably transmitted by the patient or their sexual partners (24), self-observation and regular screening for cervical dysplasia and cancer were advised for our patient (23).

Approximately 90% of DSCCs have been reported to be HPV-positive (24), with HR HPV16 identified in the majority (74 to 94%) of cases, whereas less frequently detected types were HPV2, HPV11, HPV18, HPV26, HPV31, HPV34, HPV35, HPV56, HPV58 (22, 24), and also HPV73 in five cases (23, 25–28).

HPV73 is classified under species 11 *Alpha*-PV (29) and was first identified in 1996 in oral papillomatous lesions with histological atypia obtained from a patient with HIV infection (30). According to the most recent IARC classification, HPV73 is considered a possibly carcinogenic biologic agent (group 2B) (2). However, according to the epidemiological classification system of oncogenic HPV types, HPV73 has been suggested for consideration as HR HPV type (Group 1) (31). At present, HPV73 is neither routinely tested during HPV-based cervical screening nor covered in any of the three existing prophylactic HPV vaccines: bivalent (HPV16/18), quadrivalent (HPV6/11/16/18), or nonavalent (HPV6/11/16/18/31/33/45/52/58) (32). The bivalent and quadrivalent vaccines, which cover the two most prevalent HR HPVs, HPV16/18, prevent the development of approximately 70% of cervical carcinomas, and the nonavalent vaccine, which covers an additional five HR HPV types, protects against more than 90% of cervical cancer (33).

Because DSCCs are most frequently associated with HPV16, HPV18, and HPV33 (22–24), we estimate that in the long term approximately three-quarters of DSCCs could also be prevented. Nevertheless, HPV73 and other possibly carcinogenic and HR HPV types (as classified per IARC), which are not included in the current prophylactic HPV vaccines, will cause some portion of HPV-associated neoplasms, but this portion will be very minor.

On the other hand, the existing prophylactic HPV vaccination might represent an efficacious strategy for prevention of keratinocyte carcinomas as reported recently in a case series of two elderly patients with multiple past keratinocyte tumors; they were vaccinated off-label with a quadrivalent HPV-vaccine and experienced an approximately 65% reduction in the number of newly developed SCCs and BCCs (34).

Conclusions

The presented case of HPV73-associated DSCC in an immunocompetent patient reinforces the suspected oncogenic nature of this HPV type. Analogously to cervical carcinoma and other anogenital carcinomas, we assume that the incidence of DSCC will significantly decrease in the near future due to the widespread use of effective and safe prophylactic HPV vaccines covering the great majority of HR HPV types also associated with DSCC. However, HPV73 and other possibly carcinogenic and HR HPV types (as classified per IARC), which are not included in current prophylactic measures, will cause some portion of HPV-associated neoplasms, but this portion will be very minor.

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