Association of human papillomavirus and extra-genital Bowen disease (squamous cell carcinoma in situ): A systematic review

To the Editor: Human papillomavirus (HPV) type is classified into 1 of 5 genera (α, β, γ, μ, and ν) and mucosal α-HPV can be divided into high- and low-risk, based on oncogenic potential.[1] Although controversial, HPV has been suggested as a potential etiologic factor for Bowen disease.[2,3] This study aimed to perform a systematic review on the relationship between HPV and extragenital Bowen disease and summarize the results of previous studies.

We systematically searched the PubMed and Embase databases on September 11, 2019. Only studies that detected HPV in human Bowen disease samples with polymerase chain reaction–based methods were included. As a result, 16 articles were included, and the details of our study method are provided in the Supplemental Fig 1 (available via Mendeley at https://data.mendeley.com/datasets/88fcgj65bf/1). All studies were retrospectively designed, with only 4 studies including a control group. From 16 studies, α-HPV was detected in 203 of 904 samples (22.5%). The most commonly detected type was HPV 16 (137 samples), followed by HPV 33 (9 samples). Most detected α-HPVs (178 samples; 87.7%) belonged to high-risk α-HPV types (Table I). From 7 studies, β-HPV was detected in 62 of 307 samples (20.2%; Table II). In total, HPV (α or β) was detected in 256 (28.3%) of 904 samples. Traditionally, the firm association of β-HPVs and squamous cell carcinoma or Bowen disease in patients with epidermodysplasia verruciformis supported the view that β-HPVs play a more important role in keratinocyte carcinogenesis.[1] On the other hand, some studies have questioned the role of β-HPV in Bowen disease and focused primarily on α-HPVs.[2] Although the total number of samples tested for α-HPV was much greater than those tested for β-HPV, both α-HPV and β-HPVs were detected in about 20% of tested samples. This suggests that both HPV types are associated with certain Bowen disease cases.

There were only limited numbers of Bowen disease samples that were positive for multiple HPV types (α-HPVs, 9 samples; β-HPVs, 8 samples; α-HPV and β-HPV codetection, 9 samples). As suspected, the HPV detection rate in samples from immunosuppressed patients (α-HPV 27.9%; β-HPV 40.5%) was higher than that in samples from immunocompetent patients (α-HPV 8.6%; β-HPV; 16.3%). Most studies failed to show any sex predilection for HPV detection except for 1 study[4] that found the proportion of HPV-positive cases was significantly higher among immunosuppressed females compared with males. Most studies failed to find any markers (koilocytosis, p16, pRb, ProExC, Ki67, p21, p53, PCNA, and Bcl-2) for HPV detection status, except for 1 study[5] that determined negative p53 is significantly correlated with HPV detection.

In conclusion, the evidence of associations between HPV and Bowen disease is currently weak (only 16 studies and mostly retrospective case-series without appropriate control subjects). However, studies consistently show that HPV is detected in a percentage of Bowen disease samples, implying that HPV may be involved in cutaneous carcinogenesis in specific situations. Further study is needed to confirm this relationship and state which HPV type (α or β) has a stronger association.

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Table I. Reported α-human papillomavirus detection rate in Bowen disease samples

Source	Study location	Study design	Study sample size, n				α-HPV detected detection rate, n (%)				Detected α-HPV types (n)
			IS	IC	U	Total	IS	IC	U	Total	
Aoki et al, 2019	Germany	Retrospective, with 10 control subjects	6	7	21	34	3 (50.0)	1 (14.3)	9 (42.9)	13 (38.2)	HPV 16 (13)
Perruchoud et al, 2016	Switzerland	Retrospective	0	0	11	11	0	0	9 (81.8)	9 (81.8)	HPVs 16 (6), 73 (2), and 52 (1)
Švajdler et al, 2016	Czech	Retrospective	0	127	0	127	0	13 (10.2)	0	13 (10.2)	HPVs 16 (6), 33 (2), 18 (1), 56 (1), 58 (1), 66 (1), and 81 (1)
Švajdler et al, 2016	Czech	Retrospective	25	0	0	25	3 (12.0)	0	0	3 (12.0)	HPVs 16 (1), 18 (1), and 78 (1)
Idriss et al, 2016	Germany	Retrospective	0	0	38	38	0	0	11 (28.9)	11 (28.9)	HPVs 6 (4), 16 (3), 90 (2), 11 (1), and 58 (1)
Murao et al, 2014	Japan	Retrospective	0	0	133	133	0	0	11 (8.3)	11 (8.3)	HPVs 16 (4), 33 (4), 6 (1), 52 (1), and 59 (1)
Park et al, 2013	Korea	Retrospective	0	30	0	30	0	2 (6.7)	0	2 (6.7)	HPVs 16 (1) and 33 (1)
Nakajima et al, 2010	Japan	Retrospective	1	42	0	43	1 (100)	5 (11.9)	0	6 (14.0)	HPVs 16 (6) and 58 (1), including 1 multiple HPV type infection
Sanchez-Hernandez et al, 2010	Spain	Retrospective	0	0	37	37	0	0	7 (18.9)	7 (18.9)	HPVs 16 (6), 11 (1), 35 (1), 45 (1), and unknown* (1), including 2 multiple HPV type infections
Hama et al, 2006	Japan	Retrospective, with 17 control subjects	0	0	21	21	0	0	1 (4.8)	1 (4.8)	HPV 31 (1)
Zheng et al, 2005	Japan	Retrospective, with 48 control subjects	0	41	0	41	0	3 (7.3)	0	3 (7.3)	HPVs 16 (2) and 33 (1)
Mitsuishi et al, 2003	Japan	Retrospective	0	0	55	55	0	0	26 (47.3)	26 (47.3)	HPVs 16 (7), 62 (5), 18 (3), 57 (2), 58 (2), 61 (2), 31 (1), 33 (1), 34 (1), 52 (1), 54 (1), and 73 (1), including 1 multiple HPV type infection
Clavel et al, 1999	France	Retrospective, with 20 control subjects	0	0	94	94	0	0	78 (83.0)	78 (83.0)	HPVs 16 (78), 31 (4), and 18 (1), including 5 multiple HPV type infections
Mitsuishi et al, 1997	Japan	Retrospective	0	12	0	12	0	8 (66.7)	0	8 (66.7)	HPVs 61 (2), 16 (1), 31 (1), 54 (1), 58 (1), 62 (1), and 73 (1)
de Villiers et al, 1997	United Kingdom	Retrospective	11	0	0	11	5 (45.5)	0	0	5 (45.5)	HPVs 57 (2) and unknown† (3)
Rübben et al, 1996	Germany	Retrospective	0	192	0	192	0	7 (3.6)	0	7 (3.6)	HPVs 16 (3) and unknown† (4)
Total			43	451	422	904	12 (27.9)	39 (8.6)	152 (36.0)	203 (22.5)	HPVs 16 (137), 33 (9), 31 (7), 18 (6), 58 (6), 62 (6), 6 (5), 57 (4), 61 (4), 73 (4), 52 (3), 11 (2), 54 (2), 90 (2), 34 (1), 35 (1), 45 (1), 56 (1), 59 (1), 66 (1), 78 (1), 81 (1), unknown* (1), and unknown† (7) including 9 multiple HPV type infections

IC, Immunocompetent; *IS*, immunosuppressed; U, unknown.
*Because of low DNA quality.
†Because of a putative new HPV type at the time of the study.

Table II. Reported β-human papillomavirus detection rate in Bowen disease samples

Source	Study location	Study design	Study sample size, n				β-HPV detected detection rate, n (%)				Detected β-HPV types (numbers of detected samples)
			IS	IC	U	Total	IS	IC	U	Total	
Švajdler et al, 2016	Czech	Retrospective	0	120	0	120	0	30 (25.0)	0	30 (25.0)	HPVs 9 (4), 24 (4), 8 (3), 25 (3), 5 (2), 21 (2), 93 (2), 105 (2), 20 (1), 23 (1), 36 (1), 37 (1), 38 (1), and unknown* (14), including 6 multiple HPV type infections
Švajdler et al, 2016	Czech	Retrospective	25	0	0	25	7 (28.0)	0	0	7 (28.0)	HPVs 9 (1), 21 (1), 96 (1), and unknown* (5), including 2 multiple HPV type infections
Nakajima et al, 2010	Japan	Retrospective	1	42	0	43	1 (100)	3 (7.1)	0	4 (9.3)	HPV 8 (4)
Zheng et al, 2005	Japan	Retrospective, with 48 control subjects	0	41	0	41	0	2 (4.9)	0	2 (4.9)	HPVs 27 (1) and 67 (1)
Mitsuishi et al, 2003	Japan	Retrospective	0	0	55	55	0	0	12 (21.8)	12 (21.8)	HPVs 5 (3), 17 (3), 20 (3), 38 (2), 23 (1), and unknown† (1), including 1 multiple HPV type infection
Mitsuishi et al, 1997	Japan	Retrospective	0	12	0	12	0	0	0	0	
de Villiers et al, 1997	United Kingdom	Retrospective	11	0	0	11	7 (63.6)	0	0	7 (63.6)	HPVs 20 (2), 23 (1), and unknown† (4)
Total			37	215	55	307	15 (40.5)	35 (16.3)	12 (21.8)	62 (20.2)	HPVs 8 (7), 20 (6), 5 (5), 9 (5), 24 (4), 17 (3), 21 (3), 23 (3), 25 (3), 38 (3), 93 (2), 105 (2), 27 (1), 36 (1), 37 (1), 76 (1), 96 (1), unknown* (19), and unknown† (5) including 9 multiple HPV type infections

IC, Immunocompetent; *IS*, immunosuppressed; U, unknown.

*Because of low DNA quality.

†Because of a putative new HPV type at the time of the study.

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Treatment outcomes in confluent and reticulated papillomatosis: A systematic review

To the Editor: Confluent and reticulated papillomatosis (CARP) is a rare dermatosis characterized by persistent, hyperpigmented, reticulated papules and plaques.[1] Various treatment options including antibiotics, antifungals, and retinoids have been reported[2]; however, no well-established guidelines or consensus statements exist for the management of CARP. The aim of this systematic review was to summarize CARP treatment options and their outcomes.

MEDLINE and Embase in OVID were searched on July 1, 2020, by using variations of the keywords "confluent and reticulated papillomatosis" and "Gougerot-Carteaud syndrome" (Supplementary Material available on Mendeley at https://doi.org/10.17632/s6p2cbk8kx.1). After screening, 70 studies consisting of 192 patients (mean age, 22.5 years; 53.1% male) and 278 treatment regimens, because some patients received multiple therapies, were included (Table I, Fig 1).

Oral tetracyclines were the most commonly reported drug class used as monotherapy (44.6%; n = 124/278), achieving complete resolution (CR) in 59.7% (n = 74/124) and partial resolution (PR) in 22.6% (n = 28/124) of cases, with a mean resolution period of 51.8 days. Specifically, minocycline was the most frequently used tetracycline (91.9%; n = 114/124), achieving CR in 61.4% (70/114) and PR in 21.1% (n = 24/114) of cases within 51.0 days. Other oral antibiotics (amoxicillin and azithromycin) were administered in 9.4% (n = 26/278) of cases, achieving CR or PR within 57.9 days in 92.3% (n = 24/26) of cases.

Oral and topical antifungal treatments achieved CR or PR within 31.6 days in 30.4% (n = 17/56) of cases; however, the majority of patients (62.5%; n = 35/56) did not notice any improvement. Oral and topical retinoid monotherapy resulted in CR or PR in 73.7% (n = 14/19) of cases within 68.8 days. Additionally, topical vitamin D derivatives, despite being uncommon treatment interventions, resulted in CR or PR in 85.7% (n = 6/7) of cases within 42.6 days.

Combination therapies, most commonly minocycline and various topical agents, were used in 9.0% (n = 25/278) of cases. Although CR was achieved in 36.0% (n = 9/25) within 58.8 days, no improvement occurred in 32.0% (n = 8/25) of cases. Treatment-related adverse events were reported in 1.6% (n = 3/192) of patients and included fatigue (minocycline and topical tretinoin), gastrointestinal symptoms (minocycline and topical lactic acid), and cheilitis (treatment unreported).

Many theories have postulated the role of bacterial or fungal infection in CARP.[3] We found that minocycline, a tetracycline derivative, was the most commonly used. Because minocycline inhibits the migration and function of neutrophils,[2] its anti-inflammatory and immunomodulatory effects may explain its effectiveness in treating CARP. In addition to the bacterial etiology, clinical resemblance between CARP and tinea versicolor has led researchers to propose the role of *Malassezia* species in CARP pathogenesis.[4] However, the majority of patients (62.5%; n = 35/56) in this review did not experience any improvement with antifungals. It is possible that patients who responded to antifungals had tinea versicolor or that their CARP cleared spontaneously and not in response to a specific agent.

A few limitations of this systematic review should be taken into consideration, including lack of high-quality randomized controlled trials, prospective studies, inaccessible full texts, and non-English studies. Additionally, the majority of the studies did not report adverse events, making the safety of treatments difficult to assess. Despite these limitations, our findings provide useful information to guide the clinical management of CARP. Although minocycline monotherapy yielded the highest reported CARP resolutions, further studies with large sample size are needed to confirm our findings.

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