

A case report of disseminated verrucosis secondary to ustekinumab in a patient with Crohn's disease

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Abstract

Ustekinumab is a biologic agent with Food and Drug Administration approval for the treatment of moderate-to-severe plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease. It functions to inhibit the p40 subunit common to both interleukin-12 and interleukin-23. These pro-inflammatory cytokines are implicated in autoinflammatory and autoimmune disorders, but they also play an important role in cell-mediated immunity against viral, bacterial, and fungal pathogens. Therefore, antagonism of interleukin-12 and interleukin-23 by ustekinumab may increase the risk of human papillomavirus infection or reactivation which can lead to the development of verrucae. To the best of our knowledge, there is only one published report of disseminated verrucosis secondary to ustekinumab treatment for psoriasis. Here, we present the first case report of ustekinumab-induced disseminated verrucosis occurring in the setting of treatment for Crohn's disease.

Keywords

Crohn's disease, disseminated verrucosis, human papillomavirus, ustekinumab, verruca vulgaris

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Introduction

Ustekinumab is a biologic agent currently Food and Drug Administration (FDA) approved for the treatment of moderate-to-severe plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease.¹ A human IgG1 kappa monoclonal antibody, ustekinumab binds to the p40 subunit of both interleukin (IL)-12 and IL-23 that are involved in inflammatory and immune responses. In addition to intrinsic diseases, these two pro-inflammatory cytokines are important for cell-mediated immunity against viral, bacterial, and fungal pathogens via CD4⁺ T-cells and natural killer cells.^{1–3} Due to its immunosuppressive properties, ustekinumab may increase the risk of infection and reactivation of latent infections, including human papillomavirus (HPV).^{1,3,4} Cutaneous infection with HPV may lead to the development of generalized warts also known as disseminated verrucae. While the safety and side-effect profile of ustekinumab is comparable to that of other biologics, clinical trials have not reported disseminated verrucae to be a known adverse effect of the drug.^{1,3,4} Based on a PubMed search performed in December of 2020, there is only one other case of disseminated verrucosis attributed to ustekinumab and it occurred in a patient treated for psoriasis.⁵ Here, we report the first case of disseminated verrucosis associated with ustekinumab in a patient with Crohn's disease.

Case report

A 59-year-old female with a history of Crohn's disease and hepatic cirrhosis presented to the dermatology clinic for sudden-onset, generalized warts. Physical exam was remarkable for numerous tan-colored, verrucous papules on the head, trunk, and extremities (Figure 1). Two months prior, she was started on ustekinumab for her Crohn's disease which had been quiescent for 3 years without immunosuppressive therapy post-ileocelectomy. The administration of ustekinumab involved a 390-mg intravenous infusion for induction therapy, followed by a 90-mg subcutaneous injection every

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Figure 1. Numerous skin-colored papules in a widespread distribution over the bilateral lower extremities.

8 weeks. The patient's other medications included gabapentin, trazodone, rifaximin, zinc sulfate, lactulose, spironolactone, and toremide, all of which she had used for years and tolerated well. She also had not started any new medications while receiving treatment with ustekinumab.

Biopsies of the verrucous lesions were performed. Histopathologic analysis was consistent with HPV infection (Figure 2) and polymerase chain reaction confirmed the presence of several HPV types including HPV types 2, 3, 16, 66, 93, 98, and 150. Among the 10 biopsied samples, HPV type 2 was the most frequently detected type with six positive samples (Table 1). Due to suspicion for ustekinumab-induced disseminated verrucosis, the medication was stopped. Cessation of the ustekinumab, in addition to treatment with liquid nitrogen cryotherapy and aminolevulinic acid photodynamic therapy, initially resulted in a significant decrease in the number of verrucae. However, the patient experienced a flare of her Crohn's disease and was subsequently restarted on ustekinumab by her gastroenterologist. This was associated with the development of numerous additional verrucae on the face, neck, trunk, and extremities. Despite new and ongoing verrucae, the patient decided to remain on ustekinumab. She continues to receive treatment with cryotherapy and aminolevulinic acid photodynamic therapy.

Discussion

The clinical and histologic presentations of the patient's disseminated verrucae were consistent with verruca vulgaris. Verruca vulgaris clinically presents with hyperkeratotic, dome-shaped papules, which histologically have spire-like papillae with vascular cores and elongated, inward-curving rete ridges

Table 1. Detection of HPV types in 10 biopsied samples.

Sample number	HPV type FAP-PCR ^a	HPV type PGMY/GP+ PCR ^b
1	Negative	HPV2
2	Negative	HPV16
3	Negative	Negative
4	HPV98	HPV2
5	Negative	HPV66
6	HPV93, HPV150	HPV3
7	HPV93	HPV2
8	Negative	HPV2
9	Negative	HPV2
10	Negative	HPV2

HPV: human papillomavirus.

^aFAP-PCR system detects broad spectrum of beta and gamma human papillomaviruses.^{6,7}

^bPGMY/GP+ PCR system detects broad spectrum of alpha human papillomaviruses.^{6,7}

(Figure 2).⁸ Of the nearly 200 HPV strains identified, HPV types 2 and 4 are most commonly associated with verruca vulgaris.⁹ As a result of cell-mediated immunity, the majority of HPV infections are subclinical and most wart manifestations typically resolve spontaneously within several years.⁸ However, treatment with immunosuppressive agents may compromise cellular host defenses and increase the risk and persistence of verrucae.^{8,10,11} Furthermore, immunosuppression is associated with the development of multiple verrucae.⁸

To our knowledge, this is the first case of ustekinumab-induced disseminated verrucosis that has been confirmed by HPV type determination utilizing nested consensus primer systems, which is the gold standard for HPV detection.^{6,7} The PGMY/GP+ system that was utilized demonstrated high sensitivity in a previously published sensitivity analysis.⁶ The majority of our patient's biopsies were positive for HPV type 2 consistent with the diagnosis of verruca vulgaris. Several other HPV types including types 3, 16, 66, 93, 98, and 150 were also identified. HPV type 3 is most commonly associated with verruca plana.⁸ HPV types 16 and 66 are classified as high-risk types due to their oncogenic potential.^{8,12} HPV types 93, 98, and 150 are classified as β -HPV. The risk of β -HPV infection is greater among iatrogenically immunosuppressed patients, and these patients are also more likely to be infected with multiple β -HPV types.¹³

IL-12 and IL-23 pathways play critical roles in mediating adaptive immune responses. In particular, IL-12 induces the helper T (Th)1 cell response and leads to the production of cytokines such as tumor necrosis factor (TNF)- α and interferon- γ which are important for controlling viral infections.^{2,14} IL-23 stimulates the differentiation of naïve Th cells into Th17 cells which assist in recruitment of neutrophils and macrophages via IL-17 pathway.^{14,15} Consequently, antagonism of IL-12 and IL-23 by biologics such as

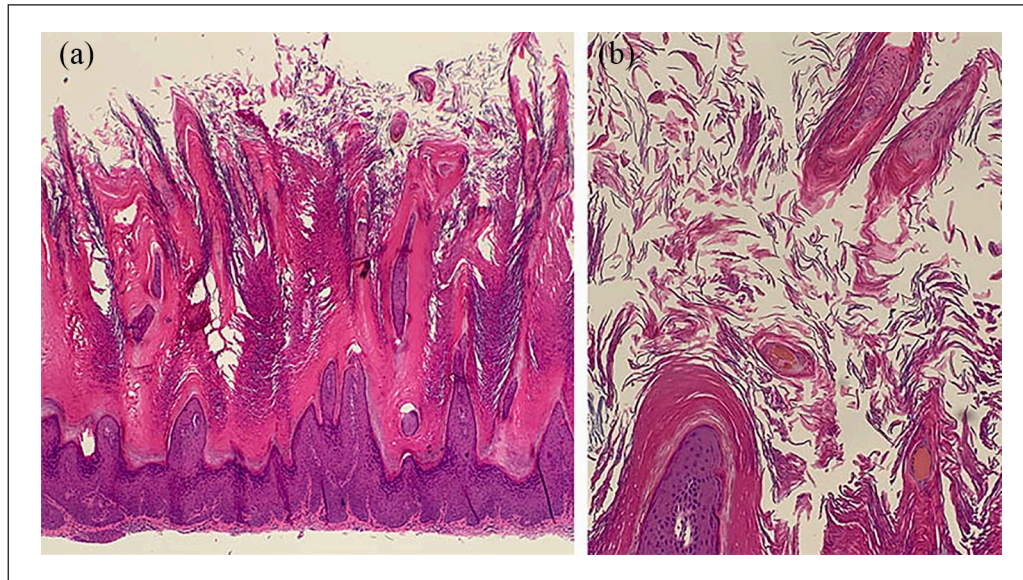


Figure 2. (a) Papillomatosis and coarse hypergranulosis prominent on the sides of the papilla with “church spire” tiered parakeratosis, and accentuation of papillary dermal vessels (H&E 40 \times). (b) Punctate regions of intracorneal hemorrhage within the tips of the papillae altogether diagnostic of verruca vulgaris (H&E 400 \times).⁸

ustekinumab can theoretically lead to impaired clearing and persistence of HPV infection in epithelial cells.^{5,10} However, the authors hypothesize that ustekinumab-induced disseminated verrucosis is more likely a result of the IL-12 blockade rather than the IL-23 blockade. This is supported by the fact that IL-12 leads to robust production of TNF- α and cases of cutaneous and genital warts have been reported in those treated with TNF- α blockers, namely, infliximab and etanercept.^{10,11}

Although the development of disseminated verrucae has been reported with other biologic agents,^{10,11} this adverse reaction has only been reported in one patient treated with ustekinumab for psoriasis.⁵ To our knowledge, this is the first case of disseminated verrucae reported in a patient being treated with ustekinumab for Crohn’s disease, which notably requires higher induction dosing and more frequent maintenance dosing than psoriasis. Physicians should be aware of this rare adverse effect and the potential for HPV infection or reactivation in patients undergoing therapy with ustekinumab and other biologic agents.

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Informed consent

The patient provided signed consent for publication of the case report and images.

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