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CASE REPORT

Eruptive Seborrheic Keratoses Following Hpv Vaccination During Ixekizumab Therapy for Psoriasis: A Case Report and Literature Review

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Abstract: Psoriasis is a chronic, recurrent, inflammatory autoimmune skin disease. The advent of biologics, such as ixekizumab, has provided a breakthrough for patients with moderate-to-severe disease by specifically inhibiting the interleukin-17A (IL-17A) mediated inflammatory cascade. The human papillomavirus (HPV) vaccine is a cornerstone in the prevention of HPV-associated malignancies, with well-established safety and efficacy profiles. However, due to the unique immune status of patients with psoriasis, cutaneous adverse events following HPV vaccination during biologic therapy have rarely been reported. Seborrheic keratosis (SK) is a common benign epidermal tumour. Its eruptive variant, known as the Leser-Trélat sign, has traditionally been associated with internal malignancies; however, recent studies suggest potential links to inflammation, pharmacological agents, and immune alterations. We report the case of a 37-year-old female with psoriasis who, after achieving stable disease control on ixekizumab, developed widespread eruptive brown macules, patches, and papules within one month of receiving a quadrivalent HPV vaccine. Histopathological examination confirmed SK, and malignancy, as well as other associated disorders, were excluded. The lesions faded following oral acitretin therapy. This case highlights the possibility that ixekizumab in combination with HPV vaccination may synergistically alter immune homeostasis, thereby precipitating eruptive SK. We discuss potential mechanisms, propose clinical management considerations, and provide insights that may inform future research and clinical practice. The ultimate aim is to contribute to the refinement of guidelines on vaccination in patients receiving biologic therapy for psoriasis, ensuring both therapeutic efficacy and patient safety.

Keywords: ixekizumab, psoriasis, HPV vaccine, seborrheic keratosis, vaccine adverse reaction, immune activation, autoimmune response

Introduction

Psoriasis is a chronic, recurrent, inflammatory autoimmune skin disease and has long been a central focus of clinical research. In recent years, the advent of biologic therapies has revolutionized the management of diseases. Among these, ixekizumab, a highly selective interleukin-17A (IL-17A) antagonist, exerts its therapeutic effect by specifically blocking IL-17A mediated inflammatory pathways. This mechanism leads to marked improvement in cutaneous lesions and quality of life in patients with moderate-to-severe psoriasis, making ixekizumab one of the first-line therapeutic options in current clinical practice.[1,2] The human papillomavirus (HPV) vaccine represents the cornerstone of primary prevention for HPV-related malignancies, including cervical cancer and oropharyngeal cancer, as well as their precancerous lesions. Its safety and efficacy have been well established in large-scale clinical trials and post-marketing surveillance.[3,4] Adverse events are typically mild and localized, such as injection-site pain, erythema, or transient systemic symptoms like fever.[5] With growing awareness of cervical cancer prevention and other HPV-associated diseases, HPV vaccination coverage has steadily increased worldwide.

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In patients with psoriasis, however, the situation presents unique challenges. This population is characterized by chronic immune dysregulation, and many therapeutic agents exert modulatory effects on immune function. Consequently, the safety and efficacy of vaccination in this group have been a topic of ongoing concern. While current clinical guidelines generally recommend HPV vaccination during periods of stable disease, reports of unusual cutaneous adverse reactions following HPV vaccination in patients undergoing biologic therapy remain exceedingly rare.[6]

Seborrheic keratosis (SK) is one of the most common benign epidermal tumours, with incidence increasing with age, and is often regarded as a cutaneous hallmark of ageing. Its precise aetiology remains incompletely understood, though genetic predisposition, ultraviolet exposure, and local keratinocyte factors have all been implicated.[7] Eruptive seborrheic keratosis (ESK), also referred to as the Leser-Trélat sign, is a rare clinical phenomenon characterized by the sudden onset of multiple, disseminated SK lesions within a short time frame. Traditionally, medical textbooks have considered ESK to represent a paraneoplastic dermatosis, most frequently associated with visceral malignancies such as gastrointestinal adenocarcinoma.[8,9] However, more recent reports have also linked ESK to inflammatory conditions, drug reactions, and dynamic alterations in immune status, thereby challenging its specificity as a marker of internal malignancy.[10]

Currently, reports describing cutaneous adverse reactions resulting from the interplay between biologic therapy induced immune modulation and vaccine-mediated immune responses are scarce. Here, we present the first documented case of ESK occurring in a patient with psoriasis receiving ixekizumab who subsequently developed eruptive lesions following HPV vaccination. This unusual case highlights the possibility that ixekizumab treatment and HPV vaccination may act synergistically to perturb immune homeostasis, thereby precipitating ESK. It further underscores the need to reappraise the etiological spectrum of the "Leser-Trélat sign" in the era of biologics—suggesting that, in addition to malignancy screening, intense immune activation events should also be considered as potential triggers.

Case Report

Patient Information and Medical History

A 37-year-old female presented with a two-year history of multiple brown macules, patches, and papules of varying size and irregular shape distributed over the trunk and extremities. The lesions first appeared on the right upper limb one month after administration of a quadrivalent HPV vaccine and subsequently spread progressively to the trunk and limbs. During the course of the disease, she underwent electrocautery and cryotherapy for lesions on the right lower limb, but recurrence was noted within one month (Figures 1A–D).

Since the onset, the patient denied experiencing headache, sore throat, iritis, oral ulcers, urethritis, abdominal pain, diarrhoea, or arthralgia. Her past medical history was notable for psoriasis of several years' duration, for which she had received ixekizumab therapy for six months.

Physical Examination

General Examination: Unremarkable.

Dermatological Examination: Diffuse distribution of light- to dark-brown macules, patches, and papules on the trunk and extremities. Lesions were smooth-surfaced, sharply demarcated, and ranged in diameter from several millimetres to several centimetres. No subjective symptoms were reported.

Ancillary Investigations

Immunological Analysis: Late T-cell activation (CD3+HLA-DR+%) was elevated at 53.63% (reference range: 6.4–43.4); NKT cell count (CD3+CD56+Abs) was 147/μL (reference range: 2–17); NKT cell percentage (CD3+CD56+%) was 8.1%; CD4+/CD8+ ratio was 1.14 (reference range: 1.2–2.0); early T-cell activation (CD3+CD69+%) was 4.95% (reference range: 0.5–3.5).

Other Laboratory and Imaging Studies: Routine blood, urine, and stool tests; liver and renal function tests; antinuclear antibody (ANA), complement, thyroid function, EBV DNA, HSV-1/2 IgM, HIV, syphilis, hepatitis B and C serology, serum IgE, electrocardiogram, chest radiograph, colonoscopy, abdominal ultrasonography, and tumor markers were all within normal limits.

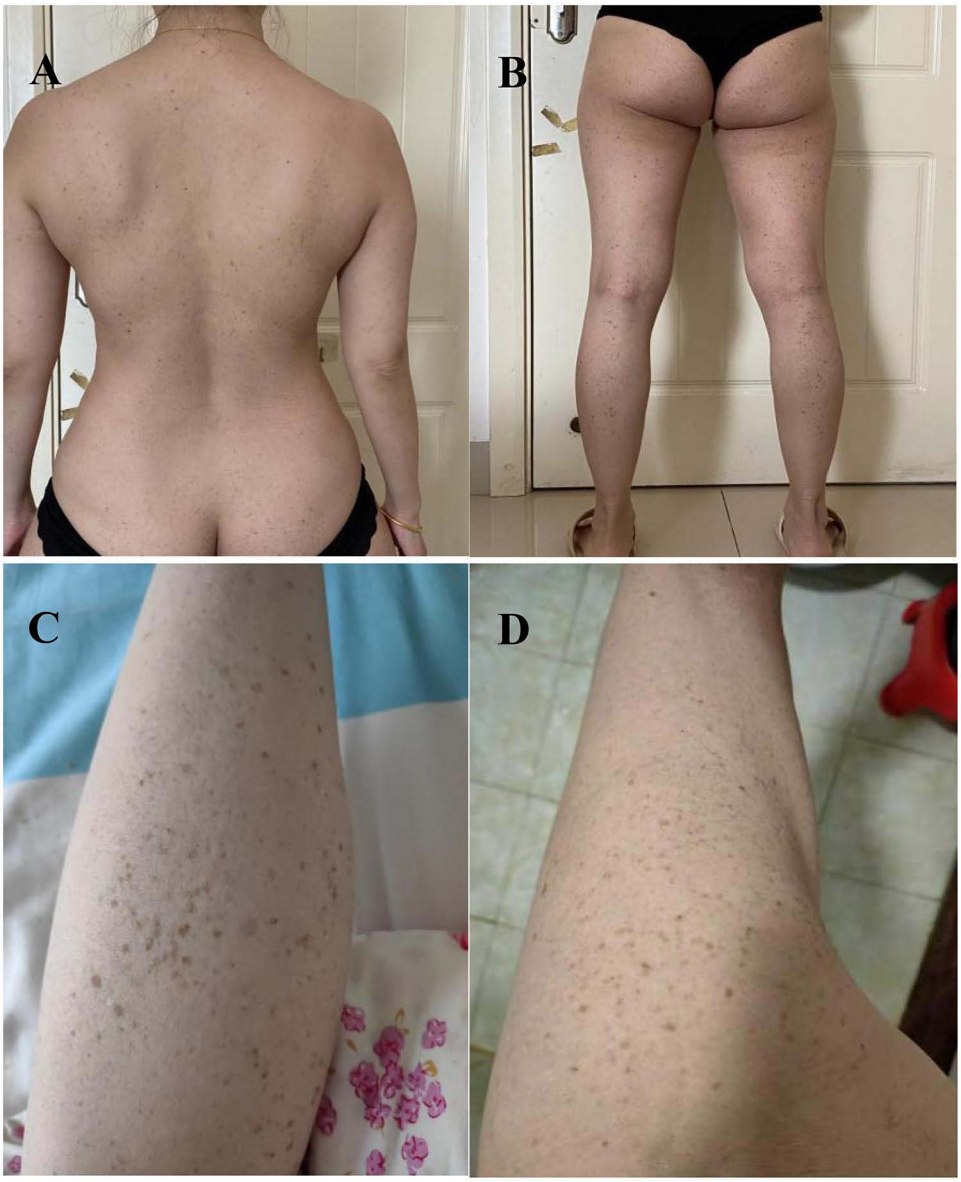

Figure 1 (**A**) [Back], (**B**) [Both lower extremities], (**C**) [Right lower leg], (**D**) [Left lower leg] showed diffuse light brown to dark brown macules, patches and papules. The lesions had a smooth surface and clear borders, with sizes ranging from several millimeters to approximately 1 centimeter.

Histopathology of skin lesions: Demonstrated basal cell hyperplasia with exophytic growth, hyperkeratosis, acanthosis, and papillomatous proliferation. Some proliferating keratinocytes contained melanin granules (Figure 2A and B).

Direct Immunofluorescence (DIF)

Negative for IgA, IgG, IgM, and C3.

HPV DNA Testing

Weakly positive for HPV16.

Based on the patient's history, clinical manifestations, and histopathological findings, a diagnosis of seborrheic keratosis was established.

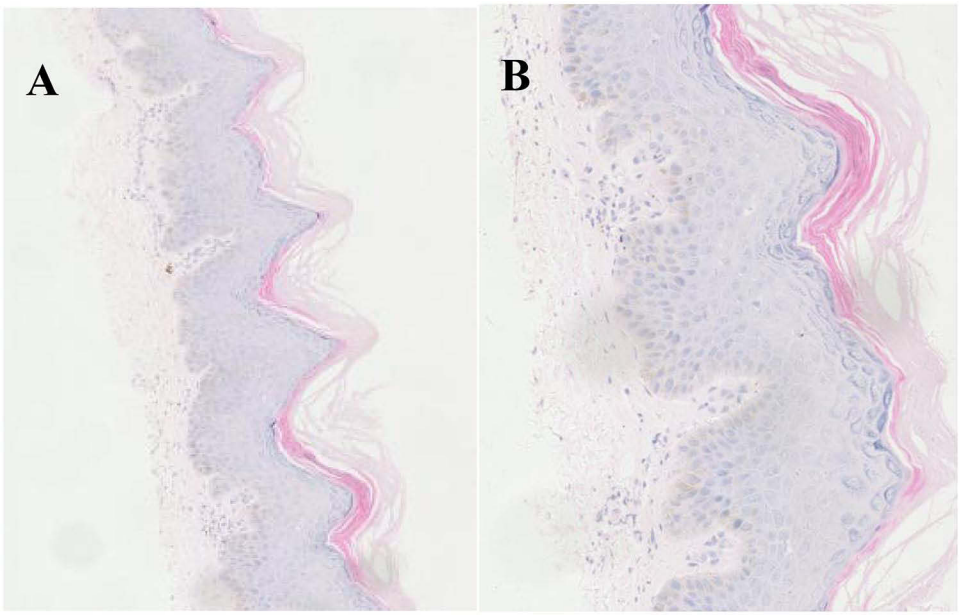

Figure 2 Hyperplasia of basal keratinocytes with outward growth was observed, accompanied by hyperkeratosis, acanthosis, and papillomatous hyperplasia. Some hyperplastic keratinocytes contained dark pigment granules. (**A**) HE staining, ×200 magnification; (**B**) HE staining, ×400 magnification (representative histological fields).

Treatment and Outcomes

The patient was treated with oral acitretin at a dose of 10 mg once daily. She reported partial fading of the pigmentation following treatment. At the time of follow-up, the lesions had not completely resolved, and the patient remains under observation.

Discussion

The distinctive feature of this case lies in the patient's concurrent history of ixekizumab therapy and HPV vaccination, with the onset of eruptive seborrheic keratoses occurring within one month after completion of the vaccination series. Before this, the patient had been receiving ixekizumab for six months, during which her psoriasis remained well controlled without notable cutaneous adverse reactions. This temporal association provides a crucial clue for investigating the potential synergistic role of ixekizumab and HPV vaccination in triggering eruptive seborrheic keratoses.

From a mechanistic perspective, ixekizumab exerts its therapeutic effect through selective binding to IL-17A, thereby suppressing its central pro-inflammatory role in the pathogenesis of psoriasis.[11] However, IL-17A is not limited to mediating inflammation; it is also critically involved in cutaneous and mucosal immune defence, antitumor immunity, and tissue repair. The interruption of IL-17A signalling may therefore influence broader aspects of immune homeostasis, potentially altering host responses to immune challenges, such as vaccination.[12]

Long-term blockade of IL-17A with ixekizumab may induce alterations in immune homeostasis. On the one hand, such disruption may attenuate the skin's ability to regulate immune responses against external stimuli, such as viral infections or vaccinations, thereby impairing its capacity to mount appropriate defence mechanisms. On the other hand, it may interfere with the normal proliferation and differentiation of keratinocytes, creating a permissive environment for the development of seborrheic keratoses. Previous studies have suggested that biologic agents, such as tumour necrosis factor-α antagonists, may increase the risk of benign or malignant cutaneous tumours in patients with autoimmune diseases.[13] Although direct evidence linking ixekizumab with seborrheic keratosis remains scarce, the potential influence of immunomodulatory therapies on cutaneous tumorigenesis warrants careful attention and further investigation.

The HPV vaccine, as an inactivated vaccine, functions by mimicking the antigenic structure of HPV to stimulate the production of specific antibodies, thereby preventing HPV infection.[14] Vaccination induces both humoral and cellular immune responses, a process that is critical for protective immunity in the general population. However, in patients with

psoriasis who already exhibit immune dysregulation and are concurrently receiving ixekizumab, this immune activation may have additional, unintended consequences.

Given that ixekizumab-treated psoriasis patients exist in a state of immune modulation, the immune response elicited by HPV vaccination could disrupt pre-existing immune equilibrium, altering the local cutaneous microenvironment. Evidence suggests that vaccine-induced immune activation may influence keratinocyte proliferative cycles or promote lesion formation through activation of specific signalling pathways such as MAPK.[15] Moreover, although HPV vaccination is commonly associated with mild local skin reactions such as erythema or pruritus-which were absent in this case-the systemic immune response triggered by vaccination may nonetheless have acted as an indirect driver of eruptive seborrheic keratoses.[16]

Traditionally, malignant tumours have been regarded as the most common associated factor in eruptive seborrheic keratosis, with gastrointestinal adenocarcinoma representing a prototypical example. Associations with ovarian cancer, breast cancer, and, more rarely, melanoma or cutaneous T-cell lymphoma have also been reported.[17] In exceptional cases, psoriasis may manifest in a paraneoplastic manner.[18] However, in the present patient, comprehensive evaluations including colonoscopy revealed no evidence of an underlying malignancy. This finding compels a reassessment of the contemporary etiological understanding of eruptive seborrheic keratosis (Leser-Trélat sign). While traditionally considered a hallmark of paraneoplastic syndromes, the negative results from extensive malignancy screening in this case strongly support a growing recognition that Leser-Trélat-like eruptions are not exclusively indicative of malignancy. Several reports have linked such eruptions to a variety of inflammatory dermatoses (eg, eczema, abrupt remission of psoriasis), severe drug reactions, and, as highlighted in this report, immune-activating events such as vaccination.[19–21] Our case provides novel and compelling evidence for this emerging perspective, suggesting that intense immune challenges during the management of immune-mediated conditions may fully recapitulate cutaneous manifestations typically associated with paraneoplastic states, thereby enriching our understanding of the etiopathogenesis of the Leser-Trélat sign.

Although cutaneous reactions to HPV vaccination are uncommon, they have been documented in prior studies and clinical practice, including lichenoid eruptions, vitiligo, and lichen planus.[22–24] To date, however, eruptive seborrheic keratosis triggered by HPV vaccination has not been reported. The occurrence of this rare event underscores the limited knowledge regarding interactions between biological agents and vaccines, highlighting the critical importance of ongoing pharmacovigilance and the timely reporting of such uncommon occurrences. Accumulation of additional cases is crucial for better characterizing the potential risks in this domain.

It is also necessary to acknowledge the primary limitations of this report. First, this is a single-case observation, and the sample size is insufficient to establish the generalizability of the potential association between ixekizumab and HPV vaccination in triggering eruptive seborrheic keratosis. Second, mechanistic insights into the interaction remain largely hypothetical, with a lack of robust experimental evidence. Furthermore, molecular biological analyses of the lesions were not performed, precluding assessment of local cytokine or growth factor expression. These limitations identify clear directions for future research, which could employ targeted molecular analyses to elucidate the intrinsic mechanisms underlying disease pathogenesis further.

In the diagnostic process of this case, careful differentiation from other cutaneous conditions is essential to exclude malignant or severe diseases. Key considerations include distinguishing paraneoplastic eruptive seborrheic keratosis (Leser-Trélat sign), which is often associated with visceral malignancies, such as gastrointestinal or respiratory tumours. A comprehensive evaluation using imaging modalities (eg, abdominal CT, chest X-ray) and tumour marker assessments is necessary to exclude an underlying malignancy;[25] normal findings can essentially rule out this condition. Differentiation from HPV-related skin lesions, such as flat or common warts, is also critical. Although both are HPV-associated, clinical and histopathological features differ: flat warts present as flattened papules with vacuolated cells on pathology, whereas seborrheic keratoses exhibit hyperkeratosis and papillomatous proliferation without vacuolation, allowing adequate distinction.[26] Actinic keratosis should also be considered; it typically arises in sun-exposed areas, shows keratinocyte atypia histologically, and carries malignant potential. In contrast, the present case involved lesions on sun-exposed trunk areas without cellular atypia, effectively excluding actinic keratosis.[27]

Based on our experience, clinical management of patients planning HPV vaccination especially those with a history of psoriasis receiving biologic therapy should include pre-vaccination assessment, close post-vaccination monitoring, and appropriate therapeutic strategies. Before immunization, immune status and biologic treatment history (eg, ixekizumab use) should be evaluated, and potential risks thoroughly discussed with patients to support informed decision-making. Post-vaccination, dermatologic follow-up for 3–6 months is recommended, with prompt dermoscopic and histopathological evaluation of new lesions to avoid diagnostic delays. For eruptive seborrheic keratoses, physical modalities such as cryotherapy or laser treatment may be employed, while maintaining ongoing psoriasis control to prevent disease exacerbation. Treatment choice should be guided by lesion number and distribution: limited lesions may respond to liquid nitrogen cryotherapy or topical agents such as 0.1% tazarotene gel, whereas extensive or hyperkeratotic lesions may require electrodessication or CO_2/Er: YAG laser therapy. Refractory cases may benefit from short-term systemic retinoids, while malignancy-associated lesions necessitate targeted treatment for the primary tumour. Patient education and strict follow-up including avoidance of self-manipulation and adherence to sun protection are crucial.[28,29] Emerging targeted therapies, such as PI3K/AKT/mTOR inhibitors, may offer additional options in the future.

Conclusion

The diagnostic and therapeutic course of this case offers essential insights for clinical practice. First, in patients with psoriasis receiving biologic therapy such as ixekizumab, clinicians should carefully evaluate disease stability, immune status, and the risk benefit profile before HPV vaccination. For patients with well-controlled disease and no significant immunodeficiency, HPV vaccination may be cautiously recommended after thorough counselling regarding potential risks. Post-vaccination, close follow-up is essential, particularly for monitoring cutaneous and mucosal reactions. Any newly emerging skin lesions should be promptly evaluated to establish a diagnosis and avoid delays in management.

This case also highlights current gaps in the literature. On one hand, there is a paucity of studies examining cutaneous adverse events following HPV vaccination in patients treated with IL-17A inhibitors such as ixekizumab, and large-scale clinical data are lacking to determine the existence and magnitude of any potential association. On the other hand, the pathogenesis of eruptive seborrheic keratosis remains incompletely understood, particularly under the combined influence of immunomodulatory drugs and vaccination, leaving clinicians without robust mechanistic guidance for diagnosis and management. Future work should include both clinical and experimental studies. Clinical observational studies should expand sample sizes to systematically evaluate the incidence of cutaneous adverse events in patients receiving HPV vaccination during ixekizumab therapy and clarify the strength of any association. Experimental studies, including in vitro cellular models and in vivo animal models, are warranted to elucidate the molecular mechanisms by which ixekizumab and HPV vaccination may influence the development of seborrheic keratoses, thereby providing a more solid theoretical foundation for disease prevention and treatment.

Furthermore, there is a need to develop comprehensive clinical guidelines for vaccination in patients with psoriasis undergoing biologic therapy. Such guidelines would standardise clinical decision-making, ensuring that patients receive adequate vaccine protection while maintaining the safety of both ongoing biologic treatment and vaccination, thereby enhancing the overall management and long-term health of this patient population.

Ethic Statement

The patient has granted permission for the images to be published along with the case report, and The Fifth People's Hospital of Hainan Province has given its approval for the case details to be disclosed after obtaining approval from its own Ethics Committee.

Consent Statement

Informed consent was provided by the patient for publication of the case.

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Disclosure

The authors report no conflicts of interest in this work.

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