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Eruptive Lentigines Confined to Resolving Psoriatic Plaques Following Treatment with Guselkumab

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ABSTRACT

Eruptive lentigines related to resolving psoriatic plaques has been well documented in the literature following successful treatment with multiple therapies. This is historically associated with light treatment but has been expanded to include other therapies such as anti-tumor necrosis factor therapies and, more recently, some biologic agents. Guselkumab (Tremfya) is an IgG1λ monoclonal antibody used in the treatment of plaque psoriasis with only 1 case of eruptive lentigines confined to resolving psoriatic plaques (ELRP) noted as a side effect. We present the second such case of ELRP associated with the successful treatment of plaque psoriasis with Guselkumab. This case study is significant because as biologic agents become more popular, it is critical to document all side effects of new therapeutic agents when encountered.

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INTRODUCTION

Psoriasis Vulgaris is a chronic condition affecting 2% of Western countries with an equal incidence in males and females.[1] Patients can experience a range of manifestations, from mild and asymptomatic to severely debilitating plaques. Mild psoriatic plaques are often treated with topical corticosteroids, whereas moderate-to-severe psoriasis often requires more intense systemic therapies such as immunomodulating biologic agents. Guselkumab (Tremfya) is an IgG1λ monoclonal antibody that binds to a subunit of IL-23, reducing pro-inflammatory cytokines that contribute to the symptoms of psoriasis.[2] Recorded guselkumab side effects thus far have included headaches and diarrhea, along with upper respiratory infections secondary to its immunosuppressive effects.[2] Dermatologic complications of guselkumab and other systemic biologic therapies for psoriasis are rare and must be documented when encountered. Lentigines are benign hyperpigmented macules with clearly demarcated borders that often appear with age and ultraviolet light exposure. Eruptive lentigines confined to resolving psoriatic plaques (ELRP) is a rare occurrence, originally described after topical or phototherapies. The condition has since been described as secondary to biologic therapies, with no clear evidence of the etiology. We present only the second documented case of ELRP after guselkumab and discuss the proposed etiology of this interesting phenomenon. With a plethora of new biologic agents available, it is critical to document all side effects when encountered.

CASE PRESENTATION

A 36-year-old female construction worker with a history of extensive chronic plaque psoriasis on the legs, arms, and trunk presented to the dermatology clinic seeking care for her psoriasis. The patient was originally started on methotrexate, which failed to relieve her condition. The patient was then placed on adalimumab (Humira) but experienced undesired weight gain, resulting in the discontinuation of the medication. Next, the patient began treatment for her psoriasis with guselkumab (Tremfya). At the follow-up visit, 3 months after guselkumab initiation, the psoriatic lesions resolved (PASI 100

response). While the plaques had resolved, eruptive lentigines developed on the arms and legs confined to only areas of resolved plaques (Figure 1). At 3 and 6-months follow up, the lentigines were asymptomatic but persistent. No treatment for the lentigines has been pursued.

DISCUSSION

Eruptive lentigines confined to areas of resolving psoriatic plaques (ELRP) is a rare phenomenon, initially described after phototherapy treatment, then after topical steroids and vitamin D analogs.[3,4] The first cases of lentigines confined to resolving psoriatic plaques secondary to systemic therapies were reported in 2008, secondary to adalimumab and etanercept therapy.[5,6] Since then, multiple biologic agents have been described, including but not limited to infliximab, ustekinumab, and secukinumab.[7,8,9] In 2019, the first case of ELRP after guselkumab treatment was reported in a 41-year-old male, presenting 2 weeks after treatment initiation and plaque clearance.[10] The patient presented is just the second known eruptive lentigines in resolving psoriatic plaques when treated with guselkumab. Today, more effective and convenient biologic agents have become the mainstay of moderate to severe psoriasis treatment.

The etiology of the lentiginous eruptions varies depending on the type of treatment for psoriasis used, with possible explanations for some treatment modalities. For example, when ELRP is secondary to phototherapy, it is proposed as secondary to an abnormal reaction to UV light since phototherapy is a well-described cause of hyperpigmentation.[3] Post-inflammatory hyperpigmentation is proposed to be the etiology when cases were reported secondary to topical therapies such as steroids or vitamin D analogs.[4] A 2019 clinical trial for apremilast, a PDE4 inhibitor, demonstrated ELRP in 5 out of 21 patients (24%) and is thought to have occurred secondary to PDE4 inhibition of melanocyte inducing transcription factor (MITF), which resulted in increased melanocyte activity.[11] While these proposed explanations seem

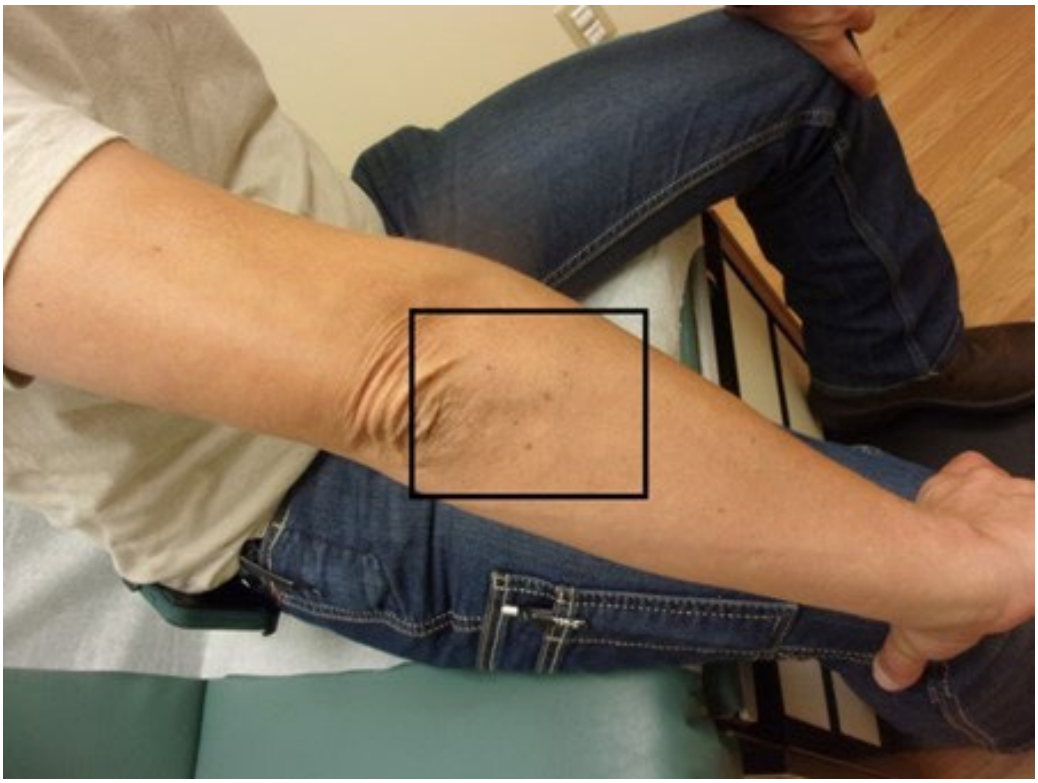

FIGURE 1. Hyperpigmented macules of eruptive lentigines on elbow in area of resolved psoriatic plaque.

straightforward, the answer to the mechanism behind the lesions when using biological therapies is not.

The mechanism of ELRP secondary to biologic therapies is unclear and potentially multifactorial, as agents affecting a range of inflammatory mediators have been indicated. In 2008, when ELRP after biologic therapy was first reported, it was suggested the phenomenon was related to the pathophysiology of psoriasis itself, not the therapy used.6 Increased levels of IL-17 and TNF-a have been documented to be present in psoriatic plaques.[12] IL-17 and TNF stimulate melanocytic growth factors such as CXCL1, CXCL2, CXCL3, and IL-8, while suppressing melanin production genes such as MC1R, MITF, SOX-10, DCT, and TYR.[13,12] When biologic agents inhibit IL-17 and TNF, the suppression of pigment production is withdrawn in the setting of plaques containing up to twice as many melanocytes, resulting in lentigines.[12-14] An increased number of normal melanocytes at the dermo-epidermal junction staining has been documented in lentigines in resolved psoriatic plaques, supporting these thoughts.[14] Furthermore, IL-17-driven degranulation of melanocytic autoantigens present in psoriatic lesions has been postulated to cause melanogenesis interference.[15,16] This idea supports the above findings of ELRP being secondary to psoriasis itself, as melanogenesis inhibition is withdrawn upon biologic initiation and reduction in IL-17-driven melanocyte autoantigen degranulation. These thoughts explain ELRP in agents that directly affect IL-17 and TNF-a but do not thoroughly explain the etiology when secondary to agents targeting other cytokines. Some authors postulate that other cytokines and factors, such as IL-23, likely help regulate melanogenesis and melanocytic growth.[12,13,17] Furthermore, IL-17 and TNF-a could be affected in the same pathway described previously, secondary to downstream effects of IL-23 inhibition. It has been suggested that mutations in signaling proteins may predispose specific individuals to greater immune modulation developing lentigines, as immune modulation may be more significant in these individuals.[18,19]

Contraindicating those findings, other cases have demonstrated an increase in melanin deposition without an associated increase in melanocytes or formation of melanocytic nests, suggesting post-inflammatory melanin production as the etiology.[5,6,16] ELRP could represent an exaggerated recovery in pigment production, associated with greater disease severity or greater inhibition of cytokines, supported by ELRP appearing after the rapid resolution of thick psoriatic plaques but not thin plaques in some cases.[13,20] With these contraindicating thoughts considered, ELRP could result from multiple different disruptions in melanocytic pathways, and the etiology is likely multifactorial.[12]

Eruptive lentigines after biologic treatment appear within the first 6 months of treatment initiation and persist chronically with little to no improvement. Minimal improvement has been documented in cases up to 5 years following the eruption of the lentigines.[13] The condition is benign, but treatment could be pursued with Q switched ruby laser, which has led to partial improvement in 1 case, and successful treatment of the lentigines in another.[13]

CONCLUSION

We present a case of eruptive lentigines confined to resolving psoriatic plaques following treatment with guselkumab (Tremfya), only the second case documented. The association of ELRP with other biologic agents has been well described. The cause is likely multifactorial, best described by increased cytokines in psoriatic plaques, which demonstrate effects on the melanocytic pathway and the rapid withdrawal and initiation of effects due to the powerful biologic agents used. Similar side effects will likely present as biologic agents continue to gain popularity. Therefore, it is important to document all possible side effects of new therapeutic agents as they are introduced to the market.

AUTHOR AFFILIATIONS

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