The development of oral hairy leukoplakia during baricitinib therapy

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INTRODUCTION

Baricitinib is an oral, selective, and reversible Janus Kinase 1/2 Inhibitor small molecule inhibitor that is approved by the US Food and Drug Administration for the treatment of refractory rheumatoid arthritis and severe alopecia areata (AA). The JAK/STAT pathway is downregulated with inhibitor therapy and functions to reduce the activity of over 50 cytokines and growth factors that are implicated in inflammatory disease states.[1] These agents deliver promising efficacy data for their approved indications but have been associated with adverse effects including serious infections and malignancy from immune downregulation. We present the case of an HIV-negative male developing oral hairy leukoplakia (OHL) while on baricitinib therapy for alopecia universalis (AU).

CASE REPORT

A 50-year-old man with a past medical history of asthma, gastro-esophageal reflux disease, and AU first presented to our clinic in July 2022 seeking treatment of his chronic AU. Family history was significant for AA in his father and maternal cousin. He had a 25-year history of AU and noted that he had previously attempted treatment in his 20s with topical, injectable, and oral steroids without improvement nor any progression of his disease. Physical examination was notable for diffuse, total body hair loss. Given the severe nature of his disease, he was started on baricitinib 4 mg orally daily after baseline laboratory screening with complete blood count, complete metabolic profile, lipid panel, and Quantiferon. At his initial follow up visit in December 2022, he had no hair regrowth; however, in March 2023 at follow up, he was first noted to have patchy hair regrowth on scalp, bilateral arms, axilla, and eyebrows. He reported tolerating the therapy without any side effects throughout this time; repeat laboratory tests including complete blood count, complete metabolic profile, and lipid panel were within normal limits. At a routine dental visit in March 2023, dental examination was notable for newly appearing white patch on lateral right tongue for which he was referred to oral surgery. Of note, no oral lesion was present on routine dental examinations 6 or 12 months prior. He underwent tongue biopsy with subsequent surgical removal of the lesion (Fig 1) which demonstrated positive in situ hybridization for Epstein Barr virus (EBV) (Fig 2) and findings consistent with OHL.

Of note, patient's social history is remarkable for an 11-year monogamous relationship with another male. He undergoes annual HIV screening which was negative in January 2023 and most recently with repeat negative in April 2023 after OHL diagnosis. He was referred to an infectious disease specialist who has and will continue to monitor for any further infectious complications while he continues with baricitinib therapy.

Abbreviations used:

AA:	alopecia areata
AU:	alopecia universalis
EBV:	Epstein Barr virus
OHL:	oral hairy leukoplakia

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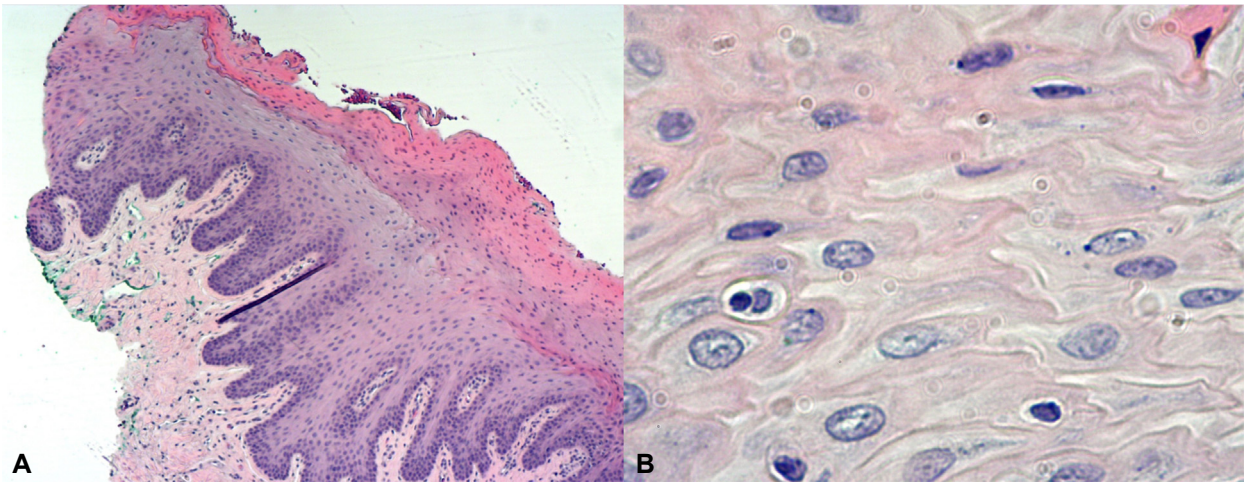

Fig 1. Oral hairy leukoplakia biopsy. Right lateral tongue pathology findings consistent with oral hairy leukoplakia at **A,** ×20 magnification showing markedly parakeratotic, acantholytic stratified squamous epithelium with a layer of vacuolated cells immediately subjacent to parakeratin, and at **B,** ×60 magnification demonstrating chromatin compaction and margination to nuclear periphery characteristic of EBV.

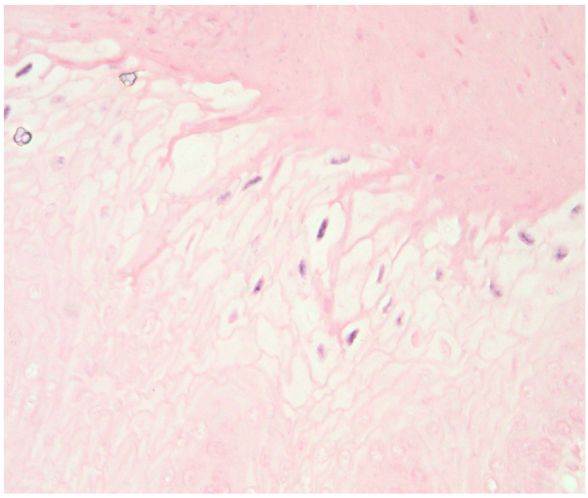

Fig 2. EBV early RNA in situ hybridization histology. Right lateral tongue histology at ×40 magnification demonstrating focally positive EBV by in situ hybridization in superficial portions of squamous epithelium.

DISCUSSION

All JAK inhibitors pose the risk of immune-related adverse events as they downregulate cytokines and growth factors involved in the adaptive immune response. Individuals are at increased risk of infection due to both their underlying disease as well as immunomodulator therapy. Notable adverse events reported with baricitinib use in trials include serious infection, malignancy, and major cardiovascular events. Baricitinib was first approved for rheumatoid arthritis in 2018 and AA in June 2022.[1] In a recent pooled analysis across 9 randomized studies and 1 long-term extension study including 3770 patients on baricitinib for rheumatoid arthritis with a median exposure of 4.6 years, the incidence rate of serious adverse events was 7.4 per 100 patient years of exposure. The overall incidence rate of serious infection for patients on baricitinib in the study was 2.58 per 100 patient years of exposure, whereas malignancy incidence rate was 0.92 per 100 patient years of exposure which appeared similar to malignancy risk in overall population.[2] Safety data are similar in baricitinib across 52 weeks of treatment specifically for AA.[3] Opportunistic infections reported with therapy in trials included tuberculosis, multidermatomal herpes zoster, esophageal candidiasis, pneumocystis, histoplasmosis, cryptococcus, cytomegalovirus, and human pappiloma virus 1 virus.[2,3]

OHL is a disease of the oral mucosa associated with EBV infection. OHL infection is predominantly found in HIV-positive patients or those with significant immunosuppression such as in those with organ transplants. In Chambers et al[4] recent multicenter study, a series of patients with non-HIV related OHL were identified; these patients, while immunocompetent, predominantly had comorbid conditions requiring inhaled +/− systemic steroid therapy. However, recent reports of immunocompetent patients without evidence of any responsible systemic diseases or medications developing OHL have emerged.[5-7] The only reports of targeted immunomodulation with JAK inhibition associated with reactivation of EBV is in cohort of steroid-refractory graft-versus-host disease.[8] The pathophysiology regarding the role of the JAK pathway in the

reactivation of EBV is not well understood but may involve a functional impairment in dendritic cells and natural killer lymphocytes involved in clearance of virus-infected cells.[9] Thus, we note the possibility that the baricitinib therapy and development of OHL are independent events in our case report. As the side effects of JAK therapy is further classified, additional studies specifically elucidating the significance and association between therapy and opportunistic infections is necessary. Our case report is notable in its report of a temporal relationship between baricitinib therapy and the development of OHL. Clinicians should be aware of this adverse event that presented during JAK inhibitor therapy in our case to allow for timely and appropriate patient management.

Conflicts of interest

None disclosed.

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