Kaposi Sarcoma Associated with Tofacitinib Use in a Patient with Rheumatoid Arthritis

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ABSTRACT

Kaposi sarcoma is a rare vascular malignancy associated with HHV-8 infection. Four variants of Kaposi sarcoma have been described: Classic, African, HIV-associated, and iatrogenic. Iatrogenic Kaposi sarcoma is typically associated with immunosuppression and organ transplantation. We present a case of iatrogenic Kaposi sarcoma associated with tofacitinib therapy. A 69-year-old woman with rheumatoid arthritis receiving tofacitinib presented with multiple firm, purple-red nodules and brown plaques on the left lower extremity and a single lesion on the right medial calf. Clinicopathologic correlation confirmed a diagnosis of Kaposi sarcoma. Tofacitinib was discontinued and she was started on Alitretinoin 0.1% gel bid. The purple-red Kaposi sarcoma nodules decreased 50% in size after 4 months and resolved at 1 year off the tofacitinib and initiation of alitretinoin gel. As the use of immunomodulators and biologics continues to expand, awareness of this association is important for prompt diagnosis and management.

KEYWORDS: Kaposi sarcoma, tofacitinib, rheumatoid arthritis, immunosuppression, HHV-8

CASE REPORT

The patient is a 69-year-old Hispanic woman with rheumatoid arthritis on tofacitinib 5 mg daily for 1 year. She presented with bilateral lower extremity edema and skin lesions primarily on the left lower extremity and single lesion on the right medial calf. The lesions were asymptomatic and slowly growing over the previous 6 months. There was no history of trauma. Physical examination revealed a well-appearing patient with multiple purple-red nodules and brown plaques ranging from 2–10 mm in size on the dorsal left foot, left lateral ankle and left calf (**Figure 1**). One 4mm round dull red-purple macule was present on the right medial calf. No other similar lesions were found on full body skin examination and no mucosal involvement was detected. Laboratory testing confirmed that the patient had a negative human immunodeficiency virus (HIV) status.

Shave and punch biopsy of the left dorsal foot and left lateral calf, respectively, was performed. The shave of a purple nodule revealed focal human herpesvirus-8 (HHV-8) positivity and increased vascularity confirmed by CD31 staining. Punch biopsy of a brown plaque demonstrated hyperkeratosis and an acanthotic epidermis. Within the upper and mid dermis, there was a subtle proliferation of slit-like vascular spaces, interspersed interstitial spindle cells, numerous dermal endothelial cell lined well-formed small blood vessels, occasional plasma cells and moderately dense lymphohistocytic inflammation (**Figure 2**). Background fibrosis, extravasated erythrocytes and hemosiderin was also present. The prominent angioplasia, inflammation and fibrosis suggested concomitant acroangiodermatitis features. Immunohistochemical staining with CD68 revealed intermingled histiocytes. CD4/CD8 immunostaining confirmed an admixed lymphoid infiltrate with a CD4:CD8

Figure 1. A and **B** show red-purple Kaposi sarcoma nodules on brown patches of dorsal left foot [**A**] and left ankle [**B**] region at time of presentation. **C** and **D** show resolution of the nodular lesions 1 year after stopping at tofacitinib and starting alitretinoin 0.1% gel.

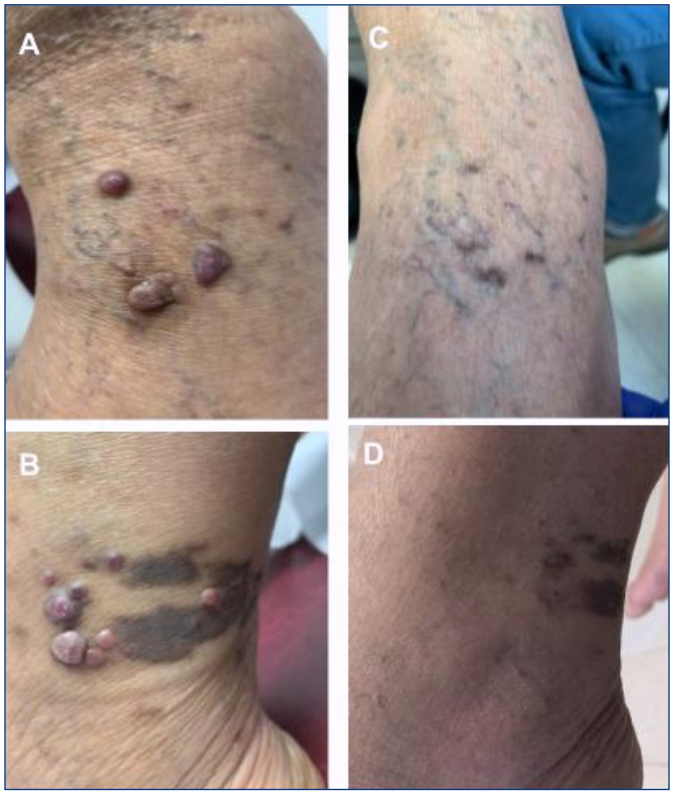
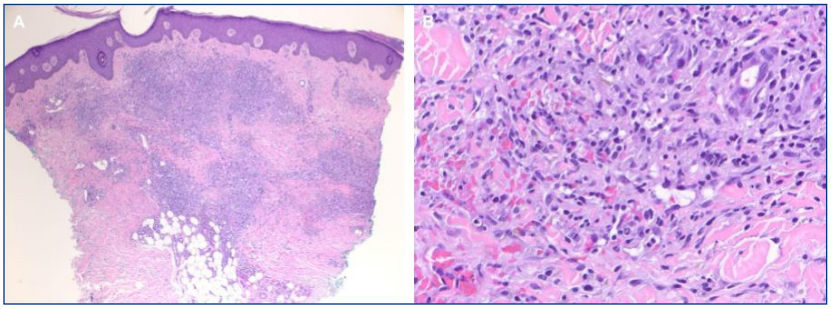


Figure 2. Punch biopsy H&E stain demonstrates nodular proliferation and admixed interstitial spindle cells with slit-like vascular spaces, extravasated erythrocytes, endothelial cells lining well-formed small blood vessels, occasional plasma cells, and moderately dense lymphohistiocytic inflammation. 4X [**A**] and 40X [**B**] magnifications.



ratio of 4:1. HHV-8 immunostaining showed occasional scattered positive nuclei. Clinicopathologic correlation confirmed a diagnosis of Kaposi sarcoma in the setting of tofacitinib therapy. Tofacitinib was discontinued. Skin lesions have notably decreased in size following cessation of tofacitinib and the start of alitretinoin gel.

DISCUSSION

Kaposi sarcoma is a vascular endothelial proliferation caused by an infection with HHV-8. Cutaneous findings of Kaposi sarcoma have a predilection for the lower extremities and they include red-purple nodules, patches, and macules, as seen in our patient. Mucocutaneous manifestations and visceral involvement have been reported, most commonly affecting the gastrointestinal tract.[1] Histopathologic analysis is required for diagnosis, particularly in order to distinguish Kaposi sarcoma from mimickers such as bacillary angiomatosis. The key histological characteristics of Kaposi sarcoma include angiogenesis of banal appearing spindle cells forming aggregates and slit-like to ectatic vascular spaces. There is accompanying microhemorrhage, single intracellular and few to many extravasated erythrocytes, hemosiderin deposition and inflammation. Immunostaining for HHV-8 aids in diagnosis. Rare cases of HHV-8 negative have been reported.[2]

Although Kaposi sarcoma may be classic, endemic/African or acquired immunodeficiency syndrome (AIDS) associated, it may present in patients with immunosuppression due to reactivation of latent HHV-8 infection. With the increased availability of antiretroviral therapy (ART), the incidence of HIV-associated Kaposi sarcoma has decreased.[3] Nevertheless, iatrogenic Kaposi sarcoma can be seen in various clinical contexts. In a large retrospective study of 137 patients with Kaposi sarcoma in Turkey by Baykal et al, 37 cases of iatrogenic Kaposi sarcoma were reported: sixteen following systemic steroid use, ten transplant patients (renal and liver) on varying immunosuppressive medications, four with myasthenia gravis (some patients receiving either systemic corticosteroids or IVIG therapy), three with rheumatoid arthritis (some patients receiving systemic corticosteroids, methotrexate, and/or leflunomide), three with topical steroid therapy use and one with congenital immunodeficiency syndrome.[4]

The development of Kaposi sarcoma in patients with rheumatoid arthritis receiving various therapies, including TNF-alpha inhibitors and triptolide, a diterpene triepoxide found in a traditional Chinese herbal remedy have been reported.[5,6] However, as noted above, there are infrequent reports of Kaposi sarcoma developing specifically in patients with rheumatoid arthritis who are receiving immunosuppressive drugs. Tofacitinib is a small-molecule immunomodulator that primarily inhibits Janus Kinase (JAK) 1 and JAK 3 (and to a lesser extent JAK 2), which are cell surface proteins that mediate cytokine-dependent signal transduction.[7] Inhibition of JAK signaling interferes with lymphocyte activation, proliferation, and function.[7] Tofacitinib is used to treat severe cases of rheumatoid arthritis, even in the setting of an incomplete response to methotrexate therapy.[7] This drug is also used in the management of other inflammatory conditions, including ulcerative colitis, psoriasis, and alopecia areata.[8-10] More recently, tofacitinib has been shown to reduce the risk of death among patients hospitalized with COVID-19 pneumonia.[11]

Adverse events related to tofacitinib therapy primarily result from immunosuppression. For example, the incidence of herpes zoster (HZ) has been found to be higher in individuals with rheumatoid arthritis on tofacitinib compared to those not on this treatment.[12] Similarly, it has been shown that the risk of cancer and cardiovascular disease is higher with tofacitinib relative to tumor necrosis factor (TNF) therapy.[13] Tocilizumab, a humanized antihuman interleukin-6 (IL-6) receptor monoclonal antibody developed in Japan has demonstrated safety and efficacy in the management of rheumatoid arthritis refractory to various treatment options including other biologics and methotrexate.[14]

Moreover, one case report has associated tofacitinib with the development of Kaposi sarcoma. Wetwittayakhlang et al describes biopsy-confirmed Kaposi sarcoma in an HIV-negative 61-year-old man after two years of tofacitinib therapy for treatment-resistant ulcerative colitis. In this patient, the Kaposi sarcoma in lesions improved slowly within 2 months of discontinuation of tofacitinib, thus suggesting a causal relationship.[15] Notably, there is one case report of an HIV-negative patient with essential thrombocythemia (ET) treated with ruxolitinib, another JAK inhibitor, who developed biopsy-confirmed Kaposi sarcoma.[16]

Our patient was treated with alitretinoin gel 0.1% which, along with the discontinuation of tofacitinib, resulted in resolution of the red-purple nodular Kaposi sarcoma cutaneous lesions. Repeat biopsy of residual brown plaque at 1

year revealed no evidence of KS; only findings consistent with drug deposition attributed to her ongoing Plaquenil use. Alitretinoin is a Vitamin A derivative that offers a non-invasive, patient-administered topical therapy to treat Kaposi sarcoma with minimal adverse effects.[17] Randomized controlled studies have confirmed the utility of alitretinoin 0.1% gel in the treatment of AIDS-related Kaposi sarcoma, although case reports have suggested that it may also be effective in patients who develop Kaposi sarcoma in the setting of a HIV negative status.[17,18]

This case highlights the importance of close surveillance for new skin lesions, particularly in the lower extremities, in iatrogenically immunosuppressed patients. With the increased use of biologics and immunomodulators to treat chronic autoimmune conditions, physicians must be familiar with the clinical presentation of Kaposi sarcoma and maintain a low level of threshold for skin biopsy to establish a prompt diagnosis.

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