VEXAS syndrome presenting as refractory cutaneous Kikuchi disease-like inflammatory pattern responding to tofacitinib

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Key words: cutaneous Kikuchi disease; janus kinase inhibitor; Kikuchi disease; Kikuchi disease-like inflammatory pattern; MxA staining; tofacitinib; VEXAS syndrome.

INTRODUCTION

VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a recently described adult-onset autoinflammatory syndrome caused by an acquired mutation of *UBA1* in hematopoietic progenitor cells. VEXAS syndrome commonly co-occurs with other conditions such as Sweet syndrome and hematologic malignancies. Herein, we describe a case of VEXAS syndrome presenting with prominent cutaneous manifestations, found to have cutaneous Kikuchi-disease like inflammatory pattern (KLIP) on histology. To our knowledge, this is the first reported case of KLIP occurring in VEXAS syndrome, extending the spectrum of VEXAS-associated diseases.

Abbreviations used:

DC:	dendritic cell
HSS:	histiocytoid Sweet's syndrome
JAK:	janus kinase
KFD:	Kikuchi-Fujimoto disease
KLIP:	Kikuchi disease-like inflammatory pattern
MxA:	Myxovirus resistance protein A
VEXAS:	vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic

CASE REPORT

A 66-year-old man presented for evaluation of a 3-year history of a rash that initially began as erythematous, tender, nonpruritic plaques on the chest, abdomen, and back. He had no fever, night sweats, weight loss, or arthralgias. The rash was not photosensitive. His medical history included hypertension and diverticulitis. He underwent an initial workup for his rash at an outside institution where a presumed diagnosis of pseudolymphoma was made based on a biopsy showing a dermal lymphocytic inflammatory process with a polyclonal T-cell receptor beta gene rearrangement. Over the subsequent 2.5 years, he was treated with topical halobetasol, topical tacrolimus, oral doxycycline, oral minocycline, and oral hydroxychloroquine with no improvement. He was started on oral prednisone (10-20 mg/day) which led to mild but incomplete improvement of his rash; prednisone tapering resulted in severe flares necessitating continuous systemic corticosteroids for over 1.5 years. Three months prior to presentation to us, numerous new lesions developed over his neck, arms, and legs. He was referred to the Columbia University Comprehensive Skin Cancer Center for further evaluation.

Physical examination revealed scattered, erythematous, round plaques and nodules ranging in size between 1 and 4 cm distributed over the neck,

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Funding sources: None.

IRB approval status: Not applicable.

Patient consent: Consent for the publication of all patient photographs and medical information was obtained by the authors prior to the manuscript submission. This consent is retained on file by the corresponding author and can be provided if necessary. The patient understands that their photographs and medical information may be published in print and online and will be publicly available.

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JAAD Case Reports 2023;38:136-40.

2352-5126

https://doi.org/10.1016/j.jdcr.2023.06.021

chest, back, arms, and legs (Fig 1, *A* and *B*). There was no evidence of skin atrophy or scarring. There was no lymphadenopathy or hepatosplenomegaly.

Three separate skin biopsies showed a reproducible morphology characterized by striking papillary dermal edema in association with an extensive mature histiocytic infiltrate in the superficial and deep dermis accentuated around blood vessels, nerves, and the eccrine coil. Prominent leukocytoclasia and vacuolar interface dermatitis were observed. The histiocytes included many macrophages exhibiting engulfed nuclear debris along with twisted serpiginous to C-shaped histiocytes (Fig 2). Immunohistochemistry demonstrated extensive positivity of mononuclear cells for CD4, CD11c, CD14, CD68, CD123, and CD163 throughout the dermis and subcutis, consistent with a mature monocyte-derived dendritic cell (DC) infiltrate (Fig 3). A subset of the monocytes also expressed granzyme. Several histiocytic elements showed myeloperoxidase (MPO) positivity compatible with an activated macrophage phenotype. There was a striking degree of Myxovirus resistance protein A (MxA) staining indicative of strong type I interferon expression throughout the sample (Fig 3, *A*). A minor T-cell component was highlighted whereby the monocyte to T-cell ratio was 5:1.

The pathologic findings were consistent with a primary cutaneous histiocytopathy of mature monocyte-derived DCs with a differential diagnosis encompassing KLIP, histiocytoid Sweet syndrome (HSS), and myeloid DC dyscrasia. The overall morphology and immunohistochemical profile were, however, most reminiscent of KLIP. While HSS has some overlapping histopathologic features with KLIP, the infiltrate in HSS is primarily MPO-positive immature myelomonocytic cells with histiocytic morphology rather than authentic histiocytes. In addition, HSS has few CD163+ cells which are typically scattered at the periphery of the main infiltrate.[1] Our case had striking CD163 immunoreactivity throughout the sample with only minor MPO positivity, making HSS less likely. Myeloid DC dyscrasia was considered less likely in light of the absent histiocytic atypia and the presence of leukocytoclasia.[2]

Laboratory evaluation revealed no significant abnormalities other than a mildly elevated erythrocyte sedimentation rate of 40 mm/hour. His hemoglobin was 14.1 g/dL with a normal MCV of 89 fL and CRP was normal. Autoimmune serologies were negative including ANA (antinuclear antibody) by indirect fluorescent antibody, anti-dsDNA, anti-Ro/SSA, anti-La/SSB, anti-Smith, anti-RNP, anti-endomysial IgA, anti-tissue transglutaminase IgA, cytoplasmic- and perinuclear-antineutrophilic cytoplasmic, anti-MPO, and anti-serine protease 3 antibodies. Bone marrow biopsy demonstrated mildly hypercellular marrow but was otherwise unremarkable. Bone marrow biopsy, flow cytometry, and positron emission tomography/computed tomography scan showed no evidence of underlying myeloproliferative disorder.

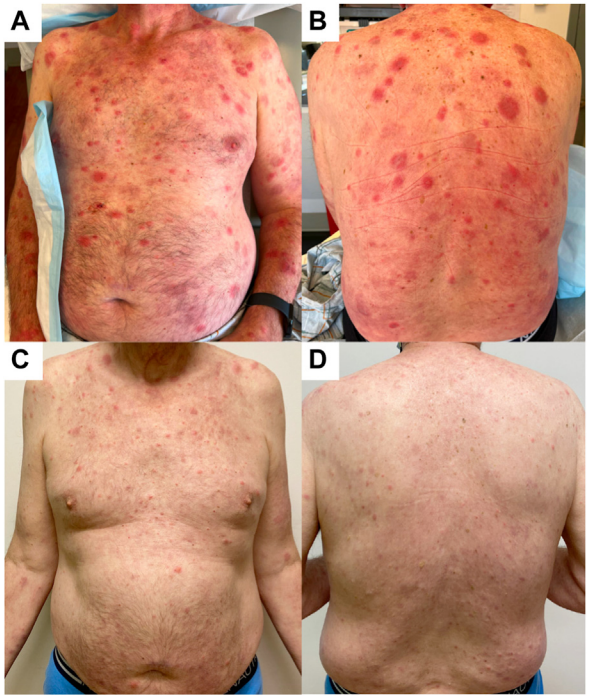

Fig 1. VEXAS syndrome presenting with Kikuchi disease-like inflammatory pattern. **A** and **B,** Erythematous, round plaques and nodules are seen on the chest, arms, and back. At this time, the patient was on oral prednisone with minimal clinical response. **C** and **D,** Significantly improved cutaneous lesions 6 months after initiating tofacitinib. *VEXAS*, Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

We made a provisional diagnosis of KLIP. Given the impressive pattern of type I interferon signaling apparent on the patient's biopsy, the patient was started on oral tofacitinib 5 mg twice daily and tapered off prednisone 2 weeks after initiating tofacitinib. He had significant improvement within 2 months. His dose was gradually increased to 10 mg twice daily. He has continued tofacitinib for more than 6 months with sustained clinical improvement (Fig 1, *C* and *D*) and no adverse effects. The patient's older age, male sex, refractory treatment course, and lack of underlying malignancy or autoimmune disease prompted genetic testing for VEXAS syndrome which revealed a pMet41Leu mutation in the *UBA1* gene, confirming the diagnosis of VEXAS syndrome. Upon repeat review of systems, the patient denied

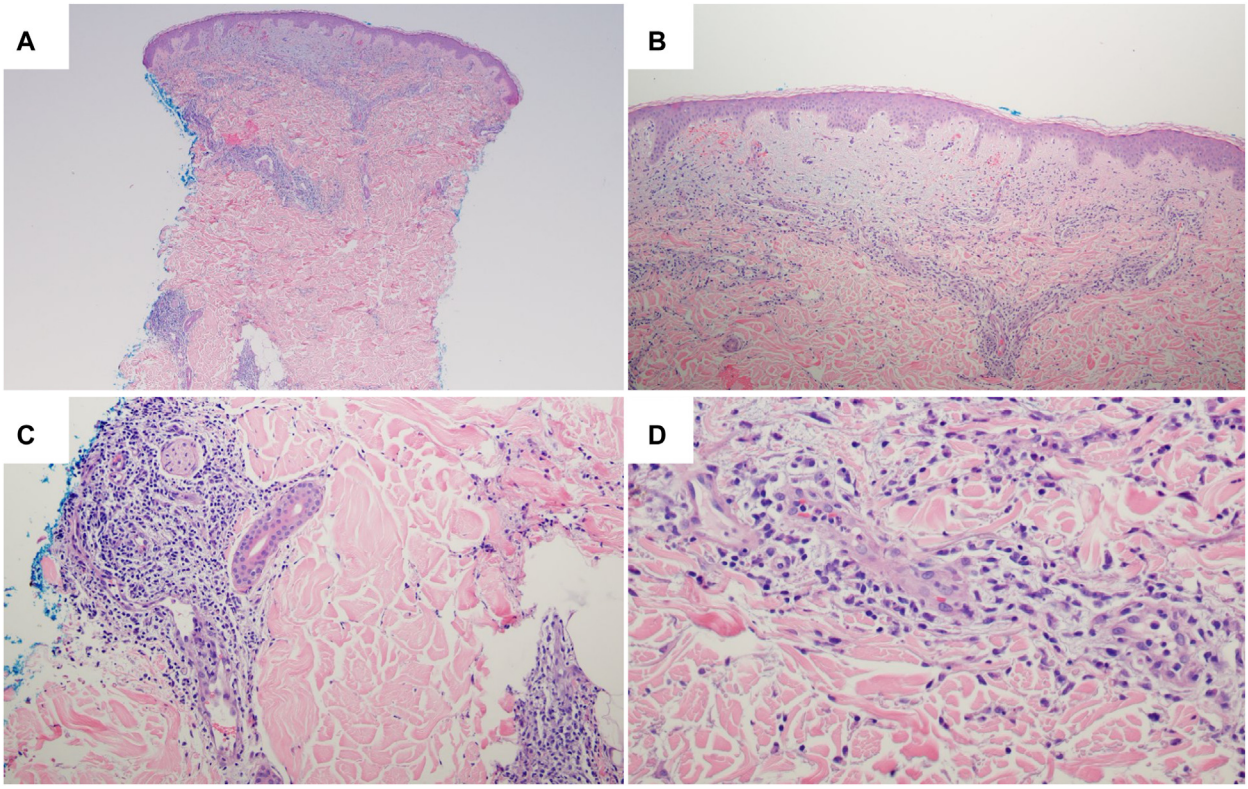

Fig 2. A, A low power view of the skin biopsy demonstrates a superficial and deep inflammatory cell infiltrate. **B,** The infiltrate assumes a somewhat band-like pattern superficially where it is accompanied by papillary dermal edema and some degree of interface change. **C,** The infiltrate exhibits a micronodular disposition within the mid and deeper reticular dermis; it manifests accentuation around nerves and involves the adventitial dermis of the eccrine coil. **D,** Higher power magnification discloses the composition of the infiltrate, being one of lymphocytes and histiocytes. The histiocytes include a number of cells that have C-shaped or serpiginous outlines. A characteristic finding is prominent leukocytoclasia. (**A-D,** Hematoxylin-eosin stain; original magnifications: **A**, 40×; **B**, 100×; **C**, 200×; and **D**, 400×).

fever, weight loss, chondritis, arthritis, shortness of breath, cough, or history of thromboembolism, but endorsed infrequent night sweats which he had previously denied at initial presentation.

DISCUSSION

VEXAS syndrome was first described in 2020 by Beck et al[3] who used a genotype-driven approach to identify men who harbored somatic mutations in *UBA1*, an X-linked gene encoding a ubiquitin activating enzyme required for hematopoiesis. Loss of UBA1 leads to defective hematopoiesis and a dysregulated pro-inflammatory state. The discovery of VEXAS syndrome unified a cohort of men presenting with previously unidentified and seemingly disparate hemato-inflammatory syndromes with multi-organ systemic involvement. Although the clinical presentation is variable, this diagnosis can be considered in men in the fifth to seventh decade of life presenting with treatment-refractory fevers, rashes, macrocytic anemia, polychondritis, pulmonary disease, thromboembolism, and vacuolization of bone marrow erythroid and myeloid precursor cells. VEXAS syndrome may be underrecognized, with one study estimating a prevalence of about 1 in 4269 men older than 50 years.[4]

Our case was a diagnostic challenge given that the patient lacked many of the common clinical features of VEXAS syndrome. However, data from a multicenter case series of 116 patients suggest that there may be several distinct clinical phenotypes with some patients presenting with a milder disease course.[5] The UBA1 p.Met41Leu mutation, for example, seems to be associated with fewer constitutional symptoms, less frequent thromboembolic events, and lower CRP levels, consistent with our patient's case. In retrospect, clues to the diagnosis were his older age and male sex, treatment-refractory rash, mildly elevated erythrocyte sedimentation rate, and hypercellular bone marrow.[6]

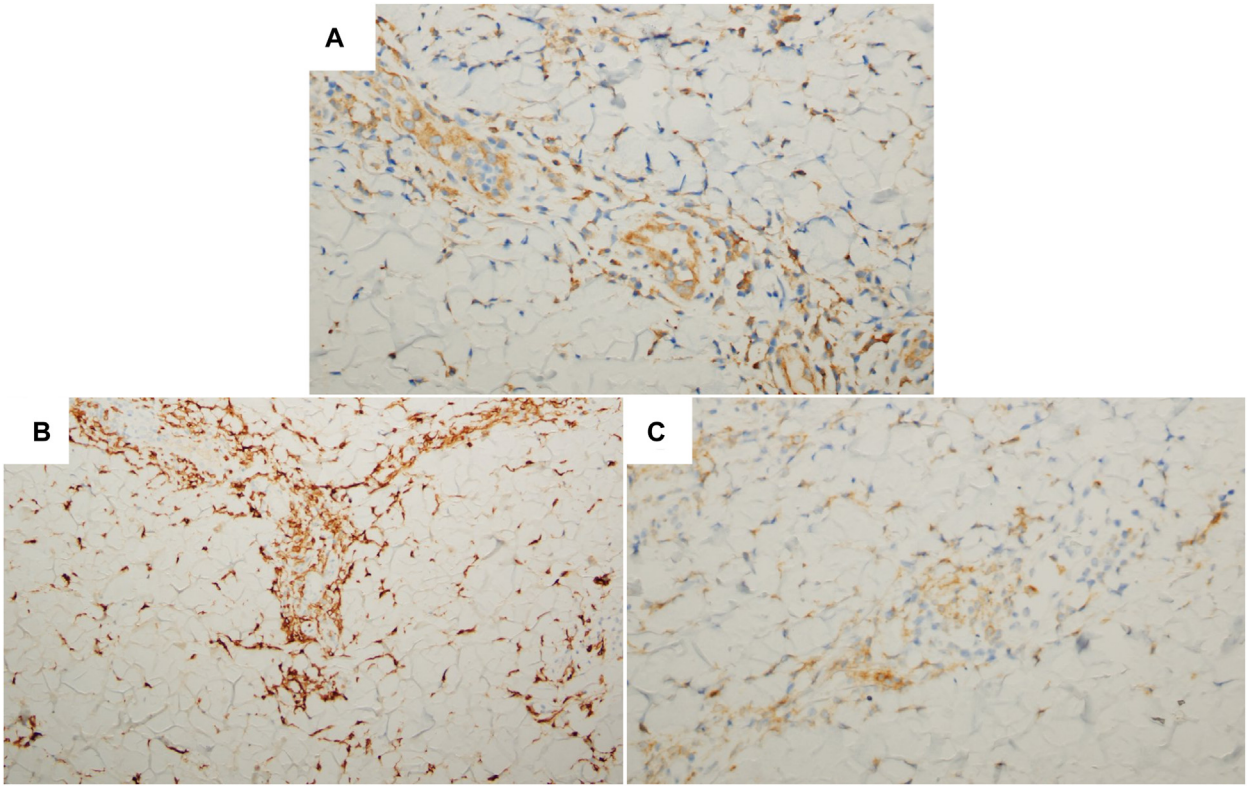

Fig 3. A, The MxA stain shows prominent immunoreactivity in endothelial cells and inflammatory cells and reflects a strong type I interferon signature. **B,** CD163 stain highlights the extensive histiocytic component of the infiltrate. **C,** Many of the histiocytic cells demonstrate CD11c staining, suggestive of a monocyte-derived dendritic cell phenotype. (**A-C,** diaminobenzidine; original magnifications: **A**, 400×; **B**, 200×; and **C**, 400×).

The most common dermatologic manifestations of VEXAS syndrome are Sweet syndrome and cutaneous vasculitis.[3,5] There are 2 reported cases of VEXAS syndrome associated with Kikuchi-Fujimoto disease, both of which presented with recurrent fevers, necrotizing lymphadenitis, and rashes.[7,8] KLIP is a rare pattern of cutaneous inflammation that shares histopathological features with classical Kikuchi-Fujimoto disease but presents with isolated cutaneous lesions without fevers or lymphadenitis.[9] To our knowledge, we report the first case of KLIP associated with VEXAS syndrome.

Although janus kinase (JAK) inhibitors have not been previously described as a treatment for KLIP, the patient did not respond to hydroxychloroquine and required continuous systemic corticosteroids which led to numerous side effects. The strong type I interferon signature on the patient's biopsy indicated that he may respond to type I interferon-blocking medications, prompting us to initiate tofacitinib prior to obtaining the genetic testing results. Indeed, the patient had significant clinical improvement with tofacitinib and was able to discontinue steroids after 1.5 years. This is not surprising considering that JAK inhibitors are a preferred treatment for VEXAS syndrome.[10] While there is limited evidence that ruxolitinib may have superior efficacy compared to other JAK inhibitors,[10] our patient has responded well to tofacitinib. Our case highlights the utility of performing MxA staining to guide therapeutic decision-making, which enabled us to initiate the patient on the appropriate medication class prior to knowledge of the final diagnosis in this case.

Hematologic malignancies, particularly myelodysplastic syndrome and plasma cell dyscrasias, are seen in up to 50% of VEXAS syndrome cases,[5] making bone marrow biopsies an important part of the initial workup. In a patient such as ours with an established diagnosis of VEXAS syndrome and baseline bone marrow biopsy negative for underlying myeloproliferative disorder, the risk of subsequently developing a hematologic malignancy is unclear. We advocate for multidisciplinary care among dermatologists, hematologists, and rheumatologists. While there is no high-quality evidence to inform monitoring protocols for these patients, a reasonable strategy includes regular follow-up with focused

histories and physical examinations as well as regular monitoring of the complete blood counts and basal metabolic panels (eg, once every 3-6 months). Additional workup should be individualized according to the patient's symptoms, exam findings, and laboratory values. For example, progressive cytopenia may prompt a repeat bone marrow biopsy.

It is crucial that dermatologists are aware of VEXAS syndrome, as skin manifestations are present in almost 90% of patients[3] and may be the predominant manifestation of this syndrome as in our case. A lack of systemic symptoms and absence of macrocytic anemia are not sufficient to rule out the diagnosis. Genetic testing for VEXAS syndrome may be considered in older males presenting with treatment-refractory dermatoses.

Conflicts of interest

Dr Geskin has served as an investigator for and/or received research support from Helsinn Group, J&J, Mallinckrodt, Kyowa Kirin, Soligenix, Innate, Merck, BMS, and Stratpharma; on the speakers' bureau for Helsinn Group and J&J; and on the scientific advisory board for Helsinn Group, J&J, Mallinckrodt, Sanofi, Regeneron, and Kyowa Kirin. Drs Fahmy, Schreidah, Lapolla, and Magro have no conflicts of interest to declare.

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