Extensive reactive cutaneous histiocytic infiltrate resembling non-Langerhans cell histiocytosis as the presenting sign of underlying vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome

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INTRODUCTION

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a newly described condition caused by mutations in the ubiquitin-like modifier activating enzyme 1 (*UBA1*) gene.[1] Affected patients have signs of marked systemic inflammation, including fever and other constitutional symptoms, elevated inflammatory markers, and hematologic abnormalities such as cytopenias. Other features are highly variable, but commonly include skin lesions, chondritis, arthritis, ocular inflammation, and pulmonary involvement. Patients are usually between 55 and 75 at onset and, given *UBA1* is found on the X chromosome, most often male.[1-5]

Cutaneous manifestations are one of the most prevalent features, found in 73% to 88% of cases.[1-3,6] Neutrophilic dermatoses represent the most common skin finding (32%-40% of cases[1,3]), with other presentations including cutaneous vasculitis, panniculitis, and urticaria. However, there has not been, to our knowledge, report of an extensive cutaneous histiocytic reaction in association with VEXAS. Here, we report a unusual case of a widespread reactive histiocytic infiltrate leading to a diagnosis of VEXAS in the setting of myelodysplastic syndrome (MDS).

Abbreviations used:

MDS:	myelodysplastic syndrome
RGD:	reactive granulomatous dermatitis
UBA1:	ubiquitin-like modifier activating enzyme 1
VEXAS:	vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic

CASE REPORT

A 66-year-old Caucasian man presented with a painful, scarring rash worsening over 2 years. He had previously been evaluated by several outside physicians and was being treated for a possible diagnosis of lupus with methotrexate and hydroxychloroquine, although autoimmune work-up was only notable for positive SS-A antibody with negative antinuclear antibody. On examination, he had annular yellow-pink plaques on the neck and upper portion of the chest (Figs 1 and 2), as well as mamillated plaques and nodules on the upper portion of the arms, chest, back (Fig 3), and upper lip. Punch biopsies were performed from the right side of the neck and breast and showed a dermal interstitial infiltrate of histiocytes, some containing foamy cytoplasms, with areas of nuclear dust and

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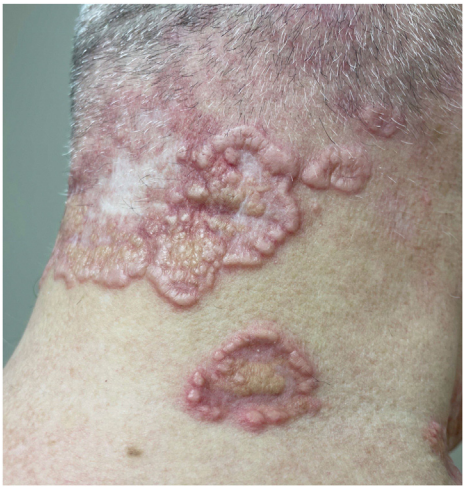

Fig 1. Annular yellow-pink plaques on the posterior aspect of the neck.

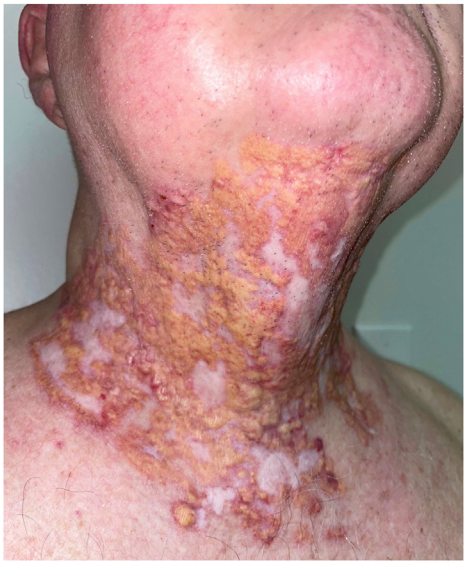

Fig 2. Annular yellow-pink plaques on the anterior aspect of the neck and upper portion of the chest.

foci of altered collagen. The absence of cholesterol clefts and Touton giant cells, along with lack of facial involvement clinically, militated against necrobiotic xanthogranuloma. Lack of associated features such as mucosal xanthomas and diabetes insipidus also suggested against xanthoma disseminatum. Overall, the findings, although difficult to interpret, were favored to represent a reactive granulomatous dermatitis (RGD).

Given the unusual findings, further work-up was performed to rule out underlying systemic associations such as malignancy. Upper endoscopy, colonoscopy, and serum protein electrophoresis were normal. Complete blood count and metabolic panel

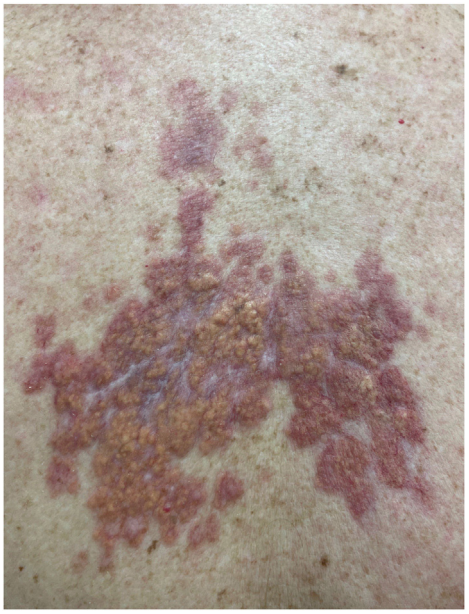

Fig 3. Yellow-pink plaques on the central back.

were unremarkable except for persistent macrocytic anemia with mean corpuscular volume of up to 111 fL that was generally attributed to methotrexate use. Other cell lineages were initially unaffected. Topical steroids and additional immunosuppressive agents were tried including mycophenolate mofetil by outside providers but without improvement.

He returned a year later with worsened widespread rash. Repeat punch biopsy was performed from the left shoulder (Fig 4). Histopathological examination demonstrated a diffuse infiltrate of histiocytes within the superficial to mid dermis, many containing abundant foamy cytoplasms, associated with scattered lymphocytes and abundant cellular debris. Extensive alteration to the collagen and early fibrinoid changes of the vessels were also noted. Stains for microorganisms (GMS, Gram, AFB, and Fite) were negative. CD68 staining highlighted a diffuse infiltrate of histiocytes, whereas CD1a and S-100 stains were negative. A VE1 stain for BRAF V600E mutation was performed and was also negative. CD3 and CD20 highlighted scant admixed lymphocytes, most of which were CD3+ T cells with only rare CD20+ B cells. Overall, the features were somewhat similar to those of the prior biopsies; however, the histiocytic infiltrate diffusely involved the papillary dermis in a sheet-like pattern, raising the possibility of a non-Langerhans cell histiocytosis, which was thus favored over RGD. The plan was therefore to start thalidomide.

Before the patient could begin treatment, he was admitted for worsening rash in addition to fevers, night sweats, and generalized weakness. Hospital

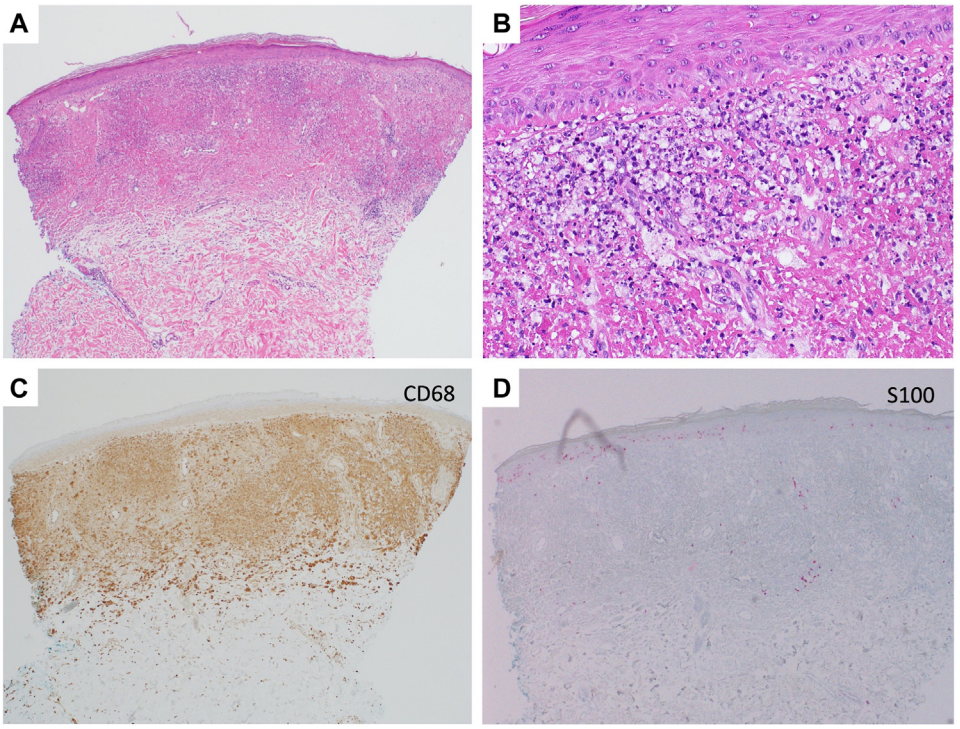

Fig 4. Histopathological examination. **A**, Low-power view of inflammatory infiltrate within superficial and reticular dermis (hematoxylin-eosin stain; original magnification: ×40). **B**, Diffuse infiltrate of histiocytes, many containing abundant foamy cytoplasms, associated with scattered lymphocytes and abundant cellular debris (hematoxylin-eosin stain; original magnification: ×200). **C**, Positive CD68 staining highlighting the infiltrates of histiocytes (original magnification: ×40). **D**, S-100 staining was negative.

work-up included a positron emission tomography-computed tomography that demonstrated diffuse bone marrow uptake and increased uptake in the spleen and several nodes. He had persistent macrocytic anemia as well as new mild thrombocytopenia. Oncology, dermatology, and rheumatology were consulted and collectively favored Erdheim-Chester disease, a form of non-Langerhans cell histiocytosis. He was started on a prednisone taper with improvement in symptoms and was discharged with close oncology follow-up. Bone marrow biopsy was subsequently performed and showed a markedly hypercellular marrow with granulocytic hyperplasia and multilineage atypia and vacuoles in small subset of myeloid and erythroid precursors, consistent with MDS. A targeted sequencing panel was also performed, which revealed a pathogenic mutation in *UBA1* (M41L with 88% variant allele frequency) and a variant of uncertain significance in *DNMT3A* (W601R, 21% variant allele frequency). Taken together, a new diagnosis of VEXAS syndrome, in the setting of MDS, was made.

The patient was subsequently started on ruxolitinib 10 mg by mouth twice daily in addition to prednisone with improvement in his systemic symptoms and rash. He is currently being evaluated for bone marrow transplant.

DISCUSSION

Our case demonstrates a striking presentation of an extensive cutaneous histiocytic infiltrate, resembling a non-Langerhans cell histiocytosis, which we propose is a reactive infiltrate in the setting of VEXAS syndrome. Such a cutaneous reactive histiocytic infiltrate has not previously been described in association with VEXAS. RGD has been associated with MDS in several cases,[7] but our patient's presentation ultimately did not fit clinically or histopathologically with classic RGD patterns.

There is no standardized treatment for VEXAS.[4] Patients often require high-dose glucocorticoids for control. Some of the most promising medications include JAK inhibitors (ruxolitinib the most effective[8]), DNA methyltransferase inhibitors (azacitidine[9]), and anti-IL-6 therapies (tocilizumab[9]). Multidisciplinary care between involved specialties is critical. Stem cell transplant may be beneficial in some cases.[10]

As in this case, many patients may have a long history of prior work-up before they are finally diagnosed. Our patient also had associated MDS, which is common in VEXAS patients (approximately 24%[1]-55%[9]). Of note, VEXAS may not be uncommon—a single-center retrospective study of over 163,000 patients examined the prevalence of somatic *UBA1* mutations through exome sequencing and found that disease-causing variants were present in 1/13,591 unrelated individuals and 1/4269 men older than 50.[6]

This case highlights the importance of further investigation in cases involving recalcitrant inflammatory skin disease. In such patients, particularly those with higher-risk demographics such as older age and male sex, further work-up for VEXAS syndrome should be considered.

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Conflicts of interest

Dr Musiek has received financial compensation through her employment on an advisory board for Kyowa, and as a principal investigator for Kyowa, Pfizer, Aristea, and Bristol Myers Squib. Drs Wang, Yokoyama, and Rosman have no conflict of interest to declare.

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