Long-term maintenance of eosinophilic dermatosis of hematologic malignancy with doxycycline

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INTRODUCTION

Eosinophilic dermatosis of hematologic malignancy (EDHM) is a cutaneous manifestation reported with various hematoproliferative and lymphoproliferative disorders, most commonly chronic lymphocytic leukemia (CLL). It is characterized as a nonspecific pruritic eruption with pleomorphic clinical presentations ranging from erythematous, urticarial papules and nodules to vesicles and bullae, making accurate diagnosis difficult, as it can mimic other conditions.[1] EDHM often has a chronic, recurrent course with differential responses to treatment modalities reported in the literature.[2] We report two cases of EDHM that initially were a diagnostic and therapeutic challenge; we hope to raise awareness of this rare entity as well as share a successful long-term treatment regimen not previously reported.

Abbreviations used:

BP:	bullous pemphigoid
CLL:	chronic lymphocytic leukemia
EDHM:	eosinophilic dermatosis of hematologic malignancy

CASE REPORTS

Case 1

An 81-year-old woman with a history of CLL experienced recalcitrant urticaria for more than 5 years. The physical examination findings ranged from localized indurated plaques with tiny tense vesicles (Fig 1, *A*) to diffuse urticarial papules and plaques with excoriations. Over the years, multiple biopsies were performed, which consistently showed a superficial and deep mixed cell infiltrate with many eosinophils suggestive of a dermal hypersensitivity reaction that was thought to be due to either a drug or an insect bite. The lesions began during the patient's fifth cycle of chemotherapy with bendamustine and rituximab and improved with a 40 mg prednisone taper over 3 months. When maintenance therapy with rituximab was restarted, the lesions recurred and did not resolve when rituximab was discontinued, making a drug reaction unlikely. A further biopsy showed similar pathology, with the addition of intraepidermal vesiculation, raising concern for bullous pemphigoid (BP) (Fig 1, *B*). A skin biopsy for direct immunofluorescence was negative for BP-specific antibodies, and the patient's lack of response while receiving maintenance rituximab made this diagnosis less likely.

Over the years, the patient was trialed on multiple therapies, including permethrin 5% cream, antihistamines such as cetirizine and clemastine, topical triamcinolone, dapsone, and narrow-band ultraviolet B phototherapy, all of which resulted in little or no improvement. When the recurrent course of her symptoms in the setting of malignancy and the histopathologic findings were considered, the diagnosis was presumed to be EDHM. Coincidentally, when an abscess developed that was treated with doxycycline, her pruritus and urticarial plaques resolved within 2 weeks but recurred after she finished the antibiotic course. She was restarted on doxycycline 100 mg twice daily and again showed

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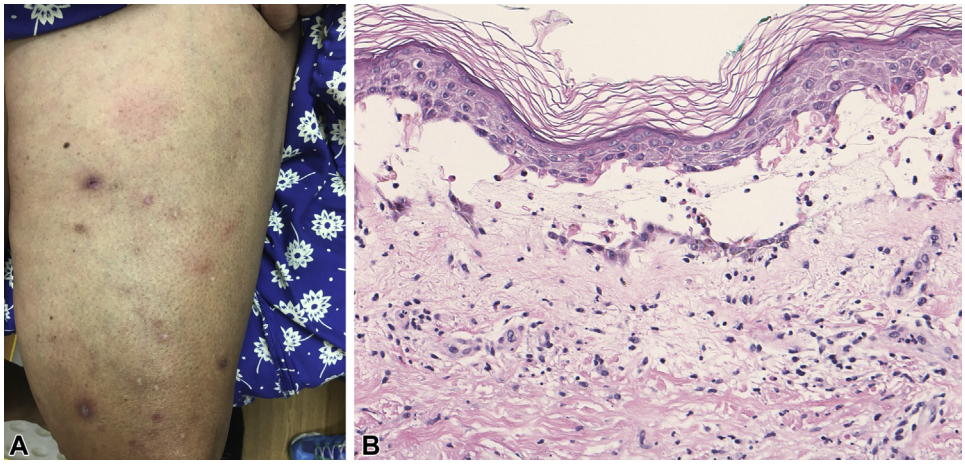

Fig 1. A, Indurated urticarial papules and plaques with excoriations. **B**, Superficial and deep mixed cell infiltrate with many eosinophils and intraepidermal vesiculation. (Hematoxylin-eosin stain; original magnification: ×10.)

improvement. Physical examination during this regimen showed no new eruptions or excoriations. Consequently, adequate control has been achieved for the past 3 years with courses of doxycycline 100 mg twice daily, decreased to once daily if the symptoms are well controlled.

Case 2

A pruritic, bullous eruption developed in a 55-year-old woman with a history of stage IV follicular lymphoma during treatment with bendamustine that persisted after transitioning to maintenance rituximab. Originally, the patient showed no improvement with topical permethrin, oral hydroxyzine, or topical hydrocortisone and mild improvement with 60 mg of prednisone tapered over 2 months. The physical examination showed diffuse round crusts and pink edematous, vesicular papules and bullae on the extremities, with the trunk mostly spared (Fig 2, *A*). Although the clinical presentation resembled BP, this diagnosis was less likely, given that the disease showed no response to rituximab. The biopsy results showed subepidermal vesiculation with a superficial and deep perivascular and periadnexal mixed cell infiltrate including many eosinophils (Fig 2, *B*). The direct immunofluorescence findings were negative. Given the oncologic history, clinical presentation, and histopathologic features, a diagnosis of EDHM was made. The patient was started again on 60 mg of prednisone to be tapered, topical triamcinolone 0.1% ointment, and doxycycline 100 mg twice daily, with improvement. Interestingly, when the patient ran out of the medications, the lesions recurred. Doxycycline was restarted alone, and the pruritus and lesions resolved within a few weeks, with adequate control lasting for more than 3 months.

DISCUSSION

EDHM is a rare paraneoplastic condition, with 208 cases described in the literature. Although it is predominantly associated with CLL (77% of patients), it has also been reported in patients with lymphomas (17%), including follicular lymphoma, other leukemia (3.5%), and other hematologic disorders (2.5%).[3] Given that EDHM is a diagnostic challenge because of its multiple clinical morphologies, the proposed criteria for diagnosis include a history of hematoproliferative disease, recurrent episodes of pruritic cutaneous eruptions, and histopathologic evidence of eosinophilic infiltration, with other possible causes excluded.[4] Differential diagnoses to consider are scabies, arthropod bites, dermatitis herpetiformis, drug reaction, eosinophilic folliculitis, eosinophilic cellulitis, disseminated zoster infection, leukemia cutis, and urticarial stage of BP.[2]

The cutaneous symptoms of EDHM can appear months to years after diagnosis of a hematologic malignancy and may even precede it. The eruptions have been found to be unrelated to the disease course, occurring when the malignancy is quiescent and during ongoing therapy.[5,6] Notably, in both of our cases, lesions appeared while the patient was receiving rituximab for CLL or follicular lymphoma and persisted after the malignancy improved. Although its pathogenesis has not been fully elucidated, EDHM is likely driven by an induced cytokine imbalance caused by neoplastic leukemic B cells with increased production of interleukin 4 and interleukin 5 by Th-2 cells, which are largely

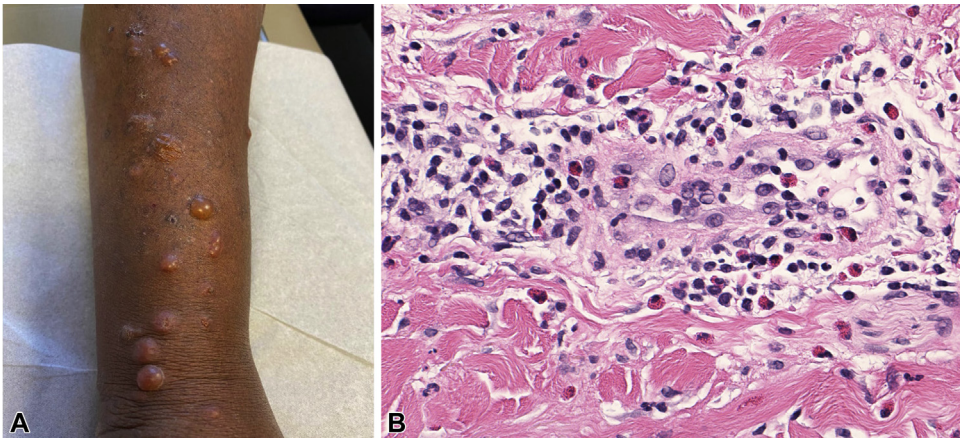

Fig 2. A, Round crusts and pink edematous, vesicular papules and bullae on the upper extremity. **B**, Perivascular mixed cell infiltrate including many eosinophils. (Hematoxylin-eosin stain; original magnification: ×40.)

responsible for the recruitment of eosinophils.[1,3,7] In some reported cases, however, improvement with chemotherapy was noted but the disease often recurred.[2,8]

EDHM has been challenging therapeutically, since various modalities, such as systemic steroids, doxycycline with or without nicotinamide, antihistamines, interferon therapy, and phototherapy, have elicited some response in the short term; however, reported maintenance therapy to prevent relapse has been largely lacking, with options such as systemic steroids or dapsone not preferred because of the adverse effects of long-term therapy.[4,9] For a longer, sustained response, dupilumab and omalizumab have been reported to be successful.[7,9] Since both of our patients' symptoms have been managed well for an extended period of time on doxycycline, likely due to its antiinflammatory properties, we suggest considering this low-toxicity and inexpensive therapy, which has not been previously reported as a long-term treatment option.[2]

Although they are not thought to be life-threatening, the refractory pruritus and lesions associated with EDHM can have a detrimental impact on patients' quality of life.[4] It is imperative to report cases with this condition in order to raise awareness, given its rarity, and to suggest possible treatment options with prolonged response that may benefit others who receive a diagnosis of this paraneoplastic disorder.

Conflicts of interest

None disclosed.

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