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Eosinophilic dermatosis in a patient with chronic lymphocytic leukemia: a rare case report

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Abstract

Chronic lymphocytic leukemia (CLL) is a type of malignant lymphoproliferative disorder characterized by a rapid and uncontrolled increase in lymphoid cells, mostly monoclonal B-cells (B-CLL). Patients with CLL may present cutaneous lesions that can be classified as either "specific" or "non-specific." In CLL patients, specific skin eruptions arise from leukemic cell infiltration, recognized histopathologically in tissue sample biopsy. Non-specific lesions encompass the majority of eruptions in CLL patients and may present as petechiae, purpura, urticaria, exfoliative dermatitis, paraneoplastic pemphigus, vasculitis, or eosinophilic dermatosis. Eosinophilic dermatosis of hematologic malignancy (EDHM) is a rare cutaneous manifestation that presents as an eruption in various locations and is characterized as papular, pruritic, and sometimes vesicular or vesiculobullous. Here we present a rare and interesting case of a 58-year-old woman with a medical history of B-CLL that was examined at our clinic for evaluation of an unspecified diffuse vesicular pruritic rash. The patient was first diagnosed with CLL 3 years earlier and followed a 6-month course of immuno-chemotherapy with rituximab, fludarabine, and cyclophosphamide. We also performed brief review of previous literature and present the results.

Keywords: allergy, diagnosis, eosinophilic dermatosis, lymphoma, paraneoplastic syndrome, surgery

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Introduction

Chronic lymphocytic leukemia (CLL) is a type of malignant lymphoproliferative disorder characterized by a rapid and uncontrolled increase in lymphoid cells, mostly monoclonal B-cells (B-CLL). This proliferation creates lymphoid cell buildup in peripheral blood, bone marrow, and other organs. Patients with CLL may present with cutaneous lesions that can be classified as either "specific" or "non-specific" (1). In CLL patients, specific or "real" skin eruptions arise from leukemic cell infiltration and are recognized histopathologically by leukemic cell presence in tissue sample biopsy, as observed in the uncommon CLL manifestation of leukemia cutis (2). Clinically, specific skin eruptions present as reddish-brown papules or nodules. Non-specific lesions encompass the majority of eruptions in CLL patients, and they may present as petechiae, purpura, urticaria, exfoliative dermatitis, paraneoplastic pemphigus, vasculitis, or eosinophilic dermatosis (3). The condition of eosinophilic dermatosis of hematologic malignancy (EDHM), first reported in 1965, was categorized as an insect bite–like reaction in patients with CLL. It was linked to latent hypersensitivity reactions to insect bites, particularly mosquitoes, although most patients presenting with this reaction frequently could not recall being bitten, and thus the term insect bite–like reaction was further questioned (4). Later the term eosinophilic dermatosis of myeloproliferative disease was proposed and was defined by the selected criteria shown in Table 1 (5).

Table 1 | **Byrd's diagnostic criteria for eosinophilic dermatosis of myeloproliferative disease (5).**

	Description
A	Pruritic papules, nodules, and/or vesiculobullous eruption refractory to standard treatment
B	Histopathology revealing eosinophil-rich superficial and deep dermal lymphohistiocytic infiltrate
C	Exclusion of other causes of tissue eosinophilia
D	Diagnosis of hematologic malignancy

Case report

A 58-year-old woman with a history of B-CLL presented at our clinic for evaluation of an unspecified diffuse vesicular, pruritic rash that developed over a period of 2 days. The patient was first diagnosed with CLL 3 years earlier. The immunophenotype of the peripheral blood, characteristic of B-CLL with a 72% percentage of B-lymphocytes, revealed the expression of CD5−/+, CD23+, CD20+ (low), and CD24+ on B-lymphocytes, whereas the ratio between kappa and lambda light-chains was 350 (kappa/lambda: 350), with normal values ranging between 0.5 and 3.0. Additional karyotyping testing was performed, which demonstrated pathological findings of an additional derivative of chromosome 9, formed by an unknown large translocation [+der(9)add(9)], a deletion in the long arm of chromosome 13 [del(13)], and the absence of a copy of chromosomes 15 and 18 (−15, −18): karyotype according to International System for Human Cytogenomic Nomenclature (ISCN) 2016: 45,XX, +der(9)add(9)(q34), del(13)(q12q21), −15 −18 (2)/ 46,XX (5). Fluorescence in situ hybridization (FISH) did not detect absence of the TP53 gene (TP53 unmutated). Finally, the analysis of immunoglobulin heavy-chain variable (IGHV) gene status revealed no mutated regions. Two years later, the patient followed a 6-month course (June 2019 to January 2020) of immunochemotherapy regimens of rituximab, fludarabine, and cyclophosphamide, following treatment initiation indications (B-symptoms, rapid increase

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in lymphocyte count, and deterioration of lymphadenopathy). Shortly after the initial response to the treatment, the patient exhibited papular, pruritic eruptions on various parts of her body, along with peripheral edema and ocular pruritus of the right eye (Fig. 1). Multiple pruritic papules ranging from 2 to 5 mm within areas of erythema were revealed upon physical examination, in addition to hard, enlarged preauricular lymph nodes that were discovered on palpation. The clinical differential diagnosis included allergic drug skin reaction, arthropod assault / papular urticaria, herpes zoster, scabies, urticarial stage of bullous pemphigoid, and eosinophilic folliculitis. Laboratory tests showed a hemoglobin level of 12.9 g/dl (normal range 12–16 g/dl) and a white blood cell count of 10,200 K/μl (normal range 3,800–10,500 K/μl). In addition, the liver enzymes aspartate transaminase (AST) and alanine transaminase (ALT) were within normal limits, whereas renal function tests (urea and creatinine) were slightly elevated, at 49 mg/dl (normal range 10–43 mg/dl) and 1.16 mg/dl (normal range 0.66–1.10 mg/dl), respectively, alkaline phosphate was 151 U/l (normal 20–140 U/l), and lactate dehydrogenase was 259 U/l (normal < 248 U/l). Immunoglobulins (Ig), including IgE and b2 microglobulin serum levels, were within normal range, with the exception of a low IgM at 26.4 mg/dl (normal range 46–304 mg/dl). Complement component 4 was elevated at 57 mg/dl (normal range 6–38 mg/dl). Antinuclear antibodies were the sole antibodies that were detected at a threshold positive level of 1/160 with the indirect fluorescent antibody (IFA) method. Serological testing for hepatitis B and C as well as HIV was also negative. Consequently, the patient was initially treated with acyclovir, amoxicillin/clavulanic acid, methylprednisolone, and levocetirizine. In the following few days, the patient's clinical condition partly improved, and treatment was continued with only methylprednisolone and levocetirizine with gradual dose tapering. Because the skin lesions persisted, a skin biopsy was performed during the following month and the histopathological findings were compatible with eosinophilic dermatosis. Immunohistochemical stains showed that the lymphocytes were positive for CD3 and negative for CD20 and PAX5 markers, indicating that the infiltrate was composed of reactive T-cell lymphocytes rather than leukemic B-cells. The infiltrate was also abundant in eosinophils (Fig. 2). These findings are consistent with eosinophilic dermatosis, which can be linked to the patient's underlying hematologic malignancy. The immunohistochemical evidence was considered along with the detected lymphadenopathy, as well as a subsequent white blood cell increase to 18,500 K/μl (normal range 3,800–10,500 K/μl), significant lymphocytosis (86%), and thrombocytopenia (106,000 K/μl, normal range 150,000–450,000 K/μl). The findings led to the patient's treatment plan being altered from only methylprednisolone to the addition of ibrutinib, an inhibitor of Bruton's tyrosine kinase (BTK). One year later, she is progressing well on solely ibrutinib treatment without the presence of new skin lesions.

Discussion

EDHM is a rare cutaneous manifestation. Initial eruptions generally appear concurrently or months to years after associated hematologic malignancy diagnosis, with rare instances of eruption prior to malignancy. The typical age of EDHM presentation in CLL patients has been shown to be between 50 and 60 years old, as in our patient (6). Clinical differential diagnosis of EDHM can be undertaken by excluding autoimmune blistering disorders (such as bullous pemphigoid and dermatitis herpetiformis) through immunofluorescence and cutaneous specific lesions of CLL through histological and immunohistochemistry examination (1). Other differential diagnoses that should be conducted include eosinophilic folliculitis, Well's syndrome, non-dermatomal distribution, and disseminated zoster virus infection (4, 7).

Currently, the condition's pathogenesis has not been elucidated, with some suggesting that leukemic cells drive a cytokine imbalance, resulting in interleukin-4 and interleukin-5 abundance, which promotes excess neoplastic B cell proliferation driving eruption. This hypothesis is reinforced by the role of interleukin-5 as a prominent eosinophile recruiting cytokine. Alternative hypotheses include that increased expression of interleukin-5 is driven by an immune stimulus presence such as a virus, drug, or insect bite along with the patient's underlying immunodeficiency (4).

Current therapeutic actions for EDHM include antibiotics, an-

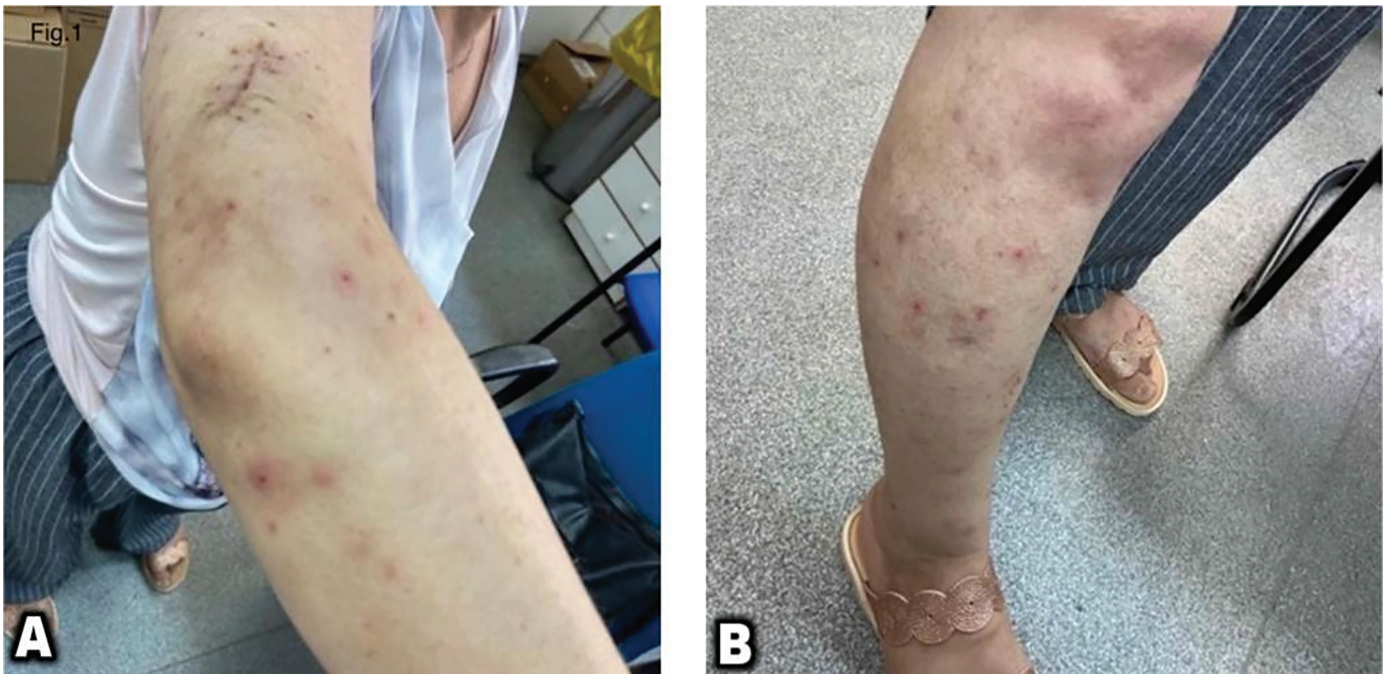

Figure 1 | (A) Close and (B) distal view of the patient's vesicular rash. Multiple erythematous-based vesicles appear in various parts of her limbs.

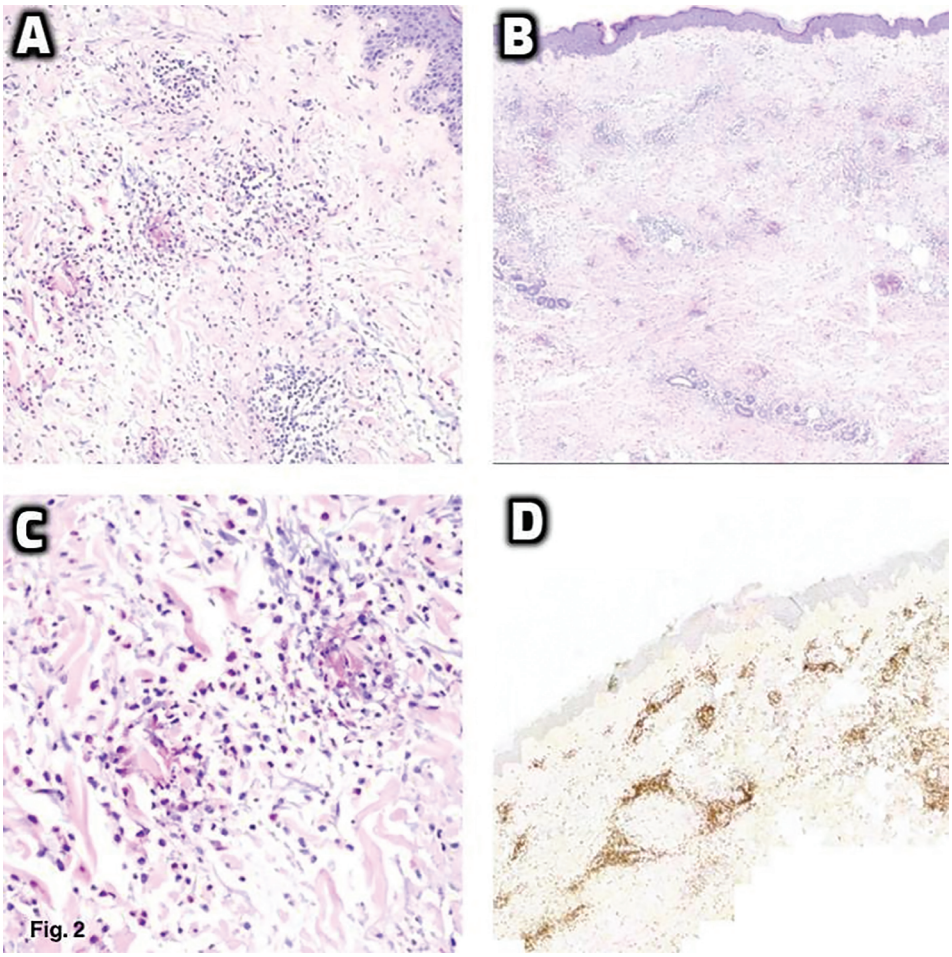

Figure 2 | (A) H&E 100× view: the epidermis is without remarkable changes, and in the dermis there is inflammatory infiltrate with many eosinophils; (B) low-power view with full-thickness dermal inflammation, many eosinophils, and flame figures; (C) H&E 200× view: closer view of the flame figures and the eosinophils; (D) immunohistochemical stain CD3+: low-power view revealing CD3+ T-lymphocytic infiltrate.

tihistamines, intravenous immunoglobulin, interferon alpha, radiation, and chemotherapy. Although some patients have been shown to benefit, most only present brief or partial improvement from therapies. Despite EDHM being a recalcitrant condition, systemic corticosteroids at doses of 0.5 to 1 mg/kg/d (7) in the active phase of treatment have been indicated as the most successful means in suppressing skin manifestations; however, dosage tapering can result in symptom recurrence. Although there has been no actual proof of a direct link between eosinophilic dermatosis and the course of the underlying disease to date, in other cases of CLL patients with eosinophilic dermatosis, as well as in ours, the onset of the skin lesions coincided with a rapidly progressing B-CLL disease course. Although the relationship between the two clinical entities remains unclear, patients seem to benefit from a therapy plan that includes immunochemotherapy treatment to control CLL disease (4). Recent research suggests a possible maintenance therapy for EDHM with low long-term toxicity in the form of omalizumab. Omalizumab is a monoclonal antibody derived from recombinant DNA that binds to the surface of B lymphocytes and free IgE in interstitial fluid and blood with specificity. Omalizumab administration following phototherapy and prednisone tapering has been shown to control EDHM in an individual case study (6).

Conclusions

Despite the patient's initial response to B-CLL treatment, after a period of 2 months she experienced signs of recurrent disease with manifestation of cortisone-resistant skin lesions and lymphadenopathy, along with significant aggravation of values in the complete blood count tests. Correlation of the medical history, clinical presentation, pathologic findings, and laboratory results established the diagnosis of eosinophilic dermatosis with hematologic malignancy. Eventually, the patient was treated with methylprednisolone tapering for the skin lesions and ibrutinib for the CLL.

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