Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2023;32:183-186
doi: 10.15570/actaapa.2023.32

A dermatological perspective: eosinophilic eruption of hematoproliferative disease as a clinical and histological dilemma

Tijana Orlic[1], Snezana Minic[1,2], Emilija Manojlovic-Gacic[2,3], Dubravka Zivanovic[1,2], Igor Kapetanovic[1] ✉

[1]Clinic of Dermatology and Venereology, University Clinical Center of Serbia, Belgrade, Serbia. [2]Department of Dermatology and Venereology, Faculty of Medicine, University of Belgrade, Serbia. [3]Institute of Pathology, School of Medicine, University of Belgrade, Belgrade, Serbia.

Abstract

The emergence of de novo or recurrent cutaneous eruptions in individuals with hematological diseases presents a challenge when determining whether they indicate secondary dissemination or an unrelated diagnosis. Eosinophilic eruption of hematoproliferative disease is a rare nonspecific manifestation accompanying lymphoproliferative disorders, including chronic lymphocytic leukemia (CLL). We present the case of a 70-year-old man with CLL in remission (previously treated with two 6-month cycles of fludarabine-cyclophosphamide plus rituximab, 2 and 5 years earlier) with an acute, disseminated polymorphic skin eruption. Skin biopsies from two sites (bulla and infiltrated nodule) were taken for histopathological examination. The pathologist reported giant spongiform vesicle formation with eosinophils with dermal and hypodermal inflammatory infiltrate composed of lymphocytes (predominantly T cells, fewer B cells) and eosinophils. Secondary neoplasm dissemination and sarcoidosis were excluded by means of immunohistochemistry. A diagnosis of eosinophilic eruption of hematoproliferative disease in the CLL patient post-chemotherapy and without active disease was established. Two weeks after skin remission, the patient worsened with enlarged lymph nodes and a leukocyte count of 291 × 10^9/l. CLL relapse was confirmed. Leukocytapheresis was performed and ibrutinib 140 mg three times daily was prescribed. Our case underscores the importance of recognizing this relatively common but underreported eosinophilic eruption associated with hematoproliferative diseases.

Keywords: hypersensitivity, insect bites and stings, leukemia, prognosis, sarcoidosis

Received: 25 July 2023 | **Returned for modification:** 10 September 2023 | **Accepted:** 9 October 2023

Introduction

In patients with hematological malignant neoplasms, whether in an active state or in remission, de novo or recurrent cutaneous eruptions are common. Around 25% of chronic lymphocytic leukemia (CLL) patients have skin changes due to either specific skin involvement by seeding malignant cells or nonspecific involvement with secondary nonmalignant etiology, affecting 45% of patients (1, 2). A particularly rare and nonspecific manifestation associated with lymphoproliferative disorders, notably CLL, is hypersensitivity to insect bites.

The exaggerated delayed hypersensitivity reaction to mosquito bites, initially defined by Weed et al. as reactionary lesions exceeding 20 mm in diameter with induration, edema, erythema, and pruritus, has been observed in 8.3% of CLL patients (3). This reaction has been termed "insect bite–like reaction" or "eosinophilic eruption of hematoproliferative disease" (EEHD) (4). The literature on EEHD in CLL primarily consists of individual case reports (4, 5) and case series (6, 7). Many patients cannot recall having been bitten, triggering an exploration of other etiologies. The presence of these lesions, particularly considering their timing in the course of the disease, can pose a diagnostic dilemma and therapeutic challenge for both clinicians and pathologists.

Case report

We present the case of a 70-year-old man with a history of CLL in remission (previously treated with two 6-month cycles of fludarabine-cyclophosphamide plus rituximab, 2 and 5 years prior) that presented to the clinic with an acute polymorphic skin eruption on the face. One month later, erythematous livid to purple infiltrated nodules and papules with dark crusts on an erythematous background appeared, and multiple blisters also disseminated on his neck, shoulders, and upper and lower extremities (Fig. 1A–C). Differential diagnosis included sarcoidosis, dissemination of primary CLL, and bullous pemphigoid. Direct immunofluorescence (DIF) of perilesional skin and indirect immunofluorescence (IIF) were negative, which ruled out bullous pemphigoid. Two separate biopsy sites were analyzed: a blister on the right hand and a nodule on the left lower leg. Histology showed extreme edema, scattered eosinophils, and extravasation of erythrocytes in the papillary dermis accompanied by perivascular and interstitial infiltrates composed of lymphocytes and dispersed eosinophils in the reticular dermis (especially on the hand, which had a gigantic spongiform vesicle with eosinophils in the lumen). Biopsy of the nodule revealed necrobiosis of collagen without mucin deposition. Alcian blue and colloidal iron staining was negative. Lymphocytic infiltrate in both biopsies revealed T cell predominance (CD3+, CD5+) and a smaller subset of B lymphocytes (CD20+, Pax5+), with individual lymphocytes being Bcl-2+ and CD23+ (Fig. 2A–D), excluding secondary dissemination of CLL.

Finally, the patient admitted to spending most of his time outdoors, but he denied insect bites. After the final clinico-histological correlation, diagnosis of EEHD / insect bite–like hypersensitivity in a CLL patient post-chemotherapy, without active disease at the time, was established.

Treatment that included cephalexin 2 grams daily, antihistamines, and local treatment as well as strict avoidance of spending time outdoors coincided and led to remission of skin lesions (Fig. 1D–F).

✉ Corresponding author: igor.kapetanovic@hotmail.com

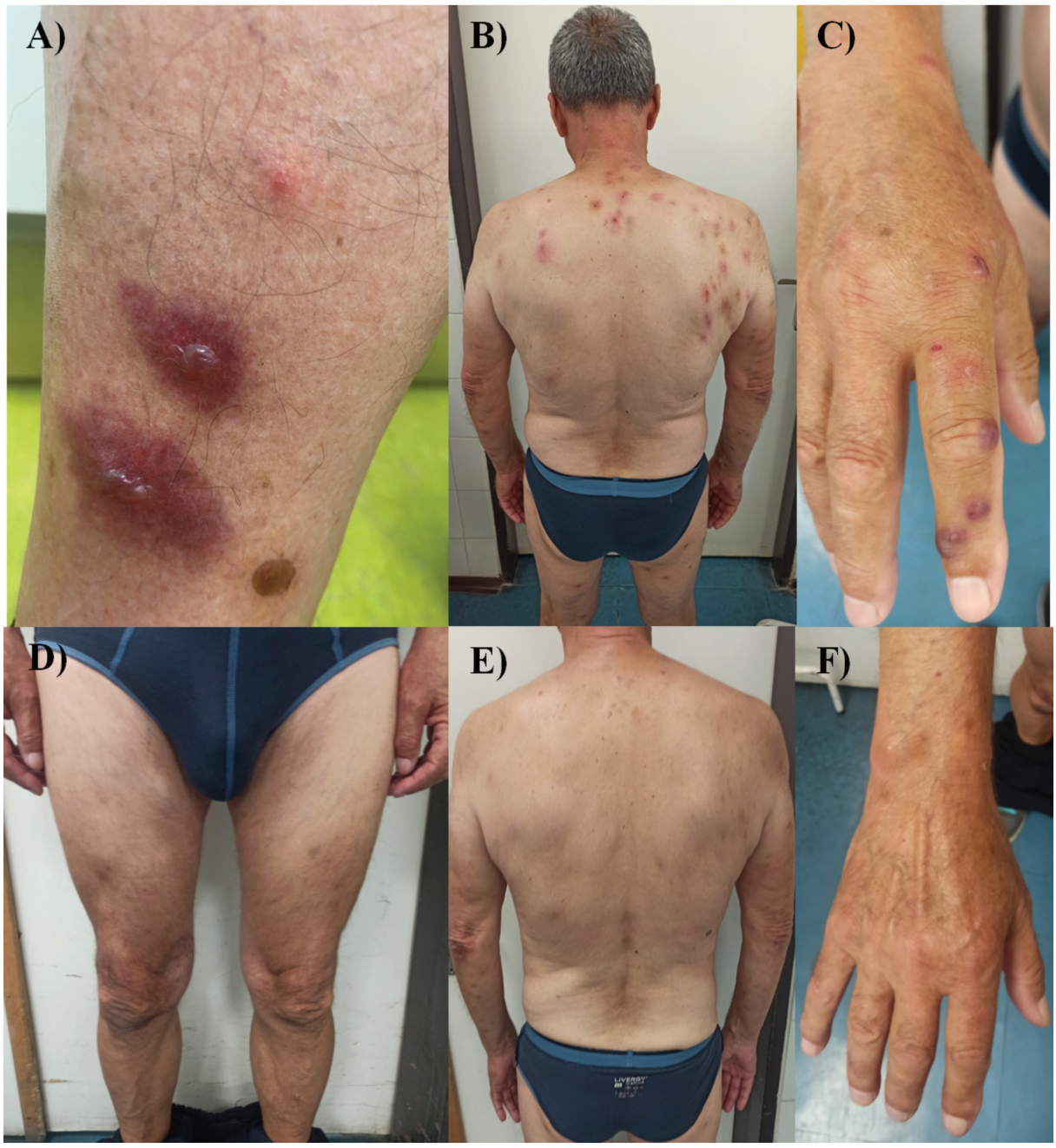

Figure 1 | (A–C) Skin lesions at admission in the patient; (D–F) skin lesions after 6 months of remission.

Two weeks after achieving remission, the patient presented with a leukocyte count of 291 × 10^9/l (normal 4.0–10.0 × 10^9/l). Over the the next 7 days, he experienced abdominal pain, weakness, sweating, splenomegaly (187 × 91 mm), and enlarged lymph nodes (axillary 20 × 20 mm, inguinal 30 × 20 mm, mesenteric 30 mm). The leukocyte count further increased to a maximum of 490 × 10^9/l. Fluorescence in situ hybridization (FISH) analysis revealed chromosome 12 trisomy. A relapse of CLL was confirmed. Subsequently, leukocytapheresis was performed and ibrutinib 140 mg three times daily was instituted.

Discussion

CLL is a malignant lymphoproliferative disorder characterized by progressive accumulation of leukemic cells in the blood, bone marrow, and lymphoid tissues and is the most common leukemia in adults in the western hemisphere (8). Deposition of leukemic cells might occur in the skin, which has been recognized as a common extranodal area involved (8). There are no concrete or specific skin localizations for secondary dissemination. Our patient's lesions were asymmetric, and both solitary as well as grouped and disseminated—that is, on the upper and lower extremities, trunk, and face. The distribution was not conclusive for any specific dermatological diagnosis. These types of polymorphic lesions have been described in leukemia cutis (4). Histopathology and immunohistochemistry excluded dissemination of CLL. Because multiple blisters arose on the skin, autoimmune blistering disorders needed to be excluded. DIF and IIF were performed and were negative.

In addition to the obvious possibility of dissemination of primary CLL, clinical features and other case reports led to consideration of another differential diagnosis. EEHD has previously been described in the literature as a nonspecific phenomenon that was occasionally observed in patients suffering from CLL (3).

A personal history of insect bites was not given and subsequently denied upon further questioning, thus complicating the diagnosis. However, there are reported cases of patients with CLL

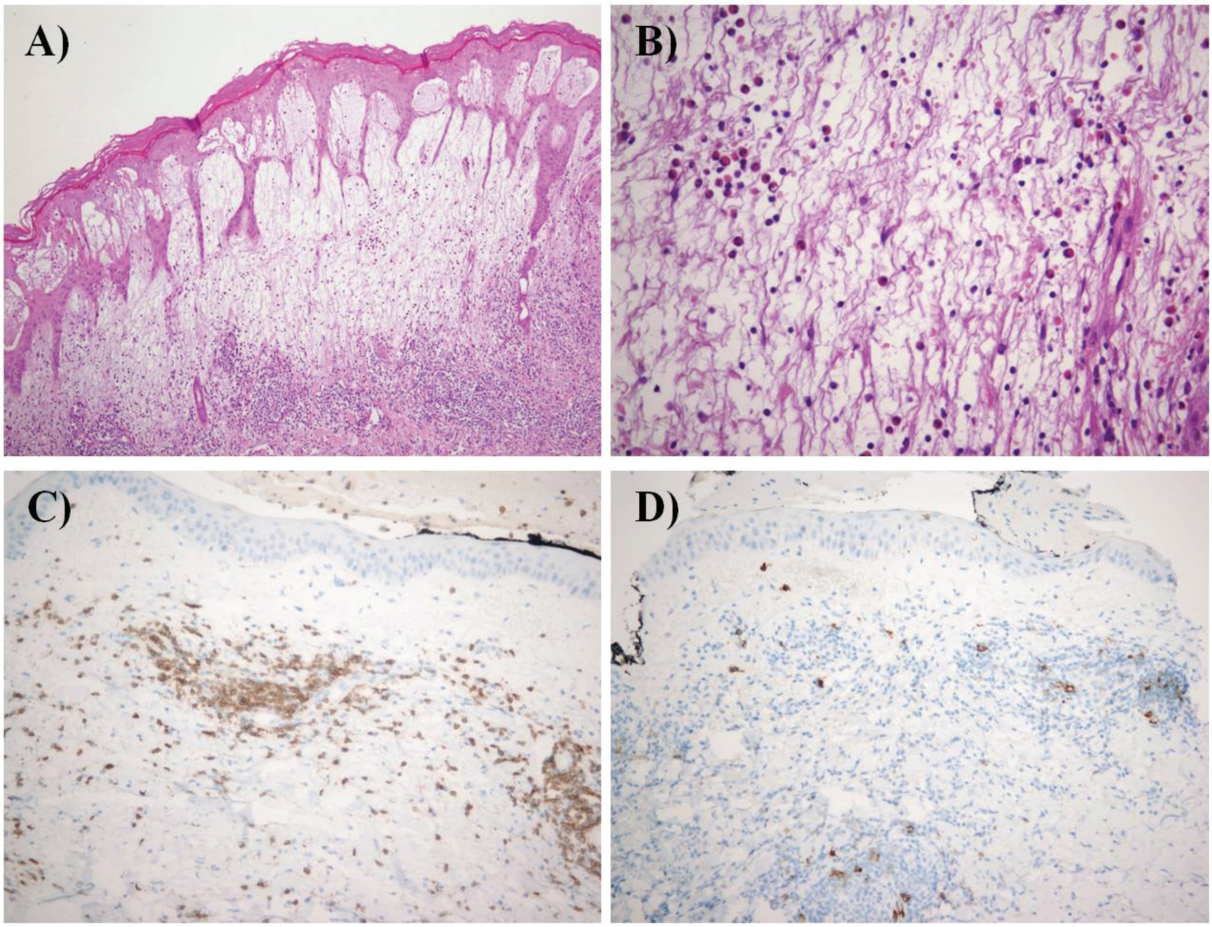

Figure 2 | (A) The diagnosis of exaggerated insect bite-like reaction is supported by extreme edema (hematoxylin and eosin, ×200) and (B) numerous eosinophils (hematoxylin and eosin, ×400) in papillary dermis; (C) perivascular infiltration consisted predominately of T (CD3+) lymphocytes (CD3, ×200); (D) B lymphocytes (CD20+) were sparse and scattered (CD20, ×200).

and this polymorphic skin occurrence in which insect bites were not recalled (9). Furthermore, the literature states that the reaction is often (as in our case) not restricted to exposed areas and is not specific during summer only (3, 9).

These skin lesions were described as an "insect bite–like reaction" by Barzilai et al. (6) and later as "eosinophilic eruption of hematoproliferative diseases" by Byrd et al. (10). Furthermore, to simplify the diagnostics, four criteria were proposed: 1) pruritic eruption of nodules, papules, and/or vesiculobullae resistant to conservative management; 2) histopathology confirming eosinophil-rich dermal lymphohistiocytic infiltrate at the superficial and deep dermis; 3) exclusion of other causes of tissue eosinophilia; and 4) a previously diagnosed hematological malignancy (10). A mixture of T- and B-cell lymphoid cell infiltrates is expected within lesions, along with prominent eosinophilic infiltration and eosinophil granule protein deposition (1). This type of histology was observed from two sites in our patient. Furthermore, our patient fulfilled all four criteria. Although helpful, these criteria state that a preexisting diagnosis of hematological malignancy is required. Later studies regarding the aspect of clinical appearance and subsequent time of onset relative to CLL had different findings. In most cases, eruptions have been reported to appear months to years after CLL was diagnosed but can also precede CLL and other hematological disorders (9). In the study conducted by Bairey et al., it was found that a bite-like reaction occurred before the diagnosis of CLL in 10 out of 46 patients. This reaction manifested 1.5 to 4.0 years before the CLL diagnosis, with a mean duration of 2.25 years. Notably, the study reported this phenomenon in six specific cases (9). It has been speculated whether there are prognostic implications for EEHD patients with CLL. Multiple studies have shown that cutaneous eruption is not related to disease activity or the course of the hematological disease (5, 6, 9). In our case, our patient had his third relapse after the diagnosis and remission of the bite-like reaction.

It is not yet understood what causes the histological changes described, and multiple theories have been proposed. One theory suggests that eosinophilic infiltration is evoked by the proliferation of malignant B cells, which is stimulated by increased secretion of interleukin-4 and interleukin-5 (1). The excess in these specific interleukins might be connected with an altered immune response, which is to be expected in patients with hematological malignancy (9). Other speculated triggering factors include chemoimmunotherapy, drugs, and bacterial infections (1). Mitteldorf et al. reported the presence of neoplastic B cells in skin infiltrate using FISH (11). Moffitt et al. concluded that, other than a toxic mechanism, it is most likely that an IgE-mediated or inflammatory cell–mediated process takes place in the pathogenesis (12).

If these skin changes appear before diagnosing a hematological malignancy or relapse, a high index of suspicion is needed and further investigation is required. The prognostic implication of EEHD is debated. Some authors (9) suggest this issue is worthy of further investigation, such as in our case, whereas others (1) are certain that the course of CLL is not related to these skin eruptions. Regardless, the patient should be observed in multidisciplinary settings and primarily by the hematologist.

In terms of treatment of cutaneous reactions specifically, there are several considerable therapeutic modalities because the lesions are mostly chronic and fairly resistant to therapy. We treated

our patient with topical corticosteroids, topical and systemic antibiotics, and systemic antihistamines. Throughout the period of treatment, he was advised not to spend too much time outdoors. Success was partial, followed by resistance for 2 months, and finally remission was achieved. Interestingly, the above therapy was given and similar during both spending time outdoors and strict avoidance. Remission coincided with a period of strict 2-week avoidance of spending time outdoors, which he finally adhered to in the summer period. Some authors have even mentioned that chemotherapy and treatment of primary disease may positively affect the skin lesions (13–15).

Conclusions

In conclusion, our case of EEHD draws attention to this condition and emphasizes the importance of raising awareness among healthcare professionals, including dermatologists, hematologists, pathologists, and primary care physicians, regarding this relatively common yet underreported eosinophilic eruption. Although studies suggest that the eruption is generally not linked to disease activity or course, unique cases such as ours demonstrate the potential for this dermatological phenomenon to either precede the diagnosis of CLL or coincide with its relapse. Thus, in the setting of symptoms and signs characteristic of CLL or a previous history of CLL accompanied by this dermatological manifestation, a high index of suspicion is warranted as well as screening and hematological evaluation or re-evaluation. We hope our case will motivate more research on this topic with larger sample sizes.

References

1. Robak E, Robak T. Skin lesions in chronic lymphocytic leukemia. Leuk Lymphoma. 2007;48:855–65.
2. Stawiski MA. Skin manifestation of leukemias and lymphomas. Cutis. 1978;21:814–8.
3. Weed RI. Exaggerated delayed hypersensitivity to mosquito bites in chronic lymphocytic leukemia. Blood. 1965;26:257–68.
4. Kim JE, Kim SC. Insect bite–like reaction with bullous lesions mimicking bullous pemphigoid in a patient with chronic lymphocytic leukemia. Ann Dermatol. 2018;30:468–72.
5. Ma CM, Chen WC, Shen JL, Lee FY, Juan CK, Chen YJ. Insect bite–like reaction in a patient with chronic lymphocytic leukemia. Dermatologica Sinica. 2016;35:155–6.
6. Barzilai A, Shpiro D, Goldberg I, Yacob-Hirsch Y, Diaz-Cascajo C, Meytes D, et al. Insect bite–like reaction in patients with hematologic malignant neoplasms. Arch Dermatol. 1999;135:1503–7.
7. Rosen LB, Frank BL, Rywlin AM. A characteristic vesiculobullous eruption in patients with chronic lymphocytic leukemia. J Am Acad Dermatol. 1986;15:943–50.
8. Wierda WG, Zelenetz AD, Gordon LI, Abramson JS, Advani RH, Andreadis CB, et al. NCCN guidelines insights: chronic lymphocytic leukemia / small lymphocytic leukemia, version 1.2017. J Natl Compr Canc Netw. 2017;15:293–311.
9. Bairey O, Goldschmidt N, Ruchlemer R, Tadmor T, Rahimi-Levene N, Yuklea M, et al. Insect-bite–like reaction in patients with chronic lymphocytic leukemia: a study from the Israeli chronic lymphocytic leukemia study group. Eur J Haematol. 2012;89:491–6.
10. Byrd JA, Scherschun L, Chaffins ML, Fivenson DP. Eosinophilic dermatosis of myeloproliferative disease: characterization of a unique eruption in patients with hematologic disorders. Arch Dermatol. 2001;137:1378–80.
11. Mitteldorf C, Tronnier M, Merz H, Haenssle HA, Bertsch HP, Schön MP, et al. Insect bite–like reactions in a patient with B-CLL: FISH analysis revealed neoplastic B-cells within the skin infiltrate. Br J Dermatol. 2012;167:944–6.
12. Moffitt JE, Golden DB, Reisman RE, Lee R, Nicklas R, Freeman T, et al. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol. 2004;114:869–86.
13. Davis MD, Perniciaro C, Dahl PR, Randle HW, McEvoy MT, Leiferman KM. Exaggerated arthropod-bite lesions in patients with chronic lymphocytic leukemia: a clinical, histopathologic, and immunopathologic study of eight patients. J Am Acad Dermatol. 1998;39:27–35.
14. Darji K, Bahram-Ali E, Dhandha M, Guo M. Mantle cell lymphoma presenting with exaggerated skin reaction to insect bites. BMJ Case Rep. 2019;12:e227590.
15. Rodríguez-Lojo R, Almagro M, Piñeyro F, Pérez-Varela L, Fernández-Jorge B, Del Pozo J, et al. Eosinophilic panniculitis and insect bite–like eruption in a patient with chronic lymphocytic leukaemia: a spectrum of the same entity. Dermatol Res Pract. 2010; 2010:263827.