Eosinophilic dermatosis of hematologic malignancy mimicking varicella zoster infection: report in a woman with chronic lymphocytic leukemia and review of the literature

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ABSTRACT

Eosinophilic dermatosis of hematologic malignancy is a rare papulovesicular eruption that presents in patients with hematopoietic disorders, particularly chronic lymphocytic leukemia. A 59-year-old woman with chronic lymphocytic leukemia who developed eosinophilic dermatosis of hematologic malignancy mimicking varicella zoster infection is described. PubMed database was searched with the key words: chronic, dermatosis, eosinophilic, hematologic, infection, leukemia, lymphocytic, malignancy, varicella, zoster. The papers generated by the search and their references were reviewed. The patient presented, on more than 20 occasions, with a dermatomal vesicular eruption. Her oncologist, based on the clinical presentation, treated each episode as recurrent varicella zoster virus infection. A complete workup of the patient not only demonstrated negative viral studies but also revealed pathologic changes consistent with eosinophilic dermatosis of hematologic malignancy on lesional skin biopsy. The recurrence of the patient’s dermatosis was less frequent when her malignancy was under better control. Eosinophilic dermatosis of hematologic malignancy may mimic other reactive dermatoses. The morphology of our patient’s recurrent dermatosis resembled varicella zoster virus infection. Disseminated zoster virus infection with dermatomal and non-dermatomal distribution should be added to the clinical differential diagnosis of eosinophilic dermatosis of hematologic malignancy.

Introduction

Eosinophilic dermatosis of hematologic malignancy was first reported in 1965 and thought to be a hypersensitivity reaction to insect bites in patients with chronic lymphocytic leukemia (CLL) [1]. Subsequent reports noted that most patients failed to recall insect bites; thus, the term “insect bite-like reaction” was established [2]. Byrd et al. later dubbed the process
infection outbreaks. Cutaneous examination showed dermatomal (Figure 1) and non-dermatomal (Figure 2) lesions with similar morphology on her back and flanks. Vesicles ranging from 2 mm to 5 mm, within areas of erythema, were present. Initial evaluation included viral cultures for herpes simplex virus and varicella zoster virus; vesicular fluid was sent for direct fluorescent antibody to these viruses. In addition, biopsies were performed for both routine staining and direct immunofluorescence to rule out autoimmune bullous diseases. The viral cultures and direct fluorescent antibody studies were negative. Microscopic examination of the skin biopsy showed an intraepidermal vesicle with eosinophils, eosinophilic spongiosis, and an accompanying diffuse and dense perivascular and periadnexal lymphocytic infiltrate with numerous eosinophils (Figure 3). Direct immunofluorescence and enzyme-linked immunosorbent assay (ELISA) studies were negative for bullous pemphigoid antigen-1 and bullous pemphigoid antigen-2.

Correlation of the clinical history, morphology, pathologic changes, and laboratory studies established the diagnosis of eosinophilic dermatosis of hematologic malignancy. Initial management included twice daily application of betamethasone dipropionate 0.05% cream, which provided relief and eventual resolution of the lesions. Two weeks later, the patient had recurrence of her lesions (Figure 4) and another skin biopsy showed similar pathologic changes. The patient was receiving investigational systemic therapy for her CLL; oral and other systemic therapies were prohibited. She continued her topical treatment.

The frequency of relapsing skin lesions was markedly reduced during periods in which her hematologic malignancy was under better control. Recently, she had an exacerbation of her CLL and antineoplastic therapy was altered. Subsequently, she has had less frequent flares of her dermatosis after being placed on obinutuzumab.

**Case Report**

A 59-year-old woman with CLL presented for evaluation of vesicular eruptions thought to be recurrent varicella zoster virus infection. She was diagnosed with CLL in 2003 but experienced several recurrences of her leukemia. Shortly after the first recurrence of CLL in 2009, she developed skin lesions that appeared in a dermatomal distribution on her back. These lesions reappeared several times, and her oncologist treated her for presumptive herpes zoster virus infection with an appropriate dosage of acyclovir on more than 20 occasions. The patient had no definitive prior history of herpes zoster virus infection; varicella zoster virus infection had never been objectively confirmed with biopsy, viral culture, or PCR amplification. However, the patient did have several complete blood counts drawn. Eosinophil percentages ranged from 1-10%, though most frequently were 4-5% (normal range 0-7%); however, absolute eosinophil count never exceeded 500 cells per ml (normal range 0-500 cells per ml). Serum IgE level was assessed and found to be 2 International Units (IU) per ml (normal range 0-99 IU/ml). Her CLL therapy initially included fludarabine, cyclophosphamide, and rituximab but later included alemtuzumab, lenalidomide, venetoclax, and obinutuzumab.

She presented to the dermatologist for evaluation of a new onset of her skin lesions; these were similar to those that her oncologist had previously treated as varicella zoster virus infection outbreaks. Cutaneous examination showed dermatomal (Figure 1) and non-dermatomal (Figure 2) lesions with similar morphology on her back and flanks. Vesicles ranging from 2 mm to 5 mm, within areas of erythema, were present. Initial evaluation included viral cultures for herpes simplex virus and varicella zoster virus; vesicular fluid was sent for direct fluorescent antibody to these viruses. In addition, biopsies were performed for both routine staining and direct immunofluorescence to rule out autoimmune bullous diseases.

The viral cultures and direct fluorescent antibody studies were negative. Microscopic examination of the skin biopsy showed an intraepidermal vesicle with eosinophils, eosinophilic spongiosis, and an accompanying diffuse and dense perivascular and periadnexal lymphocytic infiltrate with numerous eosinophils (Figure 3). Direct immunofluorescence and enzyme-linked immunosorbent assay (ELISA) studies were negative for bullous pemphigoid antigen-1 and bullous pemphigoid antigen-2.

Correlation of the clinical history, morphology, pathologic changes, and laboratory studies established the diagnosis of eosinophilic dermatosis of hematologic malignancy. Initial management included twice daily application of betamethasone dipropionate 0.05% cream, which provided relief and eventual resolution of the lesions. Two weeks later, the patient had recurrence of her lesions (Figure 4) and another skin biopsy showed similar pathologic changes. The patient was receiving investigational systemic therapy for her CLL; oral and other systemic therapies were prohibited. She continued her topical treatment.

The frequency of relapsing skin lesions was markedly reduced during periods in which her hematologic malignancy was under better control. Recently, she had an exacerbation of her CLL and antineoplastic therapy was altered. Subsequently, she has had less frequent flares of her dermatosis after being placed on obinutuzumab.
The pathogenesis of this condition is poorly understood [4]. It has been hypothesized that there is an excess of interleukin-4 and interleukin-5; this imbalance may lead to a proliferation of neoplastic B cells, which have been considered a major driver of the eruption [3,4,9]. This hypothesis is supported by the fact that interleukin-5 is the major eosinophil-recruiting cytokine [4]. Alternatively, it has been thought that neoplastic B cells drive a hypersensitivity reaction [3].

Several therapeutic options to treat eosinophilic dermatosis of hematologic malignancy have been reported. They include antibiotics, antihistamines, chemotherapy, dapsone, interferon alpha, intravenous immunoglobulin, phototherapy, and radiation [2,4,10]. Though some patients report favorable responses to therapy, overall the results have been disappointing [4]. The poor response underscores the lack of clarity of this condition’s pathogenesis [4].

In regards to prognosis, eosinophilic dermatosis of hematologic malignancy may be associated with an aggressive course of CLL [4]; our patient lends support to this observation, given her repeat recurrences of CLL. Reported complications in patients with CLL and eosinophilic dermatosis of hematologic malignancy include Richter transformation and malignant clone expansion [2,10]. An underlying state of immunosuppression is postulated as the cause for these occurrences.

Conclusion

Our patient’s recurrent skin lesions of eosinophilic dermatosis of hematologic malignancy were clinically interpreted by her oncologist to be varicella zoster virus infection because they were frequently dermatomal. However, the likelihood of over 20 episodes of herpes zoster would be unique and unexpected; hence, we were prompted to evaluate her skin lesions and exclude the diagnosis of either a viral infection or
autoimmune bullous disease. It is conceivable that our patient may have initially had zoster sine herpete, which manifests as radicular pain without rash [26]. With a background of zoster sine herpete, the patient plausibly could have developed an immunocompromised zone and therefore displayed Wolf’s isotopic response, in which a new skin disorder occurs at the site of a previously healed skin disease [27]. However, our investigation established the diagnosis of eosinophilic dermatosis of hematologic malignancy. Based on our patient’s
In the morphologic presentation of eosinophilic dermatosis of hematologic malignancy, we add disseminated zoster infection with dermatomal and non-dermatomal distribution to the differential diagnosis of this condition.

Figure 4. Distant (A) and closer (B and C) views of a linear presentation of erythematous-based vesicles of eosinophilic dermatosis of hematologic malignancy corresponding to the left L4 dermatome. [Copyright: ©2017 Bari et al.]
| Author, Year | Number of Cases | Associated Malignancy | Age; Sex | Clinical Manifestation | Histology | Management | EDHM Course | Ref |
|--------------|-----------------|-----------------------|---------|------------------------|-----------|------------|-------------|-----|
| Weed, 1965   | 8               | CLL                   | 40-76; NR | Erythematous, indurated, and pruritic lesions in areas of recent mosquito bites or areas with central punctum | Subepidermal edema with dense dermal infiltrate of eosinophils and lymphocytes | CLL was treated with chlorambucil or prednisone in most patients | Lesions resolved spontaneously within weeks | 1   |
| Rosen, 1986  | 10              | CLL                   | 37-82; 7 M, 3 W | Erythematous and pruritic bullae, nodules, and papules at various locations | Superficial and deep, perivascular, periadnexal, and interstitial infiltrate of eosinophils and lymphocytes | Treatments for CLL included prednisone, vincristine, cyclophosphamide, and chlorambucil | NR | 11  |
| Kolbusz, 1989| 1               | CLL                   | 31; W    | Recurrent eruptions of erythematous urticarial patches on the extremities and trunk | Lymphohistiocytic infiltrate with eosinophils | Diphenhydramine for skin lesions | Initial outbreaks were self-limited with no treatment; later eruptions improved with diphenhydramine | 12  |
| Davis, 1998  | 8               | CLL                   | 51-69; 6 M, 2 W | Papular and vesiculobullous lesions in various locations | All biopsies revealed lymphohistiocytic infiltrate and eosinophils in the dermis | Chemotherapy, IVIG, and glucocorticoids | 3 patients experienced improvement with chemotherapy for CLL; 1 patient improved with IVIG; 4 patients responded to oral glucocorticoids | 10  |
| Barzilai, 1999| 8               | ALL, AML, CLL (3 patients), MCL, LCL, MF | 42-72; 4 M, 4 W | Recurrent erythematous, pruritic papules and plaques at various locations | Superficial and deep perivascular and interstitial infiltrate of eosinophils and lymphocytes | Topical antipruritic agents, topical and systemic corticosteroids, systemic antihistamines | No improvement with any agent except systemic corticosteroids, though lesions recurred when steroids were tapered | 2   |
| Blum, 2001   | 1               | CLL                   | 49; M    | Admitted to the hospital after second cycle of chemotherapy with vesicles and hemorrhagic bullae on the extremities, face, and trunk | Superficial and deep perivascular dermatitis with interstitial eosinophils | Systemic corticosteroids | Lesions improved with steroids but recurred with tapered dose | 13  |
| Byrd, 2001   | 4               | AML, CLL (2 patients), MDS | 53-81; 4 M | Recurrent eruptions of erythematous, pruritic nodules and papules at various locations | Perivascular and periadnexal infiltrate with lymphocytes and eosinophils | Antibiotics, antifungals, antihistamines, colchicine, dapsone, hydroxyurea, hydroxychloroquine, isotretinoin, systemic and topical steroids, and UV-B phototherapy for skin lesions; chemotherapy started for malignancy | 2 patients’ lesions resolved during chemotherapy but recurred once it was complete, and chemotherapy was re-started to control skin lesions in these patients; 2 patients experienced improvement with phototherapy | 3   |
| Asakura, 2004| 1               | CLL                   | 46; W    | Pruritic, erythematous bullae on the extremities in the site of prior mosquito bites | NR | Cyclophosphamide and prednisolone for CLL | Skin lesions were self-limited | 14  |
| Cocuroccia, 2004 | 1         | CLL                   | 65; M    | 4-month history of recurrent pruritic bullae and papules on the extremities | Epidermal spongiosis, edema in papillary dermis, with superficial and deep, perivascular and interstitial infiltrate of eosinophils and neutrophils | Antihistamines and topical corticosteroids for skin lesions | Improvement after 10 days with mild recurrence after 2 weeks; no further lesions at 6-month follow-up | 15  |

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| Author, Year | Number of Cases | Associated Malignancy | Age; Sex | Clinical Manifestation | Histology | Management | EDHM Course | Ref |
|-------------|----------------|----------------------|---------|------------------------|----------|------------|-------------|-----|
| Dodiuk-Gad, 2004 | 2 | MCL | 61, 64; 2 M | Patient 1 with 6-month duration of pruritic, erythematous nodules and papules on the extremities; Patient 2 with 2-year history of pruritic, erythematous nodules, papules, and plaques on the extremities | Patient 1 with epidermal spongiosis and microvesicles with eosinophils, along with an upper dermal infiltrate of eosinophils; Patient 2 with dense infiltrate of eosinophils and neutrophils in the dermis | Antipruritic agents, topical and oral steroids for skin lesions in Patient 1; Patient 2 started on CHOP and rituximab | Patient 1 improved with oral prednisone but lesions continued to recur; Patient 2 improved with chemotherapy | 16 |
| Khamaysi, 2005 | 6 | CLL (3 patients) and MCL (3 patients) | 56-74; 3 M, 3 W | Pruritic and erythematous nodules, papules, plaques, and vesicles | Superficial and deep perivascular and interstitial infiltrate with eosinophils and mononuclear cells | NR | NR | 17 |
| Vassallo, 2005 | 5 | CLL (3 patients), NHL (2 patients) | NR; NR | Erythematous, pruritic bullae, papules, and plaques | Superficial and deep perivascular and interstitial infiltrate of eosinophils and lymphocytes | Antihistamines and systemic steroids for skin lesions | Improvement in skin lesions but flares continued to recur | 18 |
| Yoon, 2005 | 1 | NMZL | 46; M | 6-year history of recurrent papulovesicular eruptions at various locations | Epidermal spongiosis with focal necrosis, edema in the papillary dermis, and perivascular, periadnexal, and interstitial infiltrate of eosinophils, lymphocytes, and neutrophils | 6 courses of CHOP | Improvement in skin lesions with residual scar | 19 |
| Walker, 2007 | 1 | CLL | 69; W | 18-month history of pruritic, erythematous plaques on the extremities | Spongiotic vesiculation and infiltrate of eosinophils in the papillary dermis | Antibiotics, fexofenadine, ibuprofen, oral prednisolone, promethazine, and topical betamethasone for skin lesions; rituximab for CLL | Poor response to all agents except ibuprofen and prednisolone, which reduced severity of outbreaks; once patient was switched to rituximab, she experienced less frequent flares | 20 |
| Rodríguez-Lojo, 2010 | 1 | CLL | 63; M | 1-year history of recurrent urticarial nodules on the extremities and trunk | Infiltrate of eosinophils that involved fat lobules; later biopsies revealed dermal eosinophilic infiltrate with flame figures | Systemic steroids, topical steroids, and dapsone for skin lesions; CHOP for CLL | Recurrences were reduced with therapy for skin lesions; eruptions stopped when CLL was controlled | 21 |
| Bairey, 2012 | 48 | CLL | 33-82; 25 M, 23 F | Erythematous and pruritic macules, nodules, papules, and vesicles at various locations | Superficial and deep, interstitial and perivascular infiltrates of eosinophils and mononuclear cells | Antibiotics, antihistamines, dapsone, oral and topical steroids, phototherapy | 60% of eruptions resolved with treatment, 24% improved, and 14% had no response to therapy | 22 |
| Farber, 2012 | 1 | CLL | 73; M | 4-year history of recurrent erythematous, pruritic nodules and papules on the extremities, face, neck, scalp, and trunk | Dense superficial and deep perivascular infiltrate of eosinophils and lymphocytes | Doxycycline, hydroxyzine, and prednisone taper for skin lesions; chemotherapy started for CLL | Eruptions improved when chemotherapy started but recurred once it was completed; number of lesions and intensity of pruritus decreased but complete resolution was not achieved | 4 |

(Continued next page)
| Author, Year | Number of Cases | Associated Malignancy | Age; Sex | Clinical Manifestation | Histology | Management | EDHM Course | Ref |
|--------------|-----------------|-----------------------|----------|------------------------|-----------|------------|-------------|-----|
| Mitteldorf, 2012 | 1 | CLL | 71; F | Pruritic, erythematous papulovesicular eruptions on the face and trunk | Focal epidermal spongiosis, edema within the papillary dermis, and superficial and deep perivascular and interstitial infiltrate of eosinophils and lymphocytes | Prednisolone for skin lesions; rituximab and bendamustine started for CLL | No cutaneous improvement from chemotherapy; steroids led to complete resolution of skin lesions | 23 |
| Qiao, 2013 | 1 | CLL | 67; W | 9-month history of recurrent pruritic eruptions of bullae, papules, plaques, and vesicles on the extremities, face, and trunk | Prominent subepidermal blisters with diffuse infiltrate of eosinophils and flame figures in the dermis | Prednisone | Lesions improved within 10 days of prednisone but eruption recurred with steroid taper | 5 |
| Butzmann, 2014 | 1 | CLL | 60; W | 6-month history of lesions on the extremities; presented with excoriated papules and vesicles | Intraepidermal vesicle with eosinophils; dermis with dense perivascular lymphocytic infiltrate with eosinophils | Topical corticosteroids and oral antihistamines | Reduced recurrence rate and intensity of new lesions | 24 |
| Two, 2014 | 1 | MM | 50; M | 3-month history of pruritic vesicles on the extremities and trunk | Superficial and deep mixed perivascular infiltrate of eosinophils and lymphocytes | Topical corticosteroids for skin lesions; bortezomib, carfilzomib, and dexamethasone for MM | Vesicles disappeared at 6-week follow-up after stopping topical steroids though MM was undergoing continued therapy | 6 |
| Liu, 2015 | 1 | CLL | 45; W | 5-year history of recurrent pruritic blisters, papules, and plaques on the extremities and face | Subepidermal edema with dense nodular and interstitial infiltrate of eosinophils and lymphocytes in the dermis and subcutaneous tissue | Prednisolone for 12 months | Lesions continued to recur | 25 |
| Penn, 2015 | 1 | DLBCL | 56; W | Pruritic papular eruptions on the extremities | Superficial and deep perivascular infiltrate of eosinophils and lymphocytes | Antihistamines, intralesional glucocorticoids, and topical glucocorticoids for skin lesions; rituximab and bendamustine for CLL | Eruptions improved with systemic therapy for malignancy along with regimen of antihistamines and steroids | 7 |
| Jayasekera, 2016 | 1 | CLL | 51; M | Several week history of papules and plaques on the extremities | Epidermal spongiosis and interstitial infiltrate of eosinophils | Topical betamethasone, dapson, oral prednisolone with topical clobetasol; idelalisib and rituximab for CLL | Failed topical steroids; rash flared once oral prednisolone was tapered | 9 |
| Martires, 2016 | 1 | CLL | 68; W | 5-month history of recurrent pruritic bullae on the extremities and face | Epidermal spongiosis with superficial and deep mixed infiltrate of eosinophils, lymphocytes, and neutrophils | Methylprednisolone, prednisone, and high-potency topical glucocorticoids for skin lesions | Rate of resolution increased but lesions continued to recur | 8 |

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TABLE 1. Summary of eosinophilic dermatosis of hematologic malignancy (continued)

| Author, Year       | Number of Cases | Associated Malignancy | Age; Sex | Clinical Manifestation                                                                 | Histology                                                                 | Management                                                                 | EDHM Course                  | Ref |
|--------------------|-----------------|-----------------------|----------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------|-----|
| Bar and Cohen, 2017| 1               | CLL                   | 59; W    | 5-year history of dermatomal and non-dermatomal distribution of vesicles on the back and flanks | Eosinophilic spongiosis, intraepidermal vesicle with eosinophils, and perivascular and periaxial lymphocytic infiltrate with eosinophils | Acyclovir, topical betamethasone for skin lesions; CLL was treated with many agents but most recently the patient was started on obinutuzumab | Acyclovir was not efficacious, though topical betamethasone led to temporary resolution of skin lesions; patient experienced fewer recurrences after obinutuzumab was started | CR  |

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute monocytic leukemia; CHOP, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone; CLL, chronic lymphocytic leukemia; CR, current report; DLBCL, diffuse large B cell lymphoma; EDHM, eosinophilic dermatosis of hematologic malignancy; IVIG, intravenous immunoglobulin; LCL, large cell lymphoma; M, man; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MF, myelofibrosis; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NMZL, nodal marginal zone lymphoma; NR, not reported; Ref, reference; UV-B, ultraviolet-B phototherapy; W, woman

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