Eosinophilic folliculitis in association with chronic lymphocytic leukemia: A clinicopathologic series

Kiran Motaparthi, MD,[a] Jyoti Kapil, MD,[b] and Sylvia Hsu, MD[c]
Gainesville, Florida; Irving, Texas; and Philadelphia, Pennsylvania

Key words: chronic lymphocytic leukemia; eosinophilic folliculitis.

INTRODUCTION

Well-recognized variants of eosinophilic folliculitis (EF), also known as *eosinophilic pustular folliculitis*, include Ofuji disease, infantile EF, and HIV-associated EF, which is considered a defining illness of AIDS.

A fourth less commonly recognized subtype of EF is that associated with hematologic malignancy, in particular leukemia and non-Hodgkin lymphoma (NHL).[1] EF in HIV-negative individuals and associated with hematologic malignancy was first reported in 1993.[2] This variant of EF may be underrecognized and difficult to diagnose given the clinical scenario, morphology, and variable histologic findings, detailed in a series of 3 patients with EF in association with chronic lymphocytic leukemia (CLL) presented herein.

Abbreviations used:

BMT:	bone marrow transplantation
CLL:	chronic lymphocytic leukemia
EF:	eosinophilic folliculitis
NHL:	non-Hodgkin lymphoma
SCT:	stem cell transplantation
WBC:	white blood cell

CASE SERIES

Patient 1

A 69-year-old man with a history of CLL, and undergoing chemotherapy with fludarabine, cyclophosphamide, and rituximab, presented with a 2-week history of a highly pruritic eruption distributed over the scalp, face, neck, upper trunk, and extremities. Physical examination found scattered excoriated papules and vesicles (Fig 1, *A*). Complete blood count with differential found a peripheral eosinophilia of 10% (350/mm^3, with total white blood cell [WBC] count of 3500/mm^3). The initial clinical diagnoses considered were disseminated varicella-zoster virus infection and drug eruption; the initial histologic diagnosis rendered was papular urticaria. Skin biopsy found papillary dermal edema overlying a wedge-shaped lymphocytic infiltrate with numerous eosinophils (Fig 2, *A*); step sections showed focal involvement of the follicular infundibulum and sebaceous lobule (Fig 2, *B*). The eruption resolved after a 2-week course of prednisone but later recurred followed by gradual resolution over the course of several weeks.

Patient 2

A 75-year-old man with a history of CLL and recent chemotherapy with chlorambucil presented with a 1-month history of pruritic papulovesicles and urticarial papules distributed over the head, neck, chest, back, and arms (Fig 1, *B*). The initial clinical diagnoses considered were drug eruption and arthropod bite reaction; the initial histologic diagnosis rendered was arthropod bite reaction. Skin biopsy found superficial and deep perivascular mixed infiltrates with abundant eosinophils and infundibular vesiculation with eosinophils and follicular mucin. Marked improvement with near clearance of lesions was noted after treatment with isotretinoin (1 mg/kg/d) for 1 month.

From the Department of Dermatology, University of Florida College of Medicine[a]; Dermatopathology, Miraca Life Sciences, Irving[b]; and Department of Dermatology, Lewis Katz School of Medicine at Temple University.[c]

Funding sources: None.
Conflicts of interest: None declared.

Correspondence to: Kiran Motaparthi, MD, Department of Dermatology, University of Florida College of Medicine, 4037 NW 86th Terrace, Room 4119 Springhill, Gainesville, FL 32606.
E-mail: kmotaparthi@dermatology.med.ufl.edu and kiranmotaparthi@gmail.com.

JAAD Case Reports 2017;3:263-8.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2017.03.007

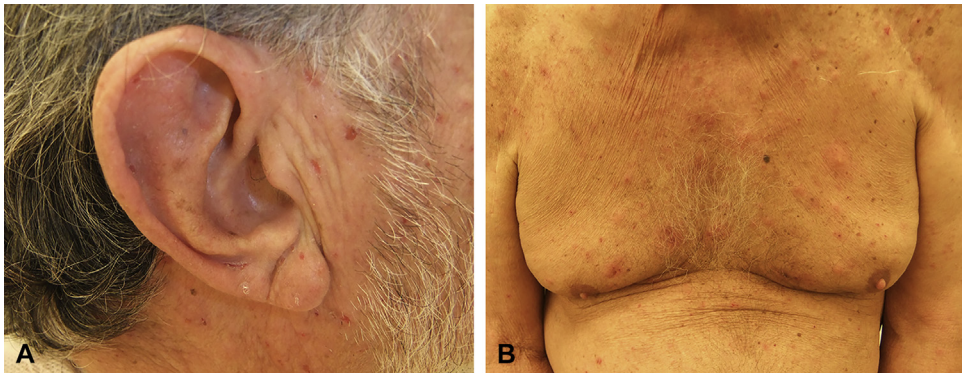

Fig 1. A, Patient 1: Excoriated papulovesicles over the ear, neck, and cheek. **B**, Patient 2: Excoriated papules, some with urticarial morphology, on the chest and arms.

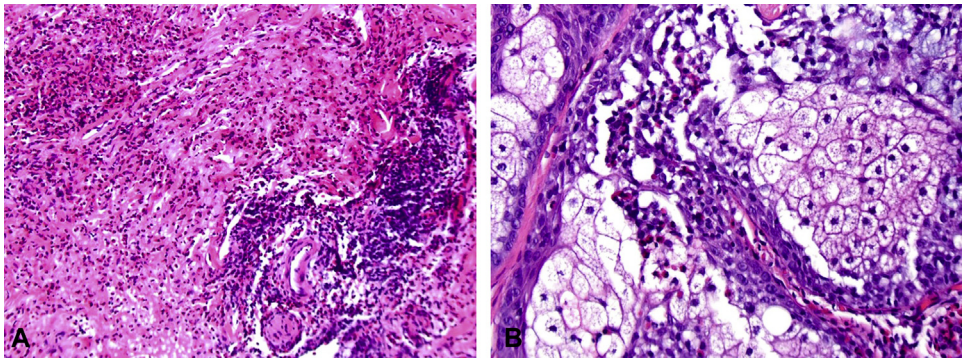

Fig 2. A, Patient 1: Florid dermal eosinophilia and perivascular lymphocytic infiltrate, simulating features of arthropod bite reaction. **B**, Eosinophils, spongiosis, and mucin within the folliculosebaceous unit. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A** and **B**, ×200.)

Patient 3

A 51-year-old man with a history of CLL and concurrent chemotherapy with fludarabine, cyclophosphamide, and rituximab, presented with a 6-week history of pruritic papules, vesicles, and rare plaques, distributed over the face with prominent involvement of the cheeks, ears, and forehead, as well as upper trunk and arms. Complete blood count with differential found a peripheral eosinophilia of 7% (343/mm^3, with total WBC count of 4900/mm^3). Initial skin biopsy found typical arthropod bite reaction, with a wedge-shape lymphocytic infiltrate with numerous eosinophils. Of note, this initial specimen lacked prominent follicular involvement. A repeat biopsy showed findings similar to those noted in patients 1 and 2. Follicular spongiosis and vesiculation with surrounding dermal edema and rare eosinophils within the folliculosebaceous unit were identified on step sections. Resolution of lesions was gradual over several months without specific treatment. Clinicopathologic characteristics of patients with EF associated with CLL are summarized in Table I.

DISCUSSION

The first subtype of EF described was Ofuji's disease, characterized as a papulopustular eruption in Asians, with formation of coalescent plaques and distributed over the cheeks, upper trunk, and upper extremities. In contrast, infantile EF favors the scalp of young males and recurs in crops of sterile pustules with eventual spontaneous remission. A third described subtype of EF is HIV associated and is an AIDS-defining illness that typically presents with urticarial papules and plaques on the head, neck, and upper trunk. Paradoxically, pustules are usually absent in the HIV-associated subtype. All forms of EF are associated with marked pruritus and may demonstrate an associated peripheral eosinophilia.[6] Importantly, histologic findings are variable and may depend on the stage of disease at the time of biopsy. Peri-infundibular lymphocytic infiltrates with variable numbers of eosinophils are seen early while infundibular spongiosis, vesiculation, and pustule formation with infiltration of folliculosebaceous units by eosinophils is seen when lesions are more well established.[1] Treatments with variable reported

Table I. Clinicopathologic features of EF associated with CLL[3-5]

Age, y	Sex	Underlying hematologic malignancy	Treatment for malignancy	Peripheral eosinophilia	Clinical description	Distribution	Clinical differential diagnosis	Notable histologic features	Initial histologic diagnosis	Treatment and clinical course
69*	M	CLL	Chemotherapy (fludarabine, cyclophosphamide, and rituximab)	10% (350/mm^3, with total WBC count 3500/mm^3)	Papules, vesicles and urticarial plaques	Head and neck, trunk, arms	Disseminated VZV infection; drug eruption	Eosinophils within sebaceous lobule and follicular infundibulum	Papular urticaria	Prednisone; recurrence then resolution over several weeks
75*	M	CLL	Chemotherapy (chlorambucil)	N/A	Papules, vesicles and pustules	Head and neck, trunk, arms	Drug eruption; insect bite reaction	Marked infundibular spongiosis with eosinophils and mucin	Insect bite reaction	Near clearance with isotretinoin
51*	M	CLL	Chemotherapy (fludarabine, cyclophosphamide, and rituximab)	7% (343/mm^3, with total WBC count 4900/mm^3)	Papules, vesicles and plaques	Face, upper trunk, arms	Leukemia cutis	Spongiosis and eosinophils within folliculo-sebaceous unit	Insect bite reaction	Gradual resolution without specific treatment
47†	F	CLL	Chemotherapy	N/A	N/A	N/A	N/A	N/A	N/A	N/A
52†	M	CLL	Chemotherapy	N/A	N/A	N/A	N/A	N/A	N/A	N/A
61†	M	CLL	Chemotherapy	N/A	Pruritic follicular papules and pustules	Face, neck, and chest	N/A	Numerous eosinophils, lymphocytes and neutrophils within pilosebaceous units	N/A	N/A
53†	M	CLL	N/A	770/mm^3	Pruritic papules, vesicles, and pustules with crusting	Face, scalp, neck, arms, back	N/A	Intrafollicular eosinophilic pustules	N/A	Initial treatment with isotretinoin ineffective; eventual outcome N/A

CLL, Chronic lymphocytic leukemia; *EF*, eosinophilic folliculitis; *F*, female; *M*, male; *N/A*, not available; *VZV*, varicella-zoster virus.
*Reported within this series.
†Previously reported in the literature.

Table II. Clinicopathologic features of EF associated with underlying hematologic malignancy other than CLL

Study	Age, y	Sex	Underlying hematologic malignancy	Treatment for malignancy	Peripheral eosinophilia	Clinical description	Distribution	Notable histologic features
Takamura et al[6]	77	M	Mantle cell lymphoma	Chemotherapy	13%	Pruritic, erythematous papules	Face, neck	Eosinophils around follicles and sebaceous glands
Takamura et al[6]	60	M	Mantle cell lymphoma	Chemotherapy	3.7%	Pruritic, follicular reddish papules	Face	Eosinophils around follicles and sebaceous glands
Bhandare et al[8]	64	F	Splenic marginal zone lymphoma	Chemotherapy	2968/mL^3	Pruritic, follicular papules and pustules	Scalp, back, proximal extremities	Follicular spongiosis with eosinophils
Zitelli et al[1]	56	M	Acute lymphoblastic leukemia	Autologous SCT	6.4%	Pruritic papules and pustules	Face, chest, and back	Intrafollicular collections of eosinophils
Sugaya et al[9]	42	M	Sézary syndrome	N/A	9.5%	Pruritic reddish follicular papules	Cheeks	Prominent follicular exocytosis of eosinophils
Rashid et al[10]	74	M	Chronic myelomonocytic leukemia	Chemotherapy	N/A	Pruritic perifollicular papules	Neck and chest	Perifollicular infiltrates with eosinophils, follicular mucin
Goiriz et al[7]	25	F	Acute eosinophilic leukemia	Allogeneic peripheral blood SCT	8.6%	Pruritic follicular papules	Axillae and trunk	Intrafollicular eosinophil collections, spongiosis and crusting
Keida et al[11]	41	M	Diffuse large B-cell lymphoma	Autologous peripheral blood SCT	12.5%	Pruritic reddish follicular papules and pustules	Upper trunk	Follicular exocytosis of eosinophils and neutrophils
Ota et al[12]	22	F	Chronic myelogenous leukemia	Allogeneic BMT	800 $\times$ 10^6/L	Pruritic red papules, coalescent erythema	Face and scalp	Eosinophilic infiltrates within follicles and sebaceous glands
Patrizi et al[4]	45	M	Acute monocytic leukemia	None	N/A	Pruritic follicular papules and pustules, urticarial lesions	Face, neck, shoulders, axillae	Numerous eosinophils, lymphocytes and neutrophils within pilosebaceous units
Vassallo et al[13]	25	F	Hodgkin lymphoma	Chemotherapy	1%	Pruritic follicular papules and pustules	Scalp and thighs	Eosinophilic exocytosis into all segments of follicle and sebaceous gland
Evans et al[14]	35	M	Diffuse B-cell NHL, intermediate type	Autologous BMT	21.6%	Pruritic papules and pustules	Face, scalp, and trunk	Eosinophil-rich pustules within follicular epithelium

Bull et al[2]	59	M	Multiple myeloma	Chemotherapy and autologous BMT	18%	Pruritic urticarial papules	Face, upper trunk, and arms	Prominent intrafollicular eosinophils
Bull et al[2]	39	F	Acute erythroid leukemia	Chemotherapy and allogeneic BMT	424 × 10^6/L	Pruritic papules	Forehead and cheeks	Follicular degeneration with perivascular eosinophils
Bull et al[2]	40	M	Acute myeloid leukemia	Chemotherapy and autologous BMT	8%	Pruritic papules and pustules	Shoulders and thighs	Numerous perifollicular eosinophils
Bull et al[2]	76	M	Waldenstrom macroglobulinemia	Chemotherapy	3.2%	Pruritic papules	Upper back	Prominent eosinophils within the follicular infundibulum
Patrizi et al[15]	31	F	Diffuse B-cell NHL	Chemotherapy and autologous BMT	12%	Pruritic follicular papules and pustules	Forehead and cheeks	Follicular spongiosis and perivascular eosinophils

BMT, Bone marrow transplantation; *CLL*, chronic lymphocytic leukemia; *EF*, eosinophilic folliculitis; *F*, female; *M*, male; *N/A*, not available; *NHL*, non-Hodgkin lymphoma; *SCT*, stem cell transplantation.

efficacies include indomethacin, topical and systemic steroids, phototherapy, isotretinoin, and, if HIV associated, highly active antiretroviral therapy. In patients with underlying hematologic malignancy, resolution with minimal specific treatment is typical, occurring after 8 weeks.[1,7]

Before this series of 3 patients, 4 patients with EF in association with CLL were reported in the English-language literature. Including this series, 6 of 7 patients have been men older than 50 years. Six of 7 patients have developed EF during or after the administration of chemotherapy. In all cases in which the clinical morphology and distribution of lesions were reported (5 of 7), pruritic papules with variable vesicles, pustules, and urticarial lesions occurred on the head and neck, upper trunk, and arms. Furthermore, in all patients with reported histopathology (5 of 7), eosinophils within some portion of the folliculosebaceous unit were demonstrated.[3-5]

Within this series, peripheral blood eosinophilia was present in 2 of 3 cases for which the results of complete blood count with differential were available. Of note, EF was not considered within the initial clinical or histopathologic differential diagnosis (Table I). In all 3 patients, the initial histopathologic diagnosis was either arthropod bite reaction or papular urticaria, based on the common finding of a superficial and deep perivascular lymphocytic infiltrate with numerous eosinophils. Repeat biopsy, review of initial specimens, and step sections for the diagnostic finding of eosinophils within the folliculosebaceous unit, in conjunction with clinicopathologic correlation, ultimately permitted accurate diagnosis. Elected treatments were varied, but gradual resolution was observed in the 3 patients.

Patients presenting with EF in association with a variety of other hematologic malignancies, such as NHL (including mantle cell lymphoma, diffuse B-cell lymphoma, and splenic marginal zone lymphoma), Hodgkin lymphoma, acute and chronic myeloid leukemias, acute lymphoblastic leukemia, multiple myeloma and Waldenstrom macroglobulinemia, and Sézary syndrome, have been reported (Table II). Uniformly reported clinicopathologic features include pruritic papules above the waist and perifollicular or intrafollicular eosinophils. Age and sex, peripheral eosinophilia, and the presence of polymorphous lesions including vesicles, papules, or urticarial lesions are variable (Table II). Additionally, the occurrence of EF after chemotherapy, bone marrow transplantation (BMT), or stem cell transplantation (SCT) is a commonly reported feature.[1,2,4-15]

Of note, a condition termed *eosinophilic dermatosis of hematologic* malignancy has also been described in the literature, with striking clinicopathologic overlap with the cases described in this series in terms of morphology, distribution, context of underlying lymphoproliferative disorder (including CLL), perifollicular and intrafollicular eosinophilia, and natural history.[16] Thus, it is likely that eosinophilic dermatosis of hematologic malignancy represents the same entity described herein—EF.

Although the pathogenesis of EF is not well understood, one potential immunologic pathway in patients with underlying hematologic malignancy is the clonal expansion of T helper 2, cells which produce interleukin-5, resulting in the stimulation of eosinophils.[4,13] Degranulation of perifollicular mast cells may also recruit eosinophils to the follicular epithelium.[2] Given the temporal relationship to chemotherapy, BMT, or SCT, EF in the context of hematologic malignancy may also represent a hypersensitivity to *Demodex* or *Malassezia* species.[13]

EF should be included in the clinical and histopathologic differential diagnosis when evaluating a patient with underlying hematologic malignancy presenting with a pruritic papulovesicular, pustular, or urticarial eruption above the waist. In patients with CLL, male sex, age older than 50 years, distribution of lesions over the head and neck and upper trunk, peripheral eosinophilia, and occurrence during or after chemotherapy are common clinical features that may help dermatologists consider EF in the differential diagnosis.[3-5] Furthermore, within this series, it was observed that a frequent initial histopathologic consideration was arthropod bite reaction/papular urticaria, and clinicopathologic correlation in tandem with careful search for eosinophils within the folliculosebaceous unit was essential for accurate diagnosis of this uncommon entity.

REFERENCES

1. Zitelli K, Fernandes N, Adams BB. Eosinophilic folliculitis occurring after stem cell transplant for acute lymphoblastic leukemia: a case report and review. *Int J Dermatol*. 2015;54:785-789.
2. Bull RH, Harland CA, Fallowfield ME, Mortimer PS. Eosinophilic folliculitis: a self-limiting illness in patients being treated for haematological malignancy. *Br J Dermatol*. 1993;129:178-182.
3. Lambert J, Berneman Z, Dockx P, Stevens W, Van Marck E. Eosinophilic pustular folliculitis and B-cell chronic lymphatic leukaemia. *Dermatology*. 1994;189(Suppl 2):58-59.
4. Patrizi A, Chieregato C, Visani G, Morrone P, Patrone P. Leukaemia-associated eosinophilic folliculitis (Ofuji's disease). *J Eur Acad Dermatol Venereol*. 2004;18:596-598.
5. Agnew KL, Ruchlemer R, Catovsky D, Matutes E, Bunker CB. Cutaneous findings in chronic lymphocytic leukaemia. *Br J Dermatol*. 2004;150:1129-1135.
6. Takamura S, Teraki Y. Eosinophilic pustular folliculitis associated with hematological disorders: a report of two cases and review of Japanese literature. *J Dermatol*. 2016;43:432-435.
7. Goiriz R, Guhl-Millan G, Penas PF, et al. Eosinophilic folliculitis following allogeneic peripheral blood stem cell transplantation: case report and review. *J Cutan Pathol*. 2007;34(Suppl 1):33-36.
8. Bhandare PC, Ghodge RR, Bhobe MR, Shukla PR. Eosinophilic pustular folliculitis post chemotherapy in a patient of non-Hogkins lymphoma: a case report. *Indian J Dermatol*. 2015;60:521.
9. Sugaya M, Suga H, Miyagaki T, Fujita H, Sato S. Eosinophilic pustular folliculitis associated with Sezary syndrome. *Clin Exp Dermatol*. 2014;39:536-538.
10. Rashid R, Hymes S. Folliculitis, follicular mucinosis, and papular mucinosis as a presentation of chronic myelomonocytic leukemia. *Dermatol Online J*. 2009;15:16.
11. Keida T, Hayashi N, Kawashima M. Eosinophilic pustular folliculitis following autologous peripheral blood stem-cell transplantation. *J Dermatol*. 2004;31:21-26.
12. Ota M, Shimizu T, Hashino S, Shimizu H. Eosinophilic folliculitis in a patient after allogeneic bone marrow transplantation: case report and review of the literature. *Am J Hematol*. 2004;76:295-296.
13. Vassallo C, Ciocca O, Arcaini L, et al. Eosinophilic folliculitis occurring in a patient affected by Hodgkin lymphoma. *Int J Dermatol*. 2002;41:298-300.
14. Evans TR, Mansi JL, Bull R, et al. Eosinophilic folliculitis occurring after bone marrow autograft in a patient with non-Hodgkin's lymphoma. *Cancer*. 1994;73:2512-2514.
15. Patrizi A, Di Lernia V, Neri I, Gherlinzoni F. Eosinophilic pustular folliculitis (Ofuji's disease) and non-Hodgkin lymphoma. *Acta Derm Venereol*. 1992;72:146-147.
16. Farber MJ, La Forgia S, Sahu J, Lee JB. Eosinophilic dermatosis of hematologic malignancy. *J Cutan Pathol*. 2012;39:690-695.