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

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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.

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/mm³, with total white blood cell [WBC] count of 3500/mm³). 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.

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

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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/mm³, with total WBC count of 4900/mm³). 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 1.

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. 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
| 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/mm³, with total WBC count 3500/mm³) | 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/mm³, with total WBC count 4900/mm³) | 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/mm³                | 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 |

*Reported within this series.
†Previously reported in the literature.

**Table I.** Clinicopathologic features of EF associated with CLL³⁻⁵

CLL, Chronic lymphocytic leukemia; EF, eosinophilic folliculitis; F, female; M, male; N/A, not available; VZV, varicella-zoster virus.
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 | 77     | M   | Mantle cell lymphoma              | Chemotherapy             | 13%                    | Pruritic, erythematous papules | Face, neck   | Eosinophils around follicles and sebaceous glands                                           |
| Takamura et al | 60     | M   | Mantle cell lymphoma              | Chemotherapy             | 3.7%                   | Pruritic, follicular reddish papules | Face         | Eosinophils around follicles and sebaceous glands                                           |
| Bhandare et al | 64     | F   | Splenic marginal zone lymphoma    | Chemotherapy             | 2968/mL³               | Pruritic, follicular papules and pustules | Scalp, back, proximal extremities | Follicular spongiosis with eosinophils                                                       |
| Zitelli et al  | 56     | M   | Acute lymphoblastic leukemia       | Autologous SCT           | 6.4%                   | Pruritic papules and pustules       | Face, chest, and back | Intrafollicular collections of eosinophils                                                    |
| Sugaya et al   | 42     | M   | Sézary syndrome                   | N/A                      | 9.5%                   | Pruritic reddish follicular papules | Cheeks       | Prominent follicular exocytosis of eosinophils                                               |
| Rashid et al   | 74     | M   | Chronic myelomonocytic leukemia    | Chemotherapy             | N/A                    | Pruritic perifollicular papules    | Neck and chest | Perifollicular infiltrates with eosinophils, follicular mucin                               |
| Goiriz et al   | 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    | 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      | 22     | F   | Chronic myelogenous leukemia       | Allogeneic BMT           | 800 × 10⁶/L            | Pruritic red papules, coalescent erythema | Face and scalp | Eosinophilic infiltrates within follicles and sebaceous glands                               |
| Patrizi et al  | 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 | 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    | 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                                       |
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. Within this series, peripheral blood eosinophilia was present in 2 of 3 cases for which the results of complete blood count were available. Of note, EF was not considered within the initial clinical or histopathologic differential diagnosis (Table I). In all 3 patients, the initial clinical or histopathologic differential 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 follicular lymphoma), and chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, and Waldenstrom macroglobulinemia, 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).

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.

| Author(s)          | Age (Yrs) | Gender | Primary Diagnosis            | Treatment                          | Eosinophils | Lesion Location                      | Comment                                      |
|--------------------|-----------|--------|------------------------------|------------------------------------|-------------|-------------------------------------|----------------------------------------------|
| 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 |

In patients with underlying hematologic malignancy, resolution with minimal specific treatment is typical. In patients with underlying hematologic malignancy, and if HIV associated, highly active antiretroviral therapy.
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. 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. Degranulation of perifollicular mast cells may also recruit eosinophils to the follicular epithelium. 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.

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.

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.

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