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Eosinophilic dermatosis of hematologic malignancy: A retrospective cohort of 37 patients from an Italian center

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3 **Title: Eosinophilic dermatosis secondary to hematologic malignancies: a retrospective cohort of 37**
4 **patients from an Italian centre.**

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42 **To the Editor,**

43 Eosinophilic dermatosis of hematologic malignancy (EDHM) is a non-specific skin disease primarily
44 associated with chronic lymphocytic leukemia (CLL).^{1,2,3} Despite being a common disease in the
45 hematology setting, often misdiagnosed as an exaggerated reaction to mosquito bites,² there is a
46 shortage of dermatology-oriented reports. Here we report on a retrospective case series of EDHM
47 carried out in our department from November 2014 to January 2017. The main results of the study
48 are listed in table 1.

49 We identified 37 patients on the basis of the proposed EDHM diagnosis criteria, which include: i)
50 known history of onco-hematological disease, ii) recurrent episodes of papules, nodules, urticarial
51 plaques or blisters with intense pruritus, iii) eosinophilic infiltration upon histopathology, and iv)
52 exclusion of other causes of tissue eosinophilia.¹ The majority suffered from indolent B-cell
53 disorders, primarily B-CLL (51%) and various types of B-cell non-Hodgkin lymphomas (30%),
54 whereas acute leukemia was observed in four patients (10%). At the time of EDHM onset, only a
55 minority of them (25%) underwent chemotherapy due to active/progressive disease.

56 The eruption was widespread , albeit mostly occurring on the lower (90%) and upper limbs (79%).
57 However, over half of the cases had lesions on the trunk and 25% reported painful lesions on the
58 face, scalp, and neck.

59 The majority of the patients presented with pruritic erythematous papules, plaques, and nodules
60 with a smooth surface and color ranging from slightly pink to bright red, or more cyanotic hues. In
61 one third of cases, tense blisters resembling Bullous Pemphigoid (BP) were evident, especially on
62 the legs (Figure 1A).

63 Skin specimens showed variably dense, mainly perivascular lymphohistiocytic and eosinophilic
64 infiltrates in the upper and mid-dermis in the majority of cases (80%), extending to the deep
65 dermis and subcutaneous fat in 20% of cases. In two cases, the histologic features resembled those

66 of Wells syndrome, revealing numerous eosinophils with flame figures in the deep dermis. Dermal-
67 epidermal detachment was observed in 10 cases, raising suspicion of BP. In these cases, direct
68 immunofluorescence was negative. No relevant epidermal changes were found, except for
69 spongiosis in two specimens (Figure 1B).

70 Almost all patients showed some clinical benefit with the proposed treatment: most of the patients
71 were treated with systemic steroids with/without concomitant topical steroids. A minority of
72 patients achieved clinical improvement with other regimens, including doxycycline with/without
73 nicotinamide and UVA1 phototherapy. The overall response rate was 93%. However, in many cases
74 (63%) the response was short-lived and the patient suffered a relapse.

75 Our study shows that EDHM potentially occurs in a wide range of hematologic cancers, with
76 differing biological behavior and of either lymphoid or myeloid origin. Due to its
77 clinical/pathological heterogeneity and its tendency to persist over long periods, it may represent
78 both a diagnostic and therapeutic challenge. The overlap with BP should be kept in mind to avoid
79 misdiagnosis and may have led to an overestimation of the BP incidence in this setting.^{1,4,5} Besides
80 systemic steroids, doxycycline, nicotinamide, and UVA1 phototherapy could be effective therapeutic
81 alternatives considering their lower long-term toxicity, but this data warrants further prospective
82 investigations.

83 To conclude, we believe that EDHM is an underestimated disorder. Although there is no evidence to
84 suggest that EDHM has a negative impact on the prognosis for the underlying malignancy, it has
85 significant negative implications for patients given its uncomfortable symptoms and chronic,
86 relapsing course. The main limitation of this study is its retrospective design. Further
87 pathophysiological insights and long-term prospective studies are advisable to gain a better
88 understanding of this disorder and optimize patient management.

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106 Table 1. Summary of the main results of the study, including demographic, clinical and therapeutic data
 107 in patients with eosinophilic dermatosis of haematological malignancies (EDHM).

Characteristic	Value
Enrolled patients	37
Male	17 (46%)
Female	20 (54%)
<i>Associated malignancies</i>	
B-cells chronic lymphocytic leukaemia	19 (51%)
B-cells non Hodgkin lymphoma	11 (30%)
Multiple myeloma/monoclonal gammopathy of undermined significance	2 (5%)
Acute leukemia	4 (10%)
Aggressive T-cell lymphoma	1 (2.5)

Age at time of hematologic diagnosis (years)	Mean = 66, range = 40-88, median = 67
Age at time of EDHM diagnosis (years)	Mean = 70, range = 41-89, median = 74
Latency between hematological diagnosis and EDHM (months)	Mean = 57, median = 40, range = 5-191
Follow up (months)	Mean = 8.7, median = 5, range = 0-34
Previous exposure to chemotherapy	27/34 (80%)
On chemotherapy at time of skin rash	7/34 (20%)
Duration of rash (months)	Mean = 7, median = 3.5, range = 1-34
<i>Seasonality</i>	
Spring	13/37 (35%)
Summer	10/37 (27%)
Autumn	9/37 (24%)
Winter	5/37 (13%)
<i>Involved sites</i>	
Head/neck	9/37 (24%)
Trunk	20/37 (54%)
Upper limbs	30/37 (81%)
Lower limbs	34/37 (91%)
<i>Type of lesions</i>	
Papules	28/37 (75%)
Plaques	17/37 (45%)
Nodules	15/37 (40%)
Vesicles	7/37 (19%)
Blisters	12/37 (32%)
<i>Therapy</i>	
Prednisolone 0.5 mg/kg/day	16/34 (46%)
Prednisolone 1.0 mg/kg/day	8/34 (23%)
Topical steroids	12/34 (35%)
Oral antihistamines	6/34 (18%)

Cyclosporine	1/34 (3%)
UVA1	2/34 (6%)
Doxycycline	4/34 (12%)
Oral nicotinamide 1g/die	4/34 (12%)
Overall response rate	28/30 (93%)
Complete responses	12/30 (40%)
Partial Responses	16/30 (53%)
No Response	2/30 (7%)
Relapse rate	12/19 (63%)
Mean relapse free interval (months)	Mean = 5, median = 4, range = 1- 14
On chemotherapy at time of relapse	3/12 (25%)

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113 **Figure legend**

114 Figure 1. A: Distinct clinical presentations of eosinophilic dermatosis of hematologic malignancy. a)
115 light pink plaque on a leg resembling Wells Syndrome. b-c) multiple erythematous papules and
116 nodules on the head and neck. d) tense blisters, some hemorrhagic, on the forearm. e) multiple,
117 monomorphic, centered erythematous papules on the trunk that persisted for months. B: Distinct
118 histopathologic presentation of eosinophilic dermatosis of hematologic malignancy. (a) Extensive
119 intra and subepidermal edema with dermal-epidermal detachment, and an intense, perivascular,
120 mixed inflammatory infiltrate with numerous eosinophils, extending from the upper into the
121 reticular dermis, resembling Wells syndrome (hematoxylin and eosin, magnification 10x). At higher
122 magnification, it becomes possible to observe flame figures, consisting of hypereosinophilic
123 collagen fibers surrounded by degranulated eosinophil granulocytes (hematoxylin and eosin,
124 magnification x40). (b) Dermal-epidermal unilocular detachment. Mixed-type inflammatory
125 infiltrate with a few superficial perivascular and dermal eosinophilic granulocytes (hematoxylin
126 and eosin, magnification x10). (c) Acanthosis and mild epidermal spongiosis. Edema of the upper
127 dermis. Presence of a moderate, inflammatory interstitial infiltrate consisting of eosinophilic
128 granulocytes in the upper and mid-dermis (hematoxylin and eosin, magnification x20).

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