

Assessment of Seasonality in Eosinophilic Dermatitis of Haematological Malignancy

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Eosinophilic dermatitis of haematological malignancy (EDHM) is a pruritic, relapsing eosinophilic skin disease primarily associated with B-cell malignancies, predominantly with chronic lymphocytic leukaemia (CLL) and B-cell lymphoma. EDHM is characterized by recurrent flares of itchy skin lesions with a diffuse distribution, e.g. nodules, blisters or cellulitis, for which the diagnosis must be established by following well-established diagnostic criteria (1–6). The pathogenesis of EDHM remains largely unknown, and mosquito bites do not appear to be a determining factor (7, 8). In the same way, although it has been initially noted (7, 9, 10) the presence of a seasonality remains to be confirmed and does not clearly appear in the most recent series (1, 2). However, seasonality of EDHM has never been specifically studied in a homogeneous cohort of patients.

MATERIALS AND METHODS

Patients with B-cell malignancies who developed EDHM were identified based on medical records from Cancer University Institute, Toulouse Oncopole databases. The research period extended from January 2014 to January 2020. Two groups of patients could be included, depending on whether a skin biopsy was available: (i) patients with histopathological analysis (1 or several biopsies) were included according to Byrd's EDHM diagnosis criteria (3); (ii) patients without an available skin biopsy, with a diagnosis based on history and clinical presentation that was considered sufficiently relevant and after systematic review using a multidisciplinary methodology.

Finally, the seasonality of the EDHM was evaluated with a retrospective and transversal methodology: (i) determination of

the date (month) of skin biopsies performed for initial diagnosis or new flare (from medical records); (ii) analysis of data concerning seasonality reported by patients and physicians: season or month of first occurrence, month of complete remission of first EDHM flare, recurrence of lesions (from medical records); (iii) a prospective telephone survey was finally conducted by 1 of the investigators in February and March 2020 (AB), assessing the persistence of EDHM in the winter period in our cohort of patients (**Table I**).

All patients provided informed consent for collection and analysis of their tumour samples and medical data. This study was approved by the IRB, Institut Universitaire du Cancer, Toulouse Oncopole (CRE IUCT-O: 2-22-03).

RESULTS

A total of 35 patients were individualized during the defined period. All included patients were examined at least once by the same referent oncodermatologist. Twenty-six of these patients (74%) had 1 or more skin biopsies available and were included according to Byrd criteria; the remaining 9 patients were included when EDHM was confirmed after a systematic multidisciplinary discussion between the referent dermatologists and the referent haematologist.

The distribution was 24 females (69%) and 11 males (31%), with a median age of 71 years. All patients presented a B-cell malignancy, of which 26 patients were followed for CLL (74%), 4 patients for follicular lymphoma (11%) and 3 patients for large B cell lymphoma (9%). All patients came from the Midi-Pyrenees region in South-West of France. None of the patients had a sig-

Table I. English translated version of the questionnaire used for the (French) patients of the cohort during the telephone survey (study carried out during the winter period, between February and March 2020) and results (n = 31)

	n	%
Do you currently suffer from skin pimples/skin problems/skin lesions (in the last month)? (if yes, do they have the same clinical presentations/characteristics all year round?)		
Yes	2	6.4
No	29	93.6
Are you currently suffering from itching (in the last month)?		
Yes	2	6.4
No	29	93.6
Have you noticed any seasonality in your skin pimples/skin problems/skin lesions and itching?		
Yes	30	96.8
No	1	3.2
Do you notice a complete disappearance/remission of pimples/skin lesions and itching in winter?		
Yes	29	93.6
No	2	6.4
Is this condition responsible for a major impairment of your quality of life?		
Yes	31	100
No	0	0
According to you, is there a relationship between pimples/skin lesions and itching and insect bites?		
Yes	9	29
No	22	71

nificant history of photosensitivity or other pre-existing eosinophilic dermatoses.

All the first episodes of EDHM occurred after the initial diagnosis of haematological malignancy, with a median delay of 4.4 years. Skin biopsies (26 patients) were systematically re-examined with complementary immunohistochemical analysis ($n=44$ available biopsies). Histopathological findings revealed a predominantly perivascular superficial and deep dermal lymphohistiocytic infiltrate, with the presence of eosinophils in all cases. A lymphocytic T-cell infiltrate was also noted in 100% with positive CD3 immunostaining, with a moderate-to-dense infiltrate in 37/44 biopsies (84%). In contrast, CD20⁺ immunostaining was inconsistently positive in only 15/44 biopsies (34%, 7 patients with CLL) with a weak infiltrate or with small clusters of B-cells. In these 7 patients, a superimposable positive CD23 immunostaining was also noted in 6 of them, suggesting a tumoural origin of B-cell infiltrate.

When available, skin biopsies (initial diagnosis, recurrence of EDHM) were performed between May and October in 94% of cases. The season corresponding to the first EDHM lesions was specified for all included patients. The period of onset was spring/summer in 32 of the 35 patients (91%). More precisely, the month of first occurrence was also known for 23 patients and ranged from April to October in 22 of them (96%) (Table II). The first EDHM lesions disappeared between October and November in 20/24 patients (83%). All other included patients ($n=31$, 89%) presented a complete remission in winter months and developed a systematic recurrence in the spring or summer periods; none presented recurrence in the winter or autumn period. Finally, the cutaneous eruption did not appear to be related to disease activity and no haematological therapy (i.e. Bruton Tyrosine Kinase inhibitors, chemotherapy, anti-CD20 rituximab or binatumumab) altered the course or recurrence of EDHM lesions.

The prospective phone survey (done in the winter period) was performed in 31 patients of the cohort. Of the

patients interviewed, 30 had noticed a seasonal pattern of EDHM (97%) and 29 of them (93%) were in complete remission of cutaneous lesions and pruritus at the time of the telephone survey (Table I). Only 2 patients described persistent lesions during the survey, with a lower intensity in wintertime. Finally, less than one-third of the patients ($n=9$, 29%) reported a potential link with mosquito bites.

DISCUSSION

The results of this study showed that EDHM activity appeared to be clearly correlated with the season, with a very significant predominance of dermatological involvement between May and September, i.e. in the summer period in the Midi-Pyrenees region in South-West of France. This is corroborated not only by the initial diagnosis of EDHM in late spring or summer in more than 90% of cases, but also by a prolonged complete regression during the winter months, as confirmed by medical records data and telephone survey in more than 90% of the patients interviewed. Moreover, we individualized a systematic annual recurrence of EDHM lesions in spring/summer in almost 90% of patients, regardless of the course of the haematological disease or its therapeutic management, which has not been highlighted before, to our knowledge. However, it can be noted that in the 2 main published series, EDHM lesions first appeared in the winter period in only 12 of the 85 patients (1, 2).

The difference between our data and those so far established could be explained by several factors, in particular because of the retrospective and multicentric nature of the majority of studies conducted in EDHM, without any specific assessment of seasonality. The current study was designed specifically to assess EDHM seasonality in a monocentric population belonging to a geographical area with a relatively mild climate, with prospective patient questioning in the winter period by the same dermatologist.

In conclusion, further research is necessary to confirm these results in other regions or countries, using a prospective methodology. EDHM remains refractory to current treatment modalities, and the identification of a clear seasonality in the development of the lesions may allow better individualization of exogenous associated factors. In particular, the possible role of ultraviolet (UV) light in triggering lesions remains to be explored. Finally, mosquito bites do not seem to represent a major or exclusive factor in this context, in view of the current results and those previously published (7, 9, 10).

The authors have no conflicts of interest to declare.

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Table II. First occurrence and complete remission of eosinophilic dermatosis of haematological malignancy (EDHM)-related skin lesions reported by patients (distribution by month – data obtained from electronic databases of the Cancer University Institute, Toulouse Oncopole)

Distribution by month	Occurrence of first EDHM-related skin lesions ($n=23$)	Complete remission of first EDHM flare ($n=24$)
January	1	0
February	0	0
March	0	0
April	2	0
May	5	0
June	3	0
July	5	0
August	2	0
September	4	3
October	1	13
November	0	4
December	0	0
Persistent skin lesions throughout the year		4
Data not available	12	11

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