Dear Editor,

Hypereosinophilic syndromes (HESs) are defined by chronic blood hypereosinophilia ≥ 1.5 × 10^9 cells L⁻¹ and tissue damage related to eosinophilic infiltration. This heterogeneous entity includes neoplastic HES (e.g. chronic eosinophilic leukaemia linked to the FIP1L1:PDGFRA fusion transcript) and reactive HES (parasitic infections, drug reactions and inflammatory and neoplastic diseases). Among the latter, the lymphoid-variant HES is linked to clonal circulating T helper 2 CD4 T cells, most commonly with a CD3⁻ CD4⁺ phenotype. Published series of lymphoid HES remain scarce.

We retrieved suspicious cases of lymphoid HES from the database of the French Reference Center for Hypereosinophilic Syndromes (CEREO). The definition of HES complied with the International Cooperative Working Group on Eosinophil Disorders criteria. CD3⁻ CD4⁺ lymphoid HES was defined by HES and an aberrant blood CD3⁻ CD4⁺ lymphoid population > 0.5% T cells, without any reactive cause of HES or chronic myeloid HES. This study was approved by the local ethics committee.

Cutaneous T-cell lymphomas (CTCLs) – mycosis fungoides (MF) and Sézary syndrome – are characterized by skin infiltration by clonal T cells. Advanced-stage CTCLs are frequently associated with eosinophilia, linked to interleukin-5 secretion. In Sézary syndrome, the immunophenotypic abnormalities of blood tumour CD4⁺ T cells may include CD7 loss, and CD3 and/or CD4 downregulation. These abnormalities may be found in lymphoid HES.

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Figure 1 Clinical characteristics of skin involvement in lymphoid-variant hypereosinophilic syndrome and associated cutaneous T-cell lymphoma. (a) Clinical manifestations of lymphoid-variant hypereosinophilic syndrome. Erythematous papules of the neck (upper left) and eczema-like lesions, predominating in the folds (upper middle image). (b–d) Clinical characteristics of CD3⁻ CD4⁺ T-cell lymphoproliferative hypereosinophilic syndrome associated with cutaneous T-cell lymphoma. (b) Hypopigmented macules on the foot in a patient with associated stage IA mycosis fungoides. (c) Erythematous infiltrated papules in a patient with primary cutaneous peripheral T-cell lymphoma not otherwise specified (lower left) and erythroderma in a patient with stage III mycosis fungoides (lower middle image). (d) Erythematous, lax plaques of the axillary fold in a patient with a diagnosis of stage I mycosis fungoides.
in institutional review board (approval number IRB12437, 1 February 2022) and was conducted according to the principles of the Declaration of Helsinki.

In total, 119 suspicious cases of HES were screened, among which 83 met the definition of lymphoid HES; 63 (76%) of these patients had cutaneous involvement. Thirty-four cases of lymphoid HES had sufficient information. Four had no detectable blood CD3−CD4+ but a CD3−CD4+CD7− population. These four patients had skin involvement (maculopapular erythema, n = 1; eczema-like lesions, n = 1; angio-oedema, n = 2); one of them later developed erythroderma and fulfilled the criteria of Sézary syndrome. Three patients had no skin involvement.

Out of 27 patients with CD3−CD4+ lymphoid HES and skin involvement, 15 were women (56%), and the median age was 48 years (range 16–81) (additional details available online: 10.6084/m9.figshare.20290704). The most frequent manifestations were angio-oedema (30%), urticaria (26%) and eczema-like lesions (26%). Three patients (11%) developed erythroderma, and three others had subcutaneous masses. A skin biopsy was taken in 15 cases, mostly showing a dermal lymphocytic infiltrate with admixed eosinophils. Skin T-cell clonality was available in eight cases, with a dominant T-cell clone in seven, identical to the blood T-cell clone.

After clinicopathological review, five cases of CD3−CD4+ lymphoid HES were found to have developed CTCL: stage I MF (n = 2), stage III MF (n = 1), Sézary syndrome (n = 1) and primary cutaneous peripheral T-cell lymphoma (PTCL), not otherwise specified (n = 1) (Figure 1). MF diagnosis was based on the presence of a dense, bandlike or interstitial, dermal infiltrate of CD3−CD4− small-to-medium mononuclear cells with atypical nuclei and epidermotropism, and a dominant skin T-cell clone (histological pictures available online: 10.6084/m9.figshare.20288619). The patient with Sézary syndrome had erythroderma, a skin biopsy consistent with Sézary syndrome, identical blood and skin T-cell clones, and two phenotypically aberrant T-cell populations in blood (CD3−CD4−CD26+, 31% and CD3−CD4+, 11% of lymphocytes). A fifth patient with subcutaneous nodules and a dense subcutaneous infiltrate of medium-size atypical lymphocytes with folliculotropism was diagnosed as having primary cutaneous PTCL, not otherwise specified. The infiltrate was CD3−CD4+ with CD7 loss, the Ki67 index was 30–40% and a dominant T-cell clone was found in skin.

The patient with stage IA MF had complete response after treatment with topical chlorhexidine gel. Two patients with CTCL (one stage IB MF and one Sézary syndrome) were treated with mogamulizumab with blood complete response (disappearance of hypereosinophilia, and CD4+CD26+ T cells < 0.25 x 107 cells mL−1 in the patient with associated Sézary syndrome) but persistent skin involvement. One is now in complete remission after allogeneic stem cell transplantation (6 months of follow-up since transplant), while the remaining patient was lost to follow-up having not responded to treatment with methotrexate, and while under treatment with oral bexarotene.

This multicentre study describes the various clinical presentations of lymphoid HES. Although primary nodal PTCL has been described during the course of lymphoid HES,4 to our knowledge, primary CTCL has not been reported so far. Lymphoid HES and Sézary syndrome share a common gene expression pattern and elevated serum levels of TARC (thymus and activation-regulated chemokine),1 a CCR4 ligand, further supporting a common pathophysiology. Indeed, CCR4 is expressed by both CTCL tumour cells and CD3−CD4+ T-cell clones in lymphoid HES.7 Further molecular studies may help characterize the mutational landscape of lymphoid HES with skin involvement, although common alterations such as STAT3 (signal transducer and activator of transcription 3) mutations, present in both CTCL and lymphoid HES,8 could be expected.

This study challenges the existing paradigms of cutaneous T-cell lymphoproliferative disorders, and shows that careful skin examination and repeated skin biopsies are warranted in lymphoid HES.

Claire Laurent,1 Guillaume Lefevre,2 Jean-Emmanuel Kahn,3 Delphine Staumont-Salle,4 Renaud Felten,5 Marie Puget,6 Thomas Moulinet,7 Irène Machelart,8 David Launay,9 Estelle Charvet,10 Jean David Bouaziz,1,10,11 Marie Jachiet,11,23 Alexandre Espitia,12 Alfred Mahr,13 Christian Le Clech,14 Marion Malphettes,15 Cécile Morice,16 Samia Mourah,12,17 Hélène Moins-Teisserenc,11,18 François Lifermann,19 Karine Soulier-Guérin,20 Alban Villate,21 Chloé Baillou,22 Aurélie Grados,23 Aïsa Robbins,24 Noemie Abisar,25 Martine Bagot,1,10,11 David Boutboul,15 Kevin Panel,26 Marie-Dominique Vignon-Pennamen,27 Jacqueline Rivet,27 Maxime Battistella,27 Mathieu Groh,26 and Adèle de Masson27 1Department of Dermatology, Saint-Louis Hospital, AP-HP, Paris, France. Correspondence: Adèle de Masson. Email: adele.demasson@aphp.fr

M. Battistella, M.G. and A.D.M. share last authorship.

A full list of affiliations is available in Appendix S1 (see Supporting Information).

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Appendix S1 Full list of affiliations.
The mean age of participants was 67 years, 100% were female, and participants had a mean age at diagnosis of 49 years. All participants had scalp involvement, and the majority of participants (79%) had eyebrow involvement. Our analysis elicited eight themes (Table 1). (i) ‘Trying to disguise it’ participants often cited not being able to style their hair in the way they desired as the most frustrating aspect of having FFA. Even after spending a significant amount of time camouflaging their hair loss, individuals worried throughout the day about their FFA being revealed. (ii) ‘Less than whole’: the loss of self-identity was a pervasive theme throughout the interviews. Participants no longer viewed themselves in the same manner that they had before their hair loss, and they felt their alopecia had removed a portion of their identity. Every participant mentioned embarrassment and feeling self-conscious from their hair loss. Fear of judgement and comments from others was an expressed daily worry. One participant expedited her retirement as a teacher owing to comments from her students on her hair loss. (iii) ‘It’s not a zebra, it’s a horse’: because of the delay in receiving a diagnosis, participants felt ‘cheated’ in that they wasted valuable time not actively treating their FFA and felt earlier intervention would have prevented much of their hair loss. (iv) ‘Not the end of the world’ while participants were distressed by their hair loss, almost all acknowledged the disease was not life-threatening and accepted that hair regrowth was unlikely. (v) ‘An ongoing battle’: the management of FFA was described as chronic and time-consuming, and many participants felt that their previous daily routines changed drastically with their diagnosis. (vi) ‘A mystery’ everyone desired a better explanation for the aetiology of FFA. Participants wanted to know whether the cause of their FFA was due to intrinsic or extrinsic factors, as many regretted that their past actions could have contributed to their hair loss. (vii) ‘Glimmer of hope’ participants all had positive experiences of being treated by a hair specialist and felt they had an ally in their fight against FFA. (viii) ‘Everything I’ve got’: when participants were asked how much they were willing to pay for a one-time guaranteed cure for their disease, they reported they would pay from $1000 to their entire life savings for a cure for FFA, with many offering $20 000 or more.

In our cohort, participants with FFA expressed the devastating effects of this progressive disease on social, professional and psychological aspects of their lives. The cultural importance and value of hair is pervasive throughout history.3 Consequently, hair loss can be an extremely traumatic experience for individuals. Past studies that evaluated the impact of FFA used quantitative measures such as the Dermatology Life Quality Index and indicated only mild disease burden.5,6 The aetiology of FFA is not well understood, and this was distressing to participants in our study. The amount of money participants in our cohort were willing to pay for a one-time cure was considerably greater than for other chronic dermatological conditions.6,7 This indicates high disease burden and that participants with FFA may be desperate for disease improvement and thus susceptible to attempt treatments that are not always beneficial for their alopecia. One limitation of our study is

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Psychosexual burden of frontal fibrosing alopecia: a qualitative interview study

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Dear Editor, Frontal fibrosing alopecia (FFA) is an immune-mediated cicatricial alopecia, first described in 1994, that has increased in prevalence over the past 30 years.1 FFA is predominantly limited to the frontotemporal hairline and affects the eyebrows in 80% of cases.2 FFA mainly occurs in postmenopausal women and is associated with hormonal, genetic and environmental factors, although a definitive aetiology remains unclear.3 Alopecia has a negative effect on patients’ quality of life (QoL) and is associated with anxiety and depression.4 Although there have been studies on the impact of cicatricial alopecia on QoL, in the past, few have focused on FFA specifically.4,5

To better understand the effects of FFA on patients’ lives, we conducted semi-structured interviews with 14 patients with a diagnosis of FFA from the Atrium Health Wake Forest Baptist Department of Dermatology. All participants were identified through our electronic medical record and recruited over telephone for participation in the study. Interviews were transcribed, underwent independent review and were coded by all the investigators using an inductive and constant comparative technique. Any discrepancies were resolved via discussion to achieve mutual agreement. The study was reviewed and approved by Wake Forest Institutional Review Board (approval IRB00078598).

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