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CONCISE COMMUNICATION

Lymphomatoid papulosis associated with myeloid neoplasm with eosinophilia and *FIP1L1::PDGFRA* rearrangement: Successful imatinib treatment in two cases

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Abstract

Lymphomatoid papulosis (LyP) is a benign condition, listed among primary cutaneous CD30+ lymphoproliferative disorders. Its typical picture consists of relapsing–remitting papular lesions and it can be encountered in the course of a hematologic disease, at times representing its first manifestation. Hypereosinophilic syndromes are a heterogeneous group of disorders characterized by persistent peripheral blood hypereosinophilia that may lead to life-threatening organ damage. Among eosinophilic disorders, the subtype identified as myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase gene fusions has aroused particular interest due to its excellent response to tyrosine kinase inhibitors, including imatinib. Here, we described the case of two 33-year-old men presenting with LyP and myeloid neoplasm with eosinophilia and *FIP1L1::PDGFRA* rearrangement who achieved complete clinical and molecular remission of both conditions a few months after starting imatinib.

KEYWORDS

FIP1L1::PDGFRA, hypereosinophilia, imatinib, lymphomatoid papulosis, myeloid neoplasm

1 | INTRODUCTION

First described in 1968 by Macaulay et al.,[1] lymphomatoid papulosis (LyP) is a chronic primary cutaneous lymphoproliferative disorder (LPD) characterized by a benign course with a tendency to relapse. A "wait-and-see" strategy may be an option as the indolent course of the disease suggests. Alternatively, treatment consists of topical steroids and phototherapy as first-line options. Low-dose methotrexate (15–25 mg weekly) also appears to have good results in controlling LyP. In particularly resistant cases, brentuximab vedotin may also be considered. Nevertheless, most patients tend to relapse.

Hypereosinophilic syndromes (HES), on the other hand, are a heterogeneous group of disorders characterized by persistent hypereosinophilia (HE) (i.e., peripheral blood [PB] absolute eosinophil count $>1.5\times10^9$/L with a minimal duration of 6 months) associated with organ damage and/or dysfunction attributable to tissue eosinophilic infiltrate and release of granule contents.[2]

In the 2022 International Consensus Classification, myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, *FGFR1* genes or with *PCM1::JAK2*, are now referred to as myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase (TK) gene fusions, emphasizing the relevance of molecular genetic changes for these conditions.

Recurrent genetic abnormalities (*PDGFRA/B*, *FGFR1*) have a low incidence among eosinophilic disorders and, in particular, *FIP1L1::PDGFRA* fusion gene median frequency has been reported

to be approximately 23% (range 3%–56%). Currently, imatinib is the drug of choice for myeloid neoplasms with eosinophilia and *PDGFRA/B* rearrangement, as its hematologic benefit has been confirmed in several studies, even at lower dosages than those used for chronic myeloid leukemia.[3]

Here we describe the case of two 33-year-old Caucasian men who presented with both these conditions, achieving complete response on imatinib.

2 | CASE REPORT

2.1 | Case 1

A 33-year-old Caucasian man was referred to our department in November 2021 due to increased eosinophil count (6.5×10^9/L) during dermatological follow-up. He had an unremarkable past medical history except for LyP diagnosed in June 2020 on a skin biopsy. Early lesions appeared in February 2018 and were characterized by self-healing papules with central ulceration and subsequent necrosis, mainly in the lower limbs (Figure 1a). Punch biopsy showed epidermal ulceration underlined by a deep, neutrophil-rich infiltrate comprising a polymorphic T-cell population, with intermixed large, immunoblastic-to-anaplastic cells with a "null" (i.e., CD2-/CD3-/CD5-/CD7-) CD4+/CD30+ phenotype, consistent with a diagnosis of type A LyP (Figure 1b,c).

In a complete blood count (CBC) performed at that time, eosinophils were only slightly increased (0.9×10^9/L). Due to persistence and recurrence of erythematous papules followed by a necrotic evolution, treatment with methotrexate 10 mg weekly was started, with initial resolution of skin lesions. In July 2021 methotrexate was stopped, leading to LyP relapse 1 week later, so that therapy was resumed.

In October 2021, routinary blood analysis showed a mild leukocytosis (13.14×10^9/L) with a significant eosinophilia (6.13×10^9/L). Serum lactate dehydrogenase level was increased (236 IU/L, normal range 135–225 IU/L), as well as vitamin B12 serum concentration (>2000 ng/mL), while IgE and triptase levels were unremarkable. An echocardiography ruled out any cardiac damage.

Second-level analyses were then performed: PB immunophenotype was not indicative of LPD. Autoimmunity tests revealed only antinuclear antibody positivity with a speckled pattern (1:160). Stools for parasites were all negative, whereas radiological investigations only detected a spleen diameter of 12.5 cm. Screening for *BCR::ABL1* p210 fusion transcript and *JAK2*V617F mutation was negative. In contrast, molecular analysis with NESTED/RT-PCR on PB was positive for *FIP1L1::PDGFRA* rearrangement, thus leading to a diagnosis of myeloid neoplasm with eosinophilia and *PDGFRA* rearrangement. Bone marrow (BM) biopsy featured only minor signs of morphologic dysmyelopoiesis, with eosinophilic hyperplasia, foci of interstitial accumulation of spindle-shaped, phenotypically nonaberrant (tryptase+/CD25-/CD2-/CD30-) mast cells, and an

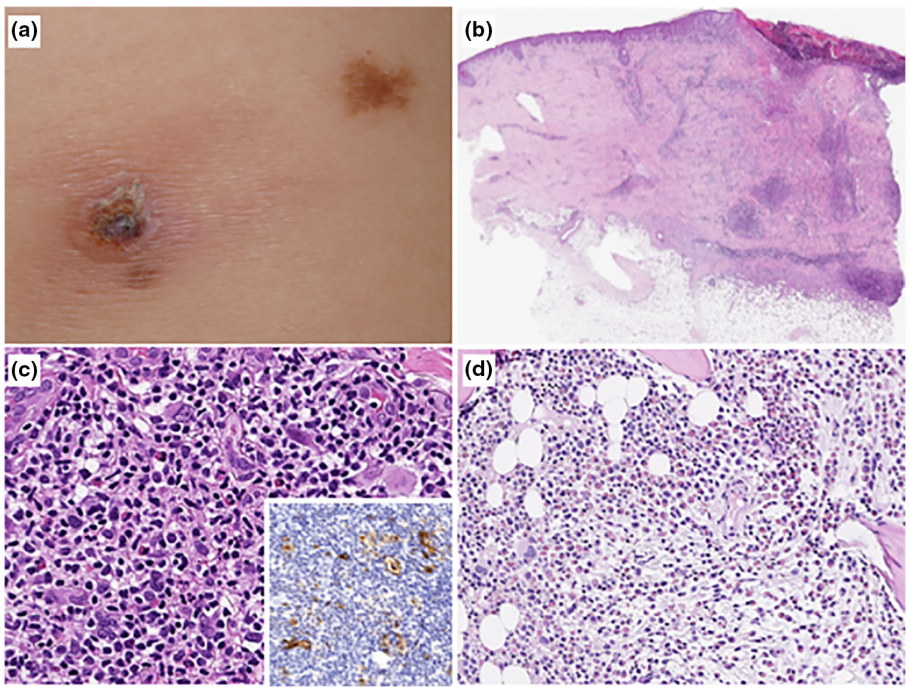

FIGURE 1 Clinical picture from patient 1 details a papular lesion with central eschar adjacent to an almost regressed lesion; morphologic detail (a) displays an ulcerated epidermis underpinned by a wedge shaped, polymorphic infiltrate (b, H/E, 20×) featuring polymorphic lymphocytes, a small amount of eosinophils and scattered CD30+ large, atypical cells (c, H/E, 400×; inset, CD30, 200×). Bone marrow biopsy (d, H/E, 200×) displays a hyperplastic eosinophilic lineage and foci of proliferation of interstitial, spindle-shaped cells consistent with mast cells.

unremarkable lymphoid infiltrate, thus being supportive of the molecular diagnosis (Figure 1d).

Methotrexate treatment was then stopped and imatinib 100 mg daily started in February 2022. After 3 months of treatment, molecular analysis on PB and BM were negative for *FIP1L1::PDGFRA* rearrangement. LyP-related skin lesions never recurred during imatinib therapy. At last follow-up after 6 months of treatment, imatinib continued to be well tolerated and further investigation of *FIP1L1::PDGFRA* rearrangement on PB was still negative.

2.2 | Case 2

In August 2018 a 33-year-old Caucasian man was referred to our department for HE. In 2018 he developed self-healing erythematous, ulcerated papules in the upper limbs with a tendency to relapse (Figure 2a). A punch biopsy was then performed showing a dermal, wedge-shaped, polymorphic infiltration comprising scattered granulocytes and plasma cells, and a predominance of small to medium predominantly CD4+ lymphocytes, with a minor component of large immunoblastic CD4+/CD30+ cells. The clinic-pathologic picture was consistent with type A LyP (Figure 2b,c).

Laboratory tests performed during dermatological follow-up revealed a normal CBC with the exception of eosinophilia (3.64×10^9/L). Autoimmunity screening and stools for intestinal parasites were negative, while serum tryptase levels were only slightly increased (19 μg/L). Radiological examinations were unremarkable, and electrocardiogram and echocardiogram showed good cardiac function.

As the immunophenotype on PB was inconclusive for LPD, a BM biopsy was obtained in September 2018 revealing eosinophilic hyperplasia (Figure 2d). Molecular analyses were negative for both *JAK2*V617F mutation and *BCR::ABL1* p210 fusion transcript, while *FIP1L1::PDGFRA* rearrangement was detected on both PB and BM, thus leading to a diagnosis of myeloid neoplasm with eosinophilia and *PDGFRA* rearrangement. Treatment with imatinib 100 mg QD was started in February 2019. After 3 months of therapy a re-evaluation was performed showing the absence of *FIP1L1::PDGFRA* rearrangement on PB, while it persisted on BM. Finally, in September 2020, 18 months from imatinib start, molecular analysis for *FIP1L1::PDGFRA* was negative on both PB and BM.

Importantly, during follow-up imatinib continued to be well tolerated and no cutaneous lesions related to LyP occurred.

3 | DISCUSSION

Prognosis of myeloid neoplasms with eosinophilia and *PDGFRA/B* rearrangements has significantly improved after imatinib introduction. Conversely, despite its minor impact on the prognosis of affected patients, LyP relapsing behavior may constitute a matter of discomfort and concern, particularly when diagnosed in the context of concurrent hematologic diseases: notably, its distinction from transformation of mycosis fungoides may be challenging.[4]

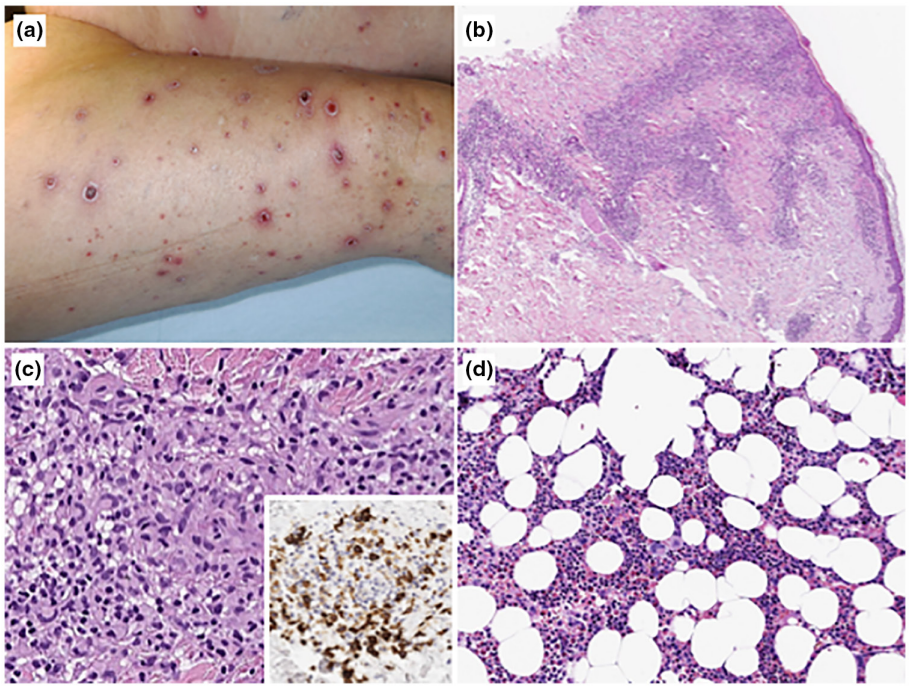

FIGURE 2 Cutaneous picture of patient 2 (a) features multiple papular, erythematous lesions at various stages of development, including ulcerated and scarring tissue. Skin biopsy (b, H/E, 20×) features a wedge-shaped infiltrate with perivascular accumulation of immunoblastic to anaplastic cells, CD30+ T cells, with an unremarkable component of eosinophils (c, H/E 400×; inset, CD30, 200×). Bone marrow biopsy (d, H/E, 200×) features minor signs of dysmyelopoieis with eosinophilic hyperplasia.

To the best of our knowledge, only 12 cases of LyP-associated HES have been reported in the literature so far. Among them, seven patients were treated with imatinib, five of whom expressed *FIP1L1*::*PDGFRA* rearrangement, and achieved a good response on both LyP and HES in all cases (Table 1).[5–11]

Why LyP can be associated with (or causal of) HES is still uncertain. HE can be secondary to clonal T-cell expansion, as in its lymphocytic variant, in which the atypical lymphocytes have been shown to release eosinophilopoietic cytokines, such as IL-5 and IL-3.[12] However, in *FIP1L1*::*PDGFRA*-positive myeloid neoplasms,

TABLE 1 Lymphomatoid papulosis and hypereosinophilia coexistence and related therapies.

Reference	Characteristics	Therapy	Main findings
LyP and its relationship to idiopathic HES[5]	(1) 48-year-old man (2) 45-year-old man (3) 47-year-old man	(1) Cyclosporine (2) Aspirin and dipyridamole (3) Prednisolone	First to described idiopathic HES in association with LyP
LyP associated with both severe HES and CD30+ large T-cell lymphoma[6]	64-year-old man	Steroids Hydroxyurea IFN-α CHOP Cyclosporine	LyP and eosinophilic count of 4×10^9/L After 6 years the patient developed a CD30+ large cell lymphoma First case of association between LyP, HES, and CD30+ large-cell lymphoma The patient was treated with CHOP but due to HE persistence, cyclosporine was ultimately proposed
Reversal of HES and LyP with mepolizumab and imatinib[7]	51-year-old man	Predinsolone Hydroxyurea Methotrexate Psoralen/UVA Mepolizumab Imatinib	51-year-old man with HES and LyP who had been unsuccessfully treated with prednisone and hydroxyurea for HE and with methotrexate and psoralen/UVA for LyP Due to organ damage caused by HES and elevated serum IL-5 levels, he was treated with mepolizumab, which transiently reduced IL-5 level and eosinophil count Two months after the last dose of mepolizumab he was given imatinib at 400 mg QD for 2 weeks, 200 mg QD for 7 months, and 100 mg QD for 11 months After starting imatinib therapy, LyP disappeared and eosinophil count normalized within a week
PDGFRA-associated HES and LyP[8]	33-year-old man	Imatinib	LyP and eosinophilic count of 5.17×10^9/L *FIP1L1*::*PDGFRA* rearrangement was detected First report of a patient with HES and LyP in whom the molecular defect responsible for HES has been identified The patient reached a complete clinical, hematological, and molecular remission He did not develop any new LyP-related skin lesion after initiation of imatinib
Long-lasting hematologic remission with imatinib therapy in idiopathic HES associated with LyP: case report[9]	32-year-old man	Hydroxyurea IFN-α PUVA Methotrexate Thioguanine Low-dose cytarabine Imatinib 100 mg	LyP and eosinophilic count of 19×10^9/L HE responded impressively to imatinib with hematologic remission achieved after 4 days of therapy
Imatinib treatment of LyP associated with myeloproliferative HES presenting the *FIP1L1*::*PDGFRA* fusion gene[10]	25-year-old man	Imatinib 100 mg	LyP and HE *FIP1L1*::*PDGFRA* was detected by FISH Both cutaneous lesions and eosinophilic count resolved rapidly after imatinib was started After a 58-month follow-up, the patient was still asymptomatic
Successful treatment with imatinib of LyP associated with myeloproliferative HES with *PDGFRA* rearrangement[11]		Imatinib 100 mg	LyP and HES with *FIP1L1*::*PDGFRA* fusion gene Treatment with imatinib was initiated at a dose of 100 mg QD After 10 days of treatment, the number of PB eosinophils had returned to normal The patient did not experience any new outbreak of LyP lesions during 20 months of follow-up and tapering of imatinib (100 mg every 2 days)

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; FISH, Fluorescence in situ Hybridization; HE, hypereosinophilia; HES, hypereosinophilic syndromes; IFN-α, Interferfero-alpha ; IL-5, Interleukin 5; LyP, lymphomatoid papulosis; PB, peripheral blood; PUVA, psoralen ultra violet A; QD, Quo Die (daily); UVA, ultra violet A.

the genetic driver is probably the major actor in eosinophil expansion. Intriguingly, at least in one patient a multilineage involvement of *FIP1L1::PDGFRA* rearrangement has been identified, including T cells, thus explaining the eponym of the disease and the increased risk of lymphoid neoplasms.[13] However, none of the tested LyP cases in the literature demonstrated the same molecular alteration in cutaneous lesions, thus suggesting an inflammatory/paraneoplastic origin in the context of an unbalanced cytokine milieu. Accordingly, it is noteworthy that once TK inhibitor therapy for myeloid neoplasms with eosinophilia and *PDGFRA* rearrangement was initiated, none of the patients had a relapse of LyP during follow-up of different durations.

Mechanisms by which imatinib might protect against LyP recurrences have not been elucidated so far. Imatinib is a powerful inhibitor of the protein tyrosine kinase Bcr-Abl, platelet-derived growth factor receptors (PDGFRA and PDGFRB) and KIT, and Ruan et al. previously observed that imatinib can hamper lymphoma growth by inhibiting PDGFRB+ associated pericytes, thus representing an antiangiogenic target with the ability to destroy neovascular integrity.[14]

Consequently, testing for *FIP1L1::PDGFRA* rearrangement should always be performed in LyP patients who present with HE at diagnosis or develop it during dermatological follow-up in light of its potential clinical and therapeutic consequences.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no potential conflicts of interest.

INFORMED CONSENT

The patients have given written informed consent to publish these cases (including the publication of images).

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