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Upadacitinib in refractory cutaneous pseudolymphoma: A case report

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Abstract

Cutaneous pseudolymphoma is a benign condition characterized by a reactive B-cell, T-cell or mixed lymphoproliferative process. Different causative agents (e.g. injected substances, tattoo, drugs and insect bites) have been described, but in many cases no cause can be identified; hence, the term idiopathic cutaneous pseudolymphoma. There are no specific guidelines for the treatment of cutaneous pseudolymphoma, and sometimes a few cases are refractory to conventional treatments. We describe a case of a 41-year-old African woman with refractory facial IgG4 pseudolymphoma successfully treated with upadacitinib.

Keywords

upadacitinib, cutaneous pseudolymphoma, JAK inhibitors

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Introduction

Cutaneous pseudolymphoma (PSL), also known as cutaneous lymphoid hyperplasia, is described as a reactive B-cell or T-cell or mixed lymphoproliferative process that histopathologically and/or clinically simulates cutaneous lymphomas.[1] Different causative agents have been described. In most cases, cutaneous PSL is elicited by drugs, such as anticonvulsants, antibiotics, antiarrhythmics and NSAIDs; in fewer cases by tattoos, vaccinations and insect bites. In addition, association with infectious agents like *Borrelia* spp., *Treponema pallidum*, human immunodeficiency virus (HIV), herpes virus, scabies and leishmaniasis has been described.[2] Idiopathic cutaneous PSL has been reported.[1]

PSL may clinically present as single or multiple erythematous to violaceous papules, nodules and plaques located on the head, neck or upper extremities.[3,4] Diagnosis requires correlations of clinical, histologic, immunophenotypic and molecular findings, and the clinical follow-up is important to support the diagnosis. Treatment options are not standardized and based on limited evidence, and include topical or intralesional corticosteroids, physical modalities or systemic anti-inflammatory or immunosuppressive drugs with variable response.[2] Here, we report a 41-year-old woman with idiopathic cutaneous PSL successfully treated with upadacitinib.

Case report

A 41-year-old woman of African origin with Fitzpatrick skin type V presented with a 5-year history of multiple facial nodules progressively increasing in size, ranging from 2 to 10 cm. Physical examination revealed multiple hyperpigmented large nodules, tough texture, on the cheekbones, left eyebrow and upper portion of the forehead (Figure 1(a)). There were no regional lymphadenopathies and no history of insect bite, trauma or drug intake. Routine haematological and biochemical investigations were within normal range. Chest X-ray and lymph node ultrasonography were negative. Serology for human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), *Borrelia burgdorferi* and Interferon-Gamma Release Assay for *Mycobacterium tuberculosis* were negative. Histopathological examination of skin biopsy taken from a nodule showed florid mixed lymphoid infiltrate with nodular architecture and lymphoid follicles

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Figure 1. At baseline, multiple hyperpigmented nodules, tough texture on the cheekbones, left eyebrow and upper portion of the forehead (a). Significant improvement of lesions after 2 months of therapy with upadacitinib 30 mg daily (b).

formation, involving the entire reticular dermis and superficial subcutis (Figure 2(a)). The lymphoid follicles presented with a true germinal center composed of an admixture of centroblasts and centrocytes and tingible body macrophages. Immunohistology revealed a normal phenotype of germinal centre cells (CD20+, CD79a+, CD10+, Bcl-6+, Bcl-2−), with a regular network of CD21+ follicular dendritic cells, high proliferation index and positivity for Tubulin3, thus excluding follicular lymphoma (Figure 2(b)). The interfollicular areas were populated by numerous T cells displaying CD3, CD5 and CD7 positivity with a ratio of CD4/CD8 of 3:1 (Figure 2(c)). Numerous mature plasma cells in the perivascular distribution and many eosinophils were also appreciated (Figure 2(d)). The plasma cells were polytypical for light chains with a Kappa/Lambda ratio close to unity, excluding primary cutaneous marginal zone lymphoma. Numerous IgG-positive plasma cells were detected in a ratio of IgG4/IgG cells of >40% (Figure 2(e)). No monoclonal T-cell and B-cell populations were detected by immunoglobulin and T-cell receptor gene rearrangement studies. A diagnosis of IgG4+ cutaneous PSL was made. In her medical history, the patient had a basal cell adenoma of the parathyroid for which she had undergone a partial parotidectomy. Previous repeated cycles of topical and systemic steroids were not effective. The patient was initially treated with hydroxychloroquine 400 mg/day and topical tacrolimus 0.1% combined with cycles of prednisone 25 mg/day, with poor benefit and recurrence of the clinical presentation when the systemic steroid was tapered. Due to the lack of benefit of previous treatments and the significant social impact of this condition, treatment with upadacitinib 30 mg/day was started. After 4 weeks, a relevant reduction in turgidity and nodule size was observed. After 6-month follow-up, the lesions continued to reduce in size with the reduction in consistency (Figure 1(b)). No adverse effects were reported.

Discussion

Cutaneous PSL is a benign condition characterized by reactive cutaneous lymphocytic infiltrates with B- or T-cell predominance or mixed. The diagnostic approach includes a combination of medical history, clinical presentation and histopathology findings, including immunohistochemistry and molecular diagnostics.[1] In the present case, the presence of multiple cutaneous nodules, a histologic picture most consistent with PSL and the presence of a lympho-plasmacytic infiltrate with a ratio of IgG4+/IgG+ plasma cells of >40%, supported the diagnosis of IgG4+ PSL.[5] The peculiarity of this case is the expression of IgG4 in cutaneous PSL, which has been rarely reported, since most are IgG1.[5] The clinical significance of this expression has yet to be established. The clinical course of cutaneous PSL can be highly variable. Some cases undergo spontaneous regression, others persist

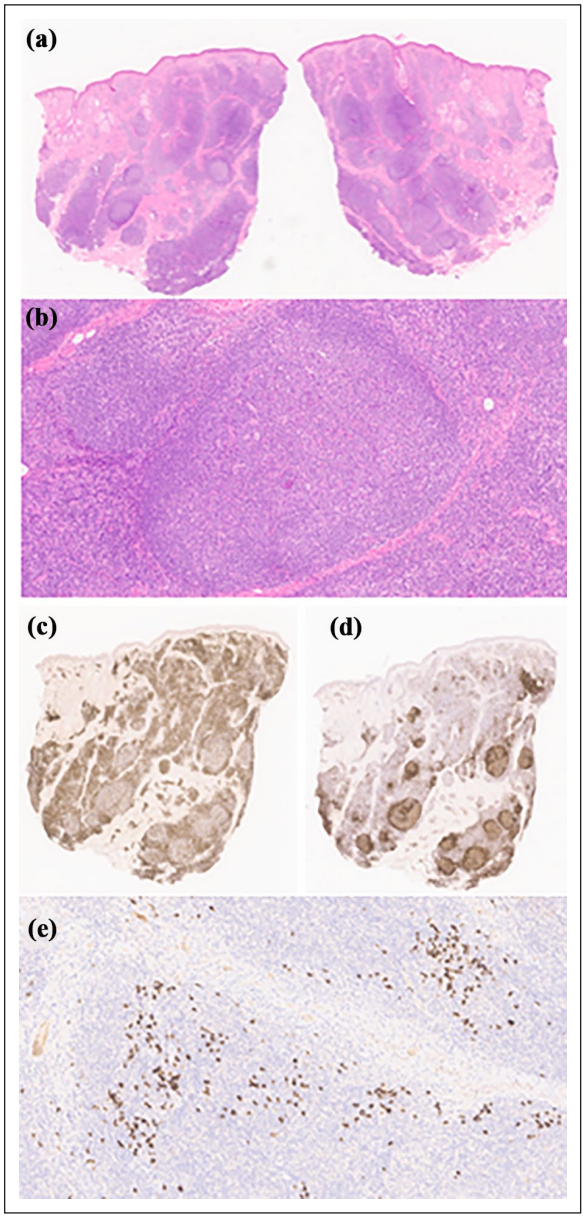

Figure 2. Dense, nodular lymphoid infiltrate in the entire dermis with involvement of superficial subcutis (haematoxylin and eosin, original magnification ×5; a). Lymphoid follicle with true germinal centre (haematoxylin and eosin, original magnification ×100; b). CD3 immunostain marking the interfollicular T cells (original magnification ×5; c). CD79a immunostain marking the B cells in nodular aggregate (immunostaining, original magnification ×5; d). IgG4+ plasma cells accounting for more than 40% of IgG+ cells (immunostaining original magnification ×100; e).

over months or even years. A re-exposure to the particular cause may incite a recurrence.[1,6] Progression or a so-called 'aggressive course' of cutaneous PSL has been rarely reported.[7,8] Removing the causative agent and avoiding re-exposure, if possible, are very important. Specific guidelines/recommendations for the treatment of cutaneous PSL are not yet available and would be needed.[1]

Treatment options include topical or intralesional corticosteroids, topical tacrolimus and systemic drugs, including corticosteroids, antibiotics, immunosuppressive agents, hydroxychloroquine, as well as intralesional or systemic interferon alpha.[1,2,9]

In this case report, the efficacy of upadacitinib in facial cutaneous PLS refractory to previous conventional treatments is presented. Upadacitinib is an oral, reversible, small-molecule Janus kinase (JAK) inhibitor engineered to have increased selectivity for JAK1.[10] The JAK1/signal transduction and activator of transcription (JAK–STAT) signalling pathway is essential for the downstream regulation of various cytokines (i.e. IFN-gamma, IL-4, IL-6, IL-13) and growth factors that contribute to a variety of developmental and homeostatic biological processes, cell proliferation and immune functions.[11,12] Through inhibition of JAK1, upadacitinib inhibits phosphorylation and activation of downstream STAT proteins. In particular, STAT1/STAT4 is a key factor for T-helper 1 (Th1) cell response, STAT3 is critical for the differentiation of Th17 cells, and STAT5 protein signals downstream of many cytokines critical for immune cell growth and immune response, and is particularly important for T and NK cells.[12,13] Upadacitinib, by inhibiting the STAT6 signalling pathway, reduces the Th2 cell differentiation and inhibits the proliferation of B cells by increasing B-cell apoptosis.[14]

This is the first patient reported in whom a refractory cutaneous facial pseudolymphoma IgG4+ was successfully treated with upadacitinib 30 mg/day. We acknowledge the limited evidence deriving from a single case report, but we think that the use of JAKs in pseudolymphomas, but also cutaneous lymphomas, can be further studied.[15]

However, caution should be taken with patients with an underlying autoimmune disease and prior immunosuppression.

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Consent for publication

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References

1. Mitteldorf C and Kempf W. Cutaneous pseudolymphoma – a review on the spectrum and a proposal for a new classification. *J Cutan Pathol* 2020; 47(1): 76–97.
2. Miguel D, Peckruhn M and Elsner P. Treatment of cutaneous pseudolymphoma: a systematic review. *Acta Derm Venereol* 2018; 98(3): 310–317.
3. Bolognia JL, Schaffer JV, Cerroni L, et al. *Dermatology*. 5th ed. Elsevier, 2024.
4. Van Vloten WA and Willemze R. The many faces of lymphocytoma cutis. *J Eur Acad Dermatol Venereol* 2003; 17(1): 3–6.
5. Tokura Y, Yagi H, Yanaguchi H, et al. IgG4-related skin disease. *Br J Dermatol* 2014; 171(5): 959–967.
6. Mitteldorf C, Geisinger E, Pleimes M, et al. T-cell pseudolymphoma in recurrent herpes simplex virus infection. *J Cutan Pathol* 2019; 46(10): 717–722.
7. Goodlad JR, Davidson MM, Hollowood K, et al. *Borrelia burgdorferi*-associated cutaneous marginal zone lymphoma: a clinicopathological study of two cases illustrating the temporal progression of *B. burgdorferi*-associated B-cell proliferation in the skin. *Histopathology* 2000; 37(6): 501–508.
8. Joseph D, Irukulla MM, Ahmed SF, et al. Radiotherapy in aggressive cutaneous pseudolymphoma: a case report and review of literature. *Radiat Oncol J* 2016; 34(1): 76–80.
9. Singletary HL, Selim MA and Olsen E. Subcutaneous interferon alfa for the treatment of cutaneous pseudolymphoma. *Arch Dermatol* 2012; 148(5): 572–574.
10. Mohamed MF, Bhatnagar S, Parmentier JM, et al. Upadacitinib: mechanism of action, clinical, and translational science. *Clin Transl Sci* 2024; 17(1): 13688.
11. Huang IH, Chung WH, Wu PC, et al. JAK–STAT signaling pathway in the pathogenesis of atopic dermatitis: an updated review. *Front Immunol* 2022; 13: 1068260.
12. Banerjee S, Biehl A, Gadina M, et al. JAK–STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs* 2017; 77(5): 521–546. (Published correction appears in: *Drugs* 2017; 77(8): 939. Erratum in: *Drugs* 2017; 77(8): 939. Erratum in: *Drugs* 2017; 77(11): 1261).
13. Dold L, Kalthoff S, Frank L, et al. STAT activation in regulatory CD4+ T cells of patients with primary sclerosing cholangitis. *Immun Inflamm Dis* 2024; 12(4): 1248.
14. Lum K, Sanchez R, Zhou C, et al. Refractory facial cutaneous B-cell pseudolymphoma successfully treated with dupilumab. *JAAD Case Rep* 2024; 46: 95–99.
15. Vahabi SM, Bahramian S, Esmaeili F, et al. JAK inhibitors in cutaneous T-cell lymphoma: friend or foe? A systematic review of the published literature. *Cancers* 2024; 16(5): 861.