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Subcutaneous panniculitis-like T-cell lymphoma with hemophagocytic lymphohistiocytosis in a psoriasis patient after sequential biologics including extended brodalumab: a case report

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Abstract

Biologic therapies have revolutionized psoriasis management, but they have also raised concerns about potential unusual adverse effects. We think this represents the first detailed case of subcutaneous panniculitis-like T-cell lymphoma with hemophagocytic lymphohistiocytosis in a psoriasis patient, confirmed clinically and histopathologically, occurring after 9 months of brodalumab treatment following multiple biologic switches. The patient's development of subcutaneous panniculitis-like T-cell lymphoma during an extended period on brodalumab, compared to other biologics, underscores the need for awareness of potential rare complications associated with this therapy.

Keywords: subcutaneous panniculitis-like T-cell lymphoma, hemophagocytic lymphohistiocytosis, psoriasis, biologics, brodalumab

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Introduction

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare subtype of cutaneous T-cell lymphoma, accounting for less than 1% of non-Hodgkin lymphomas and characterized by the infiltration of subcutaneous fat by neoplastic cytotoxic CD8+ αβ T-cells. Although previous studies have demonstrated that certain autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome, are linked to an increased risk of SPTCL (1), and psoriasis may increase the risk of cutaneous lymphoma, an association between psoriasis and SPTCL has not yet been established. In fact, there is only one case series mentioning a female patient with psoriatic arthritis before the onset of SPTCL, but without clinical pictures or pathological images (2). Biologic therapies, particularly brodalumab, are effective for managing moderate-to-severe psoriasis but have also raised concerns about potential rare adverse effects (3, 4). Moreover, given the potential dual role of interleukin (IL)-17 in tumor biology (5), the relationship between IL-17 imbalance and cancer risk remains inconclusive. Here, we present a unique case of SPTCL with hemophagocytic lymphohistiocytosis (HLH) developing in a psoriasis patient after 9 months of brodalumab treatment following biologic switches, underscoring the need for vigilant monitoring of patients on biologic therapy.

Case report

A 34-year-old female with a history of alpha-thalassemia presented to our dermatology department with itchy erythematous plaques on her trunk and legs in 2020. Physical examination revealed well-defined, small, discrete, erythematous or salmon-pink scaly papules and plaques primarily on the trunk (Fig. 1a), with a few on the lower limbs. A clinical diagnosis of guttate psoriasis was made, and treatment was initiated. However, during 1.5 years of psoriasis treatment, including topical corticosteroids with vitamin D analogs, long-term use of oral acitretin, 2 months of oral cyclosporine, and 8 months of oral methotrexate, her psoriasis remained difficult to control. She developed nail changes (Fig. 1b) and experienced several episodes of psoriasis flares, with scaly plaques coalescing to involve extensive areas of the back and lower limbs. During outpatient follow-up, we performed a skin biopsy to confirm the diagnosis of psoriasis. Histopathology demonstrated hyperkeratosis, focal parakeratosis with regular acanthosis, neutrophil aggregation in the parakeratotic layer forming Munro's microabscesses, and superficial perivascular lymphocytic infiltration in the dermis, findings supportive of the diagnosis of psoriasis (Fig. 1c, d).

Due to exacerbation of psoriasis, with the Psoriasis Area and Severity Index (PASI) score increasing from 18.6 to 39.2, the patient was started on ustekinumab 45 mg administered every 3 months. However, after 16 months, the patient still did not achieve PASI 75, and she experienced another psoriasis flare-up. Consequently, the biologic therapy was switched to guselkumab 100 mg administered every 2 months. The patient initially achieved PASI 50; however, after four doses, another psoriasis flare-up occurred. Following unsuccessful attempts to control psoriasis, we switched to brodalumab 210 mg administered every 2 weeks, based on its indication as a viable alternative for psoriasis patients that have failed to respond to tumor necrosis factor (TNF)-α, IL-12/23, or IL-17 inhibitors. After five doses of brodalumab, the patient successfully achieved PASI 90. Nonetheless, after 18 doses of brodalumab, she developed multiple tender nodules on her back and lower extremities. She also experienced fever up to 39 °C and night sweats. On physical examination, there were erythematous-violaceous subcutaneous nodules and deeply infiltrated plaques involving the left side of the back and bilateral shins (Fig. 2a, b).

Given that these skin lesions differed from her previous presentation, we immediately discontinued brodalumab and arranged a skin biopsy. Histopathological examination of the biopsy from the left upper back subcutaneous nodule revealed infiltration of

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atypical lymphocytes of variable sizes with irregular and hyperchromatic nuclei in the subcutaneous fat lobules, along with rimming of adipocytes (Fig. 2c, d). No evidence of dermal or epidermal infiltration was observed. Immunohistochemically, the atypical lymphocytes were positive for CD43, CD3, CD8, T-cell intracellular antigen (TIA)-1, and T-cell receptor (TCR)-βF1, but negative for CD20, CD4, CD56, and TCR-δ (Fig. 3). Based on these pathologic findings, a diagnosis of SPTCL was made. Furthermore, the patient developed HLH during hospitalization. She satisfied five of eight HLH-2004 diagnostic criteria, including fever over 38.5 °C for more than 7 days, neutropenia and anemia, hypertriglyceridemia (545 mg/dl; normal < 150), hyperferritinemia (3,957 ng/ml; normal < 300), and hemophagocytosis in trephine biopsy. Genetic analysis revealed no hepatitis A virus cellular receptor 2 mutation. After confirming the diagnosis of SPTCL with HLH, the patient was initially treated with dexamethasone, cyclosporine A, and etoposide according to the HLH-94 protocol (6). Subsequently, she received two courses of cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisolone for SPTCL. The systemic symptoms improved, along with some decrease in skin lesions. The patient continues to receive regular treatment and is scheduled to undergo allogeneic hematopoietic stem cell transplantation at our medical oncology department.

Discussion

To our knowledge, this is the first well-documented case of SPTCL occurring in a psoriasis patient, confirmed clinically and histopathologically. Although few cases link SPTCL with biologics (7, 8), this is the first known case of SPTCL developing after successive treatment with ustekinumab, guselkumab, and brodalumab for psoriasis. The development of SPTCL after brodalumab treatment is particularly noteworthy. Although randomized and retrospective studies have concluded that malignancy rates among brodalumab-treated patients are generally low (9), it is worth noting that, to date, the biologics that have been validated to increase certain cancer risks are primarily TNF- α inhibitors (10). Nevertheless, concerns remain regarding the potential cancer risk associated with IL inhibitors. For instance, IL-12 is involved in antitumor immunity by activating antitumor effector cells and inhibiting the proliferation of intertumoral regulatory T cells. In addition, IL-12 helps keep cancer cells in a state of equilibrium, where they remain dormant instead of becoming metastatic. Supporting this function of IL-12 in cancer surveillance, a preclinical model showed that blocking IL-12/23p40 led to increased tumor growth (11). As for IL-17, in addition to its protumoral functions, it is also crucial in antitumor immunity. Research has demonstrated

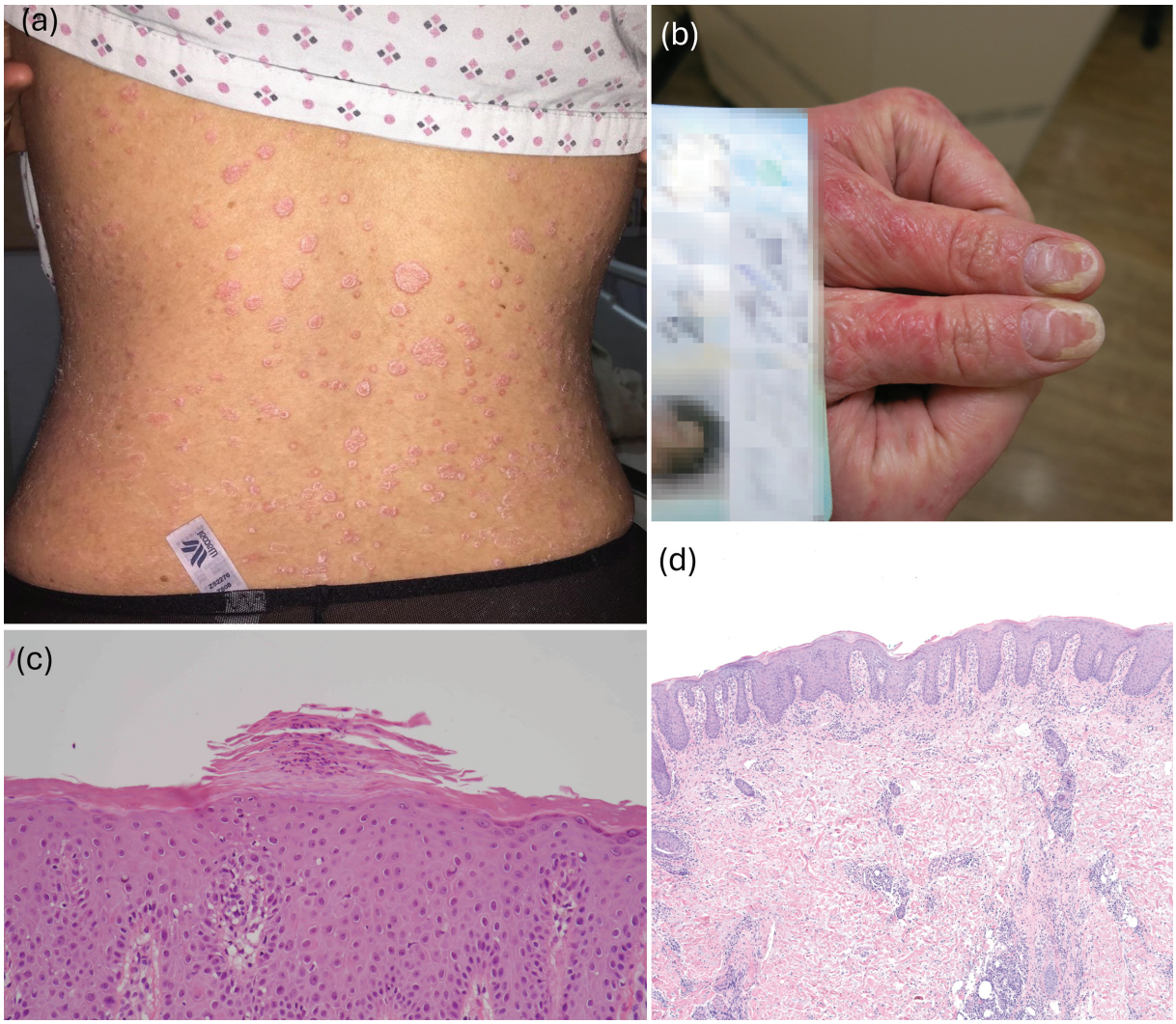


Figure 1 | (a) Clinical image showing well-defined, erythematous, salmon-pink scaly papules and plaques on the patient's back; (b) nail changes including pitting, onycholysis, and Beau's lines; (c, d) histopathological findings demonstrating regular psoriasiform acanthosis and parakeratosis with neutrophil aggregation on hematoxylin and eosin staining at 40× and 200× magnification.

that IL-17 can enhance antitumor immune responses in immunocompetent murine models (12). In the context of hematological malignancies, IL-17 has been observed to promote the development of specific cytotoxic T lymphocytes, contributing to the establishment of tumor-protective immunity (13). In addition, studies involving the transfection of human IL-17 genes into Meth-A cells have revealed that IL-17 can induce tumor-specific antitumor immunity by enhancing the expression of both major histocompatibility complex (MHC) class I and II antigens (14). Notably, during the acute phase of tumor progression, IL-17 also plays a crucial role in antitumor activity, primarily through its ability to stimulate tumor-specific cytotoxic T lymphocytes. Consequently, the dual nature of IL-17 in both promoting and inhibiting tumor growth underscores the complexity of its role in cancer biology. Moreover, an animal study demonstrated that a defective IL-17/IL-17 receptor A signaling pathway impaired antitumor CD8+ T cell immunity in murine models of melanoma and lymphoma, although its role in tumor progression remains unclear (5). Recently, a few reports have documented unusual adverse effects associated with brodalumab. A very recent, still unpublished retrospective study analyzing the Food and Drug Administration Adverse Event Reporting System database reports a mucosa-associated lymphoid tissue (MALT) lymphoma reporting odds ratio of 63.94 among patients under brodalumab treatment (3). This presents strong adverse drug event signals, suggesting that brodalumab has a higher signal intensity associated with the development of MALT lymphoma. Moreover, two case reports documented the emergence of pyoderma gangrenosum in psoriasis patients after switching biologics to brodalumab, which collectively showed a paradoxical response to brodalumab, leading to a higher degree of neutrophil activation (15, 16). Other instances of unique side effects reported during brodalumab treatment include subcutaneous lupus, sarcoidosis, palmoplantar pustulosis, and alopecia areata (17). Although our case may represent a patient susceptible to developing lymphomas due to recalcitrant inflammatory disease, and a causal relationship cannot be definitively established based

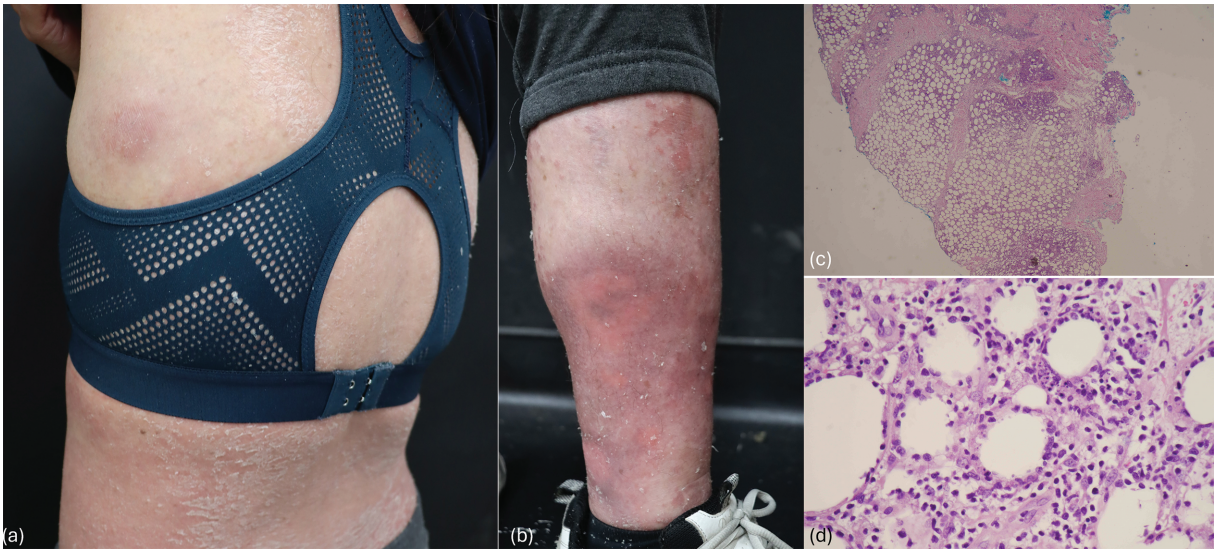


Figure 2 | (a, b) Clinical image of erythematous-violaceous subcutaneous nodules and deeply infiltrated plaques involving the left side of the back and left shin; (c) histopathology revealing atypical lymphocytic infiltrate in the subcutaneous fat lobules, with sparing of the septa, on hematoxylin and eosin staining at 20× magnification; (d) rimming of adipocytes by atypical lymphocytes with hyperchromatic nuclei, irregular nuclear membranes, and variable sizes on hematoxylin and eosin staining at 400× magnification.

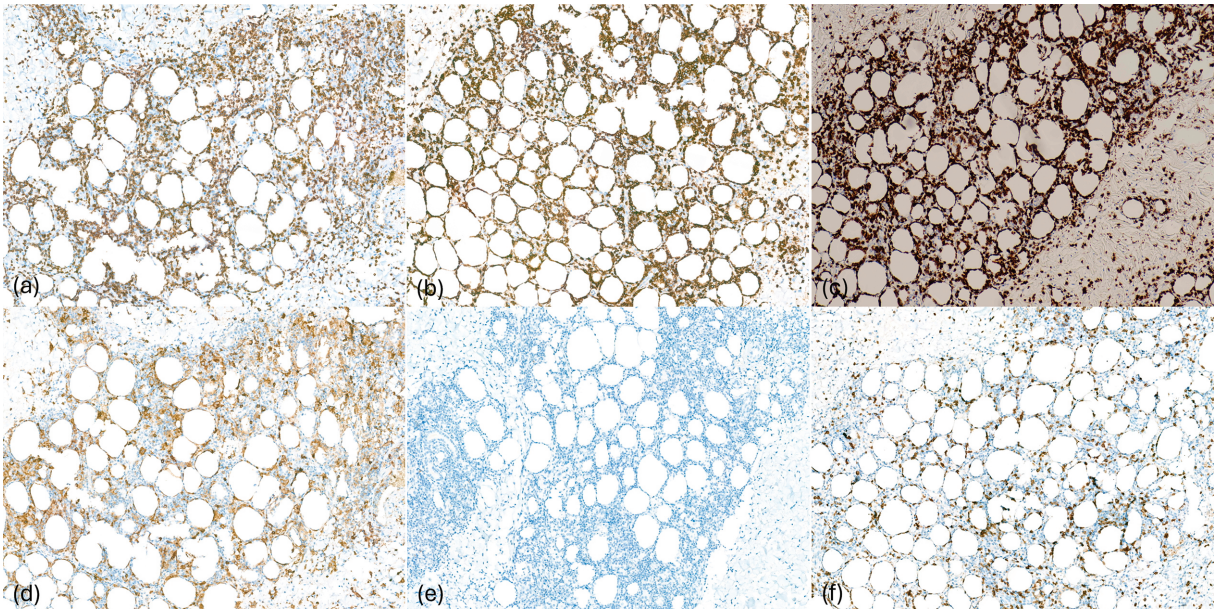


Figure 3 | (a–c) Immunohistochemistry for CD3, CD8, and T-cell receptor (TCR)-βF1 showing positivity in the neoplastic lymphocytes at 100× magnification; (d–f) immunohistochemistry for CD4, CD56, and TCR-δ showing negativity in the neoplastic lymphocytes at 100× magnification.

on a single case, the occurrence of SPTCL after extended brodalumab treatment in a psoriasis patient raises important questions about the unique adverse drug effects of IL-17 inhibitors.

Despite the development of SPTCL during brodalumab treatment, this case raises broader considerations about the safety of patients undergoing multiple successive biologic switches in psoriasis management. Although biologics have revolutionized treatment of moderate-to-severe psoriasis, our understanding of their long-term effects and rare complications continues to evolve. To date, studies on biologic switching have primarily focused on drug efficacy, with research on the safety and long-term effects of multiple switches being notably scarce. The development of SPTCL in this patient, following treatments with ustekinumab, guselkumab, and brodalumab, emphasizes the need for ongoing pharmacovigilance. Furthermore, the distinctly different presentation of SPTCL compared to the patient's previous psoriatic lesions, and the timely biopsy leading to a diagnosis of SPTCL and associated HLH, underline the need for dermatologists to be highly alert to unusual skin manifestations in patients on biologics.

Conclusions

This case report presents the first detailed documentation of SPTCL with HLH in a psoriasis patient, occurring after 9 months of brodalumab treatment following multiple biologic switches. This case contributes to the growing body of evidence suggesting that careful monitoring for unexpected complications is warranted in patients receiving brodalumab or undergoing multiple biologic switches. It also highlights the critical importance of performing skin biopsies when new or atypical lesions develop during biologic therapy.

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