Bullous Sweet's Syndrome and Pseudolymphoma Precipitated by IL-2 Therapy

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IL-2 is a key cytokine in cell-mediated immunity and currently is used in clinical trials as immunologic therapy in human immunodeficiency virus (HIV)–positive patients. Although cutaneous reactions to IL-2 therapy are common, bullous reactions are rare. We report a case of an HIV-positive patient who received multiple cycles of IL-2 therapy and developed a bullous eruption soon after each cycle was initiated. Pathology results from 2 separate outbreaks revealed a diffuse dermal neutrophilic infiltrate with leukocytoclasis. Epidermal spongiosis and focal intraepidermal vesiculation also were present. The patient discontinued IL-2 therapy but restarted 5 years later, at which time he presented with a pseudolymphomatous reaction that resolved after discontinuation of therapy. This patient is an unusual case of 2 different eruptions—Sweet's syndrome and pseudolymphoma—precipitated by IL-2 therapy in the same patient. Cutaneous eruptions to IL-2 therapy also are reviewed.

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Case Report

A 46-year-old human immunodeficiency virus (HIV)–positive man was being treated with IL-2 therapy within a clinical trial investigating the effects of IL-2 on HIV disease progression. He was scheduled for 1 cycle of IL-2 every 2 months. Each cycle consisted of 2 subcutaneous injections daily for 5 days. The Table delineates IL-2 doses received. The injection site was the abdominal area.

The patient developed a bullous eruption on the lower extremities during his first 2 cycles of IL-2 therapy, each time approximately 2 to 3 days after beginning a cycle. These blisters were treated outside of the dermatology department with gauze and bacitracin, and he was able to complete the full course of IL-2 each time.

During the third IL-2 cycle, the patient noted blisters after the first injection that increased in severity as he continued therapy. He presented to the dermatology department after completing 4 of 10 scheduled IL-2 injections in his third cycle with blisters on the arms and legs. There was no pruritus. On review of systems, he indicated that he had been having fevers and fatigue with each IL-2 cycle, which were expected side effects; he was taking acetaminophen to counteract these symptoms. There were no arthritic symptoms. His medical history was notable for HIV diagnosed in 1996, allergic rhinitis, sickle cell trait, and right inguinal hernia repair. There was no history of any notable skin disorder, except for allergies to shellfish/seafood manifested by swelling. Other medications included didanosine, stavudine, and efavirenz; acetaminophen, prochlorperazine maleate, and pseudoephedrine hydrochloride–chlorpheniramine maleate were taken as needed. On physical examination, erythematous blanchable patches and plaques were scattered on the arms and legs. Multiple tense bullae, ranging in size from pinpoint to 1 cm, were scattered along the extensor arms, inner thighs, and calves. Results of a punch biopsy revealed a diffuse dense neutrophilic infiltrate. Leukocytoclasis was present but no vasculitis. Occasional eosinophils and lymphocytes also were present. The epidermis revealed

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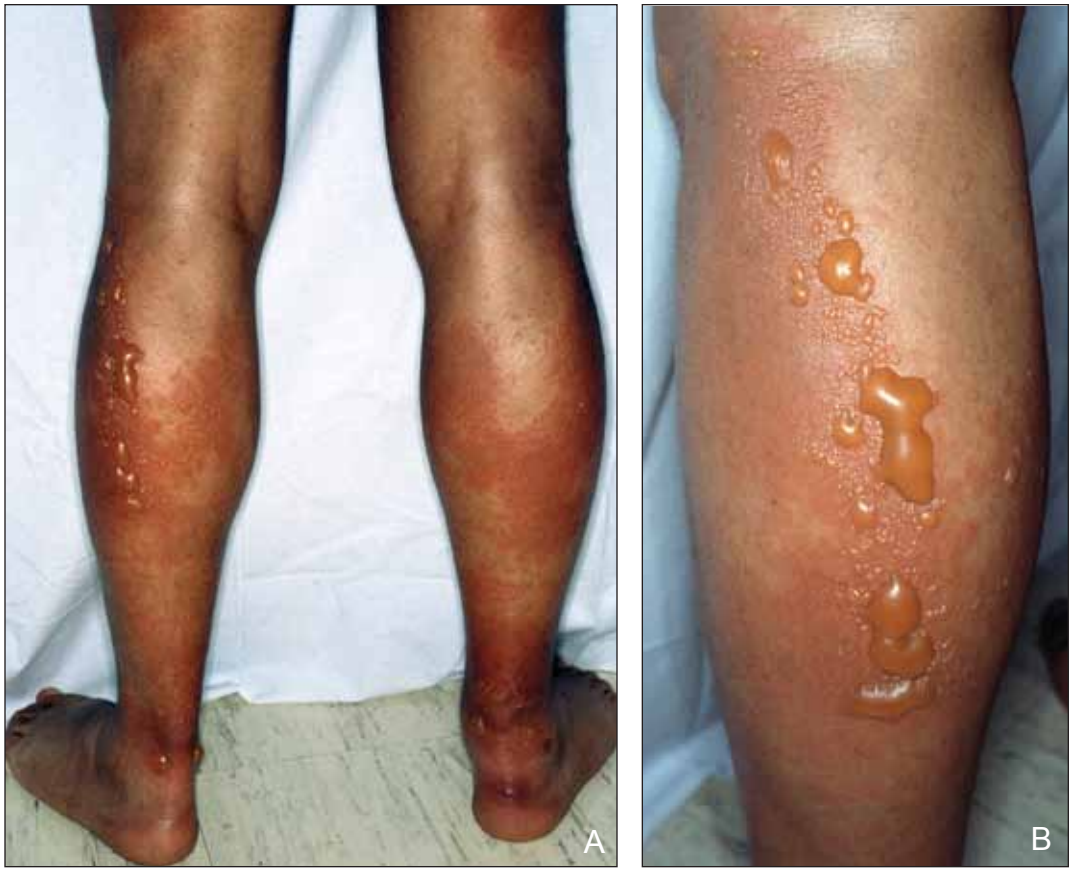

Figure 1. Erythematous edematous plaques with tense bullae on the lower legs of a patient on the third day of IL-2 therapy (fourth cycle) (A and B).

spongiosis and focal intraepidermal vesiculation. The patient was relatively asymptomatic from the eruption and completed the remaining 3 days of his IL-2 cycle. He was treated with triamcinolone acetonide ointment 0.1% twice daily and gauze dressings. At 1-week follow-up vesicles and bullae were no longer present. Some mild erythema, desquamation, and postinflammatory hyperpigmentation (PIH) remained. At 2-month follow-up only some PIH was present.

Nine months after the start of the third IL-2 cycle, the patient decided to reenter the IL-2 trial and he began a fourth cycle of IL-2 therapy. On day 3 of his fourth cycle, he again developed blisters on the lower legs. On physical examination, widespread erythematous edematous plaques were present on the arms and legs with tense bullae on the calves (Figure 1). There was no pitting edema of the lower extremities. The scalp, face, conjunctivae, palms, soles, and trunk were clear except for some erythema on his abdomen at the IL-2 injection site. Pathology results again revealed a diffuse infiltrate of neutrophils and eosinophils in the dermis with diffuse neutrophilic debris (Figure 2). No vasculitis was identified. Intraepidermal vesicles containing neutrophils and rare eosinophils were present at different levels of the epidermis. Epidermal spongiosis also was present. Direct immunofluorescence was

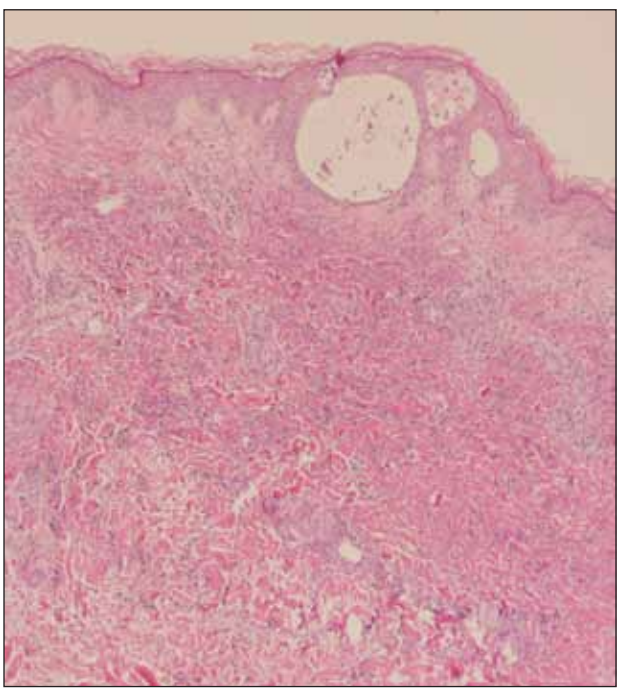

Figure 2. Pathology results revealed a diffuse infiltrate of neutrophils and eosinophils in the dermis with diffuse neutrophilic debris. No vasculitis was identified. Intraepidermal vesicles containing neutrophils and rare eosinophils were present at different levels of the epidermis, along with epidermal spongiosis (H&E, original magnification ×40).

Laboratory Data and IL-2 Dosing for Each IL-2 Cycle

IL-2 Cycle	IL-2 Dose Per Injection, million units	Increase in CD4 Lymphocyte Count	WBC,[a] $\times 10^3/\mu L$	Neutrophils, %	Eosinophils, %
1	7.5	168	12.7	70	7
2	7.5 (injections 1–8); 6.0 (injections 9–10)	406	11.7	73	11
3	6.0	187	N/A	N/A	N/A
4	4.5 (injections 1–5); then discontinued	411	8.9	73	9
5[b]	4.5	989	10.4	51	0

Abbreviations: WBC, white blood cell count; N/A, not available.
[a]Reference range, 3.8–10.6$\times 10^3/\mu L$.
[b]Five years later.

nonspecific with only C3 staining in the blood vessels. Because of the increased severity of his eruption with this cycle, we recommended terminating the IL-2 therapy. Fluocinonide ointment 0.05% applied twice daily along with local wound care was prescribed. The patient was much improved 3 days later. Although some bullae remained, he had not developed any new blisters in the interim. At 10-day follow-up all the bullae had resolved with only mild desquamation and PIH remaining.

The patient was off IL-2 therapy for almost 5 years (57 months). After that time period, he restarted IL-2 clinical trial protocol and received 4.5 million units of IL-2 subcutaneously twice daily for 5 days. On day 3 of therapy, he developed a rash but continued to complete his course of IL-2. He presented to our clinic 3 days after completing IL-2 with a pruritic rash over his body that had been improving since he completed the round of therapy. In addition, large hard bumps had developed at each of his IL-2 injection sites. This current reaction was not bullous and had not occurred with his prior courses of IL-2. On physical examination, erythematous macules in a somewhat reticulated pattern were scattered over his chest, back, posterior arms, and anterior legs. Over his abdomen there were 6 firm erythematous nodules, each approximately 2 cm in diameter (Figure 3). No lymphadenopathy was noted. A biopsy was taken from a large nodule near an injection site on his abdomen. Pathology results showed an atypical lymphoid infiltrate (Figure 4) with a predominantly $CD8^+$ T-cell population and smaller proportion of $CD4^+$ T cells. T-cell receptor gene rearrangement, L26, BerH2, and CD30 stains were negative. The patient was diagnosed with a pseudolymphomatous drug reaction to IL-2. He was taken off IL-2 clinical trial protocol and was treated with triamcinolone acetonide ointment 0.1%. At 8-day follow-up his erythematous eruption had resolved; 3 of 6 nodules had resolved, and the 3 remaining nodules were smaller.

Laboratory Data—Laboratory findings included a slight elevation in white blood cell count and mild leukocytosis (Table). Slight eosinophilia also was noted. His CD4 lymphocyte count increased after each cycle of IL-2 therapy.

Comment

IL-2 is a T cell–derived cytokine that that was originally identified in 1976 and is important for the initiation, development, and regulation of the immune response. It works to induce T cell, B cell, and natural killer cell proliferation and activation; neutrophil adhesion and chemotaxis; and activation of monocytes and macrophages. The main function of IL-2 is to promote the proliferation of T cells after antigen stimulation and to stimulate the production of lymphokine-activated killer cells (LAKs), which act against tumor cells. Currently, clinical trials are underway investigating the efficacy of subcutaneous IL-2 in patients with HIV.[1,2] Intravenous IL-2 (aldesleukin) is approved by the US Food and

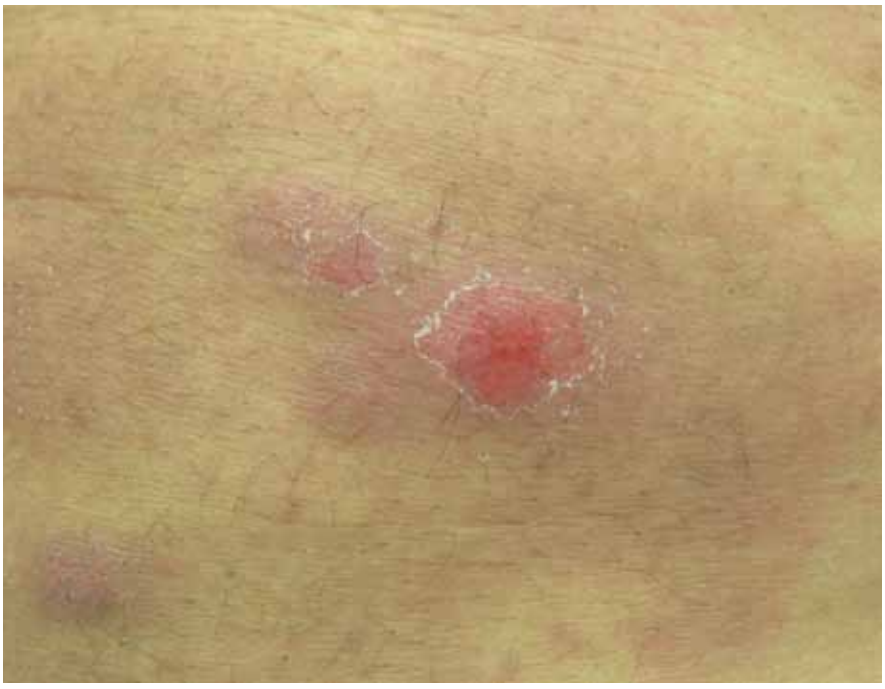

Figure 3. Five years later, the patient developed firm erythematous nodules within urticarial-type plaques at injection sites on the abdomen.

Drug Administration for the treatment of metastatic renal cell carcinoma and metastatic melanoma. It also is used as an adjuvant to chemotherapy for other tumors. Additionally, IL-2 also has been investigated for the treatment of lepromatous leprosy via intradermal injection.[3]

General Toxicities—IL-2 has notable toxicities related to its use, including fatigue, malaise, hypotension, nausea, vomiting, diarrhea, neutropenia, thrombocytopenia, renal dysfunction, and hepatoxicity. Sepsis, especially if a central venous catheter is in place, can be seen, which may be attributed to a deficiency of neutrophil chemotaxis induced by IL-2.[4] Additionally, IL-2 can induce a low-grade fever, presumably by the release of pyogenic cytokines, such as tumor necrosis factor α and interferon-γ.[5] Intravenous route of administration and higher doses are associated with more severe toxicities.

Common Cutaneous Eruptions—Cutaneous eruptions due to IL-2 therapy are common. Nondermatologic literature quotes "rash" rates of IL-2 infusions to be 20% to 100% with differences in the severity of the cutaneous reactions being dose and schedule related. In addition, a serious toxicity known as capillary leak syndrome or vascular leak syndrome frequently is seen with IL-2 therapy and is characterized by increased permeability of the endothelial cells with resultant extravasation of plasma proteins and fluid into the extravascular space. The patient may develop generalized edema as well as pulmonary edema, angina, myocardial infarction, cardiac arrhythmia, congestive heart failure, or neurologic and mental status changes.[5]

Several studies have been performed to investigate the cutaneous reactions associated with IL-2 therapy. One study by Wolkenstein et al[6] looked at 25 patients who collectively received 78 cycles of intravenous IL-2 for metastatic melanoma. Fifty-six cycles (72%) in 24 patients were associated with cutaneous eruptions. Only 1 of 25 patients did not experience a cutaneous reaction and this patient received a single cycle of low-dose IL-2. The eruptions occurred within 36 to 72 hours of beginning the IL-2 infusion. The height of most eruptions occurred on the last day of the cycle. Fifty-three of these eruptions (95%) were defined as mild, consisting of generalized erythema, pruritus, and burning. Petechiae of the lower legs occurred in 7% of the cycles, and edema of the face, palms, or soles occurred in 2% of the cycles. Regression of erythema with no cutaneous sequelae occurred in all cases after discontinuation of IL-2 therapy. Repeated cycles did not increase the cutaneous toxicity of IL-2.[6]

A study by Gaspari et al[7] prospectively looked at 10 patients with cancer receiving intravenous IL-2 and LAKs. These patients received IL-2 for 4 to 5 days, had a week off, and then received 4 days of IL-2 and LAKs. Punch biopsies in all patients were done before therapy and at the height of the eruption, either on day 5 of the IL-2 infusion or day 2 of the IL-2–LAK infusion. All 10 patients developed erythema and pruritus: 4 patients experienced mild localized erythema of the face, neck, and chest;

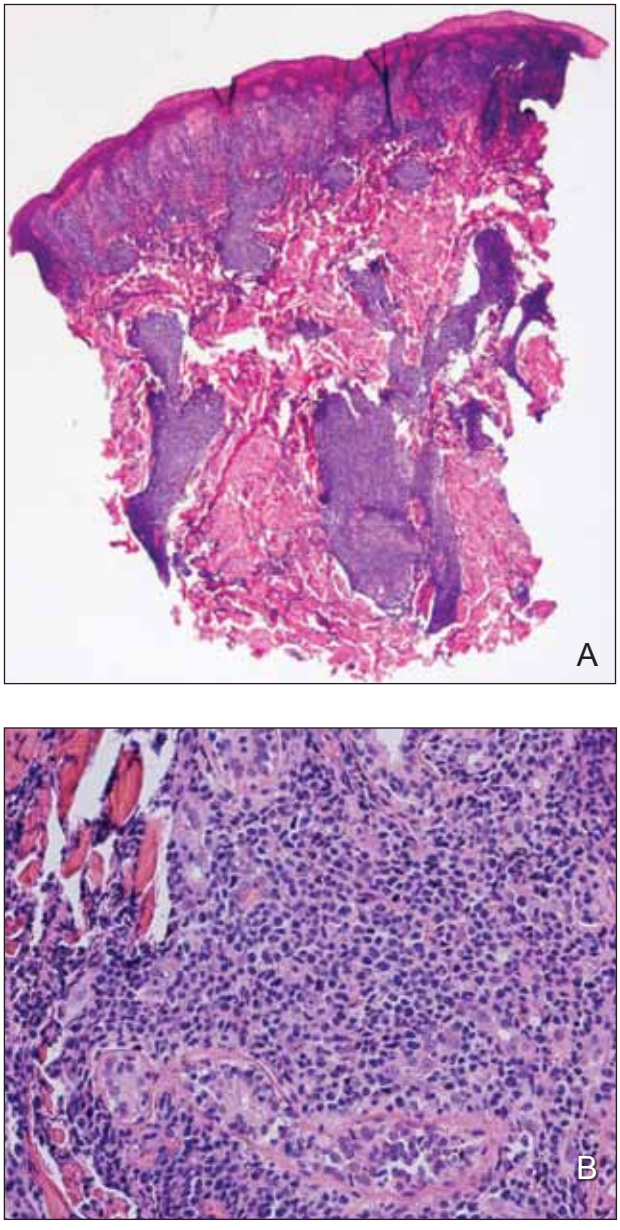

Figure 4. Pathology results from a firm nodule showed a dense atypical lymphoid infiltrate (A and B)(H&E; original magnifications ×20 and ×100, respectively).

5 patients developed generalized erythema; and 1 patient developed total body erythroderma. These eruptions started 48 to 72 hours after the end of the initial infusion and peaked at day 5 of IL-2 therapy. Erythema resolved within 48 hours of stopping the IL-2, followed by desquamation of the involved areas. The patients were symptomatically controlled with oral antihistamines and emollients. Complete resolution of the cutaneous eruption occurred in all patients within 2 to 3 weeks. The biopsy results showed spongiotic foci in the epidermis, exocytosis of mononuclear cells, focal basal vacuolar changes, rare scattered necrotic keratinocytes, mild dermal edema, and mild to moderate perivascular mononuclear cell infiltrates. These histologic changes only differed from patient to patient in severity, not in character. In addition, there was no difference noted between the histologic changes produced by the IL-2 infusion alone compared to the combined IL-2–LAK infusion, suggesting that IL-2 is responsible for these changes.[7]

In summary, cutaneous reactions to IL-2 therapy are common. Generalized erythema, pruritus, or burning can be expected to present within 48 to 96 hours after the initiation of IL-2 infusions. Resolution of these signs and symptoms should be expected within days after discontinuing IL-2, with possible subsequent desquamation. Additionally, patients should be monitored for any signs or symptoms of capillary leak syndrome.

Mucosal Involvement—In addition to cutaneous reactions to IL-2 therapy, patients also may experience mucosal involvement. In the Wolkenstein et al[6] series, 15% of cycles were associated with mucosal involvement characterized by mild glossitis, loss of lingual papillae, or painful erosions of the buccal mucosa. Gaspari et al[7] documented 7 additional patients that experienced mucosal reactions: 6 patients developed glossitis characterized by erythema, edema, and tenderness of the tongue, and 1 patient developed aphthous ulcerations of the buccal mucosa.

Hypersensitivity Reactions—An increased incidence of hypersensitivity reactions to contrast media after IL-2 therapy has been reported. Shulman et al[8] reported 70 patients receiving high-dose intravenous IL-2 for metastatic renal cell carcinoma or metastatic melanoma. Of the 74 computed tomography scans that were performed prior to IL-2 administration, no reactions to the contrast media were reported; however, 9 reactions were reported after the IL-2 therapy. These 9 reactions occurred 1 to 4 hours after the contrast media infusion and consisted of fever, chills, emesis, diarrhea, rash, wheezing, hypotension, edema, and oliguria. This study concluded that patients are at highest risk for a contrast media reaction within 2 weeks of IL-2 therapy and contrast administration should be avoided soon after IL-2 therapy.[8]

Exacerbation of Psoriasis—IL-2 administration has been associated with psoriasis flares. In a report by Lee et al,[9] 3 patients receiving IL-2 alone or combined IL-2–LAK therapy were noted to have a recurrence of their psoriasis: 2 patients developed an erythrodermic exacerbation and 1 patient developed a localized flare. All patients had resolution of their

lesions after discontinuation of IL-2 therapy and standard psoriasis treatment.[9] In the case series by Gaspari et al,[7] an additional 2 patients had erythrodermic flares in previously localized psoriasis while on IL-2 therapy. Lee et al[9] proposed that because exacerbations of psoriasis do not interfere with the antitumor response of the IL-2 therapy, it should not be considered a contraindication to treatment.

Bullous Eruptions—Although cutaneous reactions to IL-2 therapy are common, bullous reactions are rare. No prior case of IL-2–induced Sweet's syndrome has been reported, according to a PubMed search of articles indexed for MEDLINE using the terms *IL-2* (IL-2 or interleukin-2) and *Sweet's syndrome* (Sweet's syndrome, Sweet syndrome, acute febrile neutrophilic dermatosis, or Sweet disease). Few cases of bullous eruptions have been described. One case of fatal pemphigus vulgaris was reported in a patient who received IL-2 and interferon beta for poorly differentiated lymphocytic lymphoma.[10] A case of recurrent pemphigus vulgaris after IL-2 therapy for metastatic renal cell carcinoma also has been reported. This patient had been in remission for 10 years prior to IL-2 therapy.[11] Two cases of linear IgA bullous dermatosis have been associated with IL-2 therapy.[12,13] Staunton et al[14] reported 2 cases of rapidly progressive, life-threatening bullous skin eruptions. Pathology results revealed subepidermal blisters with neutrophilic and eosinophilic dermal infiltrates, and both direct and indirect immunofluorescence were negative.[14] Wolkenstein et al[6] reported 1 patient receiving IL-2 for metastatic melanoma who developed tense blisters with erythroderma on the legs. Pathology results showed severe epidermal necrosis and microvasculitis, and direct immunofluorescence was negative.[6] Hofmann et al[15] reported another case of tense bullae after IL-2 therapy for metastatic melanoma. Pathology results showed a diffuse neutrophilic infiltrate with separation of the epidermis from dermis, and both direct and indirect immunofluorescence were negative.[15] Wiener et al[16] reported a case of flaccid bullae resembling toxic epidermal necrolysis in which the patient developed rapidly spreading erythema and pinpoint pustules that resulted in superficial sloughing of large sheets of skin (estimated 75% body surface area). Histologic findings revealed subcorneal bullae, absence of acantholysis, and a prominent infiltrate of neutrophils within the epidermis and dermis.[16] A case of multifocal fixed drug eruption during IL-2 therapy for metastatic renal cell carcinoma also reported a bullous morphology in some lesions.[17] Brun Romero and Terrón Pernía[18] reported a case of bullae developing only at IL-2 injection sites in an HIV-positive woman on IL-2 for HIV therapy. Asnis et al[19] reported erythroderma and superficial bullae seen in a patient undergoing IL-2 and interferon alfa for metastatic renal cell carcinoma. No pathology was reported in these last 2 cases.[18,19]

In addition to these prior reports of IL-2–associated bullous eruptions, our patient had a clinicopathologic presentation of Sweet's syndrome. Interestingly, of the previously described bullous cases with negative immunofluorescence, the majority of them also have a neutrophilic infiltrate.

Sweet's syndrome, or acute febrile neutrophilic dermatosis, was first described in 1964 by Robert Douglas Sweet, MD,[20] and is characterized by fever, neutrophilic leukocytosis, and an abrupt onset of painful erythematous plaques or nodules, occasionally with vesicles, bullae, or pustules. Histologically, lesions consist of dense neutrophilic infiltrates of the upper dermis without leukocytoclastic vasculitis.[21] Associated conditions include acute myelogenous leukemia and less frequently other hematologic and solid malignancies. The use of certain medications has been associated with Sweet's syndrome, including minocycline,[22] oral contraceptives,[23] granulocyte colony-stimulating factor,[24] all-*trans*-retinoic acid,[25] hydralazine hydrochloride,[26] nitrofurantoin,[27] abacavir sulfate,[28] celecoxib,[29] furosemide,[30] imatinib mesylate,[31] diazepam,[32] and clindamycin.[33] Few cases of Sweet's syndrome in HIV-positive patients have been reported.[34-36] In our patient, it was believed that the eruption was secondary to IL-2 therapy rather than HIV infection given the consistent temporal relationship with IL-2 therapy.

The etiology of Sweet's syndrome is unknown. A study of cytokines in patients with Sweet's syndrome found elevated levels of IL-1, IL-2, and interferon-γ, suggesting possible involvement of type 1 helper T cells (T_H1).[37] IL-2 therapy also has been associated with a chemotactic defect in neutrophils.[38] The exact role of these cytokines in the pathogenesis of Sweet's syndrome has not been elucidated.

Pseudolymphomatous Reaction—Interestingly, after a 5-year hiatus, our patient did not develop bullous Sweet's syndrome to IL-2 but a different cutaneous eruption consistent with pseudolymphoma at injection sites. No other cases of pseudolymphoma developing in response to IL-2 therapy have been reported. Two other reports in the literature describe nodules forming at IL-2 injection sites. Klapholz et al[39] reported 5 patients with non-Hodgkin or Hodgkin lymphoma who developed painful inflamed nodules at IL-2 injection sites while on IL-2 and interferon alfa. Pathology results showed subcorneal neutrophils, vacuolar basal layer change, and superficial and deep perivascular and interstitial

lymphocytic infiltrate, which was interpreted as a fixed drug eruption.[39] Baars et al[40] presented the case of a 40-year-old woman with metastatic renal cell carcinoma who developed lymphocytic lobular panniculitis at IL-2 injection sites. Interestingly, these reactions with a nodular morphology have more of a lymphocytic rather than a neutrophilic infiltrate.

In our patient, it is possible that his immune profile changed during the 5-year hiatus, which led to a change in his response. Alternatively, a better response to treatment, with the increase in his absolute CD4 lymphocyte count being greatest during his last IL-2 cycle, may have contributed to the pseudolymphomatous response.

Conclusion

We report an unusual case of Sweet's syndrome and pseudolymphoma developing in response to IL-2 therapy for HIV disease. While cutaneous eruptions characterized by erythema, pruritus, or burning are common with IL-2 therapy, clinicians should keep in mind the rarer reactions that can present with bullous or nodular morphology.

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