

## The Cutting Edge

# Clinical Remission of Primary Aggressive CD8<sup>+</sup> Cutaneous T-Cell Lymphoma After Pralatrexate Infusion

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**Primary aggressive CD8<sup>+</sup> cutaneous** T-cell lymphoma (CTCL) is a rare, rapidly progressive peripheral cutaneous malignant condition. The rapid progression is accompanied by a dismal prognosis, despite attempts to treat with multiple treatment regimens. Herein, we report a case of primary aggressive CD8<sup>+</sup> CTCL that successfully responded to pralatrexate.

## Report of a Case

A white male patient in his 60s developed pruritic and painful plaques over his upper body. His medical history included Wegner granulomatosis, which was successfully treated with cyclophosphamide in 2006. He took no medications daily and denied any drug allergies.

A drug-related cutaneous eruption was considered at the initial evaluation, and sequential courses of corticosteroids and antibiotics for secondary impetiginization were prescribed. Biopsy specimens were sent for hematoxylin-eosin staining and direct immunofluorescence. Hematoxylin-eosin staining revealed mild epidermal spongiosis with focal vacuolar alteration along the dermoepidermal junction, dyskeratotic cells, focal exocytosis of lymphocytes, extravasated erythrocytes and superficial polymor-

phous infiltrate, parakeratosis, and intracorneal neutrophils. Immunostains showed a CD3<sup>+</sup> population with a 1:1 ratio of CD4 and CD8<sup>+</sup> cells. Results from direct immunofluorescence were negative. Overall, findings favored an acute interface inflammatory process.

The eruption progressed over months into erosions and ulcers with tumors (**Figure 1**) involving oral mucosa but sparing palms and soles. Repeated biopsies for hematoxylin-eosin staining and direct immunofluorescence ruled out a pemphigus-related disorder. The patient also appeared clinically septic and complained of malaise, anorexia, and severe pain in the skin. He was admitted for sepsis at a local hospital, underwent fluid resuscitation, and received intravenous antibiotics. Repeated biopsies showed an upper dermal bandlike CD8-predominant lymphocytic infiltrate associated with papillary dermal fibrosis and focal epidermotropism with atypia. Immunostains showed an inverted ratio of CD4 to CD8 (1:1-2), with mild decreases in CD7 and CD3 levels, and few epidermotropic CD30<sup>+</sup> cells. CD56 and granzyme B stained mononuclear cells, but there was no CD57 staining. Insufficient tissue precluded T-cell rearrangement studies. Although our differential included Mucha-Habermann disease, clinicopathologic correlation favored primary aggressive CD8<sup>+</sup> cutaneous T-cell lymphoma (CTCL)—specifically, the patient did not develop fever until months later; cutaneous lesions did not resolve spontaneously; several tumors developed on the skin; and arthritis, hemoptysis, or gastrointestinal tract bleeding were absent; however, oral mucosa was affected.

Findings from flow cytometry showed no evidence of lymphoproliferative disorder, and a positron emission tomography-computer tomography (PET/CT) scan demonstrated skin involvement without nodal or visceral involvement.

## Therapeutic Challenge

The challenge was to identify a treatment that might offer a chance of remission.

## Solution

Traditionally, advanced CTCL has been treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), with disappointing results. The track record with primary aggressive CD8<sup>+</sup> CTCL has been just as dismal. With no good therapeutic options, the patient's deteriorating clinical course convinced our team to consider the new systemic chemotherapeutic pralatrexate (Folotylin, Allos Therapeutics). He received a 30-mg/m<sup>2</sup> infusion of pralatrexate after folate and cyanocobalamin supplementation. Following the infusion, the patient developed numerous new ulcers over approximately 80% of his body surface area. The face and scalp were minimally affected, though the lower lip developed a hemorrhagic ulceration. The patient also developed neutropenia (absolute neutrophil count of 0.0/μL [normal >1500/μL]) and fever (39.0°C). These findings mirrored commonly reported Grade

Figure 1. Before Treatment



An initially pruritic eruption on the upper chest progressed to multiple painful ulcerated and eroded plaques, many with yellow crust.

3 and 4 adverse events, eg, thrombocytopenia (32%), mucosal inflammation (21%), neutropenia (20%), and anemia (17%) associated with a 30-mg/m<sup>2</sup> infusion.<sup>1</sup>

The patient was then transferred to the inpatient dermatology service at University of Miami Hospital to provide specialized cutaneous care. On arrival, the patient was given broad-spectrum antibiotics for neutropenic fever and daily filgrastim (Neupogen; Amgen Inc) injections, and he was encased in nonstick sheets with a warming blanket and covered with silver sulfadiazine paste (Silvadene cream [Hoechst Marion Roussel] mixed 1:1 with talcum powder) twice a day. Nursing left any dried paste that remained in place and reapplied paste to areas that showed visible denuded skin. A feeding tube was placed for hyperalimentation, with 2 calories per mL and advanced to 80 mL/h over 48 hours. Additional free water was given and adjusted based on daily laboratory values. This approach was adapted from the University of Miami's protocol for toxic epidermolytic necrosis.

After the patient stabilized clinically, we obtained biopsy specimens from healing skin and persistent ulcerations to determine whether the patient had benefitted from pralatrexate therapy. These biopsy results were negative for CTCL, and weekly pralatrexate infusions were restarted at a reduced dose (15 mg/m<sup>2</sup>) because of the severe adverse effects. The patient continued folate and cyanocobalamin supplementation. Because the patient experienced significant mucositis, we administered leucovorin calcium, 50 mg, every 6 hours for 6 doses starting 24 hours after pralatrexate infusion.

In total, 6 pralatrexate infusions were given (a single 30-mg/m<sup>2</sup> dose followed by five 15-mg/m<sup>2</sup> doses). The patient's skin continued to heal with supportive care and hyperalimentation. One month after discharge, 2 additional biopsy specimens of persistent ulcerations were read as negative for CTCL. At 7 months, the patient denied any new lesions and has received 2 additional 6-week infusion cycles of 15-mg/m<sup>2</sup> pralatrexate without incident (**Figure 2**). Currently, he is being monitored with clinical skin examinations and serial PET/CT scans for any hypermetabolic foci. There is no plan for further therapy unless new lesions are identified.

## Discussion

Primary aggressive CD8<sup>+</sup> CTCL is a recently recognized entity characterized by rapid progression over weeks to months of widespread tumors and/or plaques with painful ulceration of the skin, commonly with mucosal involvement.<sup>2</sup> Unlike classically indolent CTCL, metastasis is extranodal (lung, testis, central nervous system, and oral), and patients are often ill appearing. Despite dramatic clinical findings, diagnosis relies on histologic analysis to confirm, with hematoxylin-eosin demonstrating lymphocyte epidermotropism with nodular or diffuse T-cell infiltrate. While occasionally adnexal involvement, angiocentricity/angioinvasion, spongiosis or blistering, necrotic keratinocytes, and deep infiltration are seen, immunohistochemistry identifies a CD8<sup>+</sup> and CD4<sup>+</sup> population of T-cells cells with a high proliferation index (Ki-67) and CD2<sup>+</sup>/CD7<sup>+</sup>. T-cell receptor gene rearrangements can also be performed.

**Figure 2. After Treatment**



Seven months after his initial cycle of pralatrexate and aggressive supportive care, the patient's skin showed mild erythema and hyperpigmentation. Two biopsy skin specimens were negative for malignancy.

To stage a patient, PET/CT can identify often-reported early and distant metastases. Prognosis appears similar to stage IV melanoma, with 18% survival at 5 years, unlike mycosis fungoides, which is approximately 88%.<sup>3</sup>

Few therapies in managing primary aggressive CD8<sup>+</sup> CTCL have had much success. Traditional therapies used in treating CD4<sup>+</sup> CTCL, such as topical corticosteroids, chemotherapy, psoralen-UV-A, interferon alfa-2b, and photopheresis, are ineffective.<sup>1</sup> Bexarotene has been reported to stabilize more "indolent" cases that clinically progressed over a year or received concurrent total skin electron beam therapy. There is 1 case of allogeneic transplant resulting in remission after 17 months follow-up.<sup>4</sup>

Pralatrexate represents one of several potentially useful therapies for CD8<sup>+</sup> CTCL, including histone deacetylase inhibitors (eg, romidepsin).<sup>5</sup> Developed for refractory peripheral T-cell lymphomas, pralatrexate is a novel antineoplastic folate analogue that leverages fetal oncoprotein RFC-1 to enter the cell. Compared with methotrexate, pralatrexate is more than 10-fold more efficient and toxic to cells in *in vivo* studies.<sup>6</sup> In patients with CD4<sup>+</sup> CTCL, a recent phase 1 trial concluded that 15 mg/m<sup>2</sup> per week for 3 to 4 weeks was appropriate.<sup>7</sup>

This case represents, to our knowledge, the first reported use of pralatrexate in this condition. Our case report has demonstrated clinical remission and opens the door for treatment of this devastating disease. Further studies are warranted.

## ARTICLE INFORMATION

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## NOTABLE NOTES

### Joe DiMaggio's Glove

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Readers may ask: "What does the title 'Joe DiMaggio's Glove' have to do with dermatology?" The answer is found in the wonderful 1949 Rogers and Hammerstein musical "South Pacific." One of the show's most endearing characters is Bloody Mary, a Pacific Islander, about whom US Naval sailors sing: "Bloody Mary is the girl I love...Her skin is tender as DiMaggio's glove."

These lyrics not only remind us of the legendary New York Yankees center fielder, Joe DiMaggio, they also serve, through their skin and glove simile, as the introduction to a fascinating topic: the connection between dermatology and our national pastime: baseball.

Much praise goes to Shonda Schilling, wife of former pitching star Curt Schilling, for starting the Shade Foundation of America in 2002. Shonda and her foundation have promoted sun-safety awareness across the United States. Shonda herself was diagnosed as having malignant melanoma, stage 2, in 2001.

Several baseball players have been diagnosed as having malignant melanoma. One of the most heroic stories involved Jim Umbricht (1930-1964), who pitched for the Pittsburgh Pirates and the Houston Colts 45s. In 1963, Umbricht was diagnosed as having a melanoma on his right leg. He pitched the entire 1963 season, sometimes in excruciating pain. He died 6 months later.

In 2012, Baseball Hall of Fame catcher Johnny Bench was named the official spokesman for the Play Sun Smart program.<sup>1</sup> This endeavor represents a joint effort by Major League Baseball, its Players Association, and the American Academy of Dermatology to raise skin cancer awareness and offer prevention and detection tips to the baseball community. Bench himself was treated with Mohs surgery for basal cell carcinomas on both lower eyelids.

Special praise also goes to New York Mets baseball great Tom Seaver for speaking out about his battle with Lyme disease.<sup>2</sup> Seaver was first

diagnosed as having Lyme disease in 1991, when he presented with right-sided Bell palsy. In 2012, Seaver developed neurological symptoms, including memory loss and speech problems. He was diagnosed as having stage 3 Lyme disease. Fortunately, Seaver has improved with treatment.

In 1913, baseball player Jiggs Donahue died of neurosyphilis at age 34 years.<sup>3</sup> He had once played for the minor league Milwaukee Brewers team. His untimely death renewed fears about what was then called the "Milwaukee First Base Jinx." Other Milwaukee players cursed by the jinx were (1) Quait Bateman, nonfatally stabbed as a player; (2) Arthur Brown, murdered in 1911; and (3) Dan McGann, who died an apparent suicide in 1910. The jinx ended with Jiggs Donahue.

This note began with a song about Joe DiMaggio's glove and concludes with words from another New York Yankees star: Yogi Berra. Besides his baseball feats, Yogi is famous for making witty comments known as "Yogi-isms." The following example hopefully will inspire all of us to perfect our visual examination of the skin. According to Yogi: "You can observe a lot just by watchin'!"

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