Infections, autoimmune disease, bone marrow failure, medications, and total-body irradiation may induce CD4 lymphopenia, defined as a CD4 T-cell count below 300 cells/mL or less than 20% of total lymphocytes. Human immunodeficiency virus (HIV) is the most common cause of CD4 lymphopenia, with sepsis (bacterial and fungal) and postoperative states the most common causes in hospital settings. No underlying factors are found in 0.02% of CD4 lymphopenia cases, which are considered to be idiopathic. We report a patient with cutaneous T-cell lymphoma (CTCL) who developed profound CD4 lymphopenia in the setting of long-term bexarotene therapy.

Case Report
A 63-year-old man with hypertension presented to our dermatology clinic with pruritic scaly
plaques on the scalp of 4 months' duration that had progressed to full-body exfoliative erythroderma (Figure 1). He had diffuse palmoplantar keratoderma and lymphadenopathy. His only long-term medications were terazosin for benign prostatic hyperplasia and atenolol for hypertension; he reported no new medications. Laboratory evaluation revealed normal liver and kidney function. A complete blood cell count (CBC) revealed a white blood cell (WBC) count within reference range (8000/µL [reference range, 4500–11,000/µL]) but with increased eosinophils (12.9% [reference range, 2.7%]) and monocytes (11.8% [reference range, 4%]) and reduced lymphocytes (16.8% [reference range, 34%]). Flow cytometry showed a CD4:CD8 ratio of 1.18 to 1 (reference range, 0.8–4.2) (absolute CD4+ cells, 764/µL [reference range, 297–1551/µL]; absolute CD8+ cells, 654/µL [reference range, 100–1047/µL]). Skin biopsy revealed subacute spongiotic dermatitis with numerous eosinophils, exocytosis including folliculotropism, and rare atypical lymphocytes (Figure 2). Molecular studies showed T-cell receptor γ gene rearrangement. The patient did not have any other underlying conditions that would predispose him to lymphopenia. Based on these findings, a diagnosis of CTCL stage IIIA was made and agreed on by experts at the University of California, San Diego Dermatology Grand Rounds.

The patient was subsequently started on acitretin, topical corticosteroids, and hydroxyzine. However, the erythroderma progressed and he developed fever, chills, and malaise, and he was hospitalized 2 months later for intensive therapy and to rule out infection. He improved on daily wet wraps, topical steroids, oral antibiotics, and initiation of narrowband UVB therapy. He was discharged 1 week later. Acitretin was switched to bexarotene 3 months later due to peeling and cracking of the palmoplantar skin. The initial dose was 225 mg once daily, which was steadily increased over the next 4 months to a therapeutic dose of 600 mg once daily, which was much lower than the maximum dose of 400 mg/m2 daily (calculated at 750 mg/d in our patient). The patient achieved clinical remission 1 year after initiation of bexarotene in conjunction with narrowband UVB therapy. Serum eosinophils also normalized. Because there were no intolerable side effects, this dose was continued for 2 more years before it was slowly tapered to 375 mg once daily over a 1-year period. The new dose was maintained thereafter. Secondary hypertriglyceridemia and hypothyroidism, known side effects of bexarotene, developed 1 and 5 months after initiating therapy, respectively, and were treated with levothyroxine and fenofibrate. Blood counts were checked every 3 months and remained within reference range. Within the first few months of therapy, lymphocytes did trend down to 16.8%, but segmented neutrophils were normal at 59.4%. For the next 5 years the total WBC count and differential remained within reference range. T-cell subsets and flow cytometry data were not measured. No new medications were started during this period, and none of his existing medications had lymphopenia as a known side effect.

Five years after the initial diagnosis, the patient was still on bexarotene and was suspected to have pneumonia that was treated by his primary care provider with cefuroxime and azithromycin for 2 weeks with no improvement. He was then admitted to the hospital with shortness of breath, productive cough, night sweats, and dyspnea of 1 month's duration. There was no associated weight loss or fever. Notably, the skin was clear. (Figure 2. Skin biopsy at initial diagnosis revealed subacute spongiotic dermatitis with numerous eosinophils, exocytosis including folliculotropism, and rare atypical lymphocytes (H&E, original magnification ×10).)

![Figure 1. Exfoliative erythroderma at initial presentation.](image)
He was further treated for community-acquired pneumonia, first with vancomycin and ceftazidime, then with ciprofloxacin and sulfamethoxazole-trimethoprim, with no improvement. A CBC with differential was obtained on the patient’s first admission and revealed a WBC count of 3600/µL with decreased lymphocytes (8.6%), no eosinophilia, and anemia (hemoglobin, 10.5 g/dL [reference range, 33–37 g/dL]). T-cell subset studies revealed a CD4:CD8 ratio of 0.06 to 1 (absolute CD4+ cells, 6/µL; absolute CD8+ cells, 107/µL). The patient also had an elevated lactate dehydrogenase level of 1015 U/L (reference range, 100–200 U/L) and a normal comprehensive metabolic panel. A comprehensive workup, including urine and blood cultures, serum Cryptococcus and coccidioidomycosis IgG/IgM, histoplasmosis urine antigen, legionella, HIV, purified protein derivative (tuberculin), and aspergillosis galactomannan antigen panel, was negative. Blood tests for HIV and human T-lymphotropic virus also were negative. Bronchoscopy with cytology and sputum cultures for fungi, acid-fast bacteria, and viruses identified *Pneumocystis jiroveci* in the bronchial wash. Pneumocystis pneumonia was treated with intravenous clindamycin, primaquine, and leucovorin. The patient’s WBC count continued to drop over the next 2 weeks to a nadir of 1.7% with few lymphocytes noted on the differential. At that point, the bexarotene was stopped and was considered causative in inducing CD4 lymphopenia, resulting in opportunistic infection. The patient steadily improved and was discharged on sulfamethoxazole-trimethoprim prophylaxis for pneumocystis after a 4-month hospitalization.

His CD4 count slowly improved over the next 18 months; however, his skin disease recurred and progressed to exfoliative erythroderma with marked scarring alopecia (Figure 3), facial swelling, extreme pruritus, and notable eosinophilia. Repeat computed tomography was negative for extracutaneous involvement. A repeat skin biopsy showed recurrent mycosis fungoides similar to the original biopsy (Figure 4). Topical steroids and narrowband UVB therapy were restarted. A bone marrow biopsy revealed no definitive lymphoma, but the peripheral blood showed occasional CD8+ “flower cells” and no CD4+ Sézary cells. Two repeat molecular studies failed to show the T-cell receptor gene rearrangement. Localized electron beam radiation therapy, lenalidomide, and clobetasol were tried without benefit. The patient was hospitalized 3 months later and was started on wet wraps as well as weekly infusions of the histone deacetylase inhibitor romidepsin (14 mg/m² over a 4-hour period) on days 1, 8, and 15 of a 28-day cycle with rapid improvement. He experienced transient slight neutropenia with the first several treatments that quickly resolved. His skin was clear while on a regimen of triamcinolone, wet wraps, and intravenous romidepsin. He demonstrated visible improvement after 3 weekly infusions of romidepsin (Figure 5). His skin disease cleared after 9 infusions of romidepsin, and he currently remains in remission; however, he developed presumed bronchopneumonia after approximately 3 to 4 infusions. He then presented with severe headaches after his ninth infusion and was found to have cryptococcal meningitis. Romidepsin was...
stopped and he was treated with systemic antifungal therapy. His CTCL never recurred despite not restarting romidepsin.

Comment

The retinoids are chemically related to vitamin A. They regulate epithelial cell growth and are beneficial in inflammatory skin disorders and in patients with increased cell turnover as well as in skin cancer and precancer prevention/treatment. The first- and second-generation retinoids, isotretinoin and acitretin, respectively, cause anemia or leukopenia in less than 10% of patients; adverse effects are noted more commonly in doses greater than 1 mg/kg daily. Bexarotene is a third-generation retinoid drug that is more selective for retinoid X receptors. It was approved in 1991 for treatment of advanced CTCL (stages IIIB–IVB) in adult patients who have failed at least 1 prior systemic therapy. Bexarotene is noted to promote cell cycle arrest and apoptosis in CTCL cell lines. However, one study suggested that for bexarotene, inhibition of proliferation is more important than causing apoptosis in CTCL cells, and this effect is achieved through triggering the p53/p73-dependent cell cycle inhibition pathway.

Studies in patients with Sézary syndrome have shown that bexarotene changes the chemokine receptor expression in circulating malignant T cells, making them less likely to traffic to the skin (lower chemokine receptor type 4 expression), which may explain why some CTCL cases have shown improvement of skin disease on bexarotene despite progression of extradermal disease.

Bexarotene-Induced CD4 Lymphopenia

Common side effects of bexarotene include hyperlipidemia and central hypothyroidism. In addition, dose-related myelosuppression with isolated leukopenia, particularly neutropenia, also has been reported (18% of patients at a dosage of 300 mg/m²/d and 43% of patients with a dosage greater than 300 mg/m²/d). Leukopenia generally occurs within the first 4 to 8 weeks of treatment, is relatively mild (WBC, 1000–2999/µL), and generally is reversible. One review of 66 mycosis fungoides patients treated with bexarotene described a patient who developed leukopenia 15 months after initiating bexarotene therapy. The manufacturer recommends that treatment with bexarotene be continued as long as the patient is receiving benefit from the treatment. One trial of 70 mycosis fungoides patients treated with bexarotene reported response rates of 48% on bexarotene monotherapy (n=54) and 69% on bexarotene plus an additional agent (n=16). The authors noted higher response rates in patients on 2 lipid-lowering agents. They concluded that bexarotene was a safe and effective agent for treatment of cutaneous T-cell lymphoma and recommended continued treatment with a lowered dose of bexarotene in those achieving complete responses for a period of 2 years. Although the recommended initial dose is 300 mg/m²/d, bexarotene can be increased to 400 mg/m²/d after 8 weeks if no response to treatment is appreciated. Our patient was on a maximum bexarotene dose of 600 mg once daily (280 mg/m²/d) for the first 2 years, and a maintenance dose of 300 mg once daily for the next 3 years. He was not on any medicines known to induce leukopenia and he was not given any known cytochrome P450 3A4 inhibitors that could increase the toxicity of bexarotene.

The patient’s CBC was checked routinely every 2 to 3 months after he was started on bexarotene. For 5 years, the CBC and differential remained within reference range; however, his CD4 counts were not followed during those 5 years. We attribute his CD4 lymphopenia and subsequent pneumocystis pneumonia to bexarotene. After our patient’s CD4 lymphopenia was discovered, he developed a precipitous drop in his WBC and lymphocyte counts while hospitalized that worsened over a 2-week period. At this point, the bexarotene was discontinued and his WBC count slowly recovered. We believe that one of the initial antibiotics prescribed by the patient’s primary care physician at initial onset of pneumonia symptoms as an outpatient could have acted synergistically with bexarotene to worsen lymphopenia. Specifically, cefazidine, vancomycin, and ciprofloxacin have all been reported to cause leukopenia; however, it was neutropenia in these cases, not lymphopenia. Notwithstanding, the
opportunistic pneumonia and therefore CD4 lymphopenia was present prior to any antibiotic use.

The CD4 lymphopenia was unlikely due to underlying infection(s) because an extensive workup was negative, except for the pneumocystis, which likely resulted from the lymphopenia. The CD4 lymphopenia could also be idiopathic, as it has been reported in 3 patients with mycosis fungoides. All 3 patients were erythrodermic at presentation and noted to have numerous CD4+ lymphocytes in the cutaneous lesions but few circulating CD4+ T lymphocytes in the blood. The authors attributed the CD4 lymphopenia to cutaneous sequestration of CD4+ T lymphocytes. These cases contrast with our patient who was in clinical remission at the time of CD4 lymphopenia, which improved and normalized following discontinuation of bexarotene.

Conclusion
This case emphasizes the importance of monitoring for leukopenia, specifically CD4 lymphopenia, in patients on long-term bexarotene therapy. Routine CBC as well as T-cell subset counts should be performed during treatment. Rotation off bexarotene after several years of therapy should be considered, even in patients with continuous benefit from this systemic therapy.

REFERENCES