A 56-year-old man presented with multiple red-violeaceous firm, nontender nodules and plaques on the left frontal and parietal areas of his scalp (Figure 1). There was no regional lymphadenopathy. The patient denied any fever or chills. His medical history was significant for diabetes mellitus and hypertension, for which he was taking metformin, troglitazone, glyburide, and enalapril maleate. There was no personal or family history of cancer. A skin biopsy specimen from a scalp lesion showed a dense atypical lymphocytic infiltrate suggestive of malignant lymphoma (Figure 2). Results of extensive investigation including a bone marrow biopsy, lymph node biopsy, and computed tomographic scan of the chest, abdomen, and pelvis were negative for systemic lymphoma. A specimen from a repeated biopsy was submitted for flow cytometric analysis and Southern blotting for B- and T-cell receptor rearrangement. Immunophenotypic analysis showed a mixture of B and T cells. The T cells showed expression of CD3, CD5, and CD7 with markedly reduced and almost absent CD2, while the B cells expressed CD19, CD20, and CD22 with no evidence of surface immunoglobulin light chain restriction (Figure 3). This was suggestive of an atypical T-cell population. There was no T- or B-cell rearrangement on the first Southern blotting examination of the specimen; however, another examination of the specimen, which was submitted for T- and B-cell gene rearrangement analysis with restriction enzymes, demonstrated the presence of a monoclonal B-lymphocyte population indicative of a follicle center B-cell lymphoma. The patient did not want to undergo surgery, radiotherapy, or systemic chemotherapy.

The patient was initially treated with intralesional injections of triamcinolone (20 mg/mL), and the lesions improved with flattening and decrease in erythema. However, after 5 injections, 1 per month for 5 months, he reached a point where no further improvement was noted. At this time, his treatment was switched to intralesional interferon alfa. He received a total of 10 injections of 5 million units each of interferon alfa at 4-week intervals for 5 months. The patient's condition improved again with flattening of the lesions; however, the patient required monthly injections because the tumors would reappear. Topical bexarotene gel (Targretin, Ligand Pharmaceuticals Inc, San Diego, Calif), applied twice a day, was then added to the regimen. He responded very well to the combination and, within 2 months, the lesions were completely flat with no clinical evidence of recurrence (Figure 4). The patient has been applying the Targretin gel on an as-needed basis, and the need for interferon alfa injections has decreased to every 3 months. The patient has been followed up for 1 year without any recurrence.

There are many therapeutic modalities that can be used for the treatment of primary cutaneous B-cell lymphoma (CBCL). Systemic chemotherapy, including cyclophosphamide, doxorubicin, vincristine, and prednisone, as monotherapy or in combination as polychemotherapy, can be used. Fierro et al showed that the use of COP (cyclophosphamide, vincristine [Oncovin], prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) polychemotherapy resulted in response rates of 98% with a relapse rate of 33%. Santucci et al showed 100% remission rate, with two thirds of the patients having relapses. In a report by Wong and Weller, intralesional steroids were shown to be effective in controlling local skin relapses of CBCL. Furthermore, radiation therapy may be successfully combined with chemotherapeutic agents or administered alone. Berti et al demonstrated complete remission in 100% of their cases;
however, there were a large number of relapses (14/44). Piccinno et al9 also showed 100% complete remission rate with 68% relapse rate. There are also reports of intraleisional cisplatin and intraleisional interferon alfa as effective therapy. There are a couple of case reports regarding the use of intraleisional interferon alfa for CBCL. Santucci et al7 reported that 1 of the 2 patients treated had complete remission. However, the dosage and frequency of treatments were not discussed. Zenone et al5 treated 1 patient who had complete remission with intraleisional interferon alfa after failing 5 treatments of polychemotherapy and radiation. For the first 2 months the patient received 3 million units every week, then 5 million units was given every week for 4 months. Finally, the patient received 10 million units every month for 6 months. The patient had no recurrence 1 year after treatment. More recently, systemic and intraleisional rituximab, an anti-CD20 monoclonal antibody, has produced excellent response rates. We know of no published reports regarding the treatment of CBCL with Targretin or topical alitretinoin gel (Panretin, Ligand Pharmaceuticals Inc). Therefore, when considering treatment options, it is necessary to select the drug that is safe, effective, and convenient.

The use of bexarotene (Targretin), a retinoid that selectively activates the retinoid X receptors, has been used in the successful treatment of cutaneous T-cell lymphoma (CTCL), has shown substantial results in acquired immunodeficiency syndrome-related Kaposi sarcoma, and has prolonged survival of patients with non–small cell lung carcinoma and advanced renal cell carcinoma (when combined with interferon alfa).10-18 Bexarotene is a member of a class of retinoids that selectively activate the retinoid X receptors. When these receptors are activated, they function as transcription factors that regulate gene expression.10-13 These genes cause apoptosis. Retinoids that activate the retinoid A receptors have been shown to control cell differentiation and proliferation.

Oral bexarotene has been used for the treatment of CTCL. However, its use is accompanied by important adverse effects. Bexarotene use can elevate triglyceride levels, leading to pancreatitis; can cause central hypothyroidism; and can elevate transaminase levels.10,11,13,14 Laboratory evaluation has to be undertaken prior to beginning therapy with bexarotene, then weekly for the first 4 weeks and every 8 weeks thereafter, as long as the laboratory values are stable. Its use is also contraindicated in pregnancy given its teratogenic effects.

Bexarotene has recently become available in gel form. It is the first Food and Drug Administration–approved topical agent for the treatment of refractory CTCL. Phase 1 and 2 trials with stage IA and IIA CTCL yielded complete clearing of 21% of the lesions and at least 50% improvement in 63% of lesions.19,20 In phase 3 clinical tri-
als in patients with refractory or persistent stage IA, IB, and IIA CTCL, the overall response rate was 44% with a complete clearing of the lesions in 8% of the patients.21 When compared with Panretin, altretinoin (a retinoid that can bind to both the retinoid A and X receptors) in the treatment of stage I CTCL, Targretin had an overall response rate of 77%, while Panretin had an overall response rate of 67%.22 From the standpoint of adverse effects, 97% to 98% of patients participating in the phase I, 1, and 3 trials reported only pruritus (32%-33%), rash (72%-73%), and pain (22%-24%). It is not necessary to check laboratory values in patients using bexarotene gel.

Since the patient described herein responded to interferon alfa, but did not have clearing of the lesion, Targretin was added as an adjuvant topical agent. Interferon alfa works through the modification of cytokine expression. Targretin gel may work through apoptosis and other yet to be defined mechanisms. In chronic diseases, oftentimes it is more effective to use complementary combination therapy than monotherapy. Our patient had marked improvement with complete clinical resolution of the lesions on his scalp after the addition of the Targretin gel. While the patient has had a remarkable response, he still requires occasional interferon alfa injections, indicating that neither the Targretin gel nor the interferon alfa alone could control his disease. It would appear, therefore, that the combination can be effective in localized low-grade primary CBCL.

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Corresponding author: Francisco A. Kerdel, BSc, MBBS, University of Miami Department of Dermatology, PO Box 016250, Miami, FL 33136 (e-mail: Dermatology.department@hcahealthcare.com).

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