

Complete Resolution of Primary Cutaneous Anaplastic Large Cell Lymphoma With Topical Imiquimod

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ABSTRACT

Primary cutaneous anaplastic large cell lymphoma (pc-ALCL) is a CD30+ subtype of cutaneous T-cell lymphoma. It typically has a very favorable prognosis; however, traditional treatment can be expensive, invasive, and associated with significant adverse events. Imiquimod is a topical toll-like receptor approved by the Food and Drug Administration (FDA) for genital warts, actinic keratosis, and primary superficial basal cell carcinoma. In previous case reports, imiquimod has been shown to be effective against pc-ALCL. We present a case of complete resolution of pc-ALCL within 8 weeks with topical imiquimod and review the current literature.

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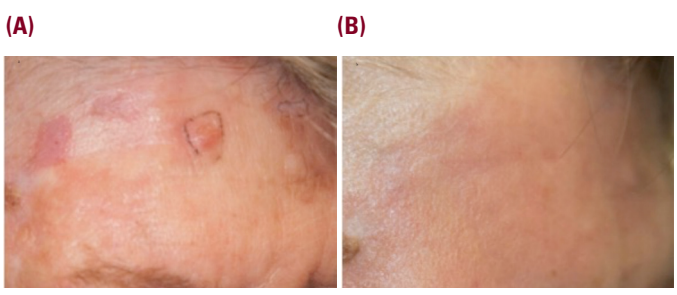
INTRODUCTION

Primary cutaneous anaplastic large cell lymphoma (pc-ALCL) is a CD30+ subtype of cutaneous T-cell lymphoma (CTCL). It typically presents as one or more nodules on the skin with a dermal infiltrate of >75% CD30+ lymphocytes.[1]

CASE REPORT

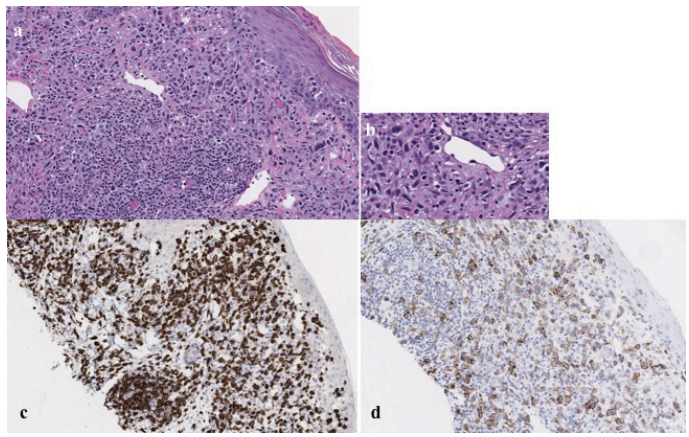
A 77-year-old Caucasian female presented for evaluation of a pink patch and papule on her forehead that appeared seven months prior. Examination revealed a 5 by 2 cm scaly pink patch on the right superior forehead with a 1 cm pink papule on the right medial forehead (Figure 1a).

FIGURE 1. Clinical appearance of pc-ALCL lesions. (A) Baseline showed pink patch with embedded 1 cm papule. (B) Lesion after eight weeks of topical imiquimod therapy.



Lesional biopsy showed dense atypical lymphocytic infiltrate composed of medium to large cells with moderate amounts of eosinophilic cytoplasm, hyperchromatic or vesicular nuclei with irregular nuclear contours, conspicuous nucleoli, and frequent mitotic figures within the dermis without a Grenz zone, with prominent involvement of epidermis (Figures 2a & 2b). Atypical cells in the epidermis and dermis were diffusely positive for CD3, CD4 and CD30 (Figures 2c & 2d), and negative for CD8, CD20, and ALK1. CD7 was negative in epidermotropic cells. Together, these findings led to a diagnosis of pc-ALCL.

FIGURE 2. Histologic findings of pc-ALCL lesions. (A) H&E of skin lesion (200x). (B) High power H&E of skin lesion (400x). (C) CD4 immunohistochemical study highlighting diffuse atypical lymphocytes (200x). (D) CD30 immunohistochemical study highlighting almost all large cells with membranous and golgi pattern of staining (200x).



Treatment was initiated with imiquimod 5% cream five times weekly and mupirocin 2% ointment two times weekly. At the eight-week follow up for possible surgical resection, the lesion was completely resolved with no adverse events (Figure 1b).

DISCUSSION

Pc-ALCL is a CD30+ T-cell subtype of CTCL. Clinically, it presents with primary or multiple erythematous papules or nodules, most commonly on the leg.[2] Pc-ALCL affects males more frequently than females (3:1), with a median age of diagnosis of 55 years. It has an indolent clinical course and five-year survival rate of 85-100%. Diffuse skin involvement, initial presentation on the head and neck, and extensive disease on a single limb are associated with a worse prognosis.[2]

Histologically, pc-ALCL is characterized by a dense dermal infiltrate comprised of >75% CD30+ lymphocytes with pale eosinophilic cytoplasm.[3] Most are positive for CD4 and demonstrate loss of CD2, CD3, and CD5. T-cell receptor gene translocations are observed in most cases.

The differential diagnosis for pc-ALCL includes systemic ALCL with cutaneous involvement, lymphomatoid papulosis (LyP), and CD30+ mycosis fungoides (MF). Compared to systemic

TABLE 1.

Reports of pc-ALCL Resolved With Topical Imiquimod

Patient No.	Age (y), Sex, Race	Clinical Presentation	Histologic	Imiquimod Regimen	Prior Therapy	Time to Resolution
1	77, Female, White	5 x 3 cm scaly erythematous patch on right superior forehead and papule on right medial forehead	Epidermal hyperplasia and atypical lymphohistiocytic infiltrate in epidermis and focal dermis. Lymphocytes positive for CD3, CD4, and CD30; negative for CD8, CD20, and ALK1.	Imiquimod 5% cream 5x/week, mupirocin 2% ointment 2x/ week	None	8 weeks
2[3]	23, Male, White	4 x 2 cm violaceous nodule on right posterior knee	Epidermal hyperplasia without epidermotropism, dermal infiltrate of lymphocytes with large, irregular nuclei and prominent nucleoli. Lymphocytes positive for CD3 and CD45RO, with >75% CD30+, CD20-.	Imiquimod 5% cream 3x/week	None	6 weeks
3[3]	55, Male, White	10 mm erythematous nodule with crust on right superior thigh	Epidermal hyperplasia, dermal infiltrate of lymphocytes with large and irregular nuclei and prominent nucleoli. Lymphocytes positive for T-cell markers and CD30.	Imiquimod 5% cream 3x/week	None	6 weeks
4[8]	25, Male, White	15 mm ulcerated erythematous nodule with central keratin plug on right nasal bridge	Polymorphous cellular infiltrate occupying dermis and part of subcutis. Sheets of atypical lymphoid cells with enlarged, horseshoe-shaped nuclei and prominent nucleoli. Lymphocytes positive for CD45, CD3, CD4, and CD30; negative for CD8, CD56, C20, ALK-protein, S-100 protein, EMA, cytokeratin, CD34, and myeloperoxidase.	Imiquimod 5% cream daily for 10 days, then q 2 days	None	4 weeks
5[9]	65, Male, Unknown	Arm	Unknown	Unknown	Multi-agent chemotherapy, MTX, topical and intralesional corticosteroids, minocycline	Unknown
6[9]	78, Male, Unknown	Temple	Unknown	Unknown	Radiotherapy, multi-agent chemotherapy, PUVA, MTX	Unknown
7[10]	63, Female, Unknown	Unknown	Unknown	Unknown	Surgery, PUVA, IFN	Unknown

Abbreviations: MTX, methotrexate; PUVA, Psoralens + UVA; IFN, interferon

ALCL, pc-ALCL is more likely to present on the head and neck and has a better prognosis.[2] LyP is not classified as a lymphoma, but rather exists on a spectrum of lymphoproliferative disorders with pc-ALCL.[3] Histologically, they are difficult to differentiate, but clinically pc-ALCL is suggested by size >2 cm and lack of the typical waxing and waning presentation of LyP. Compared to CD30+ MF with large cell transformation, pc-ALCL typically affects younger patients who lack a history of MF. Histology shows less epidermotropism and a greater number of abnormal T-cells. Clinically, pc-ALCL presents as fewer, more localized lesions that have a higher rate of spontaneous regression than in CD30+ MF.

Many traditional treatments are expensive, invasive, and associated with significant adverse events. For pc-ALCL involving few lesions, therapies include surgery and radiotherapy.[3] Multifocal lesions are treated with radiotherapy or low-dose methotrexate. Other treatment options include topical steroids, oral bexarotene, and brentuximab vedotin (BV). BV is a monomethyl auristatin E-conjugated monoclonal antibody directed against CD30 that was shown to induce complete remission from pc-ALCL in a mean of 5.2 weeks.[5] Peripheral neuropathy (57.2%) and fatigue (35.6%) are the most frequently reported adverse events. In addition, BV is administered as an infusion, and has significant financial cost. Imiquimod is a topical toll-like receptor agonist approved by the FDA for genital warts, actinic keratosis, and primary superficial basal cell carcinoma.[6] It is used off-label to treat other dermatologic conditions, including cutaneous flat warts and acyclovir-resistant herpes simplex virus infection. It is inexpensive and has a favorable safety profile with side effects including skin irritation or rash, flu-like symptoms, headache, and infection.[6] Topical imiquimod has been previously reported as effective against MF.[7]

Topical imiquimod therapy has achieved complete resolution of pc-ALCL in six other cases, summarized in Table 1.[1,8-10] For patient 4, imiquimod therapy was initiated for a presumed keratoacanthoma; biopsy results later diagnosed pc-ALCL.[8] Patients 5-7 received more invasive forms of therapy without resolution before initiating imiquimod.[9,10] All patients achieved resolution with topical imiquimod within eight weeks and reported no adverse events. Further investigation is needed to evaluate the efficacy and safety profile of imiquimod in patients with pc-ALCL.

While pc-ALCL typically has a favorable prognosis, traditional treatment may be expensive, invasive, and associated with significant adverse events. These findings highlight topical imiquimod as a possible alternative for first line therapy to treat pc-ALCL.

DISCLOSURES

None of the authors have any conflicts of interest to disclose.

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