

Pediatric Primary Cutaneous Marginal Zone Lymphoma Treated With Doxycycline

Grace C. Chan, MD; Sonia Kamath, MD

PRACTICE POINTS

- When skin biopsy reveals marginal zone lymphoma, laboratory workup should include a complete blood cell count, chemistry, and serum lactate dehydrogenase levels. If lymphocytosis is present, flow cytometry of peripheral blood cells should be performed.
- For patients with multifocal skin lesions, positron emission tomography with computed tomography is utilized to exclude systemic disease and assess lymph node involvement.
- Treatments for primary cutaneous marginal zone lymphoma include excision, topical steroids, intralesional steroids, intralesional rituximab, radiation therapy, and antibiotics.
- Doxycycline can be considered as a treatment option for pediatric patients with widespread cutaneous involvement.

Primary cutaneous marginal zone lymphoma (PCMZL) is a cutaneous B-cell lymphoma that rarely occurs in children. We present a 13-year-old boy with multiple asymptomatic erythematous papules and nodules on the trunk and arms that were confirmed on biopsy to be PCMZL. He was treated with doxycycline and intralesional triamcinolone with improvement of lesions. This case supports the use of doxycycline for the treatment of pediatric PCMZL in patients with widespread involvement despite negative *Borrelia* serology. Multiple low-risk treatment modalities may be used in conjunction to clear disease in pediatric patients.

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Case Report

An otherwise healthy 13-year-old boy was referred to pediatric dermatology with multiple asymptomatic erythematous papules throughout the trunk and arms of 6 months' duration. He denied fevers, night sweats, or weight loss. A punch biopsy revealed a dense atypical lymphoid infiltrate with follicular prominence extending periadnexally and perivascularly, which was most consistent with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (Figures 1A and 1B). Cells were positive for Bcl-2, CD23, and CD20 (Figure 1C). Polymerase chain reaction analysis of the immunoglobulin heavy and κ chain gene rearrangements were positive, indicating the presence of a clonal B-cell expansion. The patient's complete blood cell count, complete metabolic profile, serum lactate dehydrogenase, and erythrocyte sedimentation rate were within reference range. Lyme disease antibodies, *Helicobacter pylori* testing, thyroid function testing, thyroid antibodies, anti-Sjogren syndrome-related antigen A antibody, and anti-Sjogren syndrome-related antigen B were negative. Additionally, positron emission tomography (PET) with computed tomography (CT) revealed no abnormalities. He was diagnosed with stage T3b primary cutaneous marginal zone lymphoma (PCMZL) due to cutaneous involvement of 3 or more body regions.

The patient was started on clobetasol ointment 0.05% twice daily to the affected areas. After 2 months, he had progression of cutaneous disease, including increased number of lesions; erythema; and induration of lesions on the chest, back, and arms (Figure 2A) and was started

From Children's Hospital Los Angeles, California. Dr. Chan is from the Pediatric Residency Program. Dr. Kamath is from the Pediatric Dermatology Department. Dr. Kamath also is from the Department of Dermatology, Keck School of Medicine, University of Southern California, Los Angeles. The authors report no conflict of interest.

Correspondence: Grace C. Chan, MD, 4650 Sunset Blvd, Mailstop #68, Los Angeles, CA 90027 (Grchan@chla.usc.edu).
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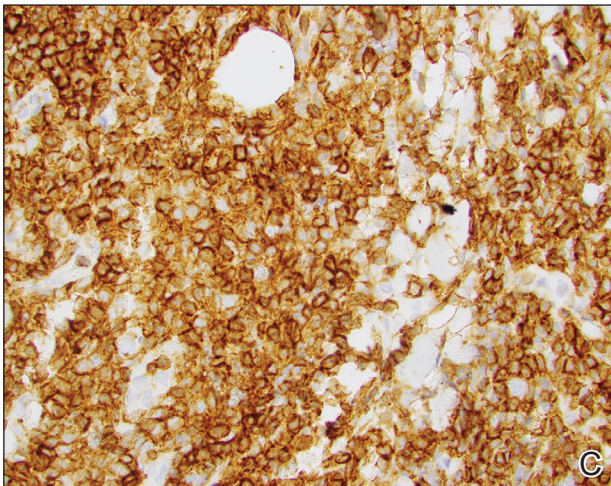
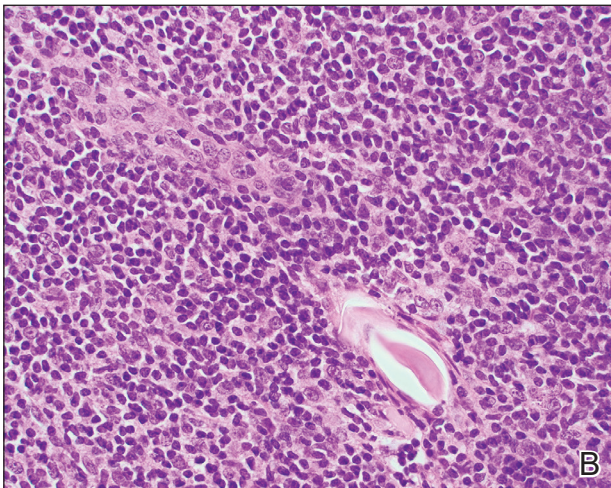
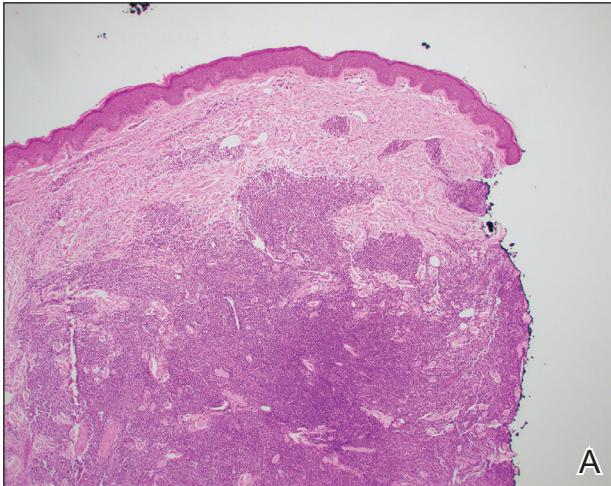


FIGURE 1. A, Histopathology revealed dense lymphoid infiltrates, predominantly in periadnexal areas, extending into subcutaneous tissue (H&E, original magnification $\times 20$). B, The lymphoid cells predominantly were small with round to irregular nuclei, dense chromatin, inconspicuous nucleoli, and scant amounts of cytoplasm (H&E, original magnification $\times 100$). C, CD20 immunohistochemistry staining highlighted expansion of B cells (original magnification $\times 200$).

on oral doxycycline 100 mg twice daily with subsequent notable improvement of the skin lesions at 2-week follow-up, including decreased erythema and induration of all lesions. He then received intralesional triamcinolone 20 mg/mL injections to 4 residual lesions; clobetasol ointment 0.05% twice daily was continued for the remaining lesions as needed for pruritus. He continued doxycycline for 4 months with further improvement of lesions (Figure 2B). Six months after discontinuing doxycycline, 2 small residual lesions remained on the left arm and back, but the patient did not develop any new or recurrent lesions.

Comment

Clinical Presentation—Primary cutaneous B-cell lymphomas include PCMZL, primary cutaneous follicle center



FIGURE 2. A, Multiple erythematous dermal papules and a scar at a biopsy site on the right arm prior to treatment. B, After treatment with clobetasol ointment 0.05% and oral doxycycline 100 mg, the dermal papules resolved with a residual hypertrophic scar at the biopsy site.

lymphoma, and primary cutaneous large B-cell lymphoma. Primary cutaneous marginal zone lymphoma is an indolent extranodal B-cell lymphoma composed of small B cells, marginal zone cells, lymphoplasmacytoid cells, and mature plasma cells.¹

Primary cutaneous marginal zone lymphoma typically presents in the fourth to sixth decades of life and is rare in children, with fewer than 40 cases in patients younger than 20 years.² Amitay-Laish and colleagues² reported 29 patients with pediatric PCMZL ranging in age from 1 to 19.5 years at diagnosis, with the majority of patients diagnosed after 10 years of age. Clinically, patients present with multifocal, erythematous to brown, dermal papules, plaques, and nodules most commonly distributed on the trunk and arms. A retrospective review of 11 pediatric patients with PCMZL over a median of 5.5 years demonstrated that the clinical presentation, histopathology, molecular findings, and prognosis of pediatric PCMZL appears similar to adult PCMZL.² Cutaneous relapse is common, but extracutaneous spread is rare. The prognosis is excellent, with a disease-free survival rate of 93%.³

Diagnosis—The diagnosis of PCMZL requires histopathologic analysis of involved skin as well as exclusion of extracutaneous disease at the time of diagnosis during initial staging evaluation. Histologically there are nodular infiltrates of small lymphocytes in interfollicular compartments, reactive germinal centers, and clonality with monotypic immunoglobulin heavy chain genes.⁴ Laboratory workup should include complete blood cell count with differential, complete metabolic panel, and serum lactate dehydrogenase level. If lymphocytosis is present, flow cytometry of peripheral blood cells should be performed. Radiographic imaging with contrast-enhanced CT or PET/CT of the chest, abdomen, and pelvis should be performed for routine staging in most patients, with imaging of the neck recommended when cervical lymphadenopathy is detected.⁵ Patients with multifocal skin lesions should receive PET/CT to exclude systemic disease and assess lymph nodes. Bone marrow studies are not required for diagnosis.^{5,6}

Associated Conditions—Systemic marginal zone lymphoma has been associated with autoimmune conditions, including Hashimoto thyroiditis and Sjögren syndrome; however, this association has not been shown in PCMZL and was not found in our patient.^{7,8} *Borrelia*-positive serology has been described in cases of PCMZL in Europe. The pathogenesis has been speculated to be due to chronic antigen stimulation related to the geographic distribution of *Borrelia* species.⁹ In endemic areas, *Borrelia* testing with serology or DNA testing of skin is recommended; however, there has been no strong correlation between *Borrelia burgdorferi* and PCMZL found in North America or Asia.^{9,10} *Helicobacter pylori* has been associated with gastric mucosal-associated lymphatic tissue lymphoma, which responds well to antibiotic therapy. However, an association between PCMZL and *H pylori* has not been well described.¹¹

Management—Several treatment modalities have been attempted in patients with PCMZL with varying efficacy. Given the rarity of this disease, there is no standard therapy. Treatment options include radiation therapy, excision, topical steroids, intralesional steroids, intralesional rituximab, and antibiotics.^{2,12-14} Case reports of pediatric patients have demonstrated improvement with excision,¹⁵⁻¹⁹ intralesional steroids,^{20,21} intralesional rituximab,²² and clobetasol cream.^{23,24} In asymptomatic patients, watchful waiting often is employed given the overall indolent nature of PCMZL. Antibiotic therapy may be favored in *Borrelia*-positive cases. However, even in *B burgdorferi*-negative patients, there have been cases where there is response to antibiotics, particularly doxycycline.^{2,15,25} We elected for a trial of doxycycline in our patient based on these prior reports, along with the overall favorable side-effect profile of doxycycline for adolescents and our patient's widespread cutaneous involvement.

Doxycycline is utilized in pediatric patients 8 years and older for numerous indications, including treatment of acne, Rocky Mountain spotted fever, and Lyme disease. Use of doxycycline in younger patients typically is avoided given the risk for dental enamel hypoplasia, tooth discoloration, and possible delays in skeletal development. Originally utilized for its antibacterial effects as an intracellular inhibitor of protein synthesis, doxycycline has been repurposed for oncologic therapies. It has been shown to have cytotoxic and antiproliferative properties in various cancer cells and also may inhibit leukemic cell migration.²⁶ In PCMZL, doxycycline initially was utilized in *Borrelia*-positive patients in Europe and found to improve disease clearance.²⁷ In patients without *Borrelia* infection, doxycycline is thought to enhance apoptosis through caspase-3 activation along with p53 and Bax upregulation.²⁸

Intralesional triamcinolone alone may not be feasible in pediatric PCMZL patients because of widespread involvement, and doxycycline may be considered as a treatment option. Multiple low-risk treatment modalities may be used in conjunction to clear disease in pediatric patients, as demonstrated in our case.

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