



# Primary cutaneous marginal zone lymphoma with leptomeningeal involvement and a durable response to rituximab

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**Key words:** central nervous system; cutaneous B-cell lymphoma; leptomeningeal involvement; primary cutaneous marginal zone lymphoma; rituximab.

## BACKGROUND

Primary cutaneous marginal zone lymphoma (PCMZL) is an indolent B-cell lymphoma, typically characterized by frequent cutaneous recurrences and rare systemic involvement. Lymph nodes, bone, and bone marrow are commonly affected sites in rare cases of extracutaneous disease. Secondary involvement of central nervous system (CNS) in confirmed PCMZL is unreported.

## CASE PRESENTATION

A 47-year-old man presented with a slowly expanding, asymptomatic lesion on the right arm of 1-year duration (Fig 1, A and B). Skin biopsy as reviewed by the Department of Pathology at Memorial Sloan Kettering Cancer Center was consistent with low-grade cutaneous B-cell lymphoma of marginal zone type (Fig 2, A and B). The immunohistochemical stains showed mixed population of cells positive for CD3 and CD20 and negative for CD10 and BCL-2. Sheets of CD20<sup>+</sup> cells showed  $\lambda$  light chain restriction (Fig 2, C and D). Findings from staging workup, including complete blood count, comprehensive metabolic profile, protein electrophoresis, serum immunoglobulin levels, and computed tomography scans of the chest, abdomen, and pelvis were within normal limits.

### Abbreviations used:

CNS:	central nervous system
CSF:	cerebrospinal fluid
PCMZL:	primary cutaneous marginal zone lymphoma
WBC:	white blood cells

New lesions subsequently developed on the patient's arms and lower back, which showed identical histology and clonal immunoglobulin heavy chain (IgH) gene rearrangement. Rapid progression of disease prompted us to perform restaging workup including repeat computed tomography scans and bone marrow biopsy, results of which were again within normal limits. The patient was treated with topical and intralesional steroids with resolution of most lesions. Follow-up every 3 to 6 months found minimal cutaneous disease for nearly 3.5 years, when a transient left facial droop developed that resolved spontaneously. He later reported persistent headaches with diplopia associated with right fourth cranial nerve palsy. The diplopia gradually resolved but then recurred with new right sixth cranial nerve palsy. Electroencephalogram and gadolinium-enhanced magnetic resonance imaging of spine and orbits were unremarkable. Cerebrospinal fluid (CSF)

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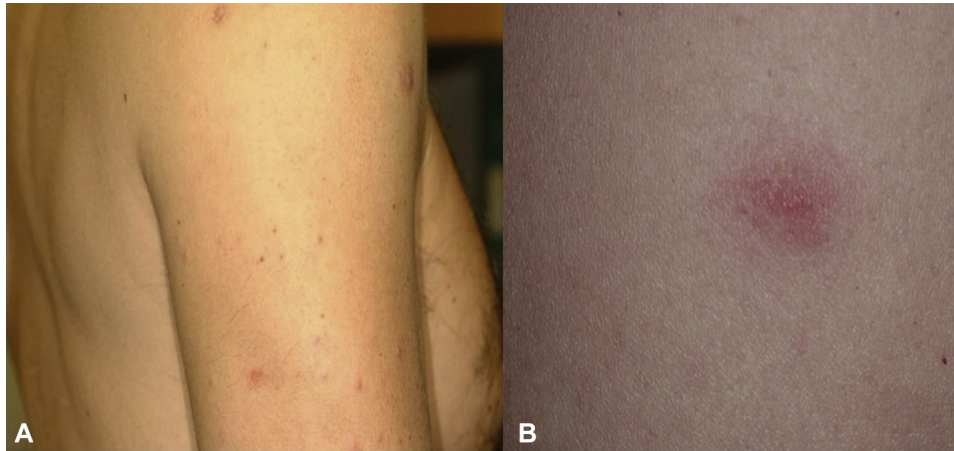
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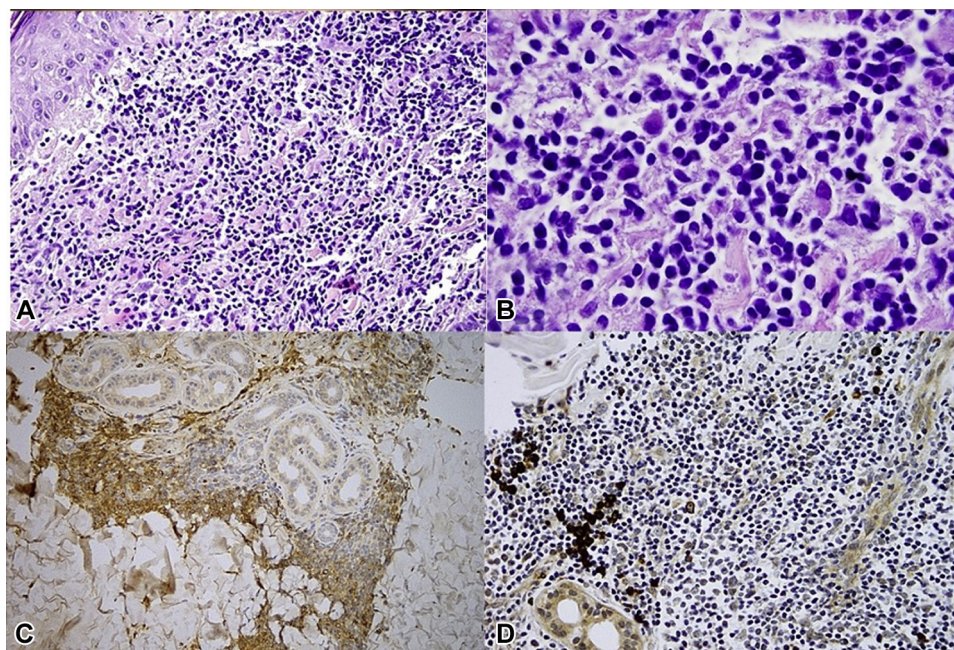
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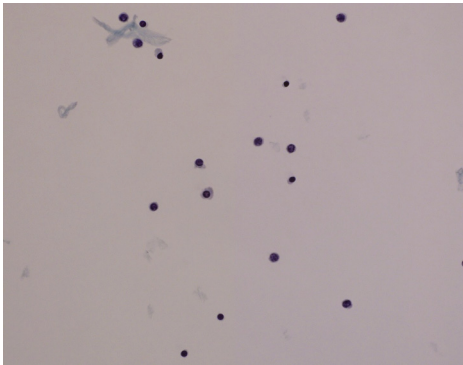
**Fig 1.** Clinical overview images. **A**, Multiple red papules on upper arm. **B**, Close-up view of the erythematous papule.



**Fig 2.** Representative photomicrographs of skin biopsies. **A**, Striking infiltrate of atypical lymphoplasmacytoid cells involving superficial and deep dermis. **B**, interstitial and perivascular infiltrate of atypical small-to-intermediate lymphocytes, some with abundant cytoplasm and plasmacytic differentiation. **C**, The B lymphocytes show a dominance of  $\lambda$  light chain. **D**, Kappa is essentially negative. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 200$ ; **B**,  $\times 1000$ .)

analysis found elevated WBCs (27 cells/ $\mu\text{L}$ , 99% lymphocytes), 71 mg/dL protein, and 62 mg/dL glucose. Cytology (Fig 3) and flow cytometric results were consistent with B-cell lymphoma, with  $\lambda$  to  $\kappa$  ratio of 41:1. Polymerase chain reaction of CSF found clonal rearrangement of IgH chain identical to the clone in skin. Positron emission tomography scan and bone marrow biopsy were unremarkable. Fluorescence in situ hybridization performed to rule out t (11; 18) (q21; q21) translocation was negative.

The patient received high-dose rituximab (750 mg/m<sup>2</sup> weekly  $\times$  4 weeks), without initial symptomatic improvement. CSF testing at 2 months found significant reduction in WBCs (5 cells/ $\mu\text{L}$ , 97% lymphocytes) and light chain–restricted B cells ( $\lambda$  to  $\kappa$  ratio of 5:1) but persistent IgH clone. A second course of high-dose rituximab led to marked improvement in headaches. CSF testing at 1 month found a WBC count of 7 cells/ $\mu\text{L}$  and 95% lymphocytes, absence of light chain restriction



**Fig 3.** Cerebrospinal fluid shows atypical lymphocytes.

( $\lambda$  to  $\kappa$  ratio of 1:1), but persistently clonal IgH. Based on clinical and pathologic improvement, he received a third course of high-dose rituximab with normalization of WBC count (2 cells/ $\mu$ L) and flow cytometry with extinguishing of IgH clone. His diplopia resolved along the way. The patient continues to be in remission with occasional cutaneous relapses since completion of treatment about 8 years ago. He follows up annually and is monitored clinically since remission.

## CONCLUSIONS

Primary cutaneous B-cell lymphomas are extranodal non-Hodgkin lymphomas that constitute approximately 25% of all cutaneous lymphomas.<sup>1</sup>

PCMZL is included in 2008 World Health Organization classification as extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue.<sup>2</sup> Extranodal marginal zone lymphoma can involve single or multiple extranodal sites like the gastrointestinal system, skin, breast, lung and orbit.<sup>3</sup>

PCMZL is a low-grade lymphoma with indolent disease course and excellent prognosis. It presents as solitary or clustered nodules or plaques on the trunk or upper extremities,<sup>4</sup> with good response to local radiation or excision. Cutaneous recurrences are common and do not affect prognosis.<sup>5,6</sup> Of 137 patients with PCMZL, 6 patients (4%) had extracutaneous disease in lymph nodes, gastrointestinal system, bone marrow, and lungs, during mean follow-up of 54 months. None had CNS involvement. All patients with extracutaneous spread had simultaneous or previous cutaneous relapses. Mean time to extracutaneous spread was 2 years and not related to extent of the disease. Cutaneous relapses were observed in 53 patients (44%) with median disease-free survival of 47 months. Patients with multifocal lesions showed higher rates of cutaneous relapse and shorter disease-free survival. Overall survival was favorable (93% at 5 and 10 years).<sup>7</sup> In

another series, CNS involvement was reported in 2% of all primary cutaneous B-cell lymphomas. Of 7 patients with primary cutaneous follicle center lymphoma who had extracutaneous spread, 3 had CNS involvement accounting for 75% of lymphoma-related deaths. None of the patients with PCMZL had extracutaneous spread.<sup>8</sup>

CNS involvement by PCMZL is not described in the literature, with the possible exception of a 71-year-old man reported from China, who presented with a dural mass.<sup>9</sup> Evaluation found a 4-year-old subcutaneous nodule on the arm that was histologically and immunophenotypically similar to a dural mass and diagnostic of marginal zone lymphoma. The diagnosis of PCMZL was made retrospectively with no staging evaluation at presentation to differentiate between primary cutaneous versus multifocal extranodal marginal zone lymphoma with skin involvement. He later underwent resection followed by chemotherapy leading to remission.

Intravenous rituximab has been used to treat multifocal PCMZL, with an overall complete response rate of 43% and duration of response between 6 and 75 months.<sup>10,11</sup> Measurable, albeit low levels of rituximab can be found in CSF after intravenous treatment with anecdotal responses reported in CNS.<sup>12</sup>

We report the first case, to our knowledge, of PCMZL with intracranial involvement. The patient responded well to rituximab and continues to be overall free of extracutaneous disease 8 years after treatment. Skin recurrences have successfully been treated with skin-directed therapy only, such as topical steroids.

Dissemination of PCMZL to CNS is distinctly unusual. Given that CNS was effectively cleared with high-dose rituximab and has not recurred despite recurrence in skin suggests that extension to CNS was a rare unique event in this patient or reflected a subpopulation of cells that had the ability to grow outside the skin. Eradicating this malignant subpopulation of cells with high-dose rituximab and lack of recurrence in CNS many years later further support the rarity of the event and low likelihood of its recurrence.

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