IgG4 expression in cutaneous marginal zone lymphoma with plasmacytic differentiation and localized amyloid deposition: A useful clue to cutaneous origin

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INTRODUCTION

Primary cutaneous lymphomas include T-cell and B-cell neoplasms limited to skin without evidence of extracutaneous disease. Cutaneous follicle center cell lymphoma is the most common cutaneous B cell lymphoma, comprising 12% of cases. Primary cutaneous marginal zone B-cell lymphoma (PCMZL) accounts for 7% of all skin lymphomas and comprises 25% to 30% of cutaneous B cell lymphoma. Cutaneous diffuse large B-cell lymphoma of the leg type is the least common at about 4% of cases.[1]

PCMZL typically presents as pink-purple, solitary or grouped papules, plaques, and nodules on the trunk and upper extremities of adults in the fifth to sixth decade with a male predominance. Biopsy typically finds a vaguely nodular nonepidermotropic, deep dermal (bottom-heavy), subcutaneous and/or periadnexal polymorphous lymphoid infiltrate. Small lymphocytes surround germinal centers with either centrocytelike or plasmacytoid morphology. Plasma cells are often increased. Lymphoma cells express CD20 and CD79a and are negative for CD5, CD10, and Bcl-6. If plasma cells are increased, they exhibit immunoglobulin light chain restriction. Clonality can be identified in about 80% of cases.[2] PCMZL and mucosa-associated lymphoid tissue (MALT) lymphomas may be preceded by chronic antigen stimulation and are the most indolent tumors in this group. Only 4% of patients have

Abbreviations used:

IgG4-RD:	IgG4-related disease
LAD:	localized amyloid deposition
MALT:	mucosa-associated lymphoid tissue
MZL:	marginal zone lymphoma
PCMZL:	primary cutaneous marginal zone lymphoma

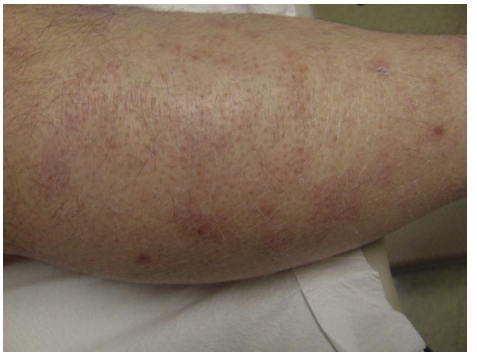

Fig 1. Erythematous macules and nodules on the lower leg in 2017.

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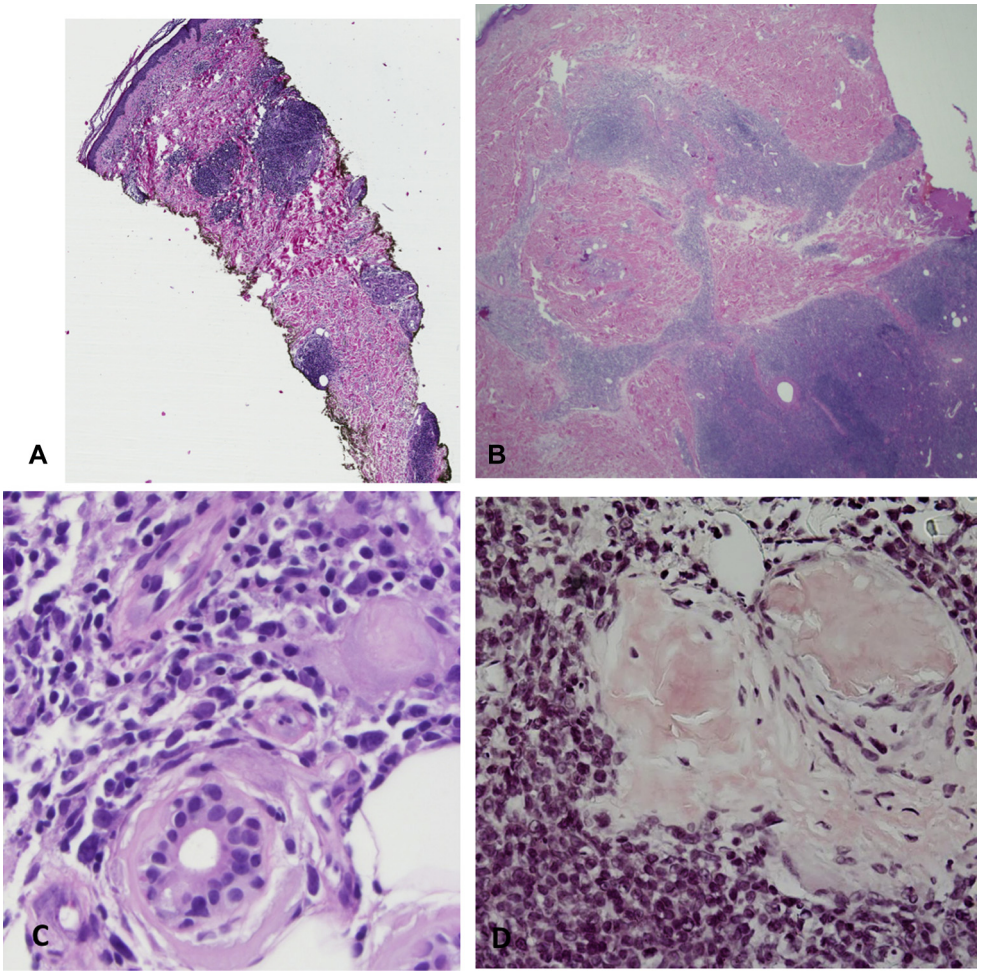

Fig 2. Similar dermal and subcutaneous infiltrate was seen in 2017 (**A**) and 2009 (**B**) samples, comprising mostly small to medium-sized lymphocytes, numerous plasma cells, and frequent immunoblasts. (**C**) Waxy hyaline deposits are seen within the infiltrate, around vessel wall, and in adnexal basement membrane and appear orange when stained with Congo red (**D**) and typical birefringence under polarized light (not shown). (**A-C**, Hematoxylin-eosin stain; original magnifications: **A** and **B**, ×20; **C**, × 400. **D**, Congo red stain; original magnification: ×200.)

extracutaneous disease, and less than 1% of patients die of disease; therefore, distinguishing PCMZL from marginal zone lymphoma (MZL) with secondary skin involvement is clinically important.[1,2]

CASE REPORT

A 59-year-old man presented with a solitary nodule of the left knee in 2009. Workup found PCMZL with dermal and subcutaneous involvement but no systemic disease after imaging studies. Treatment with 2 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) followed by radiation therapy was associated with an excellent response. One year later, new papules and nodules developed on the right arm and right leg. Radiation therapy was initiated and followed by 4 cycles of rituximab, ifosfamide, carboplatin, and etoposide (RICE). He was leukopenic, but biopsy of the marrow was unremarkable. Additional lesions did not develop until a 2017 visit when erythematous nodules were noted on the right arm and leg (Fig 1). Because of his lack of symptoms and lack of extracutaneous involvement, no systemic therapy was considered necessary. Topical imiquimod was tried but had no effect.

Review of biopsies from 2009 and 2017 found similar reports of a deep and focally superficial dermal polymorphous infiltrate comprising small to medium-sized cells and sheets of plasma cells and plasmacytoid lymphocytes (Fig 2). Extensive perivascular and periadnexal spread was present. Mitotic figures were frequent, and no necrosis was seen. Large immunoblasts were interspersed but did not form large clusters or sheets. Amorphous

Table I. Lymphoma cells immunoprofile in 2 samples

	2009 lesion (left leg excisional biopsy)	2017 lesion (right leg incisional biopsy)
CD20	Positive	Positive
CD3	Negative	Negative
CD138	Positive*	Positive*
MUM1	Positive*	Positive*
IgG	Positive*	Positive*
IgG4	Positive*	Positive*
IgM	Negative	Negative
Kappa	Positive*	Positive*
Lambda	Negative	Negative
CD21-follicular dendritic meshwork	Present (disrupted)	Absent
Congo Red	Negative for amyloid	Positive for amyloid

*In plasma cell component.

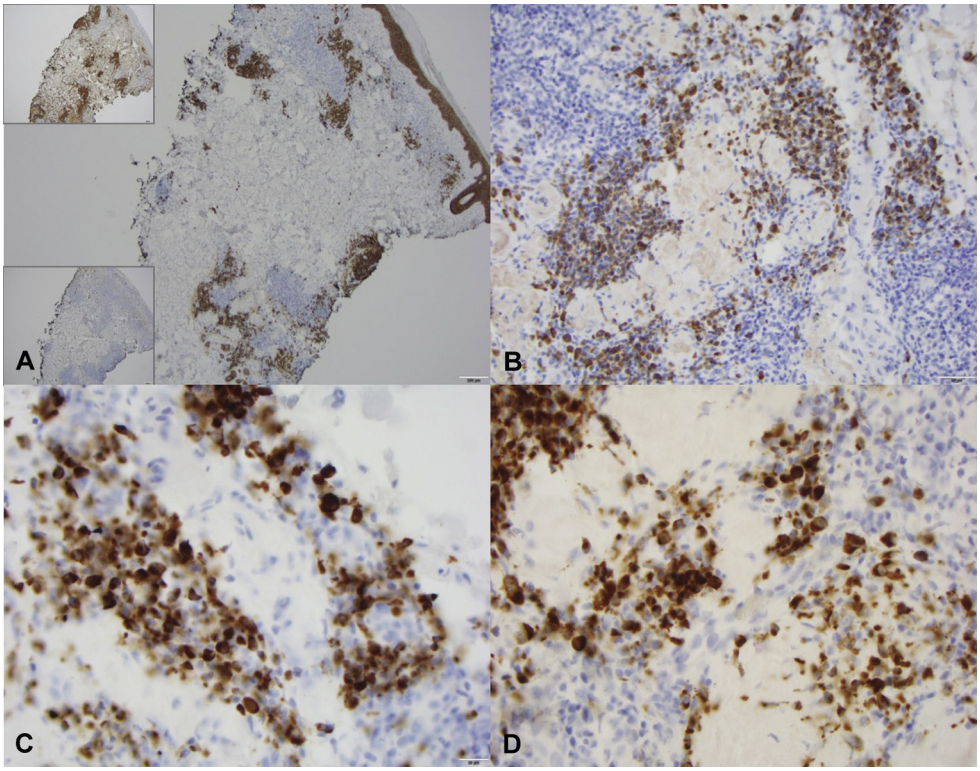

Fig 3. **A**, Plasma cells are highlighted by CD138 and are monotypic for kappa (*left upper inset*) and negative for lambda (*left lower inset*) light chains. Most plasma cells are IgG (**B**) and IgG4 (**C**, 2017 and **D**, 2009) positive with a punctate expression. Similar IgG4 labeling pattern was seen in 2009 lymphoma (**D**). (Immunohistochemistry for CD138, K, L, IgG and IgG4; original magnifications: **A**, ×20; **B**, ×200; **C** and **D**, ×400.)

eosinophilic material was associated with the lymphoid infiltrate and blood vessel walls. Congo red on the most recent biopsy (Fig 2) confirmed that this was amyloid. A comparative phenotype of the 2009 and 2017 lesions is depicted in Table I. IgG4 found a dotlike or punctate labeling pattern of plasma cells in both biopsies (Fig 3). *IgG, MALT1,* and *BCL2* loci were found intact by fluorescence in situ hybridization. Serum testing found IgG4 in normal range (20.1 mg/dL; reference range, 4.0-86.0).

DISCUSSION

PCMZL is the second most common type of cutaneous B cell neoplasm and is associated with low morbidity and mortality, raising questions about its malignant nosology.[2] PCMZL associated with plasma cell differentiation is common with 15% to

39% coexpressing IgG4.[3-5] This finding is only rarely encountered (1 of 120; 0.8%) in noncutaneous MZL.[3] IgG4 is the least common subclass of IgG, comprising approximately 4%. IgG4 has been implicated in the pathogenesis of fibroinflammatory disorders of pancreas, salivary glands, and retroperitoneum.[6]

Diagnostic criteria for IgG4-related disease (IgG-4-RD) include both histologic attributes (ie, lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis) and quantitative information (an increased number of IgG4-bearing plasma cells and an increased IgG4:IgG ratio that can vary with the site of involvement).[6] Serum levels of IgG4 are usually increased. Cutaneous IgG4-RD diagnosis is rare, requires at least 1 histologic feature and greater than 200 $IgG4^+$ plasma cells per high-power field for diagnosis, and has been proposed as a pseudolymphoma variant.[6,7] $IgG4^+$ plasma cells are increased in a variety of inflammatory, autoimmune, and neoplastic conditions and are insufficient alone for a diagnosis of Ig4-RD in the absence of typical histologic, clinical, and serologic features. Distinguishing IgG4 PCMZL from IgG4-RD on histologic grounds is usually straightforward. The absence of storiform (ie, cartwheel) fibrosis and obliterative phlebitis and presence of sheets of centrocyte-like cells, disrupted germinal centers, and plasma cells with Dutcher bodies suggest the correct diagnosis. This finding can be supported by B-cell clonality studies, which may be particularly helpful in challenging cases, small samples, or MZL mimicking IgG4-related dacryoadenitis and sialoadenitis.[8]

Localized amyloid deposition (LAD) is rare, but skin is one of the most commonly affected sites. LAD has been associated with PCMZL and autoimmune conditions and must be distinguished from systemic amyloidosis, which has a significantly more aggressive clinical course.[9] Our patient was found to have IgG4-positive plasma cells in his initial biopsy 8 years ago but no amyloid deposition at that time. Amyloid development at recurrence time was reported in a small cohort of MALT with LAD.[10] Neither finding alters the PCMZL minimal propensity for disseminated or progressive disease.[3-5,9,11] Nonamyloid monoclonal immunoglobulin light chain deposition disease can be morphologically and biologically indistinguishable from LAD and is associated with MZL or autoimmune disease as well as an indolent course. The deposits are Congo red negative and lack the typical fibrillary ultrastructure of amyloid.[12] Mass spectrometry is useful in diagnosis.[11,12] The significance of dotlike IgG4 expression pattern noted in our case and reported in the literature is unclear,[3-5] but its presence seems to be reassuring in regard to skin origin. IgG4-RD and IgG4 PCMZL may have a common pathogenesis (ie, chronic antigen stimulation), but they are distinct diseases. To our knowledge, this is the first report of IgG4 PCMZL associated with amyloid.

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