# Ataxia-telangiectasia mutated (ATM) gene mutation in a patient with primary cutaneous marginal zone lymphoma

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## INTRODUCTION

Primary cutaneous marginal B-cell lymphoma (PCMZL), a type of extranodal marginal zone lymphoma (MZL) of mucosa-associated lymphoid tissue, is a common indolent non-Hodgkin lymphoma that typically presents with solitary or multifocal papules/plaques or tumors.[1] Two types of PCMZL have been noted pathologically.[1,2] The more common subtype is characterized by class-switched immunoglobulins without C-X-C chemokine receptor 3 expression and a small proportion of neoplastic B cells.[1] A smaller subset shows a diffuse proliferation of neoplastic B cells that express immunoglobulin M (and often C-X-C chemokine receptor 3) and has a higher likelihood of extracutaneous disease manifestations.[1] Although some authors assert that many cases of PCMZL are clonal reactions to intradermal antigens, such as tick bites or tattoos,[1,3,4] the t(14;18)(q32;q21);IGH-MALT1 translocation is reported in up to 25% of PCMZLs, with t(3;14)(p14.1;q32);IGH-FOXP1 rearrangements less commonly reported.[4]

We present a patient with PCMZL with a known monoallelic mutation in ataxia-telangiectasia mutated (ATM) gene. ATM is a serine/threonine kinase that activates p53 in response to double-stranded DNA (dsDNA) damage.[5] Biallelic mutations in ATM result in the autosomal recessive disorder ataxia telangiectasia syndrome, which is associated with a 20%-30% increased risk of lymphoid and other cancers.[5] In addition, germ-line mutations of ATM have been associated with an increased risk of many types of cancer, including around a 14% risk of non-Hodgkin lymphoma.[5] We discuss the relevance of this ATM mutation in terms of prognosis and potential treatment options in patients with PCMZL.

*Abbreviations used:*

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| ATM: | ataxia-telangiectasia mutated |
| MZL: | marginal zone lymphoma |
| PCMZL: | primary cutaneous marginal B-cell lymphoma |

## CASE REPORT

A 73-year-old woman presented to the Duke Dermatology Cutaneous Lymphoma Clinic for evaluation of an 8-month history of skin lesions on her back and arms, gradually increasing in number and unresponsive to topical hydrocortisone. On examination, she had pink papules on her left and right shoulder, left upper arm, and left aspect of the back without associated bleeding, pain, or pruritus (Fig 1). Three previous outside biopsies revealed a perivascular and periadnexal infiltrate of small-sized lymphocytes, CD20 positive B cells (85%), and CD3 positive T cells. Further immunostains showed an aberrant expression of B-cell lymphoma 2, a background of plasmacytoid cells with scattered plasma cells—entirely Kappa restricted—with no expression of Lambda, and B-cell lymphoma 6 and CD10-highlighted, focally disrupted germinal centers. Molecular testing showed clonal immunoglobulin heavy chain gene rearrangement on a polyclonal background. These histologic findings were felt diagnostic of MZL, most consistent with the B cell-predominant cutaneous subtype. The outside bone marrow biopsy was negative for lymphoma, and computed tomography with contrast of her chest, abdomen, and pelvis revealed only heterogeneous-enhancing lesions in the liver, potentially representing hemangiomas. Based on the clinical presentation

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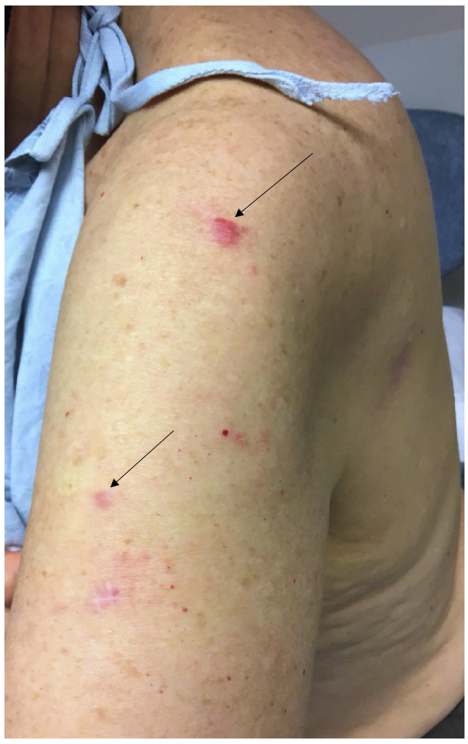

**Fig 1.** Clinical presentation of primary cutaneous marginal zone lymphoma (PCMZL), left shoulder and left arm. Scar from prior biopsy of similar papule.

and imaging as described above, the overall stage of her PCMZL was T3bN0M0.[1] The patient was prescribed Class I topical steroids with occlusion prior to consideration of radiation therapy.

As part of the patient's history, she noted prior testing for (and discovery of) an ATM mutation due to a family history of malignancy; an ATM mutation was found in her brother, who had prostate cancer, and in her niece, who did not have cancer but was tested secondary to a history of malignancy in the patient's brother and his wife. No other family members have been tested for the mutation, including a first cousin with a history of lymphoma.

## DISCUSSION

Although the testing for an ATM mutation in this patient preceded the diagnosis of PCMZL, it presents a possible genetic susceptibility in a common cancer with many questions about its etiology. There are no reports on the prevalence of ATM mutations in patients with PCMZL, but loss of ATM has been noted in both nodal and splenic MZLs.[6] ATM mutations have also been reported in both mantle cell lymphoma[7] and chronic lymphocytic leukemia, where its presence has been noted in 12% of the cases.[8] An ATM mutation may also prove to be a prognostic factor for certain cancers, as they have been associated with shorter progression-free survival in chronic lymphocytic leukemia.[8]

Although cutaneous relapses are common, PCMZL has a 5-year survival rate around 99%, with rare extension to extracutaneous sites.[1] While there is no curative treatment for this lymphoma, there may be curative treatment for individual lesions, including surgical excision, local radiotherapy,[9] or a combination of both.[9,10] Other initial treatments for limited stage I lesions include topical or intralesional steroids,[10] intralesional rituximab,[9,11] or intralesional interferon-alpha.[9,11] Recurrent or extensive skin lesions may be managed with intravenous or intralesional rituximab and, rarely, chemotherapy.[9,10] In the cases of *B. burgdorferi* infection-associated PCMZL, treatment with antibiotics (cephalosporins or tetracyclines) may be effective, although specifics on indication, treatment regimens, and antibiotic benefit are not definitive based on available literature.[9,11]

Mutations in ATM also have potential implications in treatment regimens, as cells deficient in ATM may have increased sensitivity to ionizing radiation due to inadequate double-stranded DNA repair mechanisms.[5] In our patient, who presented with PCMZL and an ATM mutation, treatment with radiation may be particularly successful due to this mechanism; however, sensitivity may lead to increased radiation-associated skin toxicity, as reported for patients with breast cancer and ATM mutations.[12] Despite this finding, the role of ATM mutations and risk of toxicity from radiation therapy remains controversial in the literature.[13] Other treatment approaches that exploit ATM mutations include synthetic lethality, in which cancer cells are killed by targeting their compensatory mechanisms of DNA repair. Although more germane to nodal cancers or chronic lymphocytic leukemia, early preclinical and animal studies suggest that the synthetic lethality of platinum drugs, nucleoside analogs (such as sapacitabine), ataxia telangiectasia and RAD3-related inhibition (using compounds such as VE821, VE822, and AZD6738), and poly (ADP-ribose) polymerase inhibitors (including olaparib) may have utility in cancers associated with ATM mutation.[5]

### Conflicts of interest

None disclosed.

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