Two cases of systemic mantle cell lymphoma involving the skin

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ABSTRACT

Mantle cell lymphoma (MCL) is a form of non-Hodgkin lymphoma that rarely affects skin. Cutaneous involvement is non-specific but usually indicates widespread disease. Herein we present two cases of MCL with secondary skin involvement. One case presented as an acneiform eruption on the face and had aberrant expression of bcl-2 and bcl-6 with weak CD5 expression. The second presented with multiple tumors on the abdomen and thighs. In both cases expression of Cyclin-D1 by the tumor cells was seen. Both patients died shortly after the diagnosis was established.

Key words: Blastoid mantle cell lymphoma, immunostaining, mantle cell lymphoma

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INTRODUCTION

Mantle cell lymphoma (MCL) is a rare type of B-cell lymphoma that represents 3%-10% of all non-Hodgkin's lymphoma subtypes. Skin involvement in this type of lymphoma is rarely seen. Most frequently, the skin lesions are accompanied by systemic symptoms, but several cases have been described with only cutaneous lesions without systemic involvement. Skin lesions may evolve before the clinical symptoms of internal organ lymphoma appear, representing the first sign of the disease. Due to the variability of its presentation that includes nonspecific papules that appear benign, a high level of suspicion is needed to recognize this lymphoma early. Herein we present two cases of the less common blastoid variant of MCL, one with aberrant expression of bcl2 and bcl6 involving the skin, highlighting the aggressive course that this disease may have, despite an inconspicuous clinical presentation.

CLINICAL CASES

Case 1

A 77-year-old man presented for routine skin exam and was noted to have slightly elevated pink papules on both his cheeks [Figure 1]. The patient otherwise had no complaints. The differential diagnoses included acneiform papules, but because these arose on sun-damaged skin, a biopsy for suspected basal cell carcinoma was performed. A shave biopsy after revealed a dense nodular and diffuse infiltrate of atypical medium-sized lymphocytes [Figure 2A and B]. The atypical lymphocytes expressed cyclin D-1, CD79a, bcl-2, and CD43. Many of the cells also expressed bcl-6. Ki-67 demonstrated a high proliferative index (approximately 90%). CD5 stained a few reactive T cells, but the tumor cells were negative [Figure 3]. Kappa and Lamba *in situ* hybridization demonstrated a sparse population of polytypic plasma cells. CD23, CD10, TdT, and CD21 immunohistochemical stains and *in situ* hybridization for Epstein–Barr virus (EBV) with EBV encoded RNA were negative. The diagnosis of blastoid variant of MCL, aberrant type was established and a workup for systemic lymphoma was recommended. Computer tomography revealed tumors involving the neck, chest, and abdomen. Bone marrow aspirate and biopsy confirmed stage IV MCL. The patient declined the offer of chemotherapy and died of lymphoma one year after the diagnosis was established.

Case 2

A 76-year-old woman with an 8-year history of systemic MCL presented with the multiple indurated papules on the abdomen and thighs. A punch biopsy showed a diffuse lymphocytic infiltrate in the dermis [Figure 4]. The atypical lymphocytes expressed cyclin D-1, CD5, CD45, CD79a, PAX5, and CD20 [Figure 5]. Weak expression of CD43

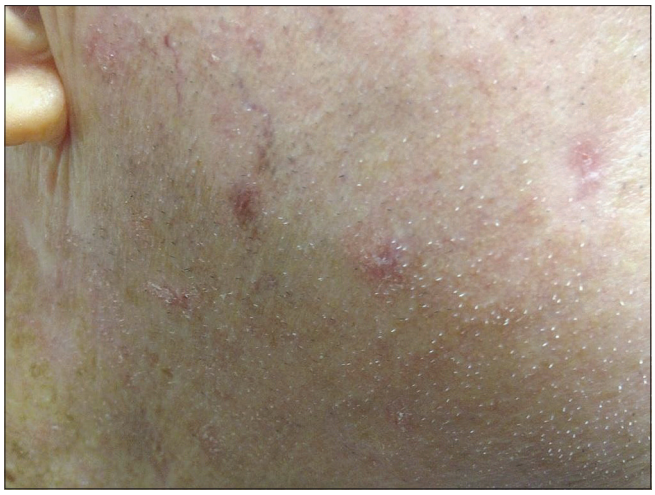

Figure 1: Multiple pink papules and sun-damaged skin of the right cheek

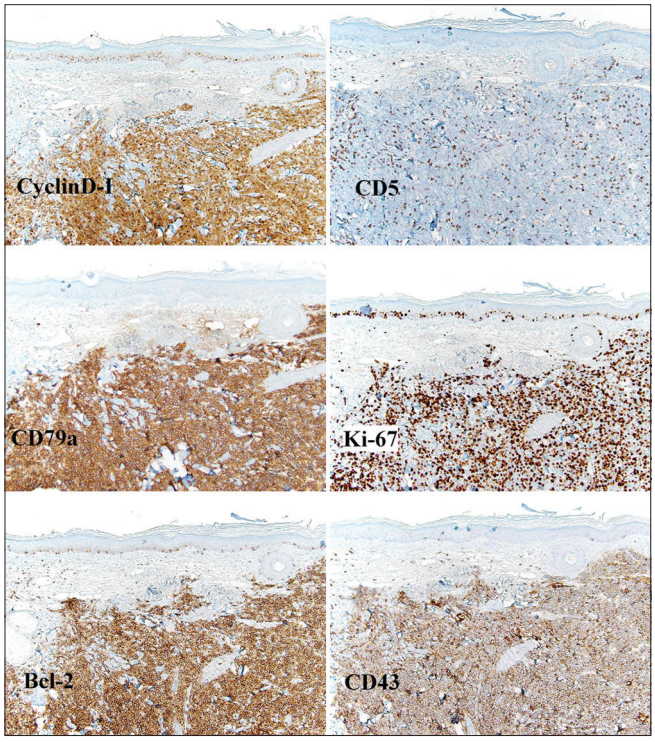

Figure 3: Immunohistochemical profile of the mantle cell lymphoma, Case 1 ×100

was seen. Ki-67 stained nearly 100% of the cells. CD3, CD4, and CD8 stained a sparse reactive T-cell infiltrate. No expression of TIA1, CD138, CD123, CD56, CD21, EBER, CD10, CD23, and TdT was seen. The diagnosis of cutaneous involvement of MCL, blastoid variant was established. The patient died of systemic lymphoma one year after the cutaneous diagnosis was made.

DISCUSSION

MCL is a non-Hodgkin's lymphoma that rarely involves the skin.[1] Skin involvement in MCL is seen predominantly in the

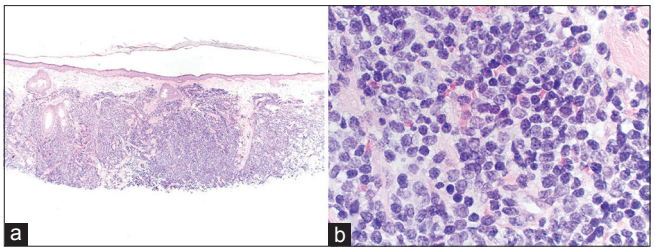

Figure 2: (a) Dense diffuse lymphocytic infiltrate with a Grenz zone. Hematoxylin and eosin (H and E) stained sections, ×40; (b) Monomorphic medium-sized atypical lymphocytes, with blast-like nuclei. H and E stained sections, ×400

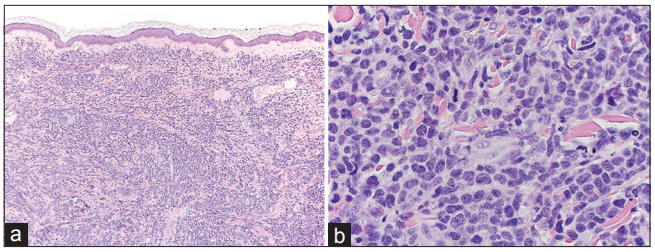

Figure 4: (a) Diffuse lymphocytic infiltrate, H and E stained sections, ×100. (b) Atypical medium-sized to large lymphocytes with multiple mitotic figures, H and E stained sections, ×600

elderly, with a median age of 65 years and a male to female ratio of 2.3:1.[2] Cutaneous involvement is rare in MCL and usually presents in the late stages of the disease. It usually indicates a poor prognostic sign, with death due to disease in the majority of patients 1–2 years after the cutaneous presentation.[3]

Skin lesions usually present as nodules or plaques, but the clinical picture may be diverse. MCL may also present as a maculopapular and petechial disseminated rash.[4] Such presentations, as well as the acneiform lesions present in our first patient may delay the diagnosis due to low suspicion for a biopsy. Skin lesions do not show any specific body site preference. In many cases and as in our first patient, skin lesions are the first visible signs of the disease. After the diagnosis is established in the skin, a thorough workup of the patient uncovers systemic involvement in the majority of cases. Several cases with isolated cutaneous involvement were reported and thought to have a more benign course, although the period of observation in the reported articles did not exceed three years.[5-9] Systemic involvement may develop several years after primary cutaneous disease.[9,10]

Classic MCL histolopathogically presents as a monotonous infiltrate of mostly small lymphocytes. This presentation should be differentiated from lymphoma with similar features, such as cutaneous involvement by chronic lymphocytic leukemia/small cell lymphoma (CLL/SLL). MCL has characteristic immunophenotypic and molecular genetic features that allow a diagnosis to be made in most cases. The infiltrate usually consists of small B cells ($CD19^+$, $CD20^+$, and $CD22^+$), co-expressing CD5 and CD43, and in most cases lacking

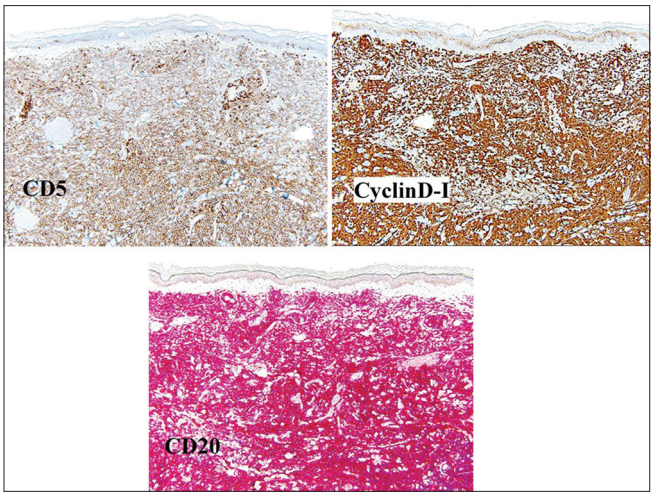

Figure 5: Immunohistochemical profile of the mantle cell lymphoma, Case 2. ×100

CD23 and CD10.[11] Typically, CD23 is positive in CLL/SLL and sometimes in follicle center lymphoma, and CD10 positivity is seen in follicle center lymphoma, helping to differentiate these from classic MCL.[12] Other B cell markers, such as CD79a seen in Case 1, will also be positive. Expression of CD5, although characteristic, is seen only in 85% cases of systemic MCL.[11,13,14] The most important immunohistochemical marker required in the evaluation of MCL is cyclin-D1. The overexpression of the *PRAD/cyclinD1* gene is the result of a chromosomal translocation t(11;14)(q13;q32), a classic feature in this subtype of non-Hodgkin's lymphoma. Expression of cyclin D1 positivity by immunohistochemistry correlates with higher mitotic index and worse prognosis.[11] Absence of cyclin-D1 is rare in skin, but has been reported.[14]

Blastoid MCL, a rare cytomorphologic variant of MCL, that is characterized by sheets of monotonous, medium-sized cells, with irregular nuclei, scant cytoplasm, and a high mitotic rate, has a more aggressive clinical course.[15] Two cytomorphologic subtypes of blastoid MCL include classic type, which is characterized by medium-sized blast-like nuclei with dispersed chromatin, and a large cell and pleomorphic variant with variable nucleoli, similar to cells of large B-cell lymphoma.[16,17] A combination of both blastoid changes and classic-type MCL may be seen.[18]

Aberrant immunophenotypic expression may occur in MCL and represents a diagnostic challenge. CLL/SLL and MCL are usually both CD5 positive, but CLL/SLL is CD23+/cyclin-D1−, whereas MCL is CD23−/cyclin-D1+.[19] However, CD23− CLL/SLL and CD23+ MCL may occur, requiring cyclin D1 to confirm MCL. Moreover, co-expression of CD10 and bcl-6, as seen in Case 1, is more typical of follicle center lymphoma, but has been reported in skin manifestations of MCL.[10,20] Cases with CD10 expression are likely to show blastoid morphology.[21] An additional challenge highlighted in our first patient was the lack of CD5 expression. The prognostic significance of aberrant expression in cutaneous MCL is unknown, but such cases, especially the pleomorphic blastoid variant, should be distinguished from diffuse large B-cell lymphoma, leg type (DLBCLLT), which rarely may express cyclin-D1.[22,23] These tumors are also very aggressive, but present with an immunophenotype that is bcL2+/MUM-1+, FoxP1+/IgM+ and usually bcl6 negative or weak.[24,25] Sox11 was recently found to be helpful in differentiating DLBCL with cyclin D1 expression and MCL.[26]

These two cases present additional examples of blastoid MCL in the skin, and highlight clinical and immunophenotypic features that may make the diagnosis challenging. More investigations and larger patient case series are needed to study the clinical and immunohistopathological features of cutaneous MCL, to determine the significance of aberrant immunophenotypic staining. A thorough workup is essential if the patient has no known history of lymphoma, followed by long-term observation for signs of systemic disease in cases of presumed primary cutaneous MCL, because appearance of the systemic involvement may be delayed.

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