Cutaneous Presentation of Mantle Cell Lymphoma

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Accepted March 16, 2010.

Mantle cell lymphoma (MCL) is a lymphoid malignancy of B-cells of the mantle zone or primary lymphoid follicle of lymph nodes. It is a moderately aggressive B-cell non-Hodgkin's lymphoma (NHL). MCL represents only 6% of all NHL (1).

MCL is listed in the new World Health Organization (WHO) European Organization for Research and Treatment for Cancer (EORTC) classification of cutaneous lymphomas that can secondarily involve the skin (2). According to this classification, "primary cutaneous lymphoma" refers to cutaneous T-cell lymphomas (CTCLs) and cutaneous B-cell lymphomas (CBCLs) that present in the skin with no evidence of extracutaneous disease at the time of diagnosis (2). The current WHO guidelines for the diagnosis of MCL rely on morphological examination and immunophenotyping with demonstration of cyclin D1 protein overexpression and/or the t(11;14)(q13;q32) translocation for confirmation (3).

There are two primary B-cell lymphomas that are more common than MCL; cutaneous marginal zone B-cell lymphoma, and primary cutaneous follicle centre lymphoma. The former is an indolent cutaneous B-cell lymphoma derived from post-germinal centre cells and characterized by a proliferation of small lymphocytes, lymphoplasmocytoid cells and plasma cells with monotypic cytoplasmic immunoglobulin. Follicle centre cell lymphoma is derived from follicle centre cells, consisting of a mixture of centrocytes and centroblasts (2, 4). Immunophenotyping assists in the differential diagnosis of these cutaneous lymphomas.

Skin involvement in MCL is very rare (1). We describe here a case of MCL involving the skin as the first manifestation of the disease, and we review the clinical features of reported cases of MCL with skin lesions.

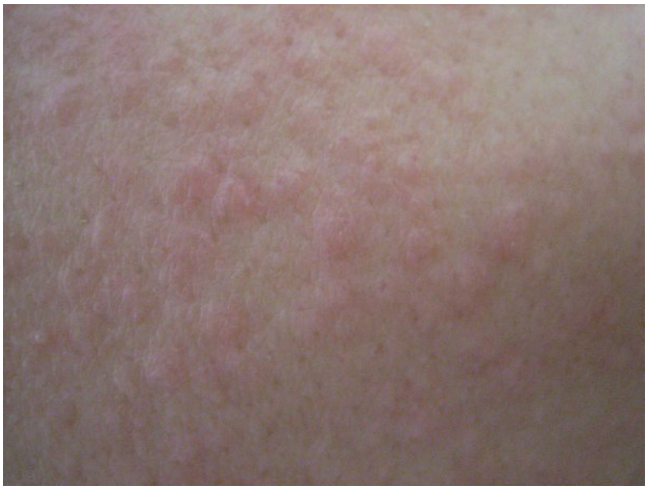

Fig. 1. Small, erythematous, slightly infiltrated papules on the back.

CASE REPORT

A 49-year-old woman was seen in our clinic because of widespread erythematous papules on the face, shoulders, back and chest that had been present for one month (Fig. 1). She had malaise, weight loss and fatigue. Multiple palpable bilateral axillary and cervical lymph nodes and hepatosplenomegaly were present.

Laboratory data showed a leukocyte count of 2300/mm^3, with 62% lymphoma cells, haemoglobin 6.9 g/dl, platelet count 78,000/mm^3 and elevated serum lactate dehydrogenase level (530 IU/l). A biopsy taken from a skin lesion showed monotonous infiltration of blastoid-type, small lymphocytes with irregular nuclear contours, very little cytoplasm and notched nuclei. There was a grenz zone with sparing of the epidermis. The growth pattern was perivascular, dense periadnexal and interstitial (Fig. 2A). MCL was diagnosed in an axillary lymph node and a skin biopsy specimen. Immunohistochemistry revealed that the neoplastic cells were CD5$^+$, CD20$^+$, CD43$^+$, CD79a$^+$, bcl-2 protein$^+$, with strong nuclear expression of cyclin D1 (Fig. 2B), and negative for cutaneous lymphocyte-associated

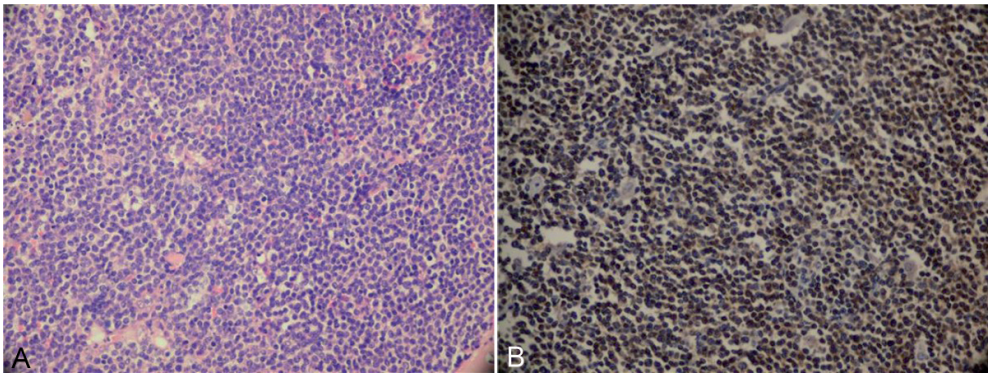

Fig. 2. Histological and immunohistochemical findings from the papules on the back. (A) Diffuse proliferation of small atypical lymphoid cells with fine chromatin (haematoxylin and eosin, ×100) and (B) cyclin D1 (immunoperoxidase, ×100).

Table I. *Mantle cell lymphoma with initially presenting skin lesions: a comparison of the medical literature*

Case (ref., year)	Age (years)/ sex	Site	Skin lesion	Other disease site	Immunohistochemistry	Outcome	Follow-up
1 (8, 1994)	65/F	Forehead	Nodules	LN, BM	CD19, CD20, CD22$^+$	DoD	11 m after diagnosis
2 (8, 1994)	77/F	Back, breast, arm	Tumoural plaques	Bronchus wall	CD5, CD22$^+$	DoD	1.5 y after diagnosis
3 (2, 1994)	51/M	Breast	Subcutaneous nodule	LN, liver, spleen	CD5, CD19, CD21, CD22, CD23, CD24, CD74$^+$	AwD	17 y after diagnosis
4 (2, 1994)	78/F	Breast, back	Nodules	None	CD5, CD19, CD21, CD22, CD24, CD38, CD74$^+$	DoD	3 y after diagnosis
5 (2, 1994)	43/M	Back, face, arm	Infiltrated plaque	LN, liver, spleen	CD5, CD19, CD20, CD21, CD22, CD23, CD24, CD25, CD45RA, CD74$^+$	AwD	
6 (2, 1994)	22/M	Breast	Nodules	None	CD5, CD19, CD20, CD21, CD22, CD23, CD24, CD25, CD45RA, CD74$^+$	AwD	5 y after diagnosis
7 (6, 2001)	61/F	Abdomen	Tumoural plaque	LN, BM, tonsils	CD5, CD19, CD20, CD45RA, Cyclin D1 CD45RA, CD74$^+$	DoD	15 m after diagnosis
8 (7, 2001)	47/M	Ear	Nodules	LN, BM	CD5, CD19, CD20, Cyclin D1$^+$	AwD	3 y after onset
9 (10, 2002)	56/M	Breast, back	Erythematous papules	LN, BM, PB	CD5, CD20, CD43, Cyclin D1$^+$	DoD	1 y after treatment
10 (10, 2002)	89/M	Breast, back, abdomen	Infiltrated purpuric plaques	LN, BM, PB	CD5, CD20, CD43$^+$	DoD	5 d after diagnosis
11 (4, 2002)	85/M	Leg	Macular rash	LN, BM, buccal mucosa	CD5, CD20, Cyclin D1$^+$	DoD	20 m after onset
12 (4, 2002)	76/M	Thigh	Nodule	None	CD5, CD20, Cyclin D1$^+$	AwD	30 m after onset
13 (4, 2002)	56/M	Chest	Nodules	BM, GI	CD20, Cyclin D1$^+$	AwD	21 m after onset
14 (4, 2002)	57/M	Legs	Maculopapular rash	LN, BM, PB	CD5, CD20, Cyclin D1$^+$	DoD	9 m after onset
15 (9, 2006)	62/M	Back, arm, chest, penis shaft	Nodules, ulcers	LN, GI, oral mucosa, tonsils, spleen,	CD5, CD20, CD43, Cyclin D1$^+$	AwD	4 m after diagnosis
16 (Our case)	49/F	Face, shoulders, back and chest	Erythematous papules	LN, BM, PB, spleen	CD5, CD20, CD43, CD79a, bcl-2 protein, cyclin D1$^+$	DoD	4 m after diagnosis

LN: lymph node; BM: bone marrow; PB: peripheral blood; GI: gastrointestinal tract; AwD: alive with disease; DoD: died of disease; y: years; m: months; d: days.

antigen (CLA). Computed tomography of the whole body revealed multiple lymphadenopathy in the cervical, supraclavicular, para-aortic and axillary regions. Bone marrow examination showed involvement by MCL. Intense uptake zones in the bilateral cervical, axillary and inguinal lymph nodes, as well as spleen were detected by positron emission tomography scan. Despite chemotherapy, the patient's general condition deteriorated, and she died 4 months after presenting with skin lesions.

DISCUSSION

MCL is positive for pan-B-cell markers (CD79a, CD19, CD20 and CD22), as well as the T-cell marker CD5 and CD43, and is usually negative for CD10 and CD23 (3, 5). Clinically, MCL usually presents in elderly patients with a median age of 65 years; males predominate at a ratio of 2.3:1. Extranodal presentation of MCL is common and may involve bone marrow, spleen, liver, gastrointestinal tract, peripheral blood, and Waldeyer's ring; however, the skin is rarely affected. Most of the patients have advanced stage MCL at the time of diagnosis (1).

Only 18 patients with skin lesions have been reported (1, 3, 6–11). Although primary involvement of the skin with MCL is rare, secondary involvement is described to occur in 17% of cases with stage IV MCL (11).

Table I summarizes the clinical and immunophenotypical features of the 16 patients who initially presented with skin lesions at the time of diagnosis of MCL. The sites were the trunk in 11 of 16 patients, followed by face and arms in 3 cases and legs in 2 cases. The most common skin involvement was nodular, whereas only one patient presented with erythematous papules similar to those of our patient. Most of the patients also had extracutaneous lesions, such as lymph node, bone marrow or gastrointestinal tract. In all cases except two, the neoplastic cells were positive for CD5. Most of the patients either died with progressive disease or showed no response to combined chemotherapy. The mean duration from diagnosis to death was 33 months.

To the best of our knowledge, there have been only 2 patients reported who presented with a primary cutaneous MCL without evident systemic involvement (patient no. 4 and 10).

MCL with skin involvement is often associated with blastoid cytological features (3). A blastoid variant is recognized as being composed either of cells having very dispersed chromatin and a high mitotic rate resembling lymphoblasts (classic type) or of larger and sometimes pleomorphic cells often with nucleoli, resembling the cells of a diffuse large B-cell lymphoma (DLBCL) (pleomorphic type) (7). Blastoid MCL can closely resemble DLBCL or B-lymphoblastic leukaemia/lymphoma (B-LBicL); we therefore advise liberal use of a stain for cyclin D1, which is almost always positive in MCL but not in DLBCL or B-LBicL.

Yatabe et al. (12) examined 151 cases of lymphoma with MCL morphology for cyclin D1 overexpression. Of

these, 128 cases (85%) showed positive nuclear staining for cyclin D1, while the remaining 23 (15%) were negative. They have suggested that cyclin D1-positive and negative groups may represent different entities and that the former closely fits the characteristics of classical, typical MCL. Recent data suggest that, although uncommon, MCL can occur if cyclin D2 or cyclin D3 or both replace cyclin D1 (13).

Although our patient was negative for CLA, one case of blastoid MCL involving skin has been shown to express CLA (7).

MCL with skin involvement is clearly associated with poor prognosis. Making a correct diagnosis is therefore important and, in younger patients especially, aggressive high-dose chemotherapy is indicated.

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