

A Case of Primary Cutaneous Marginal Zone B-cell Lymphoma

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We herein present a rare case of a 42-year-old man with primary cutaneous marginal zone lymphoma (MZL) of the B-cell type on his shin. MZL is known to be the cutaneous counterpart of MALT (mucosa-associated lymphatic tissue) lymphoma. Histopathologically, MZL is characterized by multi-nodular infiltrates of centrocyte-like and centroblast-like marginal cells with bottom-heavy patterns, lymphoplasmacytoid differentiation, typical distribution of tumor cells in the marginal zone and follicular colonization by tumor cells. This B-cell lymphoma of a benign grade should be differentiated from mantle cell lymphoma and follicular center cell lymphoma. (*Ann Dermatol* 11(2) 124~128, 1999).

Key Words: Primary cutaneous marginal zone lymphoma

Recently, the designation of MALT (mucosa-associated lymphatic tissue)-type lymphoma or cutaneous MALT lymphoma (MALToma) does not extend to the skin-involving form because there is actually no lymphoepithelial MALT in skin^{1,3}. Accordingly, primary cutaneous marginal zone lymphoma (MZL) is considered to be the cutaneous counterpart of MALToma arising from guts¹. It invariably shows a chronic indolent course without progressive nodal spreading or distant metastasis². However, until now, the concept of MZL as a disease entity has not been unified although the histopathological and immunophenotypical characteristics were partially defined³. Moreover, several cutaneous lymphomas possessing histologically borderline natures have posed the dilemma in the diagnosis of MZL:^{3,5} follicular center cell lymphoma showing marginal differentiation, mantle cell lymphoma with blastic transformation and MZL with numerous follicular colonization and immunocytoma.

We herein report a case of primary cutaneous

MZL that has not yet been reported in Korea.

CASE REPORT

A skin lesion developed on the shin of a 42-year-old man. This lesion had been present for 2 years without variation in size. A physical examination revealed an erythematous infiltrative, 3 × 3 cm nodule on his pretibial area (Fig. 1). He did not show any hepatosplenomegaly or peripheral lymphadenopathy. He had no history of other medical illnesses. A complete blood cell count did not show any specific findings except milder lymphocytosis (60%, normal ranges; 19-48%). There were no other abnormal findings in the laboratory data as follows; routine chemistry profiles, urine analysis, a peripheral blood smear, bone marrow aspiration, simple x-ray film on his leg and gastrofiberscopic examination. After the final diagnosis, the patient refused any anti-cancer therapy. The patient is currently well without any lesional progression.

Histopathological study

On hematoxylin-eosin-stained sections, a biopsy specimen of his skin lesion demonstrated multi-nodular infiltrates composed of coalescing polypotypic follicles in the lower dermis (Fig. 2). The pale tumor cells were mainly distributed in the

Received June 1, 1998.

Accepted for publication September 28, 1998.

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Fig. 1. A well-defined erythematous infiltrative nodule on his pretibial area.

Fig. 2. A biopsy specimen of his skin lesion demonstrating coalescing multi-nodular infiltrates in the lower dermis(H & E, $\times 50$).

Fig. 3. Centrocyte-like and centroblast-like marginal cells with pale cytoplasm permeating germinal centers along with active mitotic figures(H & E, $\times 400$).

Fig. 4. Lymphoplasmacytoid cells and plasma cells in the periphery of nodular infiltrates(H & E, $\times 400$).

swollen marginal zone of the follicles. Centrocyte-like and centroblast-like cells with pale cytoplasm were intermixed with small lymphocytes, giant cells, and histiocytes(Fig. 3). A permeation of reactive germinal centers by centrocyte-like tumor cells was found along with mitotic figures. In the periphery of the nodular infiltrates, lymphoplasmacytoid cells without coarse clock-face chromatin and plasma cells were found(Fig. 4). There were no lymphoepithelial structures or epithelial de-

struction at any field.

Immunohistochemical Studies

The standard avidin-biotin complex(ABC) immunoperoxidase method was performed on the frozen or paraffin-embedded skin specimens using a wide panel of monoclonal antibodies. The lymphoid infiltrates reacted with CD20(L26, DAKO, Copenhagen, Denmark)(Fig. 5-A) and CD22(Leu14, DAKO). However, none of the sections expressed

Fig. 5. Immunohistochemical findings of the infiltrating tumor cells reacting with CD20(A, $\times 200$) and surface κ -light chains(B, $\times 200$).

CD2(Leu5a, Becton-Dickinson, Sunnyvale, U.S.), CD4(Leu3a, Becton-Dickinson), CD5(Leu1, Becton-Dickinson), CD8(OKT8, Ortho Diagnostics, Raritan, U.S.), CD10(CALLA, Zymed, San Francisco, CA, U.S.), CD30(Ki-1, DAKO), CD43(Leu22, MT1, Becton-Dickinson), CD45RO(UCHL-1, DAKO), and CD56(NCAM, NKH-1, Zymed).

Also, we studied the bcl-2 expression in biopsies of the skin lesions by the labelled streptavidin biotin detection method using monoclonal mouse anti-human bcl-2 antibody(DAKO, Glostrup, Denmark, 1:100 diluted) on paraffin-embedded tissue sections. The infiltrative cells showed negative reactions to bcl-2.

Light-chain Restriction Studies

For identification of light-chain monoclonal restriction of surface IgG/M/A, the fresh specimen sections were stained using an ABC immunoperoxidase method with antisera to κ - and λ -light chains(DAKO). The infiltrative tumor cells showed positive responses to surface κ -light chains(Fig. 5-B). However, there was no positivity to λ -light chains in the tumor cells.

Ig Gene Rearrangement Analysis

We performed Southern blot analysis for detection of Ig gene rearrangement on DNA extracts from

frozen specimens of the skin lesion. After the DNA had been extracted from the specimens by a phenol-chloroform method, it was then digested with Bam HI + Hind III for JH probe, Eco RI for C probe, and Eco RI + Hind III for C probe. It was hybridized with a 32 P-labelled probe after size-fractionation by a 0.8% agarose gel electrophoresis. In this case, Southern blot analysis using three probes revealed clonality of Ig gene rearrangement.

DISCUSSION

MALT lymphoma(MALToma), a low-grade B-cell lymphoma, can occur in any mucosa-containing anatomical sites^{1,4}. According to the involved organs, MALToma has been variously nominated as follows⁵⁻⁹; MZL in the spleen, monocytoid/parafollicular B-cell lymphoma in lymph nodes, cutaneous MALT-type lymphoma or primary cutaneous MALToma or cutaneous monocytoid B-cell lymphoma in the skin. Recently, Thieblemont et al¹⁰ reported 10 cases of cutaneous MALToma among 108 patients with varied MALTomas. Also, Pelstring et al¹¹ and Bailey et al¹² demonstrated cutaneous MALTomas in 5 cases and 15 cases, respectively.

However, the confusing designation of skin-involving MALTomas is almost replaced by cuta-

neous MZL^{12,13}. Unfortunately, to date, the debate continues about the disease entity or classification of MZL; 1) MZL has been considered the prototype explaining the tumorigenesis of cutaneous B-cell lymphoma by the advocators of "marginal cell hypothesis"^{1,6,14}. 2) MZL has often been subclassified into a third "provisional group" in view of "follicular cell hypothesis"^{3,5,15}.

An etiopathogenesis of MZL or MALToma has not yet determined although the cumulative stimulants (e.g. *Helicobacter pylori*, *borrelia burdorferi*, hepatitis C virus) or autoimmune mechanisms may be implicated in the development of these lymphomas^{2,3,16,17}. In particular, *H. pylori* may provoke *H. pylori*-activated T-cell clones in that it has been detected in 80% of gastric MALT lymphoma¹⁷.

Clinically, patients with MZL show recurrent deep-seated solitary or regionally clustered nodules on extremities or the trunk^{2,18}. This slow indolent tumor usually shows asymptomatic localization and has a favorable clinical course^{19,20}. Our patient presented with a red nodule located on his shin.

Histopathologically, MZL has the characteristic findings identical with MALT lymphoma as follows^{2,5,7-9,12}; multi-nodular infiltrates composed of coalescing polytypic follicles in the lower dermis, centrocyte-like and/or centroblast-like cells (monocytoid B-cells) with clear cytoplasm, heterogenous cell components (e.g. small lymphocytes, histiocytes, eosinophils, giant cells, plasma cells), lymphoplasmacytic and/or lymphoplasmacytoid cells in the periphery of nodular infiltrates, a typical distribution of pale tumor cells in the swollen marginal zone, the permeation of germinal centers by centrocyte-like tumor cells ("follicular colonization") and Dutcher bodies at the periphery. A sole differential point of MZL from true MALT lymphoma is the absence of lymphoepithelial structures^{6,8}. Our case showed the compatible histological findings mentioned above. However, we could not find Dutcher bodies at the plasma cell rich-zone.

Immunophenotypically, MZL usually shows CD20+, CD22+, CD79a+, KiM1p+, CD5-, CD10-, CD23- and CD43-^{3,7,8,13,18}. It usually shows light-chain monoclonal restriction of surface and/or cytoplasmic IgM κ -light chain.^{2,8,18} Reactivity of tumor cells to bcl-2 is not consistent, compared with secondary follicular center cell lymphoma (FCCL)^{3,4,18}. Our case also demonstrated

CD20+, CD22+, CD5-, CD10-, CD43-, surface κ -light chain+ and negative responses to bcl-2.

Differential diagnosis from mantle cell lymphoma (MCL), FCCL and cutaneous immunocytoma (CI) may be difficult. MCL characteristically shows rapid dissemination of the lesions, vague nodularity, small monomorphous lymphoid cell population, naked follicular dendritic cells, vascular hyaline changes, eosinophilic epithelioid histiocytes and pale tumor cells compressing reactive centers without lymphoplasmacytoid differentiation²⁰. MCL invariably demonstrates CD5+, CD43+, IgM+, IgD+, PRAD-1 (cyclin-D1)+ and λ -light chain+^{20,21}. It also shows t(11;14)q(13;32) translocation and bcl-1 over-expression²⁰. FCCL shows no lymphoplasmacytoid differentiation in the periphery of nodular infiltrates^{5,20}. The principal tumor cells of FCCL are not the intermediate centrocyte-like cells or centroblast-like cells shown in MZL but rather non-cleaved centroblasts and cleaved centrocytes^{3,5,20}. Moreover, FCCL commonly demonstrates CD10+, t(14;18)+ and bcl-2 overexpression^{3,20}. CI may be difficult to differentiate from MZL in many aspects; 1) The distinctive histological findings shown in MZL are exemplified by what has been termed CI by some investigators^{20,22}. 2) It demonstrates the overlapping immunophenotypical findings with MZL (CD5-, CD10-, CD23-, cyclin-D1-)²³. However, CI possesses the unique aspects in that it invariably shows typical top heavy patterns of infiltration, cellular infiltrates vertically oriented along the course of hair follicles, marked heterogeneity of cell components resembling pseudolymphoma and variable T-cell rich portions^{22,25}. The immunotypes of CD19+, CD20+, CD22+, CD79a+ or KiM1p+ are usually lacking in CI^{20,22}.

Although all MALTomas are indolent diseases, non-gastrointestinal (GI) MALTomas including MZL seem to progress slightly more than pure GI MALTomas¹⁸⁻²⁰. For non-GI patients, a poorer outcome was associated with a poor performance status, presence of abdominal or thoracic lymph nodes, anemia, hypoalbuminemia and high β -microglobulin level¹⁰. Our case did not show these prognostic factors associated with a poorer clinical course.

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