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Case Report

Relapse of Laryngeal Mucosa-associated Lymphoid Tissue Lymphoma in the Skin

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Abstract

The prognosis for patients with lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma is good, but multifocal lesions appear in 30–40% of patients. We report a 65-year-old woman who presented with painless, firm nodules on her right arm and face. Nine years previously, the patient presented at Tzu Chi Hospital with hoarseness and a sensation of a lump in the throat. She was first diagnosed with primary MALT lymphoma of the larynx. Subsequently, multiple painless nodules were noted on her right eyelid, right axilla, and right arm. The intervals between recurrences became shorter and skin lesions relapsed more frequently. The nodules were resected and histopathology showed small B-cells including marginal zone (centrocyte-like) cells, monocytoid cells, and small lymphocytes. Most centrocyte-like cells showed positive staining for CD20 marker in the plasma membrane—this is entirely specific for B-lymphocytes. Follicular dendritic-like cells had positive staining with stromal cell-derived factor-1α (SDF1α) antibody. The nuclei of the centrocyte-like cells stained positive with CXCR4, a ligand of SDF1α. This may indicate that MALT lymphoma grows in a self-sustained microenvironment. (*Tzu Chi Med J* 2009;21(3): 261–264)

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1. Introduction

Marginal zone B cell lymphoma (MZL) can be divided to three subgroups: the extranodal mucosa-associated lymphoid tissue (MALT) type, splenic MZL, and nodal MZL. MZL occurs in 5–17% of all non-Hodgkin lymphomas, and 50–70% of MZL is MALT lymphoma. In 1983, Isaacson and Wright first coined the term MALT lymphoma (1). In 1991, researchers found that MALT lymphoma was strongly associated with *Helicobacter pylori* infection (2). Subsequently, other infections were found to cause MALT lymphoma, including *Borrelia burgdorferi* (Lyme disease) in cutaneous MALT lymphoma (3), *Chlamydia psittaci* in ocular adnexal MALT lymphoma (4), and *Campylobacter jejuni* in immunoproliferative small intestinal disease (5). Genetic alterations were also noted, including t(11;18)(q21;q21) in gastric, skin, salivary, lung, and thyroid MALT lymphoma; t(14;18)(q32;q21) in gastric, skin, salivary, lung, and liver

MALT lymphoma; and t(1;14)(p22;q32) in salivary and lung MALT lymphoma (6).

We report a patient with a relapse of laryngeal MALT lymphoma in the skin with pathology demonstrating small B-cells including marginal zone (centrocyte-like) cells, monocytoid cells, and small lymphocytes. Expression of stromal cell-derived factor-1α (SDF1α) and CXCR4 was positive in follicular dendritic-like cells and centrocyte-like cells, respectively.

2. Case report

A 65-year-old woman presented with painless, firm nodules on her right arm and face. Nine years previously, she had presented with hoarseness and a sensation of a lump in the throat at Tzu Chi Hospital and had been diagnosed with primary lymphoma of MALT of the larynx (1.5 cm in size) (7). Radiation therapy was done at Koo Foundation Sun Yat-Sen Cancer Center—after this, her symptoms disappeared. Six and 7 years later, painless nodules were reported on the right eyelid and right axilla, respectively. Two years later, another nodule was also reported in the right axilla. All nodules were resected and pathologic reports were positive for MALT lymphoma. Over the next 3 months, multiple nodules developed over the right upper extremity and forehead. The largest nodule appeared on the right arm and it enlarged insidiously to 1.2 cm in diameter. Other nodules that were deep red to violaceous infiltrated plaques or grouped nodules appeared with random distribution and in quick succession (Fig. 1). An area of infiltrated erythema on the surface surrounded some nodules.

A skin biopsy was performed on the right arm. Histopathology showed a well-defined tumor with dense small lymphocytic infiltration. No angioinvasion or epithelium invasion was found. High power views showed morphologically heterogeneous small B-cells including marginal zone (centrocyte-like) cells, monocytoid cells, and small lymphocytes (Figs. 2A and 2B). Immunoreactivity was performed including CD20 antibody (dilution titer 1:100; Dako Denmark A/S, Glostrup, Denmark), CD45RO antibody (dilution titer 1:100; Dako Denmark A/S), SDF1α antibody (dilution titer 1:50; R&D Systems, Minneapolis, MN, USA) and CXCR4 antibody (dilution titer 1:100; R&D Systems) (Figs. 2C–F). There were very few positively stained CD45RO T-lymphocytes in the tumor mass. There was positive staining for CD20 markers in the plasma membrane in B-lymphocytes, demonstrating markers entirely specific for MALT lymphoma. Follicular dendritic-like cells had positive staining with SDF1α antibody. The nuclei of the centrocyte-like cells stained positive with CXCR4, a ligand of SDF1α.

Normal liver function and renal function were noted in a serum examination. Serum lactate dehydrogenase was also within the normal range. Generalized lymphadenopathy was not found. A whole body computed tomography scan also did not show laryngeal relapse. The patient did not have fever, weight loss, or fatigue (B symptoms). The final diagnosis in this patient was a relapse of laryngeal MZL of MALT lymphoma in the skin. Systemic chemotherapy with chlorambucil 4 mg/day was given for 1 month. Six months later, a skin lesion relapsed on the face, and therapy with chlorambucil 4 mg/day was given for 3 weeks. No skin or systemic recurrence was found after 2 years of follow-up.

3. Discussion

MALT lymphoma comprises morphologically heterogeneous small B-cells including marginal zone (centrocyte-like) cells, monocytoid cells, small

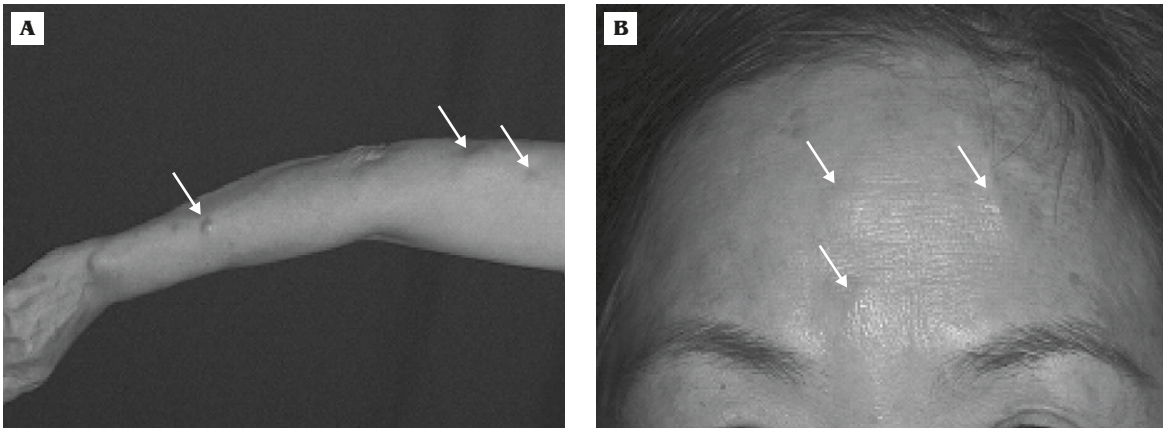

Fig. 1 — (A) Multiple violaceous, painless, firm nodules on the right arm. (B) Multiple skin-colored nodules on the forehead.

lymphocytes, immunoblasts, and centroblast-like cells. The median age of onset for MALT lymphoma is 60 years [8]. The primary sites of MALT lymphoma include the gastrointestinal tract (50%) and locations outside the gastrointestinal tract, including the lung (14%), salivary gland (14%), orbit (12%), skin (11%), thyroid (4%), and breast (4%) [4]. Multifocal lesions appear in 30–40% of patients [9]. CXCR4 and CXCR5

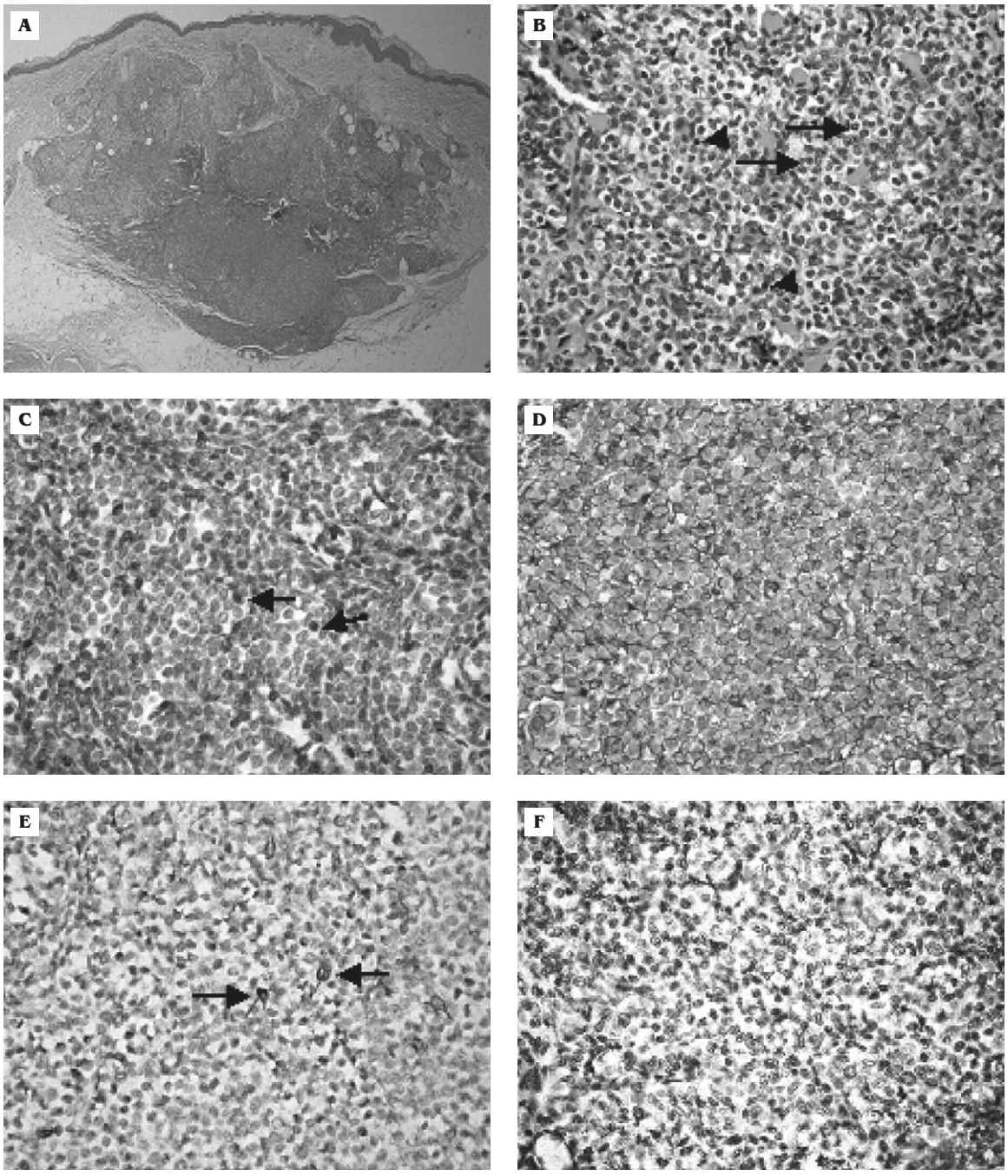

Fig. 2 — (A) A well-defined tumor with dense lymphocytes infiltrating the dermis [hematoxylin & eosin (H&E); original magnification, 125×]. (B) Centrocyte-like cells (arrows) and small lymphocytes (arrowheads) infiltrating the dermis (H&E; original magnification, 400×). (C) Expression of CD45RO-positive T cells (arrows) (H&E; original magnification, 400×). (D) Most centrocyte-like cells express CD20-positive staining of the plasma membrane of B cells (H&E; original magnification, 400×). (E) Expression of SDF1α-positive follicular dendritic-like cells (arrows) in the dermis (H&E; original magnification, 400×). (F) CXCR4-positive staining of the nucleus of the centrocyte-like cells (H&E; original magnification, 400×).

have been demonstrated as the main chemokine receptors involved in B cell homing to other tissues [10–12]. SDF1/CXCR4 interaction can induce cell migration and inflammation processes and this signal activates ERK1/2 and stimulates cell proliferation and survival in several human cancer types [13]. In addition, almost all of the tumors described so far were found to express CXCR4 and were responsive to an SDF-1 gradient [14]. This may explain why some lymphomas that express chemokine receptors have a wide dissemination to the lymph nodes, bone marrow, and peripheral blood; others are confined to a limited number of organs with minimal or no lymph node involvement.

In the patient outlined in this study, immunostaining of CXCR4 showed positive centrocyte-like cells. The expression of CXCR4 in MALT lymphoma may significantly indicate a wide organ dissemination pattern. Scattered follicular centrocyte-like cells and small stromal cells had positive staining with SDF1α antibody. This suggests that elevated tissue levels of SDF1α are associated with increased attraction of circulating cancer cells in different parts of the body and may indicate a self-sustained microenvironment in MALT lymphoma. Our patient developed MALT lymphoma in the larynx first, and the lesion disappeared after radiotherapy. The symptoms of hoarseness and a sensation of a lump in the throat have not recurred. However, the skin lesions relapsed more frequently and the intervals between recurrences became shorter. This may indicate circulatory seeding of cancer cells by SDF1/CXCR4 interaction in tumor cell growth.

Local radiation or excision is the choice for MALT, but wide organ dissemination may develop even in the absence of evident clinical symptoms. Because histological examination of the skin biopsy showed positive staining for SDF1 and CXCR4, we propose that systemic chemotherapy may be needed to treat the multifocal lesions of MALT lymphoma as early as possible. This may also suggest new avenues of treatment through elimination of CXCR4-positive cancer cells.

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