Pathol. Oncol. Res. (2008) 14:489–492
DOI 10.1007/s12253-008-9033-0

BRIEF COMMUNICATION

Tonsillar Lesions of Infectious Mononucleosis Resembling MALT Type Lymphoma. A Report of Two Cases

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Received: 25 February 2008 / Accepted: 17 March 2008 / Published online: 1 July 2008

Abstract Infectious mononucleosis (IM) is an acute lymphoproliferative disorder that typically occurs in young patients and is usually caused by Epstein–Barr virus. We report here, two cases of tonsillar lesion of IM resembling marginal zone B-cell lymphoma mucosa-associated lymphoid tissue (MALT) type. The patients consisted of an 18-year-old Japanese woman and a 36-year-old Japanese man. Both patients presented with tonsillar mass. Histologically, in one case, the tonsil showed diffuse proliferation of medium-sized lymphocytes. The medium-sized lymphocytes had round or slightly indented nuclei with a small solitary nucleoli and abundant clear cytoplasm and somewhat resembled monocytoid B-cells. In the remaining one case, the lymphoid follicles had hyperplastic germinal centers with ill-defined borders surrounded by a sheet-like proliferation of polymorphous infiltration showing a marginal zone distribution pattern. On high-power field, the interfollicular area was diffusely infiltrated by a polymorphous infiltrate of medium-sized lymphocytes with angulated nuclei somewhat resembling centrocyte-like cells, immunoblasts, plasma cells, plasmacytoid cells and histiocytes with or without epithelioid cell feature. However, there were no CD43+ B-cells in either lesion. Moreover, the polytypic nature of the B-cells was demonstrated by immunohistochemistry or polymerase chain reaction. Although MALT type lymphoma rarely affected young adults, notably, a number of cases have been reported in the tonsil. The present two cases indicated that acute IM should be added to the differential diagnosis for MALT type lymphoma in young adults.

Keywords Infectious mononucleosis · Epstein–Barr virus · Tonsil · MALT type lymphoma · Immunohistochemistry

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Introduction

Infectious mononucleosis (IM) is an acute lymphoproliferative disorder (LPD) that typically occurs in young patients and is usually caused by Epstein–Barr virus (EBV) [1, 2]. The diagnosis of infectious mononucleosis is usually based on clinical and serologic findings [1]. However, lymphoid tissue biopsy may be performed when malignant lymphoma is a clinical consideration in patients demonstrating an atypical clinical feature [1, 3, 4]. Atypical features include age over 30 years, generalized lymphadenopathy, or isolated lymphadenopathy in an unusual site, tonsillar mass, negative heterophil antibody titer or absence of atypical lymphocytosis in peripheral blood.

In such instances, diagnostic problems for surgical pathologists may arise because the histopathological features of IM may simulate those of either Hodgkin

lymphoma or non-Hodgkin lymphoma [1, 3, 4]. We report here two cases of tonsillar lesion of IM resembling marginal zone B-cell lymphoma mucosa-associated lymphoid tissue (MALT) type.

Case Reports

Case 1 An 18-year-old Japanese woman presented with bilateral tonsillar masses with exudative change accompanied by an episode of high fever. Right tonsillar biopsy was performed and she was tentatively diagnosed as having malignant lymphoma and was treated with radiotherapy (30Gy). Subsequently, laboratory studies demonstrated an elevated white blood cell count of 17800/mm^3 with lymphocytosis of 28% including atypical forms, an increased erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia and elevated lactate dehydrogenase level. Monospot test for IM was positive. There was no further treatment administered, and the patient remains well at the last follow-up 124 months later.

Case 2 A 36-year-old Japanese man presented with a left tonsillar mass and left cervical lymphadenopathy. A left tonsillar biopsy was performed and he was tentatively diagnosed as having malignant lymphoma. Laboratory studies demonstrated white blood cell count of 3800/mm^3 with a lymphocytosis of 45% including atypical forms, elevated lactate dehydrogenase level, and moderately abnormal liver function tests. Subsequent serologic tests for EBV showed the following results: a viral capsid antigen (VCA) IgG titer of 0.2 (normal range <1), a VCA IgM titer of 2.6 (normal range <1), an early antigen titer of 1.1 (normal range <1), and a nuclear antigen titer of 0.2 (normal range <1). There was no further treatment administered, and the patient was well at the last follow-up 2 months later.

Materials and Methods

Specimens were fixed in formalin, routinely processed and embedded in paraffin. For light microscopic examination, the sections were stained with hematoxylin–eosin (HE).

Immunohistochemical studies were performed using a Ventana automated (BenchMarkTM) stainer according to the manufacturer's instructions. A panel of antibodies included human immunoglobulin light chains (kappa and lambda) (Novocastra, Newcastle, UK), PS-1 (CD3; Immunotech, Marseille, France), 1F6 (CD4; Novocastra), 4C7 (CD5; Novocastra), 4B11 (CD8; Novocastra), 1B12 (CD23; Novocastra), L26 (CD20; Dako), Ber-H2 (CD30; Dako), DFT-1 (CD43; Novocastra) and CNA.42 (anti-follicular dendritic cell; Dako). Sections with known reactivities to antibodies assayed served as positive controls and sections treated with normal rabbit- and mouse serum served as negative controls.

In situ hybridization (ISH) with Epstein–Barr virus-encoded small RNA (EBER) oligonucleotides was performed to test for the presence of EBV small RNA on formalin-fixed paraffin-embedded sections using a Ventana automated (BenchMarkTM) stainer.

In Case 1, paraffin-embedded tissues from the biopsy specimen were prepared for polymerase chain reaction (PCR), and rearranged heavy-chain genes were amplified using the seminested PCR method as described by Wan et al. [5].

Results

In Case 1, the tonsil showed diffuse proliferation of medium-sized lymphocytes. There were no residual lymphoid follicles. Areas of geographic necrosis were present. The medium-sized lymphocytes had round or slightly indented nuclei with a small solitary nucleoli and abundant clear cytoplasm (Fig. 1a). The morphological findings of the medium-sized lymphocytes resembled "monocytoid B-cells (MBC) [6, 7]. Numerous small lymphocytes, plasma cells and plasmacytoid cells, and a few immunoblasts and neutrophils were also present (Fig. 1a). Single cell necrosis (apoptotic or karyorrhectic) was observed. Lymphoepithelial lesion (LeL) was not evaluated.

Immunohistochemical study demonstrated that the medium-sized lymphocytes resembling MBCs were CD3−, CD5−, CD20+, CD23−, CD30−, CD43−, bcl-2−, intracytoplasmic immunoglobulin(cIg)−. Majority of the small lymphocytes expressed CD8+ T-cells.

In Case 2, the lymphoid follicles had hyperplastic germinal centers with ill-defined borders surrounded by sheet-like proliferation of polymorphous infiltration showing a marginal zone distribution pattern (Fig. 1b). On high-power field, the interfollicular area was diffusely infiltrated by a polymorphous infiltrate of small-to-medium-sized (transformed) lymphocytes, immunoblasts accompanied by numerous of plasma cells and plasmacytoid cells (Fig. 1d). Histiocytes with or without epithelioid cell features were seen (Fig. 1c). These epithelioid cells occasionally formed small clusters (Fig. 1c). There were no Hodgkin or Reed–Sternberg-like cells. The small lymphoid cells usually had regular round nuclei, whereas medium-sized cells occasionally showed nuclear irregularities and a moderate amount of clear cytoplasm (Fig. 1d). In the interfollicular area, single cell necrosis (apoptotic or karyorrhectic) was observed, but extensive necrosis was absent. LeL was not evaluated.

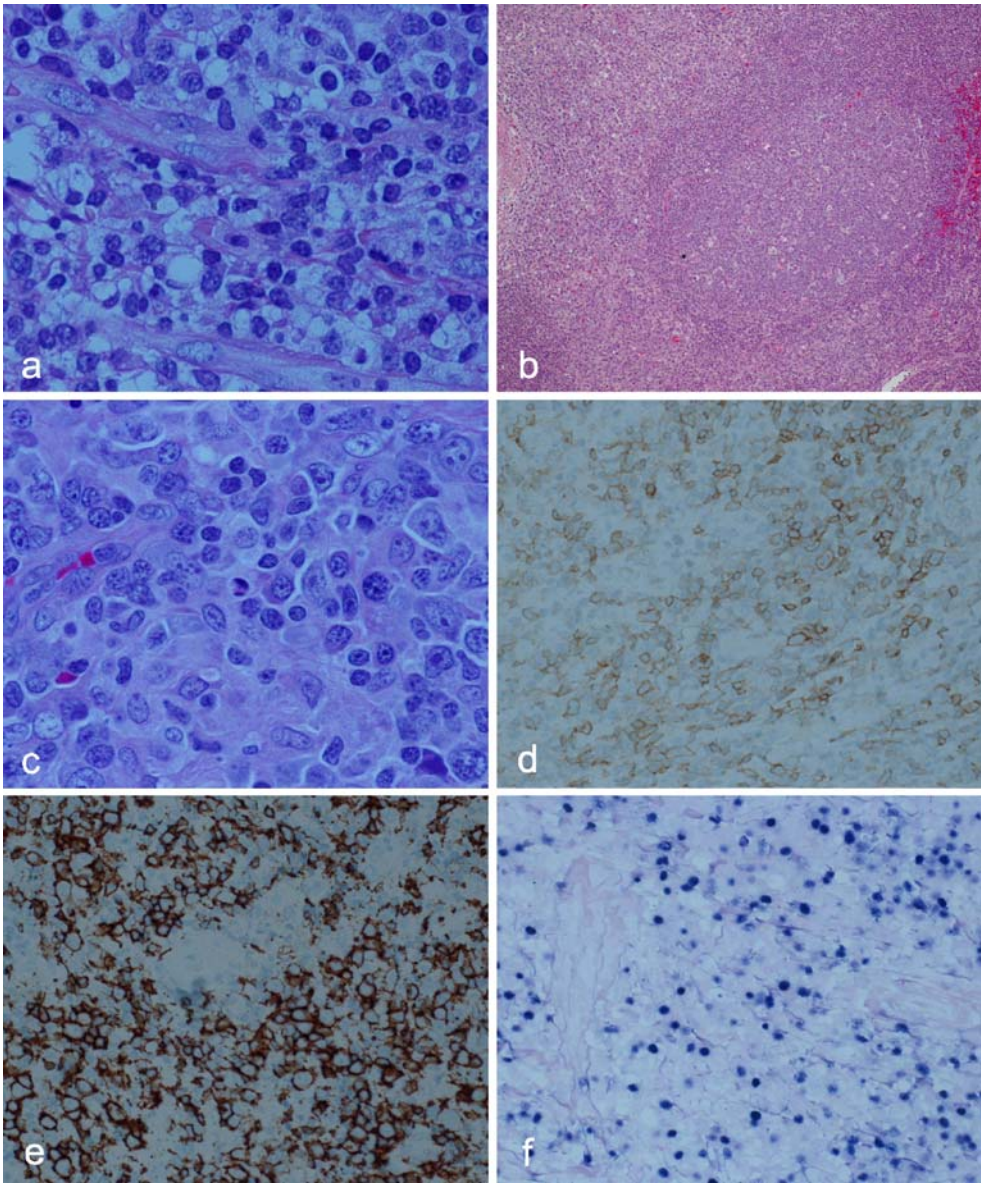

Fig. 1 **a** High-power field. The medium-sized lymphocytes had round or slightly indented nuclei with a small solitary nucleoli and abundant clear cytoplasm. Small lymphocytes, plasma cells and plasmacytoid cells, and immunoblasts and neutrophils were also present. Case 1 HE ×250. **b** Medium-power field of the tonsil. Lymphoid follicles had hyperplastic germinal centers with ill-defined borders surrounded by sheet-like proliferation of polymorphous infiltration showing a marginal zone distribution pattern. Case 1 HE ×50. **c** High-power field of Fig. 1b. The interfollicular area contained polymorphous infiltrate of small-to-medium-sized (transformed) lymphocytes, immunoblasts, plasma cells and plasmacytoid cells, and histiocytes with or without epithelioid cell features. The medium-sized cells occasionally showed nuclear irregularities and moderate amounts of clear cytoplasm. Case 2 HE ×250. **d** CD5 and **e** CD20 immunostain demonstrated the mixed nature of the small-to-medium-sized lymphocytes and immunoblasts. Case 2 ×100. **f** Numerous EBV-infected lymphocytes in the tonsil. Case 1 ×50

Staining with CD20, CD3 and CD5 showed the mixed nature of small and medium lymphocytes, and immunoblasts (Fig. 1d and e). A portion of immunoblasts were CD30 positive. There was no CD43+ B-lymphocytes. Immunohistochemical studies of light chain determinants for interfollicular plasma cells, plasmacytoid cells and B-immunoblasts including cells resembling Hodgkin cells or Reed–Sternberg cells demonstrated a polyclonal pattern. Staining with monoclonal antibody 1B12 and CAN.42 highlighted the meshwork of follicular dendritic cells (FDCs). Although, the majority of the FDC meshwork maintained a regular arrangement, a portion of the meshwork was broken into the clusters.

On ISH, there were numerous EBER+ cells in both lesions (Fig. 1f).

Genotypic studies with immunoglobulin heavy chain probes demonstrated only germ line bands in Case 1.

Discussion

Histologically, the present two cases showed similar histological findings of MALT type lymphoma [6, 7].

The medium-sized lymphocytes in Case 1 somewhat resembled MBCs in MALT type lymphoma [6, 7]. However, the medium-sized B-cells were CD43− and bcl-2− and were confirmed non-neoplastic nature [7, 8]. Moreover, PCR study demonstrated the polytypic nature of the B-cells.

Histologically, Case 2 was characterized by a marginal zone distribution pattern of atypical lymphocytes, which is a characteristic histological findings of MALT type lymphoma [6, 7]. Lymphoid infiltration was mainly composed of medium-sized lymphocytes with irregular nuclei and a moderate amount of clear cytoplasm somewhat resembling centrocyte-like (CCL) cells, immunoblasts, plasmacytoid

cells and plasma cells [6, 7]. Plasma cell differentiation has been noted in various degrees in MALT lymphoma, and the plasma cells may occasionally obscure the CCL-cells [6, 7, 9]. Moreover, a portion of MALT type lymphoma associated with prominent epithelioid cell reaction [9]. Breakage of the FDC network seen Case 2 also suggested the follicular colonization of MALT type lymphoma. However, cells resembling CCL− cells were CD20+ but CD43− [7]. The polytypic nature of the B-immunoblasts, plasmacytoid cells and plasma cells were demonstrated by the immunohistochemical study.

ISH demonstrated numerous EBER+ cells in both lesions. Finally, clinical findings including serologic data for EBV confirmed the diagnosis of acute IM.

IM showed marked histological diversity [1, 3, 4]. A previous report focused on the differential diagnosis of acute IM and Hodgkin lymphoma or peripheral T-cell lymphomas [3, 4]. Although MALT type lymphoma rarely affects young adults, notably, a number of cases have been reported in the tonsil [10, 11]. The present two cases indicated that acute IM should be added to the differential diagnosis of MALT type lymphoma in young adults.

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