Rheumatoid Arthritis/Methotrexate-associated Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type

Yosuke Matsumoto, Shigeo Horiike, Saori Maekawa, Taro Isohisa, Natsumi Sakamoto, Yoshiaki Chinen, Ryuko Nakayama, Miki Kiyota, Hisao Nagoshi, Shinsuke Mizutani, Yuji Shimura, Mio Sugitani, Tsutomu Kobayashi, Noriaki Nakai, Junya Kuroda and Masafumi Taniwaki

Abstract

This report concerns a 62-year-old man with primary cutaneous diffuse large B-cell lymphoma (PCLBCL), leg type that developed during methotrexate (MTX) treatment for rheumatoid arthritis (RA). Several tumors were observed on the left lower leg. A histological analysis showed diffuse proliferation of large neoplastic B-cells that were immunophenotypically CD10-/MUM1+/BCL6-/BCL2+ and cytogenetically had IgH/c-MYC translocation without translocation involving BCL6 or IgH/BCL2. No evidence of Epstein-Barr virus (EBV) infection was found. The discontinuation of MTX resulted in a 20-month disease-free period. No previous cases of PCLBCL, leg type associated with RA or MTX therapy have been reported. The phenotypes of our patient were partly different from those of typical PCLBCL, leg type or RA/MTX-associated lymphoma.

Key words: primary cutaneous diffuse large B-cell lymphoma, leg type, rheumatoid arthritis, methotrexate

Introduction

Primary cutaneous diffuse large B-cell lymphoma (PCLBCL), leg type is composed exclusively of large transformed B-cells and most commonly develops in the leg (1). This tumor accounts for 4% of all primary cutaneous lymphomas and 20% of all primary cutaneous B-cell lymphomas (2).

Lymphomas in rheumatoid arthritis (RA) patients, who are estimated to have a 2- to 5-fold higher risk of lymphoma than other lymphoma patients (3-6), are classified as other iatrogenic immunodeficiency-associated lymphoproliferative disorders (1). It is unclear whether the higher risk of lymphoma is due to the disease itself or the methotrexate (MTX) used in therapy, with several reports claiming that not MTX, but rather RA itself, is responsible for this increased risk (5, 7, 8). The use of MTX to treat choriocarcinoma or psoriasis has been reported to not be carcinogenic, including inducing the development of lymphoma (9, 10). On the other hand, in a number of cases, lymphoma has been found to regress following the discontinuation of MTX (11, 12).

The most common subtype of lymphoma in RA patients is diffuse large B-cell lymphoma (DLBCL) (13); however, to the best of our knowledge, no studies of PCLBCL, leg type associated with RA or MTX have ever been previously reported. The present report concerns a patient with PCLBCL, leg type that developed during MTX treatment for RA and compares the findings for this patient with those of previously reported cases of PCLBCL, leg type and RA/MTX-associated lymphoma.

1Department of Molecular Hematology and Oncology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kawaramachi Hirokoji, Japan and 2Department of Dermatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kawaramachi Hirokoji, Japan

Received for publication September 9, 2013; Accepted for publication January 8, 2014
Correspondence to Dr. Yosuke Matsumoto, yosuke-m@koto.kpu-m.ac.jp
Case Report

A 62-year-old man was seen at our hospital in June 2010 due to the presence of several progressing tumors on his left leg. He had been diagnosed with RA (American College of Rheumatology functional class 1 and Steinbrocker radiographic stage III (14)) in December 1999. Treatment with MTX (8 mg per week) was initiated in May 2001 and resulted in satisfactory control of disease progression.

A physical examination (Fig. 1), 18-fluorodeoxyglucose positron-emission tomography/computed tomography (Fig. 2a-f) and contrast-enhanced magnetic resonance imaging (Fig. 2g-i) findings showed four tumors on the left lower leg (2.5 cm×2.2 cm, 1.8 cm×1.5 cm, 3.7 cm×3.0 cm and 6.0 cm×3.0 cm), with areas of left cervical and inguinal lymphadenopathy (2.3 cm×1.4 cm and 1.2 cm×0.8 cm, respectively). The patient’s performance status was 0 according to the Eastern Cooperative Oncology Group. The serum lactate dehydrogenase level was elevated to 304 U/L (normal range: 114-243 U/L). Meanwhile, a histopathologic examination of the biopsy specimens of the leg tumor showed diffuse proliferation of large lymphoid cells with prominent nucleoli, and mitotic figures were frequently observed (Fig. 3a). An immunohistochemical and/or flow-cytometric (FCM) analysis showed that the lymphoma cells were positive for CD20, CD79a, surface IgMκ, BCL2 and MUM1 and negative for CD3, CD5, CD10 and BCL6 (Fig. 3b-h). Light chain restriction was detected (κ 57.2%, λ 1.6% by FCM). Epstein-Barr virus (EBV)-encoded small RNA in situ hybridization (EBER-ISH) produced negative results (Fig. 3i), and the EBV-DNA load was less than 20 copies/10⁶ of white blood cells. A cytogenetic analysis with G-banding of the biopsy specimen showed a normal male karyotype, 46,XY. On the other hand, fluorescence in situ hybridization (FISH) of the formalin-fixed, paraffin-embedded tissue sections detected IgH/c-MYC fusion signals (Fig. 4a) but no IgH/BCL2 fusion signals or BCL6 split signals (Fig. 4b, c). Based on these findings and in accordance with the WHO classification, the patient was diagnosed with PCLBCL, leg type (1).

Three months after the discontinuation of methotrexate, complete remission was achieved. Following a 20-month disease-free period, however, several tumors on the left leg

---

**Figure 1.** The tumors on the inside (a) and anterior portion (b) of the left lower leg

**Figure 2.** Findings of 18-fluorodeoxyglucose positron-emission tomography/computed tomography (a-f) and T1-weighted contrast-enhanced magnetic resonance imaging (g-i) of the left lower leg
Figure 3. Histopathological findings of the left lower leg tumor. Hematoxylin and Eosin staining: a: ×500, b: ×1,000. Immunohistochemistry (×500): c: CD5, d: CD20, e: BCL2, f: CD10, g: MUM1, h: BCL6 and i: EBER-ISH. The tumor cells were positive for CD20, BCL2 and MUM1 and negative for CD5, CD10, BCL6 and EBER-ISH.

Figure 4. Results of fluorescence in situ hybridization (FISH) of the formalin-fixed, paraffin-embedded tissue sections. The cut-off threshold for a positive interpretation was >5%, as calculated using a 95% confidence interval based on the normal distribution of normal peripheral blood samples. a: IGH/c-MYC fusion in the nuclei of the lymphoma cells. The orange signals represent c-MYC (8q24), and the green signals represent IGH (14q32). The arrows indicate colocalized signals (42%). b: There were no colocalized signals of green (IGH;14q32) and orange (BCL2;18q21). c: FISH using the BCL6 Dual Color, Break Apart Rearrangement Probe (Vysis, Downers Grove, IL) detected split signals in only 2.8% of the nuclei.

recurred in August 2012. Although six courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy was initiated in February 2013, the tumors remained as progressive disease.

Discussion

The subject of this report is a 62-year-old patient with PCLBCL, leg type who had been treated with MTX for RA for more than nine years. The World Health Organization and European Organization for Research and Treatment of Cancer (WHO-EORTC) classification for cutaneous B-cell lymphomas distinguishes three major groups of primary cutaneous B-cell lymphoma: primary cutaneous follicle center lymphoma (PCFCL), PCLBCL, leg type and primary cutaneous marginal zone B-cell lymphoma (PCMZL) (2, 15). PCFCL may show a partly follicular growth pattern, and, in most instances, its tumor cells express neither BCL2 nor MUM1. PCLBCL, leg type exhibits confluent sheets of medium to large neoplastic B-cells that strongly express BCL2
and MUM1 (15, 16). We diagnosed our patient with PCLBCL, leg type due to the presence of diffuse infiltration of large neoplastic B-cells expressing both BCL2 and MUM1.

A comparison of the features of PCLBCL, leg type in our and other patients and the characteristics of RA/MTX-associated lymphoma is shown in Table. Both PCLBCL, leg type and RA/MTX-associated lymphoma generally occur in elderly patients. The median age at diagnosis of PCLBCL, leg type is reported to be 76 years (17), while the mean age at the onset of lymphoma in RA patients treated with MTX is reportedly 72.2 ± 9.5 (mean ± SD) years (5). Whereas PCLBCL, leg type develops more frequently in women, the majority of whom were EBV-positive (7, 11, 12). Although, to the best of our knowledge, only one case of EBV-positive PCLBCL, leg type has been reported (22), EBV has been detected in 12-44% of lymphomas in RA patients treated with MTX (7, 8, 12, 13, 23). Some patients with RA/MTX-associated lymphoma have been reported to display regression following the discontinuation of MTX, the majority of whom were EBV-positive (7, 11, 12). Although our patient showed no evidence of EBV infection, the tumors initially regressed following the discontinuation of MTX, although they recurred after a 20-month disease-free period, as previously reported (24).

This is the first case report concerning a patient with GCB-type accounts for 58.6% of cases, according to a report by Niitsu et al. (18).

As for our patient’s cytogenetics, a FISH analysis showed IgH/c-MYC fusion; however, neither IgH/BCL2 fusion nor translocation involving BCL6 were observed. Hallermann et al. reported that, according to an interphase FISH analysis, translocations involving c-MYC, BCL6 and IgH were detected in six, five and seven of 14 patients with large B-cell lymphoma of the leg, respectively (20). Furthermore, t(14;18) and translocations involving 3q27 were reportedly detected in two and 12 of 18 RA/MTX-associated lymphoma cases, respectively (18). Our patient exhibited a BCL2 protein expression, although there was no evidence of IgH/BCL2 fusion. In patients with PCLBCL, leg type, the strong BCL2 expression is due not to t(14;18), but rather to DNA amplification of 18q21.31-q21.33 (21). On the other hand, our patient showed neither translocation involving the BCL6 gene nor a BCL6 protein expression, unlike the previously reported findings in most cases of both PCLBCL, leg type and RA/MTX-associated lymphoma (15, 16, 18).

Table. Comparison of Our Case, PCLBCL, Leg Type and RA/MTX-associated Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>Our case</th>
<th>PCLBCL, leg type</th>
<th>RA/MTX-associated lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62y.o.</td>
<td>76y.o. (median)</td>
<td>72.2 ± 9.5y.o. (mean ± SD)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>1:3-4 (Male:Female)</td>
<td>Male, 2.3; Female, 2.04 (standardized incidence ratio)</td>
</tr>
<tr>
<td>Sites of involvement</td>
<td>Left leg, left cervical and inguinal lymph nodes</td>
<td>Other sites in 10-15%</td>
<td>Extranodal in 40-50%</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>CD20+, CD79a+, BCL2+, Sm IgMk</td>
<td>CD20+, CD79a+</td>
<td>CD20+, CD79a+</td>
</tr>
<tr>
<td>Classification by Hans et al. [19]</td>
<td>CD10-, MUM1+, BCL6-</td>
<td>CD10-</td>
<td>CD10+ in 31%</td>
</tr>
<tr>
<td></td>
<td>Non-GCB</td>
<td>Non-GCB</td>
<td>MUM1+ in 52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BCL6 in 69%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GCB in 41.4%, non-GCB in 58.6%</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>IgH/c-MYC (+)</td>
<td>Translocations involving IgH, c-MYC, BCL6</td>
<td>Translocation involving 3q27 (12 of 18 cases)</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Negative</td>
<td>Positive in only one reported case</td>
<td>Positive in 12-44%</td>
</tr>
<tr>
<td>Effect of MTX</td>
<td>Recurrence after 20 months</td>
<td>Reported case</td>
<td>Tumors regress in some EBV+ cases, but grow back later</td>
</tr>
<tr>
<td></td>
<td>Disease free</td>
<td>in [22]</td>
<td>[7,8,12,13,23]</td>
</tr>
</tbody>
</table>

PCLBCL, leg type that developed during MTX treatment for RA. The clinical phenotypes of our patient were partly different from those typical of PCLBCL, leg type or RA/MTX-associated lymphoma. Briefly, our patient was 1) positive for a BCL2 expression, unlike most RA/MTX-associated lymphoma patients, 2) negative for both BCL6 translocation and the BCL6 expression, unlike most PCLBCL, leg type or RA/MTX-associated lymphoma patients and 3) responsive, at least temporarily, to the discontinuation of MTX in spite of being negative for EBV. These discrepancies between our and other cases warrant further case analyses in order to clarify the clinical characteristics of RA/MTX-associated PCLBCL, leg type.

The authors state that they have no Conflict of Interest (COI).

References