International Immunopharmacology 68 (2019) 213–217

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Preliminary report

Highly aggressive plasmablastic neoplasms in patients with rheumatoid arthritis treated with methotrexate

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ARTICLE INFO

Keywords:
Plasmablastic lymphoma
Plasmablastic plasma cell myeloma
Rheumatoid arthritis
Methotrexate-associated lymphoproliferative disorders

ABSTRACT

Patients with rheumatoid arthritis occasionally develop lymphoproliferative disorders. Methotrexate-associated lymphoproliferative disorders is a lymphoproliferative disease or lymphoma in patients treated with methotrexate for autoimmune diseases, such as rheumatoid arthritis. Here we report two rare cases of highly aggressive plasmablastic lymphoproliferative disorders in rheumatoid arthritis treated with methotrexate.

Case 1 is a 68-year-old female patient with leukemic transformation of malignant lymphoma. She received methotrexate therapy for rheumatoid arthritis for > 6 years. The patient showed rapid progressive course and died on the 2nd hospital day. After the death, we diagnosed the patient as plasmablastic lymphoma. Case 2 is an 80-year-old female patient with plasmablastic plasma cell myeloma, with a history of methotrexate treatment for rheumatoid arthritis for > 5 years. Although M-protein was decreased by chemotherapy, bone marrow examination revealed the further increase of plasmablastic cells and she died 2 months later.

The present cases were difficult to diagnose because proliferation of malignant plasmablasts was hardly predicted because neither lymph node enlargement nor an evident M-protein was observed. Both cases showed aggressive features and extremely poor prognosis. Clinicians should be aware of the underlying malignant plasmablastic proliferation when inexplicable inflammatory findings are observed in inactive rheumatoid arthritis patients.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder and synovial joints are mainly affected. In many clinical guidelines, methotrexate (MTX) is the anchor treatment for the management of the patients with RA.

RA patients have been associated with an increased risk of lymphoproliferative disorders (LPD) at a frequency 2.0 to 5.5 times higher than that in general population. Immunosuppressive states due to medication such as MTX and reactivation of Epstein–Barr virus (EBV) have been regarded as causes [1]. Here we report two rare cases of highly aggressive plasmablastic LPD in RA patients treated with MTX.

2. Case presentation

2.1. [Case 1]

A 68-year-old female with severe dyspnea, stomatitis, and epigastric pain was transferred to our hospital. She had undergone MTX therapy for RA for > 6 years without symptoms of RA such as arthralgia, joint swelling, or morning stiffness for a long period of time. Laboratory investigations revealed rapidly progressive leukocytosis (3.30×10^9/L to 29.23×10^9/L in 2 days) with 30.5% abnormal plasmacytoid cells; thrombocytopenia (46×10^9/L); elevated C-reactive protein (CRP; 13.4 mg/dL), lactate dehydrogenase (LDH; 1379 IU/L), immunoglobulin M (IgM; 2503 mg/dL), and soluble interleukin-2 receptor (sIL-2R; 5417 U/mL) levels; and reduced IgG (286 mg/dL) and IgA (100 mg/dL) levels. Although she was not tested for the presence of human immunodeficiency virus (HIV), she had no risk for HIV infection. The presence of M-protein was not evaluated. Computed tomography revealed granular and reticular pulmonary shadows. Enlargement of multiple small lymph nodes (LNs) was observed (Fig. 1A, B). Although histological examination of LNs or pulmonary lesions could not be performed due to a rapid lethal course within 2 days after admission, the histological findings of the bone marrow (BM) suggested leukemic transformation of malignant lymphoma.

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https://doi.org/10.1016/j.intimp.2019.01.014
Received 7 December 2018; Received in revised form 8 January 2019; Accepted 9 January 2019
Available online 15 January 2019

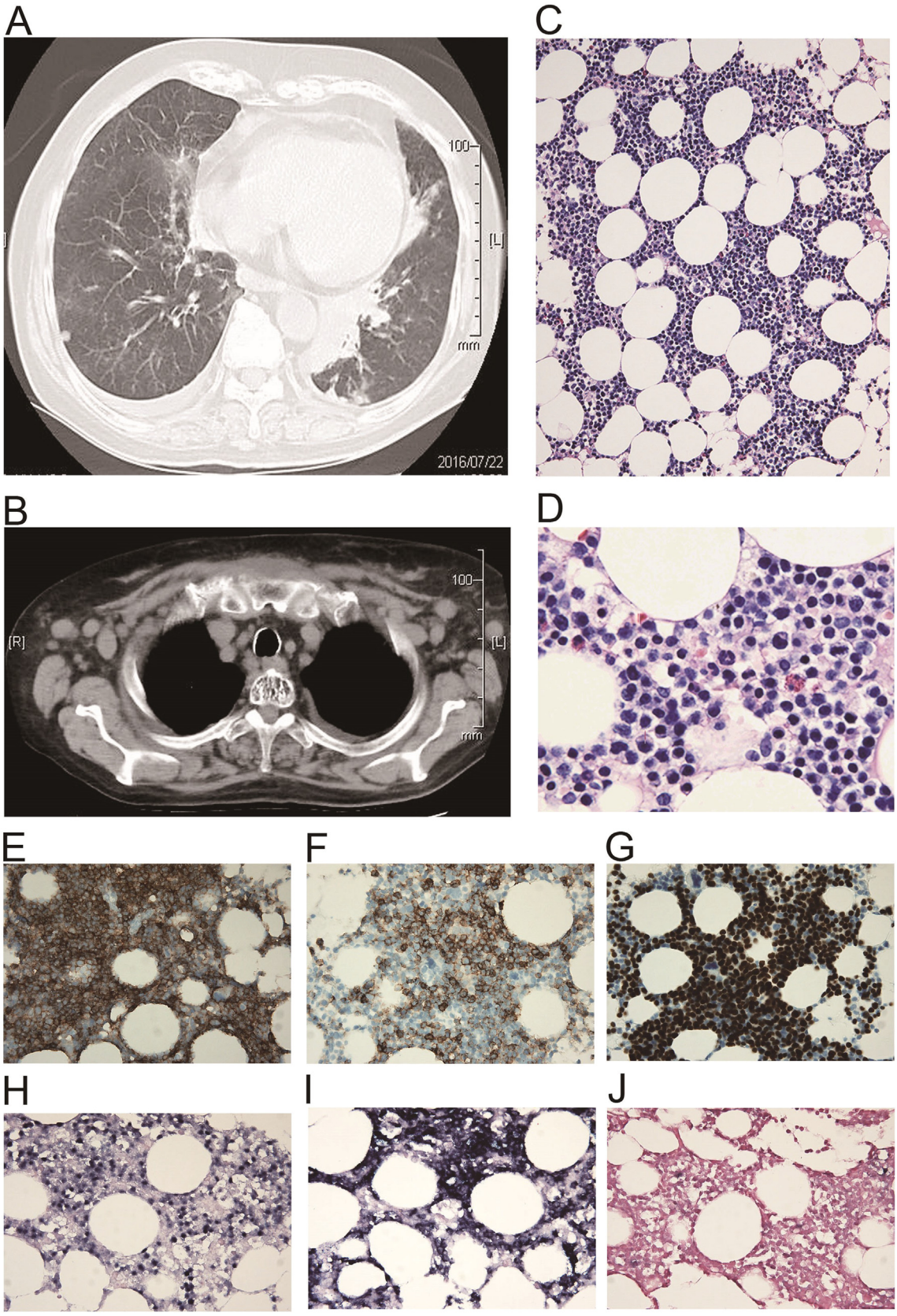

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Fig. 1. Imaging findings and bone marrow histological and immunohistochemical analyses of Case 1.
(A, B): Imaging examination
Computed tomography examination revealed granular, reticular, and ground glass shadow in the whole lung (A). Enlargement of multiple small lymph nodes was observed in the supraclavicular, axillary, mediastinal, inguinal, and abdominal regions (B).
(C–J): Histological and immunohistochemical examination of the bone marrow (BM)
Analysis of the BM exhibiting diffuse infiltration of lymphoid cells [hematoxylin and eosin (H&E) staining] (C). High-power view showing medium- to large-sized plasmablastic cells with abundant cytoplasm, large and round nuclei, and coarse chromatin (D).
(E–J) Immunohistochemical examination showing positive reactivity for CD38 (E), CD138 (F), MUM1 (G), EBER-ISH (H), and κ (I) and negative reactivity for λ (J).

Immunohistological examination showed positive reactivity for cluster of differentiation 38 (CD38), CD138, multiple myeloma oncogene 1 (MUM-1), IgM, κ, and EBV-encoded RNA in situ hybridization (EBER-ISH) and negative reactivity for CD20 and λ (Fig. 1C–J). Chromosomal analysis demonstrated normal karyotype. Flow cytometric analysis showed that tumor cells were positive for CD19 and κ (weak), and negative for CD10, CD20, CD23, CD56, and λ.

2.2. [Case 2]

An 80-year-old female with progressive anemia and severe emaciation was transferred to our hospital. She had undergone MTX therapy for RA for over 5 years and was not suffered from the typical symptoms of RA for a long period of time. LN enlargement was not observed. Laboratory analyses revealed severe anemia (Hb, 6.3 g/dL) and thrombocytopenia (48×10^9/L); elevated CRP (11.9 mg/dL), LDH (350 IU/L), IgG (2334 mg/dL), serum amyloid protein A (SAA; 1022 μg/mL), and sIL-2R (6700 U/mL) levels; and reduced IgM (13 mg/dL) level. White blood cell count was normal without abnormal cells. Only a small amount of M-protein (IgG-κ) was observed, but Bence Jones protein was not detected with almost normal serum free light chain levels (free κ, 39.7 mg/L; free λ, 18.2 mg/L; κ/λ ratio 2.18). BM examination revealed the expansion of plasmablastic cells (65%). Immunohistological examination showed positive reactivity for CD38, MUM-1, IgG, κ, and cyclinD1 and negative reactivity for CD20, CD30, λ, and EBER-ISH (Fig. 2). Chromosomal analysis demonstrated complicated karyotype (55,X,−X,+3,add(4)(q31),+5,+7,+9,add(10)(q22),+11,+14,+der(19)t(1;19)(q12;q13.4),+21,+mar1 [5]/46,XX [6]). Flow cytometric analysis showed that tumor cells were positive for CD38, CD138, CD56, CD54, and cytoplasmic κ and negative for CD19, CD20, MPC-1, CD45, CD49e, and cytoplasmic λ. Repetitive blood transfusion and chemotherapy with bortezomib and dexamethasone were performed, which decreased M-protein (815 mg/dL) and improved serum free light chain levels (free κ, 10.6 mg/L; free λ, 9.8 mg/L; κ/λ ratio 1.08). However, BM examination revealed the further increase of plasmablastic cells (79%). The patient's general condition progressively exacerbated, and she died 2 months later.

3. Discussion

Patients with RA may develop LPD (RA-LPD). The hyperimmune state of the disease itself and/or therapy-related immunosuppressive state might contribute to development of LPD.

Case 1 showed rapid progressive course and died on the 2nd hospital day. After the death, we diagnosed the patient as plasmablastic lymphoma (PBL) from the immunohistological findings, which showed

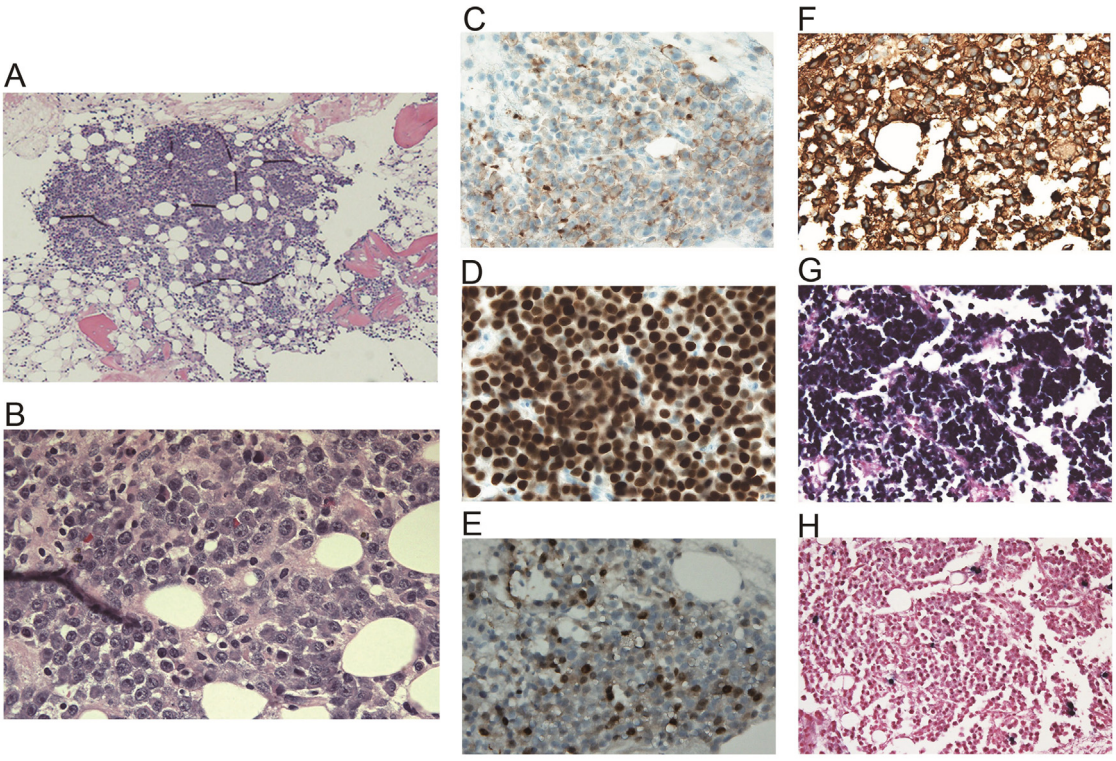

Fig. 2. Histological and immunohistochemical analyses of the bone marrow of Case 2.
Analysis of the BM exhibiting infiltration of lymphoid cells (H&E staining) (A). High-power view showing the proliferation of medium- to large-sized plasmablastic cells and some smaller cells with plasmacytic differentiation (B).
(C–H) Immunohistochemical examination showing positive reactivity for CD38 (C), MUM1 (D), cyclinD1 (E), IgG (F), and κ (G) and negative reactivity for λ (H).

positive reactivity for CD38, CD138, MUM-1, and EBER-ISH and negative reactivity for CD20 [2,3]. The prognosis of PBL patients is poor with a median overall survival between 8 and 15 months [4]. PBL is rare and is usually associated with HIV infection. However, PBL also occurs in HIV-negative individuals. In contrast to the majority of PBL patients are HIV-positive male patients, most female patients with PBL do not have HIV. The most common involved site is the oral cavity, followed by the gastrointestinal tract, LN, and skin [2]. Therefore, the stomatitis and epigastric pain observed in Case 1 may be due to oral and gastrointestinal lesions of PBL. Most HIV-negative PBL patients are elderly and immunosuppressive [5,6], suggesting a possible role of MTX-related immunodeficiency in patients with RA.

In Case 2, immunohistological examination showed positive reactivity for CD38 and MUM-1, and negative reactivity for CD20 and EBER-ISH, compatible with plasmablastic plasma cell myeloma (PCM) [3]. Myeloma cells were MPC-1-negative immature type, compatible with low secretion of M-protein despite of high tumor burden [7]. Although positive reactivity for cyclin D1 was also correlated with poorly differentiation of myeloma cells as well as large volume of infiltration [8], the relationship between cyclin D1 expression and the patients' prognosis remains unclear and controversial [9]. On the other hand, high serum level of sIL-2R in myeloma patients, as Case 2, predicts treatment resistance and poor prognosis [10].

Because of the immunophenotypic similarities between PBL and PCM [3], the diagnosis of plasmablastic malignancies might be challenging. Both PBL and PCM are positive for MUM-1, CD38, and CD138, and negative for CD20, corresponding to an immunophenotype of plasma cells. However, the expression of EBER is different; that is positive in PBL cases, but negative in PCM cases [3]. In the present cases, Case 1 was EBER-positive, and Case 2 was EBER-negative. Although many of MTX-associated LPD (MTX-LPD) patients demonstrate positive reactivity for EBER, certain cases are EBER-negative [11,12].

MTX-LPD is a lymphoproliferative disease or lymphoma which occurs in patients with autoimmune diseases such as RA, especially treated with MTX [1,11]. MTX-LPD is categorized as “other iatrogenic immunodeficiency-associated LPDs” in the World Health Organization classification [13]. Common types of MTX-LPD include diffuse large B-cell lymphoma (35%–60%) and classical Hodgkin lymphoma (12%–25%) [11].

Sometimes spontaneous regression occurs after MTX is discontinued (22–60%), but subsequent recurrence is observed in 18–45% of patients [11]. In the present cases, the effects of withdrawal of MTX were unclear, because of the quite short clinical course after discontinuance of therapy for RA in Case 1, and due to the extremely poor general condition at admission in Case 2. However, high serum levels of CRP and sIL-2R might predict persistent LPD and poor prognosis after discontinuance of MTX [14]. In that spontaneous regression could not be confirmed after cessation of MTX, the present cases were possible to be RA-LPD which occurred independently of MTX treatment. However, it has been reported that the interval between the diagnosis of RA and LPD in MTX-LPD is significantly shorter than that in RA-LPD without MTX treatment (median 132 months and 240 months, respectively) [15]. Also, in RA-LPD patients, high inflammatory activity of RA is an important driving force in LPD development [16]. The inactive state of RA at the onset of LPD and relatively short interval between the diagnosis of RA and LPD (approximately 5 and 6 years) in the present cases suggest participation of MTX therapy to LPD development.

In RA pathogenesis, predominant cytokines are mainly produced by macrophages, such as tumor necrosis factor α, interleukin (IL)-6, and IL-1β. Although MTX is a well-known antimetabolite which inhibits the metabolism of folic acid, the mechanism of MTX in the treatment of patients with RA remains to be fully elucidated. Several investigations, however, have reported the anti-inflammatory action of MTX is accompanied by changes in some cytokine expression, such as IL-6, IL-8, and IL-1β [17], and is associated with impairment of macrophage proinflammatory responses [18].

In the present cases, proliferation of malignant plasmablasts was hardly predicted because neither LN enlargement nor an evident M-protein was observed. In Case 2, SAA levels elevated irrespective of the inactive RA state. SAA has been considered to participate in the pathogenesis of chronic inflammatory diseases, such as RA [19]. Plasmablasts produce large amounts of interleukin 6 (IL-6) [20], which is a key cytokine for both multiple myeloma and RA. Moreover, IL-6 is one of the most effective cytokines to induce acute phase response such as CRP and SAA [21]. In our cases, CRP and SAA were elevated despite MTX treatment, which could reduce IL-6 production.

Here we report two quite rare and informative cases of plasmablastic LPD in RA patients treated with MTX. Both cases were difficult to diagnose and showed aggressive features and extremely poor prognosis. To the best of our knowledge, plasmablastic LPD in RA patients treated with MTX has not been previously reported, except for only one case of cutaneous plasmablastic lymphoma associated with RA [22]. Therefore, clinicians should be aware of the underlying malignant plasmablastic proliferation when inexplicable CRP and/or SAA elevation is observed in inactive RA patients.

Funding

We have no funding support.

Conflict of interest

The authors declare no conflict of interest.

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