Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2995-19
Intern Med 58: 3167-3171, 2019
http://internmed.jp

【 CASE REPORT 】

Rheumatoid Arthritis Complicated with Nasal Septum Perforation Due to Methotrexate-associated Lymphoproliferative Disorder

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Abstract:
A 44-year-old female with rheumatoid arthritis treated with methotrexate (MTX) and tocilizumab (TCZ) was admitted to our hospital with nasal pain. Nasal fiberscopy revealed septum perforation, while a membrane biopsy indicated granuloma and fibrinoid necrosis of the small artery. The patient was treated with prednisolone 30 mg/day after discontinuation of MTX and TCZ. Inguinal lymph node biopsy revealed diffuse infiltrations of atypical T-cells and Epstein-Barr virus-positive B cells. The patient was diagnosed with peripheral T-cell lymphoma due to MTX-associated lymphoproliferative disorder (MTX-LPD). We herein describe the case of a patient with nasal septum perforation due to MTX-LPD mimicking granulomatosis with polyangiitis.

Key words: nasal septum perforation, methotrexate-associated lymphoproliferative disorder, peripheral T-cell lymphoma, rheumatoid arthritis

(Intern Med 58: 3167-3171, 2019)
(DOI: 10.2169/internalmedicine.2995-19)

Introduction

Methotrexate-associated lymphoproliferative disorder (MTX-LPD) is a critical complication which can develop in patients treated with MTX (1). MTX-LPD is recognized as a lymphoproliferative disease associated with immunodeficiency (2). Although the condition is rare, its frequency is gradually increasing due to the growing number of patients that are administered MTX. The disease itself has also started to attract much attention. MTX-LPD often exhibits extranodal involvement (3); in such cases, making an accurate diagnosis may be difficult. We herein report the case of a patient demonstrating rheumatoid arthritis (RA) with nasal perforation due to MTX-LPD, mimicking the manifestation of granulomatosis with polyangiitis (GPA).

Case Report

In 2016, a 44-year-old Japanese female with RA was admitted to our hospital with a complaint of nasal pain. At age 39, the patient was diagnosed with RA and thus was treated with oral MTX. However, due to disease persistence, the patient's MTX dose was increased from 6 mg/week to 14 mg/week, and she was injected subcutaneously with 162 mg tocilizumab (TCZ) biweekly from the age of 43. On admission, the patient's vital signs were as follows: blood pressure, 141/97 mm Hg; pulse rate, 69 beats/min; and temperature, 35.7°C. Detailed physical examination revealed nasal pain and discharge accompanied by tenderness and swelling

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Received: March 11, 2019; Accepted: May 7, 2019; Advance Publication by J-STAGE: July 10, 2019
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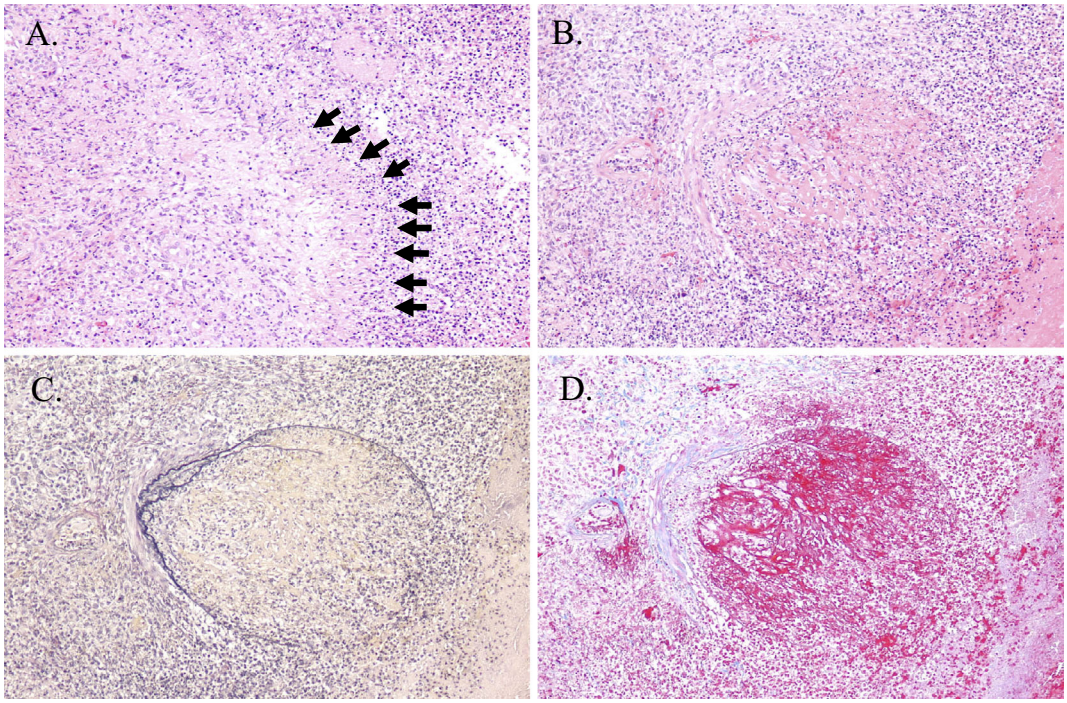

Figure 1. **Nasal membrane biopsy. (A) Black arrows indicate a palisading granuloma demarcated by H&E staining. Necrotizing vasculitis was observed by H&E staining (B). Elastic fiber staining revealed the elastic laminae of the small artery to be broken (C), while Azan-Mallory staining showed fibrinoid necrosis of the arterial wall (D). H&E: Hematoxylin and Eosin**

Table. **Patient Laboratory Data on Admission.**

<Hematology>		<Immunology>	
White blood cells	3,770 /μL	IgG	1,059 mg/dL
Red blood cells	383 ×10⁴/μL	IgA	381.9 mg/dL
Hemoglobin	12.8 g/dL	IgM	140.9 mg/dL
Hematocrit	38.3 %	Rheumatoid factor	172 IU/mL
Platelet	7.8 ×10⁴/μL	Anti-CCP Ab	33.4 U/mL
		Anti-nuclear Ab	640×
<Biochemistry>		C3	77.5 mg/dL
Total protein	6.3 g/dL	C4	12.5 mg/dL
Total bilirubin	0.8 mg/dL	MPO-ANCA	<1.0 IU/mL
AST	28 IU/L	PR3-ANCA	<1.0 IU/mL
ALT	27 IU/L		
LDH	274 IU/L	<Infection>	
ALP	268 IU/L	QuantiFERON® TB-3G	Negative
CPK	38 IU/L	EBV-DNA	420 copies/mL
Blood urea nitrogen	11 mg/dL		
Creatinine	0.46 mg/dL	<Urinary>	
C-reactive protein	<0.05 mg/dL	Protein	(±)
sIL-2R	883 U/mL	Occult blood	(-)
		Cast	(-)

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, CPK: creatine phosphokinase, sIL-2R: soluble interleukin-2 receptor, Ab: antibody, CCP: cyclic citrullinated peptide, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibodies, PR3-ANCA: proteinase 3-anti-neutrophil cytoplasmic antibodies, EBV: Epstein–Barr virus

of the bilateral wrist joints. Nasal fiberscopy revealed perforation of the nasal septum. A subsequent nasal membrane biopsy indicated granuloma and fibrinoid necrosis of the small artery (Fig. 1). Table displays the patient's laboratory data recorded on admission: myeloperoxidase- and proteinase 3-anti-neutrophil cytoplasmic antibody levels were

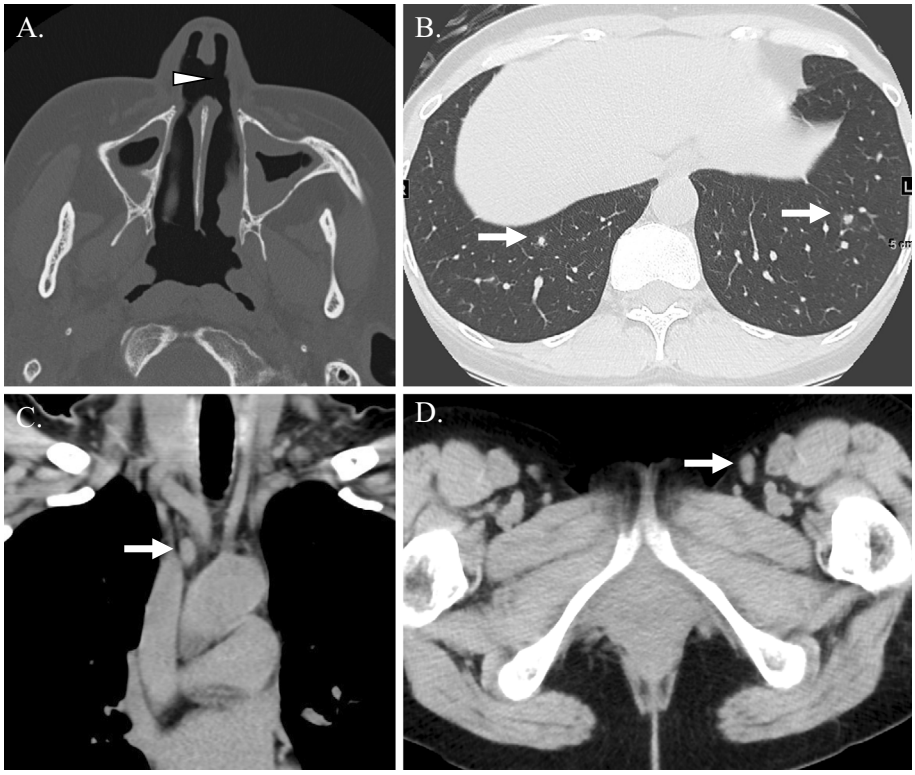

Figure 2. **CT findings. (A) Sinus CT shows nasal septum perforation (white arrowhead) and mucosal thickening of the maxillary sinus. (B) Chest CT shows multiple small nodules in the lungs (white arrows). (C) Mediastinal lymph node swelling (white arrow). (D) Abdominal CT shows left inguinal lymph node swelling (white arrow). CT: computed tomography**

within normal ranges, however, the Epstein-Barr virus (EBV)-DNA titer was found to be elevated in the peripheral blood. Computed tomography (CT) detected a perforation of the nasal septum, mucosal thickening of the maxillary sinus, multiple small nodules in both lungs, and swelling of mediastinal and inguinal lymph nodes (Fig. 2). According to these findings, GPA was suspected and the patient was treated with prednisolone (30 mg/day) following the discontinuation of MTX and TCZ. Following this, an inguinal lymph node biopsy was performed, which revealed diffuse infiltrations of atypical cells with necrosis; immunohistochemical staining of these cells mainly revealed $CD3^+$ T-cells and some $CD20^+$ and $CD79a^+$ B cells with EBV-encoded small RNA (EBER) (Fig. 3). Although the nasal membrane biopsy was re-evaluated through immunohistochemical staining, the histological findings were consistent with those from the lymph node biopsy. Thus, the patient was diagnosed with peripheral T-cell lymphoma (PTCL), not otherwise specified. In addition, positive EBER results from the biopsy specimen and elevated EBV-DNA titer in peripheral blood suggested the presence of MTX-LPD. The prednisolone dose was reduced to 2.5 mg/day within 3 months of an improvement in nasal pain after the discontinuation of MTX. Although the nasal septum perforation persisted, lymph node swelling subsequently improved, EBV-DNA titer in peripheral blood decreased and pulmonary nodules disappeared. The patient experienced no nasal involvement relapse up to 1 year after the discontinuation of MTX.

Discussion

We reported a case of RA complicated with perforation of the nasal septum due to MTX-LPD, mimicking nasal manifestation of GPA. The frequency of MTX-LPD is estimated at 0.1-0.2% in RA patients (4). The clinical features of MTX-LPD may be accompanied by extranodular lesions, the presence of EBV, and spontaneous regression after the discontinuation of MTX (3, 5, 6).

Extranodular lesions are observed in 63-79% of patients with MTX-LPD (3, 4). Making an accurate diagnosis is sometimes difficult due to the diverse and complicated nature of the pathological findings. Diffuse large B-cell lymphoma is the most frequently observed type, however, few reports exist on PTCL (7). To the best of our knowledge, this is the first case report regarding PTCL associated with MTX-LPD in the nasal cavity. Generally, T-cell lymphoma in the nasal cavity is known to cause nasal septum perforation (8). Furthermore, the pathological findings of lymphoproliferative diseases, such as Hodgkin's disease and T-cell lymphoma, rarely show evidence of necrotizing vasculitis (9, 10). The present case was therefore initially suspected to be GPA due to the pathological finding of necrotizing vasculitis in the nasal membrane biopsy. However, a re-evaluation of the nasal membrane biopsy specimen revealed background diffuse infiltration of atypical cells, with immunohistochemical staining of patient nasal membrane and

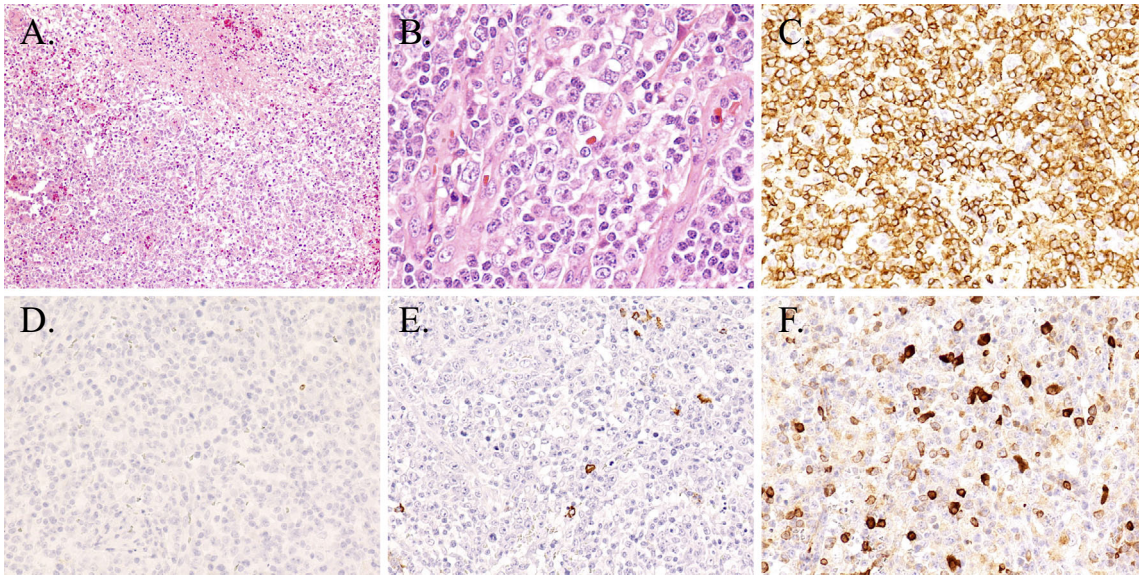

Figure 3. Inguinal lymph node biopsy. Lymph node biopsy shows loss of normal structure and diffuse infiltrations of abnormal $CD3^+$ T cells, accompanied by necrosis. $CD20^+$ and $CD79a^+$ B cells with positive Epstein-Barr (EB) virus-encoded small RNA (EBER) were observed. (A) H&E staining visualized with a low-power field. (B) H&E staining visualized with a high-power field. (C) The presence of $CD3^+$ cells indicated immunohistochemical staining. (D) $CD10^+$ cells were absent. (E) The presence of $CD20^+$ cells indicated by immunohistochemical staining. (F) The presence of $CD79a^+$ cells indicated by immunohistochemical staining. EB: Epstein-Barr, EBER: Epstein-Barr virus-encoded small RNA, H&E: Hematoxylin and Eosin

lymph node biopsies confirming the presence of MTX-LPD. It may be difficult to distinguish between lymphoma-induced vasculitis from primary vasculitis if no abnormal cells are detected in the pathological tissue.

Although the pathogenic mechanism remains unclear, one cause of MTX-LPD is an immunosuppressive reaction associated with EBV reactivation (3, 5). The frequency of positive EBER results among MTX-LPD patients is reported to ranged between 58% and 75% (6, 7). Additionally, an elevated EBV-DNA titer in peripheral blood has previously been observed in some patients (11). Ichikawa et al. reported the MTX-LPD regression rate to be significantly higher in EBV-positive patients than in EBV-negative patients (5). In the present case, the EBV-DNA titer was elevated in the peripheral blood. Furthermore, the nasal membrane and lymph node biopsies contained EBER-positive B cells. EBV-DNA titer and lymph node swelling were both reduced after the discontinuation of MTX. Based on these findings, the present case was considered to be consistent with MTX-LPD, with the nasal septum perforation considered to be a manifestation of MTX-LPD. A previous meta-analysis showed no evidence of any increased incidence of LPD due to TCZ treatment (12). Several studies have shown decreased EBV loads during TCZ treatment (13, 14). However, one study did report an exacerbation of chronic active EB virus infection during TCZ therapy (15). Further studies are therefore required to fully understand the association between LPD and TCZ administration.

Although the pathological findings seemed to indicate malignancy, the spontaneous regression which occurred after the discontinuation of MTX is a clinical feature of MTX-LPD. The frequency of a such spontaneous regression has not yet been clarified, however, it has been estimated to range between 30% and 70% (4). Inui et al. previously reported that a maximum reduction was observed 8 weeks after discontinuation of MTX (16). Thus, it may be possible to circumvent chemotherapy for approximately 8 weeks if the disease is stable. However, some patients do require chemotherapy as a result of disease exacerbation after spontaneous regression. No consensus exists regarding the optimal treatment after a regression of MTX-LPD, and the treatment safety has not been established. Rituximab may be recommended for cases of CD20 positive B-cell lymphoma. A case of LPD relapse due to TCZ re-administration has also been reported (11). Thus, careful follow-up is critical in patients with MTX-LPD.

We herein described a case of a patient with MTX-LPD complicated with nasal septum perforation. Nasal manifestation mimicked GPA due to the presence of necrotizing vasculitis in the pathological findings. The patient was eventually diagnosed with PTCL following an examination of the results from immunohistochemical staining of the nasal membrane and lymph node biopsies. Spontaneous regression was observed after the discontinuation of MTX. We believe that this case will contribute to an improved understanding of the complex clinical features of MTX-LPD.

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

Acknowledgement

The authors wish to thank the patient as well as the medical staff for their contributions to the case report.

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