CASE REPORT

Gastric Perforation due to Iatrogenic Immunodeficiency-associated Lymphoproliferative Disorder during the Treatment of Rheumatoid Arthritis

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Abstract:
A 71-year-old woman being treated with methotrexate (MTX) and tacrolimus (TAC) for rheumatoid arthritis (RA) was admitted to our hospital and underwent surgery for gastric perforation and peritonitis. An endoscopic examination six days post-surgery showed an extensive ulcer in the stomach, and a biopsy revealed diffused large B-cell lymphoma. We diagnosed her with immunodeficiency-associated lymphoproliferative disorder (LPD) and discontinued the MTX and TAC. She underwent gastrectomy due to stenosis approximately two months after the first operation, but the histopathological findings of lymphoma had disappeared. LPD should be considered as a potential cause of gastric perforation during RA treatment.

Key words: gastric perforation, iatrogenic immunodeficiency-associated lymphoproliferative disorder, methotrexate, tacrolimus, rheumatoid arthritis

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Introduction

The quality of life and prognosis of patients with rheumatoid arthritis (RA) have been improved by recent treatments, including biological disease-modifying antirheumatic drugs (DMARDs), but the clinical course of this disease varies among individual patients (1). The outcome of RA depends not only on the disease activity, including joint destruction and chronic inflammation, but also on the presence of comorbid illnesses, such as cardiovascular disease, infection, and B-cell lymphomas.

Lymphoproliferative disorders (LPDs) may occur during immunosuppressive treatment for autoimmune diseases (2). Although methotrexate-associated lymphoproliferative disorder (MTX-LPD) is well known to occur in individuals with RA, it has been reported that LPDs also develop during the use of other immunosuppressants, including anti-tumor ne-

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gests that we need to consider LPD as a differential diagnosis. Our patient’s case suggests that we need to consider LPD as a differential diagnosis. Our patient’s case suggests that we need to consider LPD as a differential diagnosis. Our patient’s case suggests that we need to consider LPD as a differential diagnosis. Our patient’s case suggests that we need to consider LPD as a differential diagnosis. Our patient’s case suggests that we need to consider LPD as a differential diagnosis. Our patient’s case suggests that we need to consider LPD as a differential diagnosis. Our patient’s case suggests that we need to consider LPD as a differential diagnosis. Our patient’s case suggests that we need to consider LPD as a differential diagnosis. Our patient’s case suggests that we need to consider LPD as a differential diagnosis. Our patient’s case suggests that we need to consider LPD as a differential diagnosis. 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Table 1. Laboratory Findings.

| WBC       | 25,000/μL | TP     | 6.8 g/dL | RF        | 23.3 IU/mL |
|-----------|-----------|--------|----------|-----------|------------|
| Seg       | 94 %      | Alb    | 2.6 g/dL | anti-CCP antibody | 9.7 U/mL   |
| Lym       | 0 %       | AST    | 25 U/L   | MPO-ANCA  | <3.5 U/mL  |
| Mono      | 3 %       | ALT    | 12 U/L   | PR3-ANCA  | <3.5 U/mL  |
| Eosino    | 0 %       | ALP    | 91 U/L   |           |            |
| Baso      | 0 %       | BUN    | 15 mg/dL | C7-HRP    | (-)        |
| RBC       | 3.90×10⁶/μL| Cre    | 0.87 mg/dL| EBV EA-DR IgG | <10 ×      |
| Hb        | 9.4 g/dL  | LDH    | 170 U/L  | EBV VCA IgM | <10 ×      |
| PLT       | 618×10⁹/μL| CRP    | 19.43 mg/dL| EBV VCA IgG | 320 ×      |
|           |           | sIL-2R | 2.208 U/mL| EBV EBNA IgG | 4.3 ×      |
|           |           | IgG    | 1,555 mg/dL| anti-HTLV1antibody | 0.2 COI |
|           |           | CH50   | 53.9 mL  |           |            |

WBC: white blood cell, Seg: segmented granulocyte, Lym: lymphocyte, Mono: monocyte, Eosino: eosinophil, Baso: basophil, RBC: red blood cell, Hb: hemoglobin, PLT: platelet, TP: total protein, Alb: Albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, BUN: blood urea nitrogen, Cre: creatinine, LDH: lactate dehydrogenase, CRP: C-reactive protein, sIL-2R: soluble interleukin-2 receptor, IgG: immunoglobulin G, IgM: immunoglobulin M, CH50: 50% hemolytic complement activity, RF: rheumatoid factor, anti-CCP antibody: anti-cyclic citrullinated peptide antibody, MPO-ANCA: myeloperoxidase antineutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3-antineutrophil cytoplasmic antibody, C7-HRP: cytomegalovirus antigenemia assay, EBV: Epstein-Barr virus, EA-DR: early antigen-diffuse and restricted, VCA: virus capsid antigen, EBNA: Epstein Barr nuclear antigen, HTLV-1: human T-cell leukemia virus type 1

Crohn’s disease causes a thickened and necrotic area in the anterior wall of the stomach. Therefore, the World Health Organization classification of tumors of hematopoietic and lymphoid tissues (4th edition, 2017) classified LPDs that are observed during immunosuppressant treatment as ‘other iatrogenic immunodeficiency-associated lymphoproliferative disorder (OIIA-LPD).’ OIIA-LPD is diagnosed based only on the patient’s history of immunosuppressant use, regardless of the pathological diagnosis.

We treated a patient with iatrogenic immunodeficiency-associated LPD that caused gastric perforation during her treatment with MTX and tacrolimus (TAC) for RA, and we confirmed that the lesion disappeared after the MTX and TAC were discontinued. While some cases of LPD in stomach have been reported, to our knowledge there is no prior report of gastric perforation due to iatrogenic immunodeficiency-associated LPD. Our patient’s case suggests that we need to consider LPD as a differential diagnosis when gastric perforation occurs during RA treatment.

**Case Report**

A 71-year-old Japanese woman with a loss of appetite for 2 months suffered from acute abdominal pain in September 2017. She was admitted to our hospital after computed tomography (CT) revealed her to have intraperitoneal free air at another hospital. She had had RA for 24 years and had been treated with MTX 8 mg/week, TAC 1 mg/day, and prednisolone 0.5 mg/day.

On admission, her body temperature was 37.5°C. She had tachycardia, but her blood pressure was 120/68 mmHg. On a physical examination, she presented with abdominal tenderness and muscular defense. Laboratory investigations showed that the white blood cell (WBC) count and C-reactive protein (CRP) levels were elevated (Table 1). Abdominal computed tomography (CT) revealed perforation of the stomach.

Under the diagnosis of acute peritonitis due to gastric perforation, we performed emergency laparotomy. We found a thinned and necrotic area in the anterior wall of the stomach, and part of the lesion was perforated (Fig. 1). Accordingly, this patient underwent omental patch repair. The thin, perforated wall was covered with omentum, and abdominal drainage was performed.

The patient’s postoperative course was eventless. On the sixth postoperative day, an endoscopic examination revealed a circumferential ulcer in the gastric body (Fig. 2), and the perforated lesion seemed to be located at the front wall side of the ulcer. Biopsy specimens of the ulcerative lesion showed atypical large lymphoid cells, and immunohistological staining revealed that the large lymphoid cells were posi-
positive for CD79a, bcl-2, and Epstein-Barr encoding region (EBER) by in situ hybridization (Fig. 3). These findings indicated diffuse large B-cell lymphoma (DLBCL). The level of lactate dehydrogenase (LDH) was within the normal range, but the level of serum soluble IL-2 receptor was high (2,208 U/mL). Other diseases capable of causing a gastric ulcer, such as cytomegalovirus infection, ischemic gastropathy, and vasculitis, were excluded.

Because the patient had been treated with MTX and TAC, we diagnosed her with iatrogenic immunodeficiency-associated LPD. An examination by fluorodeoxyglucose-positron emission tomography (18F-FDG PET)-CT showed an increased FDG uptake only around her stomach, and bone marrow involvement was not detected. Accordingly, we decided to discontinue the MTX and TAC, expecting the lymphoproliferative lesion in the stomach to disappear.

The lesion slowly healed. However, symptomatic stricture of the stomach developed approximately two months after the operation. An endoscopic examination then showed marked stenosis of the corpus (Fig. 4). We speculated that the cause of the stenosis was the growth of a lymphoma or the ulcer healing process and that she should be checked for dissemination of the lymphoma. She underwent an operation to recover her oral intake (Fig. 5). At laparotomy, there were many small nodules. In addition, the stomach adhered to the pancreas and liver. However, peritoneal lavage cytology and a peritoneal tissue biopsy showed there were no dissemination of the lymphoma. The stomach was dissected from the pancreas and liver without its injury, and distal gastrectomy and R-Y reconstruction were performed.

The histopathological examination of the excised organs showed that inflammatory cells infiltrated into the tissue, but the findings of DLBCL had disappeared (Fig. 6). As of this writing, the patient’s remission has been maintained for over a year without any elevation of the level of sIL-2R.
Patients with RA develop LPDs at a higher frequency than healthy individuals, independent of specific therapies, but DMARDs, including MTX, TAC, and anti-TNF-α therapy, may contribute to an increased risk of LPDs. We encountered a patient with RA who developed gastric perforation during treatment with MTX and TAC. The patient was diagnosed with iatrogenic immunodeficiency-associated LPD, and it regressed spontaneously after the discontinuation of the MTX and TAC.

The characteristics of iatrogenic immunodeficiency-associated LPD are spontaneous remission following the discontinuation of immunosuppressive drugs (1, 3-5) and its occurrence in extranodal lesions, such as in the gastrointestinal tract, skin, and lung, in roughly half of cases (3, 4). It was also suggested that Epstein-Barr virus (EBV) reactivation by immunosuppression is associated with the onset of
iatrogenic immunodeficiency-associated LPD (3-5). However, the influences of the type of medication used to treat RA, histopathological features, and EBV infection on the prognosis of LPD have not been clarified. Further studies are thus required to examine the associations between these factors and the prognosis of iatrogenic immunodeficiency-associated LPD.

The present patient developed LPD during treatment with MTX and TAC. Although a case series reported the onset of LPD during TAC use in RA patients (6), an observational study in Japan indicated that MTX and TAC were independent risk factors for LPD (7). Accordingly, we speculate that both MTX and TAC may have contributed to the development of LPD in our patient. The developmental mechanism of LPD in patients with RA is poorly understood, but the functional depression of cytotoxic T cell was observed in RA patients (8) and the administration of MTX causes suppression of IFN-γ-producing CD8 T cells (9). It has also been reported that TAC not only reduces the production of IL-2 by inhibiting calcineurin and suppresses the proliferation and activation of T cells but also activates regulatory T cells (10). These mechanisms increase and activate EBV levels in RA patients treated with MTX/TAC. In addition, decreased tumor immunity due to MTX/TAC and transfer of viral oncogenes through exosomes to other cells may lead to EBV tumorigenesis (11). Nevertheless, further studies are needed in order to clarify the mechanisms by which these drugs facilitate the development of LPD among RA patients.

LPD associated with RA can occur in a variety of organs, including the lungs and gastrointestinal tract. We summarized the reported cases of LPD that developed in the stomach during RA treatment in Table 2 (12-19). Ulceration was observed in many cases in gastric primary LPD with RA, but there have been no reported cases leading to gastric perforation, to our knowledge. Two types of spontaneous perforation occur in primary gastric lymphoma. One results from an ulcer and/or necrosis reaching the subserous layer, and the other results from an ulcer in a site of thin connective tissue without a tumor (20). In the present case, the ulcer and necrotic area had lymphoma cells, suggesting that the type was the first type mentioned above. When RA patients have gastric ulcers, physicians should consider the use of nonsteroid anti-inflammatory drugs (NSAIDs) and cytomegalovirus infection as potential causes. The potential development of LPD should also be considered when RA patients are treated with immunosuppressants, such as MTX and TAC. Furthermore, we should consider performing further evaluations, such as endoscopy, when patients have gas-

### Table 2. Cases of LPD that Developed in the Stomach during RA Treatment.

| Case | Age | Gender | Duration of RA | Duration of MTX total dose | Appearance of gastric LPD | Other LPD lesion | Pathology | EBER | LPD treatment | Ref. |
|------|-----|--------|----------------|----------------------------|--------------------------|------------------|------------|------|---------------|------|
| 1    | 77  | F      | 17 yrs         | 2 yrs, 5 mos 1,360 mg     | Ulcer                    | (-)              | MALT lymphoma | (-)  | Chemotherapy after MTX discontinued | 8    |
| 2    | 69  | M      | 2 yrs          | 2 yrs, 1 mo 600 mg        | n.a.                     | (-)              | DLBCL     | (-)  | Chemotherapy & radiation therapy | 9    |
| 3    | 73  | F      | n.a.           | 5 yrs n.a.                | Similar to advanced gastric cancer (type 3) | (-) | Polymorphic LPD | (+)  | MTX discontinued | 10   |
| 4    | 72  | M      | n.a.           | 10 yrs n.a.               | Ulcer                    | (-)              | T-cell lymphoma | n.a. | MTX discontinued | 11   |
| 5    | 76  | M      | 18 yrs         | 8 yrs, 8 mos 3,396 mg     | Ulcer                    | Lung, liver, spleen, ileum, lymph nodes | Lymphomatoid granulomatosis (lung) | n.a. | MTX discontinued | 12   |
| 6    | 64  | M      | 9 yrs          | 9 yrs n.a.                | Ulcer                    | Tonsil, liver, spleen, ileum, lymph nodes | Suspicion of DLBCL | n.a. | MTX discontinued | 13   |
| 7    | 77  | M      | 4 yrs          | 4 yrs 2,000 mg           | Ulcer                    | T-cell lymphoma | DLBCL | (-)  | Chemotherapy after MTX discontinued | 14   |
| 8    | 78  | F      | 18 yrs         | >2 yrs n.a.              | Similar to submucosal tumors (one of them was ulcerated) | (-) | T-cell lymphoma | DLBCL | MTX and TAC discontinued | -    |
| This case | 71 | F      | 24 yrs         | 12 yrs 3,870 mg          | Ulcer and perforation    | (-)              | DLBCL     | (+)  | MTX and TAC discontinued | -    |

**Notes:**
- **DLBCL:** diffuse large B-cell lymphoma
- **MALT:** mucosa-associated lymphoid tissue
- **EBER:** Epstein-Barr virus-encoded RNA
- **SL:** spleen
- **TAC:** tacrolimus
- **MTX:** methotrexate
- **NSAIDs:** nonsteroidal anti-inflammatory drugs
- **NA:** not available
- **SL:** spleen
- **TAC:** tacrolimus
- **MTX:** methotrexate
- **N.A.:** not available

**References:**
- 1. [Intern Med 58: 3331-3336, 2019 DOI: 10.2169/internalmedicine.2782-19](https://www.ncbi.nlm.nih.gov/pubmed/31141620)
tric symptoms.

While the treatment of RA after LPD is a clinical problem, a consensus on this treatment has yet to be reached. In our department, we experienced patients who developed relapse of RA after improvement of LPD. In cooperation with a hematologist, the patients were treated with salazosulfapyridine, abatacept, or etanercept and achieved remission. The patients have remained in remission for more than five years without recurrence of LPD.

In conclusion, we encountered a patient with RA who developed gastric perforation during treatment with MTX and TAC. She was treated successfully by the discontinuation of these drugs and resection of her stomach. An interesting point of this case is that the disappearance of DLBCL was confirmed histologically after the discontinuation of MTX and TAC. However, since the spontaneous regression of iatrogenic immunodeficiency-associated LPD in RA patients is estimated to be approximately 20-60% (1, 3-5, 13), we need to carefully follow this patient in order to monitor the potential relapse of DLBCL.

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

Shiho Toyama and Ayuko Takatani contributed equally to this work.

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