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【 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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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	3.90×10^6 /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	618×10^3 /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-HTLVIantibody	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% homolytic 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

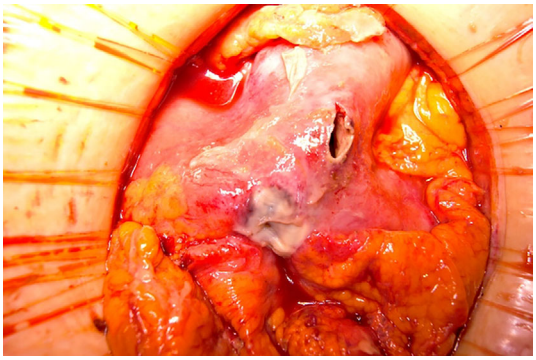

Figure 1. Macroscopic findings during surgery for gastric perforation. Perforation with a necrotic lesion in the anterior wall of corpus was detected.

crosis factor-alpha (TNF-α) therapy. 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℃. 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-

tive 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.

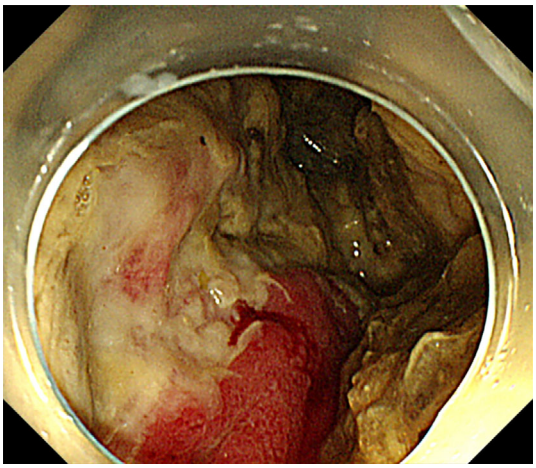

Figure 2. The findings of an endoscopic examination after the first surgery. A circumferential ulcer was observed in the body of her stomach.

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 (^{18}F-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.

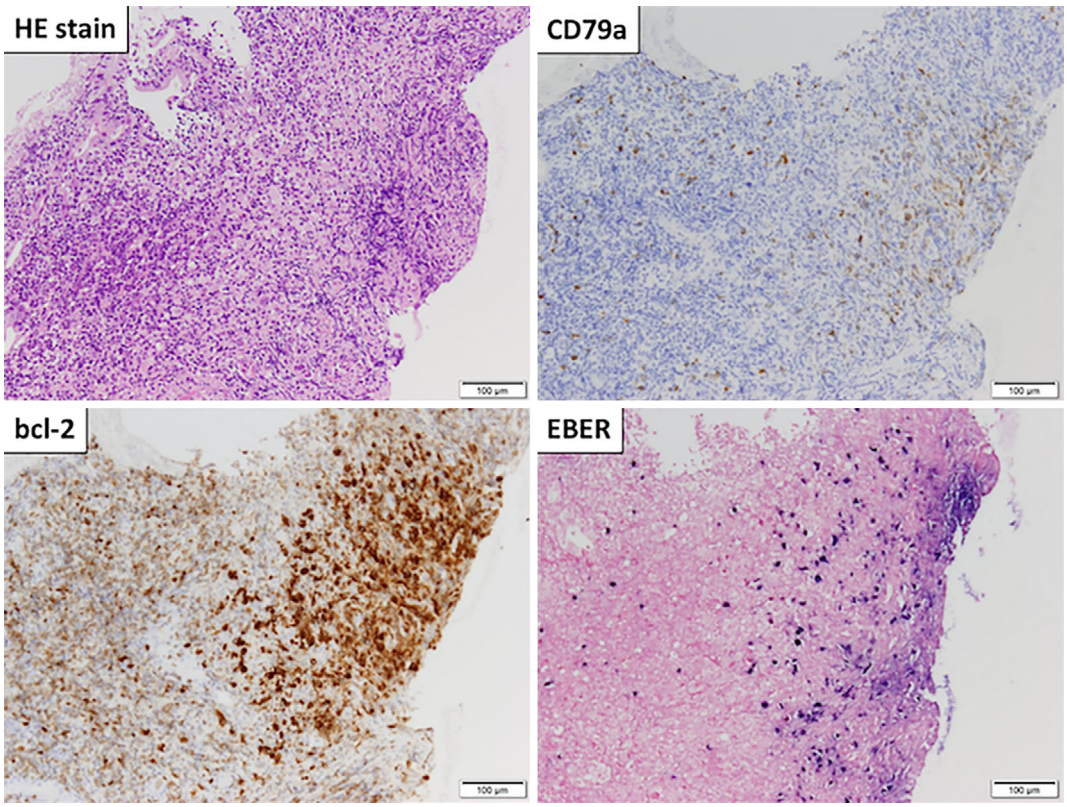

Figure 3. Results of a histological examination of the ulcer in the gastric body (Upper left: Hematoxylin and Eosin staining; Upper right: CD79a staining; Lower left: bcl-2 staining; Lower right: Epstein-Barr encoding region *in situ* hybridization). Atypical large lymphoid cells were positive for CD79a, bcl-2, and EBER on *in situ* hybridization. (bar, 100 μm).

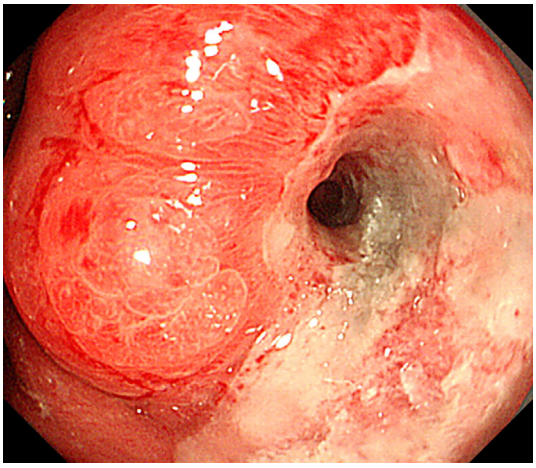

Figure 4. **The finding of an endoscopic examination 56 days after the first surgery. Marked stenosis of the corpus was observed.**

Discussion

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

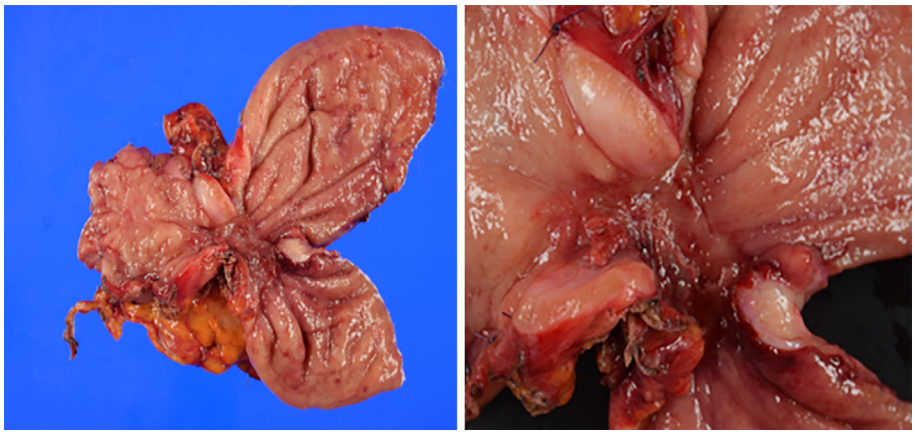

Figure 5. **Macroscopic findings of the stomach after removal. Stenosis after the ulcer was found in her stomach.**

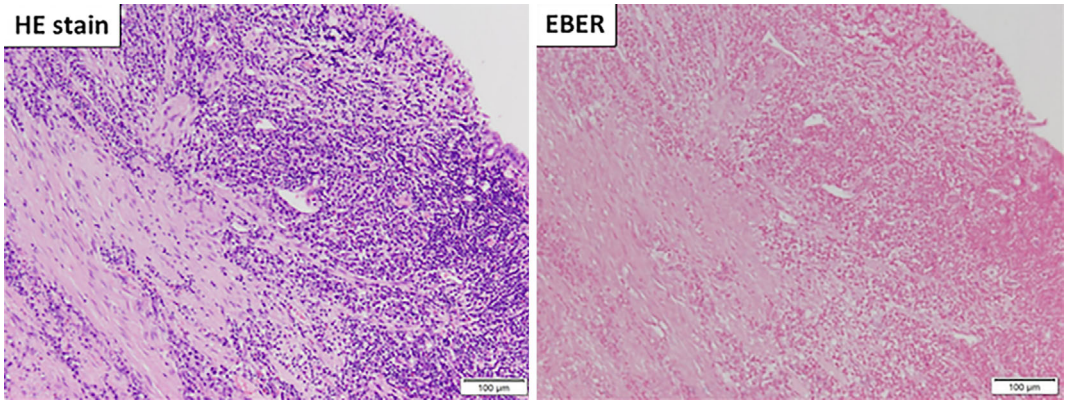

Figure 6. **Results of a histological examination of the gastrectomy (Left: Hematoxylin and Eosin staining; Right: Epstein-Barr encoding region *in situ* hybridization). Inflammatory cells were found to have infiltrated into the tissue, but the findings of DLBCL had disappeared. (bar, 100 μm). DLBCL: diffuse large B-cell lymphoma**

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

Case	Age	Gender	Duration of RA	RA treatment (onset of LPD)	Duration of MTX total dose	Appearance of gastric LPD	Other LPD lesion	Pathology	EBER	LPD treatment	Ref.
1	77	F	17 yrs	MTX, methylprednisolone	2 yrs, 5 mos 1,360 mg	Ulcer	(-)	MALT lymphoma	(-)	Chemotherapy after MTX discontinued	8
2	69	M	2 yrs	MTX, bucillamine	2 yrs, 1 mo 600 mg	n.a.	(-)	DLBCL	(-)	Chemotherapy & radiation therapy	9
3	73	F	n.a.	MTX	5 yrs n.a.	Similar to advanced gastric cancer (type 3)	(-)	Polymorphic LPD	(+)	MTX discontinued	10
4	72	M	n.a.	MTX, PSL	10 yrs n.a.	Ulcer	(-)	T-cell lymphoma	n.a.	MTX discontinued	11
5	76	M	18 yrs	MTX, PSL	8 yrs, 8 mos 3,396 mg	Ulcer	Lung, liver	Lymphomatoid granulomatosis (lung)	(+)	MTX discontinued	12
6	64	M	9 yrs	MTX	9 yrs n.a.	Ulcer	Tonsil, liver, spleen, ileum, lymph nodes	Suspicion of DLBCL	n.a.	MTX discontinued	13
7	77	M	4 yrs	MTX	4 yrs 2,000 mg	Ulcer	(-)	T-cell lymphoma	(-)	MTX discontinued	14
8	78	F	18 yrs	MTX	>2 yrs n.a.	Similar to submucosal tumors (one of them was ulcerated)	(-)	DLBCL	(-)	Chemotherapy after MTX discontinued	15
This case	71	F	24 yrs	MTX, TAC, PSL	12 yrs 3,870 mg	Ulcer and perforation	(-)	DLBCL	(+)	MTX and TAC discontinued	-

DLBCL: diffuse large B-cell lymphoma, mos: months, MTX: methotrexate, n.a.: not available, PSL: prednisolone, TAC: tacrolimus, yrs: years

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-

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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