INTERNAL MEDICINE

□ CASE REPORT □

Reactive Arthritis Caused by *Yersinia enterocolitica* Enteritis

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Abstract

We report a case of reactive arthritis (ReA) triggered by *Yersinia enterocolitica* enteritis. A 24-year-old Japanese man developed polyarthritis in the lower limbs. Two weeks prior to these symptoms, he noted diarrhea, right lower abdominal pain and a fever. *Y. enterocolitica* was not isolated from a stool culture; however, he was diagnosed with ReA based on the colonoscopic findings of a high anti-*Y. enterocolitica* antibody titer and HLA-B27 antigen positivity. Following treatment with methotrexate and steroids, his arthritis improved. This is the first reported Japanese case of ReA in the English literature after a gastrointestinal infection caused by *Y. enterocolitica*.

Key words: HLA-B27, reactive arthritis, Yersinia enterocolitica enteritis

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Introduction

Reactive arthritis (ReA) is a non-purulent joint inflammation that can be triggered by bacterial infections in the urogenital tract or gut and genetic factors, such as human leucocyte antigen (HLA)-B27 (1). *Yersinia enterocolitica* is a well-established trigger of ReA (2), and several case reports of ReA triggered by *Y. enterocolitica* have been reported in Western countries (3, 4). However, no Japanese cases of *Y. enterocolitica* triggered by ReA have been reported. To our knowledge, the present report describes the first Japanese patient with ReA that developed two weeks after the onset of acute *Y. enterocolitica* enteritis.

Case Report

A 24-year-old Japanese man presented with a 2-week of history of a fever, central abdominal pain and frequent bowel movements without blood, and the pain shifted to his right iliac region. Based on these findings, he had been diagnosed with acute enteritis and treated with an antidiarrheal drug. Two weeks later, he presented with polyarthritis of the left knee and left ankle joints and was referred to our hospital. On admission, his body temperature was 37.5℃, pulse rate was regular at 78 beats/min and blood pressure was 120/78 mmHg. He had arthralgia in the left swollen knee and ankle joints. He also had arthralgia in the bilateral sacroiliac joints. The laboratory findings at that time were as follows: hemoglobin was 13.3 g/dL, white blood count was 10,300/μL, erythrocyte sedimentation rate was 51 mm/h, and C-reactive protein was 14.1 mg/dL. The findings from liver and renal function tests were normal. Anti-citrullinated peptide antibody and antinuclear antibody tests were negative. Urinalysis revealed no abnormal findings (Table).

Abdominal computed tomography demonstrated inflammatory changes in the terminal ileum with enlarged regional mesenteric lymph modes (Fig. 1). Colonoscopy showed marked swelling in the mucosa with small ulcerations in the terminal ileum (Fig. 2A). A pathological examination demonstrated inflammatory infiltrates in the lamina propria with crypt abscess (Fig. 2B). A stool culture for *Y. enterocolitica* was negative; however, antibodies for *Y. enterocolitica* were positive with elevated titers (×5,120; normal range <×20). Serotyping of HLA class 1 was positive for B27. *Y. enterocolitica*-triggered ReA was subsequently diagnosed, and he was treated with levofloxacin (500 mg/day) for 7

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Table. **Laboratory Findings.**

Peripheral blood		**Blood glucose test**	
Red blood cells	450×10^4/μL	Glucose	101mg/dL (80-112)
Hemoglobin	13.3g/dL	HbA1c	5.7% (4.6-6.2)
White blood cells	10,300/μL	**Immunological test**	
Neut	80.9%	IgA	264mg/dL (110-410)
Ly	11.9%	IgG	1,210mg/dL (870-1700)
Eo	1.0%	IgM	157mg/dL (33-190)
Ba	0.3%	C3	154mg/dL (86-160)
Mo	5.9%	C4	26mg/dL (17-45)
Platlet	22.4×10^4/μL	CH50	45.4U/mL (30-50)
Erythrocyte sedimentation rate	51mm/hr	Rheumatoid factor	(-)
Blood chemistry		ASLO	(-)
Total protein	7.0g/dL (6.7-8.3)	ANA	(-)
Albumin	3.4g/dL (4.0-5.0)	MMP-3	171.7ng/mL (36.9-121)
Total bilirubin	0.6mg/dL (0.3-1.2)	Anti-citrullinated peptide antibody	(-)
Glutamic-oxaloacetic transaminase	20 IU/L (13-33)	Anti-SS-A antibody	(-)
Glutamic-pyruvic transaminase	36 IU/L (8-42)	Anti-SS-B antibody	(-)
Lactate dehydrogenase	187 IU/L (119-229)	Proteinase-3 anti-neutrophil cytoplasmic antibody	(-)
Alkaline phosphatase	338 IU/L (115-359)	Myeloperoxidase anti-neutrophil cytoplasmic antibody	(-)
γ-glutamyltransferase	80 IU/L (10-47)	Yersinia enterocolitica antibody	1:5120 (<1:20)
Creatinine kinase	46 IU (62-287)	(Quantitative Agglutination Test)	
Total cholesterol	182mg/dL (128-220)	**Genetic test**	
Blood urea nitrogen	14mg/dL (8-22)	Human Leukocyte Antigen	A2 A24
Creatinine	1.0mg/dL (0.6-1.1)		B27 B60
Na	137mEq/L (138-146)	**Urinalysis**	
K	4.5mEq/L (3.6-4.9)	Uric protein	(-)
Cl	103mEq/L (99-109)	Occult blood	(-)
Uric acid	5.8mg/dL (3.6-7.0)	Glucose	(-)
Ca	8.9mg/dL (8.7-10.3)	**Stool culture**	
Triglyceride	68mg/dL (30-150)	Escherichia coli	(-)
C-reactive protein	14.12mg/dL (<0.3)	Acid-fast bacilli	(-)
Ferritin	558ng/mL (20-250)		

ASLO: anti-streptolisyn-O, ANA: anti-nuclear antibody, MMP-3: Matrix Metalloproteinase-3

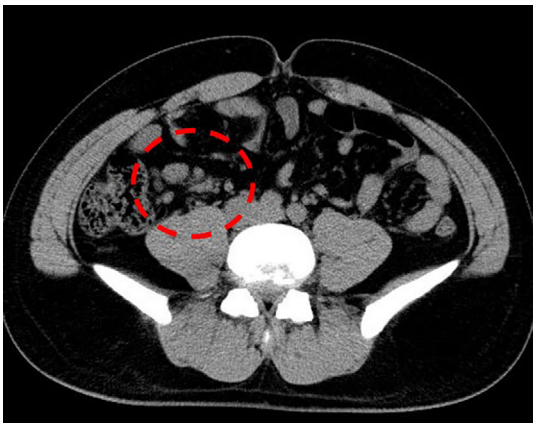

Figure 1. **Abdominal computed tomography showing regional mesenteric lymphadenopathy.**

days. His polyarthralgia did not improve; therefore, sulfasalazine (SSZ) treatment (1,000 mg/day) was started. However, the polyarthralgia was sustained; therefore, methotrexate (MTX; 8 mg/week) combined with steroid treatments was started. The patient's condition subsequently improved, and his elevated erythrocyte sedimentation rate and C-reactive protein level normalized under tapered steroid therapy plus MTX (8 mg/week) (Fig. 3).

Discussion

ReA is a type of sterile synovitis that occurs after a gastrointestinal or urogenital infection and is characterized by asymmetric arthritis predominantly affecting the lower limbs (5). The present patient developed *Y. enterocolitica* enteritis, followed by asymmetrical polyarthritis in the legs. In *Y. enterocolitica* infection, pseudoappendicitis, terminal ileitis, and mesenteric lymphadenopathy caused by *Y. enterocolitica* (6) should be kept in mind for patients presenting with symptoms resembling appendicitis. The present case had these clinical manifestations.

Enteropathogenic *Yersinia* spp. are the most frequent causative agents of human diarrhea in developed countries (7). However, the incidence of yersiniosis is largely underestimated, due to difficulty in isolating *Yersinia* from poly-contaminated stool cultures (8). Serology as a diagnostic tool for *Y. enterocolitica* infection has become more refined through the use of purified *Yersinia* outer membrane proteins (9).

The possibility that acute enteritis in the present case was caused by other enteropathic microorganisms could not be ruled out, *Y. enterocolitica* infection, at least in part, contributes to the occurrence of acute enteritis according to the serological findings.

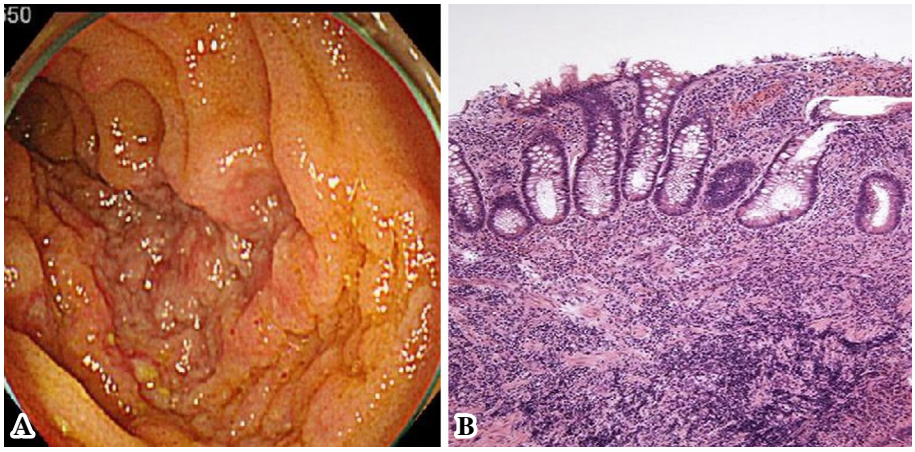

Figure 2. **A: Colonoscopic photographs showing multiple mucosal aphthae and edematous changes in the ileocecal mucosa. B: A histopathological examination of the ileocecal mucosa showing inflammatory cell infiltration and crypt abscess.**

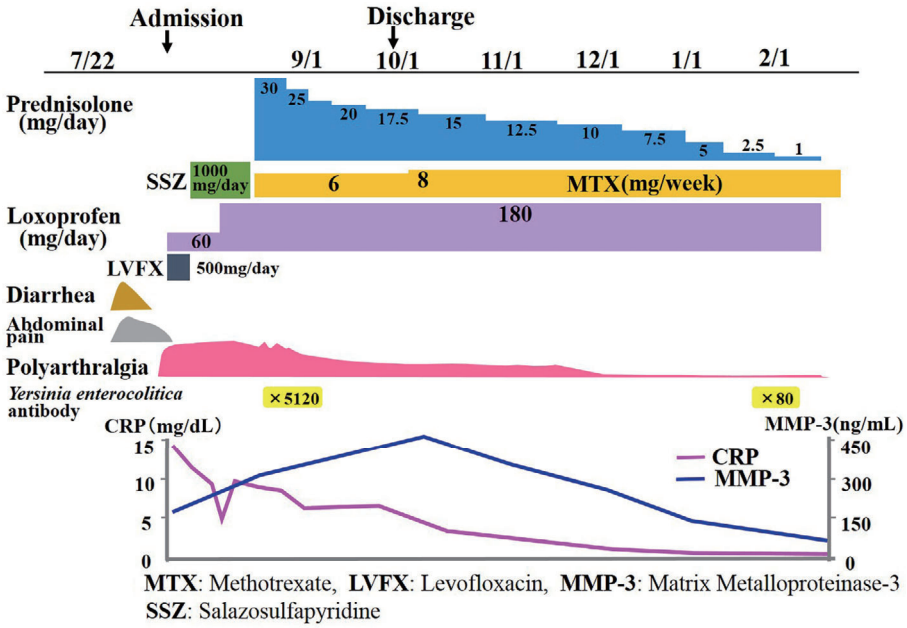

Figure 3. **Clinical course.**

In a study concerning ReA in German rheumatology clinics, as the causative enteric bacteria, *Salmonella* 11/33 (33%) and *Yersinia* 6/33 (18%) were isolated in patients with enteric ReA (10). Therefore, the frequency of ReA in adults after *Yersinia* enteric infection may not be unusual in Western countries. However, the frequency of HLA-B27 positivity is lower in Japan than in Western counties (11); thus, *Yersinia*-triggered ReA may be overlooked in Japanese patients. HLA-B27 has been shown to be a useful prognostic marker of ReA, and patients positive for HLA-B27 antigens are more likely to develop chronic or severe arthritis than those negative for it (12). HLA-B27-positive individuals are also thought to be less efficient at eliminating intracellular enteric bacteria, including *Yersinia*, than HLA-B27-negative individuals (13). The present patient exhibited HLA-B27 positivity, which may have contributed to the development of ReA following the failure to eliminate intracellular organisms or the presentation of arthrogenic peptides. Whether or not to use antibiotics in ReA is controversial. Clinical and experimental studies have clearly demonstrated that early and vigorous treatment of a triggering infection before the development of ReA is effective (14). However, in an experimental model of ReA induced by intravenous application *Yersinia enterocolitica* into rat, ciprofloxacin treatment after inoculation of the microbe, a definite effect was seen but later administration of ciprofloxacin had no effect (15, 16). Therefore, the routine use of antibiotics to treat ReA has not been established.

In chronic and severe ReA, disease-modifying antirheumatic drugs (DMARDs) are recommended for treatment (17). The most frequently used DMARD is SSZ, which has limited effectiveness in patients with ReA (18).

Another DMARD is MTX, which may be used as an alternative to SSZ in patients who are intolerant to SSZ (19). The systemic use of corticosteroids is not indicated for cases of severe joint involvement, except in short courses (1). Corticosteroids are a potent group of drugs for treating ReA. The drug should therefore be continued for a brief period in low dose and stopped gradually. If the patient later suffers from chronic arthralgia, corticosteroids should be avoided altogether. In these instances, corticosteroids have a poor therapeutic effect and cause more harm than benefit (20). Because the present patient had sustained active arthritis and was intolerant to SSZ, he was treated with prednisolone (30 mg/day) plus MTX (8 mg/week), and the steroids were subsequently tapered after his symptoms improved.

In conclusion, we described, to our knowledge, the first case of a Japanese patient with ReA that developed after acute *Y. enterocolitica* enteritis. Physicians should consider *Y. enterocolitica* infection in the differential diagnosis of patients with symptoms resembling appendicitis as well as ReA.

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

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