□ CASE REPORT □

Reactive Arthritis Caused by *Yersinia enterocolitica* Enteritis

Kazuya Honda¹, Nozomi Iwanaga¹, Yasumori Izumi¹, Yoshika Tsuji¹, Chieko Kawahara¹,
Toru Michitsuji¹, Shuntaro Higashi², Atsushi Kawakami³ and Kiyoshi Migita^{1,4}

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

(Intern Med 56: 1239-1242, 2017)

(DOI: 10.2169/internalmedicine.56.7888)

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 anti-diarrheal 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°C, 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 nodes (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 I was positive for B27. *Y. enterocolitica*-triggered ReA was subsequently diagnosed, and he was treated with levofloxacin (500 mg/day) for 7

¹Department of Rheumatology and General Internal Medicine, Nagasaki Medical Center, Japan, ²Department of Gastroenterology, Nagasaki Medical Center, Japan, ³Department of Immunology and Rheumatology, Unit of Translational Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Japan and ⁴Department of Rheumatology, Fukushima Medical University School of Medicine, Japan

Received for publication June 21, 2016; Accepted for publication August 9, 2016

Correspondence to Dr. Kiyoshi Migita, migita@fmu.ac.jp

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)
Platelet	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 B27 B60
Creatinine	1.0mg/dL (0.6-1.1)	Urinalysis	
Na	137mEq/L (138-146)	Uric protein	(-)
K	4.5mEq/L (3.6-4.9)	Occult blood	(-)
Cl	103mEq/L (99-109)	Glucose	(-)
Uric acid	5.8mg/dL (3.6-7.0)	Stool culture	
Ca	8.9mg/dL (8.7-10.3)	Escherichia coli	(-)
Triglyceride	68mg/dL (30-150)	Acid-fast bacilli	(-)
C-reactive protein	14.12mg/dL (<0.3)		
Ferritin	558ng/mL (20-250)		

ASLO: anti-streptolysin-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 countries (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 de-

velopment 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).

References

- Flores D, Marquez J, Garza M, Espinoza LR. Reactive arthritis: newer developments. *Rheum Dis Clin North Am* **29**: 37-59, 2003.
- Granfors K, Jalkanen S, von Essen R, et al. *Yersinia* antigens in synovial-fluid cells from patients with reactive arthritis. *N Engl J Med* **320**: 216-221, 1989.
- Aho K. *Yersinia* reactive arthritis. *Br J Rheumatol* **22**: 41-45, 1983.
- Foley JA, Mathews JA. Reactive arthritis due to *Yersinia enterocolitica*. *Clin Rheumatol* **3**: 385-387, 1984.
- Hannu T. Reactive arthritis. *Best Pract Res Clin Rheumatol* **25**: 347-357, 2011.
- Perdikogianni C, Galanakis E, Michalakis M, et al. *Yersinia enterocolitica* infection mimicking surgical conditions. *Pediatr Surg Int* **22**: 589-592, 2006.
- Rosner BM, Stark K, Werber D. Epidemiology of reported *Yersinia enterocolitica* infections in Germany, 2001-2008. *BMC Public Health* **10**: 337, 2010.
- Savin C, Leclercq A, Carniel E. Evaluation of a single procedure allowing the isolation of enteropathogenic *Yersinia* along with other bacterial enteropathogens from human stools. *PLoS One* **7**: e41176, 2012.
- Hoogkamp-Korstanje JA, de Koning J, Samsom JP. Incidence of human infection with *Yersinia enterocolitica* serotypes O3, O8, and O9 and the use of indirect immunofluorescence in diagnosis. *J Infect Dis* **153**: 138-141, 1986.
- Fendler C, Laitko S, Sörensen H, et al. Frequency of triggering bacteria in patients with reactive arthritis and undifferentiated oligoarthritis and the relative importance of the tests used for diagnosis. *Ann Rheum Dis* **60**: 337-343, 2001.
- Sheehan NJ. HLA-B27: what's new? *Rheumatology (Oxford)* **49**: 621-631, 2010.
- Yu D, Kuipers JG. Role of bacteria and HLA-B27 in the pathogenesis of reactive arthritis. *Rheum Dis Clin North Am* **29**: 21-36, 2003.
- Rühl M, Klos A, Köhler L, Kuipers JG. Infection and musculoskeletal conditions: Reactive arthritis. *Best Pract Res Clin Rheumatol* **20**: 1119-1137, 2006.
- Sieper J, Braun J. Treatment of reactive arthritis with antibiotics. *Br J Rheumatol* **37**: 717-720, 1998.
- Zhang Y, Gripenberg-Lerche C, Söderström KO, Toivanen A, Toivanen P. Antibiotic prophylaxis and treatment of reactive arthritis. Lessons from an animal model. *Arthritis Rheum* **39**: 1238-1243, 1996.
- Zhang Y, Toivanen A, Toivanen P. Experimental *Yersinia*-triggered reactive arthritis; effect of a 3-week course with ciprofloxacin. *Br J Rheumatol* **36**: 541-546, 1997.
- Palazzi C, Olivieri I, D'Amico E, Pennese E, Petricca A. Management of reactive arthritis. *Expert Opin Pharmacother* **5**: 61-70, 2004.
- Clegg DO, Reda DJ, Weisman MH, et al. Comparison of sulfasalazine and placebo in the treatment of reactive arthritis (Reiter's syndrome). A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* **39**: 2021-2027, 1996.
- Schumacher HR Jr. Reactive arthritis. *Rheum Dis Clin North Am* **24**: 261-273, 1998.
- Toivanen A. Managing reactive arthritis. *Rheumatology (Oxford)* **39**: 117-119, 2000.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).