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• *CASE REPORT* •

Concordance of ulcerative colitis in monozygotic twin sisters

Madoka Horiya, Satoru Kakizaki, Katsunobu Teshigawara, Yuki Kikuchi, Tetsu Hashida, Yoshio Tomizawa, Tomohiro Iida, Takashige Masuo, Hitoshi Takagi, Masatomo Mori

Madoka Horiya, Satoru Kakizaki, Katsunobu Teshigawara, Yuki Kikuchi, Tetsu Hashida, Yoshio Tomizawa, Tomohiro Iida, Takashige Masuo, Hitoshi Takagi, Masatomo Mori, Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Maebashi, Gunma 371-8511, Japan
Correspondence to: Satoru Kakizaki, **MD, PhD, Department** of Medicine and Molecular Science, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan. **kakizaki@showa.gunma-u.ac.jp**
Telephone: +81-27-220-8127 **Fax:** +81-27-220-8136
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Abstract

The etiology of inflammatory bowel disease is multifactorial and appears to combine both genetic and environmental factors. We experienced here a rare occurrence of woman monozygotic twins with ulcerative colitis (UC). A 45-year-old woman (the elder monozygotic twin) was admitted to our hospital because of bloody diarrhea occurring over 10 times per day, abdominal pain and fever. She was diagnosed as UC at the age of 22, and repeated the relapse and remission. She was diagnosed as relapse of UC and total colitis type. Her younger monozygotic twin sister also suffered from UC at the age of 22. Human leukocyte antigen was examined serologically with DNA type in both patients. DRB1*1502, which was previously shown to be dominant in Japanese patients with UC, was not observed in this case. Although the concordance in monozygotic twin in UC is reported to be 6.3-18.8%, the concordant case like this is relatively rare. We report this rare case of UC and the previously reported cases are also discussed.

Key words: Ulcerative colitis; Inflammatory bowel disease; Monozygotic twin; Human leukocyte antigen

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INTRODUCTION

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease, which is thought to be multifactorial and appears to combine both genetic and environmental factors. A number of studies have demonstrated aggregation of cases of UC in families, suggesting that patients share a genetic background. The concordance in monozygotic twin in UC is reported to be 6.3-18.8%[1-4]. Although the concordance rate is not so low, patients with twin pairs suffering from UC are relatively rare[5-9] and few observations of the twin pairs with UC have been reported[10-14]. In addition, although previous studies on the associations of UC and human leukocyte antigen (HLA) genes suggest that HLA play a role in this disease, the associations of various HLA loci with UC have yet to be fully elucidated. We experienced here a rare monozygotic twin with UC and determined their HLA serological and DNA type.

CASE REPORT

A 45-year-old Japanese woman (the elder monozygotic twin) was admitted to Gunma University Hospital with episodes of bloody mucous diarrhea occurring over 10 times per day and associated crampy lower abdominal pain and fever. She had a past history of UC at the age of 22, and was followed up by her primary physician. UC repeated the relapse and remission. Bloody diarrhea, abdominal pain and fever worsened from September 2004, and caused the admission. Physical examination was unremarkable and laboratory examination showed 105 g/L hemoglobin, 7 200 /mm^3 WBC count, 15.7×10^4/mm^3 platelets, 56 mm/h erythrocyte sedimentation rate, 52 g/dL serum total protein, 27 g/L albumin, 33 U/L alanine transaminase, 35 U/L aspartate transaminase, 67 U/L γ-glutamyl transferase, and 5.3 mg/L C-reactive protein. Perinuclear pattern of antineutrophil cytoplasmic antibodies (p-ANCA) was negative. Stool cultures for bacteria showed negative findings. Computed tomography of abdomen showed no abnormalities of liver, pancreas or biliary tract. Colonoscopy revealed a total colitis with diffusely reddish, edematous and erosive lesions, being consistent with the relapse of UC (Figure 1). Histological examination of biopsy specimen revealed depletion of goblet cells, crypt abscesses and severe lymphoplasmacytic infiltration in the mucosa, which was also consistent with UC. There were no extra-bowel complications such as primary sclerosing cholangitis. Because sulfasalazine failed to control her colitis, she was treated with intravenous prednisolone and granulocyte and monocyte adsorptive apheresis, which led her to a remission state.

Her younger sister was also diagnosed as UC at the age of 22, and was followed-up by her primary physician. She had a similar course of UC disease as her elder

Table 1 HLA alleles in the case

Serological typing		
A Locus	A2	A33
B Locus	B44	B75
DR Locus	DR13	DR15
DQ Locus	DQ1	
DNA typing		
DRB1	1302	1501
DQB1	0602	0604

sister. Although she was not admitted to the hospital, her colitis worsened in October 2004, and was treated at the outpatient clinic. She was also negative for p-ANCA and had no extra-bowel complications.

The twins were born as full-term normal deliveries and the pregnancy was not complicated. No differences in dietary habits were observed between the twins. They were non-smokers. Their parents, husbands, and daughters had no history of UC or chronic diarrheal diseases. Both twins shared the same home for 24 years, but they lived in different places since the younger sister was married and left home. For the purpose of genetic search, HLA was revealed with serological and DNA types after informed consent was obtained from each patient. HLA was identical and A2, A33, B44, B75, DR13, DR15, DQ1 were detected serologically. DRB1*1501, *1302, DQB1*0602, *0604 were observed by DNA typing (Table 1).

DISCUSSION

The pathogenesis of UC and Crohn's disease is still unknown, but the importance of genetic susceptibility has been clearly shown by epidemiological data from family and twin studies[1-4]. Several twin studies reported that the concordance rate in monozygotic twin with UC is 6.3-18.8%[1-4]. Tysk *et al*[1]. used the Swedish twin registry and inpatient hospital records to identify twins affected by inflammatory bowel disease. Among 25 000 pairs of twins identified from the Swedish twin registry, 80 twin pairs suffering from inflammatory bowel disease were found. In the UC group, 1 of 16 monozygotic pairs was concordant with the disease and the proband concordance rate among monozygotic twins was 6.3% for UC. It was reported that the pair concordance rate in monozygotic twins increases from 6.3% to 18.8% in a Swedish study[2]. Thompson *et al*[3]. also traced 144 twin pairs with inflammatory bowel disease from 16 000 members of the National Association for Colitis and Crohn's Disease, and found that 15.8% monozygotic twins with UC are concordant with the disease. These studies and case reports all indicate a higher concordance with inflammatory bowel disease in monozygotic twins than in dizygotic twins[1-4]. The prevalence and incidence of UC are much lower in Japan than in Europe and North America[15]. Although inflammatory bowel diseases are increasing also in Japan as in European countries, hospital-based investigation in 1991 revealed that the prevalence of UC is 18.12/100 000 and

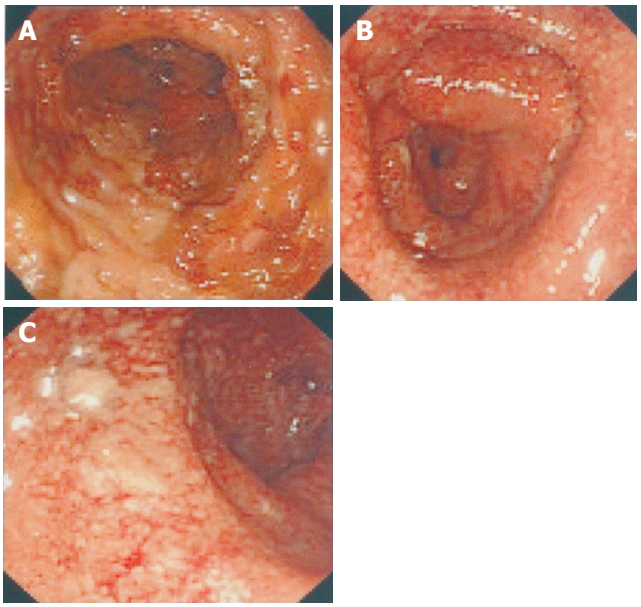

Figure 1 Colonoscopic findings in elder twin sister with UC.

the incidence is 1.95/100 000 in Japan[15]. Delivery with monozygotic twins is reported to be about 4/1 000. The twin study with UC reported that the concordance rate in monozygotic twins with UC is 6.3-18.8%[1-4]. If prevalence of UC is estimated to be 18.12/100 000, concordance rate to be 18.8% and twin delivery rate to be 4/1 000, concordance twin with UC like this case is estimated to be about 13.6/100 000 000. Thus, concordance twins with UC like this case are about only 13.6 cases in Japan. We searched concordant twins with UC using PubMed by key words ulcerative colitis and twin, and found only 22 cases (Table 2) including our case which was reported.

The apparently conflicting data on the HLA system in different studies from around the world may be explained by differences in ethnics, cases and genetic heterogeneity[16]. Replicated class II HLA includes HLA DRB1*0103 and DR2 (DRB1*1502) involved in UC susceptibility, and HLA DRB1*03 and DR4 as resistant alleles for Crohn's disease and UC respectively[16]. The strong association between HLA DR2 and UC has been reported in Japan[17], India[18], and Israel[19]. However, these alleles were not observed in our case. HLA could not explain the occurrence of UC in our case.

The role of environmental factors in the pathogenesis of inflammatory bowel disease is still controversial. The lack of complete concordance in monozygotic twin studies underlines the crucial role played by external factors in the determination of disease expression in patients with genetic susceptibility to inflammatory bowel disease. Non-smoking or a cessation of smoking is a proven risk factor for developing UC[20]. Neither of the twins in our case has ever smoked. Inversely, it has been suggested that appendectomy offers protection against the development of UC[21]. Neither of the twins in our case has received appendectomy.

Table 2 Previously reported cases and prevalence of concordant twins with UC

Author (country)	Total number of twin	IBD[1]	Ulcerative colitis[2]	Number of concordant cases	Concordance (%)	Referrence
Tysk,Halfvarson	25 000	80	16 (Monozygotic)	1 (3)	6.3 (18.8)	*Gut* 1988;29:990-996
(Sweden)			26 (Dizygotic)	0	0	*Gastroenterology*. 2003;124:1767-73
Thompson		128	38 (Monozygotic)	6	15.8	*BMJ* 1996;312:95-96
(UK)			34 (Dizygotic)	1 (Dizygotic)	2.9	
Orholm	29 421	103	21 (Monozygotic)	3	14.3	*Scand J Gastroenterol*. 2000;35:1075-81
(Denmark)			44 (Dizygotic)	2 (Dizygotic)	4.5	
Lyons (USA)	Case report			1		*Gastroenterology*. 1948;10:545
Webb (USA)	Case report			1		*Gastroenterology*. 1950;15:523-4
Bacon	Case report			1 (Dizygotic)		*Ulcerative colitis*. 1958, pp3 J.B.Lippincott Co.
Sleight	Case report			1		*Gastroenterology*. 1971;61:507-12
Sanford	Case report			1		*Am Surg*. 1971;37:512-7.
Fausa	Case report			1		*Scand J Gastroenterol*. 1972;16 (Suppl):38
Quigley (USA)	Case report			1		*Postgrad Med J*. 1982;58:112-4
Mayberry (UK)	Case report			1		*Gastroenterology*. 1983;85:1160-5
Masuichi (Japan)	Case report			1		*Nippon Shokakibyo Gakkai Zasshi*. 1995;92:1966-70
Iwaizumi (Japan)	Case report			1		*Intern Med*. 2002;41:629-32
Our case (Japan)	Case report			1		

Total number of concordant cases of ulcerative colitis in monozygotic twins. IBD[1]: number of twins, one or both pair suffered from inflammatory bowel disease Ulcerative colitis[2]: number of twins, one or both pair suffered from ulcerative colitis. UK: United Kingdom, USA: United States of America.

In summary, we have explained here a rare monozygotic twin with UC. HLA serological and DNA typing were determined. Similar twins are reported to be concordant with inflammatory bowel disease; however the concordant rate is only 6.3-18.8% and the accurate number of these cases is rare. Further accumulations of these cases are needed to clarify the contribution of genetic factors to the development of UC.

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