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ORIGINAL ARTICLE

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High frequency of unusual gastric/duodenal ulcers in patients with Behçet's disease in Taiwan: a possible correlation of MHC molecules with the development of gastric/duodenal ulcers

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Abstract The gastrointestinal (GI) involvement of Behçet's disease (BD) mainly affects the ileocecal region and colon. The gastroduodenal mucosa appears to be the least frequently involved segment of the gastrointestinal tract. The objective of this study was to assess the severity of gastric/duodenal involvement in BD patients in Taiwan. Behçet's disease was diagnosed according to the diagnostic criteria issued by the International Study Group for Behçet's Disease. We obtained and recorded clinical and laboratory data. A routine endoscopic examination with a urease test for *Helicobacter pylori* infection was arranged. Furthermore, HLA tissue typing was also performed by polymerase chain reaction with sequence-specific primers to evaluate the possible genetic loads associated with ulcer development. A total 28 BD patients, diagnosed at DaLin TzuChi hospital from 1999 to 2002, were enrolled in this study. The prevalence rate of gastric/duodenal ulceration was 43% (six patients had combined gastric and duodenal ulcers, three patients had simple gastric ulcers, and three patients had simple duodenal ulcers). No risk factors of nonsteroidal anti-inflammatory drug (NSAID) or *H. pylori* infection were found to be associated with gastrointestinal ulcers in our BD patients. All patients with peptic ulcers responded well to systemic steroids and immunosuppressant treatment in this preliminary observation. Furthermore, 7 of 12 gastric/duodenal ulcer patients (58%) carried an A2/B46/Cw1 or A11/B46/Cw1 genotype. Our data indicated that gastric/duodenal ulcers were a common manifestation in Chinese patients with BD in Taiwan in close association with the distinct genotypes of A2/B46/Cw1 or A11/B46/Cw1. A good response to systemic steroids, rather than conventional H2 blockers, might be due to downregulation of the vasculitis.

Keywords Behçet's disease · MHC · Peptic ulcer

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Introduction

Behçet's disease (BD) is a multisystem, chronic, relapsing vasculitis of unknown origin that affects nearly all organs and systems. While recurrent oral ulcerations are a "sine qua non" of BD, the frequency of extra-oral involvement of the gastrointestinal system varies widely in different countries. The most frequent extra-oral sites of gastrointestinal involvement are the ileocecal region and the colon. There are rare reports of gastric and duodenal ulcers in patients with BD in scientific journals. We had experience in treating a BD patient with repeated gastric ulcers in 1999. He was diagnosed as having Behçet's disease in 1996 with manifestations of recurrent oral ulcers, genital ulcers, erythema nodosum, and folliculitis. Hematemesis, massive tarry stool, high fever, and oral ulcer were noted and required repeated transfusion. An endoscopy examination revealed active gastric ulcers. Due to treatment failure with H2 blockers in several previous bleeding ulcer episodes, methylprednisolone pulse therapy, followed by cyclophosphamide, was prescribed for rescue of active ulcer bleeding. Dramatic improvement was noted and no new gastric ulcer has been observed since then. To further evaluate the extent of gastric/duodenal ulcer involvement in Taiwan, BD patients diagnosed from 1999 to 2002 at our hospital were enrolled in this current study.

Material and patients

Patient with Behçet's disease at rheumatology clinics of Dalin Tzuchi hospital from 1999 to 2002 were included in this study. BD was diagnosed according to the International Study Group criteria (ISG) [1]. A diagnosis of BD requires recurrent oral ulcerations plus two of the following additional findings: (1) recurrent genital ulcerations, (2) eye lesions consisting of an iritis, posterior uveitis, renal vessel occlusion, and/or optic neuritis, (3) skin lesions consisting of folliculitis, erythema nodosum, an acne-like exanthema, or a migratory thrombophlebitis, or (4) a positive pathergy test, which is an inflammatory skin reaction to an intradermal injection of saline. After admission, we obtained and recorded clinical and laboratory data including routine blood and urine analyses, erythrocyte sedimentation rate (ESR), C-reactive protein, and serum immunoglobulins from these patients. For evaluation of gastroduodenal involvement of BD in this local area, a diagnostic endoscopy was arranged for all patients. *Helicobacter pylori* infection by urease test was performed during endoscopy examination. Some patients underwent a second endoscopy examination 3 months later after treatment with systemic steroids (prednisolone 10 mg b.i.d. and cyclophosphamide 50 mg/day). Colonoscopy and barium enema were not routinely arranged but only for those patients with clinical manifestations of low abdomen pain or bloody stools. Considering the possibility of genetic loads in the pathogenesis of ulcer development, HLA tissue antigens were determined by a DNA typing technique with sequence-specific primers (SSP) (HLA-A.B.C.DR.DQ kit, Dynal Allset SSP, Dynal Biotech, Bromborough, Wirral, UK)

Results

Gastrointestinal ulcer was a relatively common manifestation in Chinese patients with BD in Taiwan. A total of 28 patients with BD were enrolled in this study. There were 14 patients who suffered from extra-oral gastrointestinal involvement determined by routine endoscope examinations (including 6 patients with combined gastric and duodenal ulcers, 3 with gastric ulcers, 3 with duodenal ulcers, 1 with anal ulcer, and 1 with a colon linear ulceration). The frequency of extra-oral GI involvement was 50% in our series (which might be an underestimate because no routine evaluation of rectocolon lesions was performed in this study). Most of our ulcer patients complained of dyspepsia, hunger pain, and epigastric pain. Two of them (patients 3 and 10) suffered severe hematemesis and bloody stools. Ten patients had previous episodes of peptic ulcers. The incidence of rectocolon lesions might be underestimated because routine colonoscopy examination was not arranged in the current study. No patient was found to have esophageal mucosa ulcerations during the examination.

Nine patients in this study had used a nonsteroidal anti-inflammatory drug (NSAID) intermittently for control of low back pain and joint pain (Table 1) at other local clinics. Only two of our ulcer patients had a history of NSAID use [patient 11 with meloxicam 7.5 mg/day for 6 months—the frequency in our series was at least 50% (no routine colonoscopy examination was performed)—and patient 20 with meloxicam 7.5 mg/day for 12 months]. It was noted, however, that duodenal ulcer and not gastric ulcer was found in patient 11, possibly not related to NSAID-induced gastric ulcer. Furthermore, only one of our ulcer patients (patient 26) had *H. pylori* infection.

In the current study, all of our BD patients had recurrent oral ulcers (100%). Twenty patients (71%) suffered from genital ulcers and 78% of our BD patients had one or more cutaneous lesions (folliculitis, erythema nodosum, and papulopustular lesion). On the contrary, only two patients had a history of iridocyclitis/uveitis. Besides, active inflammatory signs were also present simultaneously during episodes of gastric/duodenal ulcers. Leukocytosis, fever, neutrophilia, elevated ESR, and active cutaneous lesions were most frequently noted.

It was found that 7 of 12 patients (58%) with gastric/duodenal ulcerations carried an A2/B46/Cw1 or A11/B46/Cw1 genotype. On the other hand, none of the other 16 BD patients without gastric/duodenal ulcers had such genotypes. HLA-B51 genes were present in only five of our BD patients, and only one patient developed a gastric ulcer.

Discussion

Several criteria have been formed since 1969 in an attempt to aid in the diagnosis of BD. The various criteria include Mason and Bames, Japanese, O'Duffy, Zang, Dilsen, and most recently the International Study Group criteria [1]. However, there is no universally accepted definition of BD. The same patient may be classified as having complete BD by one set of criteria, while being considered to have an incomplete form of the disease by another set. The discriminatory performance in combination and in comparison with all other existing criteria sets are summarized by Kaklamani [2]. There are data that suggest that regardless of whether the BD is complete or incomplete, according to the criteria, the natural history of the disease is the same [3]. The ISG criteria compare favorably with the other criteria sets with a sensitivity 91%, specificity of 96%, and relative value of 187. All of our BD patients had oral ulcers (100%). Of 28 patients, 20 (71%) suffered from genital ulcer and 78% of our BD patients had one or more cutaneous lesions (folliculitis, erythema nodosum, and papulopustular lesion). The percentage of all the above of manifestations is similar to those described in the ISG

Table 1 Demography of patients with Behçet's disease. *EN* erythema nodosum, *GU* gastric ulcer, *DU* duodenal ulcer, *DVT* deep vein thrombosis, *ND* not done, *patho* microscopic examination of *Helicobacter* infection, *CLO* urease test for *Helicobacter* infection, *MHC* major histocompatibility complex

Patients	Sex/age	Clinical symptoms[a]	NSAID[b]	Past history of peptic ulcers	*H. pylori* infection by CLO test	Class I MHC antigen
1. Chou XX	M/61	Oral ulcer, folliculitis, genital ulcer	No NSAID		ND	A24A26B22B13Cw2Cw10
2. Chen XX	M/39	Oral ulcer, genital ulcer	Etodolac 200 mg b.i.d. for 3 months		ND	A32A2B56B7Cw1Cw2
3. Lu XX	F/44	EN, oral ulcer, folliculitis, GU, DU	No NSAID	1	CLO(−) patho: (−)	A11A33B55B58Cw10Cw12
4. Li XX	F/58	Oral ulcer, genital ulcer	No NSAID		ND	A2A11B13B58Cw10
5. Chung XX	M/23	EN, folliculitis, oral ulcer, genital ulcer	Flurbiprofen		ND	A11A26B39B58Cw7Cw8
6. Hwang XX	F/38	EN, oral ulcer, genital ulcer	No NSAID		ND	A33B56B58Cw6Cw7
7. Su XX	M/41	Oral ulcer, genital ulcer, DU	No NSAID		CLO (−) patho: ND	A2A11B46B56Cw1
8. Lin XX	F/46	Oral ulcer, genital ulcer, folliculitis	Rofecoxib 25 mg for f12 months		ND	A2B35B13Cw9Cw10
9. Tu XX	F/69	EN, Oral ulcer, DU	No NSAID	1	CLO(−) patho: ND	A2A26B46B60Cw1Cw10
10. Din XX	M/48	GU, DU, colon ulcer, oral ulcer, folliculitis	No NSAID	3	CLO(−) patho: (−)	A2A24B46B75Cw1Cw8
11. Liew XX	F/54	Oral ulcer, EN, DU	Meloxicam 7.5 mg qd for 6 months	2	CLO (−) patho: ND	A11B46B75Cw1Cw8
12. Chung X	M/38	Oral ulcer, genital ulcer, folliculitis	Diclofenac 25 mg b.i.d. for 9 months		ND	A2A24B51B62Cw1Cw4
13. Tu XX	F/41	EN, oral ulcer, genital ulcer, DU, GU	No NSAID	2	CLO(−) patho: (−)	A24B35B60Cw9Cw10
14. Lu X\X	F/48	Oral ulcer, anal ulcer, genital ulcer	No NSAID		ND	A2A32B22B15Cw8Cw15
15. Lin X	M/42	Oral ulcer, EN	No NSAID		ND	A24A11B39B40Cw8Cw10
16. Hwang XXX	F/49	Oral ulcer, genital ulcer, EN	Nimesulide 100 mg b.i.d. for 24 month		ND	A2A32B55B75Cw8Cw15
17. Liew XX	F/73	EN, oral ulcer, folliculitis, DVT, GU	No NSAID		CLO(−) patho: (−)	A2A24B46B75Cw1Cw4
18. Hwang XX	M/46	Oral ulcer, genital ulcer, folliculitis, EN, GU	No NSAID	1	CLO(−) patho: (−)	A2B51B55Cw1Cw12
19. Chen XX	M/29	EN, folliculitis, oral ulcer, genital ulcer	Diclofenac 25 mg b.i.d. for 18 months		ND	A11A33B27B58Cw10Cw12
20. Hsieu XX	F/38	EN, oral ulcer, genital ulcer, folliculitis, GU, DU	Meloxicam 7.5 mg qd for 12 months	2	CLO(−) patho: (−)	A2A11B46B60Cw1Cw7
21. Chun XX	M/38	Oral ulcer, genital ulcer, DU, GU	No NSAID	1	CLO (−) patho: (−)	A11A24B46B51Cw1Cw14
22. Chen XX	M/37	Oral ulcer, genital ulcer, folliculitis, EN	No NSAID		ND	A2A11B58B60Cw7
23. Chew XX	F/29	EN, oral ulcer, uveitis, folliculitis	No NSAID		ND	A11A24B51B60Cw7Cw14
24. Chew X	M/23	Oral ulcer, genital ulcer, DVT, EN, folliculitis	Etodolac 200 mg b.i.d. for 15 months		ND	A2A31B51B71Cw7Cw15

25. Chin XX	F/47	Oral ulcer, EN, genital ulcer, IgA nephropathy	No NSAID		ND	A2A24B55B62Cw1Cw4
26. Chung XX	F/35	Oral ulcer, genital ulcer, folliculitis, DU, GU	No NSAID	1	CLO (+)patho: (+)	A11A24B39B60Cw7Cw10
27. Lin XX	M/42	EN, oral ulcer, genital ulcer, GU	No NSAID	1	CLO(−)patho: (−)	A11B54B62Cw1Cw7
28. Kou XX	M/26	Oral ulcer, folliculitis, EN	No NSAID		ND	A11A32B7B35Cw11Cw10

[a]Cumulative symptoms and signs
[b]Drug history intermittently for low back pain and joint pain at local clinics within 3 months

criteria for BD. However, only two of our BD patients exhibited uveitis.

The frequency of gastrointestinal involvement varies in different countries, with a lower frequency in Turkey (2.8–5%), India (5.2%), and Israel (0%); a moderate frequency in France (14%), England (14%), Kuwait, and the United States (21%); and the highest frequency in Scotland (50%) and Japan (50–60%). The frequency in our series was at least 50% (no routine colonoscopy examination was performed). As for intestinal BD, some suggest it is a distinct entity of its own [4]. Ulcerations of the GI tract can be found throughout the intestine, but the most frequent area is the ileocecal region with extension to the ascending colon. Since this was not the major purpose of the current study, the true prevalence of ileocecal ulcers was not accurately estimated and needs further observations.

Compared to other parts of the gastrointestinal tract, the gastric mucosa appears to be the least frequently involved segment. Case reports of a Dieulafoy's ulcer [5] and a gastric non-Hodgkin's lymphoma associated with BD [6] have been described. Aphthous ulcers can occur in the duodenum. In two large autopsy series, a total of six patients with BD were found to have duodenal ulcers [7, 8]. Two cases of duodenal involvement in living patients have been reported [9, 10]. On the contrary, the prevalence of combined gastric/duodenal ulcers (6 of 28), simple duodenal ulcers (3 of 28), and simple gastric ulcers (3 of 28) was significantly higher in Chinese patients compared with previous reports.

In such a high prevalence of gastric/duodenal involvement of BD patients in this local area, it was found that 58% of our ulcer patients carried an A2/B46/Cw1 or A11/B46/Cw1 genotype (less than 4.6% from data of Tzu Chi Taiwan Marrow Donor Registry with over 150,000 prospective donors). On the other hand, none of the other 16 non-ulcer patients had these genotypes. It is possible that the presence of these distinct genotypes in patients might contribute to the development of gastric/duodenal ulcers in Taiwan. The role of HLA-B5(51) has been studied extensively during the past few years [11, 12]. In a recent report [13], allele HLA-B*5101 was shown to predispose to more severe diseases, such as uveitis and erythema nodosum. Japanese investigators [14] found that the BD gene is located near the HLA-B gene, but is not the HLA-B51 gene itself. Recent work suggests that polymorphism in tumor necrosis factor (TNF) and the MICA genes are noncontributory to the genetic load in BD. HLA-B51 genes were present in only five of our patients, and only one ulcer patient showed the B51 gene. It is suggested from our data that the HLA-B51 gene alone is not a contributory gene in BD and is not associated with the development of gastric/duodenal ulcerations in Chinese in Taiwan.

Only a few of our ulcer patients had risk factors of NSAID and *H. pylori* infection (two patients had histories of NSAID use but with negative survey in *H. pylori* infection; one patient had *H. pylori* infection

but with NSAID history). Two studies assessing the frequency of *H. pylori* infection in Turkish patients with BD have been reported [15, 16]. In the first, the urease positivity rate was 65% in 34 patients with BD [15]. In the second report, a higher prevalence (85%) was noted [16]. In our report, only one patient showed evidence of *H. pylori* infection (patient 26). Furthermore, only two of our ulcer patients had histories of NSAID usage (patients 11 and 20). Data of NSAID history and *H. pylori* infection did not support a correlation between ulcer formation and these risk factors. It was suggested that vasculitis rather than *H. pylori* infection or NSAID might be responsible for the high prevalence of gastric/duodenal ulcers in our patients.

In conclusion, we have demonstrated that peptic ulcer is a common manifestation in Chinese BD patients in Taiwan, although rarely mentioned in other populations. A close relationship between A2/B46/Cw1 (or A11/B46/Cw1) and the development of gastric/duodenal ulcers was found. Successful treatment of refractory gastric ulcers with steroid and cyclophosphamide might suggest that the disease itself, rather than NSAID or *H. pylori*, was responsible for the development of gastroduodenal ulcer in BD disease.

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References

1. International Study Group for Behcet's Disease (1990) Criteria for diagnosis of Behcet's disease. Lancet 335:1078–1080
2. Kaklamani VG, Vaiopoulos G, Kaklamanis PG (1998) Behcet's disease. Semin Arthritis Rheum 27:197–217
3. Thach B, Cummings N (1976) Behcet's syndrome with aphthous colitis. Arch Intern Med 136:705–709
4. Morita H, Kawai S, Kobori O, Ohya N, Sumiya M, Dohi T (1995) Incomplete form of Behcet's colitis in Japan: is it a distinct entity? Am J Gastroenterol 90:523–524
5. Arendt T, Kloehn S, Bastian A et al (1997) A case of Behcet's syndrome presented with Dieulafoy's ulcer. Z Gastroenterol 35:935–938
6. Abe T, Yachi A, Yabana T et al (1993) Gastric non-Hodgkin's lymphoma associated with Behcet's disease. Intern Med 32:663–667
7. Kasahara Y, Tanaka S, Nishino M et al (1981) Intestinal involvement in Behcet's disease: review of 136 surgical cases in the Japanese literature. Dis Colon Rectum 24:103–106
8. Chong VF, Pathmanathan R (1993) Familiar Behcet's syndrome with intestinal involvement-case reports and a review of the literature. Ann Acad Med 22:807–810
9. Ozence A, Bayraktar Y, Baykal A (1990) Pyloric stenosis with esophageal involvement in Behcet's disease. Am J Gastroenterol 85:727–728
10. Satake K, Yada K, Ikehara T et al (1986) Pyloric stenosis: an unusual complication in Behcet's disease. Am J Gastroenterol 81:816–818
11. Mizuki N, Inoko H, Ando H, Nakamura S et al (1993) Behcet's disease associated with one of the HLA_B51 subantigens, HLA-B*5101. Am J Ophthalmol 116:406–409
12. Ohno S, Ohguchi M, Hirose S, Matsuda H, Wakisaka A, Alizawa M (1982) Close association of HLA-Bw51 with Behcet's disease. Arch Ophthalmol 100:1455–1458
13. Messini H, Spyropoulou M, Papadimitropoulos M et al (1996) HLA-B5 (51) genomic analysis in Greek patients with Behcet's disease: correlation with certain disease characteristics. In: VII International Conference on Behcet's Disease. Rev Rhum Engl Ed 63:534
14. Mizuki N, Ohno SH (1996) Immunogenetics studies of Behcet's disease. In: VII International Conference on Behcet's Disease. Rev Rhum Engl Ed 63:520–527
15. Ormeci N, Gurler A, Cakir M et al (1996) Prevalence of H. pylori in Behcet's disease. In: VII International Conference on Behcet's Disease. Rev Rhum Engl Ed 63:558
16. Aksoz MK, Unsal B, Zeren I et al (1995) The upper gastrointestinal endoscopic and rectosigmoidoscopic findings in Behcet's disease. Turk J Gastroenterol 6:172–174