Frequency of pathergy phenomenon and other features of Behçet's syndrome among patients with inflammatory bowel disease

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ABSTRACT

Objective. *Crohn's disease (CD) and ulcerative colitis (UC) share common clinical features with Behçet's syndrome (BS). We surveyed UC and CD patients for pathergy phenomenon and features of BS with the aim of determining how much overlap is present between these 2 entities in a setting where BS is relatively common, the frequency of pathergy positivity in inflammatory bowel disease (IBD) patients and evaluating how International Study Group (ISG) criteria perform in differentiating IBD from BS.*

Methods. *This study was conducted among patients with CD and UC attending the gastroenterology outpatient clinic of a university hospital which is also a referral center for BS. Consecutive CD and UC patients were screened for BS using ISG criteria. Pathergy test was performed and evaluated by 2 independent observers in a masked manner.*

Results. *Ninety-three patients with CD and 130 with UC were surveyed. None of the CD patients fulfilled ISG criteria for BS while 2 of 130 UC patients did. Twenty CD patients had oral ulcers while 4 reported having genital ulcers but no scars could be observed. Twenty-two CD patients had papulopustular lesions, 2 had nodular lesions, 3 had arthritis and none had uveitis. Thirty-two UC patients had oral ulcers, none had genital ulcers, 23 had papulopustular lesions, 3 had nodular lesions, 2 had arthritis and 2 had uveitis. Pathergy test was positive according to at least one of the observers in 10/93 CD and 8/130 UC patients and according to both observers in 4/130 UC patients.*

Conclusion. *Despite similarities between the clinical features of CD and UC with BS, coexistence is uncommon. ISG criteria perform well in differentiating these diseases. About 8% of IBD patients show the pathergy phenomenon.*

Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated inflammatory condition affecting the gastrointestinal tract. Ulcerative colitis (UC) and Crohn's disease (CD) are the two major types of IBD. Extraintestinal involvement of IBD is seen in up to one third of the patients and includes dermatologic (erythema nodosum, pyoderma gangrenosum, oral mucosal lesions) rheumatologic (peripheral arthritis, sacroiliitis), ocular (anterior uveitis, episcleritis), and thrombotic (venous and arterial thrombosis) manifestations.

Behçet's syndrome (BS) is a multisystemic vasculitis which involves the skin, mucosa, joints, eyes, vascular, gastrointestinal and neurologic systems. It shares some common features with UC and CD such as oral ulcers, erythema nodosum, uveitis, arthritis, and ulcers on colonic and ileocecal mucosa. The gastrointestinal involvement of BS usually involves the ileocecal part of the intestine and may cause perforation, bleeding or obstruction leading to surgery (1, 2). The ulcers may be indistinguishable from those of CD, both macroscopically and histologically (3). The differential diagnosis might be difficult in such patients.

The original study for developing criteria for diagnosis (classification) of BS by the International Study Group for Behçet's Disease did not include or included only a few patients with inflammatoy bowel disease as controls (4). In a previous study which aimed to reassess the performance of International Study Group (ISG) criteria among patients with BS and other rheumatologic

conditions, 21 CD and 34 UC patients were studied together with 383 patients with other inflammatory diseases such as familial Mediterranean fever, rheumatoid arthritis and systemic lupus erythematosus and 302 BS patients (5). In that study 1 patient with CD and none of those with UC had fulfilled ISG criteria. However, pathergy was not evaluated in a masked manner and the number of patients with inflammatory bowel diseases was too small to evaluate how these criteria perform in differentiating these diseases.

In the current study we aimed to a) determine how much overlap is present between these 2 entities, in a population with a high prevalence of BS, b) to determine the frequency of pathergy positivity in inflammatory bowel disease patients and c) to evaluate how ISG criteria perform in differentiating inflammatory bowel diseases from BS.

Table I. International Study Group Criteria for the classification of Behçet's disease.

Recurrent oral ulceration:	Minor aphtous, major aphtous or herpetiform ulceration observed by a physician or reported reliably by patient, which recurred at least 3 times in one 12 months period
Plus two of:	
Recurrent genital ulceration:	Aphtous ulceration or scarring
Eye lesion:	Anterior uveitis, posterior uveitis or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
Skin lesions:	Erythema nodosum observed by physician or reported reliably by patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules consistent with Behçet's syndrome, observed by a physician in post-adolescent patients not on corticosteroid treatment
Positive pathergy test:	Read by physician at 48 hours, performed with oblique insertion of 20-22 gauge or smaller needle under sterile conditions

Findings applicable only in abscence of other clinical explanations.

Table II. Questionnaire which was used for evaluating features of BS.

Involvement	Questions
Oral ulcers	Do you have ulcers in your mouth ? Have you ever had any mouth ulcers in the past ? If yes, when was the first time you had a mouth ulcer? How frequently do you have ulcers in your mouth?(-- per year)
Genital ulcers	Do you have any genital ulcers? Have you ever had any genital ulcers in the past ? If yes, when was the first time you had a genital ulcer? How frequently do you have genital ulcers?(-- per year)
Acne-like lesions	Do you have acne-like lesions? Have you ever had acne-like lesions in the past ? If yes, when was the first time you had acne-like lesions?
Nodular lesions	Do you have red or purple swellings on your legs or arms? Have you ever had red or purple swellings on your legs or arms in the past ? If yes, when was the first time you had these swellings?
Joint involvement	Do you have pain or swelling in your joints? Have you ever had pain or swelling in your joints in the past? If yes, when was the first time you had pain or swelling in your joints?
Eye involvement	Do you have blurred vision, or pain or redness in your eyes? Have you ever had blurred vision, or pain or redness in your eyes? If yes, when was the first time you had blurred vision, or pain or redness in your eyes?
Vascular involvement	Dou you have swelling, pain, or redness in your calfs? Have you ever experienced swelling, pain, or redness in your calfs? Have you ever coughed up blood? Have you ever been told you have an obstruction or enlargement in your vessels?
Neurologic involvement	Have you ever had a stroke, numbness, tingling or weakness in the arms or legs, a seizure, severe head ache or double vision?

Methods

CD and UC patients followed in the gastroenterology outpatient clinic of Istanbul University, Cerrahpasa Medical School were included. This unit is a tertiary referral center with more than 800 recorded patients with inflammatory bowel disease. All patients with BS followed in the rheumatology department of Cerrahpasa Medical School who have symptoms related to the gastrointestinal system are also referred to this gastroenterology unit for further evaluation.

Consecutive IBD patients who visited the gastroenterology outpatient clinic for their routine controls and agreed to participate in this study were referred to the Behçet's syndrome research center within the rheumatology department of Cerrahpasa Medical School. The patients were questioned and examined by a rheumatologist and a dermatologist who were unaware of the diagnoses of the patients. A standard questionnaire was prepared based on the ISG criteria (Table I) (4). The questionnaire involved questions about the presence and history of oral ulcers, genital ulcers, papulopustular lesions, nodular lesions, pain and/or swelling in the joints, and eye involvement which constitute the items of ISG criteria, as well as questions about venous thrombosis, arterial aneurysms or occlusions, and neurologic involvement (Table II). Subsequently, all patients underwent a slit lamp ophthalmologic examination by an ophthalmologist experienced in BS, who was also unaware of the diagnoses.

The pathergy test was performed in all patients. Both forearms were cleaned with alcohol swabs (70%) before inserting 20-gauge disposable needles intradermally (6). Three needles were inserted to each forearm, a few centimeters apart from each other. Pathergy was evaluated 48 hours later by 2 independent observers in a masked manner. Patients put their arms through a hole in a curtain to prevent the observers from recognizing the subjects. The pathergy test was performed on the same day with the subjects of another study (7), including patients with BS, rheumatoid arthritis and healthy controls for blinding. Appearance of a papule or a pustule at the needle insertion site was

considered as a positive pathergy test. The number of reactions determined by each observer was noted, from 0/6 to 6/6.

The study was approved by the ethics committee of Cerrahpasa Medical School.

Results

Ninety-three patients with Crohn's disease (45 men, 48 women, mean age 42.8±1.3 years) and 130 patients with ulcerative colitis (58 men, 72 women, mean age 39.1±12.2 years) were included.

Among the 93 patients with Crohn's disease, 20 (21.5%) reported having 3 or more oral ulcers per year (Table III). Four (4.3%) patients reported having genital ulcers. However none of the patients including those who reported having genital ulcers had genital scars on physical examination. Twenty-two patients (23.6%) reported papulopustular lesions and in 3 of them the papulopustular lesions were on the extremities. Two patients (2.2%) reported nodular skin lesions, and 3 patients reported having (3.2%) arthritis. None of the patients had uveitis, vascular or neurological involvement.

Thrity-two of the 130 patients with ulcerative colitis (24.6%) had 3 or more oral ulcers every year (Table III). None of them reported having genital ulcers and none had genital scars on examination. Twenty-three patients (17.6%) reported having papulopustular lesions and in 2 patients these lesions were on the extremities. Three (2.3%) reported nodular skin lesions, and 2 patients reported (1.5%) arthritis episodes. Two patients had anterior uveitis. None of the patients had vascular or neurological involvement.

The skin pathergy test was evaluated as positive in 8/93 (8.6%) patients with Crohn's disease by the first observer and in 2/93 (2.2%) patients by the second observer. None of the patients were evaluated as pathergy positive by both observers. Among ulcerative colitis patients 8/130 (6.1%) had a positive pathergy test as evaluated by the first observer. Four of these patients (3.1%) were evaluated as pathergy positive by the second observer, too. Thus among the total of 223 IBD patients 18 (8.1%) had a positive pathergy test. The number of patients who were evaluated as pathergy positive by both observers was 4 (1.8%). In all of the 14 patients whose pathergy test result was discordant between the 2 observers, the test was evaluated as positive in only one of the 6 prick sites.

Overall, 2 of the ulcerative colitis patients fulfilled the ISG criteria for BS while none of the Crohn's disease patients fulfilled these criteria.

The first patient was a 48-year-old man who had presented with tenesmus and rectal bleeding seven years before. His colonoscopic evaluation showed mucosal hyperemia, edema and fragility on the distal 5 cm of rectum. Histopathologic examination revealed cryptitis, crypt abscesses and neutrophilic infiltration compatible with active ulcerative rectitis. He was treated with mesalazine rectal suppositories and had no further attacks. When he was questionned for features of BS, he reported having recurrent oral ulcers and papulopustular lesions. His pathergy test was evaluated as positive by both observers.

The second patient was a 44-year-old man who had been admitted with rectal bleeding 10 years before. Colonoscopy showed mucosal hyperemia, fragility and multiple small ulcers from rectum to transverse colon. Cryptitis, crypt distortion and crypt abscesses were detected on histopathologic examination. He is still under treatment with mesalazine and had further attacks under treatment. He is now being considered for azathioprine. When he was questionned for features of BS, he reported having oral ulcers and papulopustular lesions. His ophthalmologic examination showed anterior uveitis scar.

Table III. Features of Behçet's syndrome among ulcerative colitis (UC) and Crohn's disease (CD) patients.

	CD (n=93)	UC (n=130)
Oral ulcers	20 (21.5 %)	32 (24.6 %)
Genital ulcers	4 (4.3 %)	0
Genital scar	0	0
Papulopustular lesions	22 (23.6 %)	23 (17.6 %)
Nodular lesions	2 (2.4 %)	3 (2.3 %)
Arthritis	3 (3.2 %)	2 (1.5 %)
Vascular involvement	0	0
Eye involvement	0	2 (1.5 %)
Neurologic involvement	0	0

Discussion

This study showed that although features commonly seen in BS such as oral ulcers and papulopustular lesions were present in more than 20% of our IBD patients, there were only 2 patients (1%) who fulfilled the ISG criteria. The management of gastrointestinal involement of BS is not different from that of CD or UC (8). However it is important to determine whether such a patient has BS since serious complications involving other systems such as sight threatening panuveitis, arterial aneurysms and venous thrombosis may develop in BS patients and close follow-up is necessary.

Many case reports have been published, reporting patients with coexisting BS and UC or CD (9-14). In these reports Behçet's syndrome patients who had endoscopic and histopathologic findings resembling CD such as granuloma formation or focal cryptitis involving the crypt epithelium (9, 12), longitudinal ulcers, cobblestone appearance and anorectal fistulas (10) or findings resembling those of UC such as lead pipe appearance (11) were considered as patients who have both BS and inflammatory bowel disease. However, there are no studies comparing the histopathologic findings of gastrointestinal involvement of BS with those of CD or UC.

One might argue that the 2 patients who fulfill the ISG criteria have both BS and UC. However, oral ulcers, papulopustular lesions and anterior uveitis seen in these patients are frequently seen in UC patients. Papulopustular lesions are not a part of the clinical spectrum of IBD, but steroid use may be responsible for these lesions. Papulopustular lesions

on the extremities are considered more related to BS and these were reported only in 3 patients with CD and 2 with UC. The 2 patients who fulfilled the ISG criteria did not have papulopustular lesions on the extremities. One of the patients had a positive pathergy test, however, a positive pathergy has also been reported in other diseased and healthy controls (7). None of the patients had findings which are thought to be more specific to BS such as genital scars or posterior uveitis. Gastrointestinal findings were also more compatible with UC since cryptitis, crypt abscesses and rectitis, which were observed in the first patient, are very rare in BS and ulcers are usually single, unlike those observed in the second patient. Thus, we do not think that these 2 patients represent a true overlap of BS and UC. Although these patients fulfill the ISG criteria there is an important statement in the ISG criteria that these findings are applicable only in the abscence of other clinical explanations (4).

The ISG criteria are intended to be classification criteria rather than diagnostic criteria. The internal validity of these criteria had been addressed by weighing individual disease features and using traininig sets of patients. However the external validity has to be studied in different settings to determine whether these criteria have enough specificity to be used as diagnostic criteria, since the value of these criteria would depend on the positive predictive values in each setting such as gastroenterology, neurology or ophthalmology for BS.

This study showed that ISG criteria performed well in differentiating IBD from BS. However still more work is required to call these criteria diagnostic criteria. The diagnostic value should be further tested by including other patients who present to the gastroenterology clinic with similar findings, such as gastrointestinal tuberculosis or drug induced colitis. Especially colitis related to non-steroidal antiinflammatory drug use is an issue that should be addressed since it may be misinterpreted as gastrointestinal involvement in BS patients using these drugs for arthritis. It is also necessary to test the validity in different ethnic populations. The diagnostic value of these criteria in a gastroenterology clinic in Japan may be different from ours, since the frequency of gastrointestinal involvement in BS and thus the pretest probability may be different.

The endoscopic and histopathologic findings of CD are more likely to be confused with those of BS than UC. In the previous study by our group which assessed the performance of ISG criteria in a number of inflammatory conditions including CD and UC, there was 1 patient among 21 with CD who fulfilled ISG criteria (5). It was suggested then that the differentiation of CD from BS may be more problematic than UC. However the current study showed that there is not a significant overlap between CD and BS in terms of extraintestinal findings and none of the CD patients that we studied fulfilled ISG criteria. It should also be noted here that we have had only 2 patients with BS who were initially misdiagnosed as CD among around 400 Crohn's patients that we follow in our IBD outpatient clinic.

Another issue that this study highlighted is the frequency of pathergy positivity in UC and CD patients. As far as we know this is the first study to evaluate pathergy phenomenon in a large group of IBD patients and in a masked manner. Pathergy reaction is a well known feature of pyoderma gangrenosum lesions which are frequently related to IBD (15). However, pathergy positivity does not seem to be increased in IBD patients themselves. A positive pathergy reaction was present in 8.1% of IBD patients when the positive reading of either observer was accepted as positive, and in 1.8% when positive reading of both observers was required. This is similar to positive pathergy rates reported in rheumatoid arthritis patients and healthy individuals (7% and 3 % respectively) (7). Many of these patients were on immunosuppressive and/or steroid therapy when the pathergy test was performed. However this is unlikely to have affected the results since we have recently shown that treatment with immunosuppressives does not affect the pathergy phenomenon (16). The frequency of a disagreement between the 2 observers was 14/223 (6%). This is also comparable to what was reported in an old double blind study on the validity of the pathergy test which evaluated the interobserver and intraobserver reliability of this test (17). It should also be mentioned that the discordant results were only among those which were evaluated as 1/6 by one of the observers.

The fact that this gastroenterolgy clinic is also experienced in BS patients with gastrointestinal involvement and that the same gastroenterologist evaluates all BS patients with gastrointestinal involvement and IBD patients is both a strong point and a limitation of this study. It might be argued that patients with gastrointestinal involvement of BS have initially been excluded with scrutiny from UC and CD patients. Thus the performance of these criteria may not be as good as ours in every setting.

In conclusion, this study showed that the coexistence of BS with UC and CD is uncommon in our population and pathergy positivity is not frequent in IBD patients. ISG criteria perform well in differentiating these 2 entities, but more work is required to determine whether modifications are needed for these criteria to be used as diagnostic criteria in the setting of a gastroenterology clinic.

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