JAK2 V617F Mutation Is Not Involved in Thromboembolism in IBD

To the Editor:

Recently Janus kinase 2 (*JAK2*) mutations have been described in several Philadelphia-negative myeloproliferative disorders (MDP) as polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis, conditions complicated by thrombosis.[1] The point mutation in *JAK2* encodes a valine-to-phenylalanine change at position 617 (*JAK2* V617F) and confers constitutive tyrosine kinase activity.[2] It has been suggested that thrombosis in MPD may be due to *JAK2* mutation.

Moreover, screening for *JAK2* V617F has been carried out in a series of splanchnic, cerebral, and leg deep vein thromboses (DVTs) without overt MDP.[3,4] Results from these studies indicate that the *JAK2* V617F mutation in the absence of overt MDP is highly associated with splanchnic vein thrombosis and sporadically with cerebral thrombosis.

Thromboembolism is a disease-specific extraintestinal manifestation of inflammatory bowel disease (IBD)[5] that develops as the result of multiple interactions between acquired and genetic risk factors. Arterial and venous thromboembolism is the most important complication, representing a significant cause of morbidity and mortality in IBD patients. The most commonly detected risk factors for thrombophilia in this disease are factor V R506Q (Leiden) mutation, plasminogen activator inhibitor gene polymorphism, hyperhomocysteinemia, and antiphospholipid antibodies. However, the prevalence of these factors does not differ between patients with IBD associated with vascular complications and those with thrombosis without IBD.[6]

Different cytokines stimulate the JAK and signal transducer and activator of transcription (JAK/STAT) pathway. JAK2 is also important in vascular diseases, such as atherosclerosis in which inflammation plays an important role.[7]

The aim of our study was to investigate the frequency of the *JAK2* V617F mutation, which is the most common mutation described in MPD, in a group of 48 thrombotic IBD patients (22 with CD, 26 with UC) from Argentina ($n = 23$) and Crete ($n = 25$). The clinical characteristics of patients included in this study are reported in Table 1. No case had overt MPD, whereas some cases ($n = 4$) had a history of more than 1 thrombotic event. The diagnosis of vascular complications was defined by typical clinical characteristics and diagnostic instrumental investigation (Doppler ultrasonography, computed tomography, magnetic resonance imaging, or angiography).

Genomic DNA was isolated from peripheral blood according to an in-house DNAzol extraction procedure (Invitrogen, Breda, The Netherlands). Forty-eight patients with IBD varying in age of onset of IBD from 2 to 65 years (median 37.5 years) presented with different thrombotic events (Table 1). A semiquantitative Taqman assay was used to determine the percentage of the *JAK2* V617F mutation among wild-type DNA.

No *JAK2* V617F mutation was found in the 48 IBD patients with thrombotic complications. *JAK2* V617F mutation has been found associated with elevated hemoglobin levels and leukocytosis, which may be directly associated with the increased thrombotic risk in MPD. On the other hand, thromboembolism in IBD is not associated with elevated hemoglobin levels and leukocytosis. The finding of the absence of the *JAK2* V617F mutation in the thrombotic IBD patients suggests that other mechanisms play an important role in the pathogenesis of thrombosis in IBD. The small number of cases with splanchnic vein thrombosis in our series (but also in other IBD series), which is mainly associated *JAK2* V617F mutation, could also be an explanation of this finding.

Because recent studies in MPD have found other mutations in the gene coding for JAK2 (chromosome 9p24) such as JAK2 exon 12 mutations,[8] further study of IBD patients with these serious complications is being undertaken.

TABLE 1. Clinical characteristics and *JAK2* V617F mutation status in IBD patients with vascular complications

Number of patients	48 (Crete, 25; Argentina, 23)
Ulcerative colitis	26 (Crete, 15; Argentina, 11)
Crohn's disease	22 (Crete, 10; Argentina, 12)
Median age of onset of IBD	37.5 years
Female/male	16/32
Deep vein thrombosis of the leg	Crete, 8 UC/5 CD; Argentina, 9 UC/8 CD
Pulmonary emboli	2 UC (Crete)
Retinal venous thrombosis	2 CD (Argentina)
Splanchnic venous thrombosis	2 UC (1 Crete; 1 Argentina)
Myocardial infarction	Crete, 4 UC/2 CD; Argentina, 2 CD
Ischemic stroke	Crete, 2 UC/1 CD; Argentina, 3 CD
Presence of *JAK2* V617F mutation	0/48

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With the Great Complexity Unveiling, Can We Still Decipher the Interaction Between Gut Flora and the Host in Inflammatory Bowel Disease to Find Out the Mechanism and Cause? How?

To the Editor:

The great progress in recent years in inflammatory bowel disease (IBD) clearly demonstrated that gut bacteria play a critical role in the genesis and development of IBD.[1,2] However, on the other hand, it also revealed the extreme complexity of both gut flora and the responsive network of our body.[1,2] Molecular analysis has increased gut flora from the previous culture-based estimation of 200–300 species to between 15,000 and 36,000 species, with each of them capable of creating a specific pattern of response by the host that involves multiple immune and nonimmune cells and numerous cytokines and other bioactive molecules.[1] It would make it an extremely difficult task in attempting to find out the mechanism and cause of IBD by analysis and comparison of the unique features that each bacterial species possesses and the specific profile of response by the host that each bacterial species elicits. Can we still decipher the interaction between the gut bacteria and the host in IBD? For that purpose, we probably would have to adopt a more feasible approach. One way we can do this would be to find out those overall differences between the IBD patients and normal subjects that can be attributed to differences in gut flora. However, attention has to be paid to differentiate the noncausative metabolic or physiological changes from those with causative significance, such as the changed profile of the immune system. Even for changes in immune system, we would have to differentiate the normal, passive response from the real "aberrant" immune reaction. A large portion of the cellular and cytokine changes in IBD patients that were observed and described in the literature could be actually just a normal response of the body to the increased exposure of gut bacteria and their components or the resulting damage of the gut. Among the variety of changes in IBD patients, the increase in intestinal permeability and impairment in gut barrier function seem likely to be of primary significance. Increased intestinal permeability exists not only in IBD patients and their healthy relatives but also in the spouses of the patients,[3] making it more likely to be a special prerequisite event rather than secondary to the disease. Considering the epidemiological features of IBD, I suggest a simple scenario for how the change in gut bacteria would have increased the risk for IBD.

Reduction in gut bacteria due to inhibition by, for instance, dietary chemicals like saccharin[4]

+

Failure to get a prompt resupplement due to the improved hygiene (great reduction of bacteria in the air, water, and food)

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Impaired inactivation of digestive protease and increased luminal protease activity[5]

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Increased degradation of the protective mucus layer as a result of the synergistic effect of digestive proteases and the remaining excessive amount of bacterial glycosidases[6]

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↓

Breaking down of gut barrier function and an increase in intestinal permeability

↓

Increased infiltration of bacterial and other luminal components

↓

Inflammation and damage of the mucosa and enhanced immune response

Here I proposed a critical role for the bacteria-mediated inactivation of digestive proteases in the genesis and development of IBD. I believe digestive proteases would have played a more important role than people currently realize. For instance, the prompt massive bleeding observed in germ-free mice treated with dextran sodium sulfate (DSS)[1] would be more likely to be just simple, nonspecific digestive damage by the large amounts of digestive proteases in these animals,[6] rather than a special event involving some mysterious pathways or immune response. This notion is in accordance with the observation that similar massive bleeding also occurred in the guts of dogs shortly after ischemia, which can be effectively blocked by locally applied protease inhibitor.[7] Maybe the scenario I proposed here is too simplified. However, considering the prompt ups and downs of IBD since the last century, I strongly feel that the cause and mechanism of IBD could be much simpler than people currently conceive.

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Episodic Infliximab Treatment Induces Infusion Reactions

To the Editor:

Antitumor necrosis factor-α (TNF-α) is an important drug in the armamentarium of patients with chronic active Crohn's disease (CD). Infliximab (IFX) can be associated with the development of severe infusion reactions during treatment and retreatment, namely, acute and delayed reactions. We report 11 patients with active CD who developed infusion reactions, the reason why they had to stop IFX therapy. Eleven patients were enrolled in the study: all had active CD, refractory to steroids, and 4 were intolerant to azathioprine. The median time of CD diagnosis was 9.5 years. All patients had IFX infusions reactions: 4 acute and 7 delayed ones. Each patient started on IFX infusions (induction and episodic treatment) and then, after a variable period of time, regular scheduled therapy. Before IFX, intravenous premedication with 75 mg of prednisolone and clemastine was administered in all patients. The acute reactions started 15–30 minutes from the beginning of infusions. The clinical picture included dyspnea, facial rubor, chest pain, nausea, paresthesias, diaphoresis, tachycardia, chills, and even fever (Table 1). The median time of interruption between episodic and scheduled IFX infusions was 35 months (5–66 months) (Fig. 1). All patients were taking azathioprine. Delayed infusion reactions happened between the second and the eighth day after the last IFX infusion (Table 1). The median time between episodic and regular scheduled IFX infusions was 14.5 months (5–28 months). The clinical symptoms noticed were mainly arthralgias, especially from upper and lower members and even from the temporomandibular joint, myalgias, fever, malaise, skin eruptions all over the body, and asthenia (Table 1). The titer of autoantibodies (ANA, anti Ds DNA, anti-histones) was negative at the time of this study. There were no records about these autoantibodies during reactions. It is interesting to stress that in 50% of patients acute infusion reactions happened during the reinduction period or during the first infusion in the maintenance period. At the same time (reinfusion period), delayed infusion reactions occurred in 71% of patients. After the reaction IFX was stopped in all patients.

Herein we report 11 patients with adverse IFX reactions after retreatment with IFX on a regular schedule. All of them were treated beforehand with episodic IFX therapy. Larger intervals between IFX infusions have been associated with infusion reactions.[1] Generally, 6%–13% of CD patients receiving IFX treatment on a regular schedule develop antibodies against IFX; however, those treated with episodic infusions have a higher incidence of autoantibodies.[1] Infusion reactions have been associated with rapid formation of HACA[2]; nevertheless, in our hospital is not possible to

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TABLE 1. Clinical Description of IFX Infusion Reactions

Patients	IFX Schedule	Premedication	Infusion Reaction	Time Between IFX Infusion and Reaction	Symptoms	CPR (mg/dL)	Outcome
JPNB	On demand	Prednisolone and clemastine	Acute	30 minutes	Dyspnea, facial rubor, chest pain	7.6	Adalimumab
MDSP	On demand	Prednisolone and clemastine	Delayed	10 days	Generalized skin eruptions, fever, rubor, arthralgias of upper members	23.3	Adalimumab
ECSP	On demand	Prednisolone and clemastine	Delayed	2 days	Arthralgias of upper and lower members, fever, dyspnea,	1.7	Adalimumab
HRMG	On demand	Prednisolone and clemastine	Acute	20 minutes	Intense asthenia, malaise, nausea	50.6	Azathioprine
GMVDM	On demand	Prednisolone and clemastine	Acute	15 minutes	Parestesias, diaphoresis, tachycardia, dyspnea	15.4	Adalimumab
LAS	On demand	Prednisolone and clemastine	Acute	15 minutes	Nausea and vomiting, fever, chills	9.6	Adalimumab
ARCB	On demand	Prednisolone and clemastine	Delayed	8 days	Generalized and intense arthralgias, myalgias	11.8	Colostomy
MAMS	On demand	Prednisolone and clemastine	Delayed	3 days	Gripal syndrome, myalgias, obnubilation, fever, arthralgias of hips, knees and upper members	8.5	Adalimumab
MEVP	On demand	Prednisolone and clemastine	Delayed	10 days	Arthralgias of temporomandibular joint, myalgias, intense asthenia	23.5	Azathioprine
MARSA	On demand	Prednisolone and clemastine	Delayed	6 days	Severe asthenia, myalgias, polyarthralgias	52.7	Azathioprine
MMBR	On demand	Prednisolone and clemastine	Delayed	7 days	Generalized arthralgias, fever, myalgias, headache, asthenia	302.3	Adalimumab

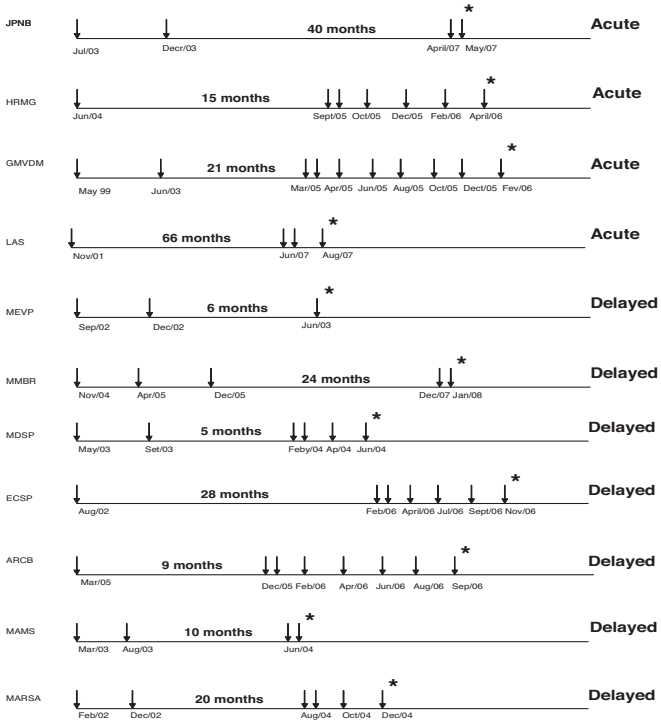

FIGURE 1. Episodic and scheduled IFX therapy. Arrows indicate IFX infusions and asterisks indicate the last infusion before reaction.

measure those antibodies. In spite of that, we measured autoantibodies making an effort to identify those with a favorable setting of antibodies formation. However, all of them were negative.

A regular IFX schedule, use of immunosuppressive medication, and pretreatment with a high dose of intravenous steroids may prevent many infusion reactions.[1] Nevertheless, all patients reported here had been premedicated with steroids and antihistamines, and the majority were immunosuppressed with azathioprine. Undoubtedly, the coadministration of immunosuppressive and antihistamines does not completely abolish the risk. A common element in all patients was a previous sporadic IFX administration (local policy) before they started on a regular schedule. Although some authors have reported a successful prophylaxis in retreated patients with prior severe reactions to IFX,[3]

we switched to a full human anti-TNF antibody[4] without any complication. In conclusion, we report that an episodic IFX schedule followed by reinduction after a long period of time is extremely immunogenic and should be a warning in clinical practice.

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Association Between Intestinal Permeability and Anti-*Saccharomyces cerevisiae* Antibodies in Patients with Crohn's Disease

To the Editor:

Anti-*Saccharomyces cerevisiae* antibodies (ASCA) are positive in 60%–80% of patients with Crohn's disease (CD).[1,2] ASCA has been used for the differentiation of ulcerative colitis (UC) from CD. The postulations of ASCA positivity in patients with CD include genetic predisposition, crossreactivity, and increased intestinal permeability, although the exact mechanism is not yet known. Forty to 60% of patients with CD also have an increase in intestinal permeability.[3] Hence, it is intriguing to know whether ASCA positivity is an epiphenomenon or a manifestation of increased intestinal permeability in patients with CD.

Of 125 patients with CD with results of intestinal permeability, we retrieved the records of 50 patients from whom sera were also available within 3 months of collection of urine for estimation of ASCA antibodies. The diagnosis of CD was made on ECCO guidelines.[4] Disease activity was assessed using the Crohn's Disease Activity Index (CDAI) and the location and behavior of the disease were classified using the modified Montreal classification. All the patients were treated according to standard guidelines.

Intestinal permeability was measured by lactulose mannitol (LM ratio) excretion in urine over 5 hours after oral ingestion of 5 g of lactulose and 2 g of mannitol. Based on the LM ratio of 22 healthy controls, the upper limit of normal for the LM ratio in our laboratory is 0.0373. All the patients and healthy subjects were instructed to abstain from nonsteroidal antiinflammatory drugs (NSAIDs) for 2 weeks prior to the test.

TABLE 1. ASCA IgG and ASCA IgA in Patients with CD

ASCA	Number (%)
Only IgA +	19 (38%)
Only IgG +	13 (26%)
Either IgG or IgA +	22 (44%)
Both IgG & IgA +	10 (20%)

A standard enzyme-linked immunosorbent assay (ELISA) was employed for qualitative detection of ASCA IgA and ASCA IgG in the serum using commercially available kits from AESKU Diagnostics (Germany). A positive and negative control along with a "cutoff" was run with each group of samples and the procedure was performed according to the instructions of the manufacturer. The cutoff value for a positive test for ASCA IgA and IgG were 15 U and 20 U, respectively.

STATA 9.0 (College Station, TX) statistical software was used for data analysis. The association between IP (LMR) and ASCA (IgG, IgA) was assessed using Spearman's correlation. The prevalence of the positivity of ASCA IgG and IgA in patients with abnormal and normal intestinal permeability was compared using chi-square tests.

Intestinal permeability was increased (LM ratio >0.0373) in 20/50 (40%) of the patients with CD. The data for ASCA IgA and ASCA IgG are shown in Table 1. No significant correlation was found between intestinal permeability (LM ratio) and ASCA IgA ($r = 0.151$, $P = 0.294$) and ASCA IgG ($r = 0.140$, $P = 0.331$). Similarly, no association was seen between ASCA positivity and increased intestinal permeability.

Saccharomyces cerevisiae is a

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"ubiquitous" yeast and is present naturally on plants and in the soil.[5] Humans are exposed to this yeast principally by food products and beverages. It is generally accepted that *S. cerevisiae* is not a pathogen, but in an immunocompromised host, fungemia with *S. cerevisiae* can prove to be pathogenic.[5] The most popular hypothesis of a positive ASCA is postulated to be increased intestinal permeability that might lead to increased exposure of yeast antigens to immune reactive cells.[6,7] However, in this study we did not find any association between abnormal intestinal permeability and ASCA positivity, as also reported by Harrer et al.[8] Therefore, an abnormal intestinal permeability may not be the cause of ASCA positivity in patients with CD.

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Pyoderma Gangrenosum Treated with Infliximab in Inactive Ulcerative Colitis

To the Editor:

A 25-year-old woman who had been diagnosed 9 years ago with ulcerative colitis (UC) (pancolitis) was referred to our gastroenterology department with a necrotic, painful skin ulcer on her left tibia without any trauma history. She first realized a skin lesion 2 months previously. At that time she had bloody stools 7 times a day while under 3 g per day sulfasalazine therapy. Her colonoscopy revealed active ulcerative pancolitis. A pyoderma gangrenosum (PG) diagnosis was first established in the gastroenterology service with dermatology consultation.

On physical examination she had a large lesion of 5 cm diameter on her left tibia. The ulcer had violaceus, inflammatory, undermined borders with pustules on a necrotic base. At admission to the hospital the laboratory results were as follows: erythrocyte sedimentation rate 55 mm/hour; C-reactive protein (CRP) 157 mg/L (normal, to 5 mg/L). The total blood count results were: white blood cell: 12,700/mL, (neutrophil: 10,100/mL, lymphocyte: 2000/mL), hemoglobin: 8.6 g/dL, hematocrit: 28%, platelet: 523,000/mL. Stool analysis showed numerous red blood cells with leukocytes and no trophozoites or ova. There was no infectious cause in the stool specimen. Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase, total bilirubin, direct bilirubin, and prothrombin time were all normal. The histological appearance was consistent with a clinical PG diagnosis. A biopsy of the ulcer showed an intense acute inflammatory infiltrate and lymphocytic vasculitis between the inflammatory infiltrate and normal dermis, consistent with PG. Bacterial and fungal cultures were all negative and did not reveal any cause of ulceration. Her bowel complaints regressed after 5 days methylprednisolone treatment (parenteral 40 mg/day), and oral methylprednisolone 32 mg/day was commenced. After 2 months at that dosage she did not have any bowel disorder but the PG lesion on her left tibia did not regress and methylprednisolone therapy was tapered at a 4 mg decrease per week and ceased. She could not tolerate azathioprine treatment due to severe gastrointestinal complaints. Cyclosporine 4 mg/kg/day intravenous for 7 days of infusion regimen followed by oral treatment at 8 mg/kg/day, giving a blood level of ≈250 ng/mL, was begun. The PG did not regress after 3 months of cyclosporine treatment (400 mg/day) either. Infliximab was commenced at 5 mg/kg; before initiation of therapy positivity of anti-nuclear antibodies and the presence tuberculous infection had been excluded. Reinfusions of infliximab were administered at the second and sixth weeks and then continued in each 8-week interval up to 11 times. The PG lesion regressed significantly after 5 infusions and completely resolved after 11 infliximab regimens (Fig. 1), leaving some discoloration of the overlying skin surface. One year later the patient is asymptomatic and has not suffered any relapse of PG.

PG is thought to be an immune-mediated, chronic ulcerating skin lesion that is characterized by deep skin ulcers with undermined edges. PG usually occurs on the lower limbs but may affect any skin surface in the body. The cause of PG remains unknown but ≈50% of cases develop in association with other conditions, inflammatory bowel disease (IBD) being the most relevant condition—30% of PG cases occur in association with IBD. Conversely, PG is seen

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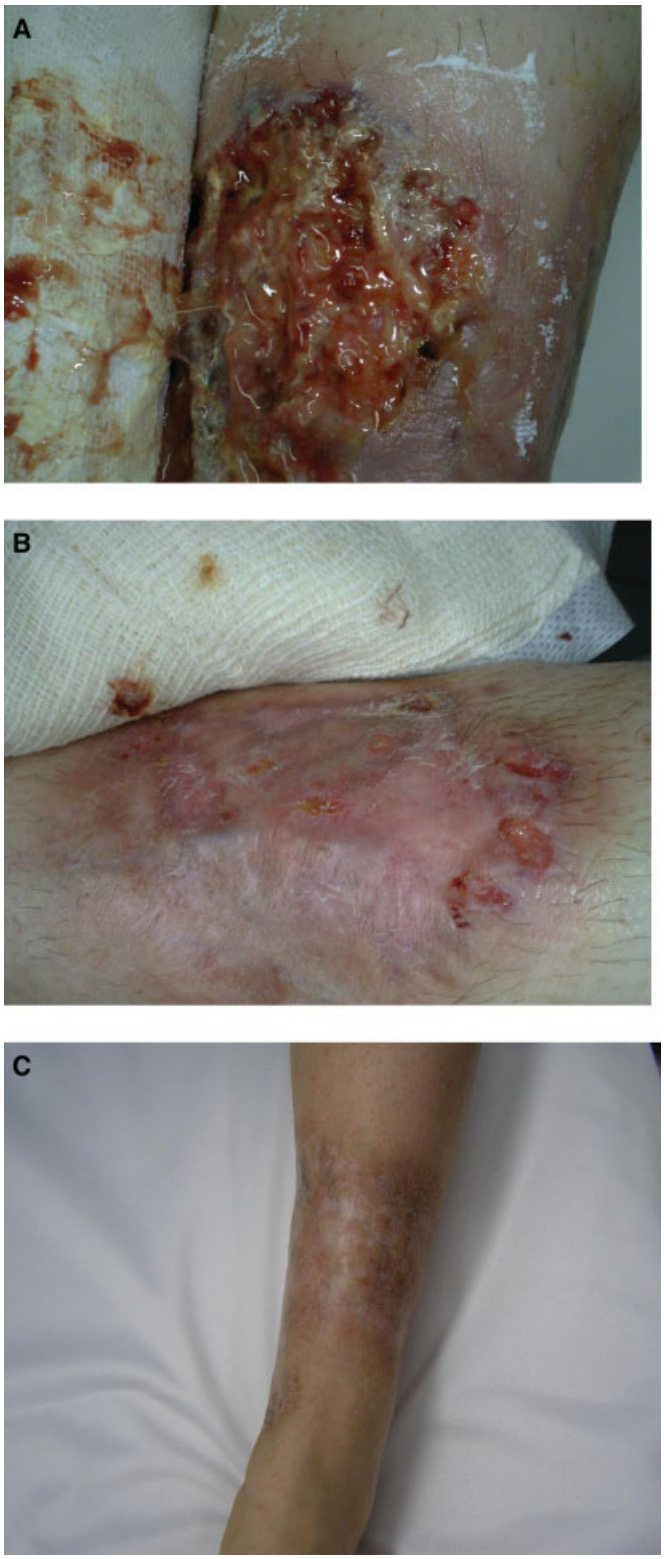

FIGURE 1. a: Pyoderma gangrenosum before the initiation of infliximab infusions. b: Pyoderma gangrenosum lesion after 5 infusions. c: Pyoderma gangrenosum lesion is completely resolved leaving only discoloration of the overlying skin after 11 infliximab infusions.

only in 1% of Crohn's disease (CD) and 3%–5% of UC.[1] PG may bear no relation to the clinical activity of the intestinal disease. However, clinical experience suggests that PG-associated IBD predicts active intestinal inflammation even if the symptoms of the gut are not overt initially.[2] The pathogenesis of PG is not fully understood but reports of cell-mediated, humoral, and complementary abnormalities as well as immune complex deposition in patients with PG and an association of PG with other immunological disorders suggest that an aberrant immune system is central to disease pathogenesis. Particularly, the documented response of PG to cyclosporine suggests that T lymphocytes play an important role in the pathogenesis.[3] Tumor necrosis factor-alfa (TNF-α) in PG has a pivotal role in skin inflammation. TNF-α increases the production of interleukin-1, leukotrienes, and neutrophil activation, thereby increasing inflammation. Infliximab is a chimeric monoclonal IgG antibody that targets membrane-bound precursors of TNF-α and prevents binding of TNF-α to its receptor. The efficacy of TNF-α is established in the treatment of fistulating type CD, rheumatoid arthritis, Behcet's disease, psoriasis, and a variety of inflammatory skin diseases.[4,5] A randomized controlled trial of 30 patients reported infliximab to be superior to placebo in the treatment of PG. Subgroup analysis suggests no difference in efficacy between the groups with or without coexisting IBD.[8] Since the clinical course of PG does not always parallel the underlying bowel disease, the mechanism of action of infliximab can differ from IBD activity.[6]

One aspect that remains unclear about infliximab therapy in refractory PG is the optimal number of doses of induction and maintenance of skin lesions. In our case 11 doses of infliximab 5 mg/kg was given (0, 2, 6 weeks, then reinfusions were repeated at 8-week intervals), achieving an im-

pressive response of the skin lesions after 5 infusions and followed by complete healing 17 months (11 infusions) later. To achieve remission methotrexate 25 mg per week intramuscular injection was commenced after the fifth infusion, permitting discontinuation of the infliximab infusions. To our best knowledge there are few case reports of infliximab treatment in PG associated with UC.[7,8] In our case infliximab was an effective and safe alternative in PG resistant to other immunosuppressive therapies in the case of UC.

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Common Biostructure of the Fecal Flora in Celiac Disease, Crohn's Disease, and Carcinoid Tumors

To the Editor:

In the April issue of *Inflammatory Bowel Diseases,* West et al[1] reported that carcinoid tumors are 15 times more common in patients with Crohn's disease (CD, 4/111) compared with controls (3/1199). The number of incidental carcinoid tumors in patients who underwent appendectomy was used as a control. The West Midlands Regional Children's Tumor Research Group showed an incidence of 1.0–1.42 cases of appendiceal carcinoid tumors per million children per year from 1957 to 1986, using the childhood population of the West Midlands Health Authority.[2] In their series, 12 carcinoids were found in 24,725 appendectomies, for a detection rate of 0.05%. Although carcinoid tumors of the appendix are rare in children, they are the most common gastrointestinal tumors in this age group. Kortbeek et al[3] reported that by chance alone, 1 carcinoid tumor should only occur every 200 years in the population of patients with inflammatory bowel disease. West et al[1] suggested that the development of carcinoid tumors may be secondary to distant proinflammatory mediators, rather than a local inflammatory effect from the adjacent CD, because none of the carcinoid tumors developed in areas of CD. Recently, we published a study on the microbial biostructure of feces using sections of paraffin-embedded punched fecal cylinders in healthy subjects ($n = 32$), patients with inflammatory bowel disease (IBD) ($n = 204$), and disease controls ($n = 227$).[4] Fluctuations in spatial distribution of 11 bacterial groups were monitored using fluorescence in situ hybridization (FISH). The microbial biostructure differed in patients with CD, ulcerative colitis, and controls allowing a specific differentiation between the two entities of IBD and other diseases. Most prominent for CD was a depletion of *Faecalibacterium prausnitzii* (Fprau $<1 \times 10^9$/mL). In this first study the depletion of *F. prausnitzii* was found also in untreated celiac disease, but in none of the other disease controls, including diverticulosis, IBS, self-limiting colitis, colonic carcinoma, and adenoma. Since 2006 we have been using FISH investigation of punched fecal cylinders routinely for the surveillance of our gastroenterological outpatients. Since our first study,[4] we have investigated over 4000 fecal cylinders in healthy subjects ($n = 62$) and patients with different gastrointestinal diseases ($n = 780$) and were able to identify a third disease, carcinoid tumors, which is associated with depletion of *F. prausnitzii*. Twelve of 23 patients with carcinoid were positive, while all other disease controls were still negative for this depletion. Brown et al[5] speculated that the coexistence may be more frequent than the literature suggests. Our data indicate that there is not just a coexistence, but an association between the pathogenesis of carcinoid tumors, celiac disease, and CD. If our assumption is correct, then carcinoids in celiac disease and CD would possibly share unique histomorphologic properties, which are absent in sporadically occurring carcinoid tumors.

It would be interesting to know what pathologists think about such a link, and whether already existing pathomorphologic data may back this hypothesis.

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