Intestinal superinfections in patients with inflammatory bowel diseases

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Crohn’s disease; IBD; Intestinal infections; Ulcerative colitis

Abstract
Background: Intestinal superinfections may occur in the setting of inflammatory bowel diseases (IBD), complicating the clinical picture and triggering flares of disease.
Aims: To report our experience with intestinal superinfections in IBD patients over a three-year period.
Methods: Charts of patients hospitalized for moderate-to-severe active disease during the observation period were reviewed, and data of patients with flares due to infections collected and analyzed.
Results: Overall, 15 out of 113 IBD patients (13.3%) had flare-ups related to intestinal infections; 143 acute flare-ups were thus documented, with 17 episodes (12%) related to infective agents, represented by Campylobacter jejuni (3 infections), Clostridium difficile (7 infections), and Cytomegalovirus (7 infections). All but two infections occurred in ulcerative colitis patients, and all responded to appropriate treatment.
Conclusions: Intestinal superinfections may complicate the clinical picture of IBD patients, increasing the diagnostic and therapeutic burden. Appropriate early diagnostic and therapeutic measures are thus needed in these patients.
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1. Introduction

The clinical course of inflammatory bowel diseases (IBD, that include ulcerative colitis (UC) and Crohn’s disease (CD)) ranges from a chronically active condition, to remission, to
intermittent flares. The determinants of these flares continue to be of great clinical interest; among the hypothesized triggers, a role seems to be played by intestinal infections. For this reason, in patients with active disease a superimposed bacterial (e.g., Clostridium difficile) or viral (e.g., cytomegalovirus, CMV) infection should be always excluded, especially in those using immunosuppressive drugs and with colonic involvement. Such evaluation should include assessment of three sets of stool samples for C. difficile, routine cultures and studies for parasites and ova.

Specific testing for sexually transmitted diseases, such as Neisseria gonorrhoeae, Herpes simplex virus, Chlamydia trachomatis/Lymphogranuloma venereum and Treponema pallidum, should be considered in specific instances, and particularly in patients with severe rectal symptoms.

The reported incidence of gastrointestinal infections among IBD patients varies between 9% and 13%, but only a few studies on this topic have been conducted.

Since the best way to treat IBD patients relies on the identification of an etiologic agent to start an effective therapy, the definition of the impact of infections in IBD patients could be relevant in this setting.

Here we report the prevalence of intestinal infections in hospitalized IBD patients in our tertiary referral center.

2. Patients and methods

All charts from IBD patients hospitalized in the Gastroenterology Section of Santa Maria della Misericordia Hospital, University of Perugia, for moderate-to-severe active disease between June 2007 and June 2010 were analyzed, retrieving those with intestinal infections. Data from culture of stool samples, including bacteria, viruses, parasites and toxins for C. difficile were collected. Concerning CMV infection, the following recommended tests were carried in case of suspicion: histopathology with immunohistochemistry (IHC), CMV-IgM and IgG serum antibodies, CMV antigenemia, and quantitative real-time polymerase chain reaction (PCR) in colonic tissue or blood. The patient was defined as CMV infected when, in addition to IgM/IgG positivity, at least one of the other tests resulted positive.

For histopathology, colonic biopsies were fixed in formalin, embedded in paraffin and stained with hematoxylin and eosin; these sections were evaluated for the typical granular eosinophilic intracytoplasmic inclusions and "owl's-eye" nuclear inclusion bodies. IHC was performed using anti-CMV monoclonal antibodies.

The following demographic and clinical variables were considered: age, sex, side of disease, clinical activity (Truelove and Witts criteria and Crohn's disease activity index (CDAI) and therapy.

C-reactive protein (CRP) value, an objective marker of inflammation, was available for all patients (normal values for our laboratory <0.5 mg/mL). Total colonoscopy with limited insufflation of air, to minimize the risk of acute traumatic dilation or perforation of the colon, was carried out in all patients at admission or during hospitalization for diagnostic purposes and for definition of presence, severity, and extent of inflammation. Tissue samples were taken from the inflamed mucosa for histological analysis and PCR.

2.1. Data analysis

Variables between infected and non-infected patients were compared by the t-test and the test for difference of proportions, where appropriate. Values of p<0.05 were chosen for rejection of the null hypothesis.

2.2. Ethical considerations

Since this was a retrospective study, no individual patient identification was involved and no study-driven clinical intervention was performed; therefore no ethical approval was necessary.

3. Results

In the observation period 113 IBD patients (54 UC and 59 CD) were admitted. Of these, 15 (13.3%) patients had flare-ups related to intestinal infections; Table 1 shows the characteristics of IBD patients, with and without infections.

Overall, 143 acute flare-ups (64 in UC and 79 in CD patients) were documented, with 17 episodes (12%) related to infective agents. Table 2 shows the clinical variables of these latter patients.

Considering the IBD subtype, infections were present in only 2 (1.8%) patients with CD.

With respect to the infective agents, these were represented by Campylobacter jejuni (1 CD, 2 UC), C. difficile (6 UC, 1 CD), and CMV (7 UC).

The median age was 34.5 (range 25–55) years in the UC/Clostridium group, 41 (range 19–64) years in the UC/CMV group, and 47 (range 25–70) years in the CD/Campylobacter group. In each group, the women represented 43%, 14% and 0%, respectively.

Extent of disease: in UC/C. difficile group 50% patients had left side involvement and 50% pancolitis, while in the UC/CMV group 87% of the patients had pancolitis and no cases of distal disease were observed. None of these patients underwent colectomy.

Table 1 Characteristics of IBD patients, with and without intestinal infections.

<table>
<thead>
<tr>
<th></th>
<th>IBD/no infection</th>
<th>IBD/infection</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>98</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>49</td>
<td>67</td>
<td>0.3</td>
</tr>
<tr>
<td>F</td>
<td>51</td>
<td>33</td>
<td>0.3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44±18</td>
<td>40±15</td>
<td>0.4</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>84±91</td>
<td>71±109</td>
<td>0.61</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>3.5±2.0</td>
<td>4.8±5.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Treatment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>16</td>
<td>67</td>
<td>0.0001</td>
</tr>
<tr>
<td>Immunosuppressors (AZA)</td>
<td>12</td>
<td>33</td>
<td>0.08</td>
</tr>
<tr>
<td>Anti-TNFα</td>
<td>2</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>45</td>
<td>33</td>
<td>0.55</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>2</td>
<td>13</td>
<td>0.03</td>
</tr>
</tbody>
</table>

α Data are presented as means (±SD).
Of the 2 CD infected patients, one had ileocolonic disease and one jejuno-ileal disease. Median CRP values were 4.9 (range 0.1–16) in the UC/Clostridium group, 4.4 (range 0.4–8) in the UC/CMV group and 8 (range 0.1–16) in the CD/Campylobacter group.

3.1. C. difficile infection

By analyzing the potential risk factors for this infection, we found that 2 (28%) of infected patients had been treated with antibiotics (amoxicillin) previously to admission. One of them had a history of recent admission in another hospital; 50% of the patients were being treated with steroids and/or immunosuppressors but none with anti-TNFα antibody. Specific antibiotic treatment for C. difficile was given to the infected patients, and the outcome was favorable in all cases.

3.2. C. jejuni infection

This pathogen was found in 17.6% patients’ flares, being probably related to the consumption of chicken meal or drinking from contaminated water sources during outdoor excursions.15

3.3. CMV infection

This infection was detected only in UC patients with moderate–severe disease and refractoriness to steroid therapy (Fig. 1, A and B). None of them had been treated with biologic agents. Clinical features of CMV infection were mainly related to the underlying UC and no cases or extraintestinal symptoms suggestive of systemic CMV infection were documented; only one HCV positive patient had altered liver function tests, probably related to the underlying disease.

Table 3 summarizes the laboratory results for CMV. CMV-PCR on colonic tissue was positive in all patients, conventional histological examination did show viral cytopathic changes in 3 cases, confirmed by IHC (Fig. 1, C and D), and all but one patients (which resulted IgM positive for a primary infection) had positive specific IgG; CMV antigenemia was positive in one patient, and blood CMV-PCR was positive in 3 patients. All patients were treated with specific antiviral therapy with a favorable outcome.

In patients treated with immunosuppressive therapy (only azathioprine was used), this was suspended immediately after confirmation of an infective cause, while steroids were gradually tapered according to the clinical status.

4. Discussion

The two more common superinfections found in our IBD population, as in other authors’ experience, were those related to C. difficile and CMV; however, we also found C. jejuni being unexpectedly common (about 20% of the overall infections). However, it must be considered that this infection represents the most frequently reported zoonotic disease in humans within the European Union,16 that it is relatively frequent in central Italy (about 9% of intestinal infections),17 and in our area is found in up to 11% of intestinal infections causing diarrhea.18

The presence of IBD was found an independent risk factor for C. difficile infection,19 and patients with colonic involvement are particularly susceptible to this infection.20 In our study we found that all but one IBD infected patients had colonic disease with moderate–severe activity and only 28% of them had a history of recent antibiotic exposure. On the other hand these patients were in treatment with immunosuppressors (azathioprine) or steroids, well known risk factors for acquisition of C. difficile.21

Although CMV gastrointestinal involvement is uncommon in immunocompetent hosts, it can occur in all locations from the mouth to the rectum;22 CMV colitis in the immunocompetent host can occur in the setting of primary infection, whereas in immunosuppressed patients it is almost always
secondary to the reactivation of latent infection. Thus, IBD patients are considered to be at high risk for CMV infection because they are frequently treated with immunosuppressive agents. However, it is worth noting that CMV infection can induce severe colitis in UC patients who have never been treated with immunosuppressive agents. This event is generally explained by the presence of abnormal mucosal surfaces that may increase the risk of this infection because CMV has a particular tropism for inflamed mucosa. Of note, CMV infection has been described as a cause of IBD relapse, and in UC patients it may display a particular severe clinical course.

Diagnosing CMV infection in IBD patients is an important, albeit controversial, issue. CMV infection, in addition to exacerbate the disease, has been found in 5%–21% of surgically resected specimens of UC; in our cohort, none of the patients with CMV infection underwent colectomy. We want to stress that it is often difficult to make an early diagnosis of CMV infection in UC patients because the symptoms of UC alone are not sufficient to distinguish the exacerbation of UC due to CMV infection from exacerbation of UC unrelated to CMV infection. The diagnosis is established by a combination of endoscopic findings, histology and immunohistochemical staining using anti-CMV monoclonal antibodies and the conventional qualitative PCR assay. Although histologic examination is often considered as the gold standard for diagnosing CMV infection in the GI tract, its sensitivity is quite low; besides, in about 40% patients the characteristic inclusions are not found.

In our series, CMV infection was diagnosed only in UC patients; all had active disease treated with steroids and were positive for IgG (only one had primary infection), suggesting a reactivation of a latent infection due to immunosuppressive therapy/disease activation. Antigenemia was positive in only one patient, and PCR resulted positive in blood in three subjects. Histological/IHC examination did show viral cytopathic changes in the 3 patients with blood PCR positivity, whereas CMV-PCR on colonic tissue was positive in all patients. Thus, once again, it is stressed that PCR on tissues probably represents, to date, the most useful tool for an early and accurate diagnosis of CMV infection in these patients.

In conclusion, intestinal superinfections in IBD patients, especially those related to CMV, although relatively infrequent, increase co-morbidity and aggravate the diagnostic and therapeutic burden of these subjects, in addition to raise the sanitary costs, especially in the light of the new therapeutic approaches. Thus, an early recognition of complicating infections with targeted therapeutic approach is needed and probably could ensure a better prognosis for IBD patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Disease activity</th>
<th>CMV IgG</th>
<th>Antigenemia</th>
<th>CMV/PCR blood</th>
<th>CMV/PCR mucosa</th>
<th>H&amp;E/IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Moderate</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Moderate</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Severe</td>
<td>IgM+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>Moderate</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>
Conflict of interest
None declared.

References

1. García Rodríguez LA, Ruigómez A, Panés J. Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. *Gastroenterology* 2006;130:1588–94.

