Concise report

Inflammatory bowel diseases in anti-neutrophil cytoplasmic antibody-associated vasculitides: 11 retrospective cases from the French Vasculitis Study Group

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Abstract

Objective. Coexistence of ANCA-associated vasculitis (AAV) and IBD is a rare condition that is rarely described in the literature. The aim of the study was to describe the main characteristics of patients presenting with both IBD and AAV.

Methods. A retrospective study of AAV patients in the French Vasculitis Study Group cohort who also had a diagnosis of IBD was conducted. We reviewed the medical records and outcomes of these patients.

Results. We identified 11 patients with AAV and IBD. Four patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) also had ulcerative colitis and seven patients with granulomatosis with polyangiitis (GPA) had Crohn’s disease. No Crohn’s disease was observed in eosinophilic GPA and no ulcerative colitis in GPA. IBD started before AAV manifestations in six cases, simultaneously in two cases and after AAV manifestations in three cases.

Conclusion. Coexistence of IBD and AAV is a rare condition. The therapeutic management of these patients includes corticosteroids in all cases and immunosuppressive drugs in some patients. Coexistence of IBD and AAV might be explained by common underlying inflammatory responses and cytokine profiles polarized towards either Th1 or Th2. Finally, in the presence of digestive manifestations in the context of AAV, the hypothesis of IBD should be assessed.

Key words: Crohn’s disease, ulcerative colitis, anti-neutrophil cytoplasmic antibody, eosinophilic granulomatosis with polyangiitis (Churg-Strauss), granulomatosis with polyangiitis.

Rheumatology key messages

- The association between ANCA-associated vasculitis and IBD is possible and exceptional.
- Th1 polarization may contribute to the association granulomatosis with polyangiitis—Crohn’s disease.
- Th2 polarization may contribute to the association eosinophilic granulomatosis with polyangiitis—ulcerative colitis.
Introduction

ANCA-associated vasculitis (AAV) is a group of small vessel necrotizing vasculitides with few or no immune deposits. According to Chapel Hill Consensus Conference Nomenclature [1], the AAV group includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic GPA (EGPA, Churg–Strauss) and single-organ AAV. In AAV, gastrointestinal involvement is observed in about 20–30% of patients. Severe gastrointestinal involvement includes bowel perforation, bleeding and pancreatitis and is associated with a poorer prognosis. This involvement is usually considered the consequence of an ischaemic process, even if this process is not always clearly demonstrated. However, vasculitis of the gastrointestinal tract was proved histologically in only 30% of patients with digestive manifestations reported by Pagnoux et al. [2]. In some exceptional cases, gastrointestinal involvement has been attributed to IBD, such as Crohn’s disease (CD) and ulcerative colitis (UC). In the present study, we describe the unusual association between IBD and AAV (IBD/AAV). Herein we report the features and outcomes of 11 patients from the French Vasculitis Study Group (FVSG) who presented with IBD/AAV.

Methods

We conducted a systematic retrospective study on AAV patients whose data had been entered into the FVSG database before March 2013. All these patients had AAV fulfilling the 1990 ACR criteria for EGPA and GPA or satisfying the revised Chapel Hill Consensus Conference definition (2012) [1]. Among the AAV patients we identified those who had a diagnosis of IBD. Then we retrieved the medical charts from the identified IBD/AAV patients and reviewed them for demographic characteristics; clinical, biological, radiological, endoscopic and histological findings; therapy; and outcome, using the same methodology as in other previous studies from the FVSG [2, 3]. Notably, all patients gave consent for use of the FVSG database information. Our study was approved by the Comité de Protection des Personnes Ile-de-France III. The diagnosis of IBD was based on criteria as described below.

The diagnosis of UC was based on criteria as described below. The data from 1697 patients were reviewed (343 MPA, 843 GPA, 511 EGPA). We identified 12 patients (6 males and 6 females) in whom AAV had been diagnosed between 1981 and 2003 and IBD between 1987 and 2013. One patient was excluded because of insufficient data on IBD. Characteristics of the patients are described in Tables 1 and 2. The mean age at diagnosis of vasculitis was 45.2 years. The diagnosis of IBD antedated the diagnosis of vasculitis in six cases [on average 5 years (range 0.3–12.0)] and was made after that of vasculitis in three cases [on average 5.5 years (range 0.8–15.0)]. Both diagnoses were made at the same time in two cases. Four EGPA patients had UC (0.78% of EGPA patients from the FVSG). Seven GPA patients had CD (0.71% of GPA patients from the FVSG). No CD was observed in EGPA and no UC in GPA. No patient had MPA.

Four patients (two males and two females; mean age 39 years at the time of EGPA diagnosis) developed both EGPA and UC (Table 1). UC antedated the diagnosis of vasculitis in two cases (24 and 144 months) and post-dated the diagnosis of vasculitis in the two other cases (10 and 180 months). All the patients had abdominal pain and bloody diarrhoea at diagnosis of UC. Endoscopic findings, according to the Montreal classification, were one proctitis (E1), one left-sided colitis (E2) and two extensive colitis (E3) (including one with pancolitis). Endoscopic findings were erosions (n = 3), superficial ulcers (n = 1) and mucosal bleeding (n = 1). Histological findings included architectural alterations (n = 3), including crypt branching and atrophy, mucin depletion (n = 3) and inflammatory features like basa plasmocytosis and lamina propria cellularity. In these cases, no eosinophilic infiltration was observed. Clinical and biological manifestations of AAV are listed in Table 1. Treatment included corticosteroids (n = 4), 5-aminosalicylic acid (5-ASA; n = 3), plasma exchange (n = 1), AZA (n = 1), CYC (n = 1), MMF (n = 1) and infliximab (n = 1). Mean follow-up was 16.4 years (range 5.3–31.0). At this time, two patients were in remission and received low-dose CSs: one with AZA and CSs and the other received oral prednisone for CS-dependent asthma.

Seven other patients [four males and three females; mean age 48.7 years (range 32.0–72.0) at the time of GPA diagnosis] were suffering from both GPA and CD (Table 1). In four cases the diagnosis of CD antedated the diagnosis of GPA (by 118, 10 and 4 months, delay not precise in 1 patient). In two cases, GPA and CD were simultaneously diagnosed and in one case CD developed 12 months after the diagnosis of GPA. The clinical and biological manifestations of AAV are listed in Table 1.
**Table 1** Clinical manifestations of patients with IBD and AAV

<table>
<thead>
<tr>
<th>Age at onset of AAV, years</th>
<th>IBD/AAV</th>
<th>Time between IBD and EGPA, months</th>
<th>Manifestations related to IBD</th>
<th>Manifestations related to AAV</th>
<th>ANCA status</th>
<th>Drugs</th>
<th>Follow-up, months</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>UC/EGPA</td>
<td>180</td>
<td>Abdominal pain, bloody diarrhoea</td>
<td>A, Asth, C, ENT, H, N, P</td>
<td>No</td>
<td>5-ASA, CS, PE</td>
<td>372</td>
<td>Low-dose CS, remission</td>
</tr>
<tr>
<td>43</td>
<td>UC/EGPA</td>
<td>–24</td>
<td>Abdominal pain, bloody diarrhoea</td>
<td>A, Asth, ENT, P</td>
<td>No</td>
<td>5-ASA, CS</td>
<td>195</td>
<td>Low-dose CS, remission</td>
</tr>
<tr>
<td>48</td>
<td>UC/EGPA</td>
<td>10</td>
<td>Abdominal pain, bloody diarrhoea</td>
<td>A, Asth, C, N, P</td>
<td>Yes</td>
<td>CS, IFX, AZA</td>
<td>63</td>
<td>CS, AZA</td>
</tr>
<tr>
<td>37</td>
<td>UC/EGPA</td>
<td>–144</td>
<td>Abdominal pain, bloody diarrhoea</td>
<td>Asth, H, N, P</td>
<td>No</td>
<td>5-ASA, CS, i.v.</td>
<td>159</td>
<td>CS, severe asthma, infectious pneumonia</td>
</tr>
<tr>
<td>65</td>
<td>CD/GPA</td>
<td>–4</td>
<td>Diarrhoea, rectovaginal fistula</td>
<td>A, C, E, ENT, N</td>
<td>No</td>
<td>CYC, CS, AZA</td>
<td>159</td>
<td>Persistent diarrhoea</td>
</tr>
<tr>
<td>72</td>
<td>CD/GPA</td>
<td>12</td>
<td>Diarrhoea, aphthous stomatitis and glossitis, perianal abscess, Diarrhoea</td>
<td>A, E, ENT, K</td>
<td>PR3</td>
<td>CYC, CS, MTX, AZA, MMF</td>
<td>45</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>41</td>
<td>CD/GPA</td>
<td>–10</td>
<td>Diarrhoea</td>
<td>N, K</td>
<td>No</td>
<td>CYC, CS, AZA, 5-ASA</td>
<td>183</td>
<td>CNS manifestations</td>
</tr>
<tr>
<td>33</td>
<td>CD/GPA</td>
<td>–118</td>
<td>Diarrhoea, stenosing ileitis, ileosigmoid fistula, perianal abscess</td>
<td>E, ENT</td>
<td>No</td>
<td>5-ASA, CS, AZA, IFX, ADA</td>
<td>249</td>
<td>Remission (anti-TNF therapy)</td>
</tr>
<tr>
<td>49</td>
<td>CD/GPA</td>
<td>0</td>
<td>Diarrhoea, aphthosis stomatitis</td>
<td>A, E, ENT, H, K, P</td>
<td>PR3</td>
<td>CYC, CS, AZA, MMF, RTX</td>
<td>72</td>
<td>Remission (rituximab)</td>
</tr>
<tr>
<td>49</td>
<td>CD/GPA</td>
<td>0</td>
<td>Bloody diarrhoea</td>
<td>ENT</td>
<td>p-ANCA</td>
<td>CYC, CS, AZA, SLZ, IFX</td>
<td>291</td>
<td>Remission (without treatment)</td>
</tr>
<tr>
<td>32</td>
<td>CD/GPA</td>
<td>Before</td>
<td>Diarrhoea</td>
<td>A, Asth, C, ENT, K, P</td>
<td>No</td>
<td>AZA, CS</td>
<td>124</td>
<td>Persistent diarrhoea</td>
</tr>
</tbody>
</table>

A: articular; AAV: ANCA-associated vasculitis; ADA: adalimumab; Asth: asthma; C: cutaneous; CD: Crohn’s disease; CS: corticosteroids; E: eye; EGPA: eosinophilic granulomatosis with polyangiitis; 5-ASA: 5-aminosalicylic acid; GPA: granulomatosis with polyangiitis; H: heart; IFX: infliximab; K: kidney; N: nervous system; P: pulmonary; p-ANCA: perinuclear ANCA; PE: plasma exchange; RTX: rituximab; SLZ: salazopyrin.
In those patients, clinical intestinal manifestations related to CD included diarrhoea (n = 6), bloody diarrhoea (n = 1) and aphthous stomatitis (n = 2). Complications of CD included fistulas (n = 2; rectovaginal and ileosigmoid), perianal abscess (n = 2) and stenosing ileitis (n = 1). Five patients were smokers (three active, two former). Extra-intestinal manifestations of CD were deep vein thrombosis (n = 2), sacroiliitis (n = 1) and axial arthropathy (n = 1). On endoscopy, disease spared the rectum in all patients; ileal involvement was present in two cases. According to the Montreal revision of the Vienna classification, the location of the disease was colonic in five cases (L2) and ileocolonic in two cases (L3). The behaviour of the CD was non-stricturing, non-penetrating in six cases (B1) and stricturing and penetrating in one case (B2B3). Two patients had perianal involvement. Colitis with ulceration was seen in six cases and stricture in one case. Histological findings showed several features in favour of CD: focal crypt architectural irregularity (n = 5), polymorph inflammation of the lamina propria (n = 4), granulomas (n = 3) and crypt abscess (n = 2) but no vasculitis lesion. The treatments included CSs (n = 7), CYC (n = 5), AZA (n = 7), 5-ASA (n = 2), MTX (n = 1), MMF (n = 2), anti-TNF drugs (n = 2) and rituximab (n = 1). Mean follow-up was 13.3 years (range 3.8–24.3): at this time one patient was lost to follow-up, three patients were in remission (one with rituximab, one with anti-TNF therapy and one without medication), two had persistent diarrhoea and one had neurological sequelae but no IBD manifestations.

**Discussion**

In the present study, EGPA is associated with UC, which antedated the onset of vasculitis in most patients. This chronological sequence has already been reported in the literature [5]. These cases suggest that the first inflammatory events leading to EGPA could begin during the inflammatory phase of UC. Notably, EGPA follows three successive phases: the prodromal phase, consisting of asthma and allergic manifestations; the second phase,
resulting from eosinophil infiltration of tissues and the necrotizing vasculitis phase, possibly several years (mean 3–4 years) after asthma. Thus EGPA could be directly linked to UC as the final step of a long-standing inflammatory process. Interestingly, experimental data are accumulating and argue that both EGPA and UC are Th2-mediated diseases. In EGPA, peripheral T lymphocytes can produce Th2-associated cytokines such as IL-4 and IL-13 [6]. In addition, IL-5 is a key cytokine in EGPA pathogenesis, as illustrated by the increased levels at the time of flares [7]. Tissue recruitment of eosinophils is also associated with Th2 lymphocytes expressing high transcript levels of Th2 cytokines (particularly IL-4, IL-5 and IL-10) [7] or the Th2 marker CD294 [8]. In EGPA, the specific recruitment of Th2 lymphocytes could be mediated by CCL17, most likely produced by dendritic cells [8]. Similarly the role of Th2 lymphocytes is also clearly documented in UC [9] and secretion of IL-5 by lamina propria CD4+ T lymphocytes is markedly increased while IFN-γ production is normal [9]. Also, the number of eosinophils is increased within the intestinal mucosa of active UC. Recent studies suggest that Th17 cells could also be implicated in the late stages of EGPA [6] as in UC (but to a lesser degree than in CD) [10]. Nevertheless, both UC and EGPA are strongly polarized towards a Th2 pattern, which could take part in the development of this association. Interestingly, in our study UC was not associated with GPA, whose physiopathology is different from that of EGPA and much less polarized towards a Th2 pattern.

In our series, all seven GPA patients had CD. Only three case reports of CD/GPA have been previously reported, but this association is probably not so uncommon since intestinal involvement of GPA mimicking CD has also been described [11]. Thus GPA can present at diagnosis as granulomatous colitis or granulomatous gastritis. Ileitis was also reported at the time of GPA relapse. As well as UC/EGPA, the association between CD and GPA could be driven by common pathogenic mechanisms. Indeed, both GPA and CD are considered granulomatous Th1-mediated diseases. In GPA, lymphocyte responses are polarized towards a Th1 pattern, in particular in the localized forms (involving ENT and lungs) of the disease [12]. The predominant Th1 pattern has also been observed in the peripheral blood CD4+ T lymphocyte populations in the granulomatous lesions, in which Th17 lymphocytes are also present [13]. Similarly CD is polarized towards Th1 and Th17 patterns, resulting in key cytokines like IFN-γ and IL-17. An increased amount of IFN-γ is produced by the T lymphocytes within the lamina propria in CD [14]. In addition, the key role of Th17 lymphocytes is now well described in human CD [10] as well as in experimental models of colitis [15]. Thus these data suggest that these lymphocyte profiles could favour the association between CD and GPA.

However, the cytokine polarization of GPA is not so clearly directed towards a Th1 pattern [12], with some forms exhibiting preferentially mixed Th1/Th2 responses [16]. Notably Th2 dominance has been observed in the nasal mucosa of some GPA patients [17]. In addition, Th17 cells and Treg have recently been demonstrated to play a key role in the pathophysiology of AAV [18] and IBD [15]. All of these different cytokine patterns and cell populations could contribute to another overlap (UC/GPA) previously reported in the literature but not observed in our study. Finally, infectious agents, already suspected as triggering factors of each disease, could activate the immune system through inflammasomes or innate and/or adaptive immunity [19, 20]. Notably, molecular mimicry with bacterial DNA was recently reported to trigger ANCA production, linking infection to autoimmunity [20]. Nevertheless, we cannot provide here any physiopathological demonstration of the mechanisms leading to IBD/AAV, since our study suffers from a lack of sample collection in addition to the difficulty of retrospective clinical data collection.

IBDs may be underdiagnosed in AAV patients. It is not excluded that the inclusion of AAV (based on glucocorticoids with or without immunosuppressive agents) may be effective against IBD development and thus lessen its frequency. Since IBD and AAV-related ischaemia can cause similar symptoms, diagnosis may be difficult. Thus we think that the hypothesis of IBD should be assessed in AAV patients with digestive manifestations. Similarly, the occurrence of extra-intestinal manifestations in IBD patients should lead to the initiation of a diagnosis procedure for AAV.

Conclusion

Our results suggest a possible and exceptional (<1% of AAV patients from the FVSG) association between IBD and AAV. Such an association should be considered in both AAV patients with intestinal manifestations and IBD patients with extra-intestinal manifestations. The possible associations (UC/EGPA and CD/GPA) might be explained by common underlying inflammatory responses and cytokine profiles.

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