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Alimentary Tract

Autoimmune cytopenias associated with inflammatory bowel diseases: Insights from a multicenter retrospective cohort

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ABSTRACT

Introduction: Autoimmune cytopenias (AIC) including autoimmune hemolytic anemia (AIHA) and immunologic thrombocytopenia (ITP) are rare immunologic disorders, scarcely reported in inflammatory bowel diseases (IBD). We conducted a multicentric retrospective study, including a case-control analysis, that aimed to describe the characteristics and outcomes of patients affected by AIC and IBD.
Method: Forty cases were recruited from 4 IBD centers and 2 AIC tertiary centers. Controls were recruited from the MICISTA registry.
Results: From the MICISTA registry, incidences were estimated at 4.1/100,000 patient-years and 12.5/100,000 patient-years after IBD diagnosis for AIHA and ITP, respectively. All AIHA patients (n = 14) had colonic involvement (13/14 with UC), whereas CD (52%) and UC (48%) diagnoses were evenly distributed among ITP patients. Compared to control IBD patients, cases were characterized by a higher frequency of extra-intestinal manifestations (37.5% vs 17%, $p < 0.001$) and by the presence of IBD severity's hallmark. AIHA and IBD ran mainly in parallel, and 12 out of 14 AIHA were warm AIHA. In isolated cases, rituximab and infliximab were efficient to treat IBD and AIC, respectively. IBD surgery may induce AIC remission in some cases.
Conclusion: Although low, incidence of AIC appears higher in IBD patients compared to the general population. The association seems to be mainly non-fortuitous, especially for colitis-associated AIHA.

1. Introduction

Autoimmune cytopenias (AIC) are characterized by the production of antibodies against blood cells responsible for the accelerated clearance and destruction of antibody-coated blood cells by tissue macrophages, predominantly in the spleen [1,2]. AIC include autoimmune hemolytic anemia (AIHA), immunologic thrombocytopenia (ITP) and Evans syndrome (both AIHA and ITP). AIHA is caused by a warm auto-antibody in 80% of the patients and by a cold auto-antibody in other patients. AIC are rare diseases with estimated incidences of 1–3/100,000 person-years for AIHA and 3–4/100,000 for ITP [3–7]. The life-time prevalence is estimated at 17/100,000 for AIHA and at 72/100,000 for ITP [5]. AIHA and ITP could be secondary to lymphoproliferative disorders, infections or solid tumors as well as autoimmune diseases such as systemic lupus erythematosus or antiphospholipid syndrome. In some cases, AIC is associated with primary immunodeficiency. In the absence of an underlying alternative cause, AIHA is defined as primary or idiopathic [8,9].

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Inflammatory bowel diseases (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) are long-standing diseases leading to chronic inflammation and damage of the gut. The pathophysiology of IBD remains poorly understood but is primarily influenced by immune disorders, environmental factors, gut microbiota and genetic inheritances [10,11]. Up to 50% of the patients with IBD experience at least one extra-intestinal manifestation, which can be present before IBD diagnosis [12,13]. Extra-intestinal manifestations are more frequent in CD than in UC and have a negative impact on the patient's quality of life [12,13]. In some cases, the activity of extra-intestinal manifestations run in parallel with the intestinal disease activity [12,13].

The association between AIC and IBD has been poorly described, leaving many unanswered questions about the pathophysiology and the management for patients with AIC and IBD [14–19]. We thus conducted a multicentric, observational, retrospective study to describe the clinical, biological and therapeutical characteristics of patients affected by both IBD and AIC. We also performed a case-control study to assess the impact of AIC on the course of IBD and vice versa.

2. Materials and methods

2.1. Study population

In this retrospective multicenter study, all the gastroenterologists from four French academic centers (Beaujon, Saint-Antoine, Saint Louis and Henri Mondor University hospitals) and all the clinical immunologists from two French academic centers (Saint Louis and Henri Mondor hospitals) were contacted and were requested to report any cases of patients who had been monitored for both IBD and AIC. The patients were recruited from the department's local database and/or the standardized hospital inpatient diagnostic dataset [20].

The diagnosis of IBD was based on the European Crohn's and Colitis Organization guidelines [21,22]. The patients with IBD-like in the context of primary immune deficiency were not included in the study. The diagnosis of ITP was based on the published standardized international criteria [6]. AIHA was defined as a hemoglobin (Hb) level below 100 g/l with at least two features of hemolysis (high reticulocyte count, low haptoglobin level, elevated lactate dehydrogenase level and/or elevated bilirubin level, with the threshold values defined according to laboratory measurements) and a positive direct antiglobulin test. The study was approved by the local institutional ethics committee.

2.2. Data collection

The physicians in charge of included patients were first contacted to complete a standardized questionnaire. An on-site visit was then conducted to collect missing data from the patients' case records (MU). At baseline, the recorded data included a detailed account of the IBD and AIC diagnosis and history, IBD phenotype according to the Montreal classification, medical and surgical treatment history and biological data.

2.3. Evaluation of disease evolution

IBD activity was assessed by analyzing the occurrence of flares, the course of corticosteroids, the use of immunomodulator or biological agents and the history of abdominal surgery. IBD activity during each year was defined as a flare-up requiring therapeutic modification related to IBD activity or the occurrence of IBD-related complications.

2.4. Efficacy of immunomodulator and biological agents on IBD and AIC

To assess treatment efficacy on AIC, the following criteria were used: (1) for ITP, a complete response was defined by a platelet count above 100×10^9/l and a partial response by a platelet count $>30 \times 10^9$/l with at least a two-fold increase of the pretreatment count according to the international consensus criteria [6]; and (2) for AIHA, a complete response was defined by an Hb level above 120 g/l in the absence of transfusion and without persistent features of hemolysis and a partial response by an Hb level above 100 g/l in the absence of transfusion with an increase of at least 20 g/l from baseline.

For IBD, treatment efficacy was assessed 6 months after treatment initiation. A complete response was defined as a Harvey–Bradshaw index (HBI) [23] score of 4 or less for patients with CD and a partial Mayo Clinic score of less than 3 with a combined stool frequency and rectal bleeding subscore of 1 or less [24,25]. A partial response was defined as a reduction in the HBI score of at least 3 points for patients with CD and as a reduction in the partial Mayo Clinic score of at least 3 points and a decrease of at least 30%, with a decrease of at least 1 point on the rectal bleeding subscore or an absolute rectal bleeding score of 0 or 1 from the baseline score for patients with UC [25].

For the case-control study as well as for the pre-post AIC analysis we considered steroids and immunodulators in the analyses only if IBD was the mian indication (e.g., if steroids were given for AIC in the context of a quiescent IBD, it was not considered as an IBD treatment in the analysis).

2.5. Case-control study

The controls were selected randomly within the MICISTA registry to match the AIC cases (four controls for one AIC case). MICISTA is an electronic database of the gastroenterology department of the Saint-Antoine Hospital [20]. All the patients who were examined in the institution from 1994 are included in the database. The data regarding medical and IBD history and follow-up are prospectively coded in the system. Case-control matching was based on the gender, birth year (±2.5 years), and type of IBD and IBD diagnosis calendar (±2.5 years). The data collection was performed using the MICISTA database and the patients' case records in the event of missing data (AA).

2.6. Statistical analysis

The data are expressed as mean ± standard deviation values or medians [interquartile range] in the case of continuous data. The nominal and ordinal data were compared using a Chi-square test or Fisher's exact test whenever appropriate, whereas the parametric data were compared using a Mann-Whitney test and Wilcoxon's matched-pair signed-rank test whenever appropriate. All the analyses were two-tailed, and p values less than 0.05 were considered to be statistically significant. All the statistical evaluations were performed using SPSS statistical software (SPSS Inc., v17, Chicago, IL, USA). All the authors had access to the study data and reviewed and approved the final manuscript.

3. Results

3.1. Study population

The medical charts from 53 patients were screened for suspected IBD-associated AIC. A total of 13 patients were excluded from the study because of either insufficient available data (n = 6) or unconfirmed AIC diagnosis (n = 7). Overall, 40 patients were

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