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Myocarditis and inflammatory bowel diseases: A single-center experience and a systematic literature review☆

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ABSTRACT

Background: Myocarditis and inflammatory bowel diseases (IBD) are rare conditions, but may coexist. Myocarditis in IBD may be infective, immune-mediated, or due to mesalamine toxicity. A gap of knowledge exists on the clinical features of patients that present myocarditis in association with IBD, especially for endomyocardial biopsy-proven cases. Our aims are: 1) to describe the clinical characteristics of patients with *an associated* diagnosis of myocarditis and IBD in a single-center hospital, 2) to perform a systematic review of the literature of analogous cases.

Methods: We retrospectively analyzed data of patients followed up at the outpatient Cardio-immunology and Gastroenterology Clinic of Padua University Hospital, to identify those with an *associated* diagnosis of myocarditis and IBD. In addition, a systematic review of the literature was conducted. *We performed a qualitative analysis of the overall study population.*

Results: The study included 104 patients (21 from our single center cohort, 83 from the literature review). Myocarditis in IBD more frequently affects young (median age 31 years) males (72%), predominantly with infarct-like presentation (58%), within an acute phase of the IBD (67%) and with an overall benign clinical course (87%). Nevertheless, a not negligible quote of patients may present giant cell myocarditis, deserve immunosuppression and have a chronic, or even fatal course. Histological evidence of mesalamine hypersensitivity is scarce and its incidence may be overestimated.

Conclusions: Our study shows that myocarditis in association with IBD, if correctly managed, may have a spontaneous benign course, but predictors of worse prognosis must be promptly recognized.

1. Introduction

Myocarditis is an inflammatory disease of the myocardium defined by established histological, immunological and immunohistochemical criteria [1]. The heterogeneity of clinical presentations, ranging from paucisymptomatic to life-threatening conditions, may render the diagnosis challenging. The diagnostic gold standard is endomyocardial biopsy (EMB) which is generally reserved to most severe cases [1], leading to difficulties in determining the actual incidence of myocarditis in the general population [2]. A diagnosis of clinically suspected myocarditis is still achievable, when EMB is not performed, according to the 2013 position statement of the European Society of Cardiology (ESC) working group on Myocardial and Pericardial Diseases [1]. Myocarditis may resolve spontaneously [3], especially mild forms; nevertheless, up to 20% of cases can evolve to dilated cardiomyopathy (DCM) with poor prognosis [4]. A wide spectrum of causes is implied in the

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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etiopathogenesis of myocarditis: infectious or toxic agents or immune-mediated mechanisms [1]. In fact, an association of immune-mediated myocarditis and systemic immune-mediated diseases (SIDs) is well-established [5]. In addition, immune-mediated origin of myocarditis and its association with SIDs are predictors of worse prognosis [5–7].

Inflammatory bowel diseases (IBD) encompass a group of chronic immune-mediated diseases, mainly Ulcerative Colitis (UC) and Crohn's Disease (CD), characterized by inflammation of segments of the gastrointestinal tract [8,9]. Pathogenesis has not been fully elucidated and is known to derive from a complex interaction between genetic and environmental factors, alterations in human microbiota and an aberrant immune system [10]. Up to one third of patients with IBD experience extra-intestinal manifestations, some of which seem to have an IBD-activity correlation [11]. Cardiovascular involvement is a supposed rare extra-intestinal manifestation of IBD [12], and apparently mostly occurs with an immune-related pathogenic mechanism [13]. The other possible cause of myocardial injury in the context of IBD is iatrogenic, in the form of hypothesized hypersensitivity reaction to 5-aminosalicilic acid (5-ASA) or its derived drugs, especially mesalamine, which is often used to cure IBD [14]. Myocarditis is a rare but potentially life-threatening comorbidity during IBD course, as described in the literature in the form of case reports [15,16]: due to the aforementioned possible difficulty of its recognition, myocarditis diagnosis may be missed or delayed, with ominous consequences on patients' prognosis.

1.1. Aims of the study

The aims of our study are:

1. To describe the clinical characteristics of patients with a diagnosis of myocarditis and IBD in a single-center tertiary hospital.
2. To perform a systematic review of the literature on case reports of myocarditis in IBD patients.
3. To analyze the overall aggregated data and to compare our single center cohort of patients with literature data.

2. Methods

2.1. Our single center experience

We retrospectively screened the database of consecutive patients followed up at the Cardio-Immunology outpatient clinic and at the Inflammatory Bowel Disease outpatient clinic of the Padua University Hospital. We included patients with diagnosis of clinically suspected or EMB-proven myocarditis that preceded, succeeded, or was concomitant with IBD diagnosis. Myocarditis diagnosis was obtained strictly following the 2013 ESC working group of Myocardial and Pericardial disease criteria [1]; for each patient, coronary artery disease (CAD) was excluded and EMB and/or CMR was obtained. In particular, CMR was analyzed according to Lake Louise criteria [17]. The diagnosis of IBD was achieved according to the 2018 European Crohn's and Colitis Organization Criteria [18]. The details on data collection process are reported in the Supplementary methods section.

2.2. Systematic review of the literature

Regarding the systematic review of the literature on case reports of myocarditis in IBD patients, the studies were identified by searching electronic databases (Medline via OvidSP, Medline via PubMed) from inception to 1st November 2021. The details on the systematic review process are reported in the Supplementary methods section.

Reports were included if they met all of the following criteria: 1) diagnosis of EMB-proven or clinically suspected myocarditis, according to the 2013 ESC Working Group of Myocardial and Pericardial diseases [1]; 2) diagnosis of IBD, in keeping with the 2018 European Crohn's and Colitis Organization Criteria [18]; 3) content of sufficient clinical data, i.e. at least demographical and/or echocardiographic or CMR data at the moment of myocarditis diagnosis. Data were extracted from each report regarding: 1) demographic patients' characteristics: age at myocarditis diagnosis, age at IBD diagnosis, sex; 2) clinical aspects of myocarditis course: presentation pattern (infarct-like, HF, or arrhythmic), clinical course (acute, chronic or fulminant), echocardiographic, ECG-graphic, CMR and EMB features; 3) clinical aspects of IBD course: type of IBD (UC, CD or indeterminate colitis), presence of signs and symptoms of IBD and pharmacological therapy at the time of myocarditis diagnosis, with particular regard to the time between 5-ASA therapy onset, if present.

Data were extracted in Microsoft Excel (Microsoft Corp, Seattle, WA), using an extraction template. Two authors (A. C. and A. S. G.) independently extracted data from reports and entered in the data extraction form. Disagreements were resolved by discussion; if no accord was reached, it was planned that a third author (M. F.) would decide. The flow diagram of the study selection process is depicted in Fig. 1, upper panel.

2.3. Analysis of the overall population

In order to perform a qualitative analysis of the characteristics of the patients from our single center cohort and the systematic literature review, we merged the data of the two patients groups.

2.4. Statistical analysis

Categorical variables were summarized by frequencies and percentages. For continuous variables, data were presented as median values with interquartile range (IQR). Data were analyzed using SPSS Statistics software for Windows (IBM SPSS Statistics for Windows, version 20).

3. Results

3.1. Our single center experience

Twenty-one patients were included (Supplementary fig. 1), 12 with clinically suspected and 9 with EMB-proven myocarditis. All patients had critical CAD ruled out via invasive coronary angiography (10 patients), coronary CT or ECG stress test. Demographic and clinical-instrumental characteristics at diagnosis and at last follow up are showed in Table 1, and raw relevant clinical data are shown in Supplementary Table 1. Majority of patients (76%) were male, Caucasian (95%, only 2 patients were Asian), and with a median age at diagnosis of 33 years (IQR 27–46). Twenty-nine % of patients had a family history of immune-mediated disease; interestingly, three patients had family history of IBD. Moreover, 29% of patients had a personal history of immune-mediated disease besides IBD: 1 of ankylosing spondylitis, 1 of acute idiopathic pericarditis, 1 of Hashimoto's thyroiditis, 1 of insulin-dependent diabetes mellitus, 1 of pernicious anaemia, 1 of autoimmune peripheral neuropathy (not shown). Eight patients had a diagnosis of RCU, and 8 of CD, in 60% of cases diagnosis of myocarditis was concomitant with a phase of activity of IBD and 62% of patients were taking mesalamine at the time of myocarditis onset, in the majority of cases for <1 month. Most patients did not report any relevant comorbidity, only one patient was hypertensive (she was 58 year old at the time of myocarditis diagnosis). The most frequent clinical presentation of myocarditis was infarct-like chest pain (57%), with less frequent HF (19%) and arrhythmic presentation (19%, 3 patients with ventricular arrhythmias, 1 of which with GCM, and 3 with supraventricular arrhythmias). Of note, one patient (5%) did not report any cardiovascular symptoms and no patient had a fulminant presentation. Troponin I and C-Reactive Protein (CRP) were abnormal in the majority of cases. The serum AHA assay was performed in 18 patients, of whom 50% tested positive. At diagnosis, the majority of patients was in New York Heart Association (NYHA) functional class I and had a preserved left

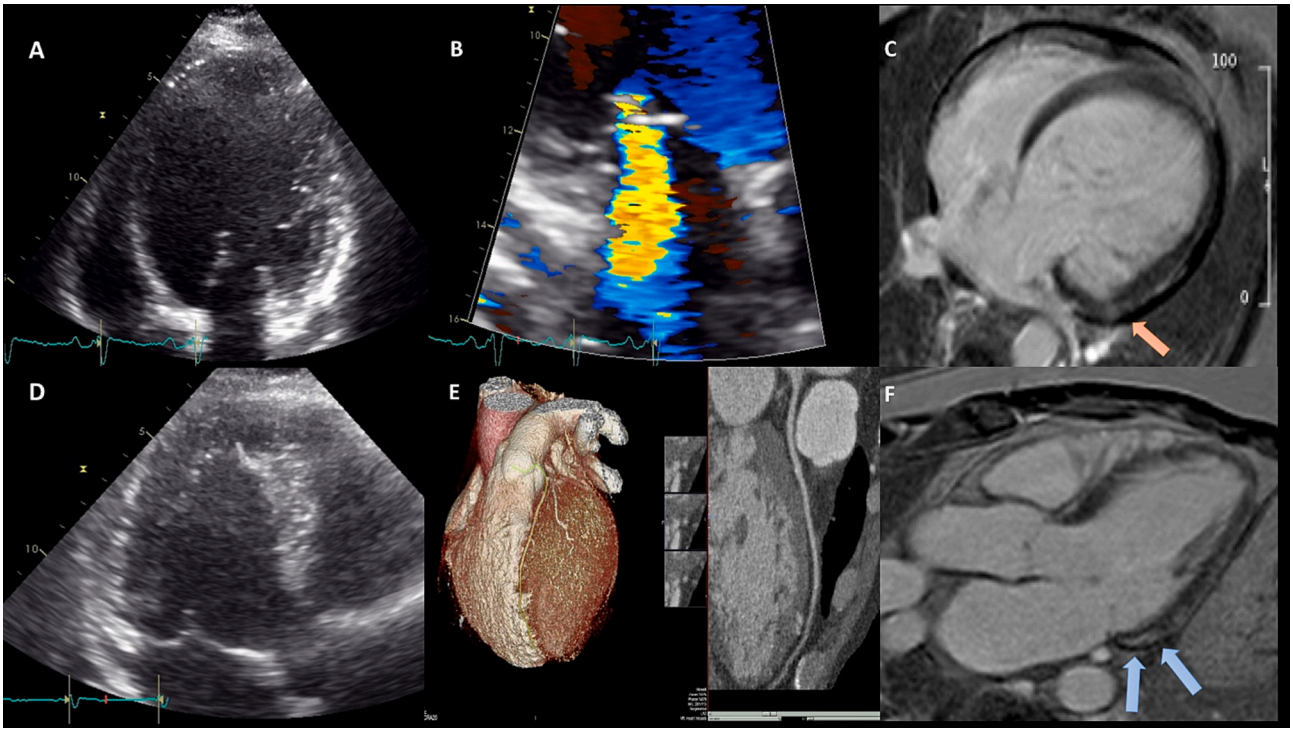

Fig. 1. Example of clinical findings of two patients with myocarditis and IBD from our single center cohort. Upper panel (case #17): 58 years-old female patient presenting to the Emergency Room (ER) following 2-weeks of exertional dyspnea. She was diagnosed with UC 1 year before that was on good control on mesalamine therapy. On ECG, new onset LBBB was diagnosed. On 2D-echocardiography, LV appeared severely dilated with LVEF 24% due to diffuse hypokinesis (A); moderate mitral regurgitation was also noted (B). CMR showed focal epicardial LGE of the inferolateral LV wall (C, orange arrow), without myocardial edema (not shown). AHA tested positive with organ-specific pattern. EMB showed lymphocytic virus-negative myocarditis, and the patient was treated with azathioprine and prednisone, with good response. Indeed, after 7 years, echocardiographic LVEF was 56%. Bottom panel (case #20): 52 years old male presenting to the ER because of syncope preceded by sudden palpitations. He was on mesalamine therapy to treat CD. ECG showed RBBB. On echocardiography, LVEF was 52% (D). A coronary CT showed absence of significant coronary artery lesions (E). CMR revealed signs of non-ischemic LGE of the inferior and lateral walls (F, blue arrows). These findings were consistent with clinically suspected myocarditis with arrhythmic presentation. During hospitalization, several ventricular tachycardia episodes were reported, but an electrophysiological study resulted negative; beta-blocker therapy was started with good control on arrhythmias. At 5-year follow up, echocardiography showed normal LVEF (67%). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ventricular function at echocardiography: indeed, the median LVEF was 56% (IQR 41.5–66.0). However, 38% of patients had LV dysfunction at diagnosis (LVEF<50%). Seventeen patients underwent CMR, which showed signs of myocardial edema in 63% of cases, and late gadolinium enhancement (LGE) in the majority of cases (87%) (Fig. 1). Five patients already were on immunosuppressive therapy (IS) at the moment of myocarditis diagnosis for IBD treatment. IS consisted of prednisone in 2 cases, azathioprine in 1 case, association of azathioprine and prednisone in 2 cases and of prednisone and cyclosporine in 1 case. No patient was treated with immune checkpoint inhibitors (ICI). Among the 9 patients undergoing EMB, 5 had a diagnosis of active lymphocytic myocarditis (Fig. 2), 2 of giant cell myocarditis (GCM) and in 1 case EMB was inadequate. In 1 case, histological diagnosis was of DCM with signs of inflammation without myocyte necrosis; it is noteworthy that this patient was on high dose intravenous corticosteroid treatment for a severe relapse of previously diagnosed CD at the time of EMB. At polymerase chain reaction (PCR), which was performed in all EMB-proven myocarditis cases, diagnosis of viral myocarditis was achieved in 1 patient, which tested positive for both Parvovirus B-19 (PVB19, >500 copies) and Epstein-Barr Virus (EBV), and was treated with antiviral therapy. Therefore, autoimmune virus-negative myocarditis was diagnosed in 89% of EMB-proven patients. Of note, none of the 5 patients who underwent EMB and was on 5-ASA therapy had clinical or histological findings consistent with hypersensitivity. In all cases, if mesalamine therapy was ongoing, it was stopped when myocarditis diagnosis was initially suspected. Details on clinical, histological and imaging data of EMB-proven myocarditis patients is reported in Supplementary Table 2.

The median duration of follow up was 40.5 months; 2 patients underwent heart transplantation (HTx), both of them with GCM diagnosis, despite combination IS, and 1 patient died of neoplastic non-cardiac cause. Four patients (19%) had myocarditis recurrence (2 with EMB-proven and 2 with clinically suspected myocarditis). At last follow-up, all remaining patients presented NYHA functional class I, 93% showed sinus rhythm and all had a normal echocardiographic LVEF (Table 1, Supplementary Table 1). One patient underwent the implantation of a CRT—D. At last follow-up, 3 patients were on IS: 1 with adalimumab, 1 with prednisone and vedolizumab and 1 with azathioprine.

3.2. Systematic review of literature results

Our literature search identified 1020 references (Supplementary fig. 2). Based on the abstract evaluation, 109 of these citations were considered potentially eligible for inclusion and their full texts were analyzed in more detail. We excluded 26 of these studies: 4 did not report a definite diagnosis of IBD, 9 did not report a definite diagnosis of myocarditis, 11 did not report an adequate amount of clinical information and 2 were in a language different from English, Italian, Spanish or French (an exhaustive list of excluded reports is shown in Supplementary Table 3). Eventually, 83 reports were considered for the analysis. The only case series which was included consisted of 2 cases (a complete list of the included reports is shown in Supplementary Table 4).

Table 2 illustrates the results of the systematic review of the

Table 1
Clinical, echocardiographic and laboratory findings of single-centre cohort patients at baseline and at last follow up.

Demographic features ($N = 21$)	N (%)
Male gender, n (%)	16 (76%)
Caucasian, n (%)	19 (95%)
Age at diagnosis, years, median (IQR)	33 (27–46)
Family history of immune-mediated disease, n (%)	6 (29%)
Immune-mediated disease, n (%)	6 (29%)
IBD diagnosis	
UC, n (%)	8 (38%)
CD, n (%)	8 (38%)
Not specified, n (%)	5 (24%)
IBD activity at the time of myocarditis onset*, n (%)	9 (60%)
Mesalamine therapy°, n (%)	13 (76%)
Start of mesalamine <30 days from myocarditis onset, n (%)	9 (69%)
Myocarditis diagnosis	
Viral infection in the 6 months before diagnosis, n (%)	4 (19%)
Infarct-like presentation, n (%)	12 (57%)
Arrhythmic presentation, n (%)	4 (19%)
Heart failure presentation, n (%)	4 (19%)
No cardiac symptoms at diagnosis, n (%)	1 (5%)
Cardiac symptoms before diagnosis, n (%)	15 (71%)
Immunosuppressive therapy at myocarditis diagnosis, n (%)	7 (33%)
NYHA I functional class, n (%)	16 (76%)
Biochemical parameters	
TnI elevation§, n (%)	13 (68%)
CRP elevation*, n (%)	12 (80%)
Positive AHA#, n (%)	9 (50%)
Electrocardiographic features	
Sinus rhythm n (%)	20 (95%)
Nonspecific IVC delay°, n (%)	3 (18%)
BBB#, n (%)	6 (33%)
QRS axis deviation°, n (%)	3 (18%)
Echocardiographic features	
LVEF§, %, median (IQR)	56.0 (41.5–66.0)
LVEDVi, ml/m2>, median (IQR)	68.0 (59.5–99.0)
CMR	
Edema <, n (%)	7 (63%)
LGE *, n (%)	13 (87%)
EMB	
Histological type, n (%)	9 (43%)
Lymphocytic myocarditis	5 (56%)
GCM	2 (22%)
DCM with inflammation without myocyte necrosis	1 (11%)
Inadequate	1 (11%)
Viral PCR positive, n (%)	1 (11%)
Clinical and instrumental findings at last follow-up	
Duration of follow-up, months, mean (IQR)	40.5 (13.1–71.9)
Dead or transplanted, n (%)	3 (14%)
Myocarditis relapse, n (%)	4 (19%)
Subacute or chronic course, n (%)	6 (29%)
NYHA I functional class >, n (%)	16 (100%)
Sinus rhythm at ECG*, n (%)	14 (93%)
LVEF°, %, median (IQR)	63.0 (61.0–67.0)
LVEDVi°, ml/m2, median (IQR)	52.0 (59.0–67.0)
Immunosuppressive therapy at last follow-up, n (%)	1 (17%)

*Data available data in 15 patients. °Data available in 17 patients. § Data available in 19 patients. # Data available in 18 patients. > Data available in 16 patients. < Data available in 11 patients.
AHA: Anti-Heart Antibodies, BBB: bundle branch block, CD: Chron's disease, CMR; cardiac magnetic resonance, CRP: C-Reactive Protein, IVC: intraventricular conduction delay, LGE: late gadolinium enhancement, LVEDVi: indexed left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, UC: Ulcerative Colitis, TnI: Troponin I, TWI: T wave inversion, EMB: endomyocardial biopsy.

literature. Patients were mostly male (71%) and relatively young (median age 39 years, IQR 21–42), and the majority had UC (64%). They mostly presented "infarct-like" myocarditis (58%) and were on 5-ASA derivative therapy (65%). Ten of the 17 available EMBs led to a diagnosis of GCM. In 92% of cases, myocarditis had a benign course. In a minor, yet not negligible, quote of patients (8%), myocarditis led to death or HTx.

3.3. Overall population analysis

Finally, we performed a descriptive analysis of the findings of the entire population. The overall population included 104 patients (21 from our single center cohort, 83 from the systematic literature review), majority of which were young (median age 31 years old, IQR 22–46) and males (72%); 59% of them had UC which was frequently treated with 5-ASA derived drugs, which in 64% of cases had been initiated less than a month before cardiovascular symptoms onset. IBD was frequently (67%) active at the time of myocarditis diagnosis. Myocarditis frequently presented with infarct-like chest pain pattern with LVEF reduction, and in 87% of cases had a complete clinical resolution. In 21% of cases myocarditis had a fulminant presentation. EMB was performed in 26 cases, 12 (46%) of which showed GCM. Other histological types were eosinophilic myocarditis in 3 cases, lymphocytic in 8 cases, inadequate in 2 cases and DCM with inflammatory cells in 1 case. Of the 3 patients with eosinophilic myocarditis, 1 case was on 5-ASA therapy. Active search for viral genome in EMB material was not performed in the majority of cases reported in literature, and only 2 cases reported viral genome presence in myocardial samples. Ten patients underwent HTx or died, 8 of which had a GCM diagnosis. At the time of myocarditis diagnosis, IBD was treated with 5-ASA or derivative in the majority of cases, but also steroids, classical immunosuppressants (especially azathioprine) and biological drugs were used; notably, infliximab was used in only 4 patients from the literature cohort.

4. Discussion

In the present study, a systematic review of published case reports was performed, and together with our 21 patients single center cohort, 104 patients were identified. Previous evidence on myocarditis and IBD association was based upon registries, case reports and expert opinions. To the best of our knowledge, this is the first clinical study to specifically address the association of myocarditis and IBD, and our 21 patients with EMB-proven or clinically suspected myocarditis and IBD represent the largest single-center cohort so far.

Cardiovascular diseases are considered atypical extra-intestinal manifestation of IBD, which more frequently affect the skin, eyes, joints, liver or other organs [19]. However, according to recent evidence, IBD patients seem to have higher risk of cardiovascular diseases, despite a relatively low rate of classical cardiovascular risk factors [20]. In the worldwide literature, we only identified 83 cases, including a single case series of 2 patients, with coexistence of IBD and myocarditis. These data would suggest that this association is rare. Indeed, in the 90s, a Danish national cohort study including 15′572 patients with IBD found a total risk of myocarditis in these patients of 4.6 per 100,000 years, with an "incidence risk ratio" of 8.3 for CD and 2.6 for UC compared to general population [21]. More recently, Shivaraj et al. investigated 1′325'547 US adult IBD patients from 2010 to 2014, and found that myocarditis was present in 0.01% patients, in particular 0.018% in UC and 0.009% in CD [22]. Notably, the relative risk of myocarditis in IBD patients was calculated relying on the estimation of myocarditis frequency in the general population [23], which is difficult to assess due to the common underdiagnosis or misdiagnosis of myocarditis [1]. Therefore, longitudinal studies are needed to define the real incidence of myocarditis in the general population and among IBD patients, and to clarify whether patients with IBD are at increased risk of myocarditis compared to the general population.

Regarding the etiology, the coexistence of myocarditis and IBD may derive by patients' predisposition to autoimmunity. Autoimmune diseases occur in patients with a genetic predisposition, and frequently more than one autoimmune disease coexist in the same patient or in members of the same family [24]. It has been recently observed that both colitis and myocarditis can appear as immune-related adverse events (irAEs) after ICI administration [25–27], suggesting an involvement of both the gastro-intestinal system and the myocardium in

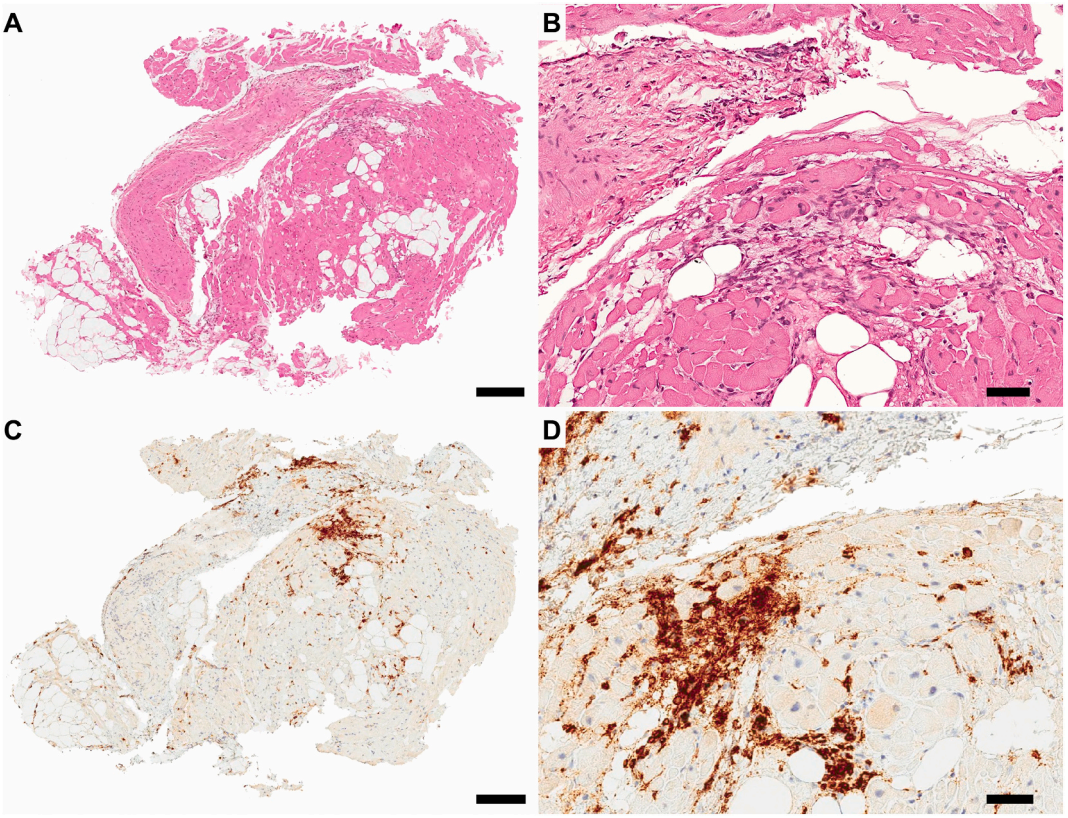

Fig. 2. Histological evaluation of a case of lymphocytic myocarditis. A) Panoramic view of the most severely involved fragment (Hematoxylin-Eosin, scale bar 200 μm). B) At higher magnification, the presence of abundant inflammatory cells coupled with myocardial necrosis and minimal fibrosis is remarkable (Hematoxylin-Eosin, scale bar 50 μm). C) Panoramic view of the same fragment with prominent lymphocytic infiltration at immunohistochemistry (CD3, scale bar 200 μm). D) Close-up of the CD3-positive lymphocytes in the largest focus (CD3, scale bar 50 μm).

deranged immune-mediated phenomena.

The role of autoimmunity in IBD is well established: native T and B cell activation is driven by "loss of tolerance" mechanisms [28], and CU patients have high frequency of anti-nuclear cytoplasmic autoantibodies (ANCA) [29]. Interestingly, molecular mimicry towards a tropomyosin isoform (hTM5) has also been identified as a causative mechanism of CU [30]. Similarly, the role of autoimmunity in myocarditis is widely recognized, either as post-infectious immune-mediated myocardial damage, or as primary organ-specific autoimmune disease [1]. In addition, non-infectious autoimmune myocarditis may occur in a variety of SIDs [31], determining worse prognosis and dictating an intensified IS regimen [6]. Autoimmune myocarditis in IBD patients may relate to exposure of shared gut and heart autoantigens [13,32], leading to release of inflammatory mediators, immune system activation and cytotoxicity to cardiomyocytes. Several findings in the present study support the hypothesis of autoimmunity as a common background of IBD and myocarditis. Firstly, in keeping with this hypothesis, the frequency of GCM observed in the overall study population was high (46% of the 26 EMB-proven cases). GCM is the prototype of autoimmune myocarditis forms and has been defined as the "most fatal of autoimmune diseases" [33]. In fact, GCM presents an ominous prognosis if not promptly recognized and treated with combination IS [34–36]. In single cases it may be triggered by viral agents, as in one patient of our series who tested positive for Parvovirus B-19 and Epstein-Barr. Secondly, in our cohort we documented a relevant quote of IBD patients with positive family and/or personal history of other SIDs. Thirdly, all the five IBD patients with EMB-proven myocarditis in our cohort of whom AHA results were available tested positive [37]. Lastly, in 67% of overall cases, myocarditis diagnosis was achieved during an active phase of IBD, indicating a possible concomitant involvement of the myocardium and the gastrointestinal tract by an altered immune system.

The other main recognized cause of myocarditis in association with IBD is a hypersensitivity reaction to 5-ASA derivatives. More than half of the IBD patients of our study were taking 5-ASA derivatives therapy; 64% of them had begun the therapy <30 days before the diagnosis of myocarditis. Mesalamine is a 5-ASA compound frequently used to treat IBD and considered to be generally safe, but various reports of cardiotoxicity are present in the literature [38]. The main recognized mechanism of myocardial injury is hypersensitivity, since complete recovery is frequently achieved after drug discontinuation [39]. Symptoms usually begin within 2 weeks after therapy initiation, but their onset may be delayed due to concomitant use of steroids, which mitigate the initial hypersensitivity reaction. Presumptive diagnosis of mesalamine-induced cardiotoxicity is mainly based on the temporal relationship between clinical onset and drug initiation, and is supported by resolution of symptoms after drug withdrawal [14]. In these mild cases, EMB is rarely performed, and myocarditis often undergoes spontaneous resolution; it is thereby possible that some cases are erroneously labeled as hypersensitivity myocarditis. Following suspected cardiotoxicity, mesalamine rechallenge is frequently not performed due to safety concerns: this exposes patients to IBD flares and requires to step up therapy to second- or third-line drugs, which could have a higher risk of toxicity [14]. Notwithstanding, our systematic review only identified a single report in which histological diagnosis of eosinophilic myocarditis with hypersensitivity features was reached through EMB [39]. Therefore, more EMB-proven studies are needed to define the real incidence and histological aspects of mesalamine-induced hypersensitivity myocarditis, since EMB is the only diagnostic tool that can identify the histological pattern of myocarditis [40].

A degree of concern may exist on the possibility of infectious myocarditis in IBD patients, which may be treated with IS therapies leading to an increased risk of opportunistic infections. In our single

Table 2
Clinical, imaging and histological data of the systematic review of literature (SRL) patients ($N = 83$) and of the overall study population ($N = 104$).

Characteristics	SRL patients (N = 83)	Overall population (N = 104)
Sex, n (%):		
-male	59 (71%)	75 (72%)
-female	21 (25%)	26 (25%)
-unknown	3 (4%)	3 (3%)
Age at myocarditis diagnosis, years, median (IQR)	39 (21–42)ˆ	31 (22–46)
IBD type, n (%):		
-UC	53 (64%)	61 (59%)
-CD	29 (35%)	37 (35%)
-undetermined	1 (1%)	6 (6%)
IBD at myocarditis diagnosis, n (%);		
-active	61 (74%)	70 (67%)
-not active	20 (24%)	26 (25%)
-unknown	2 (2%)	8 (8%)
Therapy of IBD at myocarditis diagnosis (%)*:		
-5-ASA derived drugs	54 (65%)	67 (64%)
-steroids	25 (30%)	28 (27%)
-other immunosuppressants	8 (10%)	10 (10%)
-biological agents	7 (8%)	8 (8%)
-unknown	18 (21%)	24 (23%)
Time between 5-ASA first intake and myocarditis diagnosis <30 days, n (%):	34 (63%)	43 (64%)
Myocarditis presentation, n (%):		
-infarct-like	48 (58%)	60 (58%)
-heart failure	28 (34%)	32 (31%)
-arrhythmic	7 (8%)	11 (11%)
Myocarditis course, n (%):		
-acute with clinical resolution	76 (92%)	91 (87%)
-subacute/chronic/fatal	7 (8%)	13 (13%)
Fulminant onset, n (%)	22 (27%)	22 (21%)
Relapse of myocarditis, n (%):	18 (22%)	22 (21%)
Left ventricular dysfunction at diagnosis, n (%):	52 (63%)§	60 (58%)
LVEF % at the time of diagnosis, median (IQR)	38.0 (25.0–47.0)§	41.0 (27.5–55.0)
CMR, n (%)	47 (57%)	64 (62%)
LGE on CMR#, n (%)	37 (79%)	51 (80%)
EMB, n (%)	17 (20%)	26 (25%)
Histological findings°, n (%):		
-GCM	10 (59%)	12 (46%)
-non-GCM	6 (35%)	12 (46%)
-inadequate	1 (6%)	2 (8%)
Dead or transplanted, n (%)	7 (8%)	10 (10%)

*Therapies may be present in association, i.e. steroids and other immunosuppressants. ˆData available in 81 patients. §Data available in 50 patients. #$N = 64$. °$N = 26$.

center cohort, only one patient with EMB-proven myocarditis tested positive for viral genome at PCR [41]. It is concerning that, as shown by our systematic review, active search for infectious agents in EMB material does not appear to be routinely performed, leading to possible misdiagnosis or underdiagnosis of infectious forms of myocarditis. According to the 2013 ESC Consensus, tissue obtained from EMB should always undergo viral PCR, which is the only method to rule out an infectious cause of myocarditis [1].

In the present study most IBD patients were young males with an infarct-like myocarditis presentation; this is in keeping with the known higher prevalence of infarct-like myocarditis among young males in the general population [42,43]. Regarding the type of IBD, more than half of cases were UC (59%), but this could be due to the higher prevalence of UC as compared to CD [44]. According to the only observational retrospective study exploring this issue, myocarditis is reported to be more frequent and to be associated with higher rates of cardiovascular adverse events in patients with UC than CD [22]. Our data do not allow any estimate in this sense. It is noteworthy that in our study 8 of the 10 patients who underwent HTx or died had an histological diagnosis of GCM, which represents a major predictor of adverse prognosis, in keeping with the literature [45].

4.1. Study limitations

The main limitation of the present study is its retrospective design. Regarding the systematic review of literature, the effect of selection bias towards over-representation of severe and otherwise uncommon myocarditis clinical forms, such as GCM, cannot be excluded. In addition, the majority of patients had a clinically suspected diagnosis, i.e. EMB was not performed; therefore, a description of histological features of the disease and of its prognostic relevance was not possible to perform.

5. Conclusions

Our observational data on the largest cohort of patients with IBD and myocarditis show that myocarditis in IBD has a generally benign clinical course. In the majority of cases it affects young males, presenting with infarct-like chest pain at the time of an IBD flare. Nevertheless, a relevant quote of patients may have a subacute, chronic, or even fatal course, needing advanced cardiological life support measures and prompt execution of EMB to reach a diagnosis of certainty of myocarditis as well as differentiation of infectious and immune-mediated forms. Importantly, some patients will be ultimately diagnosed with GCM, that should be managed with tailored high-intensity combination IS therapy. Apart from autoimmune etiology, mesalamine hypersensitivity should be taken into consideration, but in the absence of histological confirmation and exclusion of infectious causes, its diagnosis remains presumptive.

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CRediT authorship contribution statement

A.S. Giordani: Conceptualization, Methodology, Writing – original draft. **A. Candelora:** Conceptualization, Methodology, Writing – original draft. **M. Fiacca:** Conceptualization, Investigation, Formal analysis. **C. Cheng:** Investigation, Writing – review & editing. **B. Barberio:** Investigation, Writing – review & editing. **A. Baritussio:** Visualization, Data curation, Writing – review & editing. **R. Marcolongo:** Visualization, Writing – review & editing. **S. Iliceto:** Supervision, Writing – review & editing. **E. Carturan:** Investigation, Writing – review & editing. **M. De Gaspari:** Writing – original draft. **S. Rizzo:** Writing – original draft. **C. Basso:** Supervision, Writing – original draft. **G. Tarantini:** Supervision, Writing – original draft. **E.V. Savarino:** Writing – review & editing. **Caforio ALP:** Conceptualization, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

Nothing to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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