

The heart in inflammatory bowel disease

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SUMMARY

Cardiovascular involvement in inflammatory bowel disease (IBD) has been occasionally reported, mainly in the form of case reports. Endocardium derangement in IBD involves endocarditis and subendocardial abscess. Endocarditis may occur as a result of septicemia or due to the prolonged use of total parental nutrition (TPN) catheters or/and immunosuppression. The cause of endocarditis may be bacterial or fungal and require surgery in several cases. Prophylaxis for endocarditis in selected IBD patients is discussed. Myocarditis or perimyocarditis in IBD is reported as an autoimmune phenomenon during bowel disease exacerbations or as a side-effect of 5-aminosalicylic acid (5-ASA) formulations. Ulcerative colitis (UC) patients seem to be at a higher risk for this complication compared to Crohn's disease (CD) patients. Myocardial infarctions, selenium deficiency during TPN, the role of prolonged steroid use and the association with giant cell myocarditis are topics which need further analysis. Pericardium involvement seems to be the most frequent type of cardiovascular complication in IBD caused by drugs (5-ASA, azathioprine, cyclosporine), pericardio-colonic fistulas or unknown causes (idiopathic) and it may occasionally be the disease presenting symptom.

Coronary artery status and other factors for cardiovascular risk, such as smoking, hyperlipidemia and exercise are also discussed. Electrocardiogram and ultrasonographic changes are not so uncommon and cardiogenic sudden death in IBD is reviewed. Intracavitary coagulation abnormalities, amyloidosis, heart failure and aortitis syndrome are

topics included and discussed in this review. A list of tables contributes to a more systemic overview of this current knowledge.

Key Words: heart, inflammatory bowel disease, ulcerative colitis, Crohn's disease.

1. ENDOCARDIUM INVOLVEMENT IN INFLAMMATORY BOWEL DISEASE

An increased risk of endocarditis has been suggested in IBD patients but it has been reported in less than 30 cases¹⁻³ (Table 1). Endocardium involvement is an extremely severe condition in IBD, often leads to surgery and always needs immediate hospitalization and treatment. Endocarditis seems to occur in patients with catheters, underlying endocardium anatomic abnormalities or is a result of bacteremia during prolonged immunosuppression. Prophylactic measures and prophylactic drug administration is a topic under discussion in relation to periods of disease relapse.

a. Endocardium involvement in ulcerative colitis (UC)

Infective endocarditis during ulcerative colitis has been occasionally reported.⁴ It is usually present during disease relapse or it is the presenting symptom of an undiagnosed quiescent ulcerative colitis.⁵ Bacteremia during disease exacerbation seem to be the most probable pathophysiological mechanism of this complication. Enterococcus faecium⁶ and streptococcus⁺ bovis⁷ have been reported to be the responsible microorganisms. Children with ulcerative colitis may also be affected⁸ and an infant with UC complicated by endocarditis and cerebral infarction has been reported.⁹

b. Endocardium involvement in Crohn's disease (CD)

Microbial¹⁰ and a fatal case of tricuspid valve fungal

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Table 1. Reported endocardium involvement in inflammatory bowel disease

1. Endocarditis
a. Bacterial → enterr. Faecium
→ strept. bovis
b. Fungal → C albicans
2. Subendocardial abscess → right atrium (staph. aureus)

endocarditis due to candida-albicans¹¹ have been reported in CD patients and there is also a single case of staphylococcal right atrium abscess as a complication of prolonged central venous access for total parental nutrition¹² (TPN).

Prolonged immunosuppression and TPN seem to be the main underlying conditions leading to this severe complication. Early suspicion and Indium¹¹¹ autologous granulocyte scanning¹³ in cases with suspected abscesses are extremely important hallmarks for prompt diagnosis.

2. MYOCARDIUM INVOLVEMENT IN INFLAMMATORY BOWEL DISEASE

Myocardium involvement is a rare but severe complication of IBD. It is very often associated with pericarditis or pleural effusion in the majority of UC¹⁴⁻¹⁷ patients but it is rare in CD patients¹⁸ (Table 2). The terms myopericarditis or perimyocarditis are used to describe these kinds of coexistence. The Danish nationwide cohort study¹⁹ including 15,572 IBD patients reported 6 cases of myocarditis assessing a total risk of 4.6 per 100,000 years of risk. Comparing with the background population, an incidence ratio of 8.3 for CD and 2.6 for UC patients was assessed in that study. This study concluded that IBD patients have an increased risk of myocarditis compared with the background population although its incidence still remains low.

Table 2. Reported myocardium involvement in inflammatory bowel disease

1. myocardial infarction/coronary artery disease
2. in association with giant cell myocarditis
3. idiopathic
4. steroid induced heart muscle atrophy
5. mesalamine induced
6. selenium deficiency induced
7. in association with pericarditis

The causes of myocardium involvement in IBD do not seem to be well documented except for that of selenium (Se) deficiency during TPN²⁰ and steroid²¹ and mesalamine use²³. An interesting association with giant cell myocarditis has also been reported²⁴. Myocardial infarction is a relatively common condition in IBD patients who have additional cardiovascular risk factors.

a. Myocardium involvement in UC patients.

Drugs for UC seem to play an important role in this kind of involvement; reversible hypertrophic cardiomyopathy complicating prolonged corticosteroid therapy²¹ and acute myocarditis²² and perimyocarditis²⁵ due to mesalamine use have been reported. Acute myocardial infarction during disease exacerbation in a young patient²⁶ and a fatal case in an elderly woman²⁷ are also cases of interest. Finally, the interesting possible association of giant cell myocarditis during UC is a topic which needs further investigation^{24,28,29}.

b. Myocardium involvement in Crohn's disease

Muocardium involvement is caused by selenium deficiency during prolonged^{20,30} or short term³¹ TPN as described in 5 cases. Selenium deficiency is reversible but may result in fatal cardiomyopathy. Thus, it should always be suspected in TNP patients with palpitation, precordial pain, arrhythmias and cardiomegaly. Plasma selenium levels, erythrocyte selenium levels and glutathione peroxidase activity is of help in diagnosis and follow-up. When selenium deficiency is diagnosed, immediate oral or intravenous supplementation is of *sine qua non*. Suggested doses are 25-60 µg/day for adults and 14-30 µg/Kg/day for pediatric patients when they are metabolically stable. In selenium depleted adults a dosage of 100 µg/d i.v for 21-31 days has been recommended to reverse symptoms³¹.

The sudden death of a 29-year-old man due to ileum and atrophic change of the heart muscle³² and the association of myocarditis with subcutaneous granulomas³³ in another CD patient are also two cases of interest. Idiopathic and pediatric cases are also involved in this short catalogue³⁴.

3. PERICARDIUM INVOLVEMENT IN INFLAMMATORY BOWEL DISEASE

This seems to be the most frequent complication of heart involvement³⁵⁻⁴² in IBD (Table 3). Pericardium involvement often co-exists with myocarditis or pleural effusions, and is described as periomyocarditis or myopericarditis⁴³ and pleuro-pericarditis respectively.

Table 3. Reported pericardium involvement in inflammatory bowel disease

1. Idiopathic (disease extraintestinal manifestation)
2. CyA induced?
3. 5-ASA induced
4. AZA induced
5. Pericardio-colonic fistula
6. Pleuro-pericarditis
7. Myo-pericarditis (perimyocarditis)
8. Pericardial tamponade

Pericardium is involved in IBD cases as an idiopathic condition⁴⁴ (disease-related extraintestinal complication), as a drug side effect or due to pericardio-colonic fistulas.

In a review of 68 IBD patients with pericarditis it has been shown that UC male patients were more affected and pericarditis diagnosis was not associated with bowel disease activity in all these cases⁴⁵. In most cases, corticosteroid use was effective while, in cases of drug induced pericarditis, omission of 5-ASA therapy was sufficient. In this cohort one fatal case with myocarditis coexistence was described.

a. Pericardium involvement in UC

Acute pericarditis although it may rarely be the IBD presenting symptom, as reported in 3 cases⁴⁶⁻⁴⁸, usually occurs in long-standing IBD cases⁴⁹⁻⁵⁵. Pericardial tamponade is a rare⁵⁶⁻⁵⁹ but urgent condition and should always be intensively treated. Azathioprine-induced pericarditis due to a probable hypersensitivity drug reaction has also been reported once⁶⁰. Pericarditis due to infection and fistula between the left ventricle and transverse colon leading to death has been reported⁶¹ but this patient had a previous resection of a left ventricular apical

Table 4. Reported electrocardiographic abnormalities in inflammatory bowel disease

1. artrial fibrillation
2. supraventricular tachycardia
3. ST elevations
4. ventricular tachyarrhythmia
5. sinus bradycardia (mesalamine related)
6. atrio-ventricular block
7. autonomic vagal nerve dysfunction
8. Also all ECG abnormalities associated with endocardium, myocardium and pericardium involvement.

aneurysm, which was probably the triggering condition leading to this fatal complication.

b. Pericarditis involvement in CD patients

Acute pericardial effusion in CD patients has been reported to occur as a hypersensitivity reaction during prolonged 5-ASA⁶² or mesalamine use⁶³⁻⁶⁴, and more rarely after colonic surgery⁴⁶ or as an idiopathic (extraintestinal) disease manifestation⁶⁵⁻⁶⁷. Cyclosporin-A (CyA) has also been suggested as a possible cause of pericarditis sicca⁶⁸. Pericardial tamponade in a child with chronic monoarthritis has also been reported⁶⁹.

c. Pleuro-pericarditis in IBD

This is a rare complication, usually in combination with other extraintestinal complications of IBD. Corticosteroids, aspirin and/or indomethacin are effective drugs and can prevent tamponade⁷⁰. Patients with UC are more frequently affected than CD patients. Pleuro-pericarditis has been reported in combination with arthritis and vasculitis⁷¹ and pyoderma gangrenosum⁷². 5-ASA^{23,73} and mesalamine use⁷⁴ have also been suggested to be associated with this extraintestinal complication of IBD. Infectious and endocrinology causes should always be excluded as well as the 5-ASA induced lupus like syndrome⁷³ in IBD cases with pleuropericarditis.

4. CORONARY ARTERIES INVOLVEMENT IN IBD

Acute infarction has been reported during relapse of UC²⁶. Besides all known usual pathophysiologic conditions and risk factors, a reversible vasoconstriction diminishing blood flow to the perfused tissues followed by an ischaemia of varying severity was suggested to be involved in the pathogenesis of coronary artery involvement in CD patients⁷⁵. When coronary artery bypass grafting in UC patients with angina pectoris is needed, oral prednizone should be used during perioperative period⁷⁶. All cardiovascular risk factors for the general population are encountered in IBD patients, except for cholesterol, which seems to be significantly low, normal or below normal levels in hospitalized or malnourished IBD patients⁷⁷.

5. ELECTROCARDIOGRAPHIC CHANGES IN IBD PATIENTS

A variety of ECG changes have been reported in IBD patients⁷⁸, usually in those with UC⁷⁹ (Table 4). In a recent study, IBD patients were found to respond to labo-

ratory stressors in the same way as irritable bowel disease patients do⁸⁰. Electrocardiographic changes in endocarditis, myocarditis, pericarditis and acute myocardial infarction in IBD are exactly the same as changes as in the general population and do not attract special interest.

In UC patients, several ECG abnormalities have been reported including Wenckebach or⁸¹ complete^{14,82} atrioventricular block, atrial fibrillation with supraventricular tachycardia and ST elevations in all leads¹⁷, ventricular tachyarrhythmia²⁹ and mesalamine related sinus bradycardia⁸³ and chest pain with ECG abnormalities⁸⁴.

In CD patients under long term parenteral nutrition, cardiomegaly and arrhythmia due to selenium deficiency may be present³⁰: An autoimmune vagal nerve dysfunction study⁸⁵ suggested that a sympathetic dysfunction predominates in CD, while autonomic neuropathy is vagal in UC, but such data seem to need further clarification.

6. PHYSICAL EXERCISE AND SMOKING IN IBD PATIENTS

Epidemiological data support the role of physical activity in lowering the risk of IBD. Reduced exercise capacity after surgery, especially after extensive resections, may be observed in IBD patients⁸⁶. In a 12 week supervised walking programme⁸⁷, however it was shown that CD patients can tolerate low-intensity exercise (60% VO₂ max) of moderate duration without exacerbation of symptoms. These weeks of walking were adequate to elicit psychological and physical improvements without affecting disease activity.

The role of smoking in UC has been clarified in several studies correlating to remission of bowel symptoms but not along with cardiovascular risk^{88,89}. Nicotine use, although it seems to work experimentally in inhibiting inflammation⁹¹, was not proved effective in clinical practice and the question whether transdermal nicotine is associated with cardiovascular risk remains an important subject for discussion⁸⁹.

7. THE IBD ANGIITIS SYNDROME

Eight reported cases of patients with IBD and aortitis unrelated to endocarditis supported the idea of this IBD-angiitis syndrome. Ulcerative colitis was associated with perimyocarditis and allergic granulomatous vasculitis (Churg-Strauss syndrome) in one case⁹², CD with aortitis in another⁹³ while the other 6 cases, 5 coming

from Japan, seemed to establish the so-called UC-Takayasu aortitis syndrome. This syndrome usually affects young UC patients and it frequently needs aortic root or/and aortic valve replacement due to the aneurysmal dilatation of the ascending aorta⁹⁴ (thoracic) resulting in severe aortic insufficiency⁹⁵⁻⁹⁶ and preinfarction angina. Three of these UC-Takayasu aortitis cases also had ankylosing spondylitis and were characterized as HLA B27 related aortitis cases^{94,95,97}. In all these cases UC and ankylosing spondylitis preceded aortitis syndrome, which was diagnosed using angiographic methods. Blood studies showed positive signs of inflammatory and negative rheumatoid factor and syphilis serology, while HLA typing may be helpful. Whether a common pathophysiological basis for the associations of UC and Takayasu's aortitis exists⁹⁸ remains currently unknown.

8. HEART VALVE INVOLVEMENT IN IBD

Heart valve involvement is not so rare in IBD patients, especially in those with UC, and results from endocardium and/or aortic root involvement as previously described. The most complicated cases may need surgical valve replacement with generally good prognosis.

a. Heart valve involvement in ulcerative colitis

Aortic and mitral valve may be affected and require surgery in UC patients. Aortic endocarditis due to *Enterococcus faecium* and mitral valve leaflet aneurysm requiring surgery have been reported twice^{6,98} and mitral commissurotomy was reported in a single case¹⁰⁰.

b. Heart valve involvement in Crohn's disease

Aortic valve insufficiency⁹³, aortic regurgitation¹⁰¹ and fungal (*Candida albicans*) tricuspid valve endocarditis have been reported¹¹. Endocarditis due to TPN catheters seems to play an important role in CD heart valve involvement.

9. INTRACAVITARY COAGULATION ABNORMALITIES AND VASCULAR COMPLICATIONS IN IBD

In a large retrospective study¹⁰² thromboembolic complications developed in 1.3% of IBD patients (Table 5). In addition, less than 20 cutaneous vasculitis and arteritis associated IBD cases were also reported. The majority of these thromboembolic complications included deep vein thromboses¹⁰³ or pulmonary emboli with high mortality (25%). Peripheral arterial thrombosis, coronary thrombosis, mesenteric and portal vein thrombosis were

Table 5. Reported intracavitary abnormalities and coagulation-related complications in inflammatory bowel disease

1. subendocardial abscess (right atrium)	
2. thrombus (left ventricle)	
3. right atrium abscess	
4. superior vena cava thrombus	
5. atherosclerosis and arterial occlusion	
6. arterial occlusive disease	
7. the aortitis syndrome	
Vascular complications in IBD	
1. arterial occlusive disease	
2. superior vena cava thrombosis	
3. mesenteric thrombosis	
4. association with Churg-Strauss angiitis	
5. association with Takayasu aortitis	
6. deep vein thrombosis	
7. arteritis	
8. portal vein thrombosis	

predominantly post surgical complications, but 77% of peripheral venous thromboses occurred spontaneously. Arterial occlusive disease in 6 patients with CD showed that major arterial events in lower extremities usually occur in young, steroid dependent patients with active CD and/or prior extensive bowel resections without evidence of extraintestinal manifestations¹⁰⁴. It should be noted that all these patients showed iliac artery involvement (bilateral in three of them) and none of them had arteriographic or clinical signs of vasculitis. Microscopic atherosclerosis was evident in three patients. Five of 6 patients required revascularizations with resulted in satisfactory outcome. Smoking, dyslipidemia and family history of coronary artery disease were the most frequent cardiovascular risk factors in these patients (Table 6).

Table 6. Diagnostic procedures for heart-related pain in inflammatory bowel disease

A. Non-invasive		B. Invasive	
→ family history		→ transeophageal ultrasound	
→ physical examination		→ coronary angiography	
→ electrocardiogram		→ pericardial paracentesis	
→ echocardiogram		→ colonoscopy	
→ thalium test		→ barium enema	
→ plethysmography		(when fistula is suspected)	
→ blood examination for			
CK MB and troponine test			
→ blood cultures			

Prophylaxis with low-molecular weight heparin, warfarin and venacaval interruption (Greenfield filter) may be of help in selected cases¹⁰⁵. IBD does not seem to be a strong predisposing factor for cerebral infarction.

Left ventricular thrombus with normal left ventricular function¹⁰⁶ and right atrium thrombus due to endocardium damage and infection from a catheter tip activating coagulation system were reported in UC¹⁰⁷. In CD one case of right atrial abscess¹⁰⁸ and one case of superior vena cava thrombosis¹⁰⁹ due to malpositioned catheter tips have also been reported. These two patients presented with impaired general condition and septic shock, until the exact diagnosis was made by trans-esophageal ultrasonography and surgery was carried out successfully in one of them.

10. CARDIAC AMYLOIDOSIS

Heart amyloidosis has never been reported in UC patients. Although systemic AA amyloidosis complicating CD has been found in 0.5 to 6% in America and Europe it seems relatively rare in Japan¹¹⁰. Cardiac involvement in IBD amyloidosis is associated with an extremely poor prognosis. Colchicine¹¹¹ may be beneficial in treating this type of secondary amyloidosis, in which transplantation has been proved disappointing. Sparkling intraventricular septum appearance in echocardiography and Congo red stain positive endocardium biopsies are diagnostic hallmarks for this severe complication.

11. HEART FAILURE AND HEART-RELATED SUDDEN DEATH IN IBD

Heart failure may be the end point of all the previously reviewed cases of heart involvement in IBD with the amyloidosis being the last and most severe (Tables 7, 8). Acute heart failure may result from acute myocardial infarction, myocarditis, tamponade and valve deterioration during an endocarditis infection. Chronic heart failure is usually caused by valve and myocardium involvement, although cases of heart muscle atrophy during TPN¹¹² and corticosteroid prolonged use²¹ have also been reported.

Heart failure and cardiogenic shock due to aortic valve insufficiency have been reported in UC patients^{92,113}. An 18-year-old patient died postoperatively due to acute heart failure in a series of 23 operated UC patients¹¹⁴ and 2 out of 1407 operated UC patients died of myocardial infarction¹¹⁵. Heart-related sudden death in UC was reported to be due to myocardial infarction²⁷ or heart mus-

Table 7. Reported heart involvement in ulcerative colitis

1. Endocardium	→ infective endocarditis (bacterial)
2. Myocardium	→ myocarditis (association with giant cell myocarditis) → hypertrophic cardiomyopathy → myocardial infarction
3. Pericardium	→ tamponade → AZA-induced pericarditis → pericardio-colonic fistula → myopericarditis or perimyocarditis → pleuropericarditis
4. Heart valves	→ endocarditis → aortic root involvement – aortic valve → mitral valve aneurysm
5. Heart cavities	→ left ventricular thrombus → right atrium thrombus
6. Coronary arteries	→ vasoconstriction theory → known risk factors (except -CHOL?) → The UC-Takayasu aortitis syndrome → The UC-HLA B27 related aortitis
7. Amyloidosis	never reported
8. Idiopathic	→ drug related cases (5-ASA, mesalazine)

cle atrophy³².

Low output cardiac failure may occur in CD patients receiving long-term TPN^{10,112}. Prolonged steroid use resulting in hypertension, high risk of infection and heart muscle atrophy increases the risk for congestive heart failure in CD patients of advanced age¹¹⁶ (Table 9). Post-operative fatal heart failure was reported in an 83-year-old patient in a series of 383 operated CD patients¹¹⁷.

Intra-operative acute cardiac arrest has also been reported¹¹⁸. Among 25 (2.6%) deaths in a cohort of 1000 CD patients 3 died from acute myocardial infarction and another 10 from various neoplasms¹¹⁹.

Post-mortem heart muscle biopsy in a young man with CD who died suddenly, probably of complicated ileum, showed remarkable atrophic change in the heart muscle¹²⁰. More than one operation, very young or very old, steroid dependency any excessive cardiovascular risk factors (family history, diabetes, smoking¹²¹, hypertension, hyperlipidemia) seem to be groups at high risk of fatal heart¹²²⁻¹²³ or cerebral infarction¹²⁴ complications (Table 10). Anti-TNF therapy for CD and growth hormone may be of help in cases of heart failure in which TNF- α levels

Table 8. Reported heart involvement in Crohn's disease

1. Endocardium	→ endocarditis (fungal bacterial) → subendocardial abscess (TNP catheter)
2. Myocardium	→ Se deficiency related cardiomyopathy → myopericarditis → heart muscle atrophy (steroid induced) → myocarditis with subcutaneous granulomas
3. Pericardium	→ pericarditis after colonic surgery → 5-ASA or mesalazine induced → CyA induced? → tamponade
4. Pleuropericarditis	
5. Heart valves	→ aortic heart valve insufficiency and regurgitation → fungal tricuspid valve endocarditis → endocarditis due to TNP catheters
6. Intracavitary involvement	→ right atrial abscess
7. Coronary arteries	→ vasoconstriction theory → known risk factors (except -CHOL?)
8. Amyloidosis (secondary)	
9. Idiopathic	→ drug related cases (corticosteroid)

Table 9. Reported drugs affecting heart in inflammatory bowel disease

1. Mesalazine (mesalazine)	→ myocarditis → perimyocarditis → pericarditis → sinus bradycardia → chest pain
2. 5-ASA	→ pericarditis → lupus like syndrome (including heart)
3. Se deficiency (due to TNP)	→ cardiomegaly
4. Azathioprine	→ pericarditis
5. Steroids	→ heart muscle atrophy → hypertension → hypokalemia → reversible hypertrophic cardiomyopathy
6. Cyclosporin	→ pericarditis sicca?
7. Anti-TNF? (benefit reported in heart failure)	
8. Nicotine?	

Table 10. Overall view of cardiovascular risk factors in inflammatory bowel disease

-
- family history
 - hypertension
 - hyperlipidemia
 - smoking
 - diabetes melitus
 - poor exercise
 - previous heart event
 - corticosteroids
 - bowel surgery
 - disease exacerbation
-

were reported to be high and insulin growth factors low. TNF- α blockage and growth hormone administration¹²⁵ may improve survival and quality of life in IBD patients with end stage heart failure.

CONCLUSIONS

Pericardium involvement may rarely be the presenting IBD symptom and seems to be the most frequent type of cardiovascular complication in IBD; its main causes being drugs, pericardio-colonic fistulas or unknown causes (idiopathic). In addition, in every IBD patient, especially those with Crohn's disease, under prolonged hospitalization or/and parenteral nutrition heart-related complications may occur. Thus, although heart involvement in IBD is rare, every clinician must be aware of these extraintestinal complications. These complications have so far been reported mainly as case reports and there is not insufficient supporting evidence to regard them as true disease extraintestinal manifestations.

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