CASE REPORT

Recurrent pericarditis as an extra-intestinal manifestation of ulcerative colitis in a 14-year-old girl

Ann J. M. Van Gils[1], Sandra van Gijlswijk[2], Jan A. J. M. Taminiau[1], Fabienne Marchau[1] & Els Van De Vijver[1]

[1]University Hospital Antwerp, Antwerp, Belgium
[2]Zuwe Hofpoort Hospital, Woerden, The Netherlands

Correspondence
Ann J. M. Van Gils, Wilrijkstraat 10, 2650 Edegem, Belgium.
Tel: Tel 0032 3 821 30 34;
E-mail: ann.vangils@uza.be

Funding Information
No sources of funding were declared for this study.

Received: 21 July 2017; Revised: 24 December 2017; Accepted: 14 January 2018

Clinical Case Reports **2017; 6(8): 1538-1542**

doi: 10.1002/ccr3.1562

Key Clinical Message

Pericarditis is a known complication of mesalazine in the treatment of ulcerative colitis. This case study illustrates that after diagnostic work-up, pericarditis should not always be attributed to the use of mesalazine. It may be the presentation of an extra-intestinal manifestation of ulcerative colitis. Restarting of mesalazine should be considered.

Keywords

pediatric, recurrent pericarditis, ulcerative Colitis.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD), characterized by relapsing periods of inflammation and exacerbations. Up to 30% of patients will develop an extra-intestinal manifestation [1]. In children, the most common symptoms are associated with the skin (nodal erythema), the eyes (uveitis), the hepatobiliary tract (primary sclerosing cholangitis), and the joints (arthritis) [2]. Pericarditis is a rare complication in UC and has been described both as a side effect of therapy and as an extra-intestinal manifestation of UC [3, 4]. Pericarditis should be suspected in patients with UC complaining of chest pain or palpitations.

Case Report

We here describe a case of UC-associated recurrent pericarditis in a 14-year-old female patient. The girl was diagnosed elsewhere with pancolitis/UC with symptoms of bloody diarrhea and shoulder pain (Pediatric Ulcerative Colitis Activity Index, PUCAI = 50). Induction treatment with methylprednisolone (32 mg daily, orally) and mesalazine (2 g bidaily, orally and 1 g at night, rectally) was initiated. Methylprednisolone was gradually tapered and stopped while mesalazine treatment was continued (PUCAI = 0). Two months later, she was referred to our outpatient clinic. She presented with weight loss, bloody stools, persistent pain on the chest, and palpitations. The physical examination was normal, except for a tender but soft abdomen and a striking bouncing pulse. One week before, she suffered from a viral upper airway infection. Family health records revealed a history of myasthenia gravis and diabetes mellitus type 1 with the patient's father and UC with her uncle.

Laboratory tests showed the signs of inflammation with an increased erythrocyte sedimentation rate (ESR; 107 mm/h), C-reactive protein (CRP; 18 mg/dL), and mild anemia (Hb 9.4 g/dL). Cardiac examination revealed a normal sinus rhythm of 105 beats/min with flattened T-tops on electrocardiogram (ECG; Fig. 1). Cardiac ultrasound displayed a significant amount of pericardial fluid (Fig. 2). The pericarditis was associated with an exacerbation of UC (PUCAI = 35), and the patient was admitted to the hospital. Methylprednisolone treatment was initiated at 1 mg/kg/day. Additional examinations were performed in order to determine the etiology of the pericarditis. Serological investigations (cytomegalovirus, Epstein–Barr virus, influenza A/B virus, coxsackievirus, *Borrelia burgdorferi*) and cultures of blood, urine, sputum,

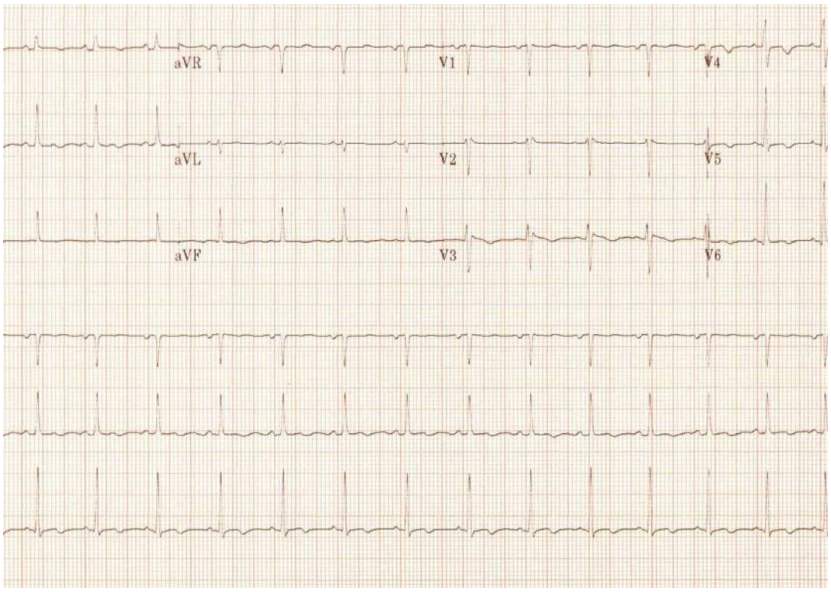

Figure 1. ECG showing normal sinus rhythm with flattened T-tops.

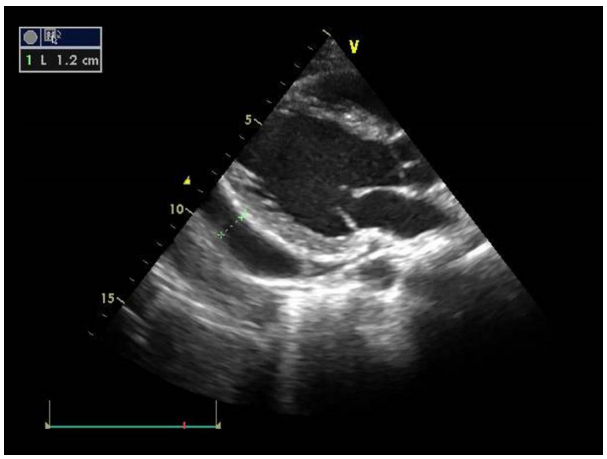

Figure 2. Cardiac ultrasound showing concentric pericardial fluid.

and throat were all negative. The autoimmune tests (antinuclear, anti-cytoplasm, and autoantibodies) were also negative, except for anti-neutrophilic cytoplasm antibodies (positive, 1/1280) and proteinase 3 (6 U/mL). Mesalazine treatment was suspended. Within 24 h after the initiation of the methylprednisolone treatment, the patient's chest pain improved and vital parameters remained stable. Cardiac ultrasound normalized within 1 week and ESR and CRP values returned to normal 2 weeks later. Subsequently, methylprednisolone therapy was gradually tapered and UC maintenance regimen with azathioprine (50 mg daily orally raised 2 weeks later to 125 mg daily, orally) was started.

Four months later, 3 weeks after the termination of the methylprednisolone treatment, the patient presented again with pain on the left side of the chest and shoulder. Again, this was preceded by a viral infection (fever, rhinitis, and coughing). ECG and cardiac ultrasound confirmed the recurrence of the pericarditis. No signs of active UC (PUCAI 0) were observed, which was confirmed by gastroduodenal- and ileocolonoscopy with biopsies. No infectious cause was found. A low-dose regimen of methylprednisolone (0.5 mg/kg/day) was restarted as therapy. The pain resolved after 5 days, and cardiac ultrasound and inflammatory parameters normalized within 1 week. Sulfasalazine was initiated as maintenance therapy of UC. Colchicine (0.5 g bidaily, orally) was added to the treatment to prevent the recurrence of the pericarditis. After gradually tapering the methylprednisolone dose, no relapse of the pericarditis was observed in the following 3 years of treatment, despite having a few viral infections. The therapy was overall well tolerated.

Discussion

We here present a case of a 14-year-old girl with UC-associated recurrent pericarditis, a rare but important extra-intestinal manifestation of the disease. To date, several cases of acute pericarditis associated with IBD in adults are reported. These reports either are true extra-intestinal manifestations of IBD or are related to the side effects of treatment with mesalazine. The prevalence of acute pericarditis as extra-intestinal manifestation in adult

Table 1. Summary of main findings about IBD related pericarditis in children

First author (Year of publication)	Population (age and sex)	IBD type	Diagnosis	IBD maintenance treatment	Etiology	Pericarditis therapy	Recurrence/info
Mukherjee et al. 2013 [6]	12 years girl	UC	Pericarditis with effusion	Mesalazine	Mesalazine	Stop mesalazine Pericardiocentesis prednisolone azathioprine	/
Atay et al. 2008 [7]	12 years boy	UC	Pericarditis with effusion	Mesalazine	Mesalazine	Stop mesalazine methotrexate	/
Raatikka et al. 2003 [8]	6 years girl	UC	Pericarditis, pleuritic	Mesalazine	Mesalazine	Stop mesalazine	5 × recurrence (mesalazine induced)
	15 years girl	UC	Pericarditis, pleuropneumonia Noonan syndrome, erythema nodosum	?	?	?	6 × recurrence
Sentongo et al. 1998[9]	16 years boy	UC	Pericarditis, pneumonia	Mesalazine	Mesalazine	Stop mesalazine prednisolone	Recurrence after start sulfasalzine
Kaiser et al. 1997 [10]	9 years girl	UC	Pericarditis with effusion	Mesalazine prednisolone	Mesalazine	Stop mesalazine	Symptoms after raising mesalazine dose
Granot et al. 1988 [11]	10 years boy	UC	Pericarditis with effusion	5-aminosalicylate prednisolone	5-aminosalicylate		
Frid et al. 1986 [12]	11 years boy	CD	Myocarditis	?	Extra-intestinal manifestation	Prednisolone	Pericarditis before diagnosis of CD
	adolescent boy	IBD	Myocarditis	?	Extra-intestinal manifestation	prednisolone	/
Levin et al. 1979 [13]	12 years girl	UC	Pericarditis	/	Extra-intestinal manifestation	Prednisolon Total colectomy	>2 recurrences
Mowat et al. 1974 [14]	15 years boy	UC	Myopericarditis	Prednisolone Sulfasalazine	Extra-intestinal manifestation	Prednisolone	5 × recurrence
Dipasquale et al. 2017 [15]	14 years boy	UC	Pericarditis	Infliximab	Infliximab	Stop infliximab	/

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

UC is 0.23% [5]. Pericarditis in pediatric IBD patients is rarely reported. So far, we could only identify 12 cases, of which seven were medication induced and four cases showed pericarditis as an extra-intestinal manifestation of IBD (one unknown case; Table 1) [6–15].

There are many known etiologies for pericarditis: infectious, drug related, systemic disease related, or idiopathic [16]. Most cases in developed countries are idiopathic or presumed viral [16]. In our patient, extensive tests (serology and cultures of blood, urine, sputum, and throat) did not reveal an underlying infectious cause in either of the times the patient was admitted.

Taking the medical history of the patient into account, including the UC maintenance treatment with mesalazine, a medication-induced pericarditis should be considered. Although pericarditis is a known side effect of the drug, it usually occurs within a few weeks after the treatment induction unless treatment was combined with methylprednisolone. The latter could delay the onset of the clinical manifestation of pericarditis. Therefore, the primary presentation of pericarditis in this patient could be induced by mesalazine. The same was true for association with a systemic disorder such as UC, by the presence of a flare-up of UC.

The second manifestation of pericarditis occurred 3 weeks after the prednisolone treatment was stopped, but as the patient did not receive mesalazine for a period of 4 months, a recurrent mesalazine-induced pericarditis was considered highly unlikely. Although sulfasalazine belongs to the same group of 5 aminosalicylates (5-ASA) as mesalazine, a treatment with sulfasalazine was added to the azathioprine maintenance treatment, to control the further manifestation of UC and to prevent future complications [17]. An immediate relapse of pericarditis could be expected within the hours after the reintroduction of 5-ASA [10]. The patient was closely monitored during the initiation of sulfasalazine treatment as a 5-ASA-associated fatal pericarditis has been reported [18]. To date, 3 years after the treatment was restarted with 5-ASA, no adverse effects were observed.

Acute pericarditis may be related to systemic disorders such as IBD [19]. At the first presentation, the patient suffered from an exacerbation of UC. Clinical, endoscopic, or histopathologic signs of exacerbation of UC however did not accompany the second presentation. This corresponds with the previous reports, where the manifestation of pericarditis was not correlated to UC disease activity [1, 5, 11, 12, 14, 15].

Idiopathic recurrent acute pericarditis (IRAP) is defined by a recurrent episode of pericarditis after a symptom-free interval of at least 4–6 weeks [16]. It occurs in 15–30% of patients with acute pericarditis [20]. The etiology is unknown, and it is suspected to be autoimmune or autoinflammatory mediated [21, 22] by the presence of pro-inflammatory cytokines in the pericardial fluid or anti-inflammatory antibodies in the blood. In the current case, only the presence of antinuclear antibody detection could be linked to IRAP as an underlying cause of the presented recurrent pericarditis (43.3% of the cases) although a genetic predisposition could not be excluded based on the available information (10% of the cases) [21].

Little is known about the specific treatment of acute pericarditis in pediatric patients. Therapy is mainly based on the treatment of acute pericarditis in adults. It is based on the relief of symptoms, the decreasing inflammation, and the prevention of recurrence [22]. Treatment options are aspirin/non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, colchicine, and immunosuppressive drugs. NSAIDs are contraindicated in systemic inflammatory diseases [22], and case reports have demonstrated NSAIDs as a causative factor of a flare-up of IBD [23]. In addition, NSAIDs monotherapy proved insufficient to treat pediatric pericarditis [8]. Therefore, acute pericarditis in IBD-patients are treated with corticosteroids as a first-line therapy. Caution should be taken as these could potentially result in a reduction in infectious agent clearance, favoring the occurrence of recurrences [22]. Low-dose corticosteroids seem to be superior to high dose for treatment failure, recurrences, hospitalization, and adverse effects. It is advised to use low dose prednisone (0.25–0.5 mg/kg/day) until the resolution of symptoms and normalization of CRP, with gradually tapering (2.5 mg/day every 2–4 weeks) [22, 24]. Treatment with corticosteroids should be used in combination with colchicine. The latter reduces symptoms and prevents recurrence [22]. Colchicine (0.5 mg once a day if $\leq$5 years or 1.0–1.5 mg divided in 2–3 doses a day if >5 years) [24, 25] can prevent the recurrences up to 50% of cases [16, 25] without a significant risk of adverse events or intolerance [24, 26]. Finally, immunosuppressive drugs, such as azathioprine, anakinra, and cyclophosphamide, can be used in refractory, noninfectious cases requiring high-dose corticosteroids [22, 24].

Conclusion

The reported case showed an unusual presentation of recurrent acute pericarditis, seen as an extra-intestinal manifestation in a pediatric patient with UC. At first presentation, the pericarditis was thought to be drug-induced. After the second episode, the pericarditis was classified as an extra-intestinal manifestation of UC, by the absence of 5-ASA or any other causative factor. Anti-inflammatory therapy was optimized, with the reintroduction of 5-ASA. This prevented the recurrence of the pericarditis and UC exacerbation.

Conflict of Interest

AJM Van Gils, S van Gijlswijk, J.A.J.M. Taminiau, F. Marchau, and E. Van de Vijver declare that they have no conflict of interest.

Authorship

AJMVG: searched the literature and approved the final version. SG: searched the literature and performed critical revision. JAJMT and FM: performed critical revision. EVDV: performed critical revision and approved the manuscript.

References

1. Greenstein, A. J., H. D. Janowitz, and D. B. Sachar. 1976. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. Medicine (Baltimore) 55:401-412.
2. Hyams, J. S. 1994. Extraintestinal manifestations of inflammatory bowel disease in children. J. Pediatr. Gastroenterol. Nutr. 19:7-21.
3. Rellecke, P., and B. E. Strauer. 2006. Chronic inflammatory bowel disease in children and cardiovascular complications. Med. Klin. 101:56-60.
4. Tunc, B., L. Fjlik, A. Ulker, and E. Parlak. 2005. Two cases of pericarditis associated with inflammatory bowel disease. Acta Medica (Hradec Kralove) 48:43-44.
5. Park, E. H., B. J. Kim, J. K. Huh, E. H. Jeong, S. H. Lee, K. B. Bang, et al. 2012. Recurrent mesalazine-induced myopericarditis in a patient with ulcerative colitis. J. Cardiovasc. Ultrasound 20:154-156.
6. Mukherjee, N., N. Pandya, B. Bhaduri, and K. Bala. 2013. Chest pain in a 12-year old girl with ulcerative colitis after therapy with mesalazine. BMJ Case Rep. 2013: bcr2012008300.
7. Atay, O., K. Radhakrishnan, J. Arruda, and R. Wyllie. 2008. Severe chest pain in a pediatric ulcerative colitis patient after 5-aminosalicylic acid therapy. World J. Gastroenterol. 14:4400-4402.
8. Raatikka, M., P. M. Pelkonen, K. Karjalainen, and E. V. Jokinen. 2003. Recurrent pericarditis in children and adolescents. Report of 15 cases. J. Am. Coll. Cardiol. 42:759-764.
9. Sentongo, T. A. S., and D. A. Piccoli. 1998. Recurrent pericarditis due to mesalamine hypersensitivity: a pediatric case report and review of literature. J. Pediatr. Gastroenterol. Nutr. 27:344-347.
10. Kaiser, G. C., D. E. Milov, N. A. Erhart, and D. J. Bailey. 1997. Massive pericardial effusion in a child following the administrator of mesalamine. J. Pediatr. Gastroenterol. Nutr. 25:435-438.
11. Granot, M., M. Rottem, and A. J. J. T. Rein. 1988. Carditis complicating inflammatory bowel disease in children. Case-report and review of the literature. Eur. J. Pediatr. 148:203-205.
12. Frid, C., B. Bjarke, and M. Eriksson. 1986. Myocarditis in children with inflammatory bowel disease. J. Pediatr. Gastroenterol. Nutr. 5:964-965.
13. Levin, E. N., D. S. Hirschfeld, and R. A. Hersch. 1979. Pericarditis in association with ulcerative colitis. West. J. Med. 130:369-370.
14. Mowat, N. A. G., P. N. Bennet, J. K. Finlayson, P. W. Brunt, and W. M. Lancaster. 1974. Myopericarditis complicating ulcerative colitis. Br. Heart. J. 36:724-727.
15. Dipasquale, V., S. M. C. Gramaglia, M. A. Catena, and C. Romano. 2018. Pericarditis during infliximab therapy in paediatric ulcerative colitis. J. Clin. Pharm. Ther. 43:107-109.
16. Fardman, A., P. Charron, M. Imazio, and Y. Adler. 2016. European guidelines on pericardial diseases: a focused review of novel aspects. Curr. Cardiol. Rep. 18:46.
17. Bezzio, C., S. Festa, S. Saibeni, and C. Papi. 2017. Chemoprevention of colorectal cancer in ulcerative colitis: digging deep in current evidence. Expert Rev. Gastroenterol. Hepatol. 11:339-347.
18. Kristensen, K. S., A. Høegholm, L. Bohr, and S. Friis. 1990. Fatal myocarditis associated with mesalazine. Lancet 335:605.
19. Bernstein, C. N., A. Wajda, and J. F. Blanchard. 2005. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology 129:827-836.
20. Fowler, N. O. 1990. Recurrent pericarditis. Cardiol. Clin. 8:621-626.
21. Maestroni, S., P. R. Di Corato, D. Cumetti, D. B. Chiara, S. Ghidoni, L. Prisacaru, et al. 2012. Recurrent pericarditis: autoimmune or autoinflammatory? Autoimmun. Rev. 12:60-65.
22. Doctor, N. S., A. B. Shah, N. Coplan, and I. Kronzon. 2017. Acute pericarditis. Prog Cardiovasc Dis 59:349-359.
23. Cappell, M. S., and A. Turkieh. 2008. Chronic pericarditis and pericardial tamponade associated with ulcerative colitis. Dig. Dis. Sci. 53:149-154.
24. Up to date, M. Imazio. Treatment of acute pericarditis. UpToDate. Available via www.uptodate.com. (Accessed June 2017).
25. Adler, Y., P. Charron, M. Imazio, L. Badano, G. Barón-Esquivias, J. Bogaert, et al. 2015. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). Eur. Heart J. 36: 2921-2964.
26. Alabed, S., G. Pérez-Gaxiola, and A. Burls. 2016. Colchicine for children with pericarditis: systematic review of clinical studies. Arch. Dis. Child. 101:953-956.