

Mesalamine-induced myopericarditis in children: a case report and a short revision of the literature

Marco Lecis¹, Francesca Stefanelli¹, Federica Montanari², Anna Rita Di Biase², Laura Lucaccioni², Lorenzo Iughetti^{1,2}

¹Post Graduate School of Pediatrics, Department of Medical and Surgical Sciences for Mother, Children and Adults, University of Modena and Reggio Emilia, Modena; ²Pediatrics Unit, Department of Mother & Child, University Hospital, Modena, Italy

Abstract. Mesalamine has a central role in the treatment of inflammatory bowel disease (IBD). Myocarditis and/or pericarditis are rare and severe side effects of mesalamine-containing drugs. We describe the case of a 14 years old boy, developing myopericarditis two weeks after starting mesalamine treatment for ulcerative colitis (UC). The adverse effect had a massive impact on the left ventricular function and required immediate intervention. Once identified as possible causative agent, mesalamine was discontinued with subsequent improvement of the clinical symptoms and laboratory findings. No recurrency nor sequelae were detected at the cardiological follow up. Mesalamine is a widely used drug for pediatric IBD treatment, although its effect on heart tissues is a rare but potentially fatal adverse reaction. At the time of presentation, in April 2021, 10 pediatric cases were reported in literature (2 children and 8 adolescents). Of them, 60% were treated with mesalamine for UC and 40% for Chron's disease (CD). Chest pain and fever were the most common symptoms at presentation (100% and 50% respectively), cough and fatigue were less represented. None of the patients developed sequelae at follow up. In patients treated with mesalamine early recognition of side effects, drug discontinuation and accurate therapy are crucial to prevent progression of the inflammation and to avoid adverse cardiovascular outcomes. (www.actabiomedica.it)

Key words: mesalamine, myopericarditis, inflammatory bowel disease, Crohn's disease, ulcerative colitis

Introduction

Mesalamine (5-aminosalicylic acid or 5-ASA) is considered the first-line treatment for inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC). Its mechanism of action is not completely understood, but the drug seems to have both anti-inflammatory and immunosuppressive properties. The most common adverse reactions are gastrointestinal discomfort, headache, skin rash and drug hypersensitivity (1).

Myocarditis, pericarditis and myopericarditis are potentially lethal adverse effects of mesalamine, rarely reported in literature (2-24) and often reversible once the drug is stopped.

Diagnosis of cardiological adverse effects is based on clinical suspicion (2-24). Physical examination is generally remarkable for tachycardia and, in some cases, for pericardial rub. Laboratory findings show elevated white blood cell count, inflammatory markers C-reactive protein (CRP), erythro-sedimentation rate (ESR) and cardiac troponin (2-24). Electrocardiogram (EKG) usually reveals nonspecific ST segment changes or T-wave changes, which could be flat, depressed or elevated T-waves, this latter being more common. Morpho-functional investigations as echocardiogram and cardiac-magnetic resonance (MRI) are often performed, showing variable degrees of left ventricular systolic dysfunction, in addition to pericardial effusion, with or without tamponade effect (2-24).

Here we report the case of a 14 years old boy, developing myopericarditis two weeks after starting mesalamine therapy for UC. This case highlights the importance of early recognition of adverse effects, because drug discontinuation and accurate cardiac therapy are crucial to prevent progression of the inflammation and avoid adverse cardiovascular outcomes.

Case report

A 14 years old male was referred to the hospital and suspected for UC after a 2 months history of intermittent abdominal pain, rectal bleeding, loose and bloody stools. Laboratory findings showed increased inflammatory markers: increased erythrocyte sedimentation rate (ESR 26 mm/h, normal value < 15 mm/h), increased C-reactive protein (CRP 1.6 mg/dl, normal value <0,5 mg/dl), elevated fecal calprotectin (179 mcg/g, normal value < 50 mcg/g), and microcytic iron-deficiency anemia (hemoglobin 10,8 g/dl, blood iron 43 µg/dl, ferritin 11 ng/ml, transferrin 324 mg/dl; normal values hemoglobin 12-15,2 g/dl, blood iron 53-119 µg/dl, ferritin 15-140 ng/ml, transferrin 215-380 mg/dl). Serological markers for IBD (Antineutrophil cytoplasmic antibodies-ANCA and Anti-Saccharomyces Cerevisiae antibodies-ASCA) were negative, as well as

radio-allergo-sorbent test (RAST) for food allergies, fecal bacterial culture, fecal viruses and fecal search for parasites. Intestinal ultrasound showed an increased wall thickness of the sigmoid and distal descending colon, as in acute inflammation, and no thickening of the last intestinal loops. Esophagogastroduodenoscopy and colonoscopy showed an active ulcerative pancolitis and the boy started mesalamine therapy at 800 mgs three times a day.

Fifteen days after starting the treatment, the boy was admitted to the emergency department with chest pain and dry-cough. Laboratory tests revealed an elevated peak concentration of cardiac Troponin I 8.140 µg/L (normal value <7µg/L), an elevated CRP concentration 19.1 mg/dL, ESR of 67 mm/h, hemoglobin level of 10.6 g/dL, and leukocyte count of 12.3 K/µL. Initial 12-lead EKG revealed sinus tachycardia with borderline T wave abnormalities in precordial leads (Figure 1).

The echocardiogram showed slightly dilated left ventricle, hypokinesia of the infero-posterolateral wall, reduced overall kinetics, an estimated ejection fraction of 40%, mild mitral insufficiency, thickening of the pericardial leaflets with a double track appearance in the postero-inferior basal area, minimal pericardial detachment at the level of the right atrium. Cardiac MRI showed images consistent with acute myocarditis (Figure 2).

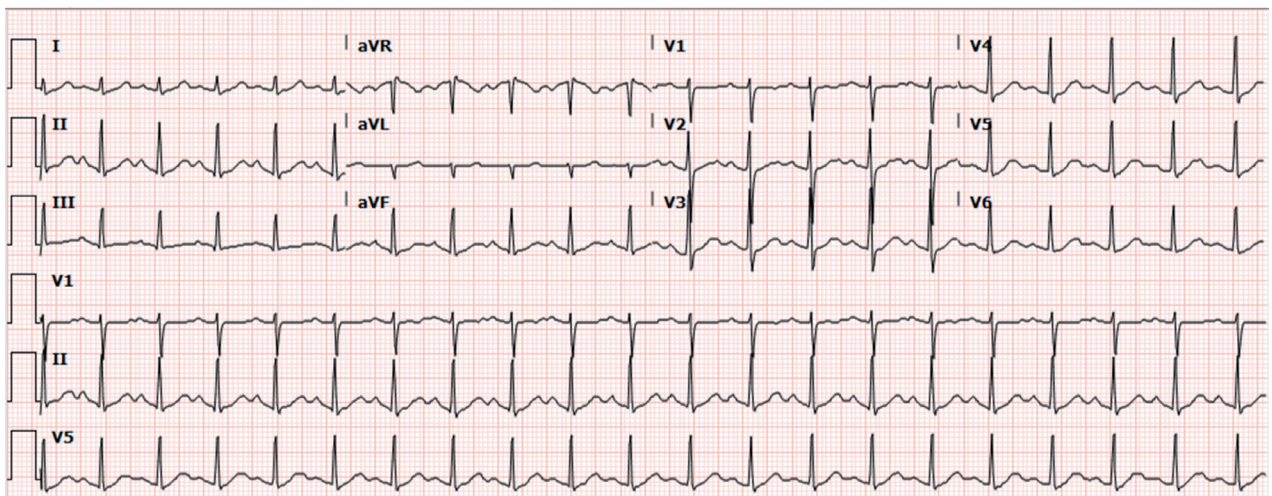


Figure 1. Electrocardiogram: twelve-lead electrocardiogram showing Sinus Tachycardia, with borderline T wave abnormalities in precordial leads.

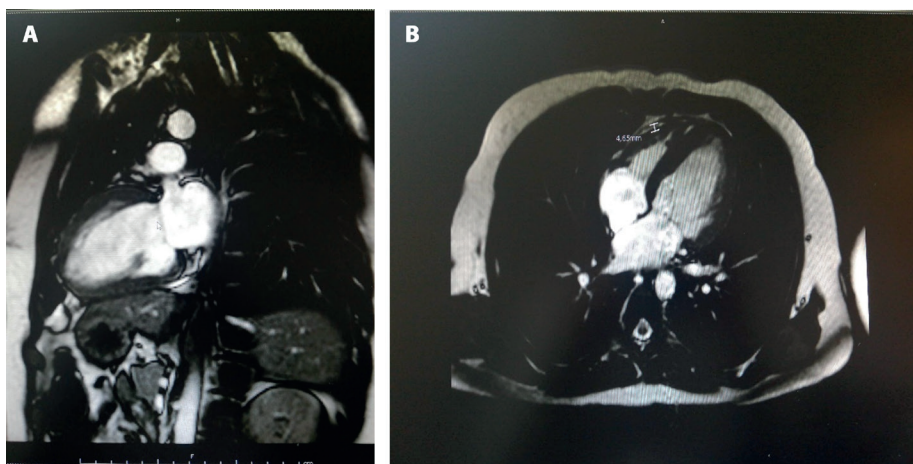


Figure 2. Cardiac MRI: images showing sagittal (a) and transverse plane (b). Modest dilation of the left ventricle and thickening of the pericardial leaflets can be observed.

Serological tests, including IgM and IgG antibodies for cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Adenovirus, Parvovirus B19 and Enterovirus, excluded an acute infection. Because of the possible iatrogenic etiology of myopericarditis, mesalamine was discontinued and corticosteroid therapy was started. Due to the left ventricular dysfunction, betablocker and ACE-inhibitor therapy was also set.

Seven days after the presentation, we observed a clear improvement of the cardiological findings: chest pain resolved, lower serum troponin I and echocardiogram showed no residual morpho-functional alterations or dyskinesia (ejection fraction of 69%). The boy was discharged, corticosteroid therapy was gradually decreased, azathioprine therapy was started, and the patient remained asymptomatic at the subsequent outpatient routine checks. Follow-up was cadenced monthly in the first three months, bimonthly in the next six months, and quarterly thereafter. The evaluation included blood tests, cardiac and inflammatory markers, EKG and echocardiography.

Discussion

Mesalamine was introduced in late 1990s as a formulation containing 5-ASA alone, with less adverse effects compared to sulfasalazine (5-ASA + sulfapyridine) and it is worldwide considered the mainstay of therapy for mild forms of IBD, mainly UC.

Mesalamine-induced myopericarditis is a rare, but potentially lethal, side effect of 5-ASA containing medications for IBD (1-24). Our patient developed cardiac symptoms two weeks after starting mesalamine treatment. The adverse effect impacted dramatically the left ventricular function, requiring both beta-blocker and ACE-inhibitor treatment and a subsequent cardiac morpho-functional follow-up.

Cardiac hypersensitivity to 5-ASA therapy has been reported in a small number of cases. It was first suggested in 1989, when a possible myocarditis was proposed (22); in 1990 the first death from myocarditis associated with mesalamine was reported (19).

The exact mechanism of mesalamine-induced myo-pericarditis is not well understood. Possible explanations include a direct toxic effect of the drug on cardiac tissues, an IgE mediated allergic reaction, a cell-mediated hypersensitivity reaction and a humoral antibody response (12, 15, 20, 22). Considering that 5-ASA intake can induce other than cardiac hypersensitive reactions involving skin, joints, eyes and lungs, an autoimmune mechanism rather than a direct toxicity seems to be the most likely cause. The improvement obtained after the drug withdrawal and the recurrence of symptoms after its re-administration also support the hypothesis (15). Kaiser et al. (12) excluded a direct toxic effect of mesalamine on the pericardium through pathological examination of pericardial tissue revealing no evidence of cell death or necrosis.

Since the lack of peripheral eosinophilia and the absence of an eosinophilic infiltrate within the pericardium, an Ig-E mediated allergic reaction was also excluded (12). A humoral antibody response, possibly with cross-reactive anti-mesalamine antibodies, seems one of the most likely mechanisms. In fact, sulfasalazine has been associated with the development of a drug-induced lupus syndrome (12). Patients with mesalamine-induced myo-pericarditis reported in literature did not meet the criteria for a drug-induced lupus syndrome, but could still have had a humoral antibody response to mesalamine that cross-reacted with cardiac tissues. Furthermore, a delayed type IV hypersensitivity reaction to 5-ASA could be a possible mechanism of the adverse effect. Jens et al. (6) carried out serial lymphocyte stimulation test on the serum of a 22-year-old woman in whom pericardial effusion occurred after initiation of mesalamine therapy. They observed that the patient's lymphocyte had an increased proliferation index when compared to controls, who showed no stimulation by the presence of 5-ASA. The initial delayed onset of symptoms followed by their immediate re-occurrence after re-exposure is consistent with hypersensitivity (6). Another possible hypothesis is the inhibition of cyclooxygenase-1 (COX1) by the drug, which may accelerate the metabolism of arachidonic acid toward lipoxygenase products such as, leukotrienes (18). This overproduction of leukotriene metabolites may induce pro-inflammatory signaling, initiating the hypersensitive reaction by liberating eosinophil-stimulating cytokines, and will lead to the myocarditis (18). However, further studies are still needed to explain the exact mechanisms underlying the development of mesalamine-induced myo-pericarditis.

Patients with myo-pericarditis caused by 5-ASA hypersensitivity typically experience onset of symptoms within 2-4 weeks after starting therapy (2-24). Cases that started later where the ones receiving high dose of steroids or immuno-modulating drugs (2,5,8,12)

Diagnosis is clinically suspected, noting classical features of fever, chest pain and dyspnea, whereas fatigue and weakness are less reported (2-24). Physical exam is generally remarkable for tachycardia and, in some cases, for pericardial rub. Laboratory findings of elevated white cell count, inflammatory markers (CRP

and ESR) and cardiac troponin along with an altered EKG strongly support the diagnostic hypothesis (4,9). Paschalis et al (7) also proposed plasma N-terminal pro-B-type natriuretic peptide (BNP) as an important marker both in the initial diagnosis and in the follow-up recovery of left ventricular structure and function. EKG usually reveals nonspecific ST segment changes or T-wave changes, which could be flat, depressed or elevated T-waves, with the latter being more common. Morpho-functional investigations as echocardiogram and cardiac-MRI are often performed, showing variable degrees of left ventricular systolic dysfunction, in addition to pericardial effusion, with or without tamponade effect (20,21). We identified in literature 10 pediatric patients (Table 1) with mesalamine-induced myopericarditis, aged between 9 and 18 years.

Overall, all of the 10 cases underwent drug discontinuation, with prompt resolution of symptoms within 48-72 hours. Four needed other pharmacological intervention: 3 were treated with prednisone and 1 with prednisolone [8, 9, 13 and 11]. None of the patients whose follow-up was reported, developed cardiovascular sequelae after drug discontinuation and pharmacological treatment.

Compared to our clinical case, the age of onset is slightly higher (mean age 15 years), with only two reports of younger patients (12,13). The interval between the initiation of therapy and the onset of symptoms, which in our case was 15 days, was generally 2-4 weeks, depending on whether or not cortisone therapy was used. Only Paschalis et al. (7) reported the use of carvedilol and ramipril in a 16 years old boy developing a myo-pericarditis, with a mild global left ventricle systolic dysfunction, two weeks after the onset of mesalamine therapy for CD. As seen in our case, the cardiac systolic function normalized after discontinuation of the drug and no sequelae were shown at follow-up.

The occurrence of pericarditis with IBD has been reported and it may occur as an extra intestinal manifestation of both UC and CD (1). The fact that mesalamine may also induce cardiac toxicity makes the differential diagnosis challenging. The chronological relation between the onset of clinical features and of 5-ASA therapy, as well as the complete resolution after its discontinuation, can help ruling out the cause.

Table 1. Summarizes the description of the clinical cases reported in the literature until April 2021.

| Age and sex | Disease | Main symptoms | Notable laboratory and imaging findings | Therapy and prognosis | Reference |
|-------------|------------------------------------|--|---|--|--------------------------|
| 9 years, F | U.C. Pericarditis | Vague retrosternal discomfort, occasional cough | Mild leukocytosis (white blood cells count of 9.700/ml, with a differential of 34% segmented neutrophils), augmented ESR (85 mm/h); Echocardiogram: pericardial effusion (2 cm) | Pericardiocentesis Discharged 3 days after surgery | Kaiser et al. (12) |
| 12 years, M | U.C. Coronary ectasia, myocarditis | Chest pain | EKG: non-specific ST-T changes, T-wave inversion in the lateral leads; Echocardiogram: low-normal to mildly depressed left ventricular systolic function with mildly prominent left main coronary artery and left anterior descending artery | Resolved within 24-36 hours after discontinuing mesalamine | Atay et al. (13) |
| 16 years, M | U.C. Coronary ectasia, myocarditis | Chest pain | EKG: nonspecific ST segment changes; Echocardiogram: mildly decreased left ventricular systolic function, with mild to moderate left ventricular dilation and coronary ectasia | Resolved few days after discontinuing mesalamine | Perez-Colon et al. (2) |
| 18 years, M | C.D. Myo-pericarditis | Pleuritic chest pain | Increased troponin I (1 ng/ml) and CK-MB (5.3 ng/ml); EKG: nonspecific ST segment changes; Echocardiogram: mildly decreased left ventricular systolic function | Resolved within 48-72 hours after discontinuing mesalamine | Nair and Cross (5) |
| 16 years, M | U.C. Pericarditis | Shortness of breath, pleuritic chest pain, myalgia | Echocardiogram: pericardial effusion | Resolved within 48 hours after discontinuing mesalamine, Recurrence after a trial with low doses of sulfasalazine | Sentongo and Piccoli (9) |
| 17 years, M | U.C. Pericarditis | Chest pain, fever | EKG: ST elevation in limb and precordial leads | Resolved within 48 hours after discontinuing mesalamine Recurrence after a trial with low doses of 5-ASA | Ishikawa et al. (11) |
| 18 years, F | U.C. Myo-pericarditis | Pleuritic chest pain | Increased troponin (1.2 ng/ml) and ESR (68 mm/h); Echocardiogram: pericardial effusion; Cardiac MRI: pericardial effusion; | Resolved within 48 hours after discontinuing mesalamine | Taha et al. (3) |

continued

Table 1. Summarizes the description of the clinical cases reported in the literature until April 2021. (*continued*)

| Age and sex | Disease | Main symptoms | Notable laboratory and imaging findings | Therapy and prognosis | Reference |
|-------------|---------------------------------|--|--|---|--------------------------|
| 18 years, M | C.D. Myo-pericarditis | Chest pain | Increased troponin (1.1 ng/ml); EKG: ST elevation | Resolved within 48 hours after discontinuing mesalamine | Sorletto et al. (8) |
| 16 years, M | C.D. Pleuro- pericarditis | Fever, non productive cough, left shoulder pain chest pain | Increased ESR (95 mm/h) and CRP (13.7 mg/dl) Echocardiogram: pericardial effusion and global hypokinesia of the left ventricle Chest radiography: left pleural effusion Drug lymphocyte stimulation tests for mesalamine: positive | Resolved within 1 week after discontinuing mesalamine | Kiyomatsu et al. (10) |
| 16 years, M | C.D. Myo-pericarditis | Fever, chest pain, dyspnea | Increased troponin (6.1 ng/ mL), CRP (24 md/dl) and BNP (2231 pg/mL). Echocardiogram: mild global left ventricle systolic dysfunction and a small posterior pericardial effusion Cardiac MRI: small effusion (11 mm) in the posterolateral and lateral walls and apex. | Carvedilol, Ramipril Resolved within 1 week after discontinuing mesalamine | Paschalis et al. (7) |

Treatment includes prompt cessation of the drug, supportive care measures and close monitoring for complete resolution of cardiovascular symptoms (20). However, some patients manifest an immediate reoccurrence of myo-pericarditis when unintentionally a 5-ASA-containing medication is re-started (6). If ventricular dysfunction is identified at diagnosis, cardiological supportive therapy is recommended including diuretics, beta-blockers, ACE-inhibitors or a combination of them (9), as in our case. Although none of the children in literature developed sequelae, monitoring the worsening of gastrointestinal manifestations once medication is stopped is recommended (20).

In conclusion, medical doctors caring for children treated with mesalamine have to be aware of this life-treating cardiac adverse effect. It is important to achieve prompt diagnosis and adequate treatment in a mesalamine-using child with IBD developing cardiac symptoms. Furthermore, patients and their care-givers should be educated regarding the cardiovascular side effects of 5-ASA and advised to seek urgent medical attention if cardiac symptoms

arise. Since most of the cases reported in literature had a favorable outcome after discontinuation of mesalamine therapy, and no long-term cardiac abnormalities were notified, early diagnosis and adequate treatment are fundamental.

Ethical Approval: Written consent for the publication of data and images was obtained from the parents of the patients.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contributions: ML and LI contributed to the conception and design. ML, LL, FS, FM and ARDB contributed to the acquisition and interpretation of data. LI revised and edited the manuscript. All the co-authors contributed to the interpretation of the data, provided critical comments and suggestions on the manuscript for important intellectual content, and all authors read the final version of the manuscript and approved it.

References

- Loftus EV Jr, Kane SV, Bjorkman D. Systematic review: short-term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. *Alimentary Pharmacology and Therapeutics*. 2004;19(2):179-89. doi: 10.1111/j.0269-2813.2004.01827.x.
- Perez-Colon E, Dadlani GH, Wilmot I, Miller M. Mesalamine-induced Myocarditis and coronary vasculitis in a pediatric ulcerative colitis patient: a case report. *Case Rep Pediatr*. 2011;2011:e524364. doi: 10.1155/2011/524364.
- Taha ME, Abdalla A, Al-Khafaji J, Malik S. Mesalamine-induced myopericarditis: a case report and literature review. 2019;10(1):59-62. doi: 10.14740/cr820.
- Waite RA, Malinowski JM. Possible mesalamine-induced pericarditis: case report and literature review. *Pharmacotherapy*. 2002;22(3):391-4. doi:10.1592/phco.22.5.391.33188.
- Nair AG, Cross RR. Mesalamine-induced myopericarditis in a paediatric patient with Crohn's disease. 2015;25(4):783-6. doi: 10.1017/S1047951114001048.
- Jenss H, Becker EW, Weber P. Pericardial effusion during treatment with 5-aminosalicylic acid in a patient with Crohn's disease. *Am J Gastroenterol*. 1990;85(3):332-3.
- Paschalis T, Paschalis M, Mandal Akj, Missouriis CG. Plasma N-terminal pro-B-type natriuretic peptide (BNP) in mesalazine-induced myopericarditis. *BMJ Case Rep* 2019;12(4):e229142. doi: 10.1136/bcr-2018-229142.
- Sorleto M, Dürrwald S, Wiemer M. Mesalazine-Induced Myopericarditis in a patient with a recent diagnosis of Crohn's disease: apropos of a case. *Case Rep Cardiol*. 2015;2015:e728310. doi: 10.1155/2015/728310.
- Sentongo TA, Piccoli DA. Recurrent pericarditis due to mesalamine hypersensitivity: a pediatric case report and review of the literature. *J Pediatr Gastroenterol Nutr*. 1998;27(3):344-7. doi: 10.1097/00005176-199809000-00015.
- Kiyomatsu H, Kawai K, Tanaka T et al. Mesalazine-induced pleuropericarditis in a patient with Crohn's disease. *Intern Med*. 2015;54(13):1605-8. doi: 10.2169/internalmedicine.54.4316.
- Ishikawa N, Imamura T, Nakajima K, et al. Acute pericarditis associated with 5-aminosalicylic acid (5-ASA) treatment for severe active ulcerative colitis. *Intern Med*. 2001;40(9):901-4. doi: 10.2169/internalmedicine.40.901.
- Kaiser GC, Milov DE, Erhart NA, Bailey DJ. Massive pericardial effusion in a child following the administration of mesalamine. *J Ped Gastroenterol Nutr* 1997; 25(4):435-8.
- Atay O, Radhakrishnan K, Arruda J, Wyllie R. Severe chest pain in a pediatric ulcerative colitis patient after 5-aminosalicylic acid therapy. *World J Gastroenterol*. 2008;14(27):4400-2. doi: 10.3748/wjg.14.44002008 21.
- Baker WL, Saulsberry WJ, Elliott K, Parker MW. Cardiac MRI-confirmed mesalamine-induced myocarditis. *BMJ Case Rep*. 2015; 2015:bcr2015210689. doi: 10.1136/bcr-2015-210689.
- Roczek M, Polak Ł, Zielińska M, Chiziński K. Myopericarditis in a patient with ulcerative colitis treated with mesalamine-Case report and review of the literature. *J Cardiol Cases*. 2014;10(3):104-107. doi: 10.1016/j.jccase.2014.05.013.
- Ibrahim A, Khalil C, Megaly M, Tawadros M, Mosleh W, Corbelli J. Mesalamine-induced myocarditis in a young athlete: can he run again? *Cureus*. 2019;11(1):e3978. doi: 10.7759/cureus.3978.
- Okoro KU, Roby MD, Bankole AA. Myocarditis secondary to mesalamine-induced cardiotoxicity in a patient with ulcerative colitis. *Case Rep Med*. 2018;2018:e9813893. doi: 10.1155/2018/9813893.
- Merceron O, Bailly C, Khalil A, et al. Mesalamine-induced myocarditis. *Cardiol Res Pract*. 2010;2010:e930190. doi: 10.4061/2010/930190.
- Kirstensen KS, Høegholm A, Bohr L, Friis S. Fatal myocarditis associated with mesalazine. *Lancet*. 1990;335(8689):605. doi: 10.1016/0140-6736(90)90387-k.
- Brown G. 5-Aminosalicylic acid-associated myocarditis and pericarditis: a narrative review. *Can J Hosp Pharm*. 2016;69(6):466-472.
- Fleming K, Ashcroft A, Alexakis C, Tzias D, Groves C, Poullis A. Proposed case of mesalazine-induced cardiomyopathy in severe ulcerative colitis. *World J Gastroenterol*. 2015;21(11):3376-9. doi: 10.3748/wjg.v21.i11.3376.
- Agnholt J, Sørensen HT, Rasmussen SN, Gøtzsche CO, Halkier P. Cardiac hypersensitivity to 5-aminosalicylic acid. *Lancet*. 1989;1(8647):1135. doi: 10.1016/s0140-6736(89)92407-0.
- Ali A, Kumaravel Kanagavelu AS, Rahimi A, et al. A Rare Case of mesalazine-induced acute myocarditis in a 19-yearold female with ulcerative colitis. *Cureus*. 2021;13(11):e20036. doi: 10.7759/cureus.20036.
- Shabtaie SA, Tan NY, Parikh RS, Papadakis KA. Concurrent Sweet's syndrome and myopericarditis following mesalamine therapy. *BMJ Case Rep*. 2018;2018:bcr2017223851. doi: 10.1136/bcr-2017-223851.

Correspondence:

Received: 31 July 2023

Accepted: 10 January 2024

Lorenzo Iughetti MD, PhD

Pediatrics Unit, Department of Medical and Surgical Sciences for Mother Children and Adults, University of Modena and Reggio Emilia

Via del Pozzo 71, Modena 41124, Italy

E-mail: iughetti.lorenzo@unimore.it