CLINICAL VIGNETTE

Mesalamine Induced Myocarditis in a 44-Year-Old Male

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A 44-year-old male with ulcerative colitis previously controlled without medication presented with worsening ulcerative colitis symptoms. He was initially started on mesalamine 4.8 gm orally daily. A month after starting mesalamine he developed sore throat and chest discomfort and presented to a local urgent care. The sore throat was present for three weeks, with chest pain noted earlier in the week described as midsternal chest tightness. Exam was unremarkable, however, EKG showed normal sinus rhythm with anterolateral and inferior lead T wave inversion (Figure 1). Labs noted elevated white cell count of 11.8 $x10^3$/uL and thrombocytosis with platelet count 521 $X10^3$/uL. Chemistries and BNP were normal. High sensitivity Troponin I was elevated at 42 ng/L (normal range <5 ng/L) and he was referred to the emergency room and admitted for further evaluation. Echocardiogram showed normal systolic LV function with ejection fraction of 60-65% and no wall motion, pericardial or significant valvular abnormalities. Cardiac catheterization showed normal coronary arteries. Infection assessment including viral studies for influenza, COVID-19, parainfluenza, adenovirus, Coxsackie were all negative. The differential diagnosis of myocarditis included viral, autoimmune and drug induced myocarditis. Clinical presentation, evaluation and rapid resolution after Mesalamine therapy was discontinued supported mesalamine induced myocarditis. Patient improved rapidly once mesalamine was discontinued with prompt resolution of both pharyngitis and chest pain. He was discharged home with resolution of all symptoms on daily aspirin 81 mg and daily metoprolol succinate 25 mg. He remained symptom free when seen one week after discharge. High Sensitivity Troponin I level decreased to 5 ng/L at one week and was normal at 4ng/L (<5ng/L) at two-week follow up.

Mesalamine (5-aminosalicylic acid or 5-ASA) is a common anti-inflammatory medication used to treat mild to moderate inflammatory bowel disease such as Crohn's disease and ulcerative colitis. Although the exact mechanism of action is uncertain, several immunomodulation effects were noted during in-vitro mesalamine studies including 5-ASA inhibition of prostaglandin and leukotriene synthesis.[1-4] Mesalamine inhibits cytokine production including TNFa and interleukins.[5-7] 5-ASA is also a free radical scavenger with an antioxidant effect in the intestinal mucosa.[8,9] 5-ASA also immunosuppresses by inhibiting antibody secretion, T-cell proliferation and leukocyte motility and function.[10-12]

Mesalamine is usually taken orally or rectally and is mainly absorbed in the colon and rectum. The most common gastrointestinal side effects include abdominal distention, nausea and vomiting, flatulence, abdominal pain, diarrhea, and constipation. Other systemic side effects are less common but can include fever, rash, headache. pharyngitis, rhinitis and abnormal liver function tests. Infrequent or rare reactions include anemia, leukopenia, aplastic anemia, liver failure, pancreatitis, nephrolithiasis, interstitial nephritis and nephrotic syndrome. Rarely Stevens Johnson syndrome has been reported.[13] Pericarditis and myocarditis are other rare side effects of mesalamine and have been documented in multiple case reports.[14-16]

Myocarditis is defined as inflammatory injury to the myocardium. If the injury also involves the pericardium, it is labeled as myopericarditis. Myocarditis can present with chest pain, dyspnea, and palpitations. More severe symptoms present in about 25% of the patients include left ventricular systolic dysfunction, ventricular arrhythmias, acute heart failure and cardiogenic shock.[17] Myocarditis can be caused by viral infections including Coxsackie, influenza, corona viruses (such as COVID-19), parvoB19. Less common causes of myocarditis include autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematous, drugs including immune checkpoint inhibitors and mesalamine, as well as vaccines including mRNA COVID-19 vaccine and smallpox vaccine.[18]

Mesalamine induced myocarditis usually occurs 2-4 weeks after initiation of therapy.[14] Patients with myocarditis typically present with chest pain, shortness of breath, fever, and fatigue. EKGs may show nonspecific ST or T wave changes. Labs usually include leukocytosis and elevated inflammatory markers such as CRP and sedimentation rate. Cardiac injury markers including elevated troponin I or T marker are often seen with acute myocarditis. Echocardiogram may show left ventricular dysfunction, however normal ejection fraction is also found. Coronary angiogram is typically normal. Cardiac MRI with gadolinium is useful in confirming the clinical diagnosis using the 2018 Lake Louis CMR criteria that include edema and myocardial scar.[18] Endocardial biopsy is less commonly performed due to lower diagnostic yield of 35%. Lower yield is due to patchy distribution of the inflammation. In addition, sampling of the epicardial and mid wall where inflammation may present is technically difficult.[19] Mesalamine induced myocarditis is typically a clinical diagnosis guided by history and elevated cardiac injury and inflammatory markers. Cardiac MRI may be useful in confirming the diagnosis. Treatment typically involves withdrawal of mesalamine treatment and supportive care. Rapid resolution of symptoms is typical, usually within 7-14 days.[14] Mesalamine induced myocarditis pathophysiology is not fully understood but hyper-

sensitivity reactions have been suggested, with antibodies against mesalamine cross react with myocardial tissue and cause inflammation.[14,20,21]

Mesalamine induced myocarditis is a rare complication of mesalamine use but important to recognize. Cardiac manifestation of myocarditis ranges from mild symptoms to severe myocardial dysfunction. Early diagnosis and withdrawal of mesalamine therapy can alleviate symptoms with rapid recovery.

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