Mesalazine-induced myalgia and creatine phosphate kinase elevation: case report and review of the literature

Stefano Festa
Riccardo Ballanti
Claudio Papi

Inflammatory Bowel Disease Unit, “San Filippo Neri” Hospital, Rome, Italy

Address for correspondence:
Stefano Festa
UOC Gastroenterologia
Ospedale “S. Filippo Neri”
Via G. Martinotti 20
00135 Roma, Italy
Phone: +39 06 33063169
E-mail: festa.stefano@gmail.com

Summary

Ulcerative Colitis (UC) is a chronic inflammatory disease of unknown etiology needing lifelong therapy. Mesalazine is the first-line treatment for induction and maintaining remission in mild-to-moderate forms. It is generally well tolerated but adverse reactions occasionally occur and for this reason are challenging from a diagnostic point of view. We present an unusual case of creatine phosphate kinase (CPK) elevation associated to myalgia following administration of mesalazine for UC. Possible explanations as well as differential diagnoses of myopathies in the setting of Inflammatory Bowel Disease are also discussed.

KEY WORDS: ulcerative colitis, mesalazine, creatine phosphate kinase (cpk), myopathies, adverse drug reactions (ADRs).

Introduction

Ulcerative Colitis (UC) is a chronic inflammatory disease of unknown etiology affecting the mucosal layer of the colon (1). Mesalazine, also known as 5-aminosalicylic acid (5-ASA), is an anti-inflammatory agent representing the mainstay therapy of this condition. Mesalazine has a topical action on colonic epithelial cells, where it is also metabolized. Given orally, rectally, or in combination in patients with mild-to-moderate UC, mesalazine represents the first-line treatment for induction and maintaining remission (2). ECCO guidelines recommend its long-term use, as it is also supposed to have chemo-preventive properties decreasing the incidence of UC associated to colorectal cancer (3).

Mesalazine is generally a well-tolerated drug with a high safety profile. Adverse drug reactions (ADRs) are usually mild and transient and are reported in up to 10-15% of patients (4). The most commonly known ADRs during mesalazine treatment include diarrhea, nausea, vomiting, abdominal pain, headache, and hypersensitivity reactions. Acute intolerance occurs in 3% and may mimic a flare of colitis (4). Occasionally, and more rarely, some patients may develop serious side effects such as acute pancreatitis, hepatitis, nephrotic syndrome, allergic lung reactions, or allergic myocarditis (4).

We report here an unusual case of creatine phosphate kinase (CPK) elevation associated to myalgia following administration of mesalazine for UC. Putative explanations of this unusual clinical picture, as well as differential diagnoses of myopathies in the setting of Inflammatory Bowel Disease (IBD), and possible pathogenic mechanisms are also discussed.

Case report

A 50-year-old man was referred to our GI unit because of bloody diarrhea (4-5 bowel movements per day with blood present in most of cases), tenesmus and crampy abdominal pain. In his past medical history there was a non-invasive papillary carcinoma of the bladder and a monoclonal gammopathy of undetermined significance for both of which he was on regular follow-up. Laboratory studies revealed that no relevant abnormalities, in particular haemoglobin, erythrocyte sedimentation rate (ESR) and C reactive protein
(CRP) were in the normal range. No pathogens ova or parasites were detected in stools. Ileo-colonoscopy showed erythema, lack of vascular pattern, friability, and small erosions up to the hepatic flexure. Ileal mucosa showed no abnormalities. Histologic examination of endoscopic biopsies showed transmucosal inflammatory infiltrate, cryptitis, crypt abscesses, and mild crypt architectural distortion. These findings were consistent with the diagnosis of extensive mild/moderate UC (Total Mayo Score = 6).

Oral and topical nesalazine was started (4g/day orally and 4g/day rectally). A rapid symptomatic relief occurred in few days and complete clinical remission within 3 weeks. After 6 weeks, topical therapy was discontinued and the patient continued oral mesalazine alone (2.4g/day) as maintenance treatment.

Six months later the patients was still in remission but, on routine laboratory test performed for his oncological follow-up, the serum CPK level was found to be elevated, 457 mg/dl (normal values: 38-176 mg/deciliter) with about 97% of the enzyme derived from skeletal muscle. Lactico-dehydrogenase (LDH), aldolase, troponin, tropomyosin and myoglobinuria were in the normal range. The peripheral white blood cell count, eosinophil included, was normal as well as autoantibodies. Thyroid and kidney function were also normal. The patient occasionally complained mild muscular discomfort at proximal legs, not affecting his normal daily activities. He denied any other drugs or herbal remedies intake. No other symptoms or signs suggestive for viruses or bacteria infections were present. Electrocardiogram and echocardiogram were normal and a neurologic evaluation that included electromyography, electoneuronography and magnetic resonance of the legs showed no findings suggestive of peripheral myopathy. A muscle biopsy was therefore considered unnecessary and, according to the above-mentioned findings, an initial diagnosis of restless legs syndrome was made.

In the following months mild muscular symptoms persisted and CPK levels increased up to six times the normal value. Mesalazine was then temporarily discontinued and a slow decrease of CPK level was observed until complete normalization along with symptoms resolution. Mesalazine rechallenge was then attempted and serum CPK levels raised again and muscular symptoms reappeared as well (Figure 1). Mesalazine was definitely withdrawn, and alternative maintenance therapy with E. Coli Nissle 1917 was started (4).

**Discussion**

We have reported the case of a UC patient, in which CPK elevation was observed together with mild muscle discomfort few months after starting mesalazine therapy. The clinical and biochemical picture resolved after mesalazine discontinuation and reappeared after mesalazine reintroduction. The occurrence of muscle disorders or isolated muscle enzyme alterations (when symptoms are...
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Mild or even absent) in the specific context of IBD can be found in three different clinical settings:
- Extra-intestinal manifestations (EIMs) of IBD
- Isolated non-pathological increased enzyme activity (or macro-CPK).
- Adverse drug reactions.

Extraintestinal Manifestation of IBD. Both Crohn’s disease (CD) and UC are often associated with EIMs, with an estimated incidence of 25% (5). A direct correlation between the presence of EIMs and the extent of colonic involvement has been found since about 75% of patients with EIMs have extensive colitis (6). Peripheral arthritis and spondylarthritides are by far the most represented EIMs in the course of IBD. Other EIMs can affect eyes (e.g. uveitis and episcleritis), skin (e.g. pyoderma gangrenosum and erythema nodosum) or liver (e.g. primary sclerosing cholangitis).

In general, muscle involvement is a rare EIM occurring in the course of IBD (6). IBD-specific entities such as orbital myositis and granulomatous myalgia syndrome have also been described (5). It is a matter of debate if IBD-associated myopathies should be considered disease-related myositis rather than coexistent autoimmune disorders affecting the muscle. However, as a possible common pathogenic mechanism of muscular involvement in IBD, an antigenic release due to bowel inflammation with subsequent antibody production and immune complex formation has been suggested (7). Colonic disease is more often associated with myopathies than small bowel involvement alone but, compared to CD, UC appears to be less frequently associated with an inflammatory myopathy. IBD usually precede the development of myositis in most patients (8). Treatment is usually aimed to control IBD activity and include salicylates, glucocorticoids, immunosuppressive or biologic agents (9). It’s noteworthy that a diagnosis of dermatomyositis or polymyositis in the context of IBD, although rarely described, should raise the suspicion of cancer or high-grade dysplasia development especially in patients with long-lasting IBD. In addition, the serum CPK should always be measured when a patient with IBD complains symptoms of myalgia and weakness (5).

In our case, clinical, laboratory and electromyography findings, as well as the clinical pattern of UC, were not consistent with a diagnosis of IBD-related myositis.

Isolated hyper-enzymemia. Elevated serum CPK is not always synonymous of muscle damage. Exceptionally, CPK electrophoresis can reveal an abnormal isoenzyme, the so-called macro-CPK, a macro-molecular complex composed of an IgA or IgG-antibody binding the CPK enzyme that, due to the high molecular weight, cannot be eliminated by the kidney. This results in an increased enzyme activity. Macro-CPK can be found either in healthy subjects or can be related to specific disease situations. Indeed, it has been postulated that macro-CPK can be induced by drugs or concomitant autoimmune, infectious or neoplastic diseases (10). Interestingly, in medical literature, macro-CPK has been previously yet reported in patients with IBD following mesalazine treatment (11).

In our case, we could not determine macro-CPK levels and a possible diagnosis of isolated hyper-enzymemia remains only speculative. Nevertheless, the possible presence of macro-CPK (theoretically attributable to several concomitant conditions such as UC, mesalazine treatment and the previous history of bladder carcinoma) could have explained the serum CPK elevation; on the other hand, the pathogenic role of macro-CPK in eliciting myalgia symptoms remains to be elucidated. Indeed, in every day clinical practice, the possibility of a macro-enzyme should be kept in mind in the presence of unexplained, isolated increased enzyme activity. It should prevent costly and unnecessary investigations.

Adverse Drug Reactions. Myalgia, and more in general myopathies, can be also related to that drugs commonly used in the management of IBD (aminosalicylates, steroids, and immunomodulators). In particular, myalgia is mentioned among the very rare ADRs of mesalazine with a reported incidence of 0.01%.

Mesalazine induced myalgia may be classified as a type B ADR (hypersensitivity reaction) being uncommon, unpredictable, unrelated to the dose and poorly understood from a pathogenic mechanism point of view. It is not a life-threatening reaction, but it can reduce quality of life and may require treatment discontinuation. Overall, 186 cases of myalgia associated to mesalazine have been reported to the WHO ADR Uppsala Monitoring Center (VigiBase, 20 December, 2015) (12). Besides the reports available in pharmacovigilance database, only two case report of myalgia/muscular damage occurring after mesalazine administration have been reported in the literature, with detailed case-description, both of them regarding paediatric patients (13, 14).

In our patient the re-administration of mesalazine and subsequent occurrence of myalgia enforced the causality assessment for the ADR occurrence.
even if the reason of CPK elevation remained unexplained. Finally, our case report is a paradigmatic case of drug-induced adverse effects. To the best of our knowledge, this case represents the first case of mesalazine induced myalgia with a documented CPK elevation in an adult IBD patient.

References