



Mesalazine Induced Pancytopenia in Crohn's Disease

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Abstract: Mesalazine, or 5-aminosalicylic acid, is an anti-inflammatory drug frequently used in patients suffering from chronic inflammatory bowel disease, and is generally well tolerated. Its most common side effects are mainly limited to gastrointestinal disorders, headaches, joint pain and skin rashes, and are generally modest and transient. Serious hematological toxicity is very rare (<1/10000), but cases of thrombocytopenia, aplastic anemia, pancytopenia and leukopenia/agranulocytosis have been reported. We report here the case of a patient with inflammatory phenotype colonic Crohn's disease on mesalazine 3g/day who presented with initial leukopenia aggravated by the development of pancytopenia.

Keywords: Mesalazine, Inflammatory Bowel Disease, Pancytopenia.

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INTRODUCTION

5-amino-salicylates (5-ASAs) have been used for decades to treat chronic inflammatory bowel disease (IBD), such as ulcerative colitis and Crohn's disease. However, 5-ASAs present a wide variety of side effects, although rare, serious, often fatal blood disorders, such as agranulocytosis, aplastic anemia, and thrombocytopenia, have been described in patients taking 5-ASA.

We present here the case of a patient with inflammatory colonic Crohn's disease on Pentasa 3g/dr who developed pancytopenia while receiving oral 5-ASA (Mesalazine, Pentasa).

OBSERVATION

This 43-year-old patient had been treated in the private sector for 2 years and was referred to our clinic for further treatment. She was treated for colonic Crohn's disease of inflammatory phenotype classified as A2L2B1 according to Montreal's

classification without anoperineal lesions, initially revealed by glairo-bloody diarrhoea evolving in remission, associated with a moderate rectal syndrome with tenesmus and false needs, and extradigestive manifestations of inflammatory peripheral polyarthralgia of the large and medium-sized joints (elbows, wrists, ankles, wrists, ankles), put on oral 5-ASA Mesalazine (Pentasa) at a dose of 2g/day as background treatment, then increased to 3g/day in the face of what was judged to be a minimal flare-up of her disease, then reduced to 2g/day 15 days later in the face of leukopenia at 2352 elm/uL, a check-up 15 days later was requested, showing pancytopenia with Hb anemia at 10.8 g/dL (normocytic normochromic anemia with reticulocytes at 82000/uL), WBC=2410 elm/uL, neutropenia at 670 elm/uL, Lymphocytes: elm/uL, plq = 130000/uL, renal function correct, ionogram correct with C-reactive protein at 4 mg/L. A myelogram showed a balanced marrow, vitamin

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levels (B9 and B12) were normal, and serum ferritin was 106ug/L.

Discontinuation of all medication was indicated, with monitoring of the blood count, which showed improvement in thrombocytopenia from day 5, and in leukopenia and anemia from day 15.

The patient was subsequently put on Azathioprine as background treatment for her disease, with good progression.

We concluded that this case was a Pentasa-associated pancytopenia, as no other cause of pancytopenia was found. In addition, our patient had not taken any other medication likely to cause blood disorders. Other causes of pancytopenia, such as a viral infection or hemophagocytic syndrome, were less likely based on the clinical course and biological tests. A definitive test for the cause of pancytopenia in this patient would be a Pentasa challenge test. However, such a provocation test is not warranted, as blood disorders following 5-ASA administration are considered to be caused by a hypersensitivity reaction and are often fatal.

DISCUSSION

Mesalazine, or 5-aminosalicylic acid, is an anti-inflammatory drug very frequently used in patients with chronic bowel disorders and is generally well tolerated, indeed, over time it has replaced sulphasalazine since it has fewer side effects [1, 2]. The mechanism of action of mesalamine preparations is attributed to modulation of the arachidonic acid metabolism with inhibition of the cyclooxygenase and lipoxygenase pathways. Additionally, mesalamine inhibits inflammatory cell functions, natural killer cell activity, plasma cell antibody production, and tumor necrosis factor activity, decreases interleukin-1 production from macrophages, and acts as a free oxygen radical scavenger [2, 3]. The most common side effects of mesalazine, such as gastrointestinal disturbances, headache, joint pain, and skin rashes, are usually of modest entity and transitory. Idiosyncratic reactions, such as nausea, diarrhoea and rashes occur in about 15% of patients and resolve on drug withdrawal. However, potentially more serious adverse reactions affecting the blood, kidney and liver may be encountered during the use of all of these drugs [2].

Severe hematological toxicity is very rare (<1/10000), but there have been reports of thrombocytopenia, aplastic anemia, pancytopenia, and leukopenia/agranulocytosis [4, 5]. Agranulocytosis is an extremely rare occurrence during treatment with mesalazine and only a very few cases have been reported in the literature. In a

United Kingdom population-based study of patients using sulfasalazine or mesalazine, among 4004 patients receiving mesalazine, there were no reports of blood dyscrasias compared to 0.26% of patients taking sulfasalazine [2-4]. Possible mechanisms of mesalazine induced hematological toxicity, include direct toxicity to hematopoietic stem cells or immunological suppression by activated cytotoxic T cells but the exact mechanism of hematological side effects remains uncertain [5]. Most reports of mesalazine-induced neutropenia were observed within the first 3 months of therapy, suggesting the possibility of a hypersensitivity reaction. However, neutropenia has been reported as early as 2 weeks or as late as 1 year after therapy was initiated [4-6], however our patient has developed hematological disorders two years after the initiation of the treatment by mesalazine. In cases of medullary aplasia, the infectious picture is accompanied by an anemic syndrome and cutaneous- mucous hemorrhagic signs reflecting the associated involvement of the red and platelet lines [6]. Majority of reported cases of mesalazine-induced cytopenia were moderate and reversed when the drug was discontinued. In the literature, on discontinuation of mesalazine, the course is considered suggestive if the blood count normalizes within one month, inconclusive if it corrects between the first and third months, not suggestive if the abnormality persists after three months [7]. In our case, the blood count normalized as soon as treatment was stopped, within the first month. In the studies reported, patients had taken oral 5-ASA in doses exceeding 1.0 g/day, but a dose-dependent relationship was not demonstrated. Casellas *et al.*, [8]. Reported a patient with leukopenia and thrombocytopenia associated with 5-ASA suppositories. For patients who have developed anaemia on mesalazine, the dosage and duration of treatment are variable, ranging from 28 days [9]. To a year or more [10, 11].

Based on this observation, we emphasize that clinical and hematological monitoring should be carried out in patients receiving 5-ASA therapy. The drug should be stopped immediately if a blood disorder is suspected.

CONCLUSION

Mesalazine is a well-tolerated drug, however, serious and potentially life-threatening hematological disorders can occur. Majority of reported cases of mesalazine-induced cytopenia were moderate and reversed when the drug was discontinued. Physicians must be aware of such unpredictable complications and consider hematological monitoring, especially during the first 3 months of therapy.

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