

Case Report

Hepatogastroentérology

# Agranulocytosis Induced By Mesalazine in Ulcerative Colitis Disease

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DOI: [10.36348/sjmps.2021.v07i11.009](https://doi.org/10.36348/sjmps.2021.v07i11.009)

| Received: 14.10.2021 | Accepted: 22.11.2021 | Published: 30.11.2021

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## Abstract

Mesalazine is a widely used and generally safe drug for the treatment of chronic inflammatory bowel diseases. Neutropenia/ Agranulocytosis rarely complicates this treatment and very few cases have been reported in the literature. Agranulocytosis is characterized by a decrease in peripheral neutrophil count to less 500 /mm<sup>3</sup>. Most reported cases presented more than three months after the initiation of treatment, and whilst many patients recovered, fatalities were reported. Cessation of mesalazine alone may not be adequate therapy and aggressive management with bone marrow evaluation, high dose of granulocyte colony-stimulating factor, or immunosuppressive therapy may be indicated. We report here the case of a patient with ulcerative colitis who developed an asymptomatic agranulocytosis during treatment with mesalazine and having spontaneously regressed after stopping treatment.

**Keywords:** Agranulocytosis, Mesalazine, Ulcerative colitis.

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## INTRODUCTION

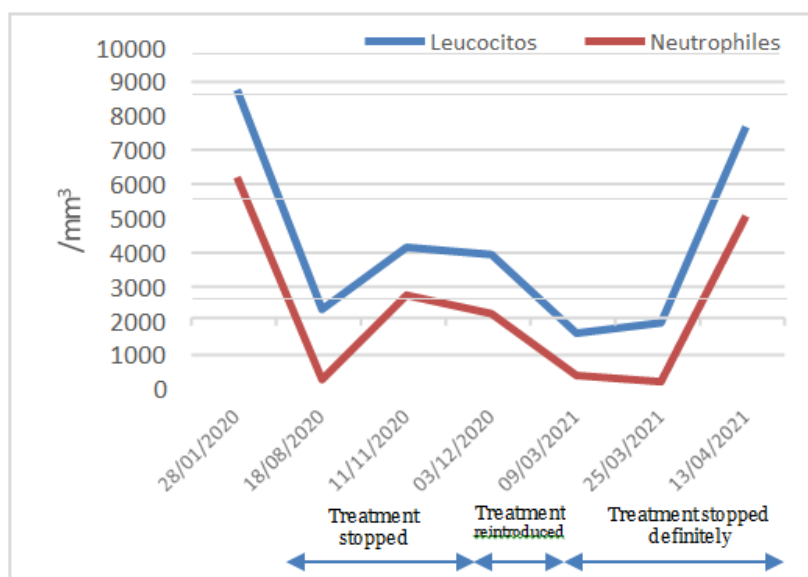
Neutropenia/ Agranulocytosis is an extremely rare occurrence during treatment with mesalazine and only a very few cases have been reported in the literature.

Here, we report the case of agranulocytosis caused by pure white cell aplasia secondary to the use of mesalazine in a 53 years-old patient with ulcerative colitis who had been receiving mesalazine treatment for about 3 years. The neutrophil count had returned spontaneously to normal after suspension of treatment.

## CASE REPORT

A 53 years old woman followed in our unit for pancolitis due to ulcerative colitis, treated by a combined oral at the dose of 3g/day and enema treatment with mesalazine, she was in clinical and histological remission.

After three years of treatment and during its biologic surveillance, Blood-chemistry tests showed a hemoglobin concentration of 12.5 g/dl with normal-sized red cells, a platelet count of 318 000/mm<sup>3</sup>, a leukocyte count of 1990/mm<sup>3</sup>, a neutrophil count of 318/mm<sup>3</sup>, liver and kidney function within the norm, and a C-reactive protein negative. The patient was asymptomatic. After other possible causes of neutropenia were ruled out (vitamin deficiencies, viral infections, immunological cause, among others), a possible iatrogenic origin was considered, suspecting that mesalazine was the main agent responsible for the neutropenia. The treatment was stopped with strict clinical and biological surveillance. The leukocyte count has normalized to 4900/mm<sup>3</sup>, the neutrophil count to 2769/mm<sup>3</sup> three months after. When we re-treated with mesalazine following a moderate flare-up, the patient reinstalls agranulocytosis to 240/mm<sup>3</sup> three months after, without complications. We have concluded an iatrogenic agranulocytosis induced by mesalazine. The treatment was stopped definitively and the results normalized two weeks later and we switched to azathioprine.



**Figure 1: Leucocyte and neutrophil count progression**

## 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 a rare and life-threatening condition, with an annual incidence of 1.1 to 4.9 cases per million population per year. Up to 50% of agranulocytosis may be induced by nonchemotherapy drugs, such as antithyroid agents and antimicrobial medications. There is often a marked increase in the incidence of agranulocytosis in elderly

patients and a predominance of women has often been suggested [6, 7]. 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, 8].

Possible mechanisms of mesalazine induced neutropenia, 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 [9]. 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 [8, 9], however our patient has developed agranulocytosis three years after the initiation of the treatment by mesalazine.

Agranulocytosis can be discovered in an asymptomatic patient when the blood count is monitored regularly in case of risky treatment, which is the case of our patient. In the elderly, the clinical manifestations of agranulocytosis are often more severe as more than two-thirds have sepsis or septic shock. In accidental 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 [9]. The risk of infection is major when the rate of polynuclear neutrophils is <500/mm<sup>3</sup> and is extreme when the rate of polynuclear neutrophils is <200/mm<sup>3</sup> [5].

Majority of reported cases of mesalazine-induced cytopenia were moderate and reversed when the drug was discontinued. Currently, the standard treatment for drug-induced agranulocytosis is discontinuation of the responsible agent (mesalazine), antibiotic treatment if the presence of infection is suspected, and proper use of granulocyte colony-stimulating factor (G-CSF)/ granulocyte-macrophage colony-stimulating factor (GM-CSF). Although their efficacy is not conclusively proven, G-CSF has minimal toxicity and may be beneficial in the management of drug-induced agranulocytosis in elderly patients [6, 9]. On discontinuation of mesalazine, the course is considered suggestive if the neutrophil count normalizes within one month, inconclusive if the neutrophil count corrects between the first and third month, not suggestive if the anomaly persists after three months [6]. In our case, the leukocyte count has normalized when we've stopped the treatment, the first one was after three months and the second one after two weeks. In the literature we've not noticed any similar case as ours, in the reintroduction of the mesalazine after stopping it.

As for antibiotic treatment, cefepime (a fourth-generation cephalosporin) is often employed as a first-line therapy for agranulocytosis with infection.

Meropenem can be used as an alternative when cefepime is not tolerated well. A recent study also demonstrated that, for severe cases (neutrophil count  $< 100/\mu\text{L}$ ), meropenem may be the superior choice for monotherapy [7].

Treatment with hematopoietic cell growth factors has been reported to decrease fatality in patients with mesalazine induced agranulocytosis. We found statistically significant associations between shorter duration of neutropenia and treatment with G-CSF or GM-CSF, regardless of whether patients had an infection at the time of diagnosis. A decreased duration of neutropenia has been shown in other retrospective studies of the effect of treatment with G-CSF or GM-CSF [2, 7].

Mortality from drug-induced agranulocytosis was in the order of 10 to 16% in European studies dating back 20 years. Currently, it is lowered to around 5%, illustrating the progress made in its recognition and therapeutic management [2, 3]. The main factors negatively influencing the prognosis are age  $> 60$  years, the neutrophil count at diagnosis  $< 100 / \text{mm}^3$ , a severe infectious state (sepsis and state of septic shock) and the presence of comorbidities (in particular a renal failure defined by serum creatinine  $> 120 \text{ mmol / L}$ ) [7].

Haematological complications are very rare amongst patients with inflammatory bowel disease who are treated with sulfasalazine or other 5-ASA-based preparations. We do not recommend any formal monitoring of the full blood count. Patients should be warned to seek medical attention if they develop symptoms such as fever, rash, severe mouth ulcers or severe sore throat, in which case the full blood count should be checked, only exception to this could be in a patient with coexistent rheumatoid arthritis where consideration should be given to checking the full blood count once at 3 months after treatment initiation [3, 8].

## 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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