CASE REPORT

Hyperleucocytosis following G-CSF treatment for sulfasalazine-induced agranulocytosis

Kenneth Chan, Redwan Farooq

Royal Free London NHS
Foundation Trust, London, UK

Correspondence to
Dr Kenneth Chan,
kennethchan1@nhs.net

Accepted 2 July 2015

SUMMARY

Agranulocytosis is a rare but serious adverse effect of sulfasalazine treatment. We present a case of a 51-year-old woman receiving sulfasalazine for inflammatory arthritis presenting with sore throat, fever, lethargy and leucopenia (white cell count $0.9 \times 10^9/L$). After 9 days of treatment with filgrastim (granulocyte-colony stimulating factor, G-CSF), her white cell count increased to $77.4 \times 10^9/L$. This case highlights the importance of recognising sulfasalazine-induced agranulocytosis and the management of hyperleucocytosis following G-CSF treatment, to prevent harmful sequelae.

BACKGROUND

Sulfasalazine is a generally safe and well-tolerated disease-modifying antirheumatic drug (DMARD), and agranulocytosis is a rare but serious adverse effect of this drug. It is important to identify this adverse effect early, as it is associated with a high mortality rate when presenting as neutropenic sepsis.

Granulocyte-colony stimulating factor (G-CSF) is a recognised treatment for neutropenia, but may result in a dramatic hyperleucocytosis, as illustrated by this case. Regular monitoring, early recognition and appropriate management of this complication of treatment is important to prevent the development of harmful sequelae.

CASE PRESENTATION

A 51-year-old woman presented with a 1-week history of sore throat, fever and lethargy. She had a background of inflammatory arthritis initially managed with local steroid injections to the hands, followed by systemic steroid injections and oral steroids. She was subsequently started on hydroxy-chloroquine as a steroid-sparing agent but due to poor tolerance of side effects, she was switched to sulfasalazine 2 months prior to admission. Her baseline full-blood count, renal function, liver function and thyroid function prior to start of treatment were all within normal range. Routine blood monitoring after increasing the sulfasalazine dose to 1 g twice daily had shown a neutropenia of $0.2 \times 10^9/L$.

On examination, the patient had a temperature of $38.8^\circ C$. She was haemodynamically stable. Cardiovascular, respiratory, abdominal and neurological examinations were unremarkable. Oral examination revealed erythema of the oropharynx and oral candidiasis. There was no lymphadenopathy or rash.

INVESTIGATIONS

The full-blood count revealed leucopenia with white cell count (WCC) of $0.9 \times 10^9/L$ (neutrophils $0.0 \times 10^9/L$, eosinophils $0.0 \times 10^9/L$, basophils $0.0 \times 10^9/L$, lymphocytes $0.8 \times 10^9/L$, monocytes $0.1 \times 10^9/L$; figure 1). Haemoglobin and platelet counts were within normal range (figure 2). Prior to sulfasalazine initiation, the patient's baseline full-blood count showed WCC of $5.0 \times 10^9/L$ (neutrophils $2.8 \times 10^9/L$, eosinophils $0.1 \times 10^9/L$, basophils $0.0 \times 10^9/L$, lymphocytes $1.7 \times 10^9/L$, monocytes $0.4 \times 10^9/L$). Baseline haemoglobin was 138 g/L and platelet count was $358 \times 10^9/L$. A blood film showed isolated severe neutropaenia with occasional activated lymphocytes.

Investigations were performed to determine the source of sepsis. The patient's chest X-ray was normal, urinalysis was negative and blood cultures yielded no growth. A throat swab was negative for haemolytic streptococci.

Further investigations were performed to identify potential alternative causes of neutropenia. Cytomegalovirus and parvovirus B19 serology were negative and Epstein-Barr virus serology showed evidence of previous infection but no active infection. Serum vitamin B₁₂ and folate levels were normal.

Figure 1 Changes in white cell count differential in response to granulocyte-colony stimulating factor.

Figure 2 Changes in haemoglobin and platelet count in response to granulocyte-colony stimulating factor.

To cite: Chan K, Farooq R. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-210709

The patient's liver function tests also showed an isolated rise in alkaline phosphatase (409 iU/L) with normal calcium and phosphate levels. Viral hepatitis serology and liver autoantibody screen were both negative. An ultrasound scan of the hepatobiliary system showed normal appearances of the liver and gallbladder, and no evidence of biliary tree obstruction.

DIFFERENTIAL DIAGNOSIS

Given the patient's history and examination findings, as well as investigations showing an isolated severe neutropenia, sulfasalazine-induced agranulocytosis was thought to be the most likely diagnosis. She was treated for neutropaenic sepsis as she presented with a fever and features consistent with an upper respiratory tract infection.

Infectious and metabolic causes of decreased neutrophil production were not supported by investigations. Accelerated neutrophil depletion, as seen in Felty's syndrome (rheumatoid arthritis, splenomegaly and neutropenia), was also considered, however, the patient did not have clinical evidence of splenomegaly. A clinical decision was made to initially manage the patient by stopping sulfasalazine and monitoring neutrophil recovery prior to further investigation. Other differential diagnoses included autoimmune neutropenia, myelodysplasia and haematological malignancy with bone marrow infiltration.

TREATMENT

Sulfasalazine was stopped immediately and the patient was started on intravenous broad-spectrum antibiotics and oral nystatin. As there was no sign of improvement in neutrophil count, G-CSF (filgrastim) 0.3 mg/day was started on day 2 of the admission. After 8 days of filgrastim treatment, the neutrophil count recovered to $0.2 \times 10^9/\text{L}$, then rapidly increased to $7.7 \times 10^9/\text{L}$ the following day (figure 1). Filgrastim was promptly stopped, however, the neutrophil count continued to rise, peaking at $33.9 \times 10^9/\text{L}$ with a total WCC of $77.4 \times 10^9/\text{L}$ on day 12. The patient's platelet count also increased over the same time period, peaking at $705 \times 10^9/\text{L}$. A repeat blood film showed a leucoblastic picture with highly toxic neutrophils, platelet anisocytosis and occasional megakaryocytes.

OUTCOME AND FOLLOW-UP

The patient was closely monitored for clinical manifestations of hyperviscosity syndrome and small vessel injury. She remained haemodynamically stable, maintained good renal function and did not develop any acute neurological deficits. She was kept well hydrated with intravenous fluids. The WCC began to decline back to normal levels by day 15 (figure 1) and, consequently, therapeutic leucoapheresis was not required.

DISCUSSION

Sulfasalazine is a commonly used DMARD and is one of the first-line therapies recommended for rheumatoid arthritis in NICE and American College of Rheumatology guidelines.^{1 2} Agranulocytosis is a rare but serious adverse effect of sulfasalazine. It is defined as a neutrophil count $<0.5 \times 10^9/\text{L}$ with or without presence of fever/signs of infection.³ Studies have shown the incidence of blood disorders attributable to sulfasalazine to be 2.6 per 1000 users.⁴ The pathogenesis is not completely understood, but is postulated to be mediated by immunological hypersensitivity or direct damage to myeloid precursors.^{3 4}

Patients usually present with non-specific symptoms such as fever, malaise and sore throat. Septicaemia occurs in about two-thirds of patients, with variable mortality between 6% and 20%, and is dependent on the duration of neutropenia.⁵ Other

poor prognostic factors include old age (>65 years), septic shock, metabolic derangements and neutrophil count $<0.1 \times 10^9/\text{L}$.³

The early initiation of empirical broad-spectrum antimicrobial agents remains the management priority for neutropenic patients presenting with fever. Patients with cancer receiving cytotoxic therapy often present with neutropenic sepsis. In high-risk patients who are expected to be neutropenic for >7 days, empirical broad-spectrum antibiotics to cover Gram-positive and Gram-negative organisms and antifungal therapy should be given until the neutrophil count $>0.5 \times 10^9/\text{L}$.⁶

G-CSF treatment, such as filgrastim, also has a role in the treatment of drug-induced agranulocytosis. Systematic reviews and meta-analyses of patients with non-chemotherapy drug-induced agranulocytosis have found that daily G-CSF significantly reduces mean time to neutrophil recovery by 2–3 days (10–7.7 days,⁷ 8.8–6.6 days⁸) and lowers the rate of septicemia and fatal infections.⁸

Hyperleucocytosis secondary to filgrastim has only been previously reported in chemotherapy patients.⁹ Similar responses have also been reported in patients receiving pegfilgrastim, the pegylated form of filgrastim, for the treatment of agranulocytosis secondary to chemotherapy and myelodysplastic syndrome.^{10 11} Pegfilgrastim has a saturable neutrophil-mediated clearance mechanism and consequently may be less prone to secondary hyperleucocytosis due to the self-regulatory effect of increased clearance with rising neutrophil count.¹⁰

Hyperviscosity syndrome is one of the reported adverse sequelae of G-CSF-induced hyperleucocytosis.¹¹ The clinical presentation may include headaches, visual and other neurological disturbances, mucosal bleeding, heart failure and manifestations of end-organ ischaemia, such as myocardial infarction and renal failure. Neutrophil activation and release of inflammatory mediators may also result in small vessel injury and capillary leakage leading to shock and cellular injury.¹²

Therapeutic leucoapheresis is a treatment option that has been used for the management of hyperleucocytosis resulting from haematological malignancies. Although it is generally regarded as safe and effective, there is limited evidence that it improves outcomes.¹³

This case demonstrated hyperleucocytosis in response to filgrastim treatment in a neutropenic patient who was not on chemotherapy. Patients with cancer receiving filgrastim may be less prone to hyperleucocytosis due to cumulative immunosuppression from multiple cycles of chemotherapy/radiotherapy. Animal studies have shown potential genetic determinants of hyperleucocytosis with G-CSF treatment.¹⁴ However, there are insufficient reported cases in the literature of this adverse effect of G-CSF treatment in humans to identify clear risk factors.

Learning points

- ▶ Agranulocytosis is a rare but serious adverse effect of sulfasalazine and regular monitoring is needed for early recognition and treatment.
- ▶ Granulocyte-colony stimulating factor (G-CSF) is an effective treatment for sulfasalazine-induced agranulocytosis but carries a risk of hyperleucocytosis.
- ▶ Regular monitoring is needed for early recognition of hyperleucocytosis. Management involves stopping G-CSF, maintenance of good hydration and close monitoring for evidence of complications, including hyperviscosity syndrome and small vessel injury. Therapeutic leucoapheresis should be considered as a treatment option.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Rheumatoid arthritis: the management of rheumatoid arthritis in adults. NICE clinical guideline; February, 2009. <https://www.nice.org.uk/guidance/cg79> (accessed 11 Jul 2015).
- 2 Singh JA, Furst DE, Bharat A, *et al.* 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:625–39.
- 3 Andres E, Maloisel F. Idiosyncratic drug-induced agranulocytosis or acute neutropenia. *Curr Opin Hematol* 2008;15:15–21.
- 4 Jick H, Myers MW, Dean AD. The risk of sulfasalazine- and mesalazine-associated blood disorders. *Pharmacotherapy* 1995;15:176–81.
- 5 Roddie P, Dorrance H, Cook MK, *et al.* Treatment of sulphasalazine-induced agranulocytosis with granulocyte macrophage-colony stimulating factor. *Aliment Pharmacol Ther* 1995;9:711–12.
- 6 Freifeld AG, Bow EJ, Sepkowitz KA, *et al.* Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011;52:e56–93.
- 7 Beauchesne MF, Shalansky SJ. Nonchemotherapy drug-induced agranulocytosis: a review of 118 patients treated with colony-stimulating factors. *Pharmacotherapy* 1999;19:299–305.
- 8 Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. *Ann Intern Med* 2007;146:657–65.
- 9 Salloum E, Stoessel KM, Cooper DL. Hyperleukocytosis and retinal hemorrhages after chemotherapy and filgrastim administration for peripheral blood progenitor cell mobilization. *Bone Marrow Transplant* 1998;21:835–7.
- 10 Snyder RL, Stringham DJ. Pegfilgrastim-induced hyperleukocytosis. *Ann Pharmacother* 2007;41:1524–30.
- 11 Heydrich BN, Schoch R, Horst HA, *et al.* Dramatic hyperleukocytosis after treatment of myelodysplastic syndrome with pegfilgrastim and darbepoetin-alfa. *Ann Haematol* 2008;87:77–8.
- 12 de Azevedo AM, Goldberg Tabak D. Life-threatening capillary leak syndrome after G-CSF mobilization and collection of peripheral blood progenitor cells for allogeneic transplantation. *Bone Marrow Transplant* 2001;28:311–12.
- 13 Parra Salinas IM, González Rodríguez VP, García-Erce JA. Therapeutic leukapheresis: 9-year experience in a University Hospital. *Blood Transfus* 2015;13:46–52.
- 14 Roberts AW, Foote S, Alexander WS, *et al.* Genetic influences determining progenitor cell mobilization and leukocytosis induced by granulocyte colony-stimulating factor. *Blood* 1997;89:2736–44.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow