Nitrofurantoin-induced agranulocytosis

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SUMMARY

Idiosyncratic drug-induced agranulocytosis is a rare life-threatening adverse reaction characterised by an absolute neutrophil count <500 cells/µL of blood. Nitrofurantoin has been associated with haematological adverse events, but few agranulocytosis cases worldwide have been reported. We present a case of a 68-year-old woman who presented with fever and agranulocytosis following treatment with nitrofurantoin. Extensive workup for agranulocytosis, including a bone marrow aspirate, was unremarkable. Treatment with nitrofurantoin was discontinued, which led to a complete recovery of the complete blood count. This case stresses the importance of monitoring treatments, given that widely used drugs are not free from severe adverse reactions.

BACKGROUND

Idiosyncratic drug-induced agranulocytosis is a rare life-threatening adverse reaction characterised by an absolute neutrophil count <500 cells/µL of blood.[1] Despite recent improvements, the mortality rate for idiosyncratic drug-induced agranulocytosis remains high, mostly due to the high rate of infectious complications.[2 3]

Nitrofurantoin is among the first-line treatment options for uncomplicated urinary tract infections in women, according to the most recent European guidelines.[4] Agranulocytosis is described as a possible adverse effect with unknown frequency in the summary of product characteristics of nitrofurantoin, but few cases worldwide have been reported.[5 6]

This report describes the diagnosis and subsequent management of a 68-year-old woman with agranulocytosis and unexplained fever associated with nitrofurantoin use.

CASE PRESENTATION

A 68-year-old woman, general practitioner, was admitted to the emergency department, due to fever for 4 days. The maximum temperature registered was 39°C. She also complained of generalised abdominal discomfort and odynophagia. There was no complaint of other respiratory, urinary or gastrointestinal symptoms.

She was diagnosed with cystitis in the previous month, 20 days before admission. At the time, urine culture was positive, and isolated *E. coli* which was susceptible to all the tested antibiotics. She was self-medicated with nitrofurantoin 100 mg three times daily for 7 days. After this period, the patient decided to perform a post-treatment urine culture. Because it remained positive for *E. coli*, the patient decided to extend the treatment with nitrofurantoin to a total treatment period of 15 days. Nitrofurantoin was discontinued 1 day before the fever started. She denied taking illicit drugs or supplements.

Past medical history included asthma, controlled hypertension, dyslipidaemia, pre-diabetes controlled with diet and exercise and biliary colic. She has never smoked. Her daily medication included fluticasone furoate/vilanterol inhaler, prednisolone and olmesartan. The patient has no known allergies.

On examination, she was normotensive with a blood pressure of 126/65 mm Hg, heart rate of 87/min, peripheral oxygen saturation of 98% and presented a temperature of 37.8°C. General examination was unremarkable. No lymphadenopathies or organomegaly were noted. The oropharynx was unremarkable.

INVESTIGATIONS

In the emergency department, complete blood count showed a decreased leucocyte count of 0.6×10^9/L (reference range 3.60–10.5x10^9/L), decreased neutrophil count of 0.10×10^9/L (reference range 1.50–7.70x10^9/L) and a decreased lymphocyte count of 0.32×10^9/L (reference range 1.10–4.40x10^9/L). Monocyte, eosinophil and basophil counts were normal. Haemoglobin and platelet levels were also within the reference range. Six months earlier, her complete blood count was unremarkable. Blood biochemistry revealed an elevated C reactive protein of 36.7 mg/dL (reference range <0.50 mg/dL). Renal function, electrolytes, liver function tests, coagulation and procalcitonin were normal. Peripheral blood smear showed an abnormal cell that could potentially be a blast. SARS-CoV-2 PCR obtained from the nasopharynx was negative. Chest radiograph was normal. Given the history of a previous urinary tract infection, a dipstick, urine culture, and renal ultrasound were performed. Urine dipstick was positive for protein and leucocyte esterase. Urine culture was negative, and renal ultrasound was unremarkable. Given the vague abdominal complaints, an abdominal ultrasound was also performed and revealed borderline hepatomegaly of 16 cm, did not reveal any lymphadenopathy or splenomegaly and, was otherwise unremarkable.

The patient was diagnosed with severe neutropenia/agranulocytosis. Following this diagnosis, all drugs were withdrawn, two sets of peripheral blood cultures were performed, meropenem was empirically initiated for febrile neutropenia, and the patient was admitted to an internal medicine ward.

While hospitalised, the patient underwent a workup for agranulocytosis. A targeted approach included checking for infections, nutritional

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deficiencies, malignancy and medications. Regarding nutritional deficiencies, levels of folate and copper were normal, while vitamin B12 and ferritin were elevated, ruling out nutritional deficiencies. Regarding infections, serology for Epstein Barr and cytomegalovirus showed previous infection, testing for Brucella, Rickettsia, Parvovirus, HIV, hepatitis B and C were all negative. Other infections were not tested given the absence of relevant epidemiological context. Peripheral blood cultures were negative. Nitrofurantoin had already been discontinued for 5 days.

Owing to the presence of an abnormal cell on the peripheral blood smear, a bone marrow aspirate was conducted to exclude acute leukaemia or myelodysplasia. Flow cytometry of the aspirate showed reactive changes, in particular reactive appearing T cells and reactive erythropoiesis. Bone marrow smear showed 3.6% blasts, no dysplasia, no abnormal cells and no further abnormalities, therefore excluding acute leukaemia.

DIFFERENTIAL DIAGNOSIS

Neutropenia or agranulocytosis requires evaluation for nutritional deficiencies, infections and medications. Given the abnormal peripheral blood smear, in this case, it was also mandatory to exclude acute leukaemia. In our patient, nutritional deficiencies and infections were ruled out. Acute leukaemia was excluded by blood marrow smear. Medication review revealed recent treatment with nitrofurantoin in an incorrect dosage and for an abnormally extended period. The time course suggests that nitrofurantoin is the most likely cause of agranulocytosis. Despite being febrile, no infection source was identified. Other possible causes of neutropenia are rheumatological and autoimmune disorders, which were not tested given the absence of clinical signs and symptoms. After an extensive workup, treatment with nitrofurantoin for uncomplicated urinary tract infection was determined to have been the most likely culprit.

TREATMENT

Her current medications were withdrawn. Due to the presence of febrile neutropenia, the patient was treated empirically with meropenem, a large spectrum antibiotic, for 7 days. She did not receive other medications while hospitalised. She did not receive granulocyte colony-stimulating factor (G-CSF).

OUTCOME AND FOLLOW-UP

During hospitalisation, complete blood count was monitored. Leucocyte count progressively trended upwards. On the second day after admission, leucocyte count was 2.1×10^9/L (reference range 3.60–10.5x10^9/L) and neutrophil count was 0.65×10^9/L (reference range 1.50–7.70x10^9/L). On the sixth day, leucocyte count returned to normal, with a value of 6.7×10^9/L and neutrophil count was also normal, with a value of 3.73×10^9/L. Haemoglobin remained normal during hospitalisation. Platelet count trended upwards, reaching a value of 480×10^9/L (reference range 140–385$\times10^9$/L) on the sixth day after admission. The patient was febrile on the first day after admission to the ward, with a temperature of 38.5°C, and subsequently remained afebrile until discharge. She was discharged after 8 days.

Three weeks later, she returned to the clinic for follow-up. Complete blood count was unremarkable. She remained asymptomatic and afebrile.

Adverse drug reaction was reported to the INFARMED (National Authority of Medicines and Health Products, I.P.) website. The patient was also referenced to a clinical pharmacology consult specialised in drug adverse reactions.

The patient consented for clinical information relating to the case to be reported in a medical publication.

DISCUSSION

Idiosyncratic drug-induced agranulocytosis is a life-threatening adverse reaction. There are two mechanisms by which drugs cause agranulocytosis: immune-mediated destruction of circulating neutrophils by drug-dependent or drug-induced antibodies; or direct toxic effects on marrow granulocytic precursors. Idiosyncratic drug reactions are thought to be immune-mediated.[7]

According to the literature, 70%–90% of acute and severe agranulocytosis cases are attributable to drugs.[8] All drugs can be implicated, particularly antibiotics.[2 9] The recommended criteria for implicating a drug as a causative agent in neutropenia are derived from an international consensus meeting.[10] Criteria are (1) onset of agranulocytosis during treatment or within 7 days of exposure to the drug, with a complete recovery in neutrophil count of more than 1.5×10^9/L within 1 month of discontinuing the drug; (2) recurrence of agranulocytosis on re-exposure to the drug; (3) exclusion criteria include history of congenital neutropenia or immune-mediated neutropenia, recent infectious disease, recent chemotherapy and/or radiotherapy and/or immunotherapy and existence of an underlying haematological disease.[3 9 11] In this case, agranulocytosis was only detected when the patient was admitted to the emergency department, 5 days after nitrofurantoin was discontinued. Fever started 4 days before admission, suggesting that agranulocytosis was already present at the time. Neutrophil count completely recovered within 11 days of discontinuing the drug, meeting criteria for a causative agent. One limitation in the approach to this case was the non-re-exposure of the patient to the presumed implicated drug. Agranulocytosis is a life-threatening condition, making re-exposure a potential risk for the patient.

Nitrofurantoin is among the first-line treatment options for uncomplicated cystitis in women with a recommended prescription period of 5 days, according to European guidelines.[4] Reported cases of agranulocytosis associated with nitrofurantoin therapy are rare despite being a frequently used drug.[5 12]

Idiosyncratic reactions with agranulocytosis are often serious, with around 50% of cases exhibiting severe sepsis and a mortality rate of 10%–20% over the last 20 years.[9 13] According to a study where 921 patients were treated with nitrofurantoin, 20 presented with blood dyscrasias, and two of the 20 resulted in fatal agranulocytosis.[14] The risk management depends on the absolute neutrophil count.[3 13] In our case, the initial neutrophil count was 0.10×10^9/L, which indicates a significant risk of infection. Neutropenic patients may not exhibit typical signs of infection. Fever is among the most common manifestations of agranulocytosis and should always be presumed to be due to infection and managed with empiric broad-spectrum antibiotics, even if there are few or no clinical signs of infection.

Treatment with haematopoietic growth factors, especially G-CSF, is associated with a significantly lower rate of infectious and fatal complications in cases with a neutrophil count $<0.1\times10^9$/L.[3 8 13] In our case, the patient had stopped the presumed implicated antibiotics several days before admission, and the authors decided to hold the haematopoietic growth factors until they had a second result of the absolute neutrophil count. Neutropenia progressively improved without haematopoietic growth factors.

In conclusion, agranulocytosis is a life-threatening condition, mostly caused by idiosyncratic drug-induced reactions. It is

important to review the patient's medication and consider this diagnosis, even in the presence of frequently used drugs.

Patient's perspective

I initially felt scared about the possibility of acute leukaemia being the diagnosis. Being a physician myself, I understand the implications of agranulocytosis and its poor prognosis. This episode made me think about the numerous drug prescriptions I have made my entire life, and the need to be constantly aware of its risk-benefit ratio. I am very thankful to the entire team for the care provided.

Learning points

- Agranulocytosis is most often drug induced.
- Fever in a neutropenic patient should always be presumed to be due to infection and managed with empiric broad-spectrum antibiotics.
- Myelodysplastic syndromes and acute leukaemia should be excluded in severe neutropenia.
- Commonly used drugs can cause severe adverse reactions.

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