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CASE REPORT
Heart failure

Pancytopenia caused by allopurinol and azathioprine interaction in a heart transplant patient: a case report

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Background Azathioprine is an immunosuppressive now less commonly prescribed after orthotopic heart transplantation. Patients with solid organ transplantation are at increased risk for numerous comorbidities including gout. Co-administration of allopurinol for gout prophylaxis and azathioprine increases the risk for severe myelosuppression due to drug–drug interactions.

Case summary A 57-year-old male with a history of heart transplant 6 years prior presented with a month of severe fatigue and shortness of breath. His admission laboratory values were notable for severe pancytopenia. Medical workup revealed no haematologic malignancy, viral infection, or other consumptive process. After extensive review, it was discovered that the patient was taking excessive allopurinol for gout. His haematologic abnormalities resolved following discontinuation of allopurinol and treatment with filgrastim and romiplostim and was able to be discharged from the hospital.

Discussion Azathioprine and allopurinol can potentially cause profound cytopenias due to the increased production of the active metabolites of azathioprine. Given the association between gout and solid organ transplantation, recognition of the risks of medication interaction as well as communication amongst health care providers and between providers and their patients is paramount.

Keywords Heart transplant • Immunosuppression • Pancytopenia • Case report

Learning points

- Immunosuppressive medications can have severe interactions with commonly prescribed medications placing transplant patients at further increased risk of infection or other complications.
- Proper dose adjustments and patient education are necessary to avoid potentially fatal complications.

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Introduction

Azathioprine is an immunosuppressive now less commonly prescribed after orthotopic heart transplantation. Patients with solid organ transplantation are at increased risk for numerous comorbidities including gout.[1,2] Co-administration of allopurinol for gout prophylaxis and azathioprine increases the risk for severe myelosuppression due to drug–drug interactions.[3] This report describes the case of a patient prescribed azathioprine for immunosuppression following heart transplantation who was found to have severe pancytopenia following self-over administration of allopurinol for gout prophylaxis.

Timeline

Two months prior to admission	Allopurinol started for gout. Azathioprine dose reduced
One month prior to admission	Worsening fatigue and shortness of breath
On presentation	Laboratory evaluation revealed pancytopenia. WBC 0.6 × 10^3/μL, haemoglobin 6.3 g/dL, and platelets 41 × 10^3/μL
Hospital Day 2	Bone marrow biopsy showed trilinear suppression
Hospital Day 4	Started on filgrastim
Hospital Day 5	Started on romiplostim
Hospital Day 15	Blood cell counts recovered and discharged with follow-up

Case presentation

A 57-year-old male presented to the emergency department with complaints of increased fatigue and shortness of breath for the past month. On initial presentation, he reported worsening dyspnoea along with presyncope and decreased appetite. He did not report any infectious symptoms or recent sick contacts and denied any easy bruising, bleeding, or weight loss. On admission vitals, he was noted to be afebrile with a heart rate of 103 b.p.m., blood pressure of 162/84 mmHg, and normal oxygen saturation. His physical examination was notable for pallor and trace lower extremity oedema but was otherwise unremarkable.

His past medical history was notable for acute lymphocytic leukaemia (ALL) diagnosed 14 years prior to presentation and treated via allogeneic stem cell transplant, orthotopic heart transplant due to non-ischaemic cardiomyopathy 6 years prior to presentation, Stage 5 chronic kidney disease, hypothyroidism, hypertension, chronic anaemia, and gout. His outpatient prescriptions included azathioprine 100 mg daily and tacrolimus 2 mg in the morning and 1 mg in the evening for immunosuppression, levothyroxine 137 μg daily, allopurinol 50 mg daily for gout prophylaxis, folic acid 1 mg daily and epoetin alpha injections once weekly for chronic anaemia, as well as torsemide 20 mg daily, diltiazem 300 mg daily, and hydralazine 100 mg three times daily.

Given his complex medical history and presentation, a clear diagnosis was not apparent but post-transplant lymphoproliferative disorder, recurrent ALL, aplastic crisis, disseminated intravascular coagulation (DIC) or other haemolytic disease, and drug-induced pancytopenia were all considered.

Laboratory data revealed pancytopenia with white blood cell (WBC) 0.6 × 10^3/μL (normal 4.5–11.0 × 10^3/μL), haemoglobin 6.3 g/dL (normal 13.9–16.3 g/dL), and platelets 41 × 10^3/μL (normal 150–450 × 10^3/μL). His metabolic panel displayed an elevated creatinine of 5.24 mg/dL, increased from a baseline of 4.5 mg/dL. International normalized ratio (INR) was measured at 1.0, fibrinogen 375 mg/dL (normal 175–450 mg/dL), d-dimer 0.64 μg/mL fibrinogen-equivalent unit (FEU) (normal 0.00–0.50 μg/mL FEU), and haptoglobin 116 mg/dL (normal 30–200 mg/dL). His initial troponin was not elevated and brain natriuretic peptide measured at 193 pg/mL (normal 0.00–100.00 pg/mL). Chest radiograph did not display any signs of acute pulmonary disease.

Initial management was focused on stabilization and he was transfused appropriately to correct his anaemia. Haematology was consulted for additional assistance. Given normal haptoglobin and coagulation studies, DIC or other causes of haemolysis were not thought to be causal. A blood smear was reviewed, which displayed decreased erythrocytes which were normal in appearance, decreased platelets, and no obvious blast cells. A bone marrow biopsy was performed on hospital day 2 which revealed trilinear suppression, with 20% cellularity without evidence of leukaemia or other lymphoproliferative disorder. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) polymerase chain reaction (PCR) and human immunodeficiency virus (HIV) studies returned without evidence of viral infection. Given the lack of evidence of malignancy on peripheral blood smear and bone marrow biopsy as well as negative viral studies, additional consideration was given to drug-induced pancytopenia. After speaking further with the patient, he admitted that he had been taking double his prescribed dose of allopurinol as an outpatient due to his gout. His 50 mg allopurinol prescription had first started 2 months prior to current presentation and at that time azathioprine dosing had been reduced from 125 to 100 mg daily. Due to gout flairs, he had been taking 100 mg of allopurinol. Allopurinol and azathioprine were subsequently discontinued on hospital day 2 and 3, respectively.

He was started on filgrastim 480 μg subcutaneously on hospital day 4 and romiplostim 1 μg/kg subcutaneously on hospital day 5 for bone marrow stimulation. Over the following days, his cell counts began to recover (*Figure 1*). He was discharged on hospital day 15. Allopurinol and azathioprine continued to be held on discharge and he was maintained on tacrolimus monotherapy for immunosuppression. On the day of discharge his WBC was measured at 9.4 × 10^3/μL, haemoglobin 8.4 g/dL, and platelets 36 × 10^3/μL. At a follow-up visit with his nephrologist 5 days after discharge, his platelet count had improved to 103 × 10^3/μL. As part of risk stratification for re-introduction of azathioprine, thiopurine methyltransferase (TPMT) levels were measured and returned at 15.4 units/mL (normal 15.1–26.4 units/mL). He remained on tacrolimus monotherapy for

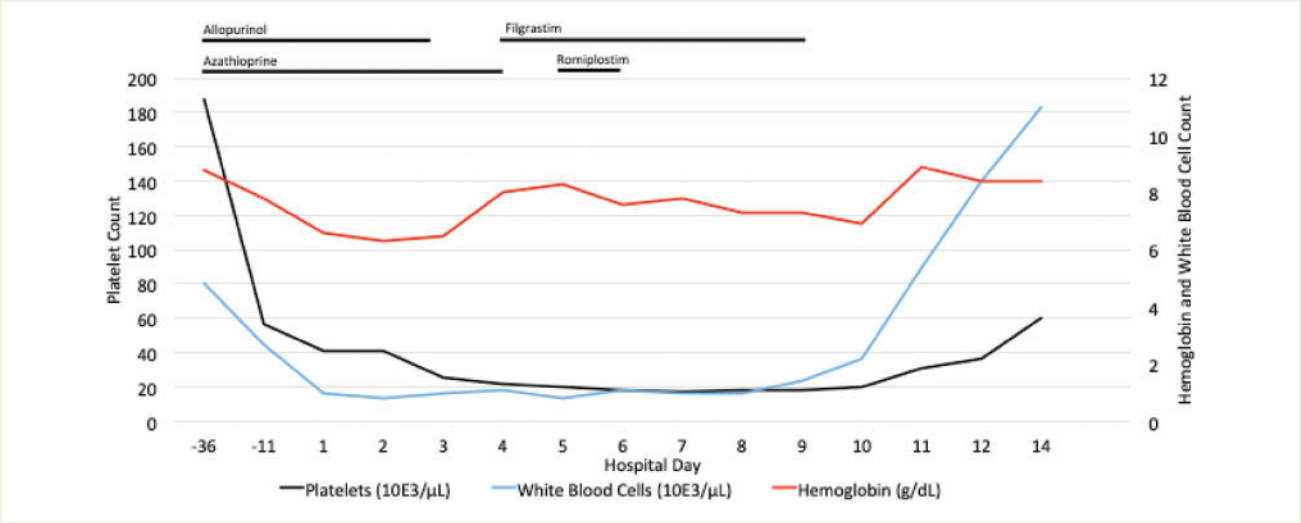

Figure 1 Complete blood cell count results during hospitalization. Temporal relationship between platelet (black), white blood cell (blue), and haemoglobin (red) daily measurements and azathioprine and allopurinol discontinuation and filgrastim and romiplostim administration.

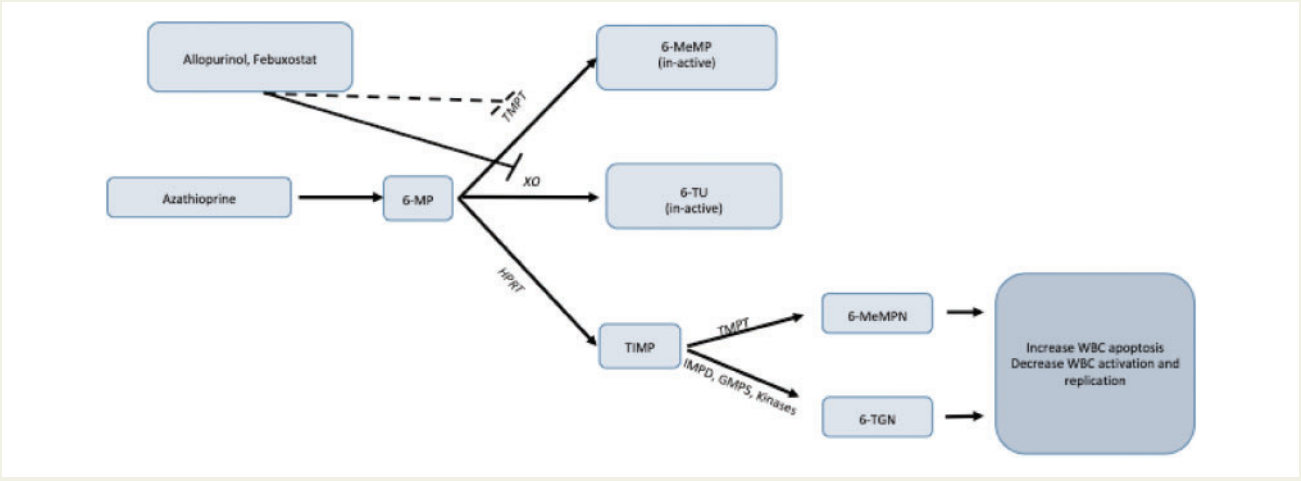

Figure 2 Metabolic pathway displaying interaction between azathioprine and allopurinol leading to pancytopenia. 6-MeMP, 6-methylthiopurine; 6-MeMPN, 6-methylmercaptopurine; 6-MP, 6-mercaptopurine; 6-TGN, 6-thioguanine nucleotide; 6-TU, 6-thiouric acid; GMPS, guanosine monophosphate synthetase; HPRT, hypoxanthine-guanine phosphoribosyltransferase; IMPD, inosine monophosphate dehydrogenase; TIMP, thioinosinic acid; TPMT, thiopurine methyltransferase; XO, xanthine oxidase.

3 months before azathioprine was reintroduced. The patient has not restarted allopurinol to date and remains free from rejection with ongoing surveillance.

Discussion

Gout has been reported in up to 28% of solid organ transplant recipients.[1] Heart transplant recipients may be at significantly increased risk due to concomitant renal disease, loop diuretic prescriptions, and the use of immunosuppressive medications.[2] Previous reports have described similar cases of azathioprine and allopurinol co-administration causing pancytopenia in heart transplant patients.[3]

Azathioprine and allopurinol can potentially cause profound cytopenias due to the increased production of active metabolites of azathioprine. Azathioprine is first converted to 6-mercaptopurine. Under ordinary circumstances, 6-mercaptopurine is partially converted to inactive metabolites via the enzymes xanthine oxidase and TPMT. However, allopurinol, which was prescribed to this patient to help control his gout flairs, acts through blockade of xanthine oxidase and TPMT. When co-administered with azathioprine, this shunts azathioprine away from the production of inactive metabolites, and towards the production of active metabolites which leads to myelosuppression and apoptosis of white blood cells (*Figure 2*). The two medications are not explicitly unable to be co-administered, however, azathioprine dosages are recommended to be reduced by 66–75% when co-administered with allopurinol.[4] Although reducing the dose of azathioprine when co-administered with allopurinol may lead to a relative decrease in the risk of myelosuppression, it does

not completely eliminate the risk.[5] Reduced clearance and accumulation of allopurinol and its metabolites in the setting of chronic kidney disease could be considered an additional risk factor, especially if allopurinol is not renally dose reduced.

In this case, the patient's dose of azathioprine was decreased but he had continued to take an increased dosage of allopurinol which placed him at increased risk for potentially fatal side effects. Following discontinuation of the suspected medications and bone marrow stimulation, his cell counts gradually improved and he was able to be safely discharged back to home. Given the association between gout and solid organ transplantation, recognition of the risks of medication interaction as well as communication amongst health care providers and with their patients is paramount. Additionally, consideration should be made for alternative treatment modalities if available.

Conclusion

Gout is common in solid organ transplant recipients but management is difficult due to potentially fatal side effects from drug interactions. In this case, a patient presented with severe myelosuppression due to azathioprine and allopurinol co-administration. This case emphasizes the need for proper dose adjustments as well as communication between members of the health care team and with their patients.

Lead author biography

Jason Feinman, MD, is a second year medical resident at the Icahn School of Medicine at Mount Sinai. He studied Biochemistry and Molecular Biology at Boston University earning a Bachelor's Degree. He earned his MD degree from Rutgers Robert Wood Johnson Medical School.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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