MEDICINAL MISHAP

Thiopurines and risk of lymphoproliferative disorders

Case

A 29-year-old male with a history of ulcerative colitis presented to his gastroenterologist for a routine check-up and reported 2 weeks of fever, night sweats and fatigue without other symptoms or signs of infection, or weight loss.

The patient had been diagnosed with ulcerative colitis at the age of 23 years and, at that time, was treated acutely with corticosteroids and started on long-term mesalazine and mercaptopurine. Five and a half years later, the mercaptopurine was ceased because he was in clinical remission. However, after 4 months off treatment, he had a colitis flare and was restarted on mercaptopurine with a good response, and was on treatment for a further 6 months before his current presentation. His full blood count and liver biochemistry results were normal when mercaptopurine was restarted, and he was having 3-monthly blood tests.

On examination, his vital signs were normal with the exception of a low-grade fever of 37.8°C. His abdomen was soft and non-tender. There were no appreciable abdominal masses or enlarged lymph nodes.

The patient's full blood count, however, revealed pancytopenia with predominantly blasts on blood film (immature atypical lymphoid cells), suggestive of a haematological malignancy. His liver biochemistry was mildly deranged with a mixed pattern; his initial pathology test results are given in Table 1.

The patient was investigated further for a haematological malignancy. An abdominal ultrasound revealed hepatosplenomegaly, with a liver span of 17 cm and spleen span of 18 cm. Bone marrow and trephine biopsy revealed hepatosplenic T-cell lymphoma (HSTCL).

Mercaptopurine, an immunosuppressant, was withdrawn, and he was started on combination chemotherapy before receiving an allogeneic haematopoietic stem cell transplant. A timeline of the patient's mercaptopurine use is given in Table 2.

Comment

This young male was diagnosed with a rare peripheral T-cell lymphoma 6.5 years after his initial diagnosis of ulcerative colitis and after a total of 6 years of mercaptopurine use (Table 2).

Table 1 Patient's initial pathology test results

Pathology test	Result	Reference range [NB1]
Full blood count		
haemoglobin concentration	107 g/L	125 to 175 g/L
white cell count	2.6 × 10^9/L	4.0 to 11.0 × 10^9/L
platelet count	86 × 10^9/L	150 to 400 × 10^9/L
blood film microscopy	predominantly blasts (immature atypical lymphoid cells)	–
Liver biochemistry		
unconjugated bilirubin concentration	1351 micromol/L	3.4 to 12.0 micromol/L
lactate dehydrogenase concentration	1348 units/L	120 to 250 units/L
Viral serology		
EBV	EBV-IgG positive and EBV-IgM negative	–

EBV = Epstein-Barr virus; IgG = immunoglobulin G; IgM = immunoglobulin M
NB1: Reference ranges are taken from the patient's laboratory results.

Varan Perananthan
Gastroenterologist[1]
Clinical Research Fellow[2]
PhD Candidate[3]

Miles P Sparrow
Gastroenterologist, and Head of Inflammatory Bowel Disease Unit[1]
Adjunct Clinical Associate Professor of Medicine[2]

Anna Foley
Gastroenterologist[1]

[1] Department of Gastroenterology and Hepatology, The Alfred, Melbourne
[2] Monash University, Melbourne
[3] Clinical Pharmacology and Toxicology Research Group, Biomedical Informatics and Digital Health, The University of Sydney

Keywords
lymphoproliferative disorders, mercaptopurine, T-cell lymphoma, thiopurines, ulcerative colitis

Aust Prescr 2024;47:91–3
https://doi.org/10.18773/austprescr.2024.020

Table 2 Patient's timeline of mercaptopurine use

Date	Event
September 2016	diagnosis of ulcerative colitis
October 2016	started on mercaptopurine
March 2022	ulcerative colitis in clinical remission; ceased mercaptopurine
July 2022	flare of ulcerative colitis; restarted mercaptopurine
January 2023	presented to gastroenterologist with a 2-week history of fever, night sweats and fatigue
February 2023	diagnosed with hepatosplenic T-cell lymphoma and started on treatment; mercaptopurine ceased

Thiopurines (e.g. azathioprine, mercaptopurine) have an important role in the treatment of inflammatory bowel disease (IBD) (including ulcerative colitis), to induce and maintain remission in patients with severe initial disease or frequent relapses. Lymphoproliferative disorders (LPDs) are a heterogeneous group of at least 70 conditions that result from clonal proliferation of B cells, T cells or natural killer cells.[1] Development of an LPD is a well-recognised, but rare, complication of thiopurine therapy.

IBD is associated with a small risk of developing an LPD, marginally higher than in the general population; however, if patients with IBD are treated with thiopurines, their risk increases 4- to 6-fold.[1-3] Other risk factors for LPDs in patients with IBD are old age, male sex, and longer duration of IBD.[3] The increased risk of developing an LPD with thiopurine use is not limited to IBD; it is also recognised in patients using thiopurines after:

- renal transplant (risk increased 6- to 20-fold)
- cardiac transplant (risk increased up to 200-fold).[4]

Newer biologic drugs can be used in combination with, or instead of, thiopurines for IBD. Large cohort studies have shown concurrent use of a thiopurine with a tumour necrosis factor (TNF) inhibitor (e.g. adalimumab, infliximab) increases the risk of developing an LPD in patients with IBD.[3]

The most common type of LPD associated with thiopurine use for IBD is Epstein-Barr virus (EBV)–positive B-cell lymphoma. This LPD occurs because of uncontrolled proliferation of EBV-positive B cells (associated with a latent EBV infection) that would normally be regulated by T cells.[1]

Despite being EBV-IgG positive, the type of LPD diagnosed in this patient was hepatosplenic T-cell lymphoma (HSTCL). Peripheral T-cell lymphomas account for 12% of all lymphoid tumours and HSTCL comprises fewer than 5% of peripheral T-cell lymphomas, highlighting that this condition is rare.[5] There have been more than 200 cases of HSTCL reported in the literature, including 62 patients with a diagnosis of IBD and 57 of these having had exposure to thiopurines.[6,7] HSTCL is strongly associated with thiopurine use in young males with IBD. The absolute risk of HSTCL in all patients taking thiopurines for IBD is 1:45,000. In males aged 35 years or younger, this increases to 1 in 7404, and for patients who are on combination therapy with a thiopurine and a TNF inhibitor, the absolute risk of HSTCL is 1 in 3534.[6]

There have also been 20 published cases of HSTCL in patients on thiopurines after solid organ transplants, suggesting a drug class effect.[6] Of the patients who developed HSTCL, thiopurines were used for at least 2 years, with a median duration of 5.5 years. Permanent cessation of a thiopurine at any point reduces the risk of HSTCL to that in the general population.[1]

The underlying pathophysiology for developing an LPD, and particularly HSTCL with thiopurine use, has not been established so individualised risk assessment is not possible. Considering LPD is rare and IBD is associated with significant morbidity, the likely benefits of thiopurine use far outweigh the potential harms and, if clinically indicated for control of disease, thiopurines should be used, with close monitoring of full blood count and liver biochemistry.[1]

For patients with IBD in prolonged clinical remission, especially males aged 35 years or younger, deprescribing thiopurines should be considered on a case-by-case basis. Although this was attempted in this patient, unfortunately it resulted in an escalation of his IBD symptoms, necessitating reintroduction of a thiopurine and his subsequent diagnosis of HSTCL.

Conclusion and recommendations

Practitioners prescribing or who have patients prescribed thiopurines should be aware of symptoms such as fever, night sweats or fatigue.

Thiopurine use is associated with an increased risk of developing an LPD. HSTCL is a rare and aggressive form of LPD strongly associated with thiopurine

use in males 35 years or younger with IBD. There is no tool to predict the risk of this disease occurring in an individual patient. The outcome for HSTCL is poor with 5-year survival rates less than 10% without allogeneic haematopoietic stem cell transplant.[8]

Thiopurines remain a cornerstone of treatment for IBD in Australia; however, deprescribing in appropriate clinical circumstances should be considered to prevent rare malignancies.

Patient consent for publication of this case study was obtained by the authors.

Conflicts of interest: Varan Perananthan was the Clinical Pharmacology Trainee participant on the Australian Prescriber Editorial Executive Committee at the time of writing. He was excluded from editorial decision-making related to the acceptance and publication of this case study.

Miles Sparrow has received research support from Gilead and Celltrion, and speaker fees from Janssen, AbbVie, Ferring Pharmaceuticals, Takeda Pharmaceuticals, Pfizer, Celltrion Healthcare, Eli Lilly and Dr. Falk Pharma. He has been on advisory boards for Janssen, Takeda Pharmaceuticals, Pfizer, Celgene, AbbVie, MSD, Emerge Health, Gilead, Bristol Myers Squibb, Celltrion Healthcare and Eli Lilly.

Anna Foley has no conflicts of interest to declare.

REFERENCES

1. Subramaniam K, D'Rozario J, Pavli P. Lymphoma and other lymphoproliferative disorders in inflammatory bowel disease: a review. J Gastroenterol Hepatol 2013;28:24-30. https://doi.org/10.1111/jgh.12015
2. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut 2005;54:1121-5. https://doi.org/10.1136/gut.2004.049460
3. Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lemann M, Cosnes J, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet 2009;374:1617-25. https://doi.org/10.1016/S0140-6736(09)61302-7
4. Lam GY, Halloran BP, Peters AC, Fedorak RN. Lymphoproliferative disorders in inflammatory bowel disease patients on immunosuppression: Lessons from other inflammatory disorders. World J Gastrointest Pathophysiol 2015;6:181-92. https://doi.org/10.4291/wjgp.v6.i4.181
5. Pro B, Allen P, Behdad A. Hepatosplenic T-cell lymphoma: a rare but challenging entity. Blood 2020;136:2018-26. https://doi.org/10.1182/blood.2019004118
6. Kotlyar DS, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2011;9:36-41 e1. https://doi.org/10.1016/j.cgh.2010.09.016
7. Shah ED, Coburn ES, Nayyar A, Lee KJ, Koliani-Pace JL, Siegel CA. Systematic review: hepatosplenic T-cell lymphoma on biologic therapy for inflammatory bowel disease, including data from the Food and Drug Administration Adverse Event Reporting System. Aliment Pharmacol Ther 2020;51:527-33. https://doi.org/10.1111/apt.15637
8. Rashidi A, Cashen AF. Outcomes of allogeneic stem cell transplantation in hepatosplenic T-cell lymphoma. Blood Cancer J 2015;5:e318. https://doi.org/10.1038/bcj.2015.43