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CASE REPORT

FATAL DRUG-INDUCED NEUTROPENIA WITH NECROTISING GASTRITIS AND SEPSIS: A CASE REPORT

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ABSTRACT

Azathioprine is an immunosuppressant widely used in the management of autoimmune and inflammatory disorders, including dermatological conditions. Despite its clinical usefulness, it is associated with a wide range of adverse effects, the most significant of which is bone marrow suppression. Necrotising gastritis is a rare and life-threatening condition where predisposing factors include immunosuppression.

This case report describes a fatal necrotising gastritis following immunosuppression due to azathioprine therapy. The clinical presentation, laboratory investigations, ultrasound scan evidence, and the autopsy findings were supportive of gastrointestinal sepsis. This fatal outcome highlights the importance of haematological monitoring, clinical vigilance, and prompt recognition of early signs of drug toxicity or infection.

Keywords: *Azathioprine, immunosuppression; necrotising gastritis*

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INTRODUCTION

Azathioprine is a purine analogue and an immunosuppressant, widely used in the management of autoimmune and inflammatory disorders, including dermatological, rheumatological, and gastrointestinal conditions[1,2]. It acts by inhibiting DNA and RNA synthesis, resulting in decreased proliferation of rapidly dividing cells[1]. Despite its clinical usefulness, azathioprine is associated with a wide range of adverse effects, the most significant of which is bone marrow suppression[1,2], which may manifest as leukopenia, thrombocytopenia, or pancytopenia, directly correlating with the patient's vulnerability to infections. Severe or rapidly progressive neutropenia may predispose patients to fulminant and fatal infections.

Necrotising gastritis is a rare and life-threatening condition characterised by widespread inflammation, mucosal necrosis, and bacterial invasion of the gastric wall. Although the pathogenesis is unclear, the predisposing factors include immunosuppression and treatment with cytotoxic drugs[3]. It typically presents with severe abdominal pain, vomiting, haematemesis, and systemic signs of sepsis. Prompt diagnosis and early surgical intervention are critical in preventing fatal complications[3,4]. The development of necrotising gastritis in the context of drug-induced neutropenia is

exceedingly uncommon, with a limited number of cases reported in the medical literature[5].

We present a fatal case of necrotising gastritis in a previously healthy elderly male following azathioprine-induced neutropenia. This case underscores the importance of timely haematologic monitoring during immunosuppressive therapy and awareness of rare gastrointestinal complications while on immunosuppressive agents[4].

CASE HISTORY

A 64-year-old male presented to a dermatologist with a recently developed rash over the upper limbs. He had no significant past medical history, took no regular medications, and was not known to have any immunological or haematological disorders. He was prescribed azathioprine 25 mg twice daily. The full blood count before starting treatment was within normal limits (total white cell count - 7000/µl, neutrophils - 44%).

Over the subsequent three weeks, the patient experienced clinical improvement of his cutaneous symptoms, with complete resolution of the rash. However, he began to notice significant hair loss during this period, although no severe systemic symptoms were recorded. Further investigations revealed marked leukopenia (3150/µl). The azathioprine therapy was discontinued, and an alternative treatment regimen was prescribed.

Despite the new treatment regimen, the patient presented to the hospital with progressive neutropenia (total white cell count - 1870/µl, neutrophils - 11.5%), high-grade fever, severe epigastric pain, and repeated episodes of profuse vomiting. He was clinically diagnosed with neutropenic sepsis, and broad-spectrum intravenous antibiotics and aggressive supportive therapy were initiated. However, he succumbed two days later.

Inward laboratory investigations showed further progression of leucopenia with critically low neutrophil counts (total white cell count - 370/µl, neutrophils - 11%). Platelet counts (281000/µl) and the haemoglobin levels (12 g/dl) were within normal limits. C-reactive protein was 289 mg/l. The ultrasound scan of the abdomen revealed thickening of the gastric and lower oesophageal walls.

An autopsy was performed. The external examination revealed diffusely thinned scalp hair that was easily detachable. No significant rash was observed. The examination of the gastrointestinal tract revealed markedly thickened and congested gastric mucosa with widespread areas of extensive necrosis (Figure 1). Both lungs showed pulmonary oedema with fatty degeneration of the liver. The other internal organs were unremarkable.

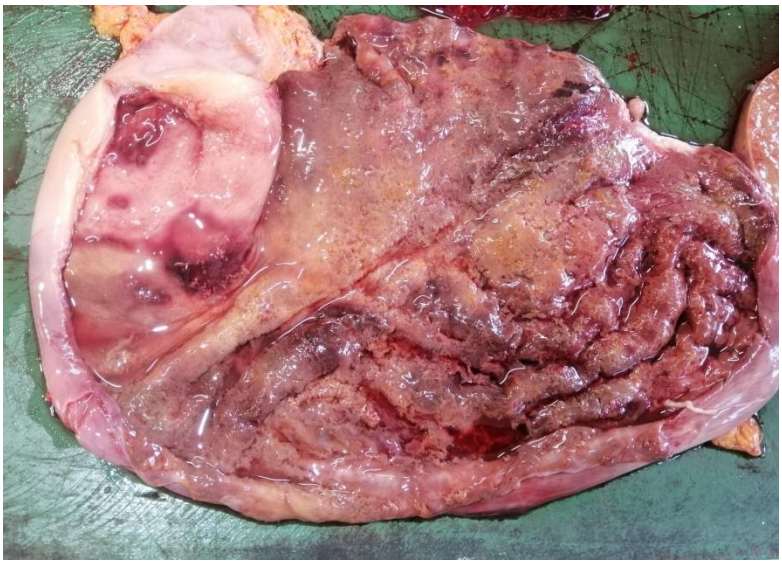

Figure 1: Specimen of the stomach demonstrating the congested and oedematous mucosa with multiple areas of necrosis.

Histopathological examination of the gastric mucosa revealed ulceration and necrosis (Figures 2 and 3), accompanied by extensive vascular congestion (Figure 4). Bacterial colonies were observed deep within the gastric mucosa (Figure 5), indicating severe infectious infiltration. There was widespread necrosis with a lack of accompanying inflammatory cellular response (Figures 2 and 3), consistent with profound neutropenia.

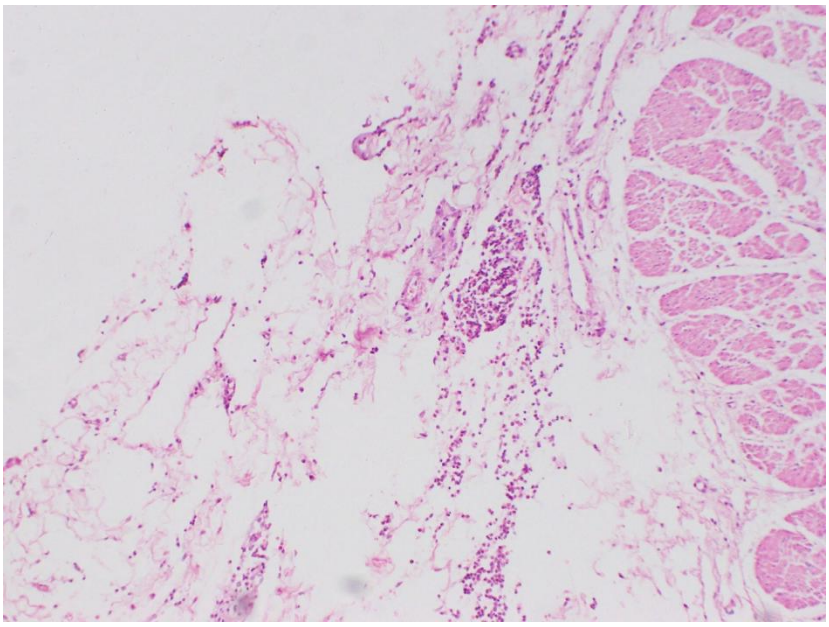

Figure 2: The surface epithelium is significantly absent, extensive tissue destruction involved beyond the superficial mucosa, with loss of normal gastric architecture. Scattered neutrophil infiltration noted (H&E x10)

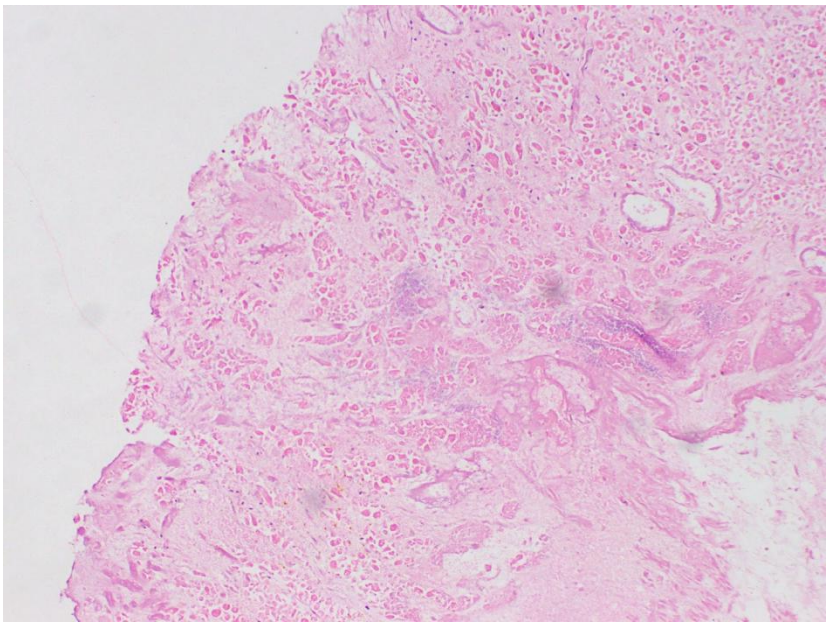

Figure 3: The gastric mucosa is largely replaced by homogeneous eosinophilic necrotic tissue and few neutrophil infiltrations with loss of normal architecture (H&E x10)

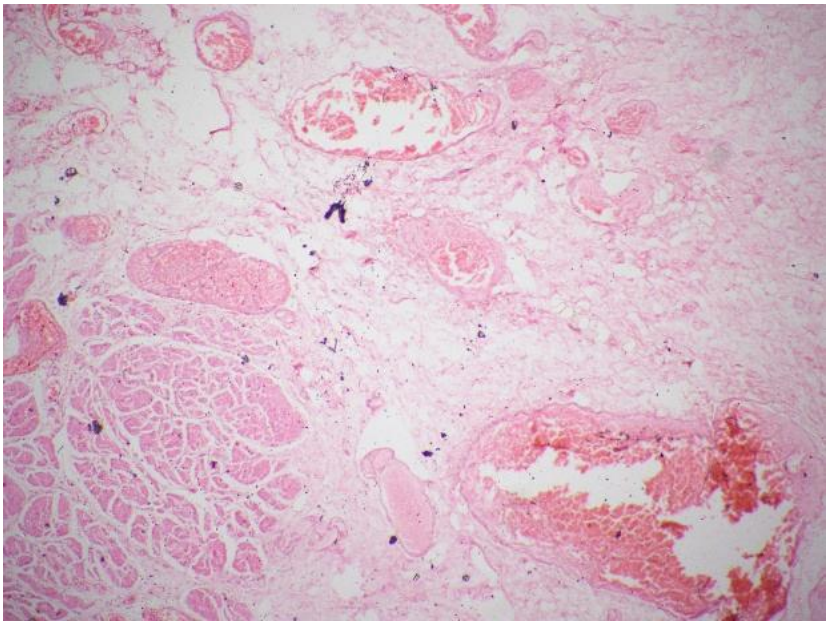

Figure 4: Micrograph of the gastric mucosa demonstrating extensive vascular congestion (H&E x10)

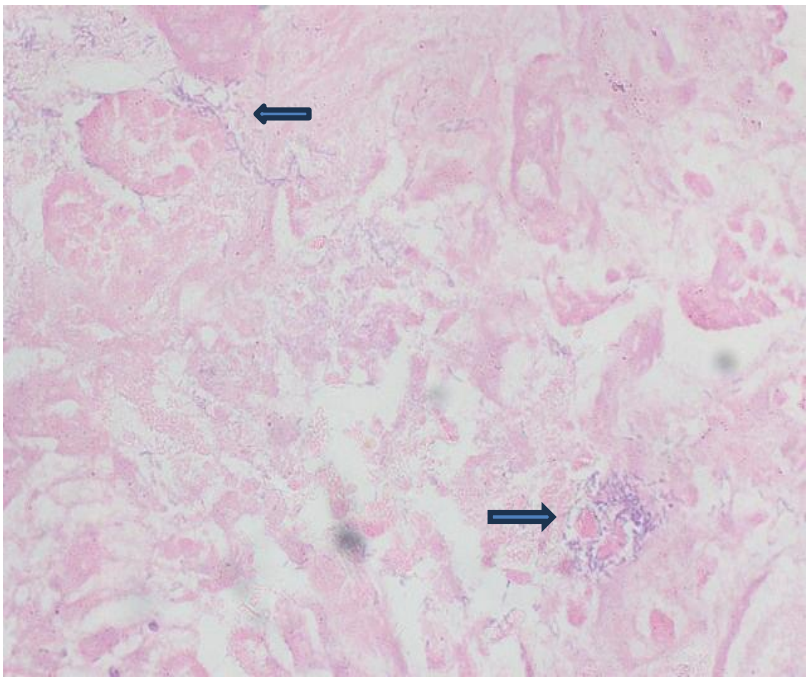

Figure 5: Micrographs of the gastric mucosa demonstrating bacterial colonies (arrows) deep within the gastric mucosa, with a few neutrophils infiltrating the necrotic tissue (H&E x10).

Considering the clinical history, laboratory investigations, and autopsy findings, the cause of death was concluded to be sepsis due to necrotising gastritis in a patient who was recently on azathioprine therapy.

DISCUSSION

This case report describes a fatal necrotising gastritis following immunosuppression due to azathioprine therapy. Azathioprine is metabolised through several pathways, including the **thiopurine methyltransferase (TPMT)** enzyme system[7]. Deficiencies or reduced activity in these pathways significantly increase the risk of drug-induced myelotoxicity[1,6]. The most serious side effect of azathioprine is bone marrow suppression, which may be life-threatening[6]. The deceased presented with alopecia following azathioprine therapy, which is an early warning sign of marrow toxicity[6]. The neutropenia progressed despite discontinuation of the drug. The rapid progression to agranulocytosis created an immunologically vulnerable state, predisposing the patient to fulminant bacterial invasion.

The clinical presentation, laboratory investigations, and the ultrasound evidence were supportive of gastrointestinal sepsis. During neutropenia, the gastrointestinal mucosa becomes susceptible to translocation of enteric organisms, often leading to severe, rapidly progressive infections[8]. In this case, autopsy examination revealed extensive mucosal necrosis, thickened and congested gastric folds, and necrotic debris, consistent with necrotising **gastritis.** Histology confirmed deep mucosal destruction with bacterial colonies penetrating the tissue and a lack of inflammatory cells, a hallmark of profound neutropenia. The lack of an inflammatory response reflects the inability of the host to mount a defence response, resulting in widespread bacterial proliferation and mucosal necrosis.

CONCLUSION

This case underscores a rare complication of azathioprine, which has precipitated severe bone marrow suppression leading to aggressive infections. The fatal outcome in this instance highlights the importance of assessing **baseline full blood counts** and TPMT levels where available before safe therapy initiation. Identifying individuals with low TPMT enzymatic activity, which is not routinely done in Sri Lanka, allows clinicians to adjust dosing or select alternative medications, thereby reducing the likelihood of severe adverse outcomes. After initiating the treatment, it is important to continue haematological monitoring, be clinically vigilant, and promptly recognise early signs of drug toxicity.

This case serves as a reminder that even widely used immunosuppressive agents can lead to life-threatening consequences, reinforcing the need for strict monitoring protocols when prescribing azathioprine. The clinicians must ensure

structured surveillance and provide clear patient education to enable timely medical intervention.

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CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

ETHICAL ISSUES

The presented autopsy case was conducted for medico-legal purposes, and this information is used for academic purposes, according to the institutional guidelines.

SOURCES OF SUPPORT

None.

AUTHOR CONTRIBUTIONS

HMJ: Conception and design of the work; the acquisition, analysis, and interpretation of data for the work; drafting the work; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. **JW:** Conception and design of the work; the acquisition, analysis, and interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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