Realgar-Indigo Naturalis Formula-Induced Acute Colitis: A Case Report

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ABSTRACT

A middle-aged woman with acute myeloid leukaemia (M3) developed abdominal pain and haematochezia after using the Realgar-Indigo Naturalis formula (RIF). After comprehensive evaluations including enhanced CT, colonoscopy, and pathological biopsy, other diseases were excluded, and medicine-related acute colitis was considered. The patient's colonic condition improved after the discontinuation of medication. The primary component of the RIF is arsenic, the only orally available arsenic-containing anti-leukaemia medicine. Arsenic exerts a direct corrosive effect on the gastrointestinal tract, resulting in inflammation and ulceration at the contact site. This type of colitis warrants further research to provide insights for clinical diagnosis. Concurrent use of this medication necessitates vigilance regarding potential intestinal side effects.

Key Words: *Realgar-indigo naturalis formula, Acute colitis, Acute myeloid leukaemia.*

How to cite this article: Lei J, Wu L. Realgar-Indigo Naturalis Formula-Induced Acute Colitis: A Case Report. *JCPSP Case Rep* 2025; **3**:34-36.

INTRODUCTION

Colitis can arise from various aetiologies, including infections, autoimmune disorders, and medications. Notably, among the medications, non-steroidal anti-inflammatory medicines (NSAIDs), immune checkpoint inhibitors, and chemotherapeutic agents are significant contributors.[1] However, the precise mechanisms by which these medicines induce colitis remain not fully elucidated. Another arsenic-containing compound, known as the Realgar-Indigo Naturalis formula (RIF), is an oral traditional Chinese medicine that includes As4S4 and has demonstrated significant efficacy in treating acute promyelocytic leukaemia (APL).[2]

In this study, we present a case in which the patient had no significant symptoms of diarrhoea or abdominal pain in the past and had a normal colonoscopy a year ago. However, a few months prior, the patient was diagnosed with leukaemia. Following treatment and subsequent improvement, the patient was placed on maintenance therapy with RIF. The patient later developed symptoms of colitis, which improved after the discontinuation of RIF. To date, very few cases of RIF-related colitis have been reported in the literature.

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Received: September 16, 2024; Revised: October 24, 2024; Accepted: November 23, 2024
DOI: https://doi.org/10.29271/jcpspcr.2025.34

CASE REPORT

A 56-year woman was admitted to the hospital with a ten-day history of abdominal pain and haematochezia. The primary symptoms included haematochezia, abdominal pain, particularly around the umbilicus, and the passage of red, watery stools three times daily. Notably, there was no vomiting, melena, chills, or fever. The patient had a history of acute myeloid leukaemia (M3 type), diagnosed a year ago, which had been managed with the oral administration of RIF and trans-retinoic acid on an alternating monthly schedule following remission. Her disease was well-controlled, and she was within her medication cycle at the time of admission. Upon admission, laboratory tests revealed a haemoglobin level of 150 g/L, immunoglobulin G concentration of 1710.0 mg/dL, and negative DNA tests for cytomegalovirus and Epstein-Barr virus. The tuberculosis infection T-cell interferon-gamma release assay (TB-IGRA) was negative. C-reactive protein was elevated at 20.0 mg/L, and the erythrocyte sedimentation rate (ESR) was 17 mm/1st hour. Lipid profile, antibody testing for Toxoplasma gondii, Cytomegalovirus (CMV), Rubella virus, and Herpes simplex virus, intestinal tumour markers, liver and kidney function tests, and electrolytes were all within normal limits. The Purified Protein Derivative (PPD) test was negative. Enhanced CT scans of the chest and abdomen showed no arterial stenosis or calcification in the colon; however, there was oedema and thickening of the colonic wall from the splenic flexure to the descending colon, suggesting an inflammatory condition, possibly ulcerative colitis (Figure 1A, B). The appendix appeared normal, with fecalith present within the lumen. Gastroscopy findings were unremarkable, while colonoscopy revealed widespread mucosal congestion, oedema, and fria-

bility throughout the colon, with spontaneous bleeding, particularly in the descending and sigmoid colon. Multiple irregularly-shaped ulcers and extensive mucosal erosions, accompanied by purple haemorrhagic nodules, were observed (Figure 1C, D). Pathological examination of the biopsy samples indicated chronic mucosal inflammation with erosion, without definitive cryptitis, crypt abscesses, granulomas, or significant crypt architectural distortion. The glandular structure was preserved (Figure 1E, F). Immunohistochemistry showed negative results for CD34, CD68, and CMV. Periodic Acid–Schiff (PAS) and silver methenamine stains were negative, thereby ruling out specific infections. The patient was managed with fasting, haemostasis, antispasmodic and analgesic medications, anti-infective therapy (ceftriaxone), microcirculation improvement, and fluid replacement. Her condition improved, and she was discharged. A follow-up colonoscopy, conducted two months after discontinuing RIF, revealed complete resolution of the colonic lesions.

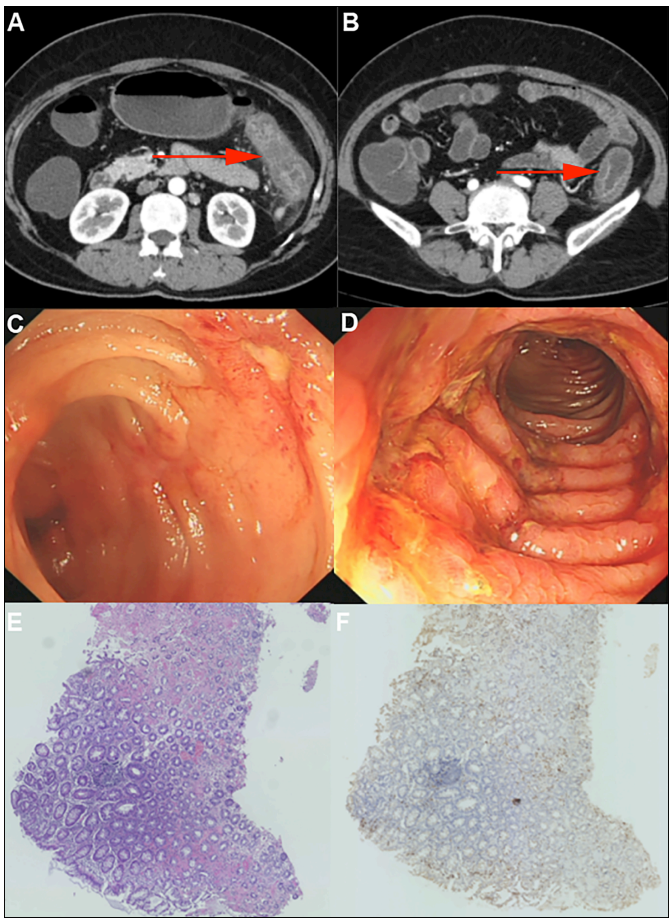

Figure 1: (A, B) The enhanced CT imaging features of the descending and sigmoid colon (red arrow points to colonic lesion). (C, D) The colonoscopic findings of the descending and sigmoid colon: Circular ulcers and diffuse longitudinal irregular ulcers. (E, F) The histopathological features of the sigmoid colon biopsy under HE staining and related viral immunohistochemical staining (× 50).

DISCUSSION

This case involved a middle-aged female with no underlying hypertension or diabetes, presenting with acute abdominal pain and haematochezia. Colonoscopy and enhanced CT indicated that the lesions were most severe in the left colon (sigmoid and descending colon). Based on the patient's history, laboratory findings, imaging, and pathology, we ruled out ischaemic colitis, infectious colitis, ulcerative colitis, malignancies, and venous thrombosis-related colitis. Given the patient's history of using specific medication before symptoms' onset and the resolution of symptoms following discontinuation, medicine-induced colitis was considered the most likely diagnosis. Arsenic and its compounds act as protoplasmic toxins by binding to key sulphydryl-containing metabolic enzymes, rendering them inactive, thereby disrupting normal cellular metabolism and leading to cell death.[3] Arsenic exerts a direct corrosive effect on the gastrointestinal tract, resulting in inflammation and ulceration at the contact site. Arsenic poisoning can manifest as diarrhoea, initially watery and later resembling rice water mixed with blood, followed by systemic failure, dehydration, hypothermia, collapse, and loss of consciousness.[4,5] Undeniably, intestinal diseases are influenced by the intervention of gut microbiota. A recent study suggests that RIF may also exert its therapeutic effects by impacting the microbiome. It can be speculated that a certain dosage of RIF, through its effect on microbial diversity, may lead to intestinal erosion and ulcerative damage.[6] With the increasing clinical use of this medicine, heightened awareness of this complication is essential, and timely management is critical. Further research is warranted to enhance our understanding of this condition.

PATIENT'S CONSENT:

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

JL: Conception and design of the study, drafting of the manuscript, acquisition, analysis, and interpretation of data.
LW: Supervision and critical revision of the manuscript for significant intellectual content.
Both authors approved the final version of the manuscript to be published.

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