

# Leflunomide-induced delayed onset colitis

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## Introduction

A 73-year-old woman with a history of psoriatic arthritis presented with worsening watery diarrhoea for 2 weeks. Initial stool cultures requested by the GP showed no growth with no relief from an anti-diarrhoeal medication given in the community. She underwent inpatient fluid resuscitation. Colonoscopy showed normal appearance of the colon and the biopsy results showed left-sided collagenous colitis along the left hemi-colon with a differential diagnosis of drug-induced colitis. She had taken leflunomide for more than 3 years and only recently developed watery diarrhoea. Her rheumatologist agreed to switch her to methotrexate, which resulted in complete resolution of the symptoms.

## Case report

A 73-year-old woman with a history of psoriatic arthritis, hypothyroidism and hypertension presented to the accident and emergency services with a progressively worsening 2-week complaint of watery diarrhoea. She was found to be clinically dehydrated with a dry tongue, low blood pressure of 95/70 mmHg, heart rate 102/minute regular with normal oxygen saturations. Systemic examination revealed some tenderness along the left iliac region with normal bowel sounds, and some psoriatic plaques in a stable phase along the front and back of her torso, thighs and legs. Rectal examination was normal. She was fluid resuscitated and abdominal X-ray findings were non-specific. Her haemoglobin level was 124 g/litre, with similar results on repeat blood tests.

She underwent axial computed tomography of the abdomen and pelvis that suggested diverticular disease of the sigmoid colon (Figure 1). Her stool cultures were negative and she underwent colonoscopy that showed a normal colonic mucosa with diverticular disease and biopsy suggesting collagenous colitis along the left hemi-colon (Figures 2 and 3). The histopathologist queried whether this could have a drug-related cause. Her medications included leflunomide 20 mg maintenance dose, amlodipine 5 mg, ramipril 5 mg and levothyroxine 50 µg, all once a day. Her case of this possible side effect was discussed with her rheumatologist, who agreed to stop leflunomide and start the patient on a lower dose of methotrexate (12.5 mg once a week) with folic acid 5 mg replacement. The patient consented to the treatment change and this resulted in dramatic cessation of diarrhoea. Repeat colonoscopy including biopsy showed complete resolution.

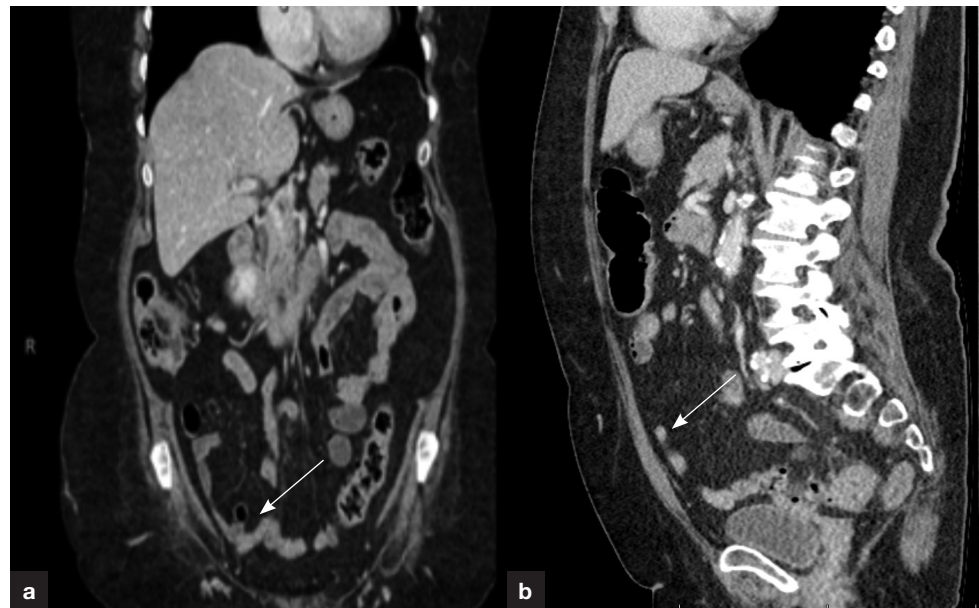
## Discussion

The mechanism of action of leflunomide is via interference with the clonal expansion of T-cells. It does so by its active metabolite A77 1726, which inhibits mitochondrial enzyme dihydroorotate dehydrogenase, an enzyme involved in the synthesis of pyrimidine (Günendi et al, 2010). Leflunomide is a well recognised oral disease-modifying antirheumatic drug along with methotrexate and sulfasalazine. Although the clinical efficacy of leflunomide in double blinded and randomised clinical trials has been found to be better than placebo, its efficacy is lower than that of methotrexate (Cohen et al, 2001; Osiri et al, 2003).

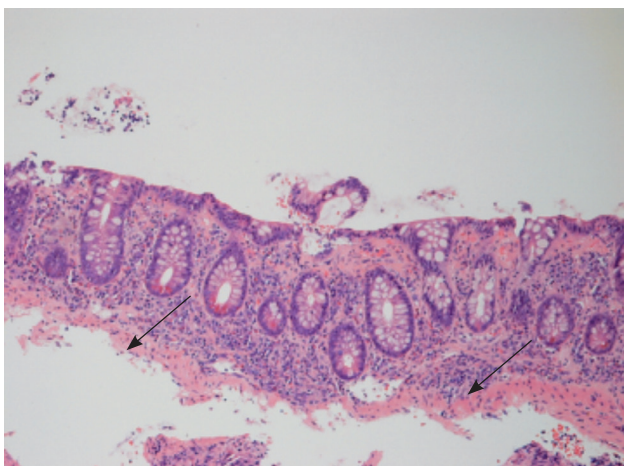
Gastrointestinal symptoms and in particular diarrhoea remain the most reported transient side effect of leflunomide use, usually only seen during the first few weeks of treatment. There is very limited information available about the delayed manifestation of colitis associated with leflunomide use. Kwok and Morosin (2019) reported a patient in Australia who was post renal transplant and had enterocutaneous fistula with chronic diarrhoea for 18 months with further acute exacerbation for 6 weeks. Günendi et al (2010) reported colitis in a patient in Turkey, with a 2-week history of diarrhoea, after 24 months of leflunomide treatment. However, the patient was also found to have aphthous ulcerative colitis on biopsy. Another case in the Republic of Ireland, from Finn et al (2006), reported a patient with typhlitis who died with aspergillosis and neutropenic sepsis who had been taking leflunomide for 1.5 years. Verschueren et al (2005) reported two cases in Belgium

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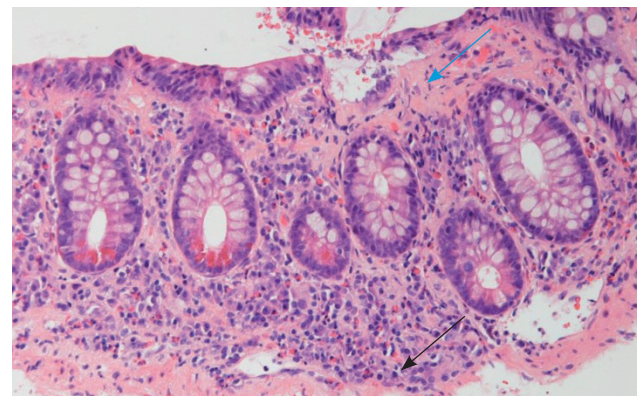
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**Figure 1.** Computed tomography of the abdomen and pelvis. a. Coronal view and (b) sagittal view showing diverticular disease of the sigmoid colon with multiple diverticuli along with long segment of wall thickening with only slight oedema associated with slight congestion of the sigmoid meso-colon (arrow).



**Figure 2.** Left colonic mucosa showing a band of subepithelial collagen deposition (arrows). Haematoxylin and eosin staining x100.



**Figure 3.** Left colonic mucosa showing thickened subepithelial collagen (blue arrow) with inflammatory cells (black arrow), including plasma cells and eosinophils, extending down to the muscularis mucosa. Haematoxylin and eosin staining x200.

following 1 year's treatment with leflunomide, with biopsy revealing ulcerative colitis in one patient, and microscopic colitis with predominant lymphocytes and plasma cells in the other. Another case reported in the United States of America showed surface erosion and increased inflammation of the lamina propria in a biopsy sample post 17 months treatment with leflunomide (Lui et al, 2020).

To the best of the authors' knowledge, this is the first reported case of leflunomide-induced collagenous colitis, and the first case to be reported with a history of watery diarrhoea 3 years after initiation of leflunomide. It remains important for clinicians to be aware of this delayed side effect that may happen after prolonged use of leflunomide.

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## Learning points

- Patients treated with leflunomide for rheumatoid arthritis, psoriatic arthritis and other rheumatological conditions complaining of persistent watery diarrhoea should be referred for colonoscopy with biopsy sampling to rule out any associated colitis.
- Leflunomide use may result in watery diarrhoea with colitis following prolonged use and clinicians should be aware of this delayed onset side effect.
- Leflunomide-associated colitis is reversible with complete resolution on stopping the treatment.

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