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CASE REPORT

Leflunomide-induced colitis in association with enterocutaneous fistula in an immunosuppressed patient with renal transplant and rheumatoid arthritis

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Abstract
We describe the case of a 68-year-old man who has a complex medical background that included renal transplantation, rheumatoid arthritis and atrial fibrillation. Because of this, he was taking a number of immunosuppressant medications including leflunomide, prednisone and tacrolimus. He had experienced chronic diarrhoea over 18 months which had acutely worsened over the 6 weeks prior to hospital presentation. Recent colonoscopies had been performed to investigate this diarrhoea with biopsies revealing acute and chronic inflammatory changes in the terminal ileum and colon. No infectious cause could be found, with all bacterial and viral stool cultures returning negative. An enterocutaneous fistula had also spontaneously developed through his renal transplant scar in the days preceding hospital admission which complicated the clinical picture. Following dose reduction of leflunomide, there was a significant improvement in the frequency and severity of the patient's diarrhoea. He continues to be managed non-operatively for his fistula as he is at high risk of peri-operative morbidity and mortality.

Keyword Leflunomide · Colitis · Enterocutaneous fistula · Immunosuppression · Transplant

Introduction

Leflunomide is an anti-rheumatoid medication that has been in clinical use since 1998. Its mechanism of action is to reduce clonal expansion of T cells and hence downregulation of the auto-immune inflammatory processes that are central to the pathophysiology of rheumatoid arthritis [1]. Almost 20% of patients experience some adverse side effects, most commonly mild diarrhoea, although life-threatening reactions have also been described. Leflunomide rarely causes colitis, with only four previous case reports existing in the literature [2–4]. In these cases, colitis developed within a maximum of 30 months from commencement of leflunomide therapy. Associations with enterocutaneous fistula formation, crypt abscesses and granulomas have never been described previously.

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Case report

A 68-year-old man was referred to the Emergency Department by his general practitioner for diarrhoea which had been present for 18 months but had acutely worsened over 6 weeks. This was associated with 10 kg of weight loss over the preceding 6 months and a new wound which had started to develop on his right anterior abdominal over the previous 2 days that was discharging enteric material.

The patient had a complex past medical history which included rheumatoid arthritis, psoriatic arthritis, right renal transplant 6 years prior for membranous glomerulonephritis and atrial fibrillation. Relevant regular medications included leflunomide 25 mg daily, prednisone 7.5 mg daily, tacrolimus 2 mg daily, pyrimethamine 25 mg daily, darbepoetin 40 µg monthly, warfarin 2 mg daily, metoprolol 25 mg daily, atorvastatin 10 mg second daily and irbesartan 150 mg daily. He had previously been on methotrexate for rheumatoid arthritis and mycophenolate as an anti-rejection medication but these were stopped several years prior due to adverse side effects. Leflunomide had been withheld in the immediate post-operative period by his treating transplant surgeon due to wound breakdown and early post-operative incisional

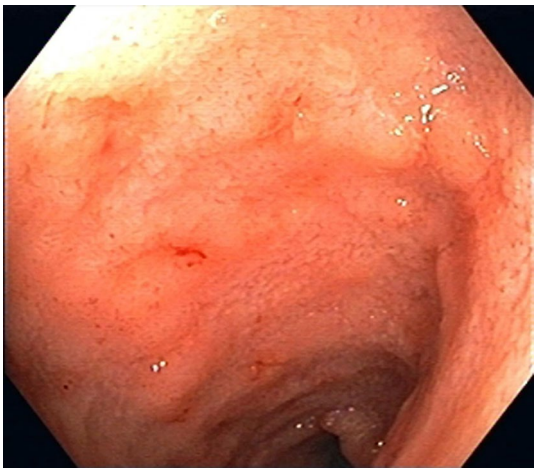

Fig. 1 Endoscopic appearance of terminal ileum demonstrating mild inflammation

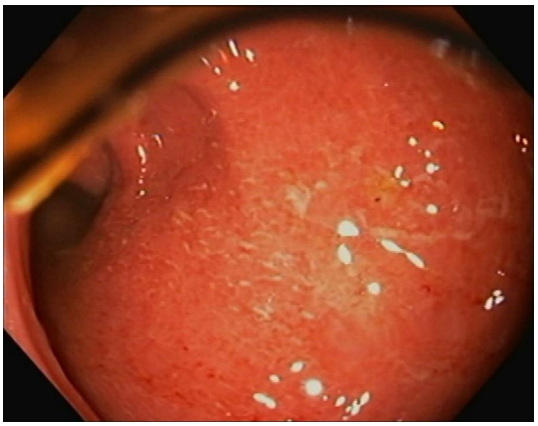

Fig. 2 Endoscopic appearance of ascending colon demonstrating moderate mucosal inflammation and surface erosions

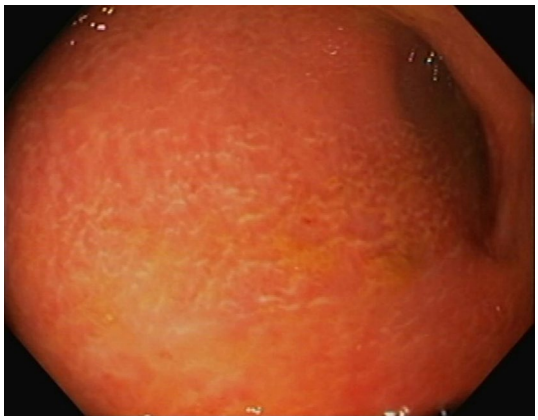

Fig. 3 Endoscopic appearance of descending colon demonstrating less marked inflammation than that seen in the ascending colon

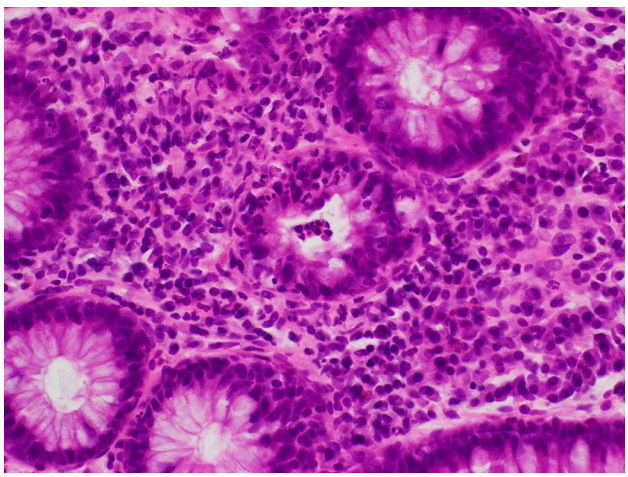

Fig. 4 Caecal biopsy demonstrating a crypt abscess (loss of normal crypt epithelium and neutrophils present within the crypt lumen)

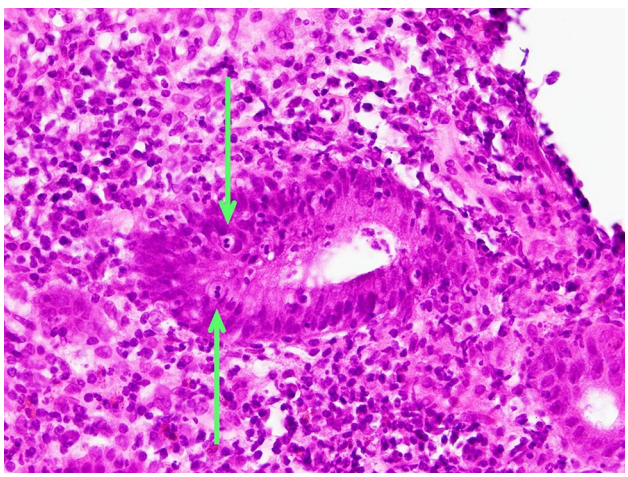

Fig. 5 Caecal biopsy demonstrating cryptitis, characterised by neutrophils (arrows) present within the epithelial layer of crypt)

hernia formation but it was recommenced approximately one year later by his rheumatologist and continued for five years until the present time.

The frequency of diarrhoea had previously been stable at up to eight episodes per day, but had recently increased to up to fifteen episodes per day. Two colonoscopies had been performed in the preceding 5 months with findings of mucosal inflammation and subtle small erosions in the terminal ileum and throughout the colon, more pronounced in the caecum and ascending colon than elsewhere (Figs. 1, 2, 3). While the terminal ileum biopsies revealed only surface erosions with mild neutrophilic infiltrates, the ascending colon biopsies revealed characteristic features of both active acute and chronic inflammation including crypt abscesses, cryptitis, scattered granulomas within the lamina propria and lymphocyte infiltration (Figs. 4, 5, 6). Although the overall appearances were not thought to be typical of Crohn's

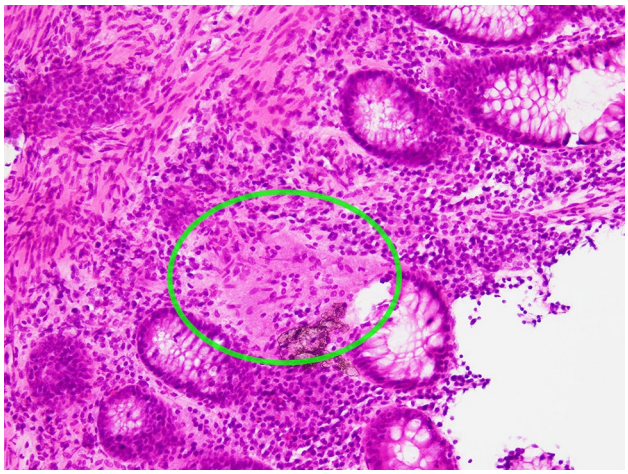

Fig. 6 Ascending colon biopsy demonstrating a granuloma (circled) with surrounding chronic inflammation (lymphocytic infiltrate)

disease, budesonide had been commenced empirically by his gastroenterologist 5 days prior to presentation.

Physical examination on presentation revealed an overweight well-looking man in no obvious distress (BMI 25.3 kg/m^2). Heart rate, temperature and oxygen saturations were normal but blood pressure was elevated at 203/68 mmHg. His abdomen was soft and non-tender with no evidence of peritonism. On the right, anterolateral aspect of his abdominal wall was a large scar from the right renal transplant performed six years earlier, at the centre of which was a 25 × 10 mm opening of an obvious enterocutaneous fistula (ECF) (Fig. 7). There was no tenderness over the transplanted kidney. His white cell count was 7.61×10^9/L (neutrophils 6.50×10^9/L, lymphocytes 0.50×10^9/L) and C reactive protein was 23 mg/L. Serum albumin was low at 26 g/L.

Numerous bacterial and viral faecal cultures (including norovirus, rotavirus, adenovirus, astrovirus, enterovirus, bocavirus and sapovirus) were performed and all returned negative results. Testing for *Clostridium difficile* antigen and toxins was also negative as was microscopy for cysts, ova and parasites. Serology was consistent with previous Epstein–Barr virus (EBV) and varicella-zoster virus (VZV) infection but there was no evidence of acute infections with these agents or cytomegalovirus (CMV). Tissue transglutaminase IgA antibodies were normal at < 1 U/mL, making coeliac disease unlikely.

Abdominal and pelvic computed tomography (CT) scans were performed and these demonstrated a large incisional hernia containing inflamed loops of small bowel superficial to the transplanted kidney in the right iliac fossa (Fig. 8). Although a definite fistula tract was not appreciated on initial magnetic resonance enterogram (MRE), a communication between the skin and terminal ileum 10-15cm proximal to the ileocaecal junction was clearly defined on a repeat MRE performed 2 weeks later and confirmed on formal sinogram (Figs. 9, 10, 11, 12). No skip lesions, mesenteric fat stranding or intra-abdominal collections were seen on any imaging modality. Output from the ECF remained low volume, draining between 5 and 50 mL per day, and it was managed conservatively with a stoma appliance to collect the effluent fluid. No dietary restriction was deemed necessary since fluid and electrolyte balance was satisfactory.

Due to ongoing diarrhoea and the medical complexity of the patient, a multidisciplinary approach was taken between specialist colorectal surgery, gastroenterology, nephrology and rheumatology teams. After review of all

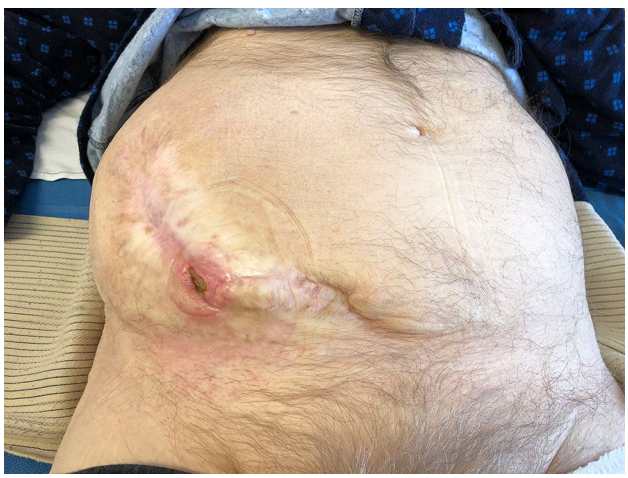

Fig. 7 Large right-sided abdominal scar from previous renal transplant associated with enterocutaneous fistula

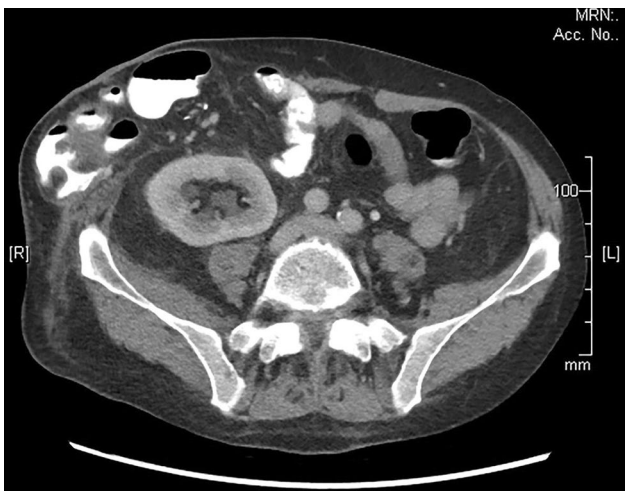

Fig. 8 Axial slice of CT Abdomen with oral contrast demonstrating close proximity of inflamed small bowel loops to overlying skin in the right iliac fossa

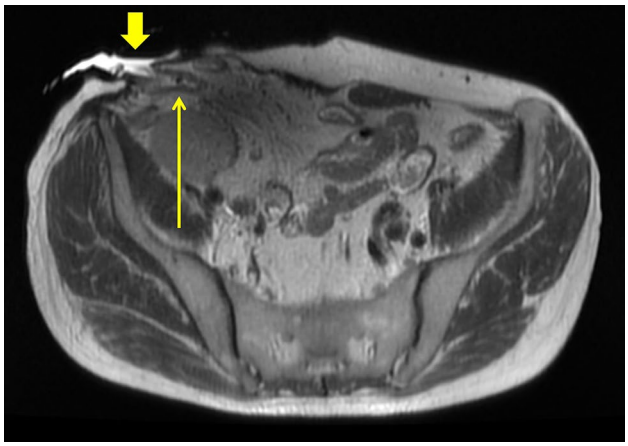

Fig. 9 Axial slice of T2-weighted MRI demonstrating mural thickening in a loop of terminal ileum (thin arrow) beneath the skin surface in the right iliac fossa with oral contrast spilling into an overlying stoma bag (thick arrow), confirming the presence of an enterocutaneous fistula

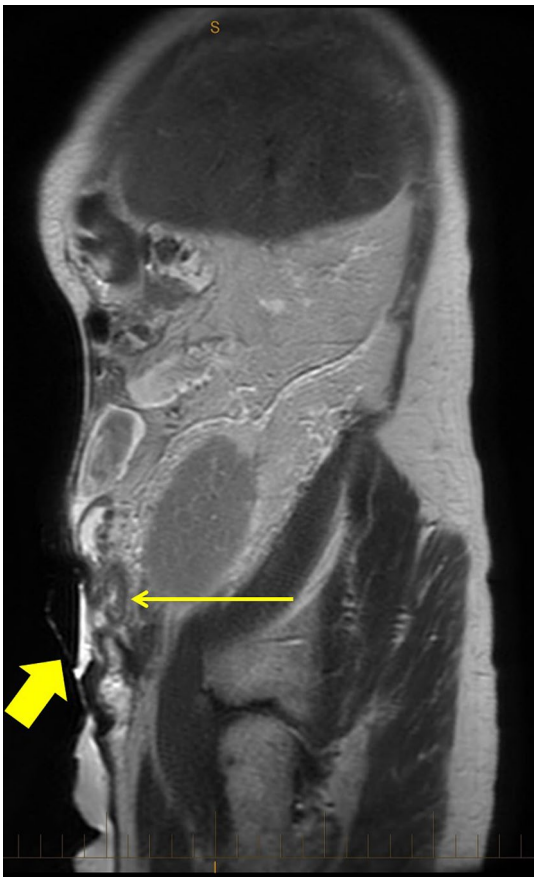

Fig. 10 Sagittal slice of T2-weighted MRI with oral contrast demonstrating a thickened loop of terminal ileum (thin arrow) beneath the skin surface in continuity with an overlying stoma bag (thick arrow)

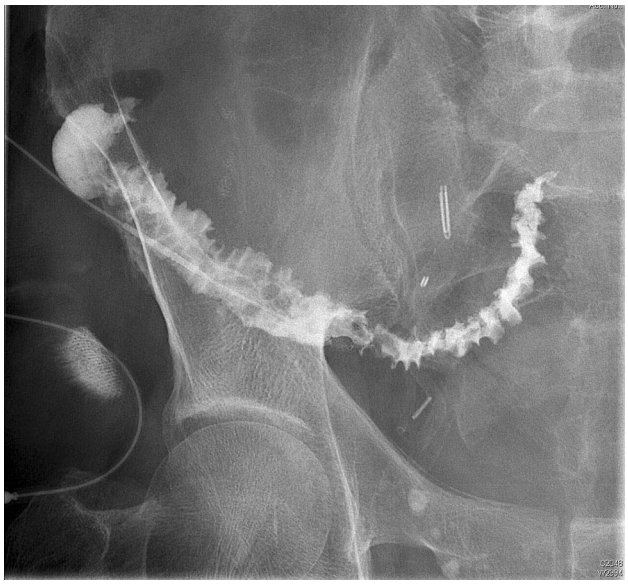

Fig. 11 Formal sinogram demonstrating opacification of small bowel loops

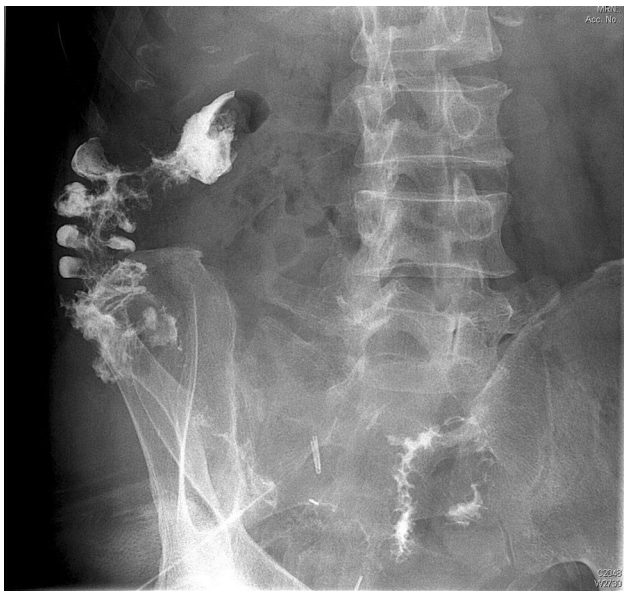

Fig. 12 Delayed images from formal sinogram demonstrating opacification of ascending colon and hepatic flexure

available results and current medications, it was decided that the most likely aetiology of the patient's diarrhoea was leflunomide-associated enteritis/colitis and that his dose should be weaned by 5 mg every month from 25 mg daily to 10 mg daily. It was agreed that non-operative management of the ECF would be most appropriate given the patient's immunosuppression, the low-volume nature of the fistula and his overall operative risk.

Seven weeks after discharge from hospital, the patient continued to keep a stool diary and reports a frequency of between two and four bowel motions per day, some of which have a normal consistency. This represents a significant improvement to his earlier reports of up to fifteen episodes of watery diarrhoea per day. Fistula output has remained stable. The temporal relationship between leflunomide dose reduction and improvement in stool frequency is highly suggestive of a causal relationship between the two, although it would be difficult to prove this definitively.

Discussion

Leflunomide is a disease-modifying anti-rheumatoid drug that is used for the treatment of rheumatoid and psoriatic arthritis and was first approved for use in USA in 1998 [1]. It acts by selectively inhibiting dihydroorotate dehydrogenase, a mitochondrial enzyme involved in pyrimidine synthesis, and therefore interferes with T-cell clonal expansion [2]. The active metabolite teriflunomide (A77 1726) has a half-life of 6 weeks and can cause a number of adverse effects which usually arise in the first 2 weeks of administration and are rare after 6 months [3]. Diarrhoea is the most common, affecting 17% of patients, while rash and hair loss may also occur. Life-threatening reactions such as interstitial lung disease and toxic epidermal necrolysis are uncommon but have been described and indicate a need for immediate treatment withdrawal [1].

Although the underlying mechanism for acute leflunomide-induced diarrhoea is not fully understood, the clinical symptoms are usually mild and respond well to medication cessation [3]. There are only four previous case reports of leflunomide-associated colitis in the literature [2–4] and in these patients symptoms developed from 10 days to 30 months after commencing treatment. Due to the rarity of the condition, there are no published data on characteristic endoscopic or histologic changes associated with leflunomide-associated colitis. Previous case reports have noted variable pathological features ranging from punctiform ulcers, haemorrhagic colitis and cryptitis to lymphocytic colitis and appearances resembling collagenous colitis [3]. One patient had severe neutropenic colitis of the caecum which resulted in transmural ischaemic necrosis [4]. However, no previous cases have reported the presence of granulomas, crypt abscesses or enterocutaneous fistulas such as those found in our patient.

A number of other anti-rheumatoid and anti-rejection medications have been implicated in drug-induced colitis, such as methotrexate, gold, non-steroidal anti-inflammatory drugs (NSAIDs) and mycophenolate [5–7]. However, our patient was not taking any of these, which excludes them as potential causative agents. The only other medication currently being administered to our patient which may have caused or contributed to his symptoms is tacrolimus, which can potentially cause gastrointestinal ulceration or perforation [8]. The timing between leflunomide cessation and symptom alleviation, however, would seem to suggest this as a more likely culprit.

We postulate that chronic leflunomide-induced terminal ileal and colonic inflammation predisposed our patient to forming an ECF, especially in the presence of a large incisional hernia with close proximity of the involved bowel loops to the overlying skin. Fortunately the underlying renal transplant graft was uninvolved in this process. There are several reasons why the ECF may not heal spontaneously or may take a prolonged period to do so, in particular his immunosuppressed state and poor wound-healing potential due to hypoalbuminaemia. Importantly, there was no evidence of undrained sepsis, neoplasia or distal obstruction which may otherwise impede spontaneous closure of the fistula.

In summary, this is an extremely rare case of leflunomide-induced colitis with a concurrent ECF in a heavily immunosuppressed patient with a renal transplant and rheumatoid arthritis. This association has not been previously described in the literature. The onset of symptoms 5 years after commencing leflunomide is unusual, since the longest latent period in previous case reports of leflunomide-induced colitis was 30 months. The presence of granulomas and crypt abscesses is also unique in this setting. The small volumes and lack of underlying infection or malignancy are favourable features that increase the likelihood of the ECF being successfully managed with a conservative approach. While there are no specific guidelines for the management of ECF in this setting, non-operative management is favoured in our patient due to his complex medical background, high operative risk and poor potential for wound healing.

Compliance with ethical standards

Conflict of interest The authors (Allan Kwok and Tia Morosin) declare that they have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid downin the 1964 Declaration of Helsinki and its later amendments.

Informed consent Written and verbal informed consent was obtained from the patient included in this case report.No personally-identifying information has been utilised.

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