Figure 1 Histological changes in colonic biopsies and tumour necrosis factor α (TNF- α) expression before and after infliximab therapy (haematoxylin-eosin and immunohistochemical stains; original magnification 125 $\times$ and 400 $\times$). (A) Active segmental colitis associated with diverticula (SCAD) characterised by a dense inflammatory infiltrate, disturbed crypt architecture, and epithelial damage, and by high TNF- α expression (B). (C) SCAD in remission characterised by regression of the inflammatory infiltrate, restoration of the epithelial damage, and profound downregulation of TNF- α expression (D).

remaining unchanged in the proximal colon (32% v 30%) (fig 1).

Increased TNF- α concentrations have been reported in both Crohn's disease and ulcerative colitis.^{5,6} For the first time, this case report showed that TNF- α overexpression was also present in SCAD. It is known that high TNF- α levels detected in Crohn's disease are reduced by infliximab therapy.⁷ Similarly, a dramatic decrease in histological activity with profound TNF- α downregulation in the SCAD tract occurred in our patient after infliximab. These observations suggest that SCAD pathogenesis may mirror the pathogenetic models proposed for IBD.

It has already been reported that SCAD can fade into a more classic ulcerative colitis picture.⁸ In our case, although the two IBD pictures presented with similar TNF- α concentrations before therapy, complete endoscopic and histological regression was limited to the SCAD tract while only partial endoscopic improvement occurred in the non-diverticular ulcerative colitis-like picture. Interestingly, persistence of histological activity was associated with high TNF- α expression. This is the first case in which two simultaneous varieties of IBD have shown a different response to infliximab in the same patient. However, due to the more aggressive clinical behaviour of the SCAD, infliximab therapy was successful in annihilating the long term steroid dependence of our patient. This implies that a much deeper knowledge of the pathogenesis of IBD needs to be pursued before preventing a patient from a potentially life saving therapy.

In conclusion, our case report showed that the pathogenesis of SCAD can be sustained by TNF- α activity and reversed by specific therapy. Moreover, an associated ulcerative colitis may show a different degree of

response to infliximab. Such different behaviours suggest that the more we struggle to unravel the inflammatory puzzle, the more puzzling the pathogenetic enigma of IBD appears to be.

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Life threatening intra-abdominal sepsis in patients on anti-TNF- α therapy

Tumour necrosis factor α (TNF- α) blocking drugs are used in the treatment of a number of inflammatory conditions. It is likely that the use of these drugs will increase. There have been reports of serious infections with these drugs.^{1–3} Doctors need to be aware of the potential for sepsis, especially as they are increasingly likely to encounter patients on anti-TNF drugs. We present two cases of life threatening intra-abdominal sepsis in patients with rheumatological conditions receiving anti-TNF drugs.

Case 1

A 60 year old male with psoriatic arthritis resistant to treatment had benefited from etanercept for six months. In rheumatology outpatients he complained of a two week history of abdominal pain. On examination he was tender in the left upper quadrant with a palpable mass. A contrast enhanced computed tomography (CT) scan demonstrated a large multiloculated splenic abscess with subcapsular extension (fig 1). Blood cultures grew *Staphylococcus aureus*. Conservative treatment with high dose intravenous antibiotics, initially with cefuroxime, metronidazole, and gentamicin on microbiological advice, had no effect. The patient became increasingly septic and after one week of conservative therapy he proceeded to laparotomy and splenectomy (fig 2). Postoperatively he developed sepsis requiring ITU admission and high dose inotropic support for five days. Histopathology of the spleen showed multiple splenic abscesses that grew *Staphylococcus aureus*. The patient made a full recovery. He

Figure 1 Computed tomography. Expansile predominantly cystic mass located within an area of hypodensity in the posterior pole of the spleen.

Figure 2 Surgical specimen consisting of the spleen with an abscess on the posterior aspect.

has received no further etanercept and has no evidence of a flare up of his arthritis six months postoperatively. He was given prophylactic low dose penicillin and anti-pneumococcal vaccination.

Case 2

A 40 year old female presented via A&E with a three day history of abdominal pain and rigors. She had been treated with infliximab for six weeks for severe rheumatoid arthritis resistant to other therapies. On examination she had a pyrexia of 39.2°C with right upper quadrant tenderness. She deteriorated with worsening sepsis and metabolic acidosis and required admission to ITU for inotropic support. Once stabilised, a CT scan of her abdomen demonstrated a large right sided hydronephrosis (fig 3). Urine cultures were negative but blood cultures grew *Escherichia coli*. After 48 hours of intravenous cefuroxime and gentamicin she improved and was discharged to the ward.

Discussion

TNF- α is an inflammatory cytokine that is essential in defence mechanisms against sepsis. However, in inflammatory arthritis it is present in both joints and blood in high concentrations. The suggestion that TNF- α is a critical cytokine in driving inflammatory diseases is supported by the success in blocking this cytokine. However, this may render the patient more prone to severe sepsis. Rheumatologists are aware of this, and screen patients for sepsis prior to starting the drugs, especially tuberculosis,^{4,5} and monitor patients for sepsis before each drug is given. Patients with a predisposition to

Figure 3 Computed tomography. Expanded non-enhancing right kidney consistent with pyelonephritis.

infection or chronic infection are ineligible for anti-TNF- α therapy. The British Society for Rheumatology has drawn up guidelines for these issues.⁶

The patients presented here had delay in initial diagnoses. This might have resulted in a worse outcome or even death. We suggest that patients who have received anti-TNF- α therapy and develop non-specific abdominal pain should proceed to urgent abdominal ultrasound or CT scan to exclude significant intra-abdominal sepsis. A further concern is that anti-TNF- α drugs may diminish the acute phase response, so that significant sepsis may not always have dramatic or acute presentations. This may lull the attending doctor into a false sense of security. Doctors who encounter patients on anti-TNF- α therapy need to be aware of the possible complications. They should be treated as if they are significantly immunocompromised, and non-specific symptoms such as abdominal pain need to be investigated intensively.

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In vivo diagnosis of collagenous colitis by confocal endomicroscopy

Collagenous colitis is a form of microscopic colitis which has recently been recognised as an entity of its own, characterised by chronic watery diarrhoea of unknown aetiology. The diagnosis of collagenous colitis relies on

histopathological examination of biopsy specimens from colorectal mucosa, which is usually of normal macroscopic appearance. The typical histological feature is diffuse thickening of the subepithelial collagen layer beneath the basement membrane and an unspecific chronic inflammatory infiltrate of the lamina propria.^{1–3}

Recently, a confocal laser endomicroscope has been developed that is integrated into the distal tip of a conventional video endoscope. This confocal laser microscope (EC-3870CIFK; Pentax, Tokyo, Japan) was designed to enable subsurface imaging of living tissue during ongoing endoscopy and allows confocal microscopy in addition to standard video endoscopy. Images are generated by intravenously administered fluorescein sodium as the fluorescent contrast agent and an argon ion laser integrated into the system that generates an excitation wavelength of 488 nm.^{4,5} For the first time, we used fluorescein aided confocal laser endoscopy for the immediate diagnosis of collagenous colitis.

A 67 year old woman was admitted to the first Medical Clinic, Johannes Gutenberg University Mainz, on July 2004, with a long history of watery diarrhoea with postprandial pain and bloating. Colonoscopy was performed using the confocal laser endoscope, enabling video endoscopy and endomicroscopy. We administered intravenously 10% fluorescein 5 ml, as a prerequisite contrast stain for endomicroscopy to enable confocal endomicroscopy of the colonic mucosa. Confocal image data were then collected at a scan rate of 0.8 frames per second (1024×1024 pixels) using an optical slice thickness of 7 μ m. Confocal images were generated simultaneously with endoscopic images. Total examination time was 36 minutes (including 12 minutes for endomicroscopy). Using this approach, cellular and subcellular structures of the colonic epithelium (surface epithelium and crypts), connective tissue, and vasculature could be seen in this patient with a lateral and axial resolution of less than 1 μ m (see fig 1). Penetration depth of the laser was approximately 250 μ m, and this depth allowed us to examine almost all parts of the colonic mucosa.

Subepithelial thickened collagenous bands could be readily identified by performing endomicroscopy. All parts of the colon were examined by placing the endomicroscopic window at the distal tip of the endoscope onto the mucosal layer. Endomicroscopic images were obtained every 15 cm within the colon. A total of 322 confocal images from six different sites were graded for the presence of collagenous bands and targeted biopsies were performed.

Biopsy specimens were fixed in 4% formalin and embedded in paraffin. Sections (4 μ m thick) were stained with haematoxylin-eosin. For assessment of the collagen band, van Gieson staining was used. Typical microscopic changes were identified endomicroscopically in four of six sites (right sided colon and transverse colon) which was confirmed by ex vivo histology in all cases.

It is well known that collagenous colitis can demonstrate a discontinuous pattern. Endomicroscopy may be well suited to target and identify affected areas. However, true specificity cannot be given in our limited series.

The patient received 9 mg of oral budesonide daily for six weeks, resulting in reduced postprandial complaints and diarrhoea.