

LETTERS TO THE EDITOR

GROWTH OF HEPATIC ANGIOMYOLIPOMA INDICATING MALIGNANT POTENTIAL

To the Editor,

Hepatic angiomyolipoma (HAML) has been considered a benign rare tumor since Ishak first described it in 1976.¹ There have been a number of reports of HAML that investigated its clinical and pathological features.^{2,3} Although the progression of radiological imaging techniques has resulted in a high detection rate and diagnostic accuracy of the liver tumor, definitive diagnosis of HAML still requires histological confirmation.⁴ Reactivity of HMB-45 confirms the definitive diagnosis

of HAML and once it is determined, surgical treatment has been avoided.^{2,3,5}

Unlike renal angiomyolipomas,^{6,7} well known to possess malignant potential, little information about malignant HAML has been available since Dalle *et al.*⁸ first described its existence in 2000. Subsequently, awareness of malignant HAML with a metastatic character has increased.^{9,10} Although all of these reports supported the existence of malignant HAML, growth activity of HAML has never been reported.

A 49-year-old woman was found to have a liver tumor in the right lobe on a medical examination. Computed tomography (CT) images with contrast medium revealed double hypervascular liver tumors (Fig. 1a,b) and a fine needle biopsy resulted in a definite diagnosis

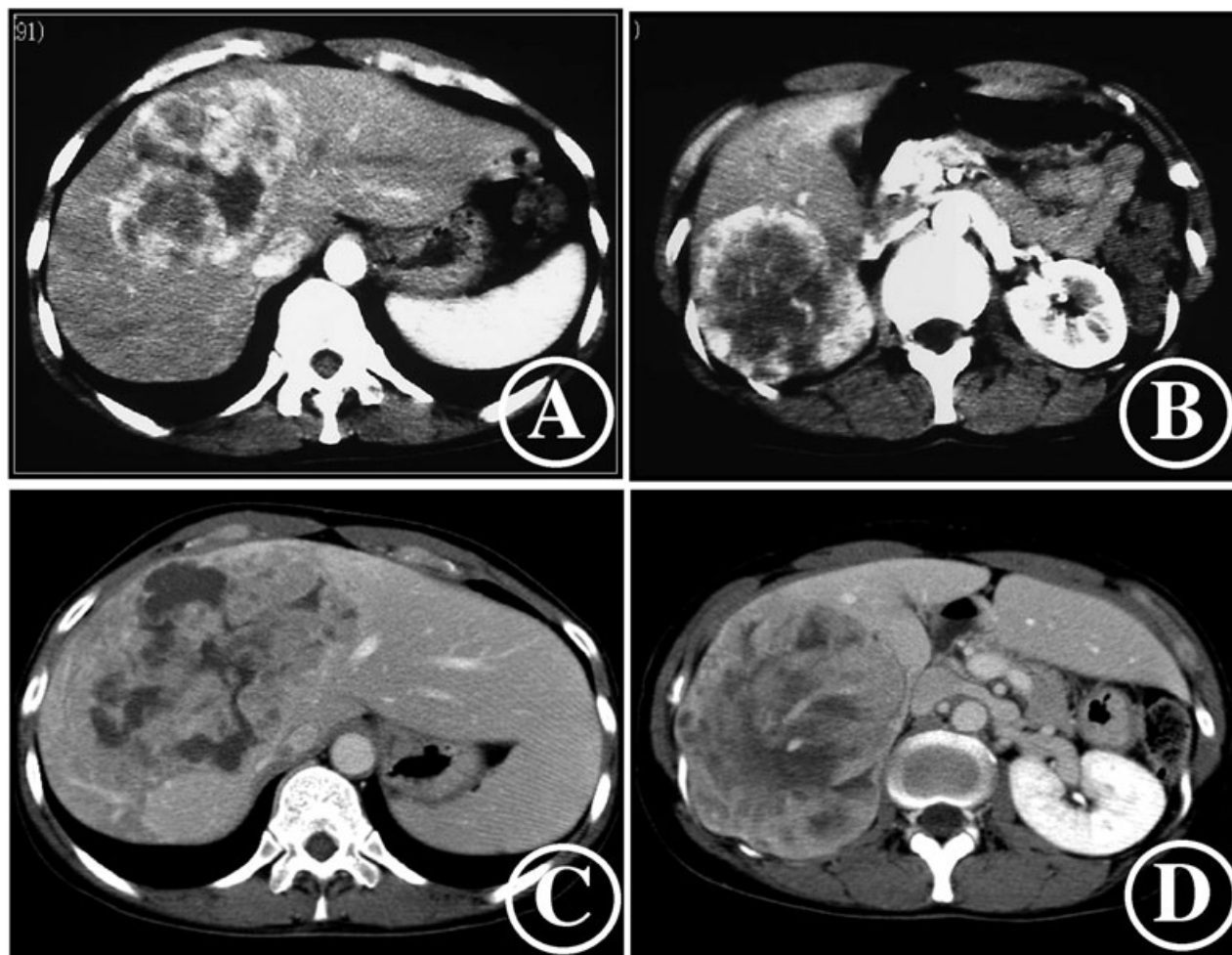


Figure 1 Computed tomography with contrast medium obtained on 3 May 2003 (a,b); 13 August 2003 (c,d). The tumor was located at segments VI and VIII. A total of 40 consecutive images were evaluated to measure the tumor volume by the computer and calculate the tumor doubling time. The volume on 3 May 2003 was 760.8 cm³ and that on 13 August 2003 was 1967.8 cm³.

of HAML. The patient was referred to our hospital and scheduled for elective surgery because of symptomatic HAML at that time.

The CT images at admission to our hospital showed that the tumor had expanded and nearly replaced the right liver lobe (Fig. 1c,d) compared to the images obtained at the previous hospital (Fig. 1a,b). No other tumor was detected by means of CT scanning and magnetic resonance imaging (MRI). Extended right trisegmentectomy was planned and successfully carried out.

We have evaluated tumor growth rate where the double tumors were located at liver segments VI and VIII. The tumor volume was calculated from 40 sequential images using a computer program. The volume on 3 May 2003 was 760.8 cm³ and that on 13 August 2003 was 1967.8 cm³. The tumor grew 2.6-fold during 102 days. The tumor doubling time was estimated to be 78.9 days. If the growth rate and the nature of the tumor was preserved from the tumor initiation, the break out of a single tumor cell was estimated to be approximately 8 years earlier.

Macroscopically, the surgical specimen was a solid mass consisting of multiple nodular formations without necrotic tissue. There was no interaction between the tumors (Fig. 2a). Immunohistochemistry showed that the myoid component predominated. The epithelioid cells possessed clear cytoplasm with a spiderweb appearance. Long spindle-shaped myoid cells possessed scant cytoplasm arranged in fascicles. The myoid cells were positive for both α SMA (Fig. 2b) and HMB-45 (Fig. 2c), which are prominent markers in the pathological diagnosis of HAML.

The clinical finding of rapid tumor growth suggested high potential for tumor malignancy. Mitotic activity was observed with eight mitoses per 10 high-power fields (HPF) without tumor necrosis. Ki-67 positive cells were found in 30% of the myoid cells (Fig. 2d). The intermediate cells, especially, were 50% positive for Ki-67 (Fig. 2e). Therefore, all observations from clinical images and pathological findings strongly suggested that the HMAL in this case could be malignant.

Hepatic angiomyolipoma has been considered a benign tumor. We found in HAML that the size of the

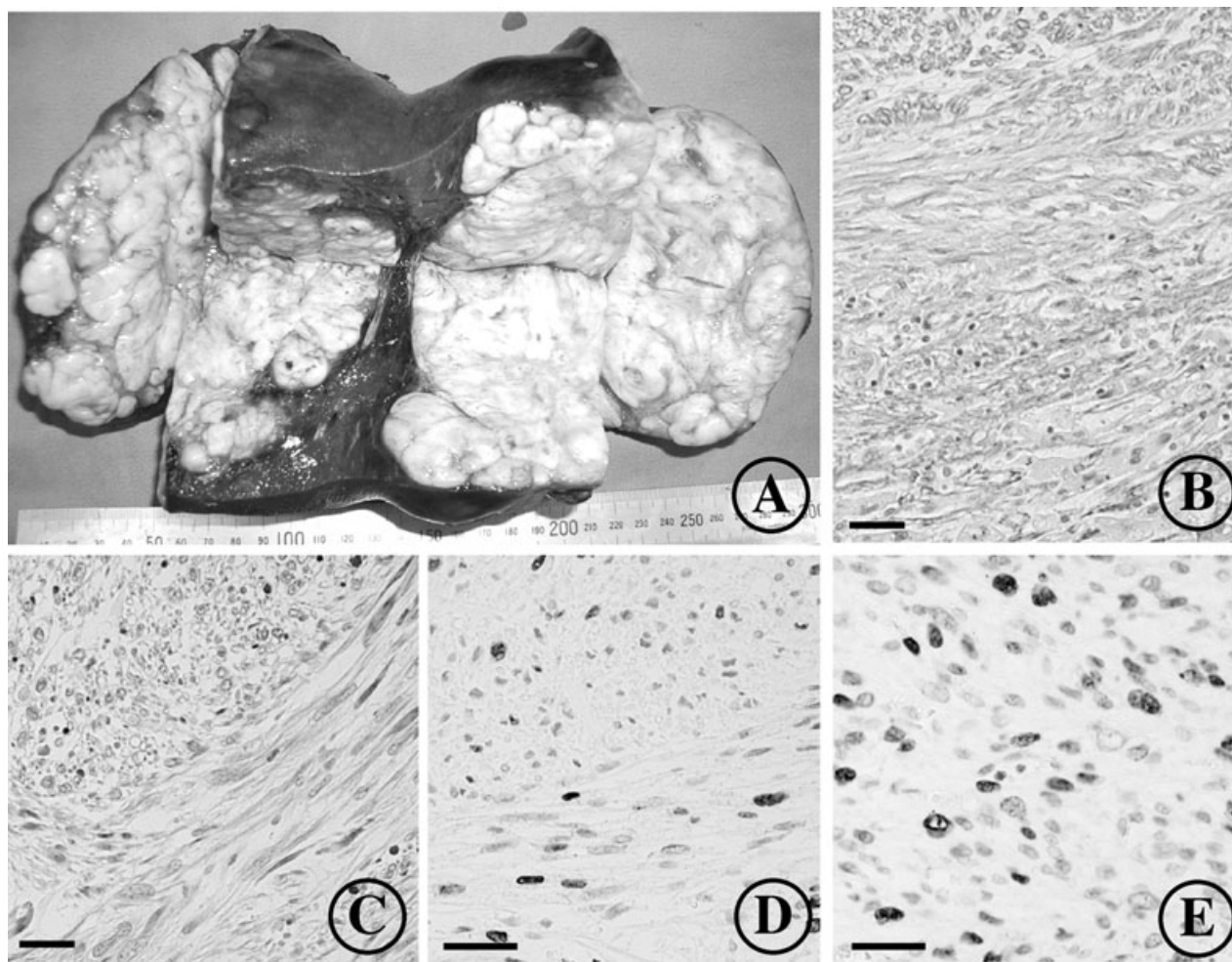


Figure 2 Gross view of the surgical specimen showed (a) a solid mass with massive nodules; (b) immunohistochemistry of α SMA; (c) MLB-47; and (d,e) Ki-67. Myoid epithelial cells are predominant (b,c). Thirty percent of polygonal epithelioid myoid cells and spindle cells were positive for Ki-67 (d). Conversely, 50% of intermediate cells were positive for Ki-67 (e). Original magnifications; $\times 200$. Scale bar, 50 μ m.

tumor increased rapidly during the wait for surgery. Pathological examination confirmed angiomyolipoma of the liver. The tumor cells were stained for HMB-45, which is a specific marker for angiomyolipoma. Furthermore, mitotic cells were observed in eight cells of 10 HPF and 30% of the cells positive for Ki-67 that supported the mitotic counts. Therefore, our case supported the malignant potential of HAML. The tumor doubling time (DT) of hepatocellular carcinomas has been reported. The median DT of hepatocellular carcinoma showing rapid growth was reported to be 56 days and to be associated with cell proliferation markers such as cyclin-D1 and Ki-67.¹¹ Conversely, the DT of malignant HAML has never been reported. The DT of the malignant HAML, which we found was 78.9 days, was as fast as that of hepatocellular carcinomas showing rapid growth. In addition, immunohistochemistry for Ki-67, in which 30% of the tumor cells were positive, supported the findings. We still do not know how the HAML acquired its malignant character in this case. However, we should consider surgery even though the pathological diagnosis is confirmed to be HAML. We recommend Ki-67 staining for HAML in addition to MLB-45 staining to determine its malignant potential. We should be aware of the presence of malignant HAML, for which surgical treatment should be considered.

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REMISSION OF ULCERATIVE COLITIS AFTER ANAPHYLAXIS

To the Editor,

We experienced a case of ulcerative colitis in which intractable enteric inflammation resolved after anaphylactic reaction to blood products. This case might help us in controlling the turbulent inflammation of ulcerative colitis.

A 64-year-old female was diagnosed in 1985 with ulcerative colitis affecting the descending colon, and was successfully treated with sulfasalazine since the remission of the second relapse in June 2000. However, in October 2001, she presented with frequent bloody diarrhea, abdominal pain and arthralgia. Accordingly, she was admitted to our hospital on 25 October 2001 for further evaluation and management. On admission, physical examination showed a bodyweight of 45 kg, height of 155 cm, temperature of 36.6°C, blood pressure of 120/70 mmHg, and heart rate of 96 beats/min. The abdomen was soft, but there was moderate tenderness in the left lower quadrant. Laboratory data included hemoglobin 10.2 mg/dL, white blood cell count 9100/mm³, serum total protein 6.2 g/dL, albumin 3.5 g/dL, and CRP 8.02 mg/dL. Colonoscopic examination showed congestion, edema and multiple irregular-shaped ulcers with bleeding extending from the rectum to the sigmoid colon. At first she was treated with steroid pulse therapy (methylprednisolone 1 g for 3 days) and thereafter with intravenous prednisolone (50 mg/day). Despite the intensive steroid therapy, the symptom and endoscopic findings (Fig. 1a) remained unchanged. Colectomy was considered. The patient required transfusion of packed blood cells for the operation. On 8 December, during the blood transfusion, she developed anaphylactic symptoms including nasal discharge, facial edema and dyspnea with laryngeal swelling. Intravenous administration of 500 mg of methylprednisolone and subcutaneous administration of 0.2 mg of epinephrine were effective against the anaphylaxis, and 5 h later, nasal discharge, facial edema and dyspnea had disappeared. From that day, the

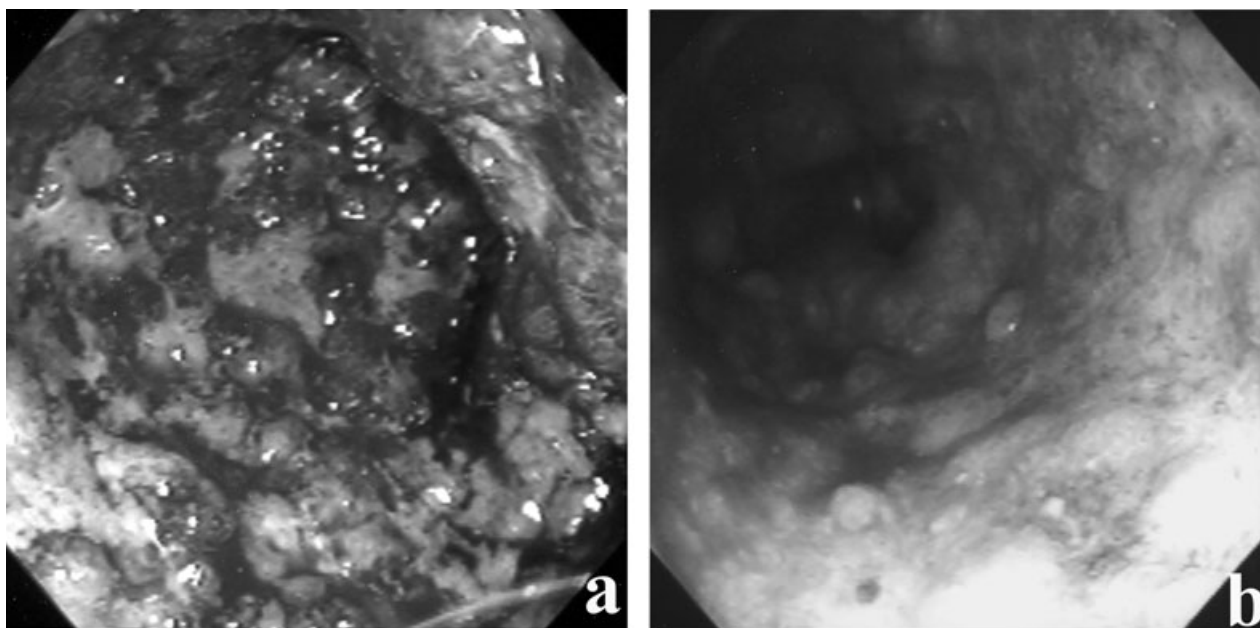


Figure 1 (a) Colonoscopy on 30 November 2001 revealed marked congestion, edema and irregular shaped ulcers. (b) Two days after the anaphylaxis, colonoscopy showed remarkable improvement of congestion, edema and ulcers.

abdominal pain and diarrhea ceased completely. On 10 December 2001, colonoscopy (Fig. 1b) showed improvement of the ulcers with scarring. The patient has been in clinical remission for 20 months since then.

Although the pathogenesis of ulcerative colitis remains to be fully understood, it likely results from unregulated immune responses to intestinal contents.^{1,2} In our case, intractable enteric inflammation that was unresponsive to standard therapy surprisingly resolved after anaphylactic reaction. We could not exclude the possibility that 500 mg of methylprednisolone when anaphylaxis occurred effected the remission of ulcerative colitis entirely. However, taking into account the fact the intensive steroid pulse therapy (methylprednisolone 1 g for 3 days) was ineffective for the treatment of symptoms, it seems that anaphylaxis suppressed the inflammation of ulcerative colitis. In an anaphylactic reaction, the interaction between antigen and IgE antibody attached to mast cells and basophiles induces an explosive release of mediators. Following Th2-type immune responses mediated by these chemical mediators such as interleukin (IL)-4, IL-5, IL-6, IL-9 and IL-13, are keys in the pathogenesis of anaphylaxis.^{3,4} Interestingly, Lee *et al.*⁵ demonstrated that IL-12 promotes differentiation on Th1 cells and inhibits the differentiation of Th0 cells into Th2, suppresses Th2 cytokine mediated anaphylactic reactions in a murine model. Recently, Summers *et al.*⁶ demonstrated that colonization of intestinal helminths was beneficial in reducing inflammation in patients with inflammatory bowel diseases (IBD), suggesting that helminths induce Th2-type immune response and also downregulate Th1 immune responses in the gut. Although ulcerative colitis is not a typical Th1-dominant disease, the induction of Th2 immune response by helminths diminishes intestinal inflammation as well as Crohn's disease. In our case,

systemic inflammation due to anaphylaxis followed by Th2-type inflammation as well as helminths might downregulate enteric inflammation.

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INFLIXIMAB IN THE MANAGEMENT OF THE EXTRA-INTESTINAL MANIFESTATIONS OF CROHN'S DISEASE

To the Editor,

Infliximab is indicated for the treatment of moderate to severely active Crohn's disease (CD) after an inadequate response to conventional therapy.¹ The management of resistant CD extra-intestinal manifestations is, however, not an indication and it is suggested that infliximab should also be considered in these circumstances (Table 1).

A 42-year-old female with ileocolonic CD suffered from erythema nodosum, pyoderma gangrenosum, episodic iritis, mouth ulcers and severe migratory polyarthritis that resulted in fecal incontinence due to decreased mobility. Active rectovaginal and perianal fistulae were present, as was severe intestinal inflammation. Her medications included salazopyrine 2.5 g/day, metronidazole 400 mg b.i.d. and ciprofloxacin 500 mg bd because she was intolerant of steroids, azathioprine and 6-mercaptopurine. The patient's erythrocyte sedimentation rate (ESR) was 123 mm/h ($n < 21$ mm/h) and C-reactive protein (CRP) 94 mg/mL ($n < 12.1$ mg/mL), while her CD activity index (CDAI) was 383 (remission < 150).

The patient received four infliximab infusions of 5 mg/kg at weeks 0, 2, 6 and 14. She ceased the antibiotics with the first infusion, continued on salazopyrine and was successfully commenced on 6-mercaptopurine. Full remission of the symptoms was achieved in 4–6 weeks. The pyoderma gangrenosum, erythema nodosum, perianal and rectovaginal fistulae healed. The migratory polyarthralgia resolved, allowing her to play golf. She has remained in complete remission for 29 months.

Pyoderma gangrenosum typically affects approximately 1% of CD patients, is difficult to treat and its activity is usually independent from the intestinal activity.² No therapy has been particularly effective, but with the advent of infliximab, published case reports that are supported here, suggest that it may induce remission.³

A 21-year-old man presented in 1991 with severe arthritis. High dose steroids achieved symptomatic resolution, which recurred on steroid reduction, but was controlled on methotrexate. After 2 years, the arthritis recurred associated with abdominal pain, per rectal (PR) bleeding and weight loss. A small bowel enema demonstrated stricturing and resection confirmed CD.

When disease recurred, the arthritis persisted despite the colitis settling with prednisone and azathioprine. In early 2001 the prednisone was weaned and late that year the patient again presented with severe colitis, erythema nodosum, iritis and polyarthritis resulting in fecal incontinence due to decreased mobility. His medications included salazopyrine 2.0 g bd, metronidazole 400 mg bd, ciprofloxacin 500 mg bd and 6-mercaptopurine 75 mg/day. Prednisone 50 mg/day was commenced due to lack of improvement. His ESR was 22 mm/h, CRP 67 mg/mL and CDAI 440.

The patient received two doses of infliximab 5 mg/kg, 8 weeks apart. Salazopyrine and 6-mercaptopurine were continued while the antibiotics were ceased prior to, and the prednisone after, the first infusion. Complete resolution of all symptoms was achieved by 4 weeks. Resolution of the polyarthritis allowed him to commence football training and he has remained in remission for the last 32 months.

Migratory arthralgia/arthritis involving the large joints occurs in 10–20% of inflammatory bowel disease (IBD) patients⁴ and may have a greater morbidity than the intestinal disease. Generally, but not always, the arthralgia/arthritis resolves with resolution of intestinal inflammation. A single dose of infliximab, however, induced complete resolution in this patient despite years of uncontrolled arthritis.

A 42-year-old man with CD pancolitis, diarrhea 10–12 times/day and 12 months of a perianal fistula that persisted despite three surgical procedures, presented with arthralgia and multiple vasculitic lesions (> 5 cm) on his legs. Salazopyrine 1.5 g t.d.s. and prednisone 80 mg/day were commenced with rapid resolution of the diarrhea and arthralgia. The rash remained and biopsy identified granulomatous vasculitis (Fig. 1), an extra-intestinal manifestation first associated with CD 20 years ago.⁵

The patient received one dose of infliximab 5 mg/kg, the prednisone was weaned and he commenced azathioprine 200 mg/day. The cutaneous granulomatous vasculitis resolved 2 weeks post infusion and the fistula healed. The patient was lost to follow-up for 15 months, but was still in remission despite ceasing the azathioprine. He recommenced azathioprine and has remained in remission for the last 36 months.

A 44-year-old man with distal colitis only controlled by prednisone 60 mg/day, olsalazine 1 g bd and 6-mercaptopurine 100 mg/day presented with a right lumbosacral, right C7 inflammatory polyradiculopathy and avascular necrosis of the left femoral head. Reduction of prednisone reactivated the colitis. He received one dose of infliximab 5 mg/kg. Although inflammatory polyradiculopathies are not known to be associated with CD, over 2 weeks all the polyradiculopathy symptoms resolved and the patient had been in remission for 20 months. The infliximab had little initial effect on the

Table 1 Extra-intestinal manifestations of inflammatory bowel disease

Independent of clinically active intestinal disease	Dependent on clinically active intestinal disease
Sacroiliitis	Migratory polyarthritis/arthropathy
Ankylosing spondylitis	Erythema nodosum
Pyoderma gangrenosum	Aphthous ulceration
Sclerosing cholangitis	Iritis
Renal stones	Episcleritis
	Venous thrombosis
	Finger clubbing

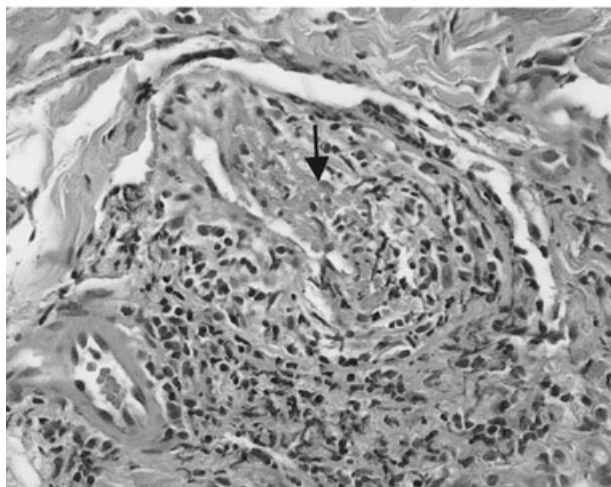
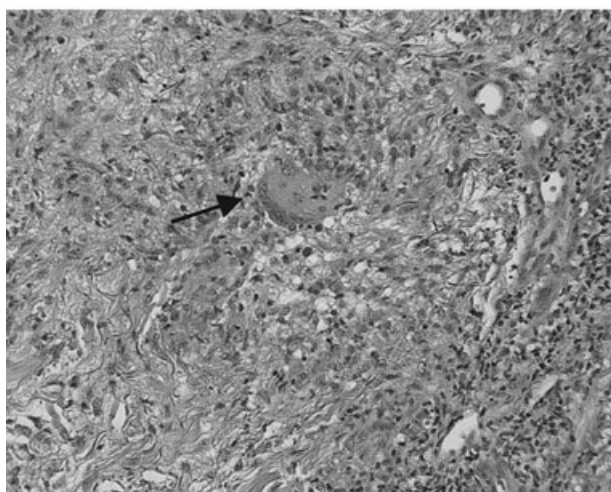
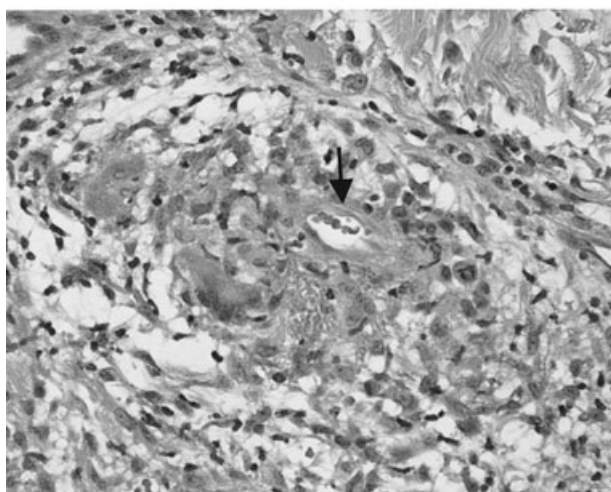
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Figure 1 Histological assessment of the painful cutaneous lesions. (a) Inflammatory cell infiltration of a dermal vessel with fibrinoid necrosis (arrow); (b) dermal granuloma with giant cell formation (arrow) not associated with a blood vessel; and (c) granuloma formation with giant cells centered around a dermal blood vessel (arrow).

distal colitis, but the prednisone dose was successfully reduced to 12.5 mg whilst maintaining remission.

The above cases are presented to highlight the use of infliximab in the treatment of the extra-intestinal manifestations of CD and infliximab has also been successful in treating hydradenitis suppurativa. In CD patients, intestinal inflammation is only part of the morbidity that effects them, and as infliximab can successfully manage all aspects of the disease, consideration should be given to its use in patients with resistant extra-intestinal manifestations, even if the intestinal inflammation seems to be under control.

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