indicate that an increase in Treg number and function, if present in the acute hepatitis phase of the infection, predicts a chronic evolution and persists over time. Interestingly, all patients with elevated Tregs and chronic evolution harboured genotype 1 virus, suggesting a possible influence of that subset on chronic evolution,⁸ perhaps through Treg triggering. Whether the elevation in regulatory T cells reported here is just a predictor of chronic evolution of HCV infection or a promoter of HCV infection chronicity, remains to be investigated.

A Perrella

Department of Infectious Disease and Immunology,
Hospital D Cotugno of Naples, Naples, Italy

L Vitiello

Department of Cellular and Molecular Biology and
Pathology, Federico II University of Naples, Naples,
Italy

L Atripaldi

Department of Infectious Disease and Immunology,
Hospital D Cotugno of Naples, Naples, Italy

P Conti

Department of Immunology, University G d'Annunzio
of Chieti, Chieti, Italy

C Sbreglia

Department of Infectious Disease and Immunology,
Hospital D Cotugno of Naples, Naples, Italy

S Altamura

Department of Cellular and Molecular Biology and
Pathology, Federico II University of Naples, Naples,
Italy

T Patarino, R Vela, G Morelli, P Bellopede, C Alone

Department of Infectious Disease and Immunology,
Hospital D Cotugno of Naples, Naples, Italy

L Racioppi

Department of Cellular and Molecular Biology and
Pathology, Federico II University of Naples, Naples,
Italy

O Perrella

Department of Infectious Disease and Immunology,
Hospital D Cotugno of Naples, Naples, Italy

Correspondence to: Dr A Perrella, Department of
Infectious Disease and Immunology, Hospital D
Cotugno, Via EA Mario 35, 80128, Naples, Italy;
alex.perrel@virgilio.it

doi: 10.1136/gut.2006.099887

Conflict of interest: None declared.

References

- 1 Davis GL, Albright JE, Cook SF, *et al.* Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl* 2003;9:331–8.
- 2 Rehmann B, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. *Nat Rev Immunol* 2005;5:215–29.
- 3 Cabrera R, Tu Z, Xu Y, *et al.* An immunomodulatory role for CD4(+)CD25(+) regulatory T lymphocytes in hepatitis C virus infection. *Hepatology* 2004;40:1062–71.
- 4 Nomura H, Sou S, Tanimoto H, *et al.* Short-term interferon- α therapy for acute hepatitis C: a randomized controlled trial. *Hepatology* 2004;39:1213–19.
- 5 Perrella A, Atripaldi L, Bellopede P, *et al.* Flow cytometry assay of myeloid dendritic cells (mDCs) in peripheral blood during acute hepatitis C: possible pathogenetic mechanisms. *World J Gastroenterol* 2006;12:1105–9.
- 6 Longhi MS, Ma Y, Bogdanos DP, *et al.* Impairment of CD4(+)CD25(+) regulatory T-cells

in autoimmune liver disease. *J Hepatol* 2004;41:31–7.

- 7 Longhi MS, Ma Y, Mity RR, *et al.* Effect of CD4+ CD25+ regulatory T-cells on CD8 T-cell function in patients with autoimmune hepatitis. *J Autoimmun* 2005;25:63–71.
- 8 Yoo TW, Donfield S, Lail A, *et al.* Hemophilia Growth and Development Study. Effect of hepatitis C virus (HCV) genotype on HCV and HIV-1 disease. *J Infect Dis* 2005;191:4–10.

Thalidomide in refractory haemorrhagic radiation induced proctitis

One of the most frequently encountered late gastrointestinal sequelae of abdominopelvic radiation therapy is radiation proctitis, occurring in 12.5–19% of patients.^{1,2} Treatment options range from drug therapy, including spasmolytics, steroids, mesalasin, and endoscopic treatment comprising argon plasma coagulation (APC), laser coagulation, and formalin application, to hyperbaric oxygen therapy and finally surgical intervention.^{3–5} We describe a patient with severe refractory haemorrhagic radiation proctitis requiring frequent blood transfusions who was successfully treated with low dose oral thalidomide.

Case report

A 78 year old female presented with a three month history of intermittent rectal blood loss. Her medical history revealed cervical cancer stage IIIB two years earlier. She had been treated with a multimodal regimen comprising chemotherapy (cisplatin 40 mg/m² at weekly intervals for six weeks) and radiation therapy (EBRT 50.4 Gy in 28 fractionated doses of 1.8 Gy plus two sessions of brachytherapy). Physical examination was unremarkable except for brisk red blood at digital rectal examination. Laboratory investigation yielded microcytic anaemia (haemoglobin 4.7 mmol/l). At colonoscopy, the distal 10–15 cm of the rectal mucosa appeared circumferentially abnormal, being highly friable and slightly bleeding, interspersed with multiple telangiectasias, compatible with radiation proctitis. Despite consecutive treatment, including topical mesalazin and/or steroid enemas, epsilon-aminocaproic acid (both orally and later topical), and several sessions of APC, no long term beneficial effect was achieved. The patient received blood transfusions at a rate of 2–3 packed cells per 2–3 weeks. Surgical options were discussed but refused. After written informed consent, low dose thalidomide was started at 50–100 mg/day. Three weeks later her haemoglobin level had remained stable after the last transfusion. Currently the patient is doing well after three months without any blood transfusions.

As illustrated by this case history, treatment of haemorrhagic radiation induced proctitis can be difficult. Because of the severe course, despite various treatment regimens and refusal of surgical intervention, other treatment options were considered. Application of formalin has been reported to effectively reduce rectal bleeding. Yet serious local adverse effects have been described in up to 19% of cases, such as painful rectal ulceration, anorectal stricture formation, and anal incontinence. Although these complications may represent the natural sequelae of radiation induced proctitis, formalin application may have contributed to the deterioration due to its direct effect on mucosal blood flow.^{3–6}

We treated this patient with low dose thalidomide with remarkable results. Thalidomide is a potent inhibitor of (neo)angiogenesis, mediated by suppression of vascular endothelial growth factor (VEGF).⁷ Bauditz *et al.* reported cessation of bleeding in otherwise refractory angiodysplasias and bleeding Crohn's disease, presumably as a result of decreased levels of VEGF during thalidomide treatment.⁸ Although the exact role of VEGF in radiation induced mucosal injury needs to be elucidated, the temporal relationship between thalidomide therapy and cessation of bleeding in our patient is highly suggestive of a causal relationship. Experimental data, suggestive of a potential role for VEGF modulation, indicate that VEGF expression is upregulated in normal rat brain after experimental intraoperative radiation therapy.⁹ Moreover, radiation induced hypoxia may perpetuate late normal tissue injury leading to progressive occlusive vasculitis, collagen deposition, and fibrosis in the presence of increased local transforming growth factor β , VEGF, and CD31, suggesting hypoxia mediated activation of the profibrinogenic and proangiogenic pathways.¹⁰

In conclusion, our preliminary experience suggests that thalidomide might be an effective treatment option in patients with refractory haemorrhagic radiation proctitis. As we are the first—to the best of our knowledge—to report this potential therapeutic effect obviating the need for surgical intervention, further clinical studies are warranted, defining the effectiveness and side effects in a larger group of patients.

M E Craanen

Department of Gastroenterology, VU University
Medical Center, Amsterdam, the Netherlands

B van Triest

Department of Radiotherapy, VU University Medical
Center, Amsterdam, the Netherlands

R H M Verheijen

Department of Gynaecology, VU University Medical
Center, Amsterdam, the Netherlands

C J J Mulder

Department of Gastroenterology, VU University
Medical Center, Amsterdam, the Netherlands

Correspondence to: Dr M E Craanen, Department of
Gastroenterology, VU University Medical Center, PO
Box 7057, 1007MB Amsterdam, the Netherlands;
me.craanen@vumc.nl

doi: 10.1136/gut.2006.099416

Conflict of interest: None declared.

References

- 1 Miller AR, Martenson JA, Nelson H, *et al.* The incidence and clinical consequences of treatment-related bowel injury. *Int J Radiat Oncol Biol Phys* 1999;43:817–25.
- 2 Chen S-W, Liang J-A, Yang S-N, *et al.* Radiation injury to intestine following hysterectomy and adjuvant radiotherapy for cervical cancer. *Gynecol Oncol* 2004;95:208–14.
- 3 de Parades V, Etienne I, Bauer P, *et al.* Formalin application in the treatment of chronic radiation-induced hemorrhagic proctitis—An effective but not risk-free procedure: a prospective study of 33 patients. *Dis Colon Rectum* 2005;48:1535–41.
- 4 Ben-Soussan E, Antonietti M, Savoye G, *et al.* Argon plasma coagulation in the treatment of hemorrhagic radiation proctitis is efficient but requires a perfect colonic cleansing to be safe. *Eur J Gastroenterol Hepatol* 2004;16:1315–18.

- 5 Jones K, Evans AW, Bristow RG, *et al.* Treatment of radiation proctitis with hyperbaric oxygen. *Radiother Oncol* 2006;**78**:91–4.
- 6 Konishi T, Watanabe T, Nagawa H. Formalin application in the treatment of chronic radiation-induced hemorrhagic proctitis induces acute deterioration of mucosal blood flow. *Dis Colon Rectum* 2006;**49**:1–2.
- 7 D'Amato RJ, Loughnan MS, Flynn E, *et al.* Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A* 1994;**91**:4082–5.
- 8 Bauditz J, Schachschal G, Wedel S, *et al.* Thalidomide for treatment of severe intestinal bleeding. *Gut* 2004;**53**:609–12.
- 9 Kim JH, Chung YG, Kim CY, *et al.* Upregulation of VEGF and FGF2 in normal rat brain after experimental intraoperative radiation therapy. *J Korean Med Sci* 2004;**19**:879–86.
- 10 Vujaskovic Z, Anscher MS, Feng QF, *et al.* Radiation-induced hypoxia may perpetuate late normal tissue injury. *Int J Radiat Oncol Biol Phys* 2001;**50**:851–5.

A case of rheumatoid arthritis with protein losing enteropathy induced by multiple diaphragmatic strictures of the small intestine: successful treatment by bougieing under double-balloon enteroscopy

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most favoured for the treatment of rheumatoid arthritis (RA) but they sometimes induce inflammation and ulceration of the gastrointestinal tract.¹ Approximately 75% of patients receiving long term NSAIDs develop inflammation in the small intestine that in rare cases results in protein losing enteropathy.^{2,3} Furthermore, NSAIDs can bring about diaphragmatic strictures in the small intestine as a consequence of ulcer healing.

We report here a patient with RA who had multiple diaphragmatic strictures in the small intestine and subsequent protein losing enteropathy, probably due to long term non-steroidal anti-inflammatory drugs use. Her intestinal stricture and protein losing enteropathy, however, were successfully corrected by bougieing under double balloon enteroscopy without resort to surgical resection.

A 57 year old Japanese woman developed RA in 1995 and was given prednisolone and NSAIDs, as well as several disease modifying antirheumatic drugs, including infliximab and etanercept. She was admitted to the Jichi Medical University Hospital in November 2005 because of lower leg oedema caused by severe hypoalbuminaemia. NSAIDs were withdrawn immediately after admission. Protein losing enteropathy was diagnosed based on ^{99m}Tc-human albumin scintigraphy and α_1 -antitrypsin clearance at 180.2 ml/day (normal range 0.4–19), although the exact cause was not specified at that time. In January 2006, she was hospitalised due to severe nausea and vomiting, difficulty eating food, and emaciation. Because a tentative diagnosis of gastrointestinal amyloidosis was not confirmed by biopsies of the stomach, duodenum, caecum, and rectum, double balloon enteroscopy was performed to examine small intestinal lesions.

A membranous stricture with a 5 mm opening was detected at the duodenum-jejunum junction. After a small balloon was placed through the stenosis aided by guide-wire equipped with a double balloon enteroscope, air was slowly pumped to inflate the balloon for bougieing the stricture (fig 1A–D). Three more diaphragmatic strictures were found in the distal portion and were treated in the same manner. The patient resumed eating without nausea or vomiting, and gained in body weight and serum albumin concentration. ^{99m}Tc-human albumin scintigraphy no longer showed signs of protein losing.

Amyloidosis is the most probable cause of protein losing enteropathy in patients with intractable RA.⁴ However, the present case demonstrates that it is also caused by diaphragmatic stricture of the small intestine that was probably induced by prolonged use of NSAIDs. Even more important is the reversibility of this lesion. After multiple strictures were corrected, to some extent, by a novel method employing double balloon enteroscopy, she recovered from loss of protein, with serum albumin level increasing from 1.5 to 3.4 mg/dl. Because all of the biopsy specimens were obtained from the relatively normal mucosa between the strictures, and revealed no pathological abnormalities, the precise mechanism of the protein losing enteropathy was not elucidated. However, in view of the spontaneous recovery after bougieing, bacterial overgrowth and increased intraluminal pressure due to stasis may be possible pathogenetic mechanisms.

Rapid progress has been made in finding pathological lesions in the small intestine using capsule endoscopy or double balloon endoscopy.^{5,6} As shown here, bougieing under double balloon enteroscopy is powerful and effective for the treatment of intestinal stenosis, especially in immunocompromised patients in whom laparotomy and surgical resection of the diseased intestine should be avoided.

Y Kamata, M Iwamoto, H Nara, T Kamimura
Division of Rheumatology and Clinical Immunology,
Jichi Medical University, Shimotsuke-shi, Japan

N Takayashiki
Department of Pathology, Jichi Medical University,
Shimotsuke-shi, Japan

H Yamamoto, K Sugano
Division of Gastroenterology, Jichi Medical University,
Shimotsuke-shi, Japan

T Yoshio, H Okazaki, S Minota
Division of Rheumatology and Clinical Immunology,
Jichi Medical University, Shimotsuke-shi, Japan

Correspondence to: Dr Y Kamata, Division of Rheumatology and Clinical Immunology, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigiken, 329-0498, Japan; y.kamata@jichi.ac.jp

doi: 10.1136/gut.2006.100446

Conflict of interest: None declared.

References

- 1 Allison MC, Howatson AG, Torrance CJ, *et al.* Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1992;**327**:749–54.
- 2 Bjarnason I, Zanelli G, Prouse P, *et al.* Blood and protein loss via small-intestinal inflammation induced by non-steroidal anti-inflammatory drugs. *Lancet* 1987;**2**:711–14.
- 3 Lang J, Price AB, Levi AJ, *et al.* Diaphragm disease: pathology of disease of the small intestine induced by non-steroidal anti-inflammatory drugs. *J Clin Pathol* 1988;**41**:516–26.
- 4 Jeong YS, Jun JB, Kim TH, *et al.* Successful treatment of protein-losing enteropathy due to AA amyloidosis with somatostatin analogue and high dose steroid in ankylosing spondylitis. *Clin Exp Rheumatol* 2000;**18**:619–21.
- 5 Yousfi MM, De Petris G, Leighton JA, *et al.* Diaphragm disease after use of nonsteroidal anti-inflammatory agents: first report of diagnosis with capsule endoscopy. *J Clin Gastroenterol* 2004;**38**:686–91.
- 6 Noshio K, Endo T, Yoda Y, *et al.* Diaphragm disease of small intestine diagnosed by double-balloon enteroscopy. *Gastrointest Endosc* 2005;**62**:187–9.

Figure 1 Diaphragmatic stricture of the small intestine and its enlargement using a double balloon endoscope and bougieing. (A) Diaphragm with a small orifice was found in the small intestine using a double balloon endoscope. (B) A balloon was placed through the diaphragmatic orifice and inflated with air to enlarge the stricture. (C) Abdominal roentgenogram showing a double balloon endoscope with a guidewire (small arrow) and inflated balloon (large arrow). (D) Enlarged orifice of diaphragmatic stricture of the small intestine.