VIRAL HEPATITIS

High incidence of allograft dysfunction in liver transplanted patients treated with pegylated-interferon alpha-2b and ribavirin for hepatitis C recurrence: possible de novo autoimmune hepatitis?

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Background: Interferon may trigger autoimmune disorders, including autoimmune hepatitis, in immunocompetent patients. To date, no such disorders have been described in liver transplanted patients.
Methods: 9 of 44 liver transplanted patients who had been receiving pegylated-interferon alpha-2b and ribavirin for at least 6 months for hepatitis C virus (HCV) recurrence, developed graft dysfunction despite on-treatment HCV-RNA clearance in all but one case. Laboratory, microbiological, imaging and histological evaluations were performed to identify the origin of graft dysfunction. The International Autoimmune Hepatitis scoring system was also applied.
Results: In all cases infections, anastomoses complications and rejection were excluded, whereas the autoimmune hepatitis score suggested a ''probable autoimmune hepatitis'' (score from 10 to 14). Three patients developed other definite autoimmune disorders (overlap anti-mitochondrial antibodies (AMA)-positive cholangitis, autoimmune thyroiditis and systemic lupus erythematosus, respectively). In all cases, pre-existing autoimmune hepatitis was excluded. Anti-lymphocyte antibodies in immunosuppressive induction treatment correlated with the development of the disorder, whereas the use of granulocyte colony-stimulating factor to treat interferon-induced neutropenia showed a protective role. Withdrawal of antiviral treatment and treatment with prednisone resulted in different outcomes (five remissions and four graft failures with two deaths).
Conclusions: De novo autoimmune hepatitis should be considered in differential diagnosis along with rejection in liver transplanted patients developing graft dysfunction while on treatment with interferon.

De novo autoimmune hepatitis (AIH) has been recently recognised as a new type of graft dysfunction affecting liver transplanted patients without a history of AIH.[1 2]

Diagnosis requires exclusion of alternative causes of allograft dysfunction and a clinical phenotype resembling classic AIH. As the classic phenotype may be modified by immunosuppression, the International Autoimmune Hepatitis Group scoring system[3] may be inappropriate for diagnosis, which may consequently depend more heavily on the exclusion of other causes of allograft dysfunction. Responsiveness to corticosteroids remains an important diagnostic cornerstone.

The hypotheses for AIH involve trigger factors, such as viruses or toxins,[4 5] and a genetic predisposition.[6 7] The loss of self-tolerance may be due to impaired negative selection of autoreactive immunocytes,[8] virus-induced polyclonal activation of lymphocytes cross-reactive to self-antigens (molecular mimicry)[9 10] and uncovering of cryptic autoantigens from tissues damaged by inflammation.[11]

In the setting of liver transplantation, calcineurin inhibitors may impair the thymic negative selection of autoreactive cells[12] and prevent the apoptosis of autoreactive lymphocytes,[13] enhancing autoreactivity. Hepatotropic viruses, whose incidence is greater because of immunosuppression, may lead to enhancement of MHC expression and polyclonal stimulation of lymphocytes, generating, through the mechanism of molecular mimicry,[14] an autoreactive, self-perpetuated immune response.

It is known that interferon (IFN), because of its immunomodulatory effects, may trigger autoimmune disorders, including AIH,[15 16] in immunocompetent patients, but there are no reports on the development of AIH in liver transplanted patients receiving IFN. We report a form of graft dysfunction with features of de novo AIH that occurred in liver transplanted patients receiving pegylated-IFN (PEG-IFN) for hepatitis C recurrence.

PATIENTS AND METHODS

From October 2001 to April 2004, 54 consecutive liver transplanted patients with recurrent hepatitis C were enrolled in a study protocol of antiviral treatment with PEG-IFN alpha-2b (Peg-Intron, Schering-Plough) 1.0 μg/kg/week and ribavirin (Rebetol, Schering-Plough) 800-1200 mg/day for at least 6 months.

Inclusion criteria were: liver transplantation for hepatitis C virus (HCV)-related cirrhosis; increased (>1.5×upper normal value) alanine aminotransferase (ALT); detectable serum HCV-RNA by qualitative assay (HCV TMA, Bayer Diagnostics) and histological features compatible with HCV reinfection.

Patients aged <18 years, or with decompensated liver disease, hepatitis B virus (HBV) or HIV infection, haemoglobin

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; ANA, antinuclear antibodies; ASMA, anti-smooth-muscle antibodies; EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; HBV, hepatitis B virus; HCV, hepatitis C virus; IFN, interferon; pANCA, antineutrophil cytoplasmic antibodies; PEG-IFN, pegylated-interferon; SLE, systemic lupus erythematosus; SVR, sustained virological response

<10 g/dl, white cell count <1500/µl, platelet count <50 000/µl, endogenous creatinine clearance <50 ml/min, cardiovascular and psychiatric disease, ongoing alcohol misuse, histological evidence of rejection and previous treatment with PEG-IFN after liver transplantation were excluded. Previous antiviral treatment with standard IFN after liver transplantation was not considered an exclusion criterion.

Liver biopsy was performed before starting treatment and evaluated by an experienced pathologist. Diagnosis of recurrent hepatitis was based on the presence of portal, periportal and lobular inflammation, with lobular acidophilic bodies or lobular hepatocytolysis. Histological activity index was assessed according to the Knodell scoring system.[17] The Banff scoring system[18] was applied to exclude acute cellular rejection. Features of chronic rejection (loss of interlobular bile ducts in ⩾50% of portal tracts accompanied by arteriopathy affecting hepatic artery branches at the hilum)[19] were also excluded.

All patients gave written informed consent to participate in the study which was conducted according to the principles of the Declaration of Helsinki.

Efficacy and safety were assessed by clinical and laboratory evaluations at each visit (carried out monthly until 6 months after the cessation of treatment). HCV-RNA viral load in serum was determined by quantitative assay (third-generation HCV bDNA 3.0, Bayer Diagnostics) before starting treatment, at the end of the first month, and every 3 months thereafter, until the end of follow-up; a qualitative assay was used when HCV-RNA fell below its detection limit. Non-organ-specific autoantibodies were tested before treatment and every 3 months thereafter, by indirect immunofluorescence.[20]

Granulocyte colony-stimulating factor (G-CSF; Granulokine, Roche, Italy) and erythropoietin (EPO; NeoRecormon, Roche, Italy) were used in cases of neutrophil count and haemoglobin falling below 1000/µl and 10 g/dl, respectively. Treatment was stopped in the event of severe side effects or sustained cytopenia despite G-CSF and EPO administration.

During the study period, 9 patients developed an unexpected form of graft dysfunction, despite on-treatment virological response (qualitative HCV-RNA negative) in 8 of them.

According to protocol, they underwent laboratory tests evaluating calcineurin-inhibitor serum levels, non-organ-specific autoantibodies, qualitative HCV-RNA and microbiological tests. Tests were also carried out to verify the regular patency of vessels and biliary tract. Liver biopsy was repeated, and if acute or chronic rejection and HCV reactivation were excluded, morphological criteria of the International Autoimmune Hepatitis Group[3] (interface hepatitis, plasma cells in the inflammatory infiltrate, rosetting of periportal hepatocytes and biliary changes) were assessed. HLA typing from donor and recipient was used to calculate the AIH score.[3] The results of typing were compared and for each locus the number of mismatches was scored as 0, 1 or 2 on the basis of the number of donor's specificities not shared with the recipient for a total amount of mismatches varying from 0 to 6.

Statistical analysis

Data were analysed using non-parametric tests, including the Mann–Whitney U test and Fisher's exact test. A p value <0.05 was considered to be significant. All data analyses were conducted using the Statistical Package for Social Science (SPSS V.11.5).

RESULTS

A total of 54 consecutive liver transplanted patients with recurrent hepatitis C were enrolled in the study (M/F 36/18; mean age 57 years, range 22–67 years; median time after liver transplant 17.5 months, range 1–151 months; genotypes 1 and 4, 46 patients; genotypes 2 and 3, 8 patients). Induction immunosuppression consisted of thymoglobulin in 5 (9%) patients, steroids in 46 (85%) and other in 3 (6%).

Maintenance immunosuppression consisted of cyclosporine or tacrolimus (with steroids in 14 patients), maintained in therapeutic range in relation to the time of liver transplant. The five patients who received induction treatment with thymoglobulin were maintained at lower tacrolimus serum level to achieve tolerance.[21]

Ten patients stopped treatment before the expected 6 months because of liver decompensation (n = 4), intolerance to treatment (n = 4), liver abscess (n = 1) and de novo hepatitis B (n = 1).

Among the 44 patients treated for at least 6 months, 9 (17%) presented unexpected liver function test abnormalities despite on-treatment virological response in 8 of them. They were evaluated according to the protocol, and in all cases infections, anastomoses complications, and acute or chronic rejection were excluded, whereas application of the AIH score suggested the diagnosis of ''probable AIH''. Revaluation of baseline data excluded the diagnosis before treatment in all cases. In all patients, antiviral treatment was withdrawn and a course of prednisone (1 mg/kg) was started. Table 1 gives a brief description of such cases.

Patient 1

Patient 1 started antiviral treatment 6 months after liver transplantation for a severe reinfection with advanced fibrosis. HCV-RNA tested negative by PCR after the first month of treatment. At month 6, an ALT flare occurred, and anti-nuclear antibodies (ANA; titre 1/40) and anti-smooth-muscle antibodies (ASMA; titre 1/40) appeared. Liver biopsy showed severe interface hepatitis with plasma cells infiltration and rosettes. The AIH score was 14. Withdrawal of antiviral treatment and treatment with steroids led to a rapid biochemical response. Nevertheless, he died 1 month later because of variceal bleeding. At that time, qualitative serum HCV-RNA was still negative.

Patient 2

Patient 2 started treatment 62 months after liver transplantation. ANA was positive (1/40) at baseline. Serum HCV-RNA tested negative from month 3. Despite persistent HCV-RNA negativity, at month 6 she presented jaundice and an ALT flare, with histological evidence of severe interface hepatitis, mild plasmacellular infiltration, rosettes, macrovesicular steatosis and worsening of fibrosis compared with baseline. The AIH score was 12. Antiviral treatment was stopped and corticosteroids were given without a significant improvement in liver tests. The immunosuppressive regimen was therefore switched from ciclosporin to tacrolimus and sirolimus. Nevertheless, she presented a relentless course of cholestatic hepatitis with progressive liver failure and died 3 months later. HCV-RNA by PCR was still negative.

Patient 3

Patient 3 started treatment at month 7 after liver transplantation, achieving rapid viral clearance. At month 10, an ALT flare occurred and ANA appeared (1/40), with histological evidence of interface hepatitis without plasmacellular infiltration, rosettes and macrovesicular steatosis. The AIH score was 10. Withdrawal of antiviral treatment and treatment with steroids led to normalisation of liver tests. After 9 months, she is still receiving low doses of steroid, with normal ALT and sustained virological response (SVR).

Table 1 Main clinical and laboratory features of patients who developed graft dysfunction

					Before antiviral treatment				During development of graft dysfunction							
Patient	Sex	Age (years)	Months after LT	HCV genotype	Knodell score	Autoantibodies	Ig*	AIH score	HCV RNA by PCR	Knodell score	Autoantibodies	Ig*	AIH score	Other findings	SVR	Outcome
1	M	65	6	1	4-3-4-3	Negative	1.5	2	Negative	5-3-4-3	ANA 1/40 ASMA 1/40	2	14	No	NA	Death for variceal bleeding
2	F	61	62	1	4-3-3-1	ANA 1/40	0.9	5	Negative	4-3-4-3	ANA 1/40	1.7	12	Macrovesicular steatosis 40%	NA	Death for graft failure
3	F	62	7	4	3-1-3-1	Negative	0.5	1	Negative	4-1-3-1	ANA 1/40	1	10	Macrovesicular steatosis 40%	Yes	Remission with steroids
4	M	59	25	1	3-1-3-1	Negative	1.2	5	Negative	5-1-4-1	ANA 1/320	1.5	10	Ductopenia†	No	Improvement with steroids despite HCV relapse
5	M	58	35	1	3-1-3-1	Negative	0.7	−1	Negative	4-1-3-3	ANA 1/40	0.9	14	Ductopenia† Autoimmune thyroiditis	Yes	Remission with triple immunosuppression
6	M	60	12	1	1-3-1-1	ANA 1/40	0.8	3	Positive	3-3-3-1	Anti-dsDNA 1/10.240	1.9	10	Macrovesicular steatosis 60%	No	Improvement with steroids despite HCV relapse
7	M	55	19	1	4-3-3-1	ANA 1/640 ASMA 1/160	1.2	5	Negative	4-3-3-3	c-ANCA 1/80 Anti-dsDNA 1/80	1.9	11	Cholangitis, SLE	No	Improvement with steroids despite HCV relapse
8	F	60	3	2	3-1-3-1	Negative	1.1	1	Negative	4-3-4-1	ASMA 1/40	1.5	10	Cholangitis Hepatic artery stenosis‡ Bile duct stenosis‡	Yes	Reenlisted for LT
9	M	66	1	1	3-1-3-1	Negative	1.2	0	Negative	5-1-4-3	AMA 1/40	2.2	10	AMA positive cholangitis§	Yes	Graft failure

AIH, autoimmune hepatitis; ANA, antinuclear antibodies; ASMA, anti-smooth-muscle antibodies; HCV, hepatitis C virus; Ig, immunoglobulin; LT, liver transplant; NA, not available (negative at time of death); PCR, polymerase chain reaction; SLE, systemic lupus erythematosus; SVR, sustained virological response.
Knodell score: periportal necrosis—intralobular degeneration and focal necrosis—portal inflammation—fibrosis.
*Immunoglobulin level (× upper normal range).
†Ductopenia did not fulfil the criteria for chronic rejection.
‡These complications occurred 2 months after the diagnosis of de novo AIH.
§Diagnosis of AIH/primary biliary cirrhosis overlap syndrome.

Patient 4
Patient 4 started treatment 25 months after liver transplantation. The virological response was achieved at month 6, when ANA became positive at high titre (1/320). At the end of treatment (month 12) an ALT flare was seen and liver biopsy showed interface hepatitis, plasmacellular infiltration and rosettes. Mild ductopenia was also present, but the criteria for chronic rejection were not fulfilled. The AIH score was 10, and steroids were started with ALT normalisation, despite a virological relapse 2 months later. He is still receiving low doses of steroids and is in good condition with normal ALT values.

Patient 5
Patient 5 started treatment 35 months after liver transplantation, obtaining a virological response after 3 months. At month 6, he developed jaundice with an ALT flare. ANA became positive at low titre (1/40) and liver biopsy showed interface hepatitis, plasmacellular infiltration and rosettes. Mild ductopenia was also present, without fulfilling the criteria for chronic rejection. Autoimmune thyroiditis was also diagnosed. The AIH score was 14. Antiviral treatment was stopped, and steroid treatment was started. No improvement in liver tests was seen and serum bilirubin further increased. Liver biopsy was repeated 1 month later, confirming the previous picture. The immunosuppressive regimen was switched from ciclosporin and steroids to a combined treatment with tacrolimus, sirolimus and steroids, with normalisation of liver tests and maintenance of SVR.

Patient 6
Patient 6 started treatment 1 year after liver transplantation, clearing virus at month 6. After 1 month, a mild increase in ALT level occurred, together with a high titre of anti-dsDNA (1/10.240; ANA 1/40 was present at baseline) and HCV-RNA reappearance. Liver histology showed interface hepatitis, plasmacellular infiltration, rosettes and macrovesicular steatosis. The AIH score was 10. Withdrawal of antiviral treatment and treatment with steroid allowed normalisation of ALT.

Patient 7
Patient 7 started treatment 19 months after liver transplantation, achieving virus clearance 6 months later. At baseline, ANA (1/640 homogeneous pattern) and ASMA (1/160) were positive. At month 11 he developed polyserositis and migrant arthritis. Perinuclear staining for antineutrophil cytoplasmic antibodies (pANCA) and anti-dsDNA (1/80) was positive. According to the ARA criteria,[22] a diagnosis of systemic lupus erythematous (SLE) was made. Low-dose steroids led to remission of SLE, and antiviral treatment was stopped at the end of month 12, achieving an end-of-treatment virological response. After 2 months, although HCV-RNA was still negative, serum bilirubin and ALT increased. Liver biopsy showed interface hepatitis, rosettes, cholangitis, ductular proliferation and biliocyte regression. The AIH score was 11. The steroid dose was increased to 1 mg/kg, with normalisation of liver tests 1 month later, although HCV relapsed.

Patient 8
Patient 8 started treatment 3 months after liver transplantation, clearing virus from the first month of treatment. At month 12, an increase of ALT, alkaline phosphatase and bilirubin was observed. No vessel or biliary tract abnormalities were detected. ASMA at low titre (1/40) became positive and liver histology showed interface hepatitis, rosettes and cholangitis. The AIH score was 10. Antiviral treatment was stopped and steroids started, with an improvement in liver tests. However, 2 months later, an increase in liver function parameters occurred again and right hepatic artery stenosis was diagnosed, with multiple right segmentary bile duct stenosis. Bilioplasty was unsuccessful and she was reenlisted for liver transplant because of a progressive worsening of liver function.

Patient 9
Patient 9 started treatment 1 month after living donor liver transplantation. No response was achieved and treatment was stopped at month 12. After 1 month, he developed jaundice and an ALT flare. No abnormalities of extrahepatic bile ducts were found. HCV-RNA tested negative and anti-mitochondrial antibodies (AMA; 1/40) tested positive (negative in the donor). Liver biopsy showed biliary aggression, ductular proliferation, severe interface hepatitis and abundant rosettes. Despite the cholestatic features, the AIH score was 10. AIH and primary biliary cirrhosis overlap syndrome were thus diagnosed. The patient was unsuccessfully treated with steroids and high doses of ursodeoxycholic acid. After 6 months, HCV-RNA persisted negative but liver function progressively deteriorated.

Risk factors
To identify potential risk factors related to the development of graft dysfunction suggestive for de novo AIH, several variables were analysed. The use of antilymphocyte antibodies as induction treatment after liver transplantation proved to be significantly associated with the development of de novo AIH ($p = 0.03$), whereas the use of G-CSF to treat neutropenia during PEG-IFN treatment showed a protective role ($p = 0.02$). In particular, among the patients who developed de novo AIH, three received antilymphocyte antibodies and none received G-CSF. No association was found between development of de novo AIH and either the recipient's or the donor's HLA-DR3/DR4, or HLA mismatches. The finding of non-organ-specific autoantibodies at baseline did not seem to increase the likelihood of graft dysfunction.

In the entire population of 54 treated patients, in addition to the 9 patients reported above, the following uncommon adverse events were observed: autoimmune gastritis in two patients, and late hepatic artery stenosis in three further patients in addition to patient 8 in this series.

DISCUSSION
De novo AIH after liver transplantation is a newly recognised condition affecting patients transplanted for disorders other than AIH.[1 2] Risk factors and pathogenesis for this disorder remain unknown, and the minimum criteria for diagnosis have not been standardised.[23]

To the best of our knowledge, no patients with de novo AIH have been described in liver transplanted patients receiving IFN or PEG-IFN for recurrent hepatitis C, although it is known that in immunocompetent patients IFN may trigger autoimmune disorders, including AIH.[16]

In this study, we describe the occurrence of a peculiar form of graft dysfunction in liver transplanted patients receiving PEG-IFN alpha-2b and ribavirin for hepatitis C recurrence. During or shortly after the treatment, 9 of 54 (17%) patients experienced unexplained abnormalities of liver tests despite HCV-RNA clearance in eight of nine patients. Graft rejection, anastomoses complications and concomitant infections were excluded in all patients. The laboratory and histological characteristics (autoantibody appearance or titre increase, severe interface hepatitis with plasmacellular infiltration and rosettes) of these patients led us to hypothesise the occurrence of de novo AIH. By applying the AIH scoring system,[3] in all patients we obtained a score suggesting ''probable AIH''. Interestingly, before treatment, the AIH score was clearly negative in all patients. The

effects of immunosuppression, concomitant viral infection and drug toxicity make the diagnosis of AIH in liver transplanted patients with hepatitis C recurrence particularly difficult. In fact, these confounding factors can influence the intensity of plasmacellular infiltration in the liver, serum levels of γ-globulins and the titre of autoantibodies. Considering these limitations, although not validated in this context, a positive AIH score[3] in this setting could be more meaningful than in non-transplanted patients. The fact that 3 of 9 patients in this series also showed other definite autoimmune disorders such as thyroiditis, overlap syndrome and SLE reinforced the hypothesis of autoimmune-mediated graft dysfunction. Further, other autoimmune manifestations such as autoimmune gastritis (n = 2) and late hepatic artery stenosis (n = 4) without hypothetical risk factors other than PEG-IFN treatment occurred in the study population, as we described previously.[24]

As compared with the reported value of about 4% in untreated patients,[1 2] the high incidence of de novo AIH in our series suggests a potential pathogenetic role of the antiviral treatment. We believe that, in a clinical setting characterised by several conditions favouring autoimmune reactions, PEG-IFN, by virtue of its immunomodulatory effects, may trigger autoimmune disorders. The fact that all but one case occurred once the patients became HCV-RNA negative may suggest that a vigorous immune response promoting virus clearance may favour tissue damage and consequent cryptic antigen release in a context of MHC interferon-induced up regulation. Epitope spreading theory, defined as diversification of epitope specificity from the initial focus on cryptic epitopes to other proteins (reviewed in Vanderlugt and Miller [25]), supports the hypothesis that tissue damage during an immune response can lead to the priming of reactive lymphocytes, regardless of the specificity of the initial insult.

When we analysed possible risk factors related to development of de novo AIH, we did not find an association either with HLA haplotype, as reported by other authors,[2] or with the finding of non-organ-specific autoantibodies at baseline. Interestingly, the use of thymoglobulin was significantly associated with the occurrence of de novo AIH, whereas the use of G-CSF seems to have a protective role. We do not have a definitive explanation for these observations, but it is well known that thymoglobulin has relevant and long-term effects on cellular response. In fact, treated patients show a persistent low percentage of T cells for at least 2 years after treatment, with low CD4/CD8 ratios and drops in CD25+ T cells.[26] We can say that the relative increase in CD8 with loss of the inhibitory role of CD25+ cells, combined with the lower serum tacrolimus levels maintained in these patients to favour tolerance, can be permissive for development of Th1-mediated autoimmune disease.

The protective effect of G-CSF may derive from its known immune modulator effects on human CD4+ T cells, skewing T-cell differentiation towards the Th2 phenotype, with consequent suppression of T cell alloreactivity.[27]

When patients developed de novo AIH, antiviral treatment was stopped and steroids were started, with different outcomes: two patients died within 3 months because of variceal bleeding and liver failure, both being HCV-RNA negative; two other patients developed progressive liver failure, maintaining SVR; the remaining five are alive in good condition on maintenance steroid treatment, with two showing SVR.

In conclusion, our findings suggest the occurrence of a new type of graft dysfunction in liver transplanted patients receiving PEG-IFN and ribavirin, not related to rejection and with features compatible with de novo AIH. We are aware that autoimmunity by definition is characterised as a loss of tolerance towards self-antigens, so the use of this term to define hepatitis affecting an allogenic organ is questionable. However, until better knowledge of the true pathogenesis of this entity is acquired, the overall clinical, histological and immunological characteristics of these disorders strongly suggest an autoimmune mechanism, and de novo AIH should be considered in the differential diagnosis along with rejection.

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EDITOR'S QUIZ

Answer

From question on page 163

All layers of the bowel wall, especially the submucosa, are expanded by extravasated erythrocytes (fig 1A) with venous engorgement and leakage through vein walls (fig 1B). These findings are typical of mesenteric venous obstruction, as commonly seen in mesenteric venous thrombosis, and distinct from jejunal haematomas associated with anticoagulation. No venous thrombi were present and arteries were normal. Venous obstruction appears to have been due to external compression. The anatomical distribution and size of the affected segments are compatible with compression of two loops of jejunum against the vertebral column by a tight lap-strap seatbelt causing localised venous occlusion without arterial compromise, resulting in venous engorgement and erythrocyte extravasation facilitated by the patient's anticoagulation. The mucosa was largely intact, confirming the acute nature of the injury, and consistent with presentation immediately after a long flight. Non-traumatic seat-belt injury should be considered in patients presenting with an acute abdomen after long-haul flights.

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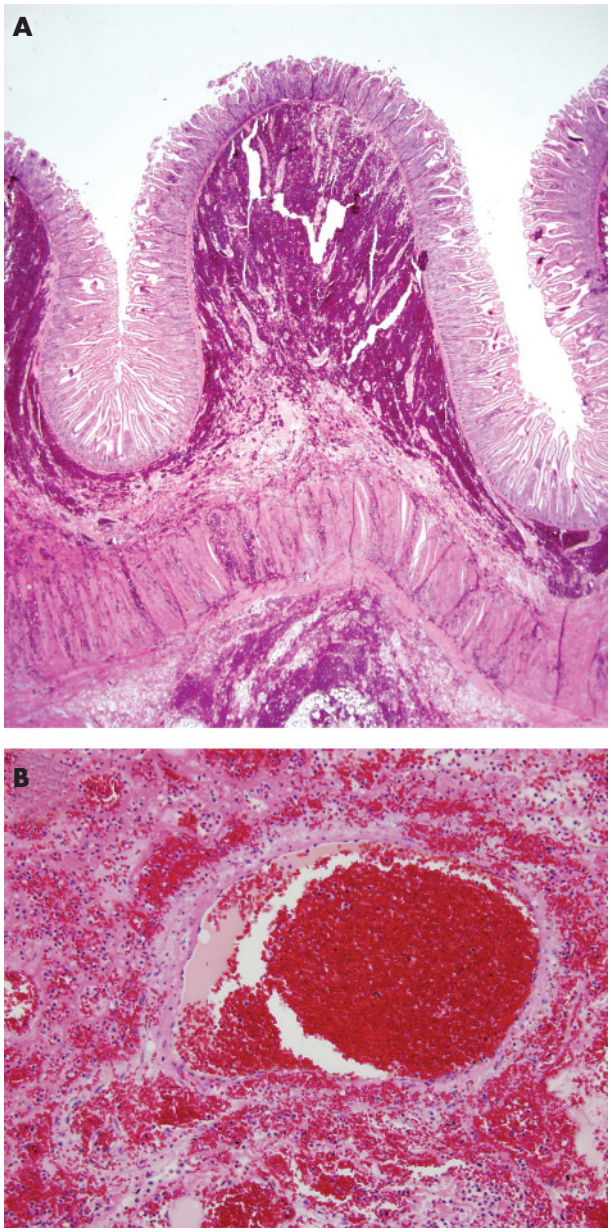

Figure 1 (A) Longitudinal section of jejunum. The virtually intact mucosa overlies the submucosa that is distended by extravasated erythrocytes. Intramural haemorrhage is also present in the muscularis propria and subserosa. (B) Submucosal vein engorged with red cells leaking through the vein walls into the surrounding connective tissue.