Crypt loss, pericapillary hemorrhage, and severe gastrointestinal graft-versus-host disease

To the Editor: The very complete study of Melson et al. [1] demonstrates the value of crypt loss as a marker of severity in acute graft-versus-host disease (GVHD) in a series of colonic biopsies in twenty seven patients. Interestingly, the authors underline that "crypt loss was not evident in the absence of accompanying apoptosis, confirming prior reports that the presence of crypt loss is specific of gastrointestinal GVHD and accompanies the presence of apoptosis".

They also report that in the three patients of their series who underwent simultaneous biopsy of the colon and upper gastrointestinal tract, severe crypt loss was also present in the duodenum. This point is important because it indicates an extensive disease of the whole digestive tract. In a previous study of ninety five patients with upper gastrointestinal biopsies [2], we also found such an extensive GVHD of the whole digestive tract in the fourteen patients with concomitant duodenal and colonic biopsies. Moreover, we found that the number of apoptotic cells was significantly correlated with the severity of GVHD in this series.

In an experimental model of acute GVHD, we demonstrated that endothelial cells, as well as epithelial cells can be the target of the allogeneic reaction, and that both types of cells undergo apoptosis through the activation of the Fas/FasL pathway [3]. In human, cutaneous endothelial cell damage was reported in chronic GVHD, with progressive loss of microvessels [4]. We also found endothelial cell apoptosis in duodenal biopsies of patients with acute GVHD, with resulting pericapillary hemorrhage, and this latter damage was significantly correlated with GVHD severity [5].

Taken together, these concordant results suggest that apoptosis of target cells, both epithelial, with crypt loss, and endothelial, with pericapillary hemorrhage, induces severe extensive damage in the digestive tract. Moreover, the loss of crypts, whose epithelium contain cells able to repair the upper part of the digestive epithelium, can also contribute to poor therapeutic response, by impairing the mechanism of digestive tract tissue repair.

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Published online 5 December 2007 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.21063

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Stroke in thalassemia: A dilemma

To the Editor: We have read the article by Karimi et al., cerebrovascular accident in β-thalassemia major and β-thalassemia intermedia [1], and would like to share our experience on the subject matter. We have recently published a retrospective chart-review study on the prevalence of thromboembolic events among 8,860 patients with thalassemia major and intermedia in the Mediterranean area and Iran [2]. We showed in that report that patients with thalassemia major (TM) have had a significantly greater risk for stroke (OR 3.72 [1.48, 9.32]; P 0.005) while patients with thalassemia intermedia (TI) had significantly greater risk to experience a thromboembolic event. We report here additional details on the clinical profile of the subset of patients who developed ischemic stroke.

Among the cohort of 8,860 thalassemics, 6,670 with thalassemia major (TM), and 2,190 with thalassemia intermedia (TI), 25 developed an ischemic stroke (17 TM and 8 TI). The diagnosis was made on clinical and radiological grounds in 64% of cases, on clinical grounds alone in 32%, and radiologically alone in 4%. Males were more than females (60% vs. 40%), and outcome was death in 36% and morbidity in 40% of cases. The 17 patients with TM (0.25%) had a mean age of 21.5 (2.5–45) years; all were on regular blood transfusion, 16 had a splenectomy before the event, and five were receiving Aspirin. Average pretransfusion hemoglobin (g/dl) was less than or equal to 10 in 15 patients, and outcome of the cerebrovascular accident (CVA) was death in eight cases. The eight patients with TI (0.36%) had a mean age of 32.3 (10–67) years; four were on regular blood transfusions, seven had a previous splenectomy, and three were on Aspirin. Average pretransfusion hemoglobin (g/dl) was less than or equal to 10 in all patients, and outcome was death in one case and morbidity in six cases.

Karimi et al. reported seven patients [5 TM (0.46%) and 2 TI (1.7%)] who developed stroke. They were all splenectomized with an average hemoglobin level of 7.5 g/%, and five of them were regularly transfused [1]. Interestingly, however, Karimi et al. forwarded the possibility of an embolic source of stoke (of cardiac origin) as suggested by the coexistence of atrial fibrillation and cardiomyopathy among the patients described in his cohort. Unfortunately, we are incapable of commenting on this suggestion (because of the limitations of our study design), but find this a plausible hypothesis that might explain why the prevalence of thrombosis among TI surpasses that among TM except in stroke and suggest testing it in a well designed manner. Finally, though not supported by strong evidence, we underline the importance of the use of anticoagulants and/or antiplatelets in the subset of patients at risk of thrombosis, especially Aspirin, being a relatively safe and useful medication in preventing arterial thrombosis. Also, the current data is still insufficient to draw meaningful recommendations on performing MRI of the brain to monitor early/subclinical vascular damage.

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Published online 8 January 2008 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.21117

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Refractory idiopathic thrombocytopenic purpura treated with the soluble tumor necrosis factor receptor etanercept

To the Editor: A 34-year-old white man presented with bruising, petechiae, and platelet counts of 3,000/μL. He was diagnosed with idiopathic thrombocytopenic purpura (ITP), an autoimmune disease in which platelets are targeted by the humoral immune system. Bone marrow biopsy, aspirates, and blood smears were normal, and serology results to rule out other antibody-based disorders were within normal range. Platelet counts had not improved after more than 2 weeks treatment with prednisone (100 mg/day). Two courses of treatment with intravenous immunoglobulins (IVIg) (1 g/kg) resulted in only temporary increases in platelet counts. Treatment with lansoprazole/amoxicillin/clarithromycin did not result in any significant change in the patient's thrombocytopenia. He underwent a splenectomy, with a temporary increase in platelet counts, followed by another drop to fewer than 10,000/μL, with manifestations of oral mucosal bleeding, 2 weeks later. Prednisone was tapered, and over the course of the next 26 months, the patient was treated with cyclophosphamide (orally and intravenously), participated in an investigational study of IDEC 131 (an anti-CD154 monoclonal antibody), and received rituximab, danazol, vincristine, colchicine, dapsone, and intermittent IVIg therapies. Response was minimal to all treatments, except for transient responses to IVIg therapy (increases in platelet counts up to 100,000/μL for 1–2 weeks, followed by drops to less than 10,000/μL). The patient had intermittent epistaxsis and a few episodes of rectal bleeding from a fissure or hemorrhoids; endoscopy ruled out related significant pathology.

On the basis of case reports in the literature [1] and the patient's failure to respond to available therapies, etanercept therapy was initiated at 25 mg twice weekly administered subcutaneously for 3 months. Etanercept is a soluble tumor necrosis factor (TNF) receptor currently indicated for the treatment of some autoimmune diseases, including psoriasis and rheumatoid arthritis [2]. During this period, the patient underwent one treatment with IVIg, 11 days after initiation of etanercept therapy. Platelets were monitored weekly and counts were generally between 20,000 and 50,000/μL. One month after finishing etanercept, his platelet count dropped to 4,000/μL, and he received another IVIg treatment, with an increase to 250,000/μL. Over the next month, platelets stabilized at $\sim$100,000/μL, but dropped to 53,000/μL $\sim$8 months after discontinuation of etanercept. He had no mucosal bleeding or petechiae. A second course of etanercept was initiated at the same dosing regimen. The patient's platelet count improved, remaining above 150,000/μL, and reached 329,000/μL when etanercept therapy was again discontinued after 3 months. Since then, the patient has had no bleeding complications, and platelet counts have remained above 200,000/μL, with no further IVIg therapy. His last platelet count, 11 months after completing his second round of etanercept therapy, was 294,000/μL. Etanercept appeared to be well tolerated in this patient, with no short-term or long-term adverse events noted.

Patients with ITP who have exhausted all therapeutic options face dire consequences from this disease, and new therapies are clearly needed. There is recent evidence that TNF may affect thrombocytopenia and platelet metabolism, providing a scientific rationale for the apparent success of etanercept in the treatment of ITP in this case and in three other patients described in the literature [1]. The patient described here, as well as 2 of the 3 patients treated by McMinn et al., [1], received etanercept therapy for up to 4 months and maintained adequate platelet counts for up to 19 months. It remains to be seen whether the morbidity and mortality associated with refractory ITP will be affected by etanercept therapy, and long-term monitoring of patients with ITP receiving this treatment is warranted.

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Published online 10 January 2008 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.21135

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Use of prothrombin complex concentrates in anticoagulation

To the Editor: We would like to respond to the review on the role of prothrombin complex concentrates (PCCs) in reversing anticoagulation by Leissinger et al. [1] We agree with the authors that evidence is accumulating PCCs being more efficacious than fresh frozen plasma (FFP) for urgent reversal of vitamin K antagonist (VKA) therapy. Though most important points were covered, we would like to adjust some of the information reported.

The authors correctly state that PCCs containing very low concentrations of coagulation factor VII (FVII) should be designated as three-factor concentrate. In the article, Cofact (Sanquin, Amsterdam, the Netherlands) was erroneously stated as three-factor concentrate with incorrect factor concentrations. In Cofact's summary of product characteristics is clearly stated that FIX concentration is fixed (25 IU/ml) and ranges of FII (14–35 IU/ml), FVII (7–20 IU/ml), and FX (14–35 IU/ml) are provided (http://www.cbg-meb.nl/IB-teksten/h17060.pdf). FVII quantity is 28–80% of FIX concentration, clearly indicating Cofact should be considered a four-factor concentrate.

The authors remark that coadministering FVII should be considered when using a three-factor concentrate in VKA reversal. That 7 of the 13 PCCs are concerned to be a three-factor concentrate is contradictory to Table II, where only six studies can be counted, of which one is supplementing FVII [2] and one is simultaneously using FFP [3], which contains FVII. These patients may be considered being treated with four factors. The study by Taberner et al. was referred as 4-factor concentrate, but the authors themselves stated using a 3-factor concentrate [4], and similar for Prothrombinex used by Crawford. Van Aart et al. used a four-factor PCC, and not a three-factor [5]. Differences in typing of PCCs influences the discussion of adverse events (AEs).

It should be stressed that all (two) AEs in the study of Van Aart et al. were possibly related to a combination of medical history, current illness and the use of PCC, but not the use of PCC alone [5]. This perspective was not stated—although it was stated for another study. Based upon the information from Table II, and with some PCCs change from three-factor to four-factor concentrate and vice versa, one would calculate slightly different numbers. Nevertheless, the number of possible thrombo-embolic complications remains low, both in the three-factor and four-factor concentrate group. Although this risk should not be neglected, we agree with the authors it is not an absolute contraindication for using PCC in urgent VKA reversal. The benefits should always be balanced against the risks.

The authors propose a study comparing efficacy of recombinant activated FVII (rFVIIa) and PCC in acute VKA reversal. This has already been performed in an animal model. It showed that PCC is more effective in reversing sustained VKA anticoagulation: haematological parameters significantly improved or normalised, and blood loss reduced to a minimum by PCC (P 0.01 rFVIIa vs. PCC) [6]. We strongly advocate a clinical study comparing haematological and clinical efficacy and safety of rFVIIa and PCC for emergency reversal of VKA therapy.

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Published online 22 January 2008 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.21142

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Etanercept therapy and acute myeloid leukemia

To the Editor: We read with great interest the study by Nair et al. on a case of myelodysplasia with acute myeloid leukemia (AML) after etanercept therapy for psoriasis [1]. The authors reviewed the literature and found only one case of AML-M2 in a patient 4 months after beginning treatment with etanercept for ankylosing spondylitis [2]. However, we published in January 2007 a similar case of AML-M2 that also developed 4 months after initiating etanercept therapy for psoriasis [3]. Of note, there was no evidence of myelodysplasia as blood cell count was normal at the beginning of the treatment [3], no dysplastic features were found on bone marrow smear and biopsy, and cytogenetic studies performed on bone marrow aspirate only demonstrated trisomy 22. In both the cases, the responsibility of the drug was disputed. Our patient had no risk factors for leukemia as he previously received only topical agents, phototherapy, and acitretin. Patients with psoriasis are not at risk for leukaemia. Transformation of myelodysplasia to AML have been described in a few patients after PUVA therapy, but its mutagenic effect on hematopoetic cells remains speculative [4,5]. As we concluded in our letter, although a fortuitous association between etanercept therapy and AML cannot be ruled out, report of such cases is required to better evaluate its incidence.

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Published online 29 January 2008 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.21140

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TNF alpha inhibition and AML

To the Editor: Dr. Bachmeyer has correctly noted that they published additional case reports of acute myeloid leukemia (AML) after TNF alpha treatment. Their article was published while ours was in press, which prevented us from referencing their work. We agree, however, with their suggestion that the temporal association between treatment with etanercept and diagnosis of AML in the three reported cases is suspicious for a cause and effect relationship. We also agree that further, long-term follow-up of all patients receiving Enbrel treatment is advisable to determine the actual statistical risk for AML after TNF-alpha inhibitor treatment.

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Published online 27 December 2007 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.21144