237-40.
4. Hunt DM, Higgs DR, Winichagoon P, Clegg JB, Weatherall DJ. Haemoglobin Cs Sp has an unstable α chain messenger RNA. Br J Haematol 1982; 51:405-13.
5. Harteveld CL, Traeger-Synodinos J, Ragusa A, et al. Multicentric origin of Hb Constant Spring [α2 codon 142 TAA-CAA]. Br J Haematol 1998; 102:50.
6. Pootrakul P, Winichagoon P, Fucharoen S, Pravatmuang P, Piankijagum A, Wasi P. Homozygous hemoglobin Constant Spring: a need for revision of concept. Hum Genet 1981; 59:250-5.
7. Schrier SL, Bunyaratvej A, Khuhapinant A, et al. The unusual pathobiology of hemoglobin Constant Spring red blood cells. Blood 1997; 89:1762-9.

Liver nodular regenerative hyperplasia after bone marrow transplant

We report an unusual liver disease which may occur after bone marrow transplantation, i.e. the collapse of hepatic lobuli followed by regenerative islets: the resulting clinical picture may mimic GvHD or a viral disease, but histology is diagnostic, showing nodular regeneration in the absence of inflammation or fibrosis.

Sir,

Liver abnormalities are frequently detected after bone marrow transplantation (BMT). Early after the transplant they may be due to drug toxicity, less frequently to venocclusive disease (VOD), viral or septic infection. Late liver impairment is often related to chronic graft-versus-host disease (GvHD), and less frequently to viral reactivation or drug toxicity. Persisting disorders are also to be expected in patients who survive a VOD.[1] A rarer post-transplant liver disorder is *nodular regenerative hyperplasia* (NRH), which is characterized by the formation of intrahepatic nodules of regenerating hepatocytes, with moderate or no fibrosis. This disorder has been associated with a number of clinical conditions of autoimmune (rheumatoid arthritis; Sjögren's, CREST or Felty's syndrome), hematologic (myelo-and lymphoproliferative disorders), or endocrine (diabetes mellitus) origin,[2] or even after prolonged administration of immunosuppressive[3] or contracceptive drugs. We report the case of a patient who had NRH nine months after an allogeneic BMT.

A 35-year old male with chronic myeloid leukemia in chronic phase received a bone marrow transplant from his HLA-identical brother in March 1998. The conditioning regimen was BuCy2; he was infused with 1.6×10^8/kg. GvHD prophylaxis was a short course of cyclosporin A and methotrexate (MTX). On day +2, after the first dose of MTX, the patient developed weight gain, painful hepatomegaly, decreased diuresis and increased bilirubin, transaminases and PAI-1. With the suspicion of an impending VOD, we discontinued MTX and all signs and symptoms disappeared. On day +33, a grade IV acute cutaneous GvHD occurred, successfully treated with high dose prednisone. At +5 months the patient presented with increased ALT, AST, γ-GT, ALP and bilirubin, in the absence of markers of viral infection. The patient was thought to have hepatic GvHD, so she underwent liver biopsy, which showed liver injury probably due to drug toxicity. All drugs were discontinued, and all liver function parameters improved; however, three months later a new wave of hepatic cytolysis and cholestasis occurred (Figure 1). A repeat liver biopsy showed hepatocyte nodular regeneration with compression of the surrounding tissue, in the absence of inflammatory cells even in portal areas and virtually no fibrosis. This picture is typical of NRH (Figure 2). No treatment was planned; liver enzymes are checked every month and continue to fluctuate. Seven months after the diagnosis of NRH, no sign of portal hypertension has appeared.

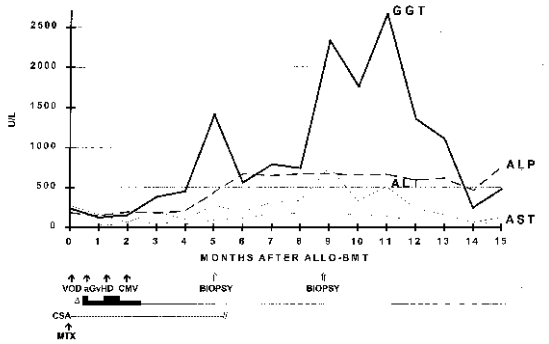

Figure 1. Post-transplant time course of liver enzymes.

The pathogenesis of NRH is not well understood. Probably it results from sinusoidal lesions causing local hypoperfusion with regenerative hyperplasia in the normally perfused surrounding areas.[4] Clinically, NRH may be confused with liver cirrhosis.[5] Fifty per cent of patients with NRH develop portal hypertension.[4] Hepatic failure, rupture of the liver, malignant transformation and gastric antral vascular ectasia syndrome are described complications of NRH.[6,7]

It is possible that post-transplant NRH is more frequent than reported, since several cases could have been clinically misdiagnosed as VOD, GvHD or drug toxicity.[8] Since no clinical or laboratory findings are specific to NRH, an informative liver biopsy is the only key to a correct diagnosis.[9] In addition, since the liver may be sequentially involved by a number of different events in the post-transplant period, repeat liver biopsies may be necessary to identify all the damaging mechanisms.

Luca Pezzullo, Pietro Muretto, Gennaro De Rosa, Marco Picardi, Anna Lucania, Bruno Rotoli

Division of Hematology, Federico II Univeristy, Naples, and Pathology Service, S. Salvatore Hospital, Pesaro, Italy.

Key words

NRH, BMT, GvHD, Liver Biopsy, LMC

Correspondence

Bruno Rotoli, M.D., via S. Pansini 5, 80131 Napoli, Italy. Phone: international+39-081-7462068 – Fax: international+39-081-7462165

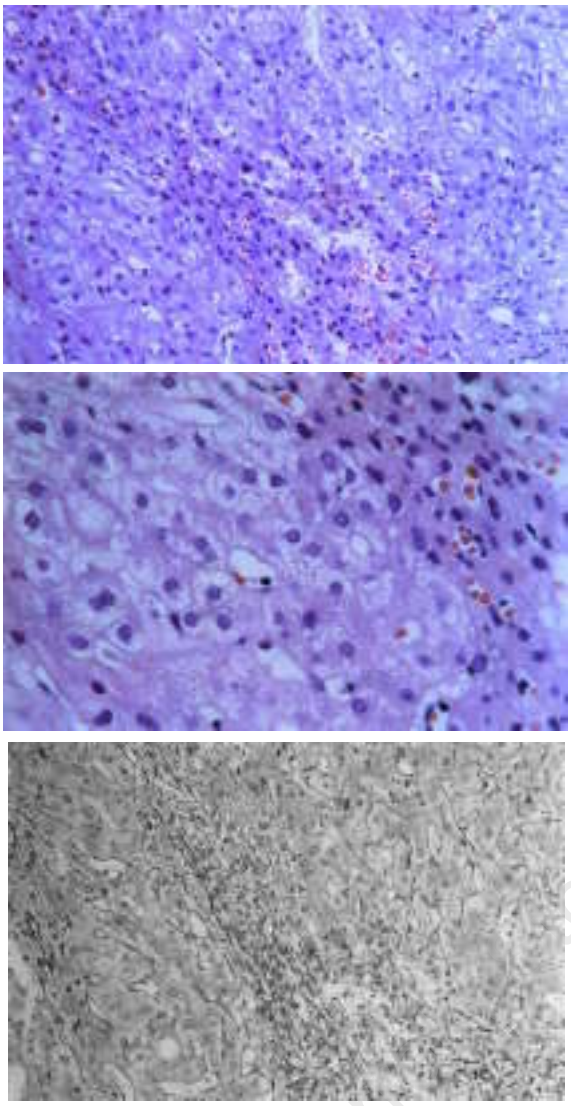

Figure 2. Post-transplant liver nodular regenerative hyperplasia. A: Two regenerative nodules compressing hepatocytes. A portal area (bottom right) shows moderate fibrosis. (HE, 400x). B: Note the absence of inflammatory cells on the boundary between regenerating and compressed hepatocytes. (HE 1000x). C: Reticular fibrosis in the compressed areas, revealed by the Gomori's staining (400x).

References

1. Richardson PG, Elias AD, Krishnan A, et al.Treatment of severe veno occlusive disease with defribotide: compassionate use results in efficacy without significant toxicity in high risk population. Blood 1997; 90(Suppl 1):252a.
2. Thung SN, Gerber MA, Bodenheimer HC Jr. Nodular regenerative hyperplasia of the liver in a patient with diabetes mellitus. Cancer 1982; 49:543-6.
3. Duvoux C, Kracht M, Lang P, Vernant JP, Zafrani ES, Dhumeaux D. Nodular regenerative hyperplasia of the liver associated with azathioprine therapy. Gastroenterol Clin Biol 1991; 15:968-73.
4. Ueno S, Tanabe G, Sueyoshi K, et al. Hepatic hemodynamics in a patient with nodular regenerative hyperplasia. Am J Gastroenterol 1996; 91:1012-5.
5. Connolly CE, O'Brien MJ. Nodular transformation of the liver: report of a case. Hum Pathol 1977; 8:350-2.
6. Stromeyer FW, Ishak KG. Nodular transformation (nodular "regenerative" hyperplasia) of the liver. A clinicopathologic study of 30 cases. Hum Pathol 1981; 12:60-71.
7. Cales P, Voigt JJ, Payen JL, et al. Diffuse vascular ectasia of the antrum, duodenum, and jejunum in a patient with nodular regenerative hyperplasia. Lack of response to portosystemic shunt or gastrectomy. Gut 1993; 34:558-61.
8. Snover DC, Weisdorf S, Bloomer J, McGlave P, Weisdorf D. Nodular regenerative hyperplasia of the liver following bone marrow transplantation. Hepatology 1989; 9:443-8.
9. Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2.500 autopsies and a new classification of benign hepatocellular nodules. Hepatology 1990; 11:787-97.

Incidence of factor v leiden and prothrombin G20210A in patients submitted to stem cell transplantation

Factor V Leiden (FVL) and prothrombin G20210A are the most common defects associated with thrombophilia. The purpose of our study was to define the incidence FVL and prothrombin 20210A in a population of patients with hematologic malignancies submitted to high dose chemotherapy and stem cell transplantation and verify the role of these mutations in the development of thrombotic complications during and after transplantation

Sir,

Factor V Leiden (FVL) and prothrombin G20210A are the most frequent mutations associated with inherited thrombophilia. They are fairly common in the general population and exert a substantial risk of development of thromboses during a subject's lifespan. The prevalences of FVL and prothrombin G20210A are 5% and 2%, respectively, in Caucasians[1] and 1.8% and 2.8%, respectively, in the general Italian population.[2,3] The relevance of these mutations prompted us to investigate their prevalence and significance in thrombotic complications after stem cell transplantation (SCT) in patients with hematologic malignancies.

Sixty-nine consecutive patients referred to our Transplant Unit were screened for FVL and prothrombin G20210A mutation. Protein C, S and ATI-II deficiency, and antiphospholipid antibodies were excluded in this series of patients. The patients' characteristics are shown in Table 1. Donor-recipient pairs were studied before allogeneic SCT in order to avoid bias from post-transplantation chimerism.[4]

Fifty-four patients are alive after a median follow-up of 31 months (range 10-69). Two out of 69 patients (2.9%) were heterozygotes for these thrombophilic mutations, one for FVL (1.4%) and one for