Dear Editor:

Bone marrow necrosis (BMN) is a rare disease, and approximately 270 cases with BMN have been reported in literature up to now [1]. Although malignant hematopoietic diseases are common causes of BMN, benign diseases and drugs including interferon alpha, fludarabine, and paracetamol may be the nonmalignant causes of this pathology [1–3]. There are no reported cases of BMN due to diclofenac in literature. We present a patient with reversible BMN due to overdose consumption of diclofenac sodium because of renal colic.

A 26-year-old male was suffering from symptoms of anemia, fever, and bone pain. He had nephrocalcinosis and was treated with diclofenac because of renal pain. Diclofenac was used intramuscularly for renal colic in a dose of 75 mg repeatedly with 30-min intervals for 12 doses. He experienced fever and bone pain 5 days after diclofenac administration. Physical examination revealed fever and pallor of skin. Remarkable laboratory findings were hemoglobin level (7.7 g/dL), leucopenia (1.6 × 10^9/L), neutropenia (0.5 × 10^9/L), and no thrombocytopenia (179 × 10^9/L). His biochemical profile revealed high levels of alkaline phosphatase (AP) 940 IU/L (normal range, 60–300 IU/L) and lactate dehydrogenase (LDH) 520 IU/L (normal range, 220–450 IU/L). Bone marrow aspiration smears showed striking necrosis and nearly absent intact hematopoietic cells, whereas bone marrow biopsy revealed BMN (100%; Fig. 1), which was graded according to the extent of necrosis in the BM biopsy described by Maisel et al. [4]. Red blood cells were transfused because of symptomatic anemia. Two months later, his physical examination and laboratory results were resolved. Nine months after his initial admission, his physical examination was normal.

Diclofenac is a pain reliever and an anti-inflammatory drug that is usually used as an analgesic in rheumatologic diseases and in general practice. Common adverse effects of diclofenac include gastrointestinal symptoms, peptic ulcer, and bleeding. Although it is usually administered at 75–150 mg daily, diclofenac was given to the patient described herein at a total dose of 900 mg/day. BMN is characterized by necrosis of the medullary stroma and myeloid tissues in large areas of the bone marrow, probably because of failure of the microcirculation. Toxic effects of chemotherapy, microvascular infarction, tumor necrosis factor, and thrombosis were blamed for the pathophysiology of BMN [1]. We believe that BMN in our patient may be due to the inflammation created by the cytokine release because of overdosed diclofenac. Although the prognosis of patients with BMN is usually poor, diseases causing BMN and the age and grade of the necrosis are the main indicators of prognosis [5]. In our case, he was young and had no other diseases. In conclusion, BMN is a rare clinical condition. It should be kept in mind that some patients may have reversible BMN due to drugs and benign diseases.

Fig. 1. BM biopsy showing eosinophilic silhouette of bone marrow between bone trabeculae (hematoxylin/eosin, original magnification 100x). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**REFERENCES**

Liposomal Amphotericin B as Antifungal Prophylaxis in Bone Marrow Transplant Patients

To the Editor: Fungal infections are common complications in immunosuppressed patients due to bone marrow transplantation (BMT). To reduce the incidence and severity of these types of infection, several prophylactic regimens with antifungal agents have been used in this population. We note that liposomal amphotericin has been used by a proportion of clinicians as a prophylactic regimen against fungal infections in BMT patients in hospitals in various countries.

However, in our search of the literature regarding this issue, we could not find evidence to support this approach. We searched for randomized controlled trials (RCTs), published in journals indexed in PubMed, Current Contents Connect, and Cochrane Library of Controlled Trials, that examined the incidence and severity of fungal infections, as well as colonization with fungi in BMT patients.

We identified only three RCTs dealing with this issue [1–3]. Table I shows characteristics of the RCTs, such as study design, number of enrolled patients, dosage of liposomal amphotericin B prophylaxis used, as well as several outcomes including mortality, fungal colonization on enrollment and after prophylactic treatment, and proven and suspected fungal infections. In one of the reviewed studies, the majority of the patients were enrolled in a nonrandomized fashion [1]. Subsequently, we combined data from the remaining two studies (that were RCTs) using the methodology of meta-analysis.

Results from the available RCTs do not provide support for the use of liposomal amphotericin B in BMT patients. Specifically, there was no difference in the occurrence of proven fungal infections (OR = 1.03, 95% CI 0.03–37.55), suspected fungal infections (OR = 0.83, 95% CI 0.47–1.45), or mortality (OR = 1.33, 95% CI 0.71–2.52) between patients using liposomal amphotericin B prophylaxis or placebo. Fungal colonization after treatment was less common in the liposomal amphotericin B prophylaxis group compared to placebo (OR = 0.39, 95% CI 0.21–0.72), however.

The results of this limited analysis do not support the practice of providing low-dose liposomal amphotericin B for antifungal prophylaxis in BMT patients. There may be some evidence for the use of azoles in a specific patient population, namely, in allogeneic BMT recipients [4,5]. Subsequently, prophylactic liposomal amphotericin B should probably be avoided in BMT patients, due to the lack of supporting evidence for its use, its high cost, and the common side effects associated with this form of antifungal prophylaxis. However, a large RCT is urgently needed to provide a definitive answer regarding the appropriate antifungal prophylaxis in BMT patients, given that the large proportion of patients undergo allogeneic bone marrow transplantation and the concerns that fluconazole, an azole frequently used in BMT patients as antifungal prophylaxis, may have some evidence for the use of amphotericin B for antifungal prophylaxis in BMT patients. Specifically, there was no difference in the occurrence of proven fungal infections (OR = 1.03, 95% CI 0.03–37.55), suspected fungal infections (OR = 0.83, 95% CI 0.47–1.45), or mortality (OR = 1.33, 95% CI 0.71–2.52) between patients using liposomal amphotericin B prophylaxis or placebo. Fungal colonization after treatment was less common in the liposomal amphotericin B prophylaxis group compared to placebo (OR = 0.39, 95% CI 0.21–0.72), however.

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Acute Promyelocytic Leukemia in an HIV-Infected Patient: A Case Report

To the Editor: A 46-year-old female was HIV-1 positive since 2001. She was treated with nelfinavir and lamivudine, but due to lipodystrophic syndrome, her medication was changed to efavirenz, achieving a CD4+ count > 500 cell/μL and HIV-RNA < 50 copies/mL. In June 2003, she stopped highly active anti-retroviral therapy (HAART) due to a gradual decrease in hemoglobin and platelets. One week before admission, she had continuous–remittent fever.


REFERENCES

A Chinese Family With Hemophilia B Leyden Due to T→A Transition at Position +6 of the FIX Gene

To the Editor: A 3-year-old Southern Chinese boy had persistent bleeding for 1 month from a tongue-biting injury. Evacuation of hematoma and repair of the tongue laceration were performed twice, initially under fresh-frozen plasma cover, which failed to stop bleeding, and subsequently with FIX replacement (upon diagnosis of hemophilia B, the FIX level was found to be 0.04 IU/mL). There was no family history of bleeding tendency. His maternal grandfather had no bleeding episodes in recent years.

The family tree, FIX genotype, FIX levels, PT, and aPTT of the patient and family members are shown (Fig. 1). Direct genomic sequencing of the patient’s FIX gene revealed a promoter mutation, nt +6 T→A. The boy is currently 7 years old, and his FIX level is still 0.04 IU/mL. His maternal grandfather (73 years old), with FIX at 0.8 IU/mL, has the same gene defect. Sequencing of the FIX promoter confirmed his mother and maternal aunt as obligate carriers. His aunt’s daughter had also inherited the defect, while his younger sister is normal.

Hemophilia B Leyden [1] is a group of point mutations within a 40-basepair (bp) region in the FIX promoter [nucleotide (nt) –26 to +13] encompassing the major transcription start sites. Patients have characteristic amelioration of disease phenotype after the onset of puberty, mediated by the action of testosterone on an androgen response element (ARE) in the promoter region [2]. Binding sites for transactivating factors, such as CCAAT/enhancer binding protein (C/EBP), hepatocyte nuclear factor 4 (HNF-4), and albumin D-site binding protein (DBP) [3–4], have also been identified in the region, such that disruption by a mutation would affect gene expression.

The numerous FIX Leyden mutations in Caucasians likely arose from common founder(s) or are recurrent mutations at Cpg dinucleotides. To date, there is only a single Asian case from Thailand (nt +8–T). We report herein the first Chinese patient with hemophilia B Leyden, carrying a nt +6 T→A defect. The clinical picture of him and his maternal grandfather with the same genetic defect conforms to the Leyden phenotype, because the grandfather now has a relatively normal FIX level (0.8 IU/mL) and no recent bleeding episodes. This mutation at nt +6 affects the first (site 1: nt +1 to +18) of five known cis-acting sites in the FIX promoter [4]. Other C/EBP and DBP binding sites at nt –77 to –99 (site 4) and nt –199 to –219 (site 5) were intact and thought to exhibit the strongest transcriptional activation [5]. At puberty, DBP binding factor is induced and acts synergistically with C/EBP to increase FIX expression [4]. Furthermore, for this nt +6 mutation, testosterone action on the normal ARE site (site 3: nt –36 to nt –22) will have an additive effect, thus raising the


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FIX level after puberty [3]. These would account for the normal FIX level in the maternal grandfather of this family.

Confirmation of hemophilia B Leyden is important for subsequent genetic counseling of carrier females. The prognosis of hemophilia B Leyden is better than for classical hemophilia B. Even if prenatal diagnosis shows an affected male fetus, mothers need not contemplate termination of the pregnancy.

Fig. 1. Southern Chinese family with hemophilia B Leyden (nt +6 T → A). The genotype (determined by direct genomic sequencing), FIX level, PT, and aPTT of all the members studied are shown. The husbands of the two daughters did not participate in the study. The proband at 7 years of age has an FIX level of 0.04 IU/mL. Normal ranges are as follows: FIX, 0.5–1.50 IU/mL; PT, 11.3–13.2 sec; aPTT, 17.6–37.6 sec. Squares symbolize male family members, circles symbolize female family members.

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To the Editor: Reports of hepatitis B virus (HBV) reactivation following treatment with rituximab have raised concern regarding use of this medication in patients who previously had a non-responding form of HBV [1,2]. We present a patient with lymphoma who received rituximab therapy and developed fulminant hepatitis B with a fatal course 3 months later.

A 21-year-old man with stage IV large B-cell non-Hodgkin lymphoma (NHL) had been treated with 3 courses of CHOP-R between July and September of 2003. The patient had a history of Evans syndrome since 5 years of age, which had been stable without a need for immunosuppressive treatment for the previous 6 years. His last transfusion was in 1995. The patient's hepatitis B surface antigen (HBsAg), surface antibody, and hepatitis B core antigen (HbcAb) were negative in 1996. His hepatitis B status immediately prior to the institution of chemotherapy is unknown. Four weeks after the last course, on day 91 of the therapy, the patient presented with cough and malaise and was admitted because of pneumonia with Respiratory syncytial virus and rapidly rising liver aminotransferase and bilirubin levels. Viral serologic investigations excluded hepatitis A and C. HBsAg was positive, and the hepatitis B core IgM was negative. A high load of HBV (2 × 10^5 copies/mL) was detected with real-time PCR. Immunoglobulin levels from September 2003 were within normal limits, and at the time of the admission, only IgM level was slightly low (44 mg/dL). Hepatic function did not recover, and the patient lapsed into coma on the 4th day of admission. Treatment with lamivudine was started at this point; however, the patient succumbed to hepatic failure 15 days after admission on day 106 of therapy for lymphoma.

Reactivation of HBV in four patients with lymphoma following treatment with rituximab may prove fatal [2–4]. This information is available at the FDA’s Medwatch website [3].

The negative core IgM in the presence of a positive HBsAg excludes a recent exposure to HBV, but it is possible the infection was acquired during therapy, and an IgM response could not be attained because of rituximab-induced B-cell depletion. His fatal outcome underscores the importance of screening for HBV and an IgM response could not be attained because of rituximab-induced B-cell depletion. His fatal outcome underscores the importance of screening for HBV exposure to HBV, but it is possible the infection was acquired during therapy, and an IgM response could not be attained because of rituximab-induced B-cell depletion. His fatal outcome underscores the importance of screening for HBV exposure to HBV, but it is possible the infection was acquired during therapy, and an IgM response could not be attained because of rituximab-induced B-cell depletion.

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References
Near-Total Resolution of Multicentric Castleman Disease by Prolonged Treatment With Thalidomide

To the Editor: We previously reported successful treatment of a patient with multicentric Castleman disease (MCD) with thalidomide [1]. At the time of initial diagnosis, the patient had extensive lymphadenopathy, ascites, a pericardial effusion, profound anemia, and thrombocytopenia. A biopsy of a lymph node was consistent with a diagnosis of Castleman disease. The patient was initially treated with steroids alone, but her condition continued to deteriorate rapidly. Because systemic manifestations of Castleman disease are believed to be potentiated by cytokines, in particular IL-6, thalidomide treatment was initiated approximately 1 month after diagnosis. The patient showed dramatic improvement, with complete resolution of the cytopenias, ascites, and pericardial effusion after 2 months of treatment. The initial dose of 300 mg of thalidomide per day was decreased to 200 mg per day due to the development of mild peripheral neuropathy. After 40 months of continuous thalidomide therapy, the patient is asymptomatic and has returned to work full-time, and has no impairment of activity due to her residual mild neuropathy. The patient does, however, have persistent lymphadenopathy that has shown no substantial changes by CT scan, compared to previous studies.

Because of her excellent performance status, a second lymph node biopsy was performed to assess the need for continued thalidomide therapy. The biopsy showed nonspecific changes, however, and focal Castleman-like features, including minimal “onion skinning” and occasional atretic/sclerotic germinal centers (Fig. 1) were also observed. Because this second lymph node biopsy had focal features characteristic for at least minimal persistence of Castleman disease, the patient was advised to continue thalidomide therapy indefinitely.

The data regarding potential side effects of long-term use of thalidomide is very scarce. To our knowledge, thalidomide does not carry many of the long-term side effects commonly associated with steroid or immunosuppressant therapy, such as osteoporosis, cataract formation, bone marrow toxicity, or increased susceptibility to infections. Fishman et al. reported long-term thalidomide treatment in a patient with Crohn disease, who tolerated 5 years of thalidomide treatment without development of mild peripheral neuropathy. Similarly, our patient has received more than 40 months of continuous thalidomide therapy and has good control of her disease, with only minimal peripheral neuropathy and without impairment of her daily activity. Thus, for now, the risk-to-benefit ratio is in favor of continued thalidomide therapy in our patient.

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TABLE I. Hematological and Molecular Data of a Family Affected With Hb D-Punjab(β)-Thalassemia

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mother</th>
<th>Son 1</th>
<th>Son 2</th>
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<td>10</td>
<td>39</td>
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<tr>
<td>RBC (1012/μL)</td>
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<td>6.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>9</td>
<td>13.4</td>
<td>12.1</td>
<td>16.8</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>30.1</td>
<td>38.4</td>
<td>36.5</td>
<td>48.6</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>52.0</td>
<td>56.0</td>
<td>61.0</td>
<td>83.1</td>
</tr>
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<td>MCH (pg)</td>
<td>15.5</td>
<td>19.5</td>
<td>20.1</td>
<td>28.7</td>
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<tr>
<td>MCHC (g/dL)</td>
<td>29.9</td>
<td>34.9</td>
<td>33.0</td>
<td>34.6</td>
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<tr>
<td>Hb D-Punjab (%)</td>
<td>—</td>
<td>76.7</td>
<td>78.1</td>
<td>42.6</td>
</tr>
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<td>Hb A2 (%)</td>
<td>5.6</td>
<td>5.2</td>
<td>5.3</td>
<td>2.9</td>
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<td>Hb F (%)</td>
<td>4.5</td>
<td>18.1</td>
<td>16.6</td>
<td>1.95</td>
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<td>β0β1BV1S1.1 (G:A)</td>
<td>βD-Punjab β0V1S1.1 (G:A)</td>
<td>βD-Punjab β0V1S1.1 (G:A)</td>
<td>β0βD-Punjab</td>
</tr>
<tr>
<td>β-Chain haplotype</td>
<td>III(+ + + + +)</td>
<td>I[+ + + + + +]</td>
<td>I[+ + + + + +]</td>
<td>I[+ + + + + +]</td>
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<tr>
<td>XmnI site 5’ to 3’</td>
<td>+/+</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
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*The order of the sites 5’ to 3’ is as follows: HindII 5’ to the e-globin gene, HindIII within IVS 2 of the Gγ and Aγ-globin genes, HindIII within and 3’ to pseudo-beta (βδ)-globin gene, AvaII within IVS 2 of the β-globin gene, and BamHI 3’ to the β-globin gene.
Response to Peginterferon Treatment in Hepatitis C Virus-Associated Splenic Lymphoma With Villous Lymphocytes

To the Editor: The prevalence of HCV infection is high in patients with splenic lymphoma with villous lymphocytes (SLVL) [1,2]. There are studies showing the benefit of antiviral treatment with interferon and ribavirin in HCV-infected SLVL [3]. Herein we report SLVL in a patient with HCV-associated active viral hepatitis who recovered after antiviral treatment.

A 61-year-old male was admitted with complaints of abdominal pain and distention. His medical history was unremarkable. On physical examination, the spleen was palpable 18 cm below the costal margin. Complete blood cell count showed mild anemia (hemoglobin 11 g/dL) and thrombocytopenia (84,000/mm3). Peripheral blood smear showed a differential count of 85% lymphocytes, most of which had villous cytoplasmic projections. Liver and renal function tests were normal. Abdominal computed tomography revealed splenomegaly (265 mm), multiple intra-abdominal lymphadenopathies, heterogeneity of hepatic parenchyma, and enlargement of the portal vein. Anti-HCV antibody was positive as well as HCV RNA with 500,000 copies. Serum cryoglobulin was negative. Bone marrow biopsy was performed because of marked lymphocytosis and revealed 37% mature lymphocytes, some having villous projections. CD23, CD22, CD20, CD19, and CD45 were positive and CD5, CD103 and CD11C were negative on immunophenotyping of bone marrow. TRAP (tartrate-resistant phosphatase) stain for differential diagnosis with hairy-cell leukemia showed negative staining. With all of these data, we diagnosed the patient with SLVL. Treatment with pegylated interferon and ribavirin was initiated. He tolerated peginterferon and ribavirin without difficulty. Six months after starting treatment, his serum HCV RNA was negative, the size of spleen had decreased to 130 mm, and the size of the lymphadenopathies had also decreased. Control bone marrow biopsy and peripheral blood smear were normal.

SLVL is a B-cell neoplasm with an indolent course. Patients usually present with moderate to massive splenomegaly and hepatomegaly. The frequent HCV positivity seen with SLVL supports the etiological linkage between HCV infection and lymphomagenesis. Pathophysiological studies suggest that the immunological response to HCV antigens induces clonal B-cell proliferation [2,3]. To our knowledge, the effects of antiviral treatment on SLVL is limited, but there are promising results; Hermine et al. treated HCV-positive SLVL patients with interferon, with and without ribavirin, and complete remission was achieved in eight of 9 patients [3,4]. Arcaini et al found that treatment with interferon can lead to regression of the lymphoma [5]. Prolonged treatment over 12 months may be needed because discontinuation of antiviral therapy can cause relapses. Antiviral therapy alone is not suggested for clinically aggressive disease.

It is well known that peginterferon is well-tolerated and has fewer side-effects than interferon. Moreover, in HCV-positive patients the response rate with peginterferon is higher than interferon. To our knowledge, this is the first case of SLVL in the literature treated with peginterferon, and a good response was achieved without significant side effects. In conclusion, we emphasize that, in patients with SLVL secondary to HCV infection, peginterferon may be a better alternative to interferon, considering its higher activity against HCV, better tolerability, and side-effect profile.

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Fig. 1. (A) Initial lymph node biopsy demonstrates florid Castleman disease with atretic follicles (dark arrow) with hyalinized vessels (light arrow) and “onion skin” layering of lymphocytes. (B) Lymph node biopsy after prolonged thalidomide with near-total resolution of previous changes, now with predominantly normal follicles (dark arrow).
REFERENCES


