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LETTERS AND CORRESPONDENCE

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Systemic Anaplastic Large Cell Lymphoma in a Child Presenting With Bone Marrow Involvement and Clinical Features of Acute Leukaemia

To the Editor: Anaplastic large cell lymphoma (ALCL) presenting with bone marrow (BM) involvement is not common [1]. We report a child of systemic ALCL whose clinical presentation was more akin to acute leukemia and the initial diagnosis was made on the BM biopsy.

A 12-month-old girl presented with marked pallor and fever of 2 months duration. On examination she had hepatosplenomegaly bilateral small cervical and axillary lymphadenopathy. A clinical diagnosis of acute leukemia was suggested. Complete blood count revealed haemoglobin of 8.0g%, leukocyte count of $16 \times 10^9/cm^2$ and platelet count of $82 \times 10^9/cm^2$. Serum uric acid and calcium were normal, and she was sero-negative for human immunodeficiency virus. Peripheral blood smear revealed normocytic normochromic red cell morphology. Differential count revealed a shift to the left with 5% myelocytes, 3% metamyelocytes. Blasts were not seen. BM aspirate showed a normocellular marrow with normal hemopoietic cells. Atypical cells were not seen. BM trephine biopsy was normocellular, but showed a focus of large, atypical tumor cells with multilobated, pleomorphic, embryo-like nuclei, prominent nucleoli, and moderate to abundant agranular cytoplasm. The tumor cells showed positivity for CD30, CD45, CD45RO (UCHL1), ALK-1 and epithelial membrane antigen. ALK-1 expression was seen both in the cytoplasm and in the nucleus (Fig. 1). Immunostains for cytokeratin, CD68, CD3, CD20, and CD15 were negative (antibodies were procured from DAKO, Denmark). A diagnosis of systemic ALCL was made. Following the BM biopsy, a cervical lymph node (LN) biopsy was performed. The LN revealed involvement of the sinuses and perifollicular regions by cells with similar cytological and immunophenotypic characteristics. The child's general condition rapidly deteriorated and she died within the week.

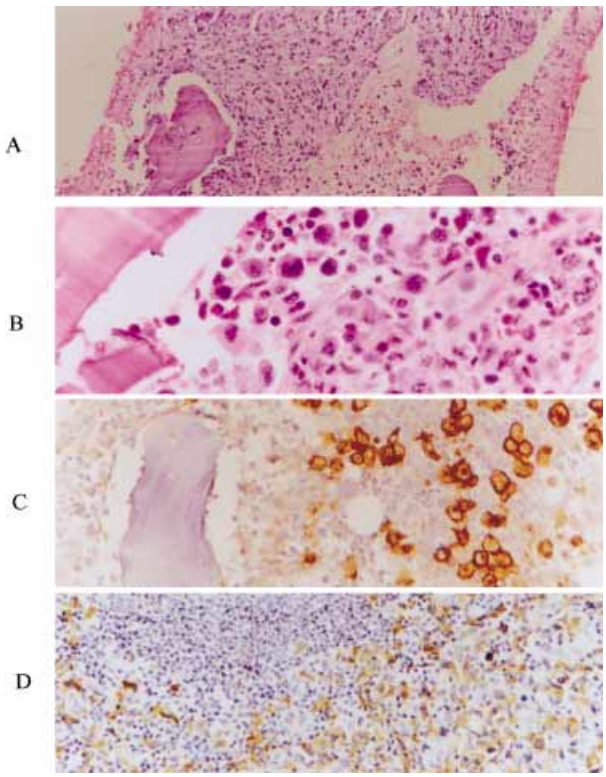

Fig. 1. (A) Bone marrow core biopsy showing involvement by atypical cells; (B) Higher magnification showing the morphologic details of the tumor cells in the bone marrow; (C) CD30 expression seen on membrane and in golgi zone of tumor cells in the bone marrow; and (D) ALK-1 expression in the tumor cells in the lymph node. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

ALCL in children tends to involve LNs and extranodal sites including skin, soft tissues, lungs and bones [1–2]. About one-fifth of ALCL patients have BM involvement at presentation. The BM involvement in ALCL shows a significant association with anemia and peripheral blood cytopenias [3]. The latter aspect of ALCL, as was noted in the current case, may mislead to a diagnosis of acute leukemia.

ALCL cells express CD30, a molecule that belongs to the tumor necrosis factor receptor superfamily. The binding of CD30 receptor to its ligand (CD30L) induces pleiotropic biologic activities that include proliferation, activation, and apoptosis in the CD30 expressing cell [4]. The CD30-CD30L interaction is also capable of inducing reverse signalling, i.e. mediating an effect on the CD30L expressing cell [5]. However, the effects of reverse signalling are not fully characterized. In the bone marrow, erythroid precursors, a proportion of myeloid cells and a subset of megakaryocytes express CD30L [6]. The possible interactions between CD30 expressing ALCL cells and CD30L expressing hemopoietic cells following BM involvement in ALCL is not known. Can these interactions lead to suppression of normal hemopoiesis and/or apoptosis of the ALCL cells?

To the best of our knowledge, ours is the first case of ALCL diagnosed in the BM biopsy. Further, ALCL patients may have a clinical picture akin to acute leukemia and careful morphological evaluation of BM is essential.

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Lamivudine Therapy for Acute Hepatitis B Infection Following Peripheral Blood Stem Cell Transplantation

To the Editor: A 60-year-old male patient was diagnosed with Ig Aκ-type stage IIIA multiple myeloma (MM). VAD chemotherapy regimen (vincristrine 0.4 mg/day, adriamycine 9 mg/m^2, dexamethasone 40 mg/day for 4 days) was commenced. After 4 courses of chemotherapy, disease status was evaluated as primary resistant disease. High-dose chemotherapy with peripheral blood stem cell transplantation (PBSCT) was scheduled. The pre-transplant conditioning regimen consisted of cyclophosphamide 4 g/m^2, etoposide 200 mg/m^2/day for 3 days, and granulocyte colony stimulating factor. Post-transplantation granulocyte and platelet recovery was observed on days 9 and 11, respectively. Before platelet engraftment, 2 units of platelet concentrates were transfused to the patient. Four months after PBSCT, during routine control HBs Ag positivity was observed with normal ALT and AST levels. Further investigation showed the following results: Hbe Ag positive; anti-HBc Ig G and M negative; hepatitis B virus (HBV) DNA positive (6 pg/ml); anti-delta and anti-HCV negative. Both HBs Ag and antibody were negative in pre-transplant routine tests. One month after HBs Ag detection the patient was suffering from progressive weakness, nausea, loss of appetite, and dark urine. Laboratory test results were as follows: ALT 858 IU/L; AST 950 IU/L; total bilirubin 3.5 mg/dL; direct bilirubin 2.3 mg/dL; alkaline phosphatase 200 IU/L; prothrombin time 14.5 sec; anti-HBc Ig M positive; HBV DNA positive (20 pg/mL). As anti-HBc Ig M was positive, acute hepatitis B infection but not reactivation in the post-PBSCT setting was diagnosed. Lamivudine 200 mg/day was commenced aiming to reduce the risk of chronicity and fulminant liver failure in an immunocompromised patient. During follow up ALT, AST, and bilirubin levels progressively declined after an initial flare up and symptomatic improvement was observed. HBV DNA became negative, and anti-HBe antibody developed. Lamivudine was ceased after anti-HBe antibody appeared. Two weeks after the cessation of lamivudine, the patient's performance status was very well and HBV DNA remained negative.

HBV is transmitted frequently by blood or needle contact. After the introduction of the more sensitive assays, the rates of transfusion-associated hepatitis B infection largely decreased, although it has not been eliminated completely [l]. Acute hepatitis B infection is usually mild, and the risk of chronicity or fulminant liver failure is low in immunocompetent adults. The risk of chronicity and on occasion fulminant hepatic failure is greatly increased in immunocomprimised patients [2]. In untreated patients with MM, a decreased primary antibody response is a consistent picture [3]. PBSCT is increasingly being used in MM. Following PBSCT a prolonged lymphopenia and specifically a $CD4^+$ T-cell deficiency relative to $CD8^+$ levels lasts for years [4].

Nucleoside analogues are effective for both the therapy of chronic hepatitis B infection in immunocompetent patients and for controlling reactivation in immunocomprimised patients [5,6]. Recently lamivudine has been reported to be effective in acute hepatitis B infection in an immunocompetent patient [7]. Nucleoside analogue therapy in acute hepatitis B infection in an immunocomprimised setting has not been reported previously. Our observation indicates that nucleoside analogues may be effective in preventing mortality and morbidity in acute hepatitis B in the immunocompromised patients. Early institution of nucleoside analogues may prevent severe liver injury during immunological recovery by supressing HBV replication and decreasing the number of infected hepatocytes. Controlling HBV replication may confer an advantage for producing anti HBe response. Improving the patients' quality of life, especially in incurable conditions, should also have great importance.

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Unusual Case of Coronary Artery Disease in a Patient With Severe Hemophilia B

To the Editor: Patients with hereditary thrombophilia may have an increased risk of ischemic heart disease (IHD) [1]. It is believed that IHD risk is reduced in hemophiliacs [2], but case reports of severe coronary atherosclerosis in hemophiliacs have been reported [3]. We report an unusual case of IHD in a young patient with Christmas disease.

A 31-year-old Chinese man with severe hemophilia B (1% Factor IX activity) and right knee arthropathy, was treated with intermittent cryoprecipitate replacement from age 3 to 24, and then *Konyne* therapy. He was started on interferon (5 MU 3× per week) and ribavirin (1 g daily) for hepatitis C. Three months later, he suffered from palpitations and exertion related chest discomfort. An electrocardiogram showed sinus tachycardia with ischemic ST segment changes. A thyroid function test showed thyrotoxicosis, with grossly elevated anti-thyroid antibody titres. There was no history of thyroid disease, hypercholesterolemia, diabetes, hypertension, or IHD in the past health or in the family history (including one hemophiliac brother on interferon and *Konyne*). Interferon was stopped and thyrotoxicosis was treated with propylthiouracil (300 mg daily). The chest pain continued, and a coronary angiogram showed near complete occlusion of the left anterior descending artery and first septal branch (Fig. 1a), with widespread vessel irregularities. He underwent percutaneous coronary angioplasty and stenting with full factor replacement and heparinization (Fig. 1b). Post-operatively, he was kept on ticlopidine (100 mg × 2 daily) and aspirin (100 mg daily) for 1 month. Six months afterward, he remained angina free. No IHD risk factors were identified on repeat blood testing.

We present an unusual case of young-onset severe IHD in a hemophilia B patient with no cardiovascular risk factors, unmasked by interferon-induced thyrotoxicosis. The case illustrated a number of interesting points. Hematologists should be aware of the fact that severe atherosclerosis can still occur in severe hemophilia [4]. In hemophiliacs, IHD may be under-diagnosed, due to reduced life expectancy due to bleeding and HIV [5] and arthropathy-restricted exercise demands under normal metabolic conditions. Vascular interventions, however, can be routinely undertaken with full factor replacement as for any normal patient [6]. Finally, there is an apparent excess of reports of IHD in the less common hemophilia B patients [7–10]. Even high-purity factor IX can still contain pro-thrombotic activated factor impurities and can cause paradoxical venous thrombosis [11]. The extent of possible arterial damage by such agents remained unknown and may be revealed as more hemophiliacs survive into middle age [5].

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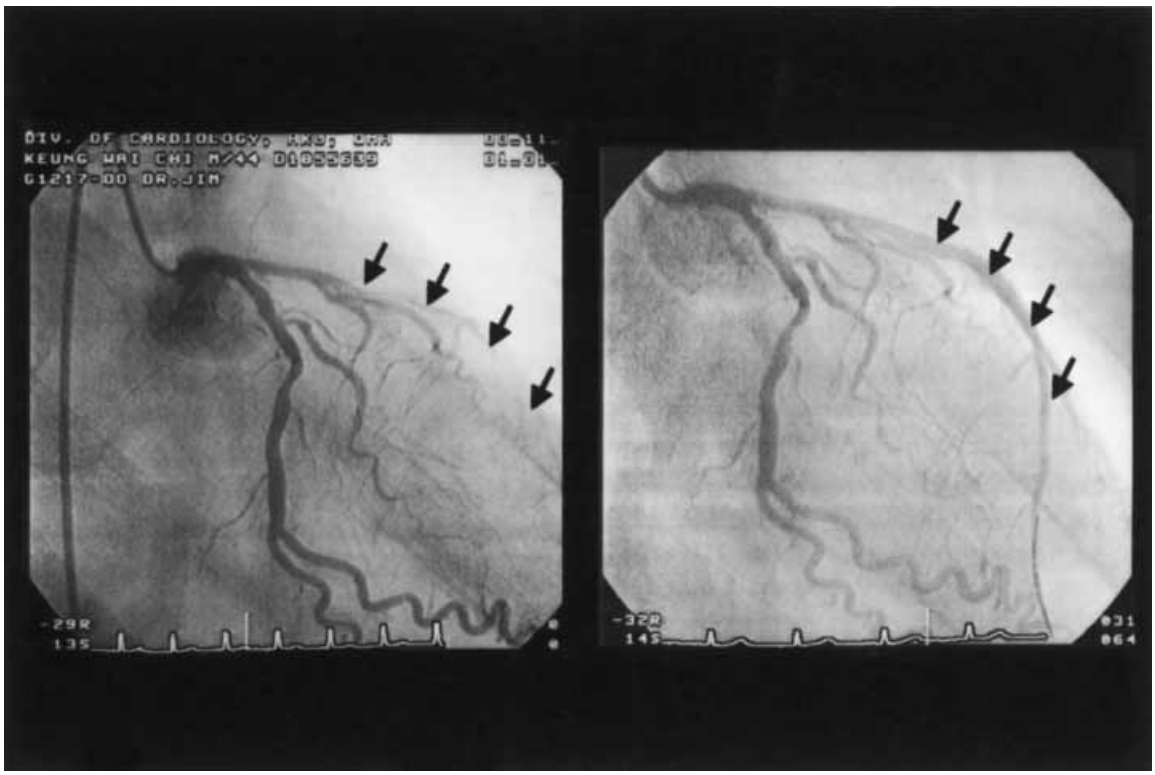

Fig. 1. RAO caudal view two-vessel coronary angiogram on cine-film showing 95% stenosis in the middle of the anterior descending artery (left panel) causing almost complete with occlusion of distal run-off (arrows), and post angioplasty and stenting angiogram (right panel) showing 75% reopening with satisfactory downstream perfusion (arrows).

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Transient Demyelinating Neurologic Lesions in a Patient With Idiopathic Hypereosinophilic Syndrome

To the Editor: Hypereosinophilic syndrome (HES) is a disorder caused by infiltration of multiple organs by mature eosinophils with peripheral eosinophilia higher than 1.5×10^9/l during more than 6 months and with exclusion of other causes of eosinophilia. The most important organs involved are the heart and central nervous system (CNS). There are scarce data on CNS magnetic resonance (MR) changes in these patients after treatment [1,2]. We report a patient with HES who developed neurological symptoms, with multiple demyelinating lesions on MR study that improved after α-interferon treatment.

A 34-year-old man was admitted due to epigastric pain, fever, and spleen enlargement. Laboratory studies showed a white blood cell (WBC) count of 250×10^9/l with 220×10^9 mature eosinophils/l. The determination of autoantibodies, stool samples for ova and parasites, and tumour markers were negative. The IgE level was normal. A bone marrow aspirate and biopsy showed normal cellularity with 80% mature eosinophils. Cytogenetic study was normal and bone marrow PCR study for *BCR/ABL* rearrangement was negative. The echocardiographic examination was normal. The patient received hydroxyurea (3 g per day, p.o.) with no response. After 7 days of treatment the patient developed headache, bradypsychia, left hemiparesis, and ataxia. MR study showed multiple supratentorial and infratentorial white matter lesions, hypointense on T_1-weighted images and hyperintense on T_2-weighted images (Fig. 1A). The CSF pressure, glucose, proteins, and IgG levels were normal, without oligoclonal bands or

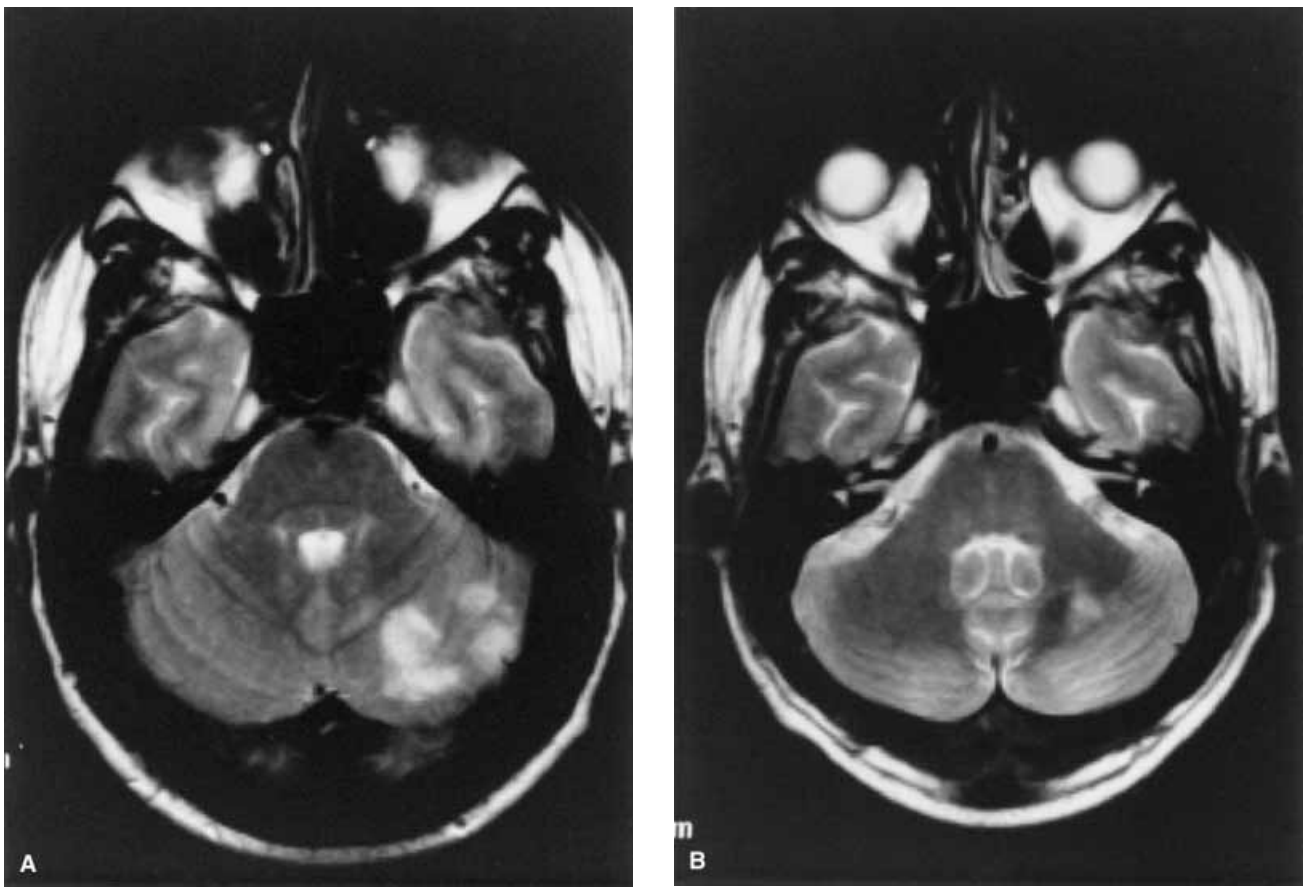

Fig. 1. (A) CNS MR imaging in T_2-weighted sequences showing demyelinating lesions involving the cerebellum. (B) Marked improvement of cerebellar MR lesions after α-interferon therapy.

eosinophils. Prednisone (80 mg per day, i.v.) and α-interferon (3×10^6 UI/day, s.c.) were administered, and the absolute WBC count progressively decreased to a normal level (eosinophil count 0.7×10^9/l) while neurological dysfunction improved. The demyelinating lesions had nearly disappeared by the second MR (Fig. 1B). In spite of treatment, the eosinophil count progressively increased and the patient developed respiratory failure with isolation of *Streptococcus viridans, Candida* spp., and *Aspergillus niger* in the bronchoalveolar lavage. Liposomal amphotericin B (400 mg/d, i.v.) and imipenem (500 mg/6 hr, i.v.) were given without response. The patient developed ventricular dysfunction refractory to vital supportive treatment and died. At autopsy, visceral infiltration by eosinophils mainly involving the heart (with multiple areas of fibrosis and necrosis) and lungs was found. The histologic study of the CNS showed white matter demyelination in the cerebellum, brainstem, and spinal cord.

Neurologic involvement, especially peripheral is frequent in HES [3,4]. When CNS is involved (15% cases), dementia is frequently observed. Neurological injury include direct eosinophilic infiltration, thrombosis, and the effect of the proteins released by eosinophils, such as eosinophil cationic protein, major basic protein, and eosinophil-derived neurotoxin [5].

Intracranial lesions are rarely observed by imaging techniques. Abnormal high signal areas in T_2-weighted sequences can be observed by MR. In the present case, there were areas of demyelination in the cerebellar hemispheres and in the paraventricular white matter of the brain. It is of note that there was a clinical improvement and disappearance of the enhancement in T_2-weighted sequences in a second MR after steroid and α-interferon treatment. Such a changes in MR images have not been previously referred. Unfortunately, the response to treatment was transient, and the patient died due to severe involvement of the heart and lungs with only small foci of demyelination observed at autopsy.

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