Itraconazole-enhanced vindesine neurotoxicity in adult acute lymphoblastic leukaemia

To the Editor: Itraconazole, an azole with broad spectrum of fungal activity, has been used for the prevention and empirical therapy of invasive fungal infections (IFIs). Severe neurotoxicity following treatment with itraconazole and vincristine has been reported in 25 patients [1–5]. Here we presented two adult acute lymphoblastic leukemia (ALL) patients developed neurotoxicity after treated with itraconazole and another vinca alkaloids, vindesine.

Case 1: A 20-year-old male was admitted to our hospital because of fever and night sweat in December 2004. He was diagnosed as having ALL according to the FAB criteria. He was treated with one courses of DVP regimen and achieved complete remission. This patient was readmitted to our hospital for consolidation on August 2005. He was treated with hyper-CVAD chemotherapy and vindesine was used in day 4 and day 11, respectively. Because he has a history of pulmonary IFI, antifungal prophylaxis with itraconazole solution was started on day 2. Nine days after itraconazole was started, some symptom of paralytic ileus including abdominal pain, abdominal bloating, cramps, inability to pass flatus, or stool were presented. An X-ray of the abdomen shows bulging loops of intestine and some fluid levels were present. He was diagnosed to have paralytic ileus secondary to neurotoxicity caused by itraconazole and vindesine. After the itraconazole was stopped, his paralytic ileus was improved rapidly. This patient received autologous peripheral blood stem cell transplantation in February 2006 and remains in remission at present.

Case 2: A 37-year-old female was admitted to our hospital because of fever and petechia in April 2005. A diagnosis of B-cell/T-cell biphenotypic acute leukemia was established based on the results of morphological assay and flow cytometry analysis. She was commenced on induction chemotherapy as for ALL (dexamethasone, Idarubicin, and vindesine). Among them, vindesine was used in day 1, day 8, and day 15, respectively. She presented as pulmonary infection with fever, cough, and expectoration in day 9. Emperical antifungal treatment with itraconazole injection was initiated. Five days after itraconazole was started, some symptom of neurotoxicity including limbs anesthesia, abdominal pain, abdominal bloating, cramps, inability to pass flatus, or stool were presented. An X-ray of the abdomen shows that some fluid levels were present. After the itraconazole and vindesine were discontinued, these symptoms were resolved rapidly. Unfortunately, she died of intracranial hemorrhage on day 28 of induction chemotherapy.

Since Böhme first described enhanced severe vincristine neurotoxicity associated with itraconazole in four adults with ALL in 1995 [1], there are 21 cases that have been reported in children [2–5]. The combined use of vinca alkaloids and itraconazole results in the enhanced neurotoxicity by the inhibition of cytochrome P450-mediated metabolism of vinca alkaloids and leading to increased plasma levels of the drug. The most frequent symptoms described were constipation, abdominal pain, paralytic ileus, and neuropathy. Here we presented two other adult ALL patients who developed neurotoxicity after coadministration of itraconazole and vindesine. Given the interaction of itraconazole with vinca alkaloids leading to severe and even potentially fatal toxicities, the combined use of these drugs should be avoided.

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Acute immune thrombocytopenia associated with Hepatitis E in an adult

To the Editor: A 34-year-old male, nonsmoker, presented with an episode of massive painless hematuria. He reported having generalized fatigue, malaise, and loss of appetite of 1-week duration prior to presentation. Past history was unremarkable for any significant illness, drug or vaccine exposure, allergy, substance abuse or high-risk sexual behavior. On examination the patient was normotensive, alert, icteric, and had nonpalpable purpura around his ankles. He had a tender hepatomegaly (liver span 18 cm) and nonpalpable spleen. Chest X-ray and ultrasound examination of abdomen were normal. Laboratory investigations revealed isolated thrombocytopenia (13×10^9/L), mild conjugated hyperbilirubinemia with transaminitis (aspartate aminotransferase 1,224 U/L, alanine aminotransferase 783 U/L), and normal alkaline phosphatase, serum protein, γ-glutamyl transferase, prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer levels. Urinalysis showed hematuria (numerous erythrocytes per high-power field) without dysmorphic changes, urinary casts or protein, suggesting nonglomerular origin of hematuria. Patient was transfused with platelet concentrates, and a bone marrow aspirate revealed normocellular marrow with large, immature megakaryocytes. No hemophagocytes or emperipolesis was seen. Serum was positive for IgM and IgG anti-Hepatitis E virus (HEV) antibodies, thus confirming a HEV infection. Serologic tests were negative for anti-HAV IgM, Hepatitis B and C, Epstein-Barr virus, cytomegalovirus, toxoplasma specific IgM, Dengue virus, leptospirosis, rubella, parvovirus B19, and HIV. No growth was seen on blood and urine cultures. ELISA for direct antiplatelet antibodies was positive. Coombs' test, antinuclear antibody, anti-ds DNA, antiphospholipid antibodies, anticardiolipin, cryoglobulins, and antithyroid antibodies were negative. Quantitative serum immunoglobulins and complement levels were also normal. Intravenous immunoglobulin (IVIG, 1.0 g/kg/day IV for 2 days) was administered from the second day of admission, and by the end of sixth day, the platelet count rose to 75×10^9/L. There was a gradual dip in counts by the end of 13th day of admission to 40×10^9/L, and platelet numbers persisted around this level for the next 8 weeks. Repeat testing at 12 weeks showed absence IgM anti-HEV antibodies, higher IgG anti-HEV titre, normal platelet counts, and normal liver function tests. At the last follow-up visit, 5 months after the presentation, the patient was doing well.

The case is unusual because immune thrombocytopenic purpura, although reported with other hepatotropic viruses, has not been reported as an isolated association with acute hepatitis E infection. HEV, a nonenveloped, single-stranded RNA virus, and recently classified under family Hepeviridae, is a major cause of sporadic as well as epidemic hepatitis and is no longer confined to Asia and developing countries [1]. On the basis of seroprevalence, an estimated one-third of worlds population has been infected [2]. Symptomatic HEV infection is most common in young adults of age 15–40 years and commonly presents with a self-limited syndrome of fever, jaundice, anorexia, abdominal pain, and an enlarged tender liver. Extensive literature search revealed only one reported case of acute Hepatitis E where an immune mechanism was assumed as the basis of the concomitant thrombocytopenia and glomerulonephritis [3]. In view of various corroborating features like

TABLE I. Clinical Characteristics and Outcomes of Patients with Severe RPH Complicating BM Trephine Biopsy

No. of cases	Eight cases reported from 1971 to 2006 (including the present case)
Age (years)	50–80
Sex	Female: 5; Male: 3
Disease	PV: 4; chronic myeloid leukaemia: 1; lymphoma: 1; osteoporosis: 3; renal osteodystrophy: 1; obesity: 2
Biopsy site	Posterior: 6; anterior: 2
Time lapse biopsy-symptoms	Immediate: 3; delayed (hours to days): 5
Clinical sequela	Shock: 3; femoral neuropathy: 4; hydronephrosis: 1
Diagnostic procedure	Angiogram: 3
Treatment	Conservative: 4; embolization: 1; surgery: 3
Outcome	Complete recovery: 6; partial recovery: 1; neurological deficit: 1
Technical difficulties or inexperienced operators	4 cases; not stated: 4 cases

Adapted with modifications from Ref. [1].

isolated thrombocytopenia and otherwise normal peripheral blood smear, normal urinalysis, normocellular marrow, presence of antiplatelet antibodies, response to IVIG, and apparent absence of other causes of thrombocytopenia, the present case fits the accepted diagnostic criteria of immune thrombocytopenic purpura [4]. In conclusion, Hepatitis E can be considered in the absence of other common associations of autoimmune thrombocytopenia. As seen in our patient, one might also expect recovery of the platelet counts with the resolution of IgM antiHEV response in such cases.

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Massive retroperitoneal hematoma with secondary hemothorax complicating bone marrow trephine biopsy in polycythemia vera

To the Editor: Bone marrow (BM) trephine biopsy is rarely associated with significant bleeding even in patients with severe thrombocytopenia. Risk factors commonly associated with bleeding are myeloproliferative disease and aspirin therapy. Retroperitoneal hematoma (RPH) is an uncommon complication of BM biopsy, with less than 10 cases reported to date, of which 3 cases were patients with polycythemia vera (PV) [1] (Table I). However, none of these patients had concurrent hemothorax.

A 56-year-old overweight and postmenopausal woman was admitted for transient ischemic attack. The hemoglobin was 22.6 g/dl, hematocrit 68.6%, leukocytes 13.5 $\times$ 10^9/l, and platelets 338 $\times$ 10^9/l. The coagulation profile was normal. She received aspirin 75-mg once daily and undergone phlebotomy. BM biopsy was performed with a Jamshidi needle from the right posterior superior iliac spine (PSIS), without immediate complications. One centimeter bony tissue was obtained after repeated attempts. Twelve hours after the biopsy, the patient complained of severe right-sided abdominal pain. Examination revealed blood pressure of 90/50 mmHg, pulse 100 bpm, distended abdomen, and a tender swelling over the right lumbar region. Contrast-enhanced CT showed a massive RPH (12 $\times$ 14 $\times$ 10 cm^3) at the right iliac fossa displacing the inferior vena cava and iliac vessels and compressing the right ureter resulting in hydronephrosis, and no contrast extravasation. Aspirin were discontinued at once. Over the next few days, she developed increasing breathlessness, hypoxemia (arterial pO_2 50–60 mmHg on air), and anemia (lowest Hb 11 g/dl) associated with massive right pleural effusion. Needle aspiration of the pleural cavity revealed frank blood. Pulmonary embolism was excluded by CT pulmonary angiography. She was treated conservatively with analgesics and blood transfusion. In the following days, the abdominal pain, hypoxemia, and anemia improved. The patient was discharged well 2 weeks after the BM biopsy following resolution of the RPH and hemothorax.

Factors that possibly contributed to the RPH in our patient included the procedure, iliac bone, PV, and antiplatelets. BM biopsy performed at the PSIS can be technically difficult in the presence of excessive adipose tissue around the hips as noted in our patient. Additionally, it is possible to penetrate the iliac bone in patients with osteopenia (particularly in older and postmenopausal woman like our patient) [2]. Bleeding is a well-known complication of PV and usually occurs in the skin or mucosa, while spontaneous RPH has been described only in one PV patient [3]. Aspirin alone was less likely to contribute to the acute RPH, as there was no bleeding at the biopsy site. In the present case, injury to a branch of the right iliac artery due to penetration of the needle through the iliac spine was the likely cause of RPH. The qualitative platelet defects due to aspirin and PV could have contributed to the continuous bleeding resulting in the extensive RPH and secondary hemothorax.

There are only few reports of hemothorax secondary to hemoperitoneum. Pratt and Shamblin [4] postulated that large volume of free fluid in the abdomen is capable of directly traversing the diaphragm to enter the pleural spaces via two main mechanisms, (i) a diaphragmatic defects, usually congenital, and (ii) the dynamic action of fluid which separates the liver and diaphragm and allows greater stress to bear on the right hemidiaphragm.

RPH can be managed conservatively in most cases [1]. The presence of contrast extravasation (which was absent in our patient) is highly suggestive of significant arterial bleeding and is a factor predictive of failure of conservative treatment, and therefore, an indication of immediate surgical or angiographic intervention [5].

This report demonstrated that BM biopsy, while generally safe could occasionally present with potentially fatal complications, even if performed by an experienced personnel. Hence, it should only be performed when there is a clear indication. Prior to BM biopsy, we recommend stopping all antiplatelets or anticoagulants, and close observation of high-risk patients over an extended period.

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Epstein-Barr virus associated pneumonia in an adult patient with severe aplastic anaemia: Resolution after the transient withdrawal of cyclosporine

To the Editor: In severe aplastic anemia (SAA) patients during immunosuppressive treatment, infectious complications are caused by either bacteria or fungi and rarely by viruses [1]. The latter are mainly due to cytomegalovirus (CMV) and herpes simplex virus, and almost never are of clinical relevance [1,2]. Recently, the first case of Epstein-Barr virus (EBV) reactivation with infectious mononucleosis-like symptoms has been reported in a SAA patient undergoing a second treatment with antithymocyte globulin (ATG) and cyclosporine A (CyA), in whom the resolution required the withdrawal of CyA and the administration of rituximab. It has been suggested that ATG could be a risk factor for EBV-related disease even out of the allogeneic bone marrow transplantation (alloBMT) setting, and that rituximab is the most effective therapy [3].

We report the first case of pneumonia following EBV reactivation in an adult patient with SAA and discuss issues related to its diagnosis and clinical management. A 26-year-old Caucasian man, EBV seropositive, with refractory SAA, presented fever on day +29 of a second course with rabbit ATG and CyA. Complete cultural and molecular examinations of peripheral blood (PB) and bronchoalveolar lavage fluid (BALf) for bacterial, fungal, and viral pathogens (CCME) resulted negative. Blood CMV antigenemia (CMVAg) resulted strongly positive, showing 112 nuclei/200,000 cells, with a CMV quantitative polymerase-chain reaction (CMVqRTPCR) of 67,760 copies/mL (Fig. 1A). Pulmonary high-resolution computed tomography (pHRCT) resulted negative. Treatment with gancyclovir (5 mg/kg/b.i.d.) was started, as reported for the pre-emptive therapy of CMV infection in immunosuppressed patients [4]. CMVAg disappeared 3 days later. Because of persisting fever and leukopenia (Fig. 1A), empirical first and second line antibiotic and antifungal therapies, including liposomal amphothericin B, have been added. Nonetheless, symptoms persisted and 1 week later he developed hypoxia and dyspnoea. A second pHRCT showed right basal interstitial pneumonia (Fig. 1B). Blood EBV qRT-PCR showed 21,923 copies/mL. EBV serology showed weak positivity for immunoglobulin (Ig) M antibodies against EBV "early antigen" (EA), negativity for IgM against EBV "viral capsid antigen" (VCA), and strong positivity for IgG antibodies against EBV EA, VCA, and nuclear antigen consistent with viral reactivation. CCME, including all respiratory viruses, CMVAg, and CMVqRTPCR resulted negative either on blood or BALf. BALf was positive for EBV DNA by PCR (50 copies/mL). Cytologic and immunophenotypic analysis of BALf revealed a marked polyclonal CD8+ T-lymphocytosis with activation markers, namely, HLA-DR+, CD45+, CD57+, but not red blood cells. Cytologic and immunophenotypic analysis of PB showed an increase of T lymphocytes, predominantly CD8+ T cells with the same phenotypic features. A very low number of B cells was detected (Fig. 1C). A diagnosis of EBV pneumonia was suspected. CyA was promptly withdrawn. After 1 week fever resolved, and after 2 weeks pHRCT and respiratory functions resulted normal. EBV viremia progressively disappeared in 1 month. CyA was reintroduced and maintained at therapeutic levels without further EBV reactivation (Fig. 1A).

EBV pneumonia is a rare occurrence either in immunocompetent or immunocompromised subjects [5]. So far, only one case of a primary EBV infection complicated with pneumonia has been reported in a pediatric alloBMT patient, successfully treated with rituximab and corticosteroids [6]. Recurrent findings appear to characterize EBV pneumonia: positive EBV on blood and BALf, a predominantly monomorphous infiltrate of polyclonal CD8+ T-cells in BALf, and ground-glass opacities, localized predominantly to the lung bases at the HRCT [5,6]. In our case, the low level of EBV in BALf may be related to the high intersubject and intrasubject variability of the quantitative PCR analysis in measuring the amount of viral load upon BAL specimens from immunocompromised patients [7,8]. Nonetheless, the association of a high blood viral load with signs and symptoms of organ disease and with the identification of the virus from the involved organ, in the absence of other pathogens, makes the viral etiology very likely [9].

In SAA patients, EBV infection has been reported as a common subclinical finding, nearly always self-limiting [2]. However, at least those patients undergoing multiple treatment with ATG and presenting clinical signs of infection, like the patient reported by Calistri et al. [3] and ours, should receive close monitoring for EBV. Lung involvement should be suspected when respiratory symptoms and high EBV viremia appear. The sole withdrawal of immunosuppression, although for a limited time period, may be sufficient to achieve a stable clinical remission, avoiding even the administration of rituximab, which may unnecessarily exacerbate the immune deficiency in these immunosuppressed patients.

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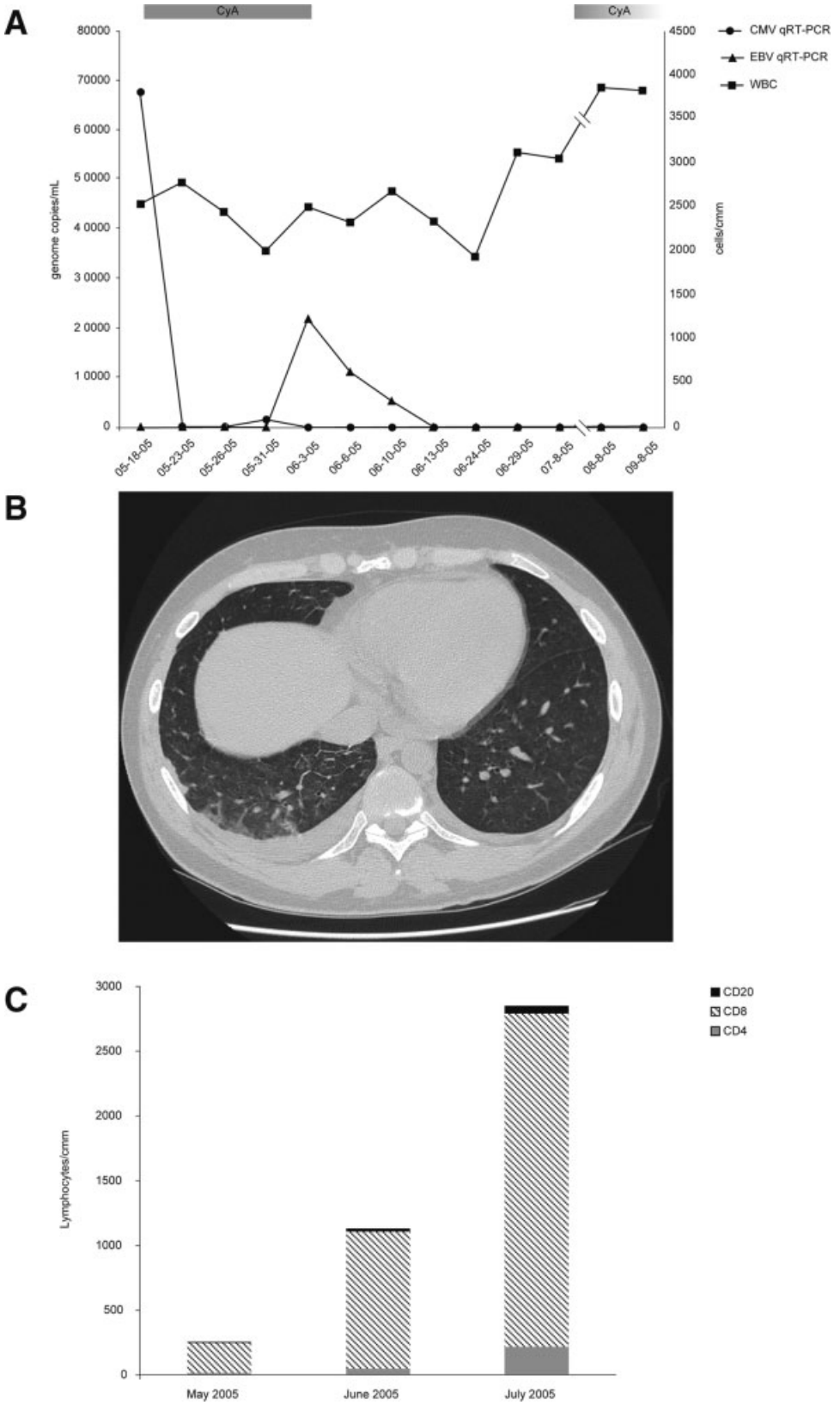

Figure 1. A: Kinetics of CMV and EBV viremia, as measured by qRT-PCR, correlation with the CyA administration, and the white blood cell (WBC) count of the patient. B: Patient's pulmonary HRCT showing bilateral pleural effusions and ground-glass opacities in the right lower lobe, on the day of highest EBV viraemia, and BAL execution (06-3-05). C: Lymphocyte count of the patient with cell subpopulations during the course of the disease and at resolution. Line with circles, CMV viremia; line with triangles, EBV viremia; line with squares, WBC count; grey rectangles, CyA treatment; grey columns, CD4+ cells; striped columns, CD8+ cells; black columns, CD20+ cells.

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