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LETTERS AND CORRESPONDENCE

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Bone Marrow Embolism After Bone Marrow Aspiration and Biopsy

To the Editor: We had performed a bone marrow aspiration and biopsy on a 49-year-old male patient in the intensive care unit as part of diagnosis-oriented investigations. The autopsy revealed bone marrow samples within the lung alveoli with no obvious fractures in the iliac crest.

We discuss herein the likelihood of bone marrow embolism after such a procedure.

In the pertaining literature, a case of pulmonary bone marrow embolism following cardiac massage is reported [1], but in our patient cardiac massage was not performed because of the gravity of his underlying disease.

Fat and bone marrow embolism following total hip arthroplasty is a well-known entity and the increase in intramedullary pressure produced by mechanical intervention during the procedure is proposed to be responsible [2]. In a case similar to ours, trauma to the iliac crest is presented as a possible cause of fat embolism after bone marrow harvesting [3]. A risk of fat and bone marrow embolism is reported after intraosseous infusions in children [4]. Death from fat embolism as a complication of intraosseous phlebography is defined as well [5].

We believe that the bone marrow embolism in our patient was a direct result of the mechanical exposure during the bone marrow aspiration and biopsy procedure, as in the similar cases mentioned above, and it should be taken into consideration as a possible complication.

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Hepatocellular Carcinoma on Cirrhosis-Free Liver in a HCV-Infected Thalassemic

To the Editor: Hepatocellular carcinoma (HCC) is a severe complication of cirrhosis of whatever etiology, and it affects prognosis. The main causes of cirrhosis are alcoholic liver disease, chronic hepatitis C (HCV) and B virus (HBV) infection, and iron overload. Furthermore, HCC rarely develops in the absence of cirrhosis [1,2].

Due to periodical transfusions, many patients with β-thalassemia are often infected with either HCV, HBV, or both, particularly those born before the 1990s [3]. Despite the introduction of desferrioxamine at the end of the 1970s, cardiac complications continued to be the main cause of death of thalassemics in the second and third decades of life until recently. Very few patients survived long enough to develop HCC. In fact, only one case of HCC had been reported in β-thalassemia [4]. The recent outcome improvement has allowed HCC to develop. A recent multicenter Italian retrospective study identified 23 cases of HCC in thalassemia syndromes [5]. Because of this concern, our policy was a strict HCC ultrasound (US) screening program in all patients with thalassemia syndromes.

In September 2003, a 63-year-old woman with IVS 1–6 homozygous β-thalassemia underwent abdominal US. She had been regularly transfused since she was 16, soon after splenectomy, and was on therapy with desferrioxamine. Clinical conditions were good, apart from repeated bone fractures due to osteoporosis. She was positive for HCV antibodies (Ab), HBsAb, HBcAb, and HCV RNA. Previous liver US (18 months before) had shown no focal lesion. Clinically, she did not have any sign of cirrhosis. Biochemistry was the following: Hb 9 g/dL, PLT 212,000/mm^3, AST 57 U/L, ALT 60 U/L, bilirubin 1.8 mg/dL, albumin 3.8 g%, INR 1.1, PTT 26 sec, liver iron concentration 4.5 g/dw, ferritin 500 ng/dL, α-fetoprotein 4 ng/dL. Liver US showed a 2.5-cm lesion between segments II and III and no signs of portal hypertension. The lesion was considered to be suggestive for HCC by spiral CT. The patient underwent surgery (II and III liver segmentectomy), and histology showed a well-differentiated hepatocellular carcinoma not infiltrating the margin of resection. The surrounding liver was cirrhosis-free (Ishak staging 2/6). To date, the patient is well and shows no signs of HCC recurrence after 4 months of follow up.

To our knowledge, no previous well-documented case of HCC on cirrhosis-free liver in thalassemia has been reported. In thalassemia, iron overload is often associated with either HCV or HBV infection, and this association increases the probability of HCC development. Moreover, increased survival

of thalassemics due to the development of better chelating drugs will surely make HCC a major problem for thalassemics in future. Nowadays the outcome of HCC can be improved by various treatments, and when HCC develops in absence of cirrhosis, liver surgery can be curative [1,2]. However, early detection of HCC is mandatory. Our experience suggests that US screening should be performed strictly in thalassemia syndromes, particularly when there is either HCV or HBV infection or sustained iron overload.

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Acute Renal Failure in a Patient With Paroxysmal Nocturnal Hemoglobinuria and Autoimmune Hemolytic Anemia

To the Editor: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic disorder characterized by hemoglobinuria and venous thrombosis. Kidney involvement is usually benign and secondary to chronic tubular deposition of hemosiderin [1]. Paroxysmal nocturnal hemoglobinuria (PNH) is occasionally complicated with acute renal failure due to effects of medication and exposure to infections [2]. We report a case of PNH and drug-induced AIHA in a 51-year-old man who developed reversible acute renal failure caused by acute tubular necrosis requiring hemodialysis.

A 51-year-old Japanese man who was diagnosed with PNH at the age of 42 years suffered from acute pharyngitis. He was treated with an antibiotic (cefcapene) and NSAIDs (ibuprofen and loxoprofen). After 3 days, urine output decreased and oliguria persisted for 2 days. He was therefore admitted to Jichi Medical School in February 2003. Physical examination revealed conjunctival anemia and leg edema. Results of laboratory studies showed a decreased hemoglobin level (5.1 g/dL), decreased hematocrit (14.8%), decreased platelet count ($13.7 \times 10^4/\mu L$), normal white blood cell count (6,200/μL with normal differential count), normal total bilirubin (0.83 mg/dL) and , direct bilirubin (0.24 mg/dL), and increased levels of blood urea nitrogen (127 mg/dL), creatinine (18.16 mg/dL), and lactic dehydrogenase (4,614 IU/L). Urine hemosiderin was detected without proteinuria. The results of a direct Coombs' test were positive, the level of haptoglobulin was decreased (< 10 mg/dL; normal, 45–32 mg/dL) and the level of cold agglutinin titer was high (256, normal < 32). Bone marrow aspiration was hypocellular (nucleated cells, $3.3 \times 10^4/\mu L$; megakaryocytes, 56/μL). A diagnosis of acute renal failure due to hemolysis attack of PNH and that of drug-induced AIHA was made. Blood transfusion with washed red cells and administration of diuretic drugs were started. One day after admission, hemolytic attack was not observed, but oliguria persisted and renal function had deteriorated. Hemodialysis (HD) was started 2 days after admission. The patient's hemodynamic condition was stable during HD. After seven sessions of hemodialysis, the patient's renal function improved. One month later, the results of a direct Coombs' test turned to be negative and a characteristic low-intensity pattern of the renal cortex in T2-weighted magnetic resonance images was observed [3].

The drug exposure was thought to have induced AIHA in this patient because the results of a direct Coombs' test turned to be negative when he had recovered from the acute hemolysis attack and renal failure [4]. Because magnetic resonance imaging suggested injury of the renal tubules caused by hemosiderin deposition and because proteinuria and hematuria were not observed, it is likely that the renal failure was caused by acute tubular necrosis. In an intravascular hemolytic state, hemosiderin damages the renal tubules. Reduced glomerular filtration and tubular damage caused by infection and drugs might have been involved in the renal failure. Patients with PNH may develop renal failure due to infection and drugs. Careful management of patients with PNH is therefore needed.

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Intracerebral Hematoma Following Intrathecal Administration of Methotrexate in a Patient With Non-Hodgkin's Lymphoma

To the Editor: Lumbar puncture (LP) is associated with post-dural puncture headache (PDPH) in approximately 37% of cases [1] and rarely with intracranial hemorrhage presenting either as subdural hematoma (SDH) or intracerebral hematoma (ICH) [2]. SDH is a well-recognized complication of bone marrow transplantation with an incidence of 2–2.7%, usually

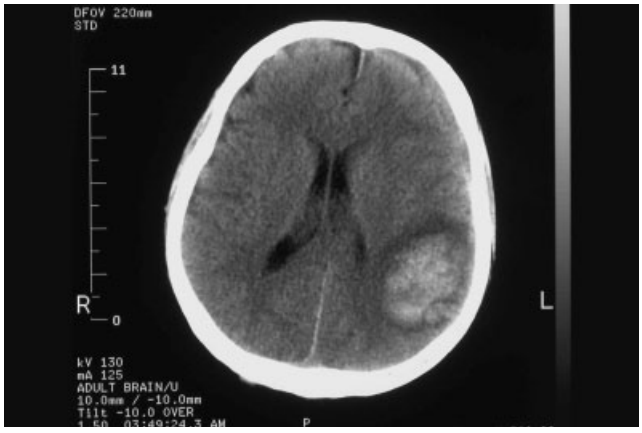

Fig. 1. CT scan of the brain: large intracerebral hematoma in the left parietal region (5 cm × 4 cm) with right brain displacement.

following intrathecal administration of methotrexate [2,3]. ICH has been well documented following LP for spinal anesthesia [4], lumbar myelography [5], and intrathecal methotrexate for hematological malignancies [2] with a much lower prevalence than SDH.

A 67-year-old man with relapsed high-grade non-Hodgkin's lymphoma (NHL) presented with confusion and a deteriorating state of consciousness. The first day of the second cycle of chemotherapy, he underwent intrathecal methotrexate infusion. Twenty-four hours following LP, he developed positional headache, drowsiness, and nausea. The symptoms persisted for 6 days, and then he had generalized seizures. There was no history of head trauma. A computed tomography (CT) scan of the brain showed a large ICH in the left parietal region with brain swelling and a midline shift (Fig. 1). Tonicoclonic seizures continued despite intravenous treatment with phenytoin, dexamethazone, and mannitol. Coagulation studies showed normal prothrombin, partial thromboplastin time, and fibrinogen and a platelet count of 75×10^9/L. His hemoglobin was 9.7 g/dL, and his white blood cell count was 1.2×10^9/L. Examination of cerebrospinal fluid (CSF) revealed lymphomatous meningeal infiltration. Four days later, expansion of the hematoma was demonstrated on the CT of the brain. Right-sided hemiparesis and headache persisted over the following weeks. The patient died 3 months later of progressive disease.

PDPH and intracranial hemorrhage presenting either as SDH or ICH seem to share a common pathogenesis. CSF leakage results in decreased intracranial pressure, leading to compensatory expansion of intracerebral veins. The loss of CSF volume may induce traction of pain-sensitive receptors and intracranial vessels, resulting in rupture of either subdural or intracerebral veins. The postural character of headache could be attributed to the increase of traction and stretching of intracranial structures when the patient moves from the supine to the upright position.

In patients receiving bone marrow transplant for hematological malignancies, intrathecal methotrexate, PDPH, coagulation disorders, and prior history of head trauma were considered as risk factors for the development of intracranial hemorrhage [2]. The onset of PDPH was usually within 48 hr, but it may be delayed for up to 2 weeks [1]. Among the hematological malignancies complicated by SDH, NHL was rather rare [2,3]. Intracranial hemorrhage usually developed in the presence of underlying intracranial pathology [3]. The delay in diagnosis of intracranial hemorrhage described in the literature ranged from 3 to 60 days [2,3]. Despite the well-recognized association with PDPH, this complication continues to be overlooked because of its scarcity.

Intracerebral hemorrhage may be a rare but life-threatening complication of lumbar puncture. The prolonged and unresolving character of PDPH warrants heightened clinical awareness for the complication of intracranial hemorrhage.

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Echocardiographic Abnormalities in Brazilian Sickle Cell Patients

To the Editor: We read with great interest the recent paper presented by Ahmed et al. [1], and we would like to briefly report our experience with the echocardiographic status of sickle cell patients. Cardiac manifestations and pulmonary hypertension (PH) are significant causes of morbidity and mortality of patients with sickle cell anemia (SCA) [2–4]. Chronic anemia is associated with several changes in cardiovascular hemodynamics, such as dilatation and hypertrophy [4]. On the other hand, pathophysiology of PH in SCA is associated with sickle cell-related vasculopathy, chronic hypoxia, pulmonary scarring from repeated episodes of thromboembolism, pulmonary infections, and high pulmonary blood flow secondary to the anemia [2,3].

The present study involved 75 SCA patients (hemoglobin SS), 41 females and 34 males, with a mean age of 27.3 years (range 15–74 years).

Conventional echocardiography was carried out in all patients without painful or hemolytic crisis or infection in the previous 4 weeks. The participants were then retrospectively evaluated from January 1980 to October 2003. PH was diagnosed as pulmonary artery systolic pressure values of 30 mmHg or above. The hemoglobin level, fetal hemoglobin (HbF) level, age, sex, β-globin haplotype, past medical history of episodes of chest syndrome and pulmonary infection were compared with echocardiographic findings and presence or absence of PH. Data obtained were analyzed by Fisher's test.

The results of the evaluated markers are shown in Table I. Similar to previous studies [1,4,5], the left ventricular mass was increased in 66 (88%) patients, but no important left ventricular systolic abnormalities were observed. The shortening fraction was shown to increase in 14 (18.6%) patients, and the ejection fraction was decreased in only one (1.3%) patient. In contrast to Ahmed et al. [1], despite PH being the most frequent complication shown (26%), no significant association with prior pulmonary infection or acute chest syndrome was observed. Similarly, clinical variables such as age, sex, mean hemoglobin, and HbF were not significantly different.

TABLE I. Echocardiographic Features of Sickle Cell Anemia Patients (n = 75)

Variable	Patients mean (range)	Reference
AO (mm)	29.8 (21.0 to 38.0)	21.0 to 37.0
LA (mm)	40.8 (31.0 to 53.0)	28.0 to 40.0
RV (mm)	23.0 (12.0 to 36.0)	10.0 to 26.0
IVS (mm)	8.4 (6.0 to 11.0)	7.0 to 11.0
LVPW (mm)	8.4 (6.0 to 11.0)	7.0 to 11.0
LVDD (mm)	53.7 (41.0 to 65.0)	38.0 to 52.0
LVSD (mm)	32.9 (24.0 to 47.0)	26.0 to 34.0
SF (%)	38.2 (27.0 to 57.0)	30.0 to 40.0
EF	0.68 (0.53 to 0.87)	>0.55
VLV (ML)	104.7 (58.2 to 171.0)	
LVMI (g/m^2)	140.7 (79.2 to 171.0)	Male < 135 Female < 111

Abbreviations: AO, aorta; LA, left atrium; RV, right ventricle; IVS, interventricular septum; LVPW, left ventricular posterior wall; LVDD, left ventricular diastolic dimensions; LVSD, left ventricular systolic dimensions; SF, shortening fraction; EF, ejection fraction; VLV, volume of the left ventricle; LVMI, left ventricular mass index.

The β-globin haplotype was studied in 25 patients: 8 (32%) with PH and 17 (68%) without this complication. Four individuals were Benin haplotype homozygotes, 10 Bantu were homozygotes, and 11 patients showed Bantu/Benin haplotype. We observed a strong predominance of Benin allele (64%) in the group without PH that could be associated as being a protector factor for PH, but, unfortunately, no firm conclusion can be established due to the low number of cases analyzed ($P = 0.66$).

Two (8.7%) participants died: a 48-year-old man (PASP of 64 mmHg) and a 28-year-old woman (PASP of 34 mmHg), 18 months and 4 months after diagnosis of PH, respectively.

In conclusion, we agree with Ahmed et al. [1] that Doppler echocardiography is useful in evaluating the prognosis of these patients. With respect to risk factors for PH in SCA, however, we did not observe a correlation between this complication and infections and acute chest syndrome.

The relevant literature about the influence of β-globin haplotype on PH pathophysiology is, however, extremely limited. Therefore, further studies are required to confirm this observation and compare treatments, prognoses, and survival.

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T-Cell-Mediated Pure Red-Cell Aplasia in Systemic Lupus Erythematosus: Response to Cyclosporin A and Mycophenolate Mofetil

To the Editor: Pure red-cell aplasia (PRCA) is a hematologic syndrome characterized by anemia, normal platelet and granulocyte counts, and severe reduction or absence of erythroid precursors in the bone marrow, associated with drugs, human parvovirus-B19 infection, thymoma, and disorders of humoral or cellular immunity. A 34-year-old woman with a 5-year history of systemic lupus erythematosus (SLE) presented with severe anemia, reticulocytopenia, and absence of erythroid precursors in the bone marrow, which led to the diagnosis of PRCA. Parvovirus-B19 DNA was undetectable by polymerase chain reaction assays in bone marrow and serum. Serologic studies for parvovirus revealed presence of IgG and absence of IgM antibodies, however, consistent with past exposure. Bone marrow immunohistochemistry for parvovirus was negative. Cytogenetic analysis was normal. Serum erythropoietin level was elevated to 585 (normal range, 4–21 mU/mL). There was no radiographic evidence for thymoma.

The clinical course was characterized by transfusion-dependent anemia. She was treated with immunosuppressive therapy with corticosteroids followed by a course of intravenous immune globulin, oral cyclophosphamide, a trial of recombinant human erythropoietin, and anti-CD20 (rituximab) without response. Hematopoietic progenitor cell assays demonstrated the absence of burst-forming unit-erythroid (BFU-e) colony formation in vitro (Fig. 1A). This defect was completely restored following T-cell depletion of the patient's peripheral blood mononuclear cells. Formation of myeloid colonies (CFU-GM) was normal and appeared to increase following T-cell depletion. The addition of the patient's plasma to progenitor cultures of a healthy donor did not inhibit BFU-e formation, suggesting the absence of humoral suppression of erythropoiesis. The patient was started on cyclosporin A (2.5 mg/kg/day, later increased to 5 mg/kg/day) and mycophenolate mofetil (1,500 mg/day). Three months later, reticulocytosis was noted and hemoglobin levels stabilized without further red cell transfusion requirements (Fig. 1B).

In patients with SLE who develop anemia with reticulocytopenia and require continued red-cell transfusions, diagnosis of PRCA should be considered. The development of PRCA in patients with SLE has been attributed to autoimmune mechanisms such as autoantibodies directed against erythroid progenitors [1] or erythropoietin [2] as well as T-cell-mediated mechanisms [3]. Response to treatment with cyclosporin A was reported in cases refractory to corticosteroids [4,5]. In our patient, the results of in vitro hematopoietic progenitor cell assays implicate T-cell-mediated suppression of erythropoiesis as the possible pathogenic mechanism. This case illustrates that laboratory evaluation with hematopoietic progenitor cell assays, including T-cell-depleted cultures, may be useful, particularly in refractory patients, to guide therapy for patients with PRCA associated with SLE.

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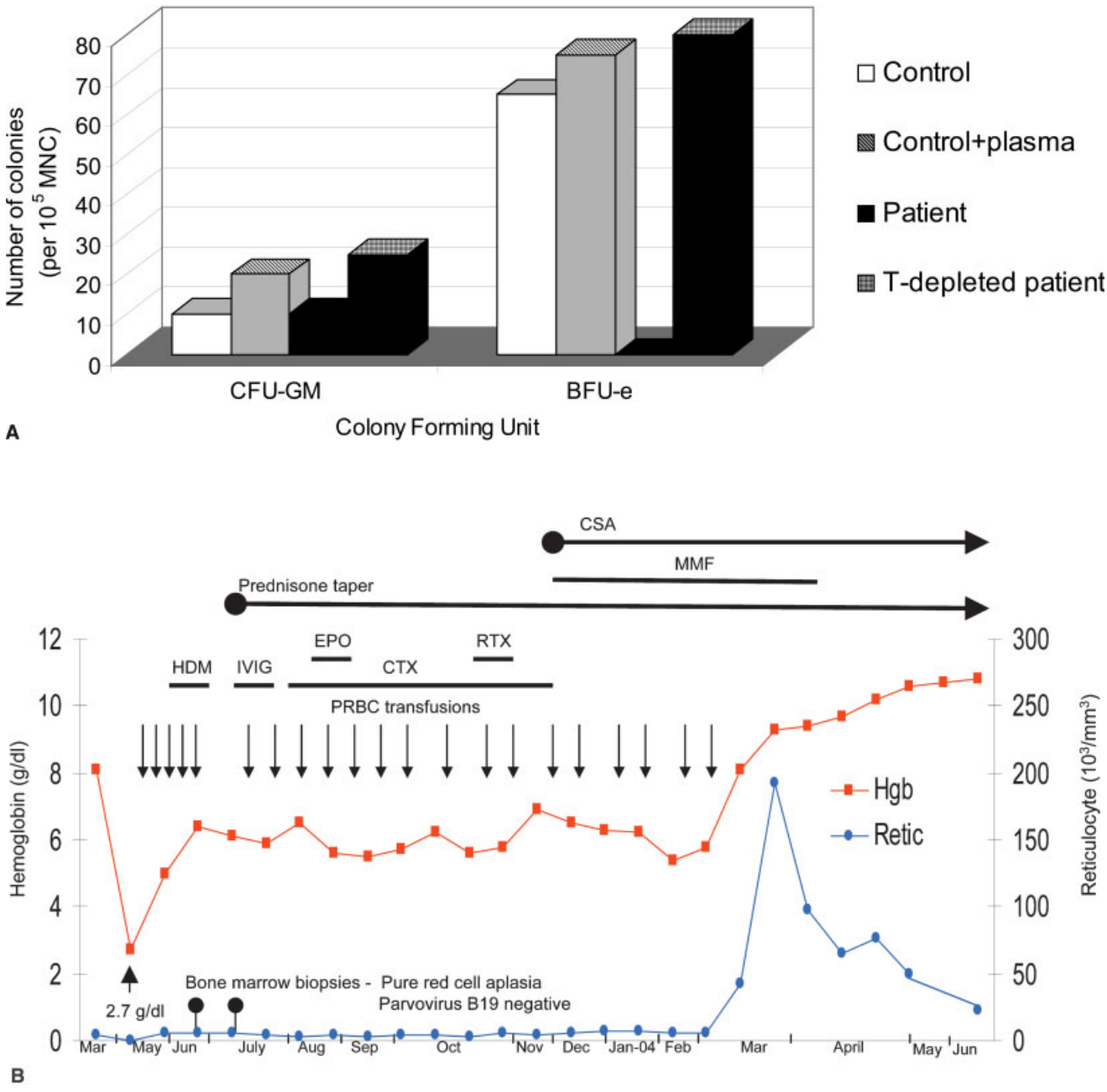

Fig. 1. (A) Depletion of T cells restores in vitro erythroid colony formation in hematopoietic progenitor cell assays. Peripheral blood mononuclear cells (MNC) from the patient and a healthy control were plated in methylcellulose medium (Methocult^{TM} GF H4434, StemCell Technologies, Vancouver, British Columbia, Canada), and hematopoietic colonies were scored after 14 days. To investigate for humoral suppression of BFU-e formation, the patient's plasma was added to cultures of control MNCs. Depletion of patient's T cells was performed using anti-CD3 antibody and magnetic separation of MNCs (Miltenyi Biotech, Auburn, CA). Abbreviations: CFU-GM, colony forming units-granulocyte/macrophage; BFU-e; burst forming units-erythroid. (B) Clinical course of pure red-cell aplasia. Three months after the initiation of CSA and MMF, the patient exhibited a clinical response with reticulocytosis and stabilization of hemoglobin levels allowing discontinuation of red-cell transfusions. Each vertical arrow represents the transfusion of 2 units of packed red blood cells (PRBC). Abbreviations: CTX, oral cyclophosphamide (1 mg/kg/day); EPO, recombinant human erythropoietin (Procrit 40,000 units/week subcutaneously for 4 weeks); HDM, pulse high-dose methylprednisolone (1 g/day for 2 doses); PRED, prednisone (1 mg/kg/day, tapered); IVIG, intravenous immune globulin (0.4 g/kg/day for 5 days); RTX, anti-CD20 rituximab (375 mg/m^2/week for 4 weeks); CSA, cyclosporin A; MMF, mycophenolate mofetil. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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Cough Mixture Abuse in Pregnancy, Folate Deficiency, and Neural Tube Defects?

To the Editor: A 26-year-old Chinese woman presented with symptoms of depression for psychiatric treatment, 8 months after delivery. She was an ex-smoker and a social drinker, and this was her first pregnancy. She attended an antenatal visit only once at 28 weeks. Routine blood screening was negative for iron deficiency, thalassemia, and TORCH, viruses but she declined ultrasound screening and subsequent follow-up. She proceeded to full gestation with uneventful suction evacuation delivery of a boy with an Apgar score of 7. Physical examination showed spina bifida cystica aperta from the L2 vertebra, with concurrent hydrocephalus and epidural clot. After several operations, the child still suffered from neurogenic bladder and paraplegia. There was no family history of congenital birth defects or spontaneous abortion. However, the mother showed excessive dental caries and admitted to cough mixture abuse (300 mL daily) before and during conception, stopping after 3 months of gestation. Retrospective review of delivery records showed no anemia (hemoglobin 11.8 g/dL) and only mild macrocytosis (MCV 97 fL), with no documentation of folate levels.

The incidence of neural tube defects in studies of Caucasians ranged from 0.06% to 0.2%, with 60–80% of cases being spina bifida. Serum and ultrasound screening has greatly reduced the birth prevalence. The incidence in the general population of Hong Kong was estimated to be 0.08% for spina bifida and 0.02% for anencephaly, rising to 0.4% for high-risk pregnancies [1]. Folate deficiency in the first trimester is by far the commonest recognized cause, and universal aggressive supplementation may reduce 70% of cases. Periconceptional supplements have been advocated for epileptics, thalassemics, and patients with family histories of neural tube defects [1,2]. Although overt dietary folate deficiency is rare in Hong Kong [3], we have recently reported a novel association between cough mixture abuse and severe folate deficiency [4]. Cough mixture abuse is an emerging problem and accounted for 1.8% of 5,642 annual new registered abusers locally (2001 figures), including 12% females (data from Action Committee Against Narcotics, Hong Kong Government). This is the first report of birth defects in young female abusers, suggesting that periconception abuse may cause disastrous fetal consequences. The risk is impossible to document by epidemiological means and may be better confirmed by animal models. Nevertheless, proper warnings in drug labels and heightened professional awareness of this novel hazard would be prudent.

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Acute Hemolytic Transfusion Reaction by Anti-P_1 Antibody in Pregnancy

To the Editor: Anti-P_1 antibody commonly found in P_2 individuals (P_1 antigen negative) reacts optimally at low temperature ($< 25°C$) and is not generally clinically significant. Rare examples of anti-P_1 reactive at 37°C and fixing complement, causing acute or delayed hemolytic transfusion reactions, have been reported [1,2].

We present a case of a 25-year-old Indian female, second gravida, with 32-week period of gestation, who presented in emergency with symptoms of severe anemia. Her hemoglobin was 3.2 g/dL; RBC morphology on peripheral smear was suggestive of dimorphic anemia. She gave no history of previous blood transfusion or fetal loss. One unit of packed red blood cells (PRBC) was requested in emergency. Her blood group was typed as B Rh-positive. One unit of B Rh-positive PRBC was cross-matched using the immediate spin cross-match technique due to the urgent request. On transfusion of 10–15 mL of blood, she developed fever (39.2°C), chills, and rigors along with respiratory distress (respiratory rate rose from 24/min to 44/min).

The transfusion reaction workup showed no clerical error. No ABO incompatibility was found between donor unit and the patient's blood group. Auto control was negative at room temperature, 4°C, and 37°C. Pre- and post-transfusion direct antiglobulin tests (DAT) were negative. Pre- and post-transfusion samples were re-cross-matched. These were found incompatible on extended incubation (30 min) at room temperature (1+ agglutination) and at 37°C (2+ agglutination). The repeat pre-transfusion immediate spin cross-match was compatible. An antibody identification panel determined specificity to be that of anti P_1. The patient was found to be P_2, while her husband and first-born 3-year-old child had P_1 antigen on their red cells. On DTT treatment of her serum, the antibody was found to be of IgM type. Plasma hemoglobin was 17 mg/dL (normal 0–5 mg/dL) with no hemoglobinuria. Serum bilirubin was 2 mg/dL with an unconjugated fraction of 1.2 mg/dL. Methemoglobin reduction test for glucose-6-phosphate dehydrogenase deficiency was negative. The bacteriological culture report of the patient's blood and the donor unit revealed that the blood samples were sterile. Two units of PRBC, which were P_1 antigen negative, were cross-matched and were IAT (indirect antiglobulin test) compatible. This transfusion episode was uneventful.

Acute hemolytic transfusion reactions by clinically significant anti-P_1 antibody, although reported, are very rare. In the index case, previous pregnancy was the most probable source of anti-P_1 alloimmunization. Although the anti-P_1 antibody was IgM in nature it was clinically significant. However, there was no risk of hemolytic disease of the newborn. Anti-P_1 antibody was missed on immediate spin cross-match but was detected on extended incubation for half an hour. The first unit that was cross-matched was 2 weeks old, and it has been reported that P_1 antigen deteriorates on storage [3]. Due to emergent need for transfusion, a complete IAT cross-match was not conducted, which could have prevented such a reaction. In our center as in most parts of the country, antibody screening during antenatal care is done only for Rh-negative pregnancies instead of it being a routine practice for all pregnancies. Thus, a screening practice needs to be adopted for all irregular antibodies in all antenatal cases to prevent such reactions in future.

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Can the *Helicobacter pylori* Eradication Regimen Induce Platelet Recovery in *H. pylori*-Negative Patients With Idiopathic Thrombocytopenic Purpura?

To the Editor: Recent studies in Italy and Japan have shown that some idiopathic thrombocytopenic purpura (ITP) patients infected with *Helicobacter pylori* (*H. pylori*) could be treated by eradication of *H. pylori* [1–3]. However, the mechanism of improvement of ITP after bacterial eradication remains obscure, and one study in Japan also reported a case in which eradication of *H. pylori* that failed resulted in platelet recovery, suggesting that a bacterium other than *H. pylori* may play a crucial role in some cases of ITP [2]. We therefore investigated the effect of the *H. pylori* eradication regimen in *H. pylori*-negative ITP patients to determine if this treatment is specific to *H. pylori*.

Seven patients (all females) with ITP whose *H. pylori* test was negative were evaluated; mean age was 43.9 years (range, 18–76 years). ITP was defined by idiopathic thrombocytopenia (platelets $< 100 \times 10^9$/L) when other causes had been excluded, without megakaryocytic hypoplasia in the bone marrow. Five of the 7 patients had chronic ITP (duration > 6 months) and had received prednisolone therapy. Two patients with a disease duration of < 6 months proved to have chronic ITP later. One patient had also previously undergone splenectomy. *H. pylori* infection was assessed by ^{13}C urea breath test (UbiT®-IR300, Otsuka Pharmaceutical Co., Tokyo, Japan). One patient (No. 4 in Table I) with a positive result in the ^{13}C urea breath test was determined to be *H. pylori*-negative because her serum antibodies (enzyme-linked immunosorbent assay) and histological examination of the stomach were negative. The *H. pylori* eradication regimen included amoxicillin (750 mg twice daily), clarithromycin (400 mg twice daily), and lansoprazole (30 mg twice daily) for 1 week. Approval for this study was obtained from the Institutional Review Board of Tohoku University, and informed consent was provided by each patient according to the Declaration of Helsinki. Platelet counts were assessed 6 months after the end of treatment.

As shown in Table I, no significant increase in the platelet count was observed in any of the patients tested. This was in contrast to our experience with *H. pylori*-positive ITP patients, in which 10 out of 15 showed platelet recovery within 3 months by the same regimen (unpublished data). Two other series, which dealt with 3 and 10 patients, respectively, have also shown that the *H. pylori* eradication regimen could not induce platelet recovery in *H. pylori*-negative ITP patients [3,4]. From these findings, a nonspecific effect of this treatment on the platelet counts seems unlikely.

Recently, negative results as to the efficacy of eradicating *H. pylori* in ITP patients have been reported [4], and the differences in the bacterial strains have been implicated as the cause of discrepancy in clinical responsiveness [5]. Further studies are needed to elucidate the mechanisms by which some patients with ITP improve with eradication of *H. pylori*, but, whatever the mechanisms are, our present data support the rationale for pursuing the mechanisms directly related to *H. pylori*.

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TABLE I. Clinical and Laboratory Characteristics of 7 Female *H. pylori*-Negative Patients With ITP*

Patient no.	Age	Disease duration (months)	Previous treatment	PAIgG (ng/10^7 cells)	^{13}C UBT (delta)[a]	*H. pylori* antibodies[b]	Platelets ($\times 10^9$/L)	
							Before	After (at 6 mo)
1	30	88	PSL, Sp	110.4	1.8	1.2	2.4	2.4
2	34	68	PSL	199.1	1.5	ND	2.5	3.9
3	72	89	PSL	80.5	0.8	1.1	7.0	8.8
4	76	2	None	ND	3.6	1.1	1.1	0.5 (at 5 mo)
5	37	85	PSL	ND	0.2	1.1	4.0	6.5
6	40	216	PSL	167.5	−3.2	ND	5.5	5.0
7	18	4	None	58.2	0.7	0.9	4.7	5.3

*Abbreviations: UBT, urea breath test; PSL, prednisolone; Sp, splenectomy; ND, not done.
[a]^{13}C urea breath test result is positive for >2.5‰.
[b]*H. pylori* antibody result is positive for >1.7.

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