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LETTERS AND CORRESPONDENCE

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Osteoporosis—An Unusual Presentation of T-Cell Lymphoma

To the Editor: Skeletal involvement in lymphomas is not commonly seen [1,2]. Osteoporosis as the first manifestation of T-cell lymphoma has been very rarely documented [2]. We report one such case. A 35-year-old man presented with radicular pain, progressive weakness, and diminished sensation in both lower limbs for 1 year following a trivial trauma. There was no other significant history. He denied history of addiction or drug intake. His dietary calcium intake was adequate. He had been treated with calcium supplements. General physical examination revealed pallor. Spleen was palpable 5 cm below the costal margin on abdominal examination. Neurological examination of lower limbs showed spasticity on both sides with reduced power (right > left) with exaggerated knee and ankle jerks and extensor planters. All modalities of sensation were impaired in the lower limbs. Rest of neurological and systemic examination was normal. Investigation showed hemoglobin 6.5 g/dL, total leukocyte count 5200/mm^3 (N37 L60 M02 E01), platelets 0.3 million/mm^3. The renal, liver function tests, and serum electrolytes (including calcium and phosphorus) were normal with elevated serum lactic dehydrogenase 1067 IU/L. X-ray of the spine showed compression of D 12 vertebra, which was confirmed by magnetic resonance imaging. Dual-energy X-ray absorptiometry (DEXA) showed T score of -5.0 at spine and -4.4 at hip. Ultrasound of the abdomen confirmed splenomegaly. Search for metabolic causes of osteoporosis (serum parathyroid levels, serum 1,25-dihydroxy calciferol levels, thyroid function tests, and serum cortisol levels) and malabsorption (upper gastrointestinal endoscopy with duodenal biopsy, barium meal follow through, anti-endomysial antibodies) were not fruitful. Urinary calcium was normal (test performed for 24 hr). On immunoelectrophoresis, M band was not seen. Bone scan showed increased tracer uptake in all the skeletal bones. Bone marrow trephine revealed hypercellular marrow with effacement of marrow spaces by mature lymphocytes (CD3+ and CD19−; Fig. 1). Contrast-enhanced computed tomogram of the chest and abdomen showed only splenomegaly. Serology for HIV was negative (serology for HTLV was not available). Diagnosis of osteoporosis with non-Hodgkin's lymphoma (T-cell) stage IV was made. The index case was a young active male who developed compression fracture of spine. Osteoporosis as confirmed by bone densitometery was the underlying cause. Since no other cause could be found after extensive evaluation, osteoporosis in this case was attributed to lymphoma.

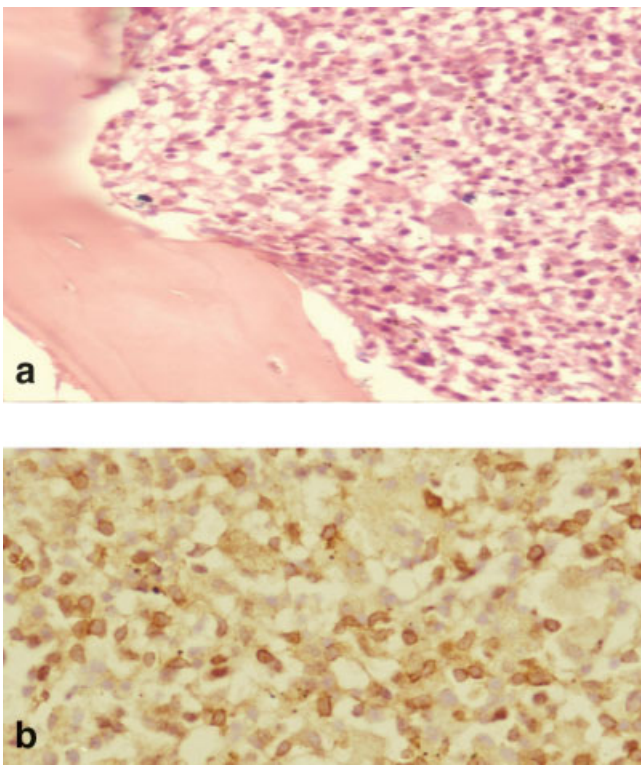

Fig. 1. Bone marrow biopsy (40×) showing diffuse sheets of lymphocytes (a), which on immunostaining showed CD3 positivity (b). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Osteoporosis is defined as reduction in bone mass or density (T score of < -2.5 on DEXA) [3]. Among the risk factors are increasing age, genetic factors, low calcium diets, smoking, alcohol, sedentary life styles, endocrinal causes, chronic diseases, and drugs. Osteoporosis also occurs in hematological malignancies most notably multiple myeloma. It is unusually encountered in lymphomas mostly B cell (lymphoplasmacytoid) [1]. In an extensive review of literature there was only anecdotal data of T-cell lymphomas presenting as osteoporosis [2]. A bone-resorbing factor "lymphocyte OAF" secreted by activated T lymphocytes was thought to be responsible [2]. This has been supported by some other studies [4].

We present this case because osteoporosis a first manifestation of T-cell lymphoma is extremely unusual. At this moment pathogenesis can only be speculated due to paucity of such cases.

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Cardiac Tamponade as the Presenting Symptom of Chronic Myelogenous Leukemia

To the Editor: In 2004, a 40-year-old man was admitted to hospital with one-week history of chest discomfort and progressive dyspnea. Physical examination revealed the spleen was enlarged below the left costal margin, no skin lesions, and no palpable peripheral lymphadenopathy. Abdominal ultrasound showed an enlarged spleen, normal venous flow, and no lymphadenopathies. Laboratory data showed white blood cell (WBC) of 80×10^9/L, platelets 114×10^9/L, and hemoglobin 97 g/L. The differential blood count showed 37% neutrophils, 27% metamyelocytes, 18% promyelocytes, 10% lymphocytes, 4% myelocytes, 3% basophils, and 1% eosinophils, with normocytic normochromic erythrocytes. By echocardiography, a large pericardial effusion was confirmed (see Fig. 1). Bone marrow aspiration revealed hypercellularity, E/M ratio of 1/11 with 3% blasts, 5% eosinophilic, and 3% basophilic series. The leukocyte alkaline phosphatase score was 20 (control 150). The Philadelphia chromosome was seen in all metaphases analyzed, and bcr-abl rearrangement was demonstrated by polymerase chain reaction analysis. Blood cultures, PPD test, the levels of immunoglobulin, and complement were normal. The diagnosis of cardiac tamponade and chronic phase chronic myelogenous leukemia (CML) were established, and a percutaneous drain was placed echocardiographically. Initially 800 mL of hemorrhagic pericardial fluid was removed. Gram and Ziehl-Nielsen stains and cultures on his pericardial fluid were negative. After drainage, the patient's symptoms improved rapidly. Treatment with hydroxyurea was started, which resulted in a decrease of leukocytes. After 3 months, the pericardial effusion disappeared entirely. The patient was discharged with a stable WBC ranging between 5,000 and 15,000 mL under treatment with hydroxyurea. But neither transplanatation nor ST1-571 or interferon-α treatment were given to the patient because of his economic problems. The patient is still in chronic phase and there was no reaccumulation of fluid at 20 months.

Approximately 50% of CML patients are asymptomatic at presentation. The most frequent complaints are fatigue, abdominal fullness, left upper quadrant fullness, and decreased exercise tolerance. Pericardial effusion in chronic phase of CML is a rare occurrence and associated tamponade is extremely rare and has been described in only a few case reports [1–4]. The causes of pericardial effusion may be related to leukemic infiltration, extramedullary hematopoiesis, infections, and bleeding in CML. In addition, STI-571 may also cause cardiac tamponade during treatment in chronic phase of CML [5]. What is interesting here is that cardiac tamponade as the first presenting of chronic phase of CML, and he was successfully treated with pericardiocentesis and hydroxyurea.

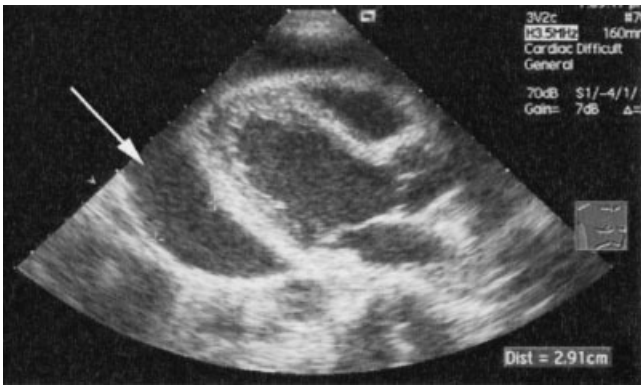

Fig. 1. Echocardiogram showed a massive pleural effusion (arrow).

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Splenic Infarction in an African-American Male With Sickle Cell Trait

To the Editor: Splenic infarction with sickle cell trait (SCT) was first documented among black servicemen flying in unpressurized aircraft during the Korean War [1]. Symptoms typical of splenic infarction include epigastric pain with migration to the left upper quadrant over 48 hr, fever, anorexia, and vomiting. Diaphragmatic irritation may cause decreased respiration, splinting, [1] and is often associated with sympathetic left lower lobe pleural effusion [2]. Serum laboratory data often show acutely increased lactate dehydrogenase, mild anemia, and increased platelets [1].

We present a 51-year-old African-American male with sickle cell trait and hepatitis C with left upper quadrant pain for 3 days and hematemesis. The patient had been using heroin for pain relief after being drug free for 6 years. He admitted being an avid exerciser including over the week prior to admission despite warm outdoor temperatures and his abdominal symptoms.

In the emergency room he was tachycardic, tachypneic, normotensive, and hypoxic with bibasilar crackles, and soft abdomen without visceromegaly. Pertinent serologies included white blood cell count of 25,000 with 80%

neutrophils, hematocrit of 36%, blood urea nitrogen of 27, creatinine of 3.4, bilirubin of 1.5, amylase of 271. Lipase, AST, ALT, alkaline phosphatase, PT, and PTT, platelet count and mean corpuscular volume, electrocardiogram were normal. Fractional excretion of sodium was 0.4%. Chest X-ray showed minimal atelectasis. Noncontrast abdominal computed tomography (CT) showed left lower lobe atelectasis. Gastric lavage with saline cleared after 200 cc.

Esophagogastroduodenoscopy showed esophagitis and gastritis. With hydration renal failure resolved within 24 hr. Repeat chest X-ray on hospital day 2 revealed new left pleural effusion. Thoracentesis indicated no infection, negative cytology, and an exudative effusion. Left upper quadrant pain persisted. Abdominal visceral arteriogram was done showing patent splenic vasculature, no signs of ateritis, but complete splenic infarction. Thrombocytosis developed during hospitalization. Electrophoresis was consistent with sickle cell trait. Peripheral blood smear was normal. He remained hypoxic throughout hospitalization and was discharged on supplemental oxygen.

The patient's course is consistent with subacute splenic infarction. Etiology of splenic infarction in patients with SCT is incompletely understood. It has been demonstrated before that patients in unpressurized airplane cabins at 15,000 feet elevation have as much as 5% red blood cell sickling [3]. Most splenic infarctions associated with SCT have been documented during mountain traveling or flying at high altitudes in unpressurized cabins [4]. This patient lived at an altitude of $\sim$4,500 feet all of his life with no recent moves to higher elevation.

Although no proof exists it has also been suggested that other factors including dehydration, infection, drugs, and muscular exertion may play a role [2]. His clinical presentation and laboratory data clearly indicate significant dehydration on admission. This combined with hypoxia and reported muscular exertion prior to admission account for a potential multifactorial etiology of splenic infarction.

This case is important as it documents a rare occurrence of an event incompletely understood. Further study is needed to ascertain more information regarding the etiology of the association of SCT and splenic infarction.

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Long Standing Priapism as Presentation of Lymphoma

To the Editor: Long standing priapism due to malignant lymphoma is a rare incident. The occurrence of a patient with 6-month priapism due to large-cell lymphoma of B-cell origin is reported.

A 50-year old man presented with a 6-month history of painless priapism. Medical history was unremarkable except for mild pain in the inguinal regions for the past 2 months, which had recently increased in severity. Upon admission, the patient was feeling well with no fever, lymphadenopathy, or organomegaly. Examination revealed a painless erection and a flaccid glans. Rectal examination demonstrated normal sphincteric tonus and a normal prostate. Laboratory studies were within normal limits. Detumescence did not occur after aspiration and injection of epinephrine nor with a corporo-glandular shunt. Cavernosonography revealed no passage of contrast material from the midshaft to the base of the penis. Duplex penile ultrasound confirmed a high flow priapism. Color Doppler ultrasound of the inguinal region demonstrated bilateral femoral deep vein thrombosis with iliac extension. Computerized tomography revealed a mildly enlarged prostate, subcuticular, bilateral, inguinal soft tissue masses (4 × 4 cm^2 in the right, 2.5 × 3 cm^2 in the left), and an enlarged corpus cavernosum. Excisional biopsy of the right subcuticular inguinal mass revealed diffuse, high-grade, large-cell type stage II malignant lymphoma of B-cell origin,. The patient was put on anticoagulant therapy (heparin followed by coumadin). He was treated with chemotherapy consisting of cyclophosphamide, adriamycin, and prednisone causing resolution of the priapism after three weeks of therapy. Color Doppler ultrasound of the penis during follow-up revealed low flow in the right cavernosal artery and normal flow in the left. The patient claimed that he was unable to achieve an erection since the treatment began.

Non-Hodgkin's lymphoma is a heterogeneous group of lymphoid malignancies. Diffuse large B-cell lymphomas are the most frequently occurring non-Hodgkin's lymphoma, which are clinically aggressive and have a wide variety of clinical presentations [1]. More than in any other subtype, diffuse large B-cell lymphoma presents in extranodal sites, the most common being the gastrointestinal site [2]. They appear in all age groups, disseminate rapidly, and appear in unusual sites. However, unlike the other subtypes in this group, the diffuse large B-cell lymphoma subtype is a chemotherapy-curable lymphoma.

Involvement of the penis by malignant B-cell lymphoma is uncommon and has not been reported in the literature. The pathogenesis of the malignant priapism is thought to be secondary to tumor infiltration of the corpora cavernosa [3]. The infiltrate causes stasis or thrombosis of the venous system resulting in an irritation of the neural pathways and an erect penis. The route of spread to the corpora cavernosa is by retrograde venous and lymphatic spread, arterial embolism, and direct invasion of the tumor. In our case, it appears that the underlying disease caused stasis in the venous system resulting in bilateral femoral venous thrombosis with iliac extension. To the best of our knowledge, this is the first published case of long standing priapism caused by malignant B-cell lymphoma.

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Rediscovery of the Susceptibility of G6PD Deficient Persons to Methemoglobinemia From Oxidant Drugs, and to Hemolysis From Methylene Blue

To the Editor: I read with interest the case report by Foltz et al. [1] on the methemoglobinemia from Triapine followed by hemolysis from methylene blue in a G6PD deficient Filipino patient. The authors have rediscovered observations that my group made over 43 years ago. In our 1962 paper [2], we

demonstrated that oxidant drugs that are not very hemolytic in G6PD deficient subjects cause over 10-fold more methemoglobin formation in G6PD deficient subjects than in normals. The drug we used to demonstrate this effect was nitrite. It appears that Triapine is a drug of this type, and produced much methemoglobin in the G6PD deficient patient of Foltz et al. [1], whereas it does not do so in non-G6PD deficient patients, and produced little or no hemolysis in their patient.

Foltz et al. [1] then undertook to treat the patient's methemoglobinemia with methylene blue, and the patient had an acute hemolytic episode. At about the same time as our earlier article we had shown that methylene blue causes hemolysis in G6PD deficient subjects [3]. All our work was done in subjects with the A type G6PD deficiency, common in African Americans, and presumably the patient of Foltz et al. [1] was of a more severe type deficiency, leading to the relatively pronounced reactions to Triapine® and methylene blue.

Since GGPD deficiency is very common in some populations, it would behoove the manufacturers to provide a warning about the use of the drug in G6PD deficient patients because of methemoglobinemia, and about the risks of treating with methylene blue should methemoglobinemia occur.

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Hiccups and Severe Hyponatremia Associated With High-Dose Cyclophosphamide in Conditioning Regimen for Allogeneic Stem Cell Transplantation

To the Editor: A 55-year-old man was diagnosed with Philadelphia-positive (Ph^1) acute lymphoblastic leukemia (ALL) and CNS involvement. He was treated according to the Swedish national protocol for ALL with addition of imatinib. After induction treatment, prophylactic intrathecal therapy was commenced with methotrexate and the patient entered a complete hematological and cytogenetic remission. Subsequently, he underwent allogeneic peripheral stem cell transplantation from an unrelated one-locus HLA mismatched donor. The conditioning regimen was Bu/Cy without TBI. Intravenous busulfan 220 mg and cyclophosphamide 4,100 mg with antithymocyte globulin (ATG) was introduced. At the same time, with infusion of cyclophosphamide the patient got MESNA and 31 of 5% glucose for hyperhydration and prevention of hemorrhagic cystitis. The patient developed hiccups at the start of chemotherapy. On the second day of cyclophosphamide infusion, the patient developed severe hyponatremia, 121 mmol/l; K, 3.3 mmol/l; Cl, 81 mmol/l; Hb, 92 g/l; WBC, 0.9×10^9/l; Plt, 40×10^9/l and had nausea and vomiting with persistent hiccups. There were no CNS symptoms except for insomnia. Plasma osmolality was 266 mosm/kg, urine osmolality 234 mosm/kg, and urine-Na 27 mmol/l. Complete water restriction was prescribed and the patient's serum natrium raised to 125 mmol/l 6 hr later and to 131 mmol/l 24 hr after the beginning of water restriction. The patient was thirsty but felt much better and the next day serum natrium was 135 mmol/l. The hiccups were gone.

Severe hyponatremia and other metabolic complications during the first 100 days after allogeneic stem cell transplantation are not unusual. The occurrence of severe metabolic abnormalities is correlated with inferior clinical outcome. Age over 40 and the type of conditioning regimen, especially the use of high-dose cyclophosphamide, are risk factors associated with hyponatremia [1]. The consequences of hyponatremia can be life threatening with convulsions and central pontine myelinolysis. Clinical clues to the presence of hyponatremia could be long-lasting or intractable hiccups [2]. Even though hiccups could have variable etiologies they can be an important sign of hyponatremia and can be seen with high-dose cyclophosphamide therapy in the setting of conditioning regimen for allogeneic stem cell transplantation. In this situation, we strongly recommend laboratory analysis of serum electrolytes even several times a day to avoid severe hyponatremia and provide unobstructed continuation of conditioning regimen [3].

We believe that the problem of hiccups is underrepresented in the hematological literature and that hiccups can be a sign of severe hyponatremia, which can be a consequence of hyperhydration and/or high-dose cyclophosphamide therapy.

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