Hypercaldemia, multiple osteolytic lesions, and acute renal failure: a rare presentation of B-cell acute lymphoblastic leukemia

TO THE EDITOR: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy [1]. Anemia, hepatosplenomegaly, and generalized lymphadenopathy are common findings in B-cell ALL [2]. Although bone pain is a common symptom of being in almost 40% of cases, hypercalcemia and frank osteolytic lesions are very rare in ALL [3, 4]. Additionally, while about 7% of cases are diagnosed as the kidney involvement of ALL by intravenous pyelogram, it is uncommon that acute renal failure presents these primary manifestations [5, 6]. We report a rare case of B-ALL with prominent ostalgia and impaired kidney functions.

CASE
A 14-year-old girl presented with a 3-month history of generalized body aches. The pain started initially in the lower back and then progressed to both legs and chest. There was no history of epistaxis, gum bleeds or bleeding from any mucosal site. On physical examination, the patient had generalized lymphadenopathy involving bilateral submandibular, posterior cervical, upper deep cervical, and superficial inguinal nodes each measuring less than 0.5 cm in diameter. Fine needle aspiration cytology (FNAC) was performed on the posterior cervical lymph node. There was localized tenderness over the chest and legs. The liver and spleen were palpable with stiffness and tenderness. Initial complete blood cell count (CBC) showed hemoglobin level of 8.5 g/dL, white blood cell (WBC) count of 9.4×10^9/L, and platelet count of 137×10^9/L. Peripheral blood smear examination showed normocytic normochromic red blood cells without abnormal cells or blasts, and WBC differential count of 72% neutrophils, 25% lymphocytes, 1% eosinophils, and 2% monocytes. As shown in Table 1, the patient had marked elevated blood urea and serum creatinine with hypercalcemia and reversal of the albumin-globulin ratio. Radiographs of skeletal system was done which showed multifocal osteolytic lesions in skull, vertebral bodies, sacrum, pelvic bones, ribs and femur as well as loss of lumbar lordosis, collapsed T12 vertebral body with biconcave end plates along with mild wedging of L4 vertebra, end plate irregularities, and sclerosis at multiple levels (Fig. 1). Ultrasonography showed echogenicity for grade 1 renal parenchymal disease with mild-degree of hydronephrosis for both kidneys and scant amounts of ascites in the abdomen. Parathyroid hormone levels were at a normal level of 12.4 pg/mL. Serum protein electrophoresis was performed for confirming monoclonal gammopathy, but showed a normal pattern. Bone marrow aspirate examination showed diffuse

| Clinical chemistry tests       | Result     | Reference range |
|-------------------------------|------------|-----------------|
| Urea                          | 171 mg/dL  | 15–40 mg/dL     |
| Creatinine                    | 3.6 mg/dL  | 0.9–1.8 mg/dL   |
| Sodium                        | 141 mEq/L  | 133–145 mEq/L   |
| Potassium                     | 4.3 mEq/L  | 3.8–5.0 mEq/L   |
| Chloride                      | 107 mEq/L  | 96–106 mEq/L    |
| Calcium                       | 13 mg/dL   | 8.5–11 mg/dL    |
| Phosphate                     | 2.3 mg/dL  | 2.4–4.1 mg/dL   |
| Uric acid                     | 7.6 mg/dL  | 1.9–7.5 mg/dL   |
| Total bilirubin               | 0.4 mg/dL  | 0–2 mg/dL       |
| Direct bilirubin              | 0.2 mg/dL  | 0.2–1.0 mg/dL   |
| AST                            | 6 U/L      | 10–40 U/L       |
| ALT                           | 26 U/L     | 7–56 U/L        |
| Total protein                 | 6.8 gm/dL  | 0.3–8.0 gm/dL   |
| Albumin                       | 2.7 gm/dL  | 3.5–5.5 gm/dL   |
| A/G ratio                     | 0.65       | 0.8–2.0         |

Fig. 1. (A) Bone marrow aspiration shows the presence of 64% blasts with high N/C ratio, scant cytoplasm, fine chromatin, and prominent nucleoli. (B) Radiographs of skull (C) pelvis (D) vertebrae showing multiple osteolytic lesions.
Fig. 2. The blasts population showed expression of CD19, TdT, and CD79a, consistent with B-cell acute lymphoblastic leukemia.

infiltration of blasts, which were twice the size of lymphocytes with scant basophilic cytoplasm. Only occasional myeloid and erythroid precursors were seen (Fig. 1). Flow cytometry identified the blasts population showing CD45 negative, CD19 positive, CD79a positive, and TdT positive which was consistent with a diagnosis of pre-B-cell ALL (Fig. 2). The modified BFM protocol was administered to the patient with sufficient hydration. The patient currently has been receiving consolidation phase 1 chemotherapy without remarkable complications.

**DISCUSSION**

Bone pain is a one of the prominent symptom of acute lymphoblastic leukemia. Jonsson et al. [3] reported that severe pain overshadowing other symptoms of ALL was present in 18% of the patients. On the other hand, hypercalcemia and frank osteolytic lesions are rarely found. Hypercalcemia arising from malignancy is a frequent complication in adults, but little has been recognized regarding that of children. In a previous study, hypercalcemia did not seem to affect the prognosis of patients with ALL [7]. Hypercalcemia arising from malignancies is a result of increased bone resorption at metastatic bone lesion and humoral factors associated with calcium metabolism [8]. In particular, parathyroid hormone-related peptide (PTHrP) is one of the most common causes of hypercalcemia in ALL. Shimonodan et al. [9] revealed the fact that elevated PTHrPs in ALL come from lymphoblasts, associated with its frequent relapses and poor prognosis. Additionally, other leukemic blasts-producing cytokines including transforming growth factor-α, tumor necrosis factor, interleukin-1, and prostaglandin E2 may affect these phenomena [10]. Although leukemic infiltration of the kidney is usually asymptomatic, it can lead to bilateral renal enlargement, acute kidney injury (AKI), or secondary hypertension [11]. If recurrent hyperuricemia and AKI are persistent, it may be an early presentation of childhood leukemia and need to examination of bone marrow and kidney [12].

In conclusion, hypercalcemia, multiple osteolytic lesions, and acute renal failure are uncommon in ALL, but can be initial manifestation of the diseases and may lead to early diagnosis of those. Therefore, clinicians keep in mind the possibility of ALL, when patient presented with unexplained hypercalcemia, multiple osteolytic lesions, and/or acute renal failure.

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JAK2 exon 12 mutation-positive myeloproliferative neoplasm associated with recurrent thromboembolism

TO THE EDITOR: Detailed analysis of Philadelphia (Ph) chromosome-negative myeloproliferative neoplasms, essential thrombocythemia (ET), and polycythemia vera (PV) paved the way for the recognition of Janus kinase 2 (JAK2) as a potential genetic factor [1]. While most cases of these diseases are related to JAK2 V617F, some are associated with JAK2 exon 12 mutation. JAK2 exon 12 mutation is a rare phenomenon that is not yet well studied. Although, the presence of JAK2 exon 12 mutation is linked to PV and ET, its phenotypic features are not clear, especially in cases without ET and PV. The JAK2 exon 12 G571S variant has also not been studied well, and its phenotypic features are unknown. We present a case of recurrent deep vein thrombosis (DVT) and pulmonary embolism that had a negative coagulation workup, but was positive for JAK2 exon 12 (G571S) mutation. The presented case suggests a possible relationship between JAK2 exon 12 mutation and recurrent thrombosis. While JAK2 V617F is inherently related to thrombotic events, irrespective of the platelet level, JAK2 exon 12 might have similar procoagulant effects. It is hypothesized that further molecular studies can reveal the underlying factors that cause this co-occurrence.

CASE
A 38-year-old Hispanic woman with a past medical history of pulmonary embolism, DVT, and asthma was seen for an evaluation of her recurrent episodes of thrombosis. She had experienced three episodes of DVT and one episode of pulmonary embolism. The first episode of DVT occurred 5 years ago, and the second episode happened 3 years ago. The pulmonary embolism occurred 1 year ago, following the third episode of DVT. Each DVT episode presented with lower leg edema and pain, and was confirmed by lower extremity ultrasound. The pulmonary embolism episodes presented as shortness of breath and low oxygen saturation.

She was given the following medications to take at home: Ipratropium-Albuterol (Duoneb Neb), 3 mL by inhalation every 4 hours as needed, and warfarin sodium (Coumadin), 12 mg orally once daily. However, she was non-adherent to the use of warfarin. The notable aspects of her family history were that her mother had diabetes mellitus and hypertension, while her father had colon cancer at age of 42. She was a current smoker and had been smoking 2 packs of cigarettes daily for 20 years. She denied alcohol and drug use. A review of systems was non-contributory.

A recent complete blood cell count revealed the following: white blood count 11.1×10^9/L, hemoglobin level 14.9 g/dL,