Renal involvement at diagnosis of pediatric acute lymphoblastic leukemia

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Abstract

Acute leukemia is the most common type of cancer in pediatric patients. This type of cancer accounts for a third of all childhood cancer cases. More than half of pediatric acute leukemia patients show signs and symptoms such as hepatomegaly, splenomegaly, pallor, fever and bruising at the time of diagnosis. In early stages of acute lymphoblastic leukemia (ALL), nephromegaly and other renal manifestations such as high blood pressure (HBP) and renal failure are uncommon, although renal infiltration and nephromegaly are common in advanced-stage pediatric patients. This is a retrospective case report with a critical appraisal of the existing evidence from the literature. We present a clinical case of a child with HBP associated with bilateral nephromegaly which resolved after chemotherapy treatment. This patient presented with HBP that required pharmacological treatment, likely owing to nephromegaly. All HBP secondary causes were rejected. Nephromegaly was resolved after chemotherapy treatment, and antihypertensive medication was discontinued. Nephromegaly and HBP are rare manifestations of ALL debut in pediatrics. The present case report illustrates this unusual combination and Suggests clinicians to consider malignancy as its causal factor, especially if the symptoms are accompanied by other suggestive extrarenal manifestations.

Introduction

Acute leukemia is the most common type of cancer in pediatric patients, accounting for a third of all cases of childhood cancer. More than half of acute leukemia pediatric patients show signs of hepatomegaly, splenomegaly, pallor, fever and bruising at diagnosis.1 During advanced stages of ALL, renal infiltration and nephromegaly are common in pediatric patients. However, nephromegaly and other renal manifestations such as HBP and renal failure are not common at the beginning of the disease.2 Nephromegaly can be attributed to leukemic infiltration, hypertrophy or hyperplasia of parenchymal cells.3,4 HBP is associated with steroid treatment,2 acute renal failure, narrowing or occlusion of intrarenal arteries and leukemic infiltration.5 HBP associated with nephromegaly at the time of diagnosis of ALL is usually moderate, transient and does not require pharmacological intervention.2,4,5 Here, we report a case of a pediatric patient with nephromegaly and HBP at the time of diagnosis of ALL. With ALL treatment, nephromegaly was resolved, but the patient required pharmacological treatment for hypertension.

Case Report

A 3-year-old Caucasian boy presented at pediatric emergency with a 3-day history of fever, petechiae on eyelids and pallor. Personal and family history was unremarkable. He was born from a full-term uncomplicated pregnancy with a normal postpartum course.

Physical examination of the patient showed a weight of 16.1 kg, height of 101 cm and blood pressure of 114/76 (>95th percentile).6 A complete blood count on the day of admission showed the following results: WBC count 12,300/µL with 86% blasts, platelets 16,400/µL, hemoglobin 7.9 g/dL. Lactic dehydrogenase was slightly elevated at 383 U/L (reference value: 85–227 U/L), erythrocyte sedimentation rate was 91 mm/h (reference value: 0–13 mm/h) and C-reactive protein value was 6.67 mg/dL (reference value: 0–0.3 mg/dL).

The rest of the blood chemistry tests were normal (electrolytes, urea nitrogen, serum creatinine, uric acid, bicarbonate, lactate and transaminases). Coagulation tests (prothrombin time and partial thromboplastin time) and urinalysis was also normal. Serological tests for cytomegalovirus, human immunodeficiency virus, Epstein-Barr virus and hepatitis B and C were negative. Abdominal ultrasound showed enlarged kidneys with normal echo-Doppler findings of renal vessels. Computed tomography (CT) of the abdomen showed kidneys enlarged for age and body surface area, with longitudinal diameter of the right kidney 9.5 cm (Z score + 4.75) and of the left kidney 9.0 cm (Z score + 3.97).3 Normal corticomedullary differentiation and non-dilated pelvicalyceal system were observed (Figure 1). The liver was also enlarged, with longitudinal diameter of the right hepatic lobe 12.1 cm (reference value: 6.9–10.9 cm)

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| Author (ref) / year | No | G | Age (yrs) | Kidney size (longitudinal and transverse diameters, cm) | Other kidney compromise | Diagnostic Imaging | Kidney biopsy | Other organ involvement | Nephromegaly | Outcomes |
|---------------------|----|---|-----------|--------------------------------------------------------|-------------------------|------------------|--------------|------------------------|-------------|---------|
| Arora (19) / 2019   | 1  | M | 2         | RK: 11×5.2; LC: 12×6.1                                 |                         | USG; bilaterally enlarged kidneys and prominence of bilateral pelvic calyceal system. Abdomen CT: bilateral enhanced kidney and mild compression of bilateral pelviccalyceal system. | ND           | NR                     | Nephromegaly | Complete remission on USG of nephromegaly after 1 month of treatment | NR |
| Sherief (8) / 2015  | 2  | F | Case 1: 4 | Case 1: RK: 8.5×3.5; LC: 7.8×3.1                      |                         | Case 2: Acute kidney injury Case 1: USG; bilateral renal enlargement with hyperplastic pattern and poor corticomedullary differentiation. MCT: bilateral symmetrical homogeneous enlarged kidneys and poor corticomedullary differentiation. Case 2: USG; markedly enlarged kidneys with mild increased renal parenchymal echogenicity. MCT bilateral diffuse renal enlargement with significantly thinned renal capsule with dilated both pelviccalyceal systems. | ND           | Case 1: lymphadenopathy Case 2: CNS infiltration | Nephromegaly | Complete remission on ultrasonography of nephromegaly at the end of induction. Case 2: marked reduction of kidney size at day 28 | Case 1: CNS enlarged 11 months after the end of therapy. Case 2: died from sepsis in consolidation phase of therapy |
| Estem (15) / 2011   | 1  | F | 5         | RK: 10×4.3; LC: 11×4.5                                |                         | Urinary tract infection | USG; bilateral renal enlargement | Diffuse interstitial high grade hematolymphoid malignant infiltration | NR          | Nephromegaly | Complete remission within 8 weeks of therapy | Remission after two years of treatment |
| Mantat (11) / 2010  | 1  | F | 0.7       | RK: 10.7×5.0; LC: 10.2×5.5                            |                         | Multiple dilated tubular structures in cortex and medulla. Abdomen CT: bilateral smooth kidneys. | NR           | Splenomegaly; CNS compromise | Nephromegaly | Complete recovery at palpation after first week of therapy | Deceased after 2 weeks of chemotherapy due to febrile neutropenia |
| Aguayo (10) / 2009  | 1  | M | 1.5       | RK: 14; LC: 11                                       |                         | USG; bilateral renal enlargement with mild hydronephrosis in right kidney and left kidney with mild echocystisis. Abdomen CT: mass within bilateral nephromegaly. | NR           | NR                     | Nephromegaly | Nephromegaly | Nephromegaly | Nephromegaly | Nephromegaly | Remission after two years of treatment |
| Chin (30) / 2008    | 1  | M | 18        | RK: 13.1; LC: 13.4                                   |                         | Kidney failure and severe metabolic acidosis | USG; bilateral renal enlargement of both kidneys | Abdomen CT: diffuse enhancement of both kidneys | NR          | Nephromegaly | Nephromegaly | Nephromegaly | Nephromegaly | Remission after two years of treatment |
| Al (8) / 2008       | 1  | M | 6         | Both kidneys: 15                                    |                         | Acute kidney injury | USG; bilaterally enlarged kidneys with hyperplastic pattern and loss of corticomedullary differentiation. MCT: bilaterally enlarged kidneys and loss of corticomedullary differentiation. | NR           | Nephromegaly | Nephromegaly | Nephromegaly | Nephromegaly | Remission after two years of treatment |
| Martins (2) / 2008  | 1  | F | 0.4       | RK: 8.6×4.1; LC: 8.7×4.4                             |                         | USG; bilaterally enlarged kidneys with hyperplastic pattern. Abdomen CT: bilaterally enlarged kidneys. | NR           | NR                     | Nephromegaly | Nephromegaly | Nephromegaly | Nephromegaly | Nephromegaly | Remission after 7 months of treatment. |
Table 1. Summary of previous cases reported.

| Author (ref) / year | No | G | Age (yrs) | Kidney size (longitudinal and transverse diameters, cm) | Diagnostic Imaging | Kidney biopsy | Other organs involvement | Nephromegaly | Outcomes |
|--------------------|----|---|-----------|---------------------------------------------------------|-------------------|---------------|------------------------|--------------|----------|
| Pradeep (4) / 2008 | 1  | M | 7         | RK: 15.1×6.3, LK: 14.4×5.3                              | HBP               | Presence of blasts similar to those seen in the peripheral smear and bone marrow | NR          | NR        | NR       |
| Boueva (16) / 2005 | 1  | F | 1.8       | Both kidneys: 14×5                                      | USG bilateral non-obstructive enlargement with hyper-echogenic parenchyma. Of interest is the presence of fine corticomedullary differentiation involving both kidneys. | Extensive infiltration of small renal vessels by NBL. No other evidence of disease. | NR          | At the end of the 1st month of therapy, plasma creatinine values, kidney dimensions, and parenchymal features became normal | NR          |          |
| Gupta (21) / 1985  | 3  | M | Case 1: 2 | Case 1: lymphadenopathy                                 |                  |               |                          |              |          |
| Gilboa (12) / 1983 | 4  | M | Case 1: 8 | Case 1: RK: 15.2; LK: 16.2                               |                  |               |                          |              |          |

Abbreviations: RK: Right Kidney; LK: Left Kidney; MRI: Magnetic Resonance Image; MCT: Multislice Computed Tomography; BUN: Blood Urea Nitrogen; HBP: High Blood Pressure; IVU: Excretory urogram; CT: Computed Tomography; NR: Not reported; ND: Not Done; CALLA: Common Acute Lymphoblastic Leukemia Antigen.
(Figure 2). The spleen and other abdominal viscera had no alterations.

Bone marrow aspirate showed 88% cellularity with 84% lymphoblasts. The immunotyping was compatible with precursor B-cell acute lymphoblastic leukemia (CD19+, CD10+, CD34+, weak CD45+, CD20+/− (50%), weak CD38+, cyIgM-, cyMPO-, CD81+, CD123+). The cytogenetic analysis was normal, and the cerebrospinal fluid cytology was negative. A renal biopsy was not performed because the suspicion of acute leukemia was confirmed by the findings in peripheral blood and bone marrow.

In the first three days of hospitalization, blood pressure continued to be above the 99th percentile+5 mmHg for age, height and sex in more than 50% of measurements without treatment with corticoids. There was no documented target organ damage (heart, retina or kidney). Treatment with amlodipine was started at 0.3 mg/kg/d with adequate response.

On the third day of hospitalization, the patient started chemotherapy for intermediate-risk ALL according to ALLIC (Acute Lymphoblastic Leukemia Intercontinental) 2009 protocol (prednisolone, vincristine, daunorubicin and L-asparaginase) and received intrathecal methotrexate. The patient presented a good hematological response in peripheral blood and bone marrow on the eighth and fifteenth day, respectively.

Kidney function was normal during the entire treatment. At the end of the induction phase of chemotherapy, a second abdominal ultrasound was performed. The size of the liver returned to its normal range and there was a decrease in the size of both kidneys.

Discussion

Acute leukemia is the most common type of cancer in pediatric patients. In the United States, between 2,500 to 3,500 new cases of ALL in children are diagnosed every year, with an incidence of 3.4 cases per 100,000.1

In a meta-analysis with 33 studies and 3,084 children with leukemia, the most commonly associated signs and symptoms reported were: hepatomegaly (64%), splenomegaly (61%), pallor (54%), fever (53%), bruising (52%), recurrent infections (49%), fatigue (46%), back pain (43%), hepatosplenomegaly (42%), lymphadenopathy (41%), bleeding tendency (38%) and rash (35%). Usually, ALL affects the bone marrow, but extramedullary involvement in liver, spleen or lymph nodes is also observed.8,10
The frequency of nephromegaly in ALL patients is variable; they have been reported to be between 2% and 24%. Two etiologies of nephromegaly have been described: the first one is renal infiltration, which is more frequent in advanced stages of the disease, and it has been found in up to 50% of autopsies in pediatric patients. The second is hypertrophy or hyperplasia of parenchymal cells.

Renal infiltration can be diffus or nodular. In most cases, it only involves the cortex and is symmetrical and bilateral. In pediatric patients, diffuse infiltration is more frequent. When renal infiltration occurs, it can be associated with the involvement of other organs such as the central nervous system, testicles and skin.

Kidney infiltration in ALL is almost always asymptomatic and detected by the presence of a palpable abdominal mass. Abdominal ultrasound, computerized tomography scan, and nuclear magnetic resonance (MRI) and intravenous pyelography can all be used for diagnosis.

In renal ultrasound, leukemic infiltration may be suspected by the presence of enlarged kidneys with a hyperechogenic pattern or by the presence of hypoechochogenic nodular lesions in the kidney cortex. Loss of corticomedullary differentiation and other abnormalities such as cystic or pylocical dilatation are also observed.

Unlike patients with lymphoma, children with leukemia generally do not require imaging tests such as routine CT or MRI at diagnosis or follow-up. In leukemia cases, the findings in peripheral blood, bone marrow, and cerebrospinal fluid, are almost always sufficient. Tests such as CT or MRI are performed when a diagnosis of related diseases or other complications is required. Therefore, it is difficult to establish the exact incidence of renal manifestations due to leukemia based on imaging tests.

Differential diagnoses of described changes on radiographic images include infection, lymphoma, nephroblastomatosis, cysts, angiomyolipoma or metastasis, polycystic kidney disease, renal vein thrombosis, renal diseases with organized deposits, duplication of the pelvic system, glycogen deposition diseases, Beckwith-Wiedemann syndrome and renal tumors, among others.

In most cases reported, after the start of ALL treatment, there is an improvement in renal size, even after the first cycle of chemotherapy. Therefore, if abnormalities on radiographic images persist, a renal histopathological study may be considered.

The impact of renal leukemia infiltration on the prognosis and survival of children with ALL is uncertain. The few studies that analyze the burden of kidney infiltration on prognosis of ALL are contradictory.

Kidney injury and HBP rarely occur in patients with ALL. Table 1 summarizes some pediatric cases reported in the literature with nephromegaly and other types of kidney compromise as primary manifestations of ALL.

HBP is usually moderate and transient, and no pharmacological treatment was required to control it in any of the reported cases. Hypertension in a patient with leukemia almost always occurs in the course of the disease. It is associated with treatment, especially long-time steroid usage, acute kidney injury and narrowing or occlusion of intrarenal arteries or leukemic infiltration. Proteinuria, hematuria or leukocyturia at diagnosis of ALL are exceptional.

Unlike the observations in most previous reports, in this case, hypertension occurred at the onset of the disease, required pharmacological treatment and was not associated with other comorbidities such as renal failure, hematuria, proteinuria, hyperuricemia, hypervolemia or other causes of secondary hypertension. This suggests that leukemic infiltration is not only the cause of hypertension but also the etiology of renal enlargement.

In the present case report, we hypothesize that hypertension may be related to nephromegaly. This hypothesis is supported by the improvement of HBP after the chemotherapy treatment, which allows the decrease of the dose of antihypertensive medications; the absence of white organ involvement, (which suggests a HBP of short evolution); the absence of risk factors for essential hypertension and the absence of secondary causes.

Conclusions

Nephromegaly and HBP are rare manifestations of early stages of ALL in pediatric patients. The present case report describes this unusual combination and recommends clinicians to consider malignancy as its causal factor, especially if these symptoms are accompanied by other suggestive extrarenal manifestations.

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