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 review 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).[7] 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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Table 1. Summary of previous cases reported.

Author (ref) / year	No	G	Age (yrs)	Kidney size (longitudinal and transverse diameters, cm)	Other kidney compromise	Diagnostic Imaging	Kidney biopsy	Other organs involvement	Nephromegaly remission	Outcomes
Arora (19) / 2019	1	M	2	RK: 11×5.2 LK: 12.3×6.1		USG: bilaterally enlarged kidneys and prominence of bilateral pelvicalyceal system Abdomen CT: bilateral enlarged kidney and mild compression of bilateral pelvicalyceal system	ND	NR	Complete remission on USG of nephromegaly after 1 month of treatment	NR
Sherief (8) / 2015	2	F	Case 1: 4 Case 2: 1.1	Case 1: RK: 8.5×3.5; LK: 7.8×3.1 Case 2: RK: 12.3×5.5; LK: 12.2×5.7	Case 2: acute kidney injury	Case 1: USG: bilateral renal enlargement with hyperechogenic pattern and poor corticomedullary differentiation. MRI: bilateral symmetrical homogenous enlarged kidneys and poor corticomedullary differentiation Case 2: USG: markedly enlarged kidneys with mild increased renal parenchymal echogenicity. MCT: bilateral diffuse renal enlargements with significantly thickened renal capsule with dilated both pelvicalyceal systems	ND	Case 1: lymphadenopathy Case 2: CNS infiltration	Case 1: complete remission on ultrasonography of nephromegaly at the end of induction Case 2: marked reduction of kidney size at day 28	Case 1: CNS relapsed 11 months after the end of therapy Case 2: died from sepsis in consolidation phase of therapy
Erdem (13) / 2011	1	F	5	RK: 10×4.3 LK: 11.1×4.5	Urinary tract infection	USG: bilateral renal enlargement	Diffuse interstitial high grade hematolymphoid malignant infiltration	NR	Renal size normalized within 8 weeks of therapy	Remission after two years of treatment
Mantan (11) / 2010	1	F	0.7	RK: 10.7×5.0 LK: 10.2×5.5	NR	USG: bilateral renal enlargement, multiple dilated tubular structures in cortex and medulla. Abdomen CT: enlarged smooth kidneys	NR	Splenomegaly, CNS compromise	Renal size normalized at palpation after first week of therapy	Deceased after 2 weeks of chemotherapy due to febrile neutropenia
Aguayo (10) / 2009	1	M	1.3	RK: 14 LK: 11	NR	USG: bilateral renal enlargement with mild hydronephrosis in right kidney and left kidney with mild pelviectasis. Abdomen CT: massive bilateral nephromegaly	CALLA-negative, pre-B cell lineage acute lymphoblastic leukemia	NR	NR	NR
Cho (20) / 2008	1	M	18	RK: 13.1 LK: 13.4	Kidney failure and severe metabolic acidosis	Abdomen CT: diffuse enlargement of both kidneys	NR	NR	Renal size normalized in abdominal CT within 8 weeks of therapy	6 months after the diagnosis, patient went to an allogeneic peripheral blood stem cell transplant with persistent and complete remission for 9 months after.
Ali (8) / 2008	1	M	6	Both kidneys: 15	Acute kidney injury	USG: bilaterally enlarged kidneys with hyperechoic pattern and loss of corticomedullary differentiation. MRI: bilaterally enlarged kidneys and loss of corticomedullary differentiation	NR	Lymphadenopathy	Renal size normalized in abdominal ultrasound after the completion of induction chemotherapy	NR
Martins (2) / 2008	1	F	0.4	RK: 8.6×4.1 LK: 8.7×4.4	NR	USG: bilaterally enlarged kidneys with hyperechoic pattern. Abdomen CT: bilaterally enlarged kidneys.	NR	NR	Renal size normalized	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)	Other kidney compromise	Diagnostic Imaging	Kidney biopsy	Other organs involvement	Nephromegaly remission	Outcomes
Pradeep (4) / 2008	1	M	7	RK: 15.1×6.3 LK: 14.4×5.3	HBP	USG: bilaterally enlarged kidneys with solid diffuse relatively hyperechoic texture of both kidneys. Abdomen CT: moderate bilateral renal enlargement; altered homogenously hypodense, diffuse, renal parenchymal changes involving the entire cortex	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	Acute kidney injury	USG: bilateral non-obstructive nephromegaly with hyperechogenic parenchyma. of interstitial tissue by MRI: bilateral nephromegaly	Extensive infiltration small round cells surrounding relatively well-preserved renal structures. Immunoperoxidase studies were compatible with pre-B proliferation	NR 1st month of therapy, plasma creatinine values, kidney dimensions, and parenchymal features became normal	At the end of the	NR
Gupta (21) / 1985	3	M	Case 1: 2 Case 2: 1	NR	Case 2: acute kidney injury the infundibula and the pelvis	Case 1: IVU: marked symmetrical enlargement of both kidneys with considerable stretching of the calyces, Case 2: massive lymphoblastic infiltration Case 2: IVU: marked bilateral renal enlargement with stretching of the calyces, the infundibula and the pelvis. Renal angiogram: no suggestion of a tumor, but both kidneys showed marked enlargement with stretching of the intra-renal arteries.	Postmortem examination Case 1: vacuolization of the convoluted tubules but no leukemic infiltration	Case 1: lymphadenopathy Case 2: lymphadenopathy, CNS compromise	NR	Case 1: deceased of intractable diarrhea Case 2: deceased
Gilboa (12) / 1983	4	M	Case 1: 8 Case 2: 12 Case 3: 5 Case 4: 12	Case 1: RK: 15.2; LK: 16.2 Case 2: RK: 15.8; LK: 14.8 Case 3: RK: 20; LK: 20	Case 1: acute kidney injury, HBP Case 2: acute kidney injury Case 3: acute kidney injury Case 4: microscopic hematuria and splenomegaly	Case 1: IVU: bilateral enlargement of the kidneys with impaired contrast medium excretion and bilateral pelviocaliceal deformity without hydronephrosis. Selective renal arteriography: marked stretching and separation of the segmental arteries and occlusion of the lobar branches Case 2: IVU: bilaterally enlarged kidneys with poor contrast medium excretion Case 3: IVU and USG: Grossly enlarged kidneys without evidence of obstruction in the urinary tract. CT of abdomen: massive enlargement of the kidney but no retroperitoneal masses Case 4: IVU: kidneys with normal collecting system, size and configuration	Case 1: severe infiltration of the interstitium and of some glomeruli with lymphoblastic cells. Case 2: severe lymphoblastic infiltration of the interstitium, with focal tubular compression Case 3: severe lymphoblastic infiltration of the interstitium Case 4: focal interstitial mononuclear infiltration with mild increase in mesangial cellularity	Case 1: arthralgia Case 2: hepatosplenomegaly and lymphadenopathy Case 3: NR Case 4: lymphadenopathy	Case 1: NR Case 2: renal size normalized one month later Case 3: renal size normalized after the treatment Case 4: NR	Case1: deceased 8 months after diagnosis with lymphomatous involvement of the CNS Case 2: NR Case 3: died of widespread malignancy 15 months after the initial presentation Case 4: died 2 months after the initial presentation

Abbreviations: RK: Right Kidney; LK: Left Kidney; MRI: Magnetic Resonance Image; MCT: Multislice Computed Tomography; CNS: Central Nervous System; HBP: High Blood Pressure; IVU: Excretory urogram; CT: Computed Tomography; NR: Not reported; ND: Not Done: CALLA: Common Acute Lymphoblastic Leukemia Antigen.

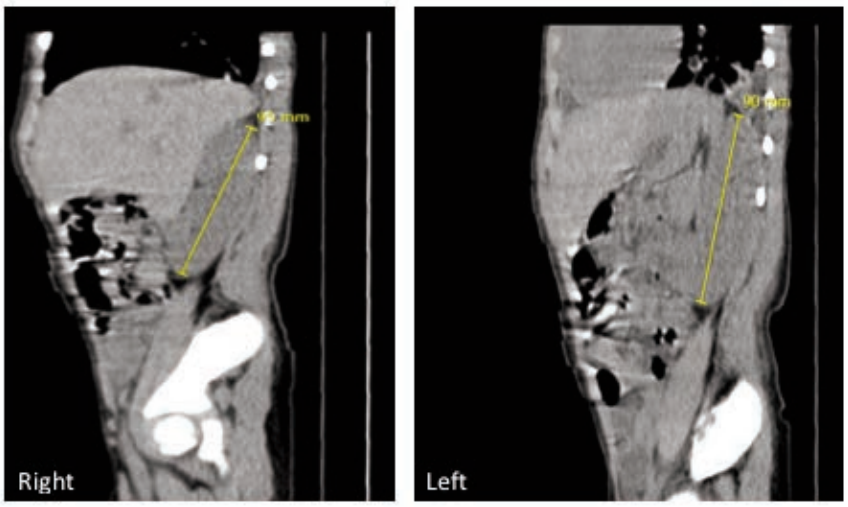
(Figure 2). The spleen and other abdominal viscera had no alterations.

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.[6,7] 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 in 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.



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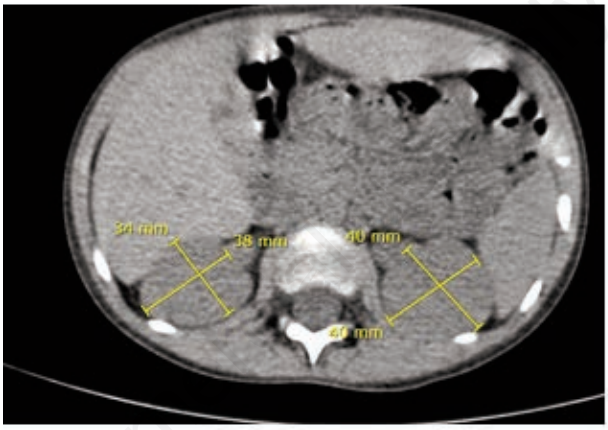

Figure 1. Computed tomography of the abdomen. Panel A: right and left kidney longitudinal diameters - Panel B: transversal diameters.

Discussion

Acute leukemia is the most common type of cancer in pediatric patients.[8] 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%).[9] Usually, ALL affects the bone marrow, but extramedullary involvement in liver, spleen or lymph nodes is also observed.[8,10]

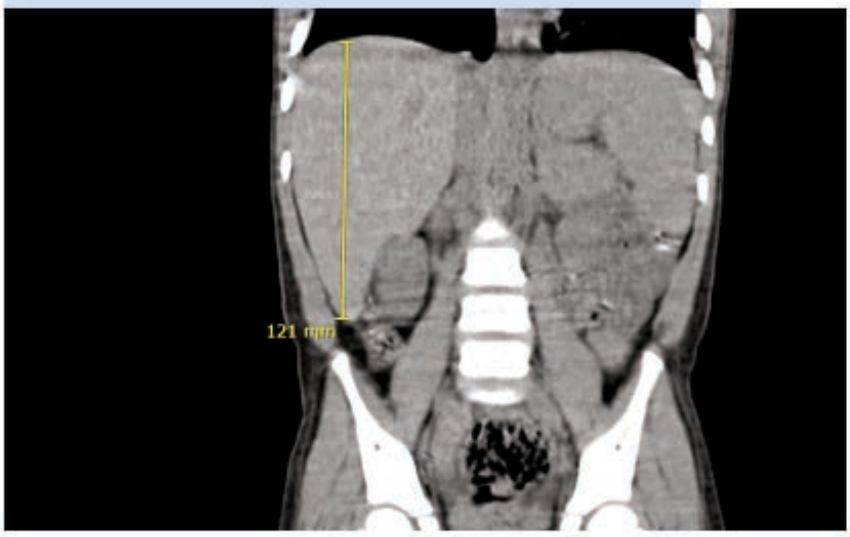

Figure 2. Computed tomography of the abdomen. Liver longitudinal diameter.

The frequency of nephromegaly in ALL patients is variable; they have been reported to be between 2% and 24%.[3,8,11,12] Two etiologies of nephromegaly have been described: the first one is renal infiltration, which is more frequent in advanced stages of the disease,[5,8,13] and it has been found in up to 50% of autopsies in pediatric patients.[14] The second is hypertrophy or hyperplasia of parenchymal cells.[3,4]

Renal infiltration can be diffuse or nodular. In most cases, it only involves the cortex and is symmetrical and bilateral.[4,11,13,15] In pediatric patients, diffuse infiltration is more frequent.[12,13,16] When renal infiltration occurs, it can be associated with the involvement of other organs such as the central nervous system, testicles and skin.[11]

Kidney infiltration in ALL is almost always asymptomatic and detected by the presence of a palpable abdominal mass.[2,4,11,16] Abdominal ultrasound,[2] computerized axial tomography scan,[5,17] nuclear magnetic resonance (MRI) and,[8] intravenous pyelography can all be used for diagnosis.[3,12,18]

In renal ultrasound, leukemic infiltration may be suspected by the presence of enlarged kidneys with a hyperechogenic pattern,[2,5,8,16] or by the presence of hypoechogenic nodular lesions in the kidney cortex,[11] loss of corticomedullary differentiation and other abnormalities such as cystic or pyelocaliceal dilatation.[8]

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.[15]

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.[2,10,13,15]

In most cases reported, after the start of ALL treatment, there is an improvement in renal size, even after the first cycle of chemotherapy.[8,11,13] Therefore, if abnormalities on radiographic images persist, a renal histopathological study may be considered.

The impact of renal leukemic 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.[10,13,17,18]

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,[2] acute kidney injury and narrowness or occlusion of intrarenal arteries or leukemic infiltration.[12] Proteinuria, hematuria or leukocyturia at diagnosis of ALL are exceptional.[12]

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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