

Urolithiasis in Children with Acute Lymphoblastic Leukemia

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Abstract: *Background:* Urinary tract lithiasis(UTL) requires careful intervention, especially when associated with other diseases. The purpose of this study was to assess the outcome of symptomatic UTL in children with acute lymphoblastic leukemia (ALL) and to evaluate its correlation with the anti-neoplastic treatment phase and drugs, and to assess the need for intervention, results, complications and follow-up.

Procedure: The charts of 350 patients with ALL (1990-2008) were retrospectively evaluated. Signs and symptoms, methods of diagnosis, complications, treatment approach, resolution, anti-leukemic treatment phase when the UTL was diagnosed, drugs used and interference on ALL treatment were recorded.

Results: A total of 12/350 patients (3.4%) had UTL (14 stones). The median age was 7.6 years. Pain was present in 60%, hematuria in 20% and both in 20%. The median stone size was 4mm (3- 13.8mm). Three patients required hospitalization (pain) and one had chemotherapy discontinued due to severe hematuria and blood support. At the time of diagnosis of UTL, four patients were in the induction phase with corticosteroids, four were in the maintenance phase with corticosteroids, two were in the maintenance phase without corticosteroids, and one had a recurrence after therapy, and two were off-therapy. 11/13 episodes of UTL had spontaneous resolution, two underwent successful extracorporeal shockwave lithotripsy, and one patient remains with an asymptomatic stone.

Conclusions: 3.4% of children with ALL presented symptomatic UTL. While the majority of cases have been resolved spontaneously, hospitalization and delay in chemotherapy have increased morbidity in these children.

Keywords: Acute lymphoblastic leukemia, children, glucocorticoids, stone, urolithiasis.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a malignancy that affects 1:25,000 children under 15 years of age per year, and it is the second most common cancer in childhood [1, 2]. In southern Brazil, ALL had an incidence of 22.59 cases per million inhabitants less than 15 years of age from 1991 to 1995 [3]. It is a highly curable disease, reaching 80% of survival in our days[1, 4-7]. Corticosteroids are essential in the treatment of these children, but their short and long-term side effects are of concern, mainly hypercalciuria and bone demineralization and urinary tract lithiasis [4, 8-15].

Urinary lithiasis is presented by 15% of the general population, and 2 to 3% are represented by children [16-18], i.e., an incidence of approximately 0.3 to 0.45%. In the United States an incidence of 1 in 1,000 to 1 in 7,600 pediatric hospital admissions has been reported [19-22]. In Germany, the prevalence of urinary tract lithiasis was 0.6% among people less than 20 years of age [23].

With the survival improvement of children treated for ALL, concerns about reducing the complications of its treatment are prevalent. However, few studies have been conducted to date reporting the incidence of urolithiasis in children treated for ALL. Howard *et al.* found the presence of renal lithiasis in 0.9% of their pediatric patients with ALL [14].

The type of corticosteroid used (prednisone or dexamethasone), and the dose and duration of treatment have been studied due to the increased incidence of osteoporosis in this population. It is possible that bone demineralization induced by the use of steroids causes hypercalcemia by increasing the urinary calcium excretion with a consequent risk of urolithiasis [13, 24-27].

In this study, we evaluated the occurrence of urolithiasis in children with ALL in our center, the characteristics of the clinical presentation of stones (signs and symptoms), complications, the need for interventional treatment, morbidity, and whether there is relationship between the phase of treatment and the drug schedule in the development of urinary lithiasis.

PATIENTS AND METHODS

This is a retrospective study involving the charts of 350 children with ALL, who were admitted from 1990 to

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2008 to the pediatric hematology/oncology and urologic clinics of the University of Sao Paulo in order to disclose those with symptomatic urinary lithiasis and who had undergone treatment for ALL. The incidence of urolithiasis in this population was evaluated as were the characteristics of the clinical presentation, complementary methods used to diagnosis lithiasis, the need for interventional treatment, and the occurrence of complications due to the stone or the treatment. The Mann-Whitney test was used to compare both groups (patients with ALL and urinary lithiasis versus patients with ALL without urinary tract lithiasis) in relation to age, sex, chemotherapy schedule, and ALL risk classification. Significance was established by $p < 0.05$. We assessed the influence of initial leukocyte count, age group (0-10 and more than 10 years) and the use of corticosteroids during maintenance therapy in the development of urinary lithiasis (χ^2 test).

RESULTS

Urolithiasis was found in 12 of 350 patients (3.4%), with a total of 14 stones (one patient had 2 stones and one patient had a recurrence). Six patients were male, 11 were white and 1 was Afro-American. The median age of the diagnosis of ALL was 7.6 years (range 28 months to 18 years) in the group with urinary lithiasis, compared with 5.2 years (range 2 months to 19.6 years) in the group without lithiasis. There were no significant differences in the distribution of sex, treatment or leukemia risk category (standard or high risk) between both groups. Pain was present in 60% of cases, hematuria in 20% of cases and both in 20%.

Ultrasonography was able to make the diagnosis in twelve of the thirteen episodes of stones, and one case required a computed tomography scan. The size of the stones ranged between 3 and 13.8mm (median 4 mm).

Table 1: Clinical Characteristics, Treatment and Follow Up of Children with Acute Lymphoblastic Leukemia and Urolithiasis

Patient	sex	Age at ALL diagnosis (mo)	Age at lithiasis diagnosis (mo)	Phase of ALL treatment	N Stones (size mm)	Metabolic disturbances	Lithiasis resolution	outcome	morbidity
1	M	168	211	Maintenance without corticoid	1 (5mm)	No	SWL	Stone free	Lithiasis relapse after 9 mo
2	F	68	72	Maintenance without corticoid	1 (3mm)	No	Spontaneous elimination	Stone free	Hospitalization Blood transfusion
3	F	138	236	Off therapy	1 (13 mm)	No	SWL	Stone free	-
4	M	43	58	Maintenance with corticoid	2 (9 and 6 mm)	No	Litocit Spontaneous elimination	Stone free	-
5	F	28	61	Maintenance with corticoid	1 (3mm)	No	Spontaneous elimination	Stone free	hospitalization
6	M	34	34	Induction	1 (13.8mm)	Hyperuricemia	Spontaneous elimination	Stone free	hospitalization
7	F	185	185	Induction	1 (3mm)	Hyperuricemia, hypocalcemia	Spontaneous elimination	Stone free	Hospitalization Chemotherapy delay
8	M	210	238	Maintenance with corticoid	1 (3mm)	Hypocitratemia, osteoporosis	Spontaneous elimination	Stone free	hospitalization
9	F	56	181	Off therapy	1 (2mm)	No	Spontaneous elimination	Stone free	hospitalization
10	M	171	172	Induction	1 (5mm)	hypocalcemia	Spontaneous elimination	Stone free	hospitalization
11	M	54	64	Maintenance with corticoid	1 (3mm)	No	Observation	1 residual stone <3mm	-
12	F	114	115	Induction	1 (5mm)	No	Spontaneous elimination	Stone free	hospitalization

Three patients required hospitalization for symptom relief. Among the 14 stones, 11 were spontaneously eliminated, and 2 patients required an interventional procedure to successful elimination of the stone (e.g., extracorporeal shockwave lithotripsy). One patient remains with a 3- mm asymptomatic stone. In one patient, it was necessary to withdraw chemotherapy due to stone treatment.

Four patients presented with urolithiasis during the induction phase of ALL treatment, which included corticosteroids, four were in the maintenance phase with corticosteroids, two were in the maintenance phase without corticosteroids and two had finished therapy (Table 1). Currently, all patients remain in complete remission of ALL, and none of the patients died. Only one patient had a recurrence of lithiasis at nine months after the initial event, when he was out of treatment.

No individual or familiar risk factors for urolithiasis were detected in any patient.

There were no statistically significant differences between the groups of patients with ALL with and without urinary lithiasis regarding age ($p = 0.088$), age group (from 0-120 months and 121 months or more: $p = 0.142$), gender ($p = 1.000$), race ($p = 0.845$), ALL risk category ($p = 0.767$) and ALL treatment protocol ($p = 0.253$) or between the use of corticosteroids in the maintenance phase and occurrence of urinary lithiasis ($p = 0.724$). We detected a statistically significant association between leukocyte count at the time of diagnosis of ALL and the occurrence of urinary lithiasis ($p = 0.041$), where 4.7% of patients with up to 50,000 leukocytes/mm³ developed urinary lithiasis compared to 0% of patients with more than 50,000 leukocytes/mm³.

DISCUSSION

In 2007, in our general pediatrics center, we found a frequency of 0.08% for urinary lithiasis considering all queries. On the pediatric nephrology and pediatric urology services, the frequency was 0.8%. The frequency of symptomatic UTL found in this study was 3.4% in the pediatric hematology/oncology department, showing a higher occurrence in children with ALL compared with data on general admissions (non published data). Considering that in the general population, 15% of people are affected by stones and that 2 to 3% of cases are represented by children (about 0.3%) [9, 16-18], we can say that the rate of

3.4% for lithiasis in children with ALL is higher than that in the general pediatric population. Moreover, this frequency was almost four times higher than the incidence of 0.9% found in a similar study conducted in the United States [14].

It was not possible to determine if some of the patients already had stones at the time of diagnosis of ALL because this was a retrospective study, and we do not routinely perform abdominal ultrasound as a work up for children with ALL if they are asymptomatic. We were thus restrained to the observation of the two diseases occurring concurrently. There were no statistically significant differences between the groups of patients with ALL with and without urinary lithiasis regarding age ($p = 0.088$), age group (from 0-120 months and 121 months or more - $p = 0.142$), gender ($p = 1.000$), race ($p = 0.845$), ALL risk category ($p = 0.767$) and ALL treatment protocol ($p = 0.253$).

There was also no statistically significant association between the use of corticosteroids in the maintenance phase and the occurrence of urinary lithiasis ($p = 0.724$), unlike the finding in a similar study conducted in the United States [14]. We have to take on the possibility of type II error in the detection of the relationship between the use of corticosteroids and the stone occurrence because of the small number of patients.

The median leukocyte count at the time of diagnosis of ALL was 8,140/mm³ for the group with lithiasis and 15,550/mm³ for the remaining group, which was not statistically different ($p=0.077$). However, we found a statistically significant association between the leukocyte count at the time of diagnosis of ALL and the occurrence of urinary lithiasis ($p = 0.041$), where 4.7% of patients with up to 50,000 leukocytes/mm³ developed urinary lithiasis compared to 0% of patients with leukocyte count over 50,000 leukocytes/mm³, and this is probably a bias due to the small number of patients with UTL.

In our study, pain, both abdominal and flank, was present in 80% of patients, and hematuria was found in 40%. There was no reported case of concomitant urinary infection (all urine cultures were negative), but one patient had fever as one of the symptoms. In the general pediatric population, hematuria is found in 33 to 90% of children of all ages with urinary lithiasis [10]: 94% of adolescents and 56% of children 0 to 5 years have lumbar pain. Urinary tract infection is a frequent presentation in preschool-aged children [28].

Hospitalization was required in 25% of patients due to a stone, and one of them (8.3%) had his ALL treatment interrupted due to intense pain and hematuria, requiring blood transfusion and special care. Only two patients needed interventional approach, and, in all cases, extracorporeal shockwave lithotripsy (ESWL) was successful. Generally, the indication for ESWL in children is for stones measuring 5 mm or more [18], and 6 patients fulfilled this criterion. However, the risk-benefit was taken into account, and ESWL was not considered due severe leukopenia and thrombocytopenia. In those patients, spontaneous stone elimination occurred with exclusive clinical support. Two patients received SWL. No more serious complications were observed, and all patients are alive.

Only one patient (8.3%) had a stone recurrence with spontaneous resolution. Studies in the last century have found a recurrence rate of 16% in the general pediatric population within nine years after the initial episode and, ranging from 3.7 to 67% [12, 28], and children with ALL and urinary lithiasis presented a 35% rate of recurrence [14].

Because we observed an increased occurrence of calculi in children with ALL in our center and this situation can lead to comorbidities and even a delay in anti-neoplastic treatment, some measures can be taken to screen for and prevent stones [29]. These include high hydric ingestion, sodium restriction and patient metabolic profile. Periodic routine abdominal ultrasonography for the search of UTL in children with ALL is justified only in a prospective study with the goal of early stone detection and precocious interventions, and minimizing complications, such as pain, bleeding, admission and ALL treatment interruption.

Moreover, it is important to counsel the patient's family about the importance of the early detection of stones and the most common symptoms of presentation. In case of the spontaneous elimination of a stone, it must be collected and taken for laboratory analysis to determine its composition.

One criticism of our study was the lack of access to stones and their analysis, because patients did not keep them. Inaccessibility to stones hinders the determination of a cause for the stone formation in the analyzed population.

Although the composition of the stone can also be suspected by helical computed tomography without

contrast, and the differentiation of stones of calcium compounds or not through Hounsfield unit patterns, this method has the disadvantage of exposing children to high doses of radiation.

Laboratory analysis of samples of blood and urine is important to determine factors predisposing to the formation of calculi and may be used in routine clinical evaluation of the treatment of ALL in children to minimize the formation of new stones by monitoring blood and urinary calcium, uric acid, citrate, phosphate, oxalate and urinary culture and periodic ultrasonography [30].

CONCLUSION

In our experience, children with ALL undergoing to chemotherapy have a high chance of developing urolithiasis, with an occurrence of 3.4%. While the majority of cases had spontaneous resolution, hospitalization and a delay in chemotherapy increased the morbidity in the children and two patients required interventional treatment (extracorporeal shockwave lithotripsy). These study data suggest the need to search for and prevent urolithiasis in our children with ALL.

GRANT

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