

Clinical and ultrasonographic findings associated with testicular infiltration in pediatric patients with leukemia

Hallazgos clínicos y sonográficos asociados a infiltración testicular en pacientes pediátricos con leucemia

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Abstract

Background: Testicular infiltration is infrequent in pediatric patients with leukemia and can be confused with other testicular conditions. **Objective:** To analyze the presence of clinical and radiological features suggestive of testicular disease and its histological association with leukemia infiltration. **Method:** Retrospective and analytical observational study that included patients with diagnosis of leukemia who underwent biopsy for suspected testicular infiltration. The relationship with the variables analyzed were diagnosis, reason for taking the biopsy, ultrasound findings, stage of treatment, induration, increased volume and pain, with testicular infiltration. **Results:** Eighteen patients were included; 11 of them with microlithiasis, of which one reported infiltration (odds ratio: 0.075; $p = 0.026$), no association was found between ultrasound findings and the presence of infiltration. Clinical findings were significantly associated with positive biopsies. **Conclusions:** No risk association was found with the ultrasound findings such as microlithiasis and hypoechoic imaging. The clinically evident testicular disease (testicular enlargement and testicular induration) has a significant statistic association with the presence of leukemia infiltration.

Keywords: Leukemia. Testicular involvement. Overt testicular disease. Microlithiasis. Testicular biopsy.

Resumen

Antecedentes: La infiltración testicular en pacientes pediátricos con leucemia es infrecuente y puede ser confundida con otros padecimientos testiculares. **Objetivo:** Analizar la presencia de características clínicas y radiológicas sugestivas de enfermedad testicular y su asociación histológica con infiltración por leucemia. **Método:** Estudio observacional retrospectivo y analítico que incluyó a los pacientes con diagnóstico de leucemia sometidos a biopsia por sospecha de infiltración testicular. Se analizó la relación con las variables diagnóstico de base, motivo de toma de biopsia, hallazgos ultrasonográficos, etapa del tratamiento, induración, aumento de volumen y dolor, con infiltración a testículo. **Resultados:** Se incluyeron 18 pacientes; de ellos, 11 con microlitiasis, de los cuales solo uno reportado con infiltración (odds ratio: 0.075; $p = 0.026$). No se encontró una asociación entre los hallazgos ultrasonográficos y la presencia de infiltración. Los hallazgos clínicos se asociaron significativamente con biopsias positivas. **Conclusiones:** No se encontró una asociación de riesgo con los hallazgos por ultrasonido, como microlitiasis e imágenes hipocogénicas. La enfermedad testicular clínicamente evidente (incremento de volumen e induración testicular) tiene una asociación estadísticamente significativa con la presencia de infiltración por leucemia.

Palabras clave: Leucemia. Infiltración testicular. Enfermedad clínicamente evidente. Microlitiasis. Biopsia de testículo.

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Introduction

Acute lymphoblastic leukemia¹ is the most common oncological disease in childhood, accounting for approximately 30% of cancer cases in children. In recent decades, the survival of patients with leukemia has improved dramatically, with cure rates exceeding 80%¹. Despite the improvement in outcomes with treatment, leukemia relapse continues to be a problem. Depending on the site and timing of the relapse, the treatment may have better or worse outcomes. In the case of relapses associated with the central nervous system or the testicle, the prognosis is better than when relapse occurs in the bone marrow², being the latter the most frequent.

Traditionally, the testicle has been considered a "sanctuary" organ due to its blood-testis barrier, which causes poor penetration of drugs³. In testicular relapse, the disease is usually localized in the interstitial spaces, while in advanced cases, infiltration may involve the seminiferous tubules³. The pathophysiology of testicular infiltration is controversial; it is currently believed that various testicular factors may control the penetration and proliferation of lymphoblasts, which, combined with the poor penetration of cytotoxic drugs, could lead to the persistence of latent cells that would cause relapse⁴.

Clinically demonstrable testicular disease usually manifests as painless testicular enlargement, which is rare at diagnosis and occurs in 2% of cases, while hidden infiltration can be diagnosed by biopsy in up to 25% of new diagnoses^{5,6}. However, due to significant rates of false negatives, routine testicular biopsy during induction, maintenance, or at the end of treatment is not recommended⁷.

In an attempt to reduce the number of false negatives and the number of unnecessary biopsies, hidden testicular infiltration has been attempted to be diagnosed by imaging modalities, such as ultrasound, which has not achieved evidence of adequate diagnostic sensitivity⁸, largely because ultrasound findings are nonspecific, reporting increased volume, focal or diffuse hypoechoic lesions that can be homogeneous, and even an appearance similar to primary testicular neoplasms, orchitis, testicular torsion, or other infiltrative disorders, such as lymphoma or sarcoidosis⁹. In a study conducted in Mexico, Dorbeker-Azcona et al.¹⁰ highlight a poor correlation of positive ultrasounds for infiltration with the results found in fine-needle aspiration biopsy.

Next, we analyze the presence of clinical characteristics and ultrasonographic findings commonly considered suggestive of testicular disease and their association with histological reports of leukemia infiltration obtained by incisional biopsies.

Method

This is an observational, retrospective, descriptive, and analytical study, with a case-control design, which included patients diagnosed with acute lymphoblastic or myeloblastic leukemia who underwent testicular biopsy to rule out infiltration. The clinical records of all testicular biopsies performed at our hospital between June 2015 and March 2021 were obtained, and patients diagnosed with acute lymphoblastic leukemia were included. The baseline diagnostic variables, reason for biopsy, ultrasonographic findings, and stage of treatment were descriptively analyzed, and a case-control analysis was performed, defining cases as patients who presented leukemic infiltration in the testicular parenchyma and controls as those whose biopsy yielded a negative result. Each of the following variables was considered as exposure factors: presence of testicular microlithiasis, testicular enlargement, induration, and testicular pain; and their association with a positive histological result for leukemia infiltration was assessed. IBM SPSS Statistics 25 was used as a statistical tool.

Results

A total of 21 patients were obtained, 18 of whom were included and 2 were excluded (due to incomplete medical records and a history of testicular neoplasm). Fourteen out of the total included (77.6%) were T-cell acute lymphoblastic leukemias, 1 (5.6%) was a biphenotypic acute lymphoblastic leukemia, 1 (5.6%) a B-cell acute lymphoblastic leukemia, 1 (5.6%) was an acute myeloid leukemia M4, and 1 (5.6%) an acute myeloid leukemia M3 (Fig. 1). Twelve (66%) were in the induction phase, 3 (16.7%) in the maintenance phase, and 3 (16.7%) were being monitored (Fig. 2). The reasons for requesting a biopsy were: testicular enlargement in 1 (5.6%), testicular pain in 2 (11.1%), testicular induration in 1 (5.6%), ultrasound suggestive of infiltration in 6 (33.3%), and isolated microlithiasis by ultrasound in 8 (44.4%) (Fig. 3). In the analytical study of the variables with a case-control model, a total of 11 patients with testicular microlithiasis were

Table 1. Results of the variables with the case-control model

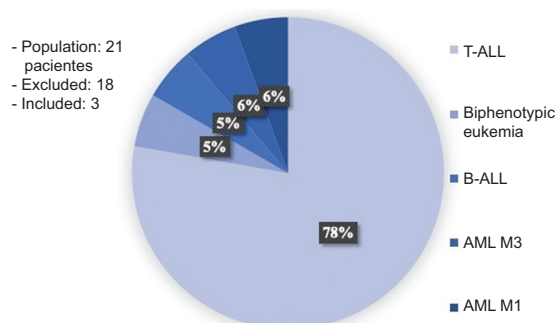
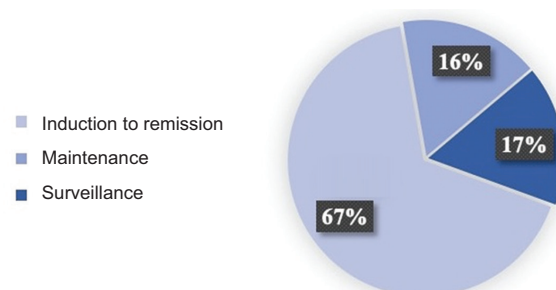
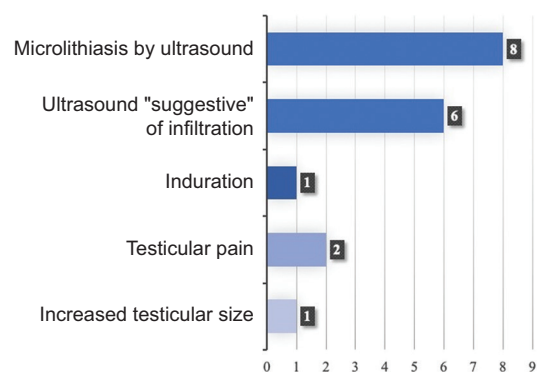
Findings	No. of cases	Cases positive to infiltration	OR	95%CI	p
Pain	2	0	1.45	1.045-2.02	0.32
Increased volume	3	3	7.5	2.06-27.25	0.002
Induration	4	4	14	2.11-92.54	< 0.001
Microlithiasis	11	1	0.075	0.006-0.954	0.026
Hypoechogenic images	8	3	2.4	0.29-19.78	0.41

found, 1 of whom had leukemia infiltration, with an odds ratio (OR) of 0.075 (95% confidence interval [CI]: 0.006-0.954; $\chi^2 = 4.92$; $p = 0.026$). Regarding patients with testicular enlargement ($n = 3$), all had leukemia infiltration (OR, 7.5; CI95%, 2.065-27.25; $\chi^2 = 9.36$; $p = 0.002$). Similar results were found for patients with induration, as none of the 4 with this clinical finding had a negative biopsy (OR, 14.0; CI95%, 2.11-92.5; $\chi^2 = 13.37$; $p < 0.001$). Regarding testicular pain and the presence of hypoechoic images by ultrasound, statistically significant results were not found (Table 1).

Discussion

The specific treatment for managing testicular leukemia has been a matter of discussion in multiple publications. Typically, optimal therapy for relapse in the testicle includes systemic chemotherapy and local radiotherapy with doses of 2400 cGy to both testicles¹¹. With the advent of new treatment regimens in the 1970s, such as the use of high-dose methotrexate, the risk of testicular relapse has significantly decreased, so that with current regimens, the incidence has declined to around 5%^{12,13}. These findings have led us to omit testicular irradiation for patients with testicular leukemia at the diagnosis of the disease who received intensive chemotherapy, provided they lacked evident testicular disease at the end of induction to remission^{6,14}.

We should mention that, currently, the treatment outcomes and prognosis for patients with occult testicular disease, vs those with evident isolated relapse, have been similar, and for this reason, testicular biopsies to document occult disease during the treatment period or at the end of it have fallen into disuse¹⁵.

**Figure 1. Type of leukemia in the studied population.****Figure 2. Treatment phase in the studied population.****Figure 3. Reasons for requesting testicular biopsy.**

In an attempt to reduce testicular biopsies, although the use of imaging modalities has been implemented to establish a correlation with the presence of the disease, the radiological findings that are significantly related to leukemic infiltration in the testicular parenchyma are not well defined, leading many radiologists to issue reports based on their personal experience. Testicular microlithiasis is among the findings commonly associated with malignancy, largely due to its association with germ cell neoplasms^{16,17}, characterized by multiple small echogenic focal lesions < 3 mm in diameter that can be focal or diffuse and are limited to the testicles, generally asymptomatic¹⁸. In our series, we decided to analyze specific findings, whether clinical or radiological, as exposure factors to compare with the results of incisional biopsies, in contrast to what was Dorbeker-Azcona et al.¹⁰ did who compared positive ultrasound findings and patients with clinical suspicion with the presence of infiltration as reported in biopsies. In our study, contrary to what would be expected, an even lower risk of leukemia infiltration was found in patients with microlithiasis (OR, 0.075; 95% CI, 0.006-0.954; $\chi^2 = 4.92$; $p = 0.026$). For those patients in whom ill-defined hypoechoic images were found within the testicular parenchyma, a positive risk association was found, with an OR of 2.4, but without statistical significance (95% CI: 0.29-19.78; $p = 0.41$), probably due to the limited number of patients in this study. Similar to what Klein et al.⁸ reported, adequate sensitivity has not been achieved for the ultrasound diagnosis of testicular leukemia infiltration.

Considering that the diagnosis of occult disease has not shown an improvement in patient survival, this study also analyzed the correlation between the clinical characteristics of evident disease, such as volume increase and induration, finding a strong, statistically significant association with leukemia infiltration (volume increase, OR, 7.5 and $p = 0.002$; induration, OR, 14.0 and $p < 0.001$). Although leukemia infiltration is generally asymptomatic, the relationship between testicular pain and infiltration was analyzed, finding a 2.4 times greater risk (95% CI, 1.045-2.02; $p = 0.32$).

Conclusions

Clinically evident disease with symptoms such as volume increase and induration has a strong, statistically significant association with the presence of

leukemia infiltration. Microlithiasis is not a suggestive finding of leukemia infiltration.

The presence of hypoechoic ultrasound images, as well as testicular pain, appear to have a positive relationship with the presence of leukemia in the testicle; however, more studies are needed to demonstrate this assertion.

Currently, there is no non-invasive diagnostic study for testicular infiltration, possibly due to a lack of studies associating specific imaging findings with this condition.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

References

1. Marwaha R, Trehan A, Bansal D, Kulkarni K. Testicular relapse in childhood acute lymphoblastic leukemia: the challenges and lessons. *Indian J Cancer*. 2010;47:134.
2. Kaplan JA. Leukemia in children. *Pediatr Rev*. 2019;40:319-31.
3. Kuo TT, Tschang TP, Chu JY. Testicular relapse in childhood acute lymphocytic leukemia during bone marrow remission. *Cancer*. 1976;38:2604-12.
4. Banavali S, Shama G, Bhagwat R, Pai S, Kurkure P, Nair C, et al. Isolated testicular relapse in acute lymphoblastic leukemia — effective treatment with the modified CCG-112 protocol. *Indian J Cancer*. 2005;42:65.
5. Kim Tae H, Brynes Russell K, Lui V-S, Hargreaves HK, Hawkins HK, Woodard J, et al. Pretreatment testicular biopsy in childhood acute lymphocytic leukaemia. *Lancet*. 1981;318:657-8.
6. Hijiya N, Liu W, Sandlund JT, Jeha S, Razzouk BI, Ribeiro RC, et al. Overt testicular disease at diagnosis of childhood acute lymphoblastic leukemia: lack of therapeutic role of local irradiation. *Leukemia*. 2005;19:1399-403.
7. Pizzo PA, Poplack DG, Adamson PC, Blaney SM, Helman L. Principles and practice of pediatric oncology. 7th ed. Philadelphia: Wolters Kluwer; 2016. p. 2150-5. Disponible en: <http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=1473212>
8. Klein EA, Kay R, Norris DG, George CR, Richmond B. Noninvasive testicular screening in childhood leukemia. *J Urol*. 1986;136:864-6.
9. Lupetin AR, King W, Rich P, Lederman RB. The ultrasound diagnosis of testicular leukemia. *Ultrasound Med Biol*. 1983;(Suppl 2):423-6.

10. Dorbeker-Azcona R, Cárdenas-Cardos R, Braun-Roth G, Morales-Hernández E. Diagnóstico de infiltración testicular por medio de biopsia por aspiración con aguja fina en pacientes con leucemia aguda. *Gac Mex Oncol.* 2009;8:69-74.
11. Steinfeld AD. Radiation therapy in the treatment of leukemic infiltrates of the testes. *radiology. Radiology.* 1976;120:681-2.
12. Hustu HO, Aur RJA. Extramedullary leukaemia. *Clin Haematol.* 1978;7:313-37.
13. Chessells JM, Veys P, Kempinski H, Henley P, Leiper A, Webb D, et al. Long-term follow-up of relapsed childhood acute lymphoblastic leukaemia. *Br J Haematol.* 2003;123:396-405.
14. Pui C-H. Is testicular irradiation necessary for patients with acute lymphoblastic leukemia and testicular relapse? *Pediatr Blood Cancer.* 2018;65:e26977.
15. Nachman J, Palmer NF, Sather HN, Bleyer WA, Coccia PF, Lukens JN, et al. Open-wedge testicular biopsy in childhood acute lymphoblastic leukemia after two years of maintenance therapy: diagnostic accuracy and influence on outcome — a report from Children's Cancer Study Group. *Blood.* 1990;75:1051-5.
16. Cooper ML, Kaefer M, Fan R, Rink RC, Jennings SG, Karmazyn B. Testicular microlithiasis in children and associated testicular cancer. *Radiology.* 2014;270:857-63.
17. Yee WS, Kim YS, Kim SJ, Choi JB, Kim SI, Ahn HS. Testicular microlithiasis: prevalence and clinical significance in a population referred for scrotal ultrasonography. *Korean J Urol.* 2011;52:172.
18. Yesil S, Tanyildiz HG, Sahin G. How should we monitor boys with testicular microlithiasis? *Pediatr Hematol Oncol.* 2016;33:171-7.