Case Report

Gallbladder Burkitt's Lymphoma in a Child Living with HIV: A Case Report

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Gallbladder Burkitt's Lymphoma in a Child Living with HIV: A Case Report

Nathalia Lopez Duarte [1,2,3,*], Ana Paula Silva Bueno [2,4], Bárbara Sarni Sanches [1,2,5], Gabriella Alves Ramos [2], Layanara Albino Batista [3], Thalita Fernandes de Abreu [1,2,6], Marcelo Gerardin Poirot Land [1,2,4,5,†] and Cristiane Bedran Milito [1,7,†]

1 Faculty of Medicine (FM), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, 21941590, Rio de Janeiro, Brazil;
2 Martagão Gesteira Institute of Pediatrics and Childcare (IPPMG), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, 21941912, Rio de Janeiro, Brazil;
3 Internal Medicine Department, Central Air Force Hospital (HCA), Rio de Janeiro, 20261005, Rio de Janeiro, Brazil;
4 Pediatric Hematology Service, Martagão Gesteira Institute of Pediatrics and Childcare (IPPMG), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, 21941912, Rio de Janeiro, Brazil;
5 National Institute of Science and Technology in Childhood Cancer Biology and Pediatric Oncology (INCT BioOncoPed), Porto Alegre, 90035903, Rio Grande do Sul, Brazil;
6 Infectious and Parasitic Diseases Service, Martagão Gesteira Institute of Pediatrics and Childcare (IPPMG), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, 21941912, Rio de Janeiro, Brazil;
7 Department of Pathology, Faculty of Medicine (FM), Clementino Fraga Filho University Hospital (HUCFF), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, 21941617, Rio de Janeiro, Brazil.
* Correspondence: author: nathalialopez@ufrj.br;
† These authors contributed equally to this work.

Abstract: Malignant lymphoma is an unusual form of gallbladder neoplasm. Almost all of these tumors are diffuse large B-cell lymphomas or mucosa-associated lymphoid tissue-type lymphomas. Herein, we report a rare case of a gallbladder Burkitt's lymphoma (BL) in a child living with HIV. As far as we are concerned, this is the first report in the pediatric population and in an individual living with HIV. The patient attended the Federal Hospital of Lagoa, Rio de Janeiro, Brazil, underwent cholecystectomy and the postoperative pathological analysis of the gallbladder revealed a diagnosis of BL. Also, HIV serology was performed and returned positive. She was transferred to the Martagão Gesteira Institute of Pediatrics and Childcare for oncological treatment, dying from sepsis and disease progression about 18 months later. Patient did not undergo ART/cART. Previous cases of gallbladder BL were analyzed to characterize the clinicopathological features. BL can occur in the gallbladder both in the context of HIV infection and in the pediatric population. Biopsy is mandatory in cases with suggestive findings of lymphoma, and an early diagnosis can change the course of the disease. Furthermore, the case highlights the importance of an early initiation of ART/cART in people living with HIV (PLWH).

Keywords: Burkitt's lymphoma; gallbladder; malignant lymphoma; gallbladder cancer; HIV; pediatric; case report; Brazil

1. Introduction

Malignant gallbladder lymphoma is particularly uncommon [1–5]. Mostly, patients diagnosed with this disease are referred for surgery with the diagnostic hypothesis of gallbladder adenocarcinoma or cholecystitis. That is because preoperative diagnosis is exceedingly challenging. Although several reports have documented malignant gallbladder lymphomas, most of these malignancies are diffuse large B-cell lymphomas (DLBCL) or Marginal Zone Lymphomas (MZL) [3,5–6], and only three reports have previously documented gallbladder Burkitt's lymphoma (BL) [1,7–8]. Herein, we report the first case of a child with gallbladder BL. It is also the first case of a patient living with HIV diagnosed with this type of lymphoma.

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2. Detailed Case Description

2.1. Case Presentation

2.1.1. Chief Complaints

A five-year-old black female child, from Rio de Janeiro, RJ, Brazil, attended the hospital, Federal Hospital of Lagoa (HFL), Rio de Janeiro, Brazil, with a complaint of vomiting, abdominal pain, diarrhea, and jaundice for four days.

2.1.2. History of Present Illness

Symptoms started four days before presentation with recurrent vomiting, abdominal pain, diarrhea, and jaundice.

2.1.3. History of Past Illness

The patient was previously healthy. She was born on 09/03/94, delivered by normal birth, without complications. Prenatal care was complete. Exclusive breastfeeding was maintained until she was two years old. On 06/16/99, she started vomiting, presenting abdominal pain, diarrhea, jaundice and itching. Furthermore, the patient complained of B symptoms like fever, night sweats, and weight loss. She was admitted to the HFL on 06/20/99 and diagnosed with intestinal subocclusion caused by *Ascaris lumbricoides*. A clinical treatment was conducted with a single dose of albendazole 400 mg orally. Despite the treatment, she developed severe cholangitis and underwent an emergency cholecystectomy on 07/15/99. The postoperative pathological examination of the gallbladder revealed a diagnosis of BL. Due to the suspicion of possible immunodeficiency, on 07/28/99, HIV serology was performed, and returned positive.

2.1.4. Personal and Family History

The patient's family denied any family history of malignant tumors or other chronic diseases. After the patient's diagnosis, an HIV serology (enzyme-linked immunosorbent assay - ELISA) was performed on the patient's mother on 07/28/99, with a positive result. There is no history of blood transfusion or physical/sexual abuse of the child. The diagnosis of vertical transmission (VT) of HIV was then established.

2.1.5. Physical Examination

The patient was presenting abdominal pain, dehydration, and jaundice in the physical examination on 06/20/99. She was afebrile at the moment. There were presence of abdominal pain on diffuse palpation, absence of Murphy's sign, and absence of visceromegaly or masses. No swollen lymph nodes were found. No other changes were found on physical examination.

2.1.6. Laboratory Examination

On 07/28/99, HIV serology was performed, which returned positive. On 07/30/99, $CD4^+$, $CD8^+$, and viral load measurements were carried out, which showed the following values: $CD4^+$ 2.00%, $CD8^+$ 45.00%, and viral load 200,000 copies/mL (log 4.20). The immunological status of the patient was classified using the CDC clinical category and immunosuppression stage (N/A/B/C and 1/2/3/unknown, respectively) at the date of diagnosis. So, at this point, the patient was classified as C3 according to CDC clinical criteria [9,10].

2.1.7. Imaging Assessment

No imaging tests related to the condition in question were performed prior to surgery or to histopathological analysis.

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2.2. Further Diagnostic Work-Up

As previously said, the patient underwent an emergency cholecystectomy on 07/15/99 and the postoperative histopathological examination of the resected specimen, that occurred on 07/16/99 at the Department of Pathology of Clementino Fraga Filho University Hospital (HUCFF/UFRJ), revealed the diagnosis of BL.

The macroscopic examination showed a gallbladder measuring 4cm x 1.0cm x 0.9cm. The serosa was opaque, and the wall thickened and white, with a firm consistency. The specimen was re-evaluated by a hematopathologist on 08/19/22 (C.B.M), who confirmed the diagnosis of BL through microscopic analysis and with immunohistochemical study according to WHO, 2022 [11]. Morphological analysis revealed diffuse proliferation of intermediate-sized cells, with small nucleoli invading and destroying the bladder wall, with a high apoptotic and mitotic index. The neoplastic cells showed positivity for CD20, CD10, Ki67 99%, and EBER by in situ hybridization (EBER1) [11,12]. There are five photographs of the sample in question below (Figures 1–5).

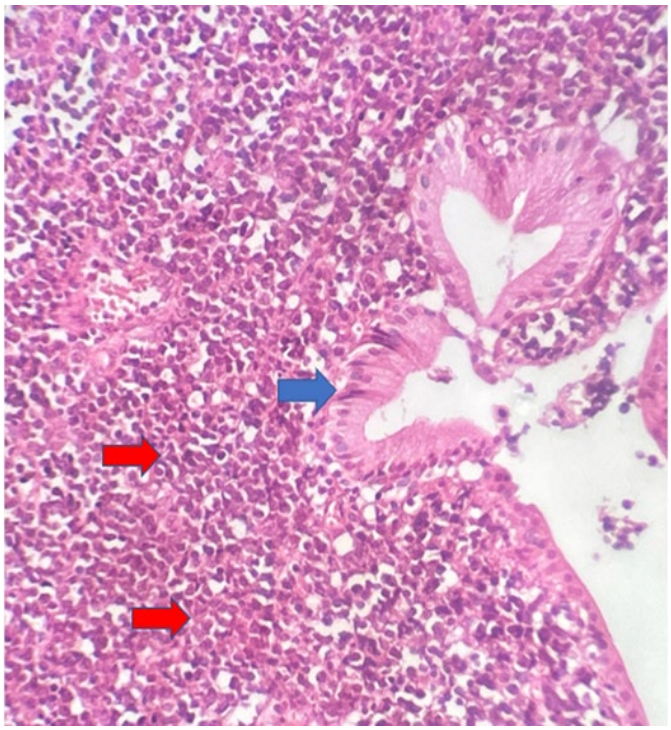

Figure 1. Gallbladder BL. Neoplasm consisting of intermediate-sized cells (red arrows) located in the gallbladder chorion (blue arrow). 10X magnification.

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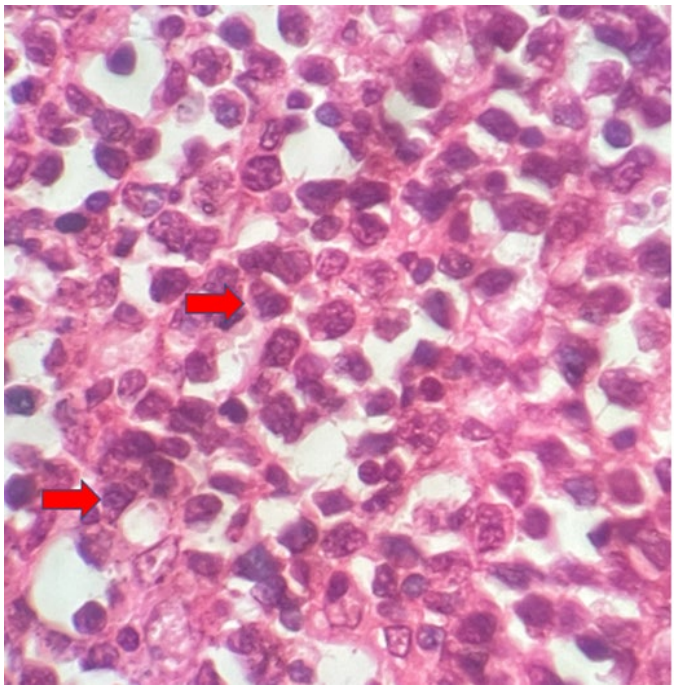

Figure 2. Intermediate-sized cells, with evident nucleoli and diffuse proliferation (red arrows). 40X magnification.

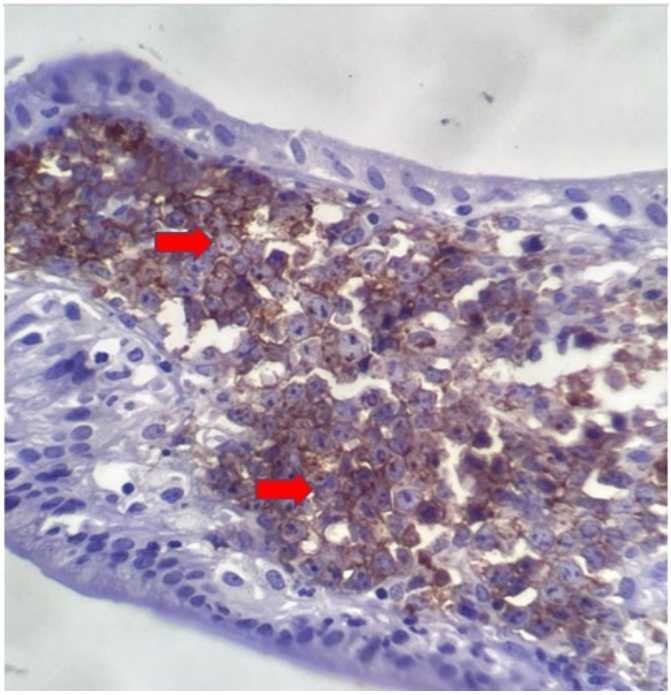

Figure 3. Diffuse immunostaining of cell membrane with anti-CD20 antibody in neoplastic cells (red arrows) and anti-CD10 antibody. 40X magnification.

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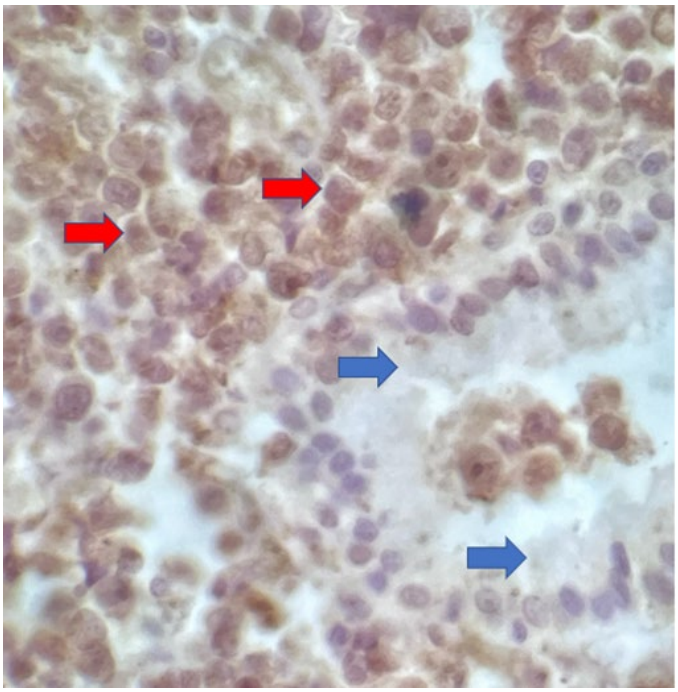

Figure 4. Nuclear immunostaining with anti-Ki67 antibody in all neoplastic cells (red arrows) and negativity in the gallbladder epithelium (blue arrows). 40X magnification.

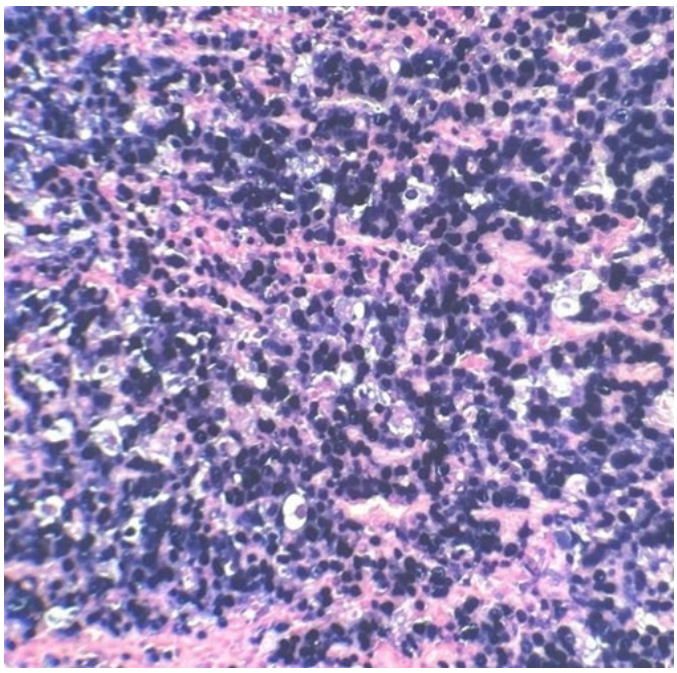

Figure 5. HIS technique showing positivity (blackish nuclei) for the EBER1 probe.

2.3. Final Diagnosis

Combined with the patient's medical history, the final diagnosis was gallbladder BL. This is an AIDS-defining malignancy (ADM), codified as 2A85.6 (BL) according to ICD-11 MMS [13].

2.4. Treatment

During her hospitalization at HFL, she presented several infectious complications and probable a *Pneumocystis jirovecii* pneumonia with associated respiratory failure. Then, the use of corticosteroids and intravenous sulfamethoxazole/trimethoprim (SMX + TMP) was initiated.

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She was transferred to the Martagão Gesteira Institute of Pediatrics and Childcare, the pediatric hospital of Federal University of Rio de Janeiro (IPPMG/UFRJ) on 07/31/99 for oncological treatment. Until that moment, she was not using prophylaxis or antiretroviral therapy/combined antiretroviral therapy (ART/cART). She arrived at IPPMG/UFRJ presenting hemodynamic instability, cutaneous-mucous parlor, sweating, grade III protein-energy malnutrition, hepatomegaly (palpable 8 cm below the right costal margin), and abdominal distension. The patient still had not swollen lymph nodes or other visceromegaly. Chest and abdominal x-ray showed no changes. Lastly, the patient remained without signs of neurological impairment. Current laboratory tests of the admission: hemoglobin (Hb) 7.3 g/dL, hematocrit (Ht) 19%, 3,000 leukocytes/mm^3 (43% neutrophils, 30% lymphocytes, and 17% monocytes) and 485,000/mm^3 platelets. On 08/03/99, bone marrow aspirate was performed, with infiltration by FAB (French-American-British Classification) L3 type blasts (>25%) and normal cerebrospinal fluid at the same date. A radiograph of long bones showed lytic lesions in the femur, bilaterally. A review of the bone marrow aspirate slide confirmed the diagnosis of L3 acute lymphoblastic leukemia (L3-ALL) at the time, now classified as BL according to the latest WHO review, 2022 [11]. Lymphoma was classified as stage IVB according to Murphy classification [14], and a Performance Status (PS) 4 was attributed to the patient.

On 08/04/99, after stabilization of the pulmonary infectious condition, the m-BACOD protocol [15] was started with the use of granulocyte-colony stimulating factor (G-CSF), due to the patient's poor PS. Lactate dehydrogenase (LDH) was 220 IU/L on 08/15/99. After four cycles of chemotherapy, with the disease progressing, NHL-BFM 95 [16] was started, together with the G-CSF. An important point is that the patient was kept off ART/cART by a medical decision since this was the best strategy considered at that time for cases when the patient was also undergoing chemotherapy treatment [17].

On 09/23/00, she was in clinical remission at the end of chemotherapy.

On 10/04/00, she had a relapse in the spinal cord and the central nervous system (CNS). A computerized tomography (CT) of the chest and abdomen scan revealed generalized lymphadenopathy. LDH dosage at this time was 998 Ul/L. The patient evolved with a progressive clinical deterioration, making it impossible to start a new chemotherapy protocol.

2.5. Outcome and Follow-Up

The patient died from sepsis and disease progression on 12/24/00.

3. Discussion

Malignant lymphoma of the gallbladder is a rare type of gallbladder malignancy, which encompasses 0.1%-0.2% of all gallbladder tumors [1–4]. In prior reports, the majority of them were described to be DLBCL or MZL [3,5]. In all medical literature, just three reports had documented Gallbladder BL [1,7,8]. The present case report grants some interesting clinical information once it is the first Gallbladder BL described in the pediatric population and in an individual living with HIV.

Affording to the diagnostic criteria of gastrointestinal lymphoma, which was defined by Dawson et al. [18] and Lewin et al. [19], the case in question is considered as a "secondary" gallbladder BL, because it included extra-gallbladder lesions, which probably occurred before gallbladder infiltration. Some days after surgery (24 days), the patient underwent an investigation in a quaternary hospital, which diagnosed an L3-ALL. There was no CNS infiltration. Besides this, an x-ray of long bones showed bilateral lytic lesions in the femurs.

Gastrointestinal symptoms (vomiting, abdominal pain, diarrhea, and jaundice) were notable and led the patient to seek medical assistance. It is well known that gallbladder BL can be presented as a localized disease that mimics gallbladder cancer. Ono et al. [4] reported imaging descriptions of malignant lymphomas, showing that high-grade malignant lymphomas can exhibit solid and bulky masses or unconventional wall thickening. Because BL is a highly aggressive and rapidly progressive disease, some extranodal sites are generally involved at the time of diagnosis, as in our case report [20].

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In children living with HIV (CLWH) the incidence of malignant neoplasms is higher. This substantial increase is related to a high frequency of non-Hodgkin's lymphomas (NHL), particularly B-NHL (like BL), Kaposi's sarcoma (KS), leiomyosarcoma and Hodgkin's lymphoma (HL) [9,21–25].

When lymphomas and HIV occur simultaneously in children with immature immune systems, it can cause serious consequences. HIV-related lymphomas are typically linked to immune dysregulation, as HIV infection causes a depletion of both cellular and humoral immunity [24,26–33]. In this population, lymphomas are often detected at a late stage with the involvement of tissues outside the lymph nodes, and usually with a rapid and aggressive progression [22,23,25,34]. It is widely acknowledged that the presence of HIV infection significantly worsens the prognosis for children and adolescents with lymphoma, even with the use of antiretroviral therapy and chemotherapy [35–41].

The accurate antiretroviral therapy reduced morbidity and mortality in people living with HIV (PLWH) since it inhibits viral replication and restores immunological surveillance [42–45]. So, starting ART/cART as soon as possible is related to a better recuperation of CD4+ T-cell counts and, consequently, to the reduction of problems caused by HIV immunosuppression - such as opportunistic infections and malignant neoplasms [42,46].

In the context of immunosuppression due to HIV infection, ART/cART, in combination with chemotherapy, has the highest priority in BL treatment, even if higher than surgery [1,40–42,46]. Unfortunately, the patient died from sepsis and disease progression about 18 months after the lymphoma diagnosis despite the early beginning of chemotherapy (around 20 days after surgery and histopathological analysis). It is noteworthy that the patient did not undergo ART/cART in any moment during the treatment, although she had been treated in a reference center for HIV and cancer treatment in Brazil (IPPMG/UFRJ). In reality, at this time (1999-2000), antiretroviral therapy was not yet recommended in similar cases by Brazilian Ministry of Health guidelines [17]. In a recent work published by our research group, it was observed that patients who achieved complete remission, but did not recover CD4+ levels, had inferior survival rates with higher relapse occurrence and infections related to the rescue protocols instituted [41]. Nowadays, the role of antiretroviral therapy is well-established for a better prognosis of PLWH precisely because it prevents the appearance and recurrence of malignant tumors, especially lymphomas [10,22,40–42,46].

Even though the precise preoperative diagnosis of gallbladder malignant lymphoma is difficult, some previous reports [3,4,47,48] have suggested the possibility of an accurate preoperative suspicion of lymphoma centered on imaging analysis. Unfortunately, in the case in question, we did not have access to modern imaging resources for evaluation and comparison with other reports. In addition, the patient had an emergency cholecystectomy due to an initial inaccurate diagnosis (intestinal subocclusion by Ascaris lumbricoides), with rapid progression to cholangitis probably because of an obstruction caused by the tumor. Furthermore, the correct mass location in the topography of the gallbladder was not documented in the medical records. As this is a case from 1999, some information were lost and valuable data for a contemporary case report were not collected. However, this did not harm the diagnosis and the focus of the discussion, once biopsy assessment is the gold standard diagnostic procedure in any lymphoma investigation [1,47,49].

Another important point of our case is the presence of EBV in the sample, confirmed by EBER1 [12]. Transcription of non-polyadenylated RNAs EBER1 and EBER2 is a constant feature of all EBV latent infection patterns and is, therefore, the best marker to demonstrate infection by this oncogenic virus [50–53]. It is known that EBV is linked to the development of a variety of HIV-related lymphomas [54–57] and it is present in 60% of BL cases in PLWH [22]. In sub-Saharan Africa, LB is endemic, and its risk increases both with increasing anti-EBV antibody titers and with HIV infection, for example [58]. Therefore, our finding corroborates the medical literature. However, the role of EBV in malignancies in CLWH across a range of Western countries in the post-cART era still is not fully recognized.

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4. Conclusions

BL can occur in the gallbladder, especially in the context of immunosuppression - such as caused by HIV infection. As far as we concern, this is the first case report of a gallbladder BL in a pediatric patient. Furthermore, it is the first one reported in a patient living with HIV. It is already known that BL should be contemplated in the differential diagnosis of a gallbladder tumor, and biopsy is mandatory for diagnosis and early beginning of chemotherapy. Neoplasms may present themselves more aggressively in immunosuppressed patients. In this scenario, an early diagnosis can change the course of the disease. Furthermore, the case highlights the importance of an early initiation of ART/cART in PLWH. For this reason, this report is so important, since gallbladder BL should also be considered a differential diagnosis in this population.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of Instituto de Puericultura e Pediatria Martagão Gesteira (IPPMG/UFRJ) (Ethics Committee approval number: 2,504,586; date of approval: 21 February 2018) and Hospital Universitário Clementino Fraga Filho (HUCFF/UFRJ) (Ethics Committee approval number: 2,581,674; date of approval: 5 April 2018).

Informed Consent Statement: Patient consent was waived as this case report used data previously collected for medical care.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

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Conflicts of Interest: The authors declare that they have no conflict of interest to disclose.

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