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Case Report

Primary osseous Burkitt lymphoma with nodal and intracardiac metastases in a child

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ABSTRACT

Burkitt lymphoma (BL) is the most frequent non-Hodgkin lymphoma in pediatric patients, accounting for approximately 34% of the cases of lymphoma in children. This subtype of non-Hodgkin lymphoma was first described in 1958 as a monoclonal proliferation of B cell lymphocytes. Cardiac involvement of BL in association with osseous compromise and lymphadenopathy is rare and poorly documented. We report a case of femur primary BL in an 8-year-old boy with metastatic cardiac involvement, retroperitoneal and iliofemoral lymphadenopathy, and hepatosplenomegaly. We highlight the diagnostic challenge in a patient with clinical nonspecific findings and systemic disease.

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Clinical case

An 8-year-old boy was referred to our hospital with a 1-month history of fever and a growing mass in the left inguinal region. Physicians first treated the mass as an infectious adenitis without satisfactory evolution. During the physical examination, a 10 × 5 cm, hard, mobile, and not very painful mass was found in the left inguinal region. In addition, the patient had a grade III/IV systolic heart murmur with inspiratory splitting of s2. Magnetic resonance (MR) of the left thigh, abdominal ultrasound, and echocardiography was ordered.

MR showed multiple lymphadenopathies forming conglomerates of 7.5 × 5.8 × 7 cm in size that surrounded the iliac vessels, the inguinal, and the left popliteal regions. The femoral lymph nodes were greatly increased in size with inflammatory changes. Incidentally, an aggressive soft tissue mass was identified in the left distal femoral metaphysis (Fig. 1). Complementary knee X-rays showed an eccentric lytic lesion involving the medial cortical border without associated fractures (Fig. 2). Abdominal ultrasound showed hepatosplenomegaly and enlarged retroperitoneal lymph nodes with sizes up to 3.7 cm (Figs. 3 and 4). The echocardiography

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Fig. 1 – Left thigh contrast-enhanced magnetic resonance (MR). (A) Axial T1-weighted postcontrast fat saturation images. Note the enlarged femoral lymph nodes forming a mass with inflammatory changes. (B) coronal short TI inversion recovery (STIR), T1-weighted precontrast and postcontrast with fat suppression images. Aggressive soft tissue lesion in the distal metaphysis of the left femur, with marked bone edema, heterogeneous enhancement, and fine periosteal reaction. There is no joint effusion and no soft tissue mass.

revealed a mobile mass in the right atrium adhered to the tricuspid valve (Fig. 5).

With the described findings, the orthopedic oncology group had in mind a bacterial endocarditis with secondary distal femoral osteomyelitis vs a soft tissue sarcoma with intracardiac involvement. A cardiac MR was ordered for better evaluation of the cardiac compromise (Fig. 6).

Laboratory tests showed hypochromic microcytic anemia, C-reactive protein of 3.96, and a lactate dehydrogenase of 312 U/L. Bone marrow aspiration was normal.

With the above findings, the possibility of bacterial endocarditis with osteomyelitis was remote. Other entities were considered, mainly lymphoproliferative disease and Ewing sarcoma. Incisional biopsies of the left thigh mass and distal femur bone lesion were performed. The results of the bone and lymph node pathology showed a malignant lymphoid infiltrate with intermediate size cells and extensive necrosis. Lymphoid cells expressed CD20, bcl-6, and CD10 markers, and

they were negative for BCL-2, MUM1, and TdT (Fig. 7). The diagnosis of IVA-stage Burkitt lymphoma (BL) with nodal and extranodal compromise was made.

The patient underwent a karyotype test for 46 XY translocation (4; 11) (q21; q23), which was negative and was treated with AA chemotherapy (cytarabine, etoposide, ifosfamide) with a satisfactory clinical evolution.

Discussion

Lymphoma is a form of cancer that affects the immune system, specifically lymphocytes. There are two broad types of lymphoma: Hodgkin's or non-Hodgkin's. BL is a form of non-Hodgkin's lymphoma in which it starts in immune cells called B-cells [1,2].

Denis Burkitt described BL for the first time in Uganda in 1958. The World Health Organization classifies it in three



Fig. 2 – Antero-posterior and lateral X-ray of the left knee. Type IC geographic lytic lesion in the metaphysis of the left distal femur with fine periosteal reaction and partially defined sclerotic borders.

types: endemic, sporadic, and immunodeficiency related. The endemic form is more frequent in Africa and New Guinea, and it has a relation with Epstein-Barr virus infection in 95% of the cases. The sporadic form, also called the American form, is present in North America, Northern and Eastern Europe, and Asia and has a relation with Epstein-Barr virus in 15% of the cases. The immunodeficiency-related form mainly occurs in HIV-infected patients. However, it can also occur in patients with congenital immunodeficiencies [1].

BL is a monoclonal proliferation of B-lymphocytes classified as a poorly differentiated lymphocytic lymphoma [2]. It is the most frequent non-Hodgkin lymphoma subtype in children, corresponding to approximately 34% of cases of lymphoma in infancy. BL is the fastest growing lymphoma in children and has a duplication time of 24–48 hours. Even with

this aggressiveness, it is curable and highly sensitive to chemotherapy. Therefore, early diagnosis and rapid treatment onset is essential [3]. Additionally, it is more frequently in boys than in girls, with a ratio of 1.3:1 to 8.8:1. It appears most commonly at the age of 8 years with a presentation range of 0–20 years old. Abdominal involvement occurs in 22.5 % of the cases, being the more frequent presentations pelvic masses (45%) and focal hepatic lesions (17%) [1,4,5].

Diagnostic approach

The diagnosis of BL like other non-Hodgkin lymphomas is histologic. Images are essential to determine the severity and extent of the involvement. The most commonly used

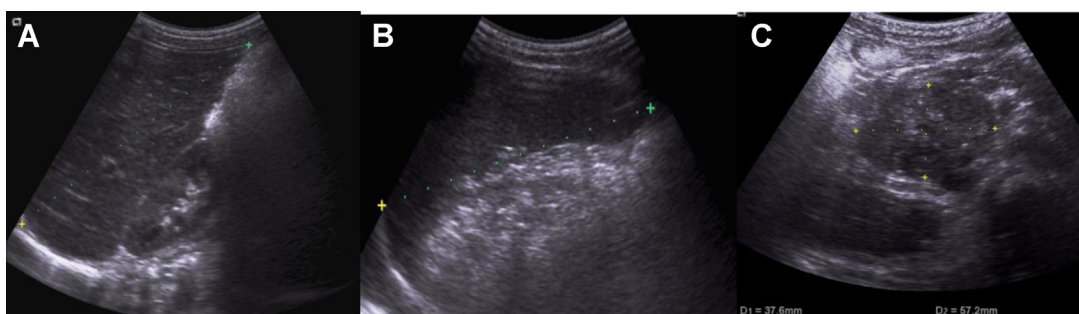


Fig. 3 – (A) Hepatomegaly, (B) splenomegaly, and (C) retroperitoneal lymphadenopathies.

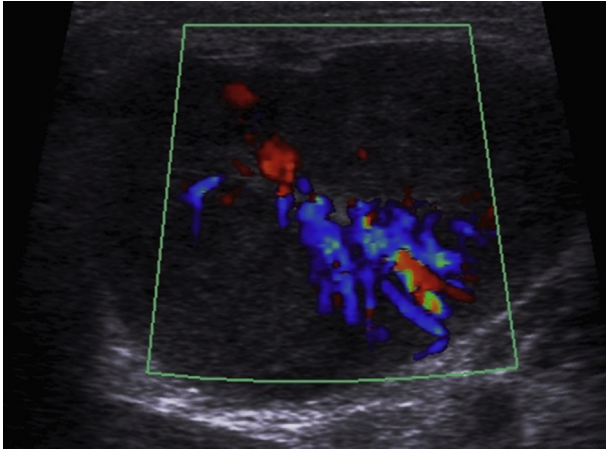


Fig. 4 – Left iliofemoral lymphadenopathies. Note the hypoechoogenicity, altered morphology and lost of the normal fatty hilum. There is central vascularization with color Doppler evaluation.

techniques are computerized tomography (CT), PET/CT, and bone scintigraphy. Ultrasound is the first image in most cases, and CT would often follow ultrasound to allow a more global assessment for bowel and visceral involvement as well as tumor staging. Because of concerns about radiation risk to oncology patients, particularly those who are children, with repeat imaging examinations, the role of MR is likely to increase [6,7]. PET/CT has become the preferred functional imaging technique both for initial staging and for evaluation response to treatment in children with BL because of a shorter interval between injection and imaging, completion of the studies in only a few hours, and improved image quality. PET/CT has been shown to reveal disease sites that were not previously identified, leading to upstaging of the disease [7]. PET/CT also has better dosimetry, which is particularly important when imaging children, in comparison with bone scintigraphy [3,7].

Clinical characteristics

Pediatric patients with BL usually have extranodal involvement, especially in the abdomen, in approximately 31% of the cases [8]. Clinical features are diverse and depend on the location of the disease. Usually, manifestations are secondary to compression, obstruction, or infiltration of structures by a tumor. The most common symptoms are abdominal pain, palpable abdominal mass, nausea, emesis, and intestinal obstruction due to secondary compression, intussusception, and acute appendicitis. Weight loss, fever, and other symptoms are commonly present in systemic disease, but they are less common in BL than in other lymphomas [4,7]. Other manifestations include obstructive ictericia when there is compression of the bile duct, kidney failure caused by tumor infiltration, or extrinsic obstruction secondary to a large mass [6].

Gastrointestinal involvement caused by non-Hodgkin lymphomas, including BL is rare, and usually affects the small intestine, ileum, cecum, and appendix [6]. Proximal gastrointestinal tract involvement is even more unusual [4].

Regarding solid organ involvement, liver disease caused by BL occurs in 17% of the cases and the most common findings in CT scans are single or multiple focal low attenuation lesions [2]. Spleen involvement shows diffuse splenomegaly. The most common renal involvement caused by BL includes nephromegaly (90%), focal kidney masses (30%), and hydronephrosis caused by ureteral obstruction (50%). Pancreatic involvement occurs in approximately 10% of the cases [3]. Lymph node involvement in the mesentery and retroperitoneum caused by BL commonly appears as abdominal pelvic masses, which can be unique or multiple. Mesenteric and retroperitoneal masses with calcifications have been reported in aggressive non-Hodgkin subtypes, specifically in BL [2,3].

Heart involvement caused by BL is extremely rare and can appear as infiltrative disease, generating secondary restrictive symptoms [9]. The other type of cardiac involvement reported

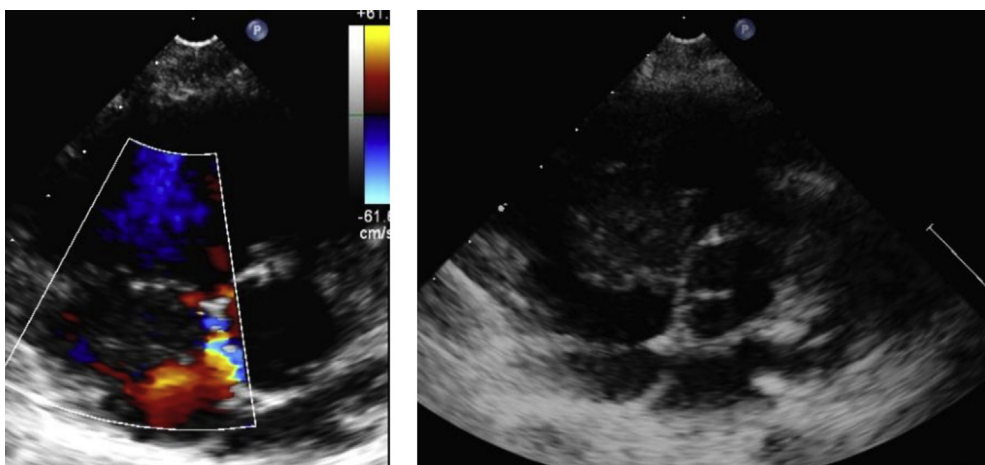


Fig. 5 – Transthoracic echocardiography. Mobile, noncalcified 1.8 × 2 cm mass in the right atrium, adhered to the lateral leaflet of the tricuspid valve without flow obstruction.

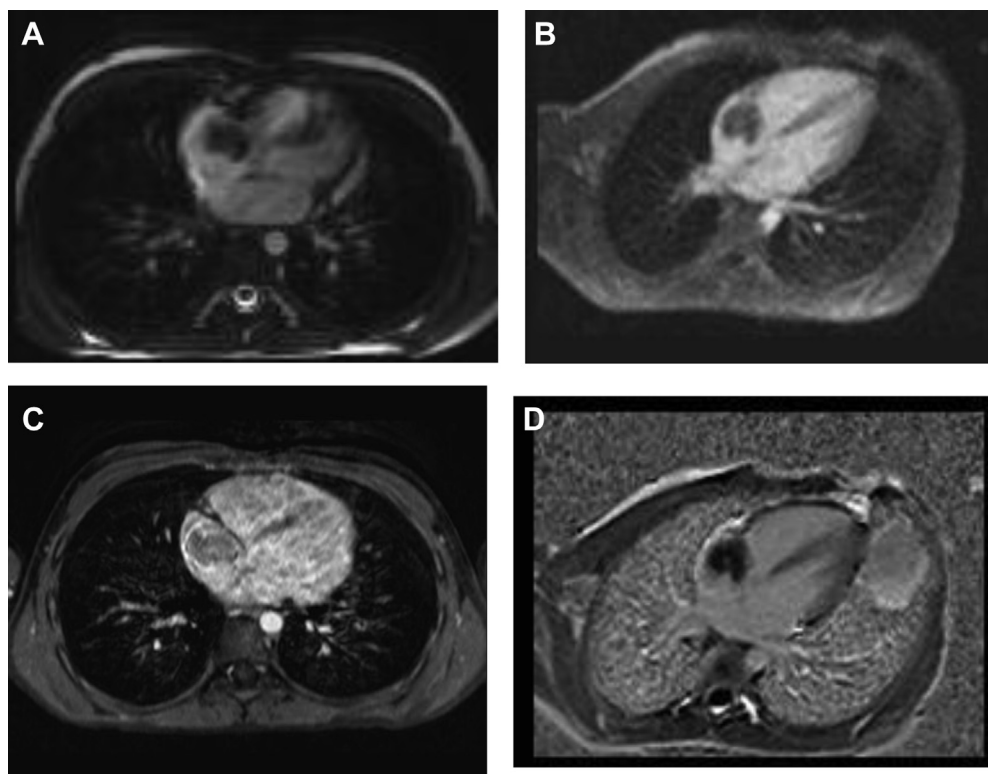


Fig. 6 – Cardiac magnetic resonance (MR). (A) Axial T2-weighted image, (B) horizontal long-axis perfusion images, (C) T1-weighted contrast enhanced with fat saturation images, (D) delayed enhancement sequences. Right atrial mass measuring 3 cm which is slightly hyper intense to the myocardium in T2 and has a discrete enhancement after contrast administration. The mass has a heterogeneous intensity in delayed enhancement sequences.

in literature is a soft tissue mass, like the one our patient had at the level of the right atrioventricular union [2,5,9].

Lymphomas can involve bone marrow or cortex of long bones. Bone marrow involvement has been described to be more frequent in non-Hodgkin than in Hodgkin lymphoma [8]. Primary non-Hodgkin lymphomas of the bone generally occur with an infiltrative and osteolytic pattern that affects mainly the metaphysis of the femur, humerus, or tibia in 75% of cases, while metastatic compromise commonly involves the spine [1,4,8].

Because of the high cell replication rate in non-Hodgkin lymphoma, BL is highly sensitive to systemic chemotherapy and complications like tumor lysis syndrome may initially occur. Treatment includes the use of chemotherapy drugs,

with frequent use of different regimens for the disease as FAB/LMB (groups B and C), BFM90/95 (R3 and R4 group) [4–6]. Free of disease survival rates range from 20% to 85% at 3 years for patients who were diagnosed initially with advanced disease (stage IV) [4,6,8]. Our patient received chemotherapy with the regimen LNH BFM95, which includes the use of glucocorticoids, cyclophosphamide, doxorubicin, methotrexate, cytarabine, etoposide, in addition to intrathecal chemotherapy supported with colony-stimulating factors. The patient received management blocks VAA-BB-CC-AA-BB-CC with good tolerance and an outstanding response from the start of the prophase.

In patients with nonendemic forms of the disease, the most common site of involvement is the abdomen, including

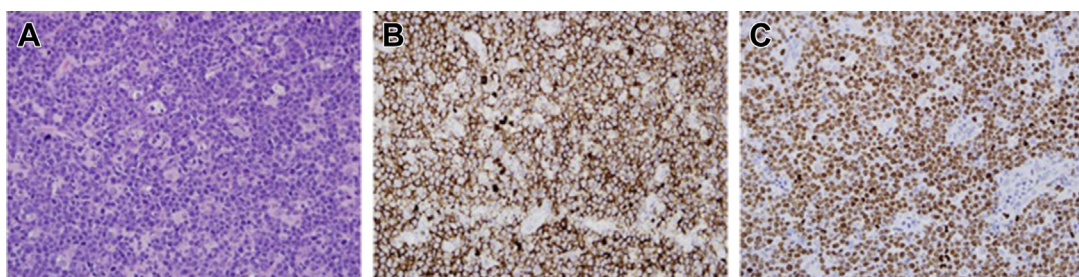


Fig. 7 – (A) Hematoxylin and eosin 40 \times . Malignant lymphoid infiltrate with intermediate size cells and extense areas of necrosis. Positive CD20 expression (B) and a Ki 67 of 100% (C).

the gastrointestinal tract. Other unusual reported sites include the following: testicular, breast, thyroid gland, skin, epidural space, bone, and pancreas [4–6]. Concomitant intracardiac lymphomatous disease has been described recently in a case series, where only 9% of the patients had histopathologic confirmation of BL. The main clinical symptom was heart failure [5].

Conclusion

We have submitted this interesting case because until this moment and to our knowledge, a pediatric case of primary bone BL with nodal and extranodal involvement including intracardiac disease has not been reported. In this specific case, this occurs in a boy whose clinical presentation and laboratory tests are bizarre. Proper multidisciplinary approach and treatment leads to favorable outcomes in pediatric BL.

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