Burkitt lymphoma associated with human immunodeficiency virus infection and pulmonary tuberculosis

A case report

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Abstract
Introduction: The association of human immunodeficiency virus (HIV) infection with Burkitt lymphoma is related to the presence of Epstein Barr virus infection and the impact of the HIV antigen on the expansion of B-polyclonal cells. In Southeast Europe, the association is rare, and recognizing this is important in the therapeutic decision to increase patient survival rate. The association of HIV with Burkitt lymphoma and tuberculosis is even more rarely described in the literature.

Patient concerns: We present the case of a 40-year-old patient who presented with a 3-week history of fever (max. 38.7 °C), painful axillary swelling on the right side, lumbar pain, gait disorders, headache, and night sweats. Clinical manifestations included marked weight loss (about 30 kg in the last 2 months before his admission).

Diagnosis: A LyCD4 count of 38/μL and a HIV1 viral load of 384,000/mm³, classified the patient into a C3 stage. A biopsy of the right axillary lymph node was performed for suspected ganglionic tuberculosis due to immunodeficiency. Histopathological examination confirmed the diagnosis of Burkitt lymphoma. Cultures on Löwenstein-Jensen medium from sputum harvested at first admission were positive for Mycobacterium tuberculosis.

Interventions: Highly active antiretroviral therapy, chemotherapeutic agents for Burkitt lymphoma, anti-tuberculous drug therapy, neurosurgical intervention of spinal cord decompression, and antibiotic therapy of the associated bacterial infection.

Outcome: Burkitt lymphoma disseminated rapidly, with central nervous system, spinal cord, osteomuscular, adrenal, and spleen involvement. The evolution under treatment was unfavorable, with patient death occurring 6 months after diagnosis.

Conclusions: The association of HIV infection with Burkitt lymphoma and tuberculosis is rare in the highly active antiretroviral therapy (HAART) era, posing prompt and multidisciplinary therapeutic management issues. Similar cases of HIV-TB and Burkitt lymphoma association have been described, but none of the other cases showed the involvement of the central nervous system or of the bilateral adrenal glands.

Abbreviations: BL = Burkitt lymphoma, CT = computed tomography, DA-EPOCH-R = dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab, HAART = highly active antiretroviral therapy, HIV = human immunodeficiency virus, MRI = magnetic resonance imaging, TB = tuberculosis.

Keywords: Burkitt lymphoma, dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab, highly active antiretroviral therapy, human immunodeficiency virus infection, pulmonary tuberculosis.

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Informed consent: Written informed consent was obtained from the patient’s parents for publication of this case report and any accompanying images. The study was accepted by the Ethics Committee of the hospital and they encouraged publishing the article. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

The authors have no conflicts of interest to disclose.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

The association of human immunodeficiency virus (HIV) infection with Burkitt lymphoma (BL) is 261 times higher than that in the general population and is linked to the presence of Epstein Barr virus infection and the impact of the HIV antigen on the expansion of B-polyclonal cells. In some areas, the incidence of BL in HIV patients is 23 per 100,000 persons (like in southern Louisiana), compared with the Southeast Europe where the association is rare. Recognizing this association is important and improving the prognosis of the disease.

2. Case report

We present the case of a 40-year-old patient with HIV infection associated with disseminated Burkitt lymphoma, with central nervous system, spinal cord, osteomuscular, adrenal, and spleen involvement and pleuropulmonary tuberculosis, a case that posed particular treatment problems.

Table 1

Evolution of the main laboratory examinations during hospitalization.

| Parameter                      | Values                  | Reference value |
|--------------------------------|-------------------------|-----------------|
| Hemoglobin                     | 11.3g/dL 11.3g/dL 10.5g/dL 9.9g/dL 9.4g/dL 8.4g/dL | 12–15g/dL       |
| Hematocrit                      | 33.0% 30.7% 27.9% 26.4% 24.1% | 37–47%          |
| WBC                             | 7.060×10⁶/μL 4.320×10⁶/μL 2.640×10⁶/μL 0.19×10⁶/μL 0.20×10⁶/μL 7.72×10⁶/μL | 4–10×10⁶/μL     |
| Differential blood count:       |                         |                 |
| Neutrophils                     | 54.3% 40.2% 26.2% 25% 86.8% | 30–75%          |
| Lymphocytes                     | 22.5% 14.4% 5.3% 5% 0.9% 10.1% | 2–10%           |
| Monocytes                       | 19.4% 14.4% 5.3% 10% 1% | 1–4%            |
| Eosinophils                     | 3.8% 0.4% 0.4% 0.4% 0.4% 0.4% 0.4% | 1–2%            |
| Basophils                       | 0% 0% 0% 0% 0% 0% 0% | 1–2%            |
| Thrombocytes                    | 228×10³/μL 218×10³/μL 206×10³/μL 80×10³/μL 64×10³/μL 247×10³/μL 150–400×10³/μL | 9.9–12.3s       |
| Prothrombin time, s             | 12.6s 12.1s 13s | 0.80–1.1        |
| INR                             | 1.1 1.06 1 |                 |
| Hemoculture                     | Negative |                 |
| Fibrinogen                      | 488.8mg/dL 572.9mg/dL | 170–420mg/dL    |
| C-reactive protein              | 54.22 81.68 | 61.47           |
| ESR                             | 100 75 | 0–20mm/h        |
| AST                             | 33UL 24UL | 5–34UL          |
| ALT                             | 31UL 44UL | <55UL           |
| Hepatitis B surface antigen     | Negative |                 |
| Hepatitis C antibodies          | Positive |                 |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus.
Immunohistochemical staining of the lymph node revealed the following: few CD3+ and CD5+ reactive T lymphocytes; diffuse atypical positive lymphoid population for CD10 and CD20. On CD23 and CD30 staining, no positive lymphocytes were found in the atypical lymphoid population. BCL2 expression was negative on BCL2 immunohistochemical staining. In addition CyclinD1 and DBA44 staining were negative, with a Ki67 score of 90% (CD10+, CD20+, BCL2−, CyclinD1−, Ki 67−90%, CD23−, CD30−) (Fig. 1).

For the same suspicion of ganglionic tuberculosis due to immunodeficiency, sputum was harvested for cultures on Lowenstein-Jensen medium. An acid-fast bacillus (AFB) stain for Mycobacteria on a sample of sputum was also performed. The stain was applied on a direct and concentrated smear. The result was a negative AFB smear.

Antiretroviral therapy with Raltegravir, Emtricitabine, and Tenofovir Disoproxil Fumarate was initiated. The recommendation was also made to initiate the Burkitt lymphoma treatment. Unfortunately, the patient seeking a second opinion postponed the beginning of the treatment.

The patient returned after a month to the emergency department with right facial paralysis, paraplegia, and loss of the beginning of the treatment.

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Cranial and lumbar magnetic resonance imaging (MRI) was performed, and revealed intracranial and intraorbital lesions with dural extension, invasion of the cranial bone structures, bilateral adrenal nodes (6 cm in diameter on the right side, and 4 cm on the left side), hepatosplenomegaly, bilateral pleural effusion, and multiple vertebral, sacral, and femoral lesions (complete description is available as supplementary material, http://links.lww.com/MD/F456).

A computed tomography (CT) scan reassessment of the patient was performed, and revealed intracranial and intraorbital lesions with dural extension, invasion of the cranial bone structures, bilateral adrenal nodes (6 cm in diameter on the right side, and 4 cm on the left side), hepatosplenomegaly, bilateral pleural effusion, and multiple vertebral, sacral, and femoral lesions (complete description is available as supplementary material, http://links.lww.com/MD/F456).

Cranial and lumbar magnetic resonance imaging (MRI) was performed, and the findings were the following: multiple disseminated restrictive tumor masses in the scalp, with transverse disseminated and dural invasion; bilateral restrictive, massive paravertebral muscle masses, larger on the right side, with intrathecal invasion from L2 to S2 and complete stenosis of the spinal canal at the L3 to L5 level. The presence of a prevertebral and para-aortic lymph node metastasis of approximately 3 cm was also confirmed (Figs. 2–4).

The patient was referred to the Department of Neurosurgery, where a L3–L4 and L4–L5 laminectomy was performed. Subsequently, he was referred to the Department of Hematology for the therapeutic management decision regarding Burkitt lymphoma. Biopsies from the excised tumors were taken, and histopathological examination confirmed Burkitt lymphoma. The microscopic appearance corroborated with the immunohistochemical aspect of positive lymphoid population for CD10, CD20, and Ki67 and a negative expression of BCL2 indicates a Burkitt lymphoma, allowing its differentiation with diffuse large B-cell lymphoma and non-classifiable B-cell lymphoma with intermediate aspects between diffuse large B-cell lymphoma and Burkitt lymphoma.

Bone marrow examination revealed an infiltration by peroxidase-negative blasts cells of 6% to 36%.

DA-EPOCH-R therapy was initiated (rituximab 700mg/etoposide 96 mg day 1–4, sindovine 0.77 mg/d day 1–4, endoxan 1450 mg/d day 5, and doxorubicin 20 mg day 3–4) associated with filgrastime 48 MU SC on day 5, preceded by cyclophosphamide 200 mg, 2×1 vial/d and prednisone 60 mg/m²/d for 5 days.

The initiation of radiotherapy was delayed due to the medullary aplasia that occurred after the treatment, and it was initiated after the correction of the blood count.

During the hospitalization period in the Department of Hematology, an episode of diarrhea occurred, which was confirmed to be related to a Clostridium difficile infection. C difficile infection was diagnosed according to the guidelines published by the European Society of Clinical Microbiology and Infectious Diseases using 2 highly sensitive tests: GDH EIA (glutamate dehydrogenase enzyme immunoassay) and toxin A/B EIA, both tests were positive. The episode of CDI has been managed with oral vancomycin 4×125 mg per day for 14 days (Figs. 5–8).

Cultures on Löwenstein-Jensen medium from sputum harvested at first admission were positive for Mycobacterium tuberculosis, after 6 weeks of incubation.

Highly active antiretroviral therapy and Burkitt lymphoma chemotherapeutic agents were combined with anti-tuberculosis drug therapy (with rifabutin, pyrazinamide, ethambutol, and isoniazid). The evolution was unfavorable with the patient’s death occurring 6 months after diagnosis.

3. Discussions

Burkitt lymphoma is the most aggressive form of non-Hodgkin lymphoma with B lymphocytes,[21] with endemic or sporadic evolution, or being associated with immunodeficiency syndromes; HIV infection, congenital immunodeficiency syndromes or in allografted patients.[3,4] It is characterized by a particularly high rate of proliferation (approximately 100%),[3] with cells doubling time of 24 hours and cytogenetic specific changes of the c-MYC proto-oncogene. Cases associated with HIV infection represent 30% to 40% of non-Hodgkin lymphoma associated with HIV infection. Disseminated forms of BL with central nervous system involvement represent 20% to 30% of cases. In the history of HIV therapy, the association of HIV infection with non-Hodgkin lymphoma was 60 to 200 times higher than that in the general population.[6]

There have been cases of BL with lymph node, hepatic, and pancreatic localization,[7] sometimes with an obstructive jaundice
evolution. Also there have been cases of BL with cardiac involvement, concurrently with extradural lumbosacral lesions or ethmoidal sinuses and cerebral (temporal) impairment. Central nervous system involvement in HIV-infected patients is appropriate for differential diagnosis, especially in cases with focal neurologic deficits, with opportunistic infections such as cerebral toxoplasmosis. Disseminated BL with lymph nodes, central nervous system, and bilateral adrenal gland involvement associated with tuberculosis in an HIV-infected patient has yet not been described by other authors.

The evolution of our case is extremely reserved, having as unfavorable prognostic factors, the CD4+ cell count below 100 cells/µL, age over 35 years, and an advanced stage of the disease (BL stage IV).

Similar cases of HIV-TB and Burkitt lymphoma association have been described, cases with dissemination at an oropharyngeal, mediastinum, or pleural level, and none of these cases presented with involvement of the central nervous system or of the bilateral adrenal glands.

HAART therapy associated with DA-EPOCH±Rituximab (administered according to CD4+ lymphocyte counts) appears to be associated with the best survival rate like CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine).

The present case describes an association of HIV infection with disseminated LB and pulmonary tuberculosis initially with the absence of imaging changes. Regarding the HIV-infected patient who is in the last stage of HIV infection (AIDS), the risk of reactivation of a latent TB infection increases by approximately 20-folds and each third death is attributed to TB. According to the Joint United Nations Programme on HIV/AIDS, in 2016, worldwide, 1.2 million new cases of TB associated with HIV infection were recorded. According to the data published by the European Centre for Disease Prevention and
Control, 58,994 cases were recorded in Europe in 2016, of which 13,617 cases in Romania\cite{20}, of which 9,222 cases with pulmonary localization, 10.5% being multidrug-resistant, and 5.6% pandrug-resistant TB forms\cite{21}, motivating the clinician’s prudence in the investigation of TB in HIV-infected patients. Imaging changes may be absent in coinfected HIV/TB patients or may be atypical\cite{21}, so the decision to investigate patients for TB by smear, culture, Xpert MTB/RIF assay, or molecular diagnosis is absolutely necessary for countries where TB infection is endemic/epidemic.

The presence of mediastinal adenopathy may be the only imaging change in pulmonary TB in HIV-infected patients with CD4+ cell counts below 200 cells/μL\cite{22,23}. It is estimated that 60% to 68.8% of TB cases in patients in the last stage of HIV infection are associated with mediastinal/hilar adenopathy\cite{24,25}.

In our case, the aspect of the CT scan of the thorax and a negative AFB smear seemed to be sufficient to rule out a possible HIV-TB coinfection, but the dynamic imaging changes correlated with positive cultures on Löwenstein-Jensen medium confirmed the diagnosis. Susceptibility testing of the *M tuberculosis* isolated
strain demonstrated conservation of sensitivity to treatment and allowed the use of first-line therapy drugs (rifabutin, pyrazinamide, ethambutol, and isoniazid). TB treatment was initiated after the first month of HAART and Burkitt lymphoma chemotherapy, without developing immune reconstitution inflammatory syndrome. The patient partially recovered neurologically and was able to move his legs but only in a supine position. At 3 months after the initiation of HAART therapy the CD4+ cell count was 178 cells/μL. Unfortunately at 6 months the patient’s death was attributed to Burkitt lymphoma.

4. Conclusions
Burkitt lymphoma is a rare form of non-Hodgkin lymphoma associated with HIV infection, which classifies the patient in the AIDS stage. The rapid progression to dissemination or amelioration of the patient’s condition depends on the

*Figure 4. MRI sequences. MRI=magnetic resonance imaging.*
promptness of initiating the HAART-associated with cytostatic therapy.

**Author contributions**

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