Nodal Epstein-Barr virus-positive T-cell/NK-cell lymphoma associated with immunodeficiency: a rare condition looking for recognition

Cristiane Rúbia Ferreira[a], Aloísio Felipe-Silva[a], Fernando Peixoto Ferraz de Campos[b],
Maria Cláudia Nogueira Zerbini[c]

ABSTRACT

The authors describe a peculiar form of Epstein-Barr virus (EBV)-associated T-cell lymphoma in an HIV-positive patient presenting an aggressive clinical course. Unlike most other EBV-positive T-cell/natural-killer (NK)-cell lymphomas, the disease was characterized by predominant nodal involvement at presentation. T-cell lineage was confirmed by T-cell receptor-rearrangement, and neoplastic cells exhibited strong and diffuse CD56 expression. A marked intravascular component was detected in the skin, the liver, and the lung parenchyma. This entity was not predicted in the WHO 2008 classification, but has been recently identified in immunocompromised patients. This case report refers to a middle-aged man with AIDS, who presented a 4-month history of weight loss, fever, hepatosplenomegaly, peripheral and deep-chain lymphadenopathy. A blood smear showed lymphocytosis with a marked presence of atypia. The outcome was unfavorable and the patient could not be treated. The autopsy revealed multivisceral involvement, including lymph nodes, spleen, bone marrow, liver, lungs, skin, and kidneys.

Keywords
Lymphoma, T-cell; Killer Cells, Natural; Epstein-Barr Virus Infections; Acquired Immunodeficiency Syndrome; Autopsy.

CASE REPORT

A 54-year-old Afro-Brazilian male patient sought the emergency unit complaining of right lower limb pain, which had been worsening over the past 3 days. He also presented a 4-month history of weight loss (10 kg) accompanied by weakness, progressive lethargy, sporadic fever, and the presence of non-tender tumors in the axillary and groin regions. He smoked 10 packs/year, drank 30-40 g of alcohol daily for more than 10 years, used marijuana and cocaine, and had unprotected sexual intercourse. Physical examination

on admission disclosed an ill-looking patient, who was hypoactive, drowsy, pale, and dehydrated. Enlarged, non-tender lymph nodes, measuring up to 2 cm, were palpable in the axillary, cervical, and inguinal chains. The cardiac and pulmonary examinations were unremarkable; however, the abdomen was mildly distended, with tender hepatosplenomegaly. The right lower limb showed an asymmetric edema. Echo Doppler showed a thrombosis from the right common femoral vein until the ipsilateral popliteal

[a] Anatomic Pathology Service – Hospital Universitário – Universidade de São Paulo, São Paulo/SP – Brazil.
[b] Department of Internal Medicine – Hospital Universitário – Universidade de São Paulo, São Paulo/SP – Brazil.
[c] Department of Pathology – Faculdade de Medicina – Universidade de São Paulo, São Paulo/SP – Brazil.

vein. Laboratory work up of admission is summarized in Table 1.

The peripheral blood film exhibited the presence of 23% of large to medium-sized lymphocytes, some of them with vacuoles, basophilic cytoplasm, and fine chromatin with two to three nucleoli (Figure 1A).

Brain, nasal, and nasopharyngeal computed tomography (CT) were normal. Thoracic CT showed axillary and mediastinal lymphadenopathy (Figure 2),

and the abdominal examination showed splenomegaly with a probable area of infarction; and retroperitoneal, mesenteric, and bilateral inguinal lymphadenopathy (Figure 3).

The patient was submitted to a fine-needle aspiration biopsy of the left inguinal lymph node, which was further excised. The fine-needle aspiration cytology showed hypercellular smears with discohesive cells, irregularly folded nuclei, scant cytoplasm,

Table 1. Initial laboratory work-up results

Exam	Result	RV	Exam	Result	RV
Hemoglobin	11.9	12.3-15.3 g/dL	Ionized Ca++	1.57	< 1.32 nmol/dL
Hematocrit	36.8	36.0-45.0%	ALT	53	9-36 IU/L
Leukocytes	12.2	4.4-11.3 × 103/mm3	AST	162	10-31 IU/L
Segmented	36	45-70%	TB	0.4	0.3-1.2 mg/dL
Eosinophil	2	1-4%	TP	4.9	6-8 g/dL
Basophil	1		Albumin	2.1	3-5 g/dL
Lymphocyte	58%	18-40%	AP	109	50-250 IU/L
Atypical Ly	++++		γGT	102	2-30 IU/L
Monocytes	1	2-9%	LDH	2670	120-246 IU/L
Platelets	135	150–400 × 10³/mm³	CRP	63	< 5 mg/L
INR	1.26	1.0	Anti-HIV	Positive	
Urea	39	5-25 mg/dL	Anti-HCV	Negative	
Creatinine	0.52	0.4-1.3 mg/dL	Anti-HBs/c*	Positives	
Potassium	4.6	3.5-5.0 mEq/L	Syphilis	Negative	
Sodium	137	136-146 mEq/L	Anti-HTLV-1	Negative	

*Anti-HBs and anti-HBc; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CRP = C-reactive protein; γGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; INR = international normalized ratio; TB = total bilirubin; TP = total protein.

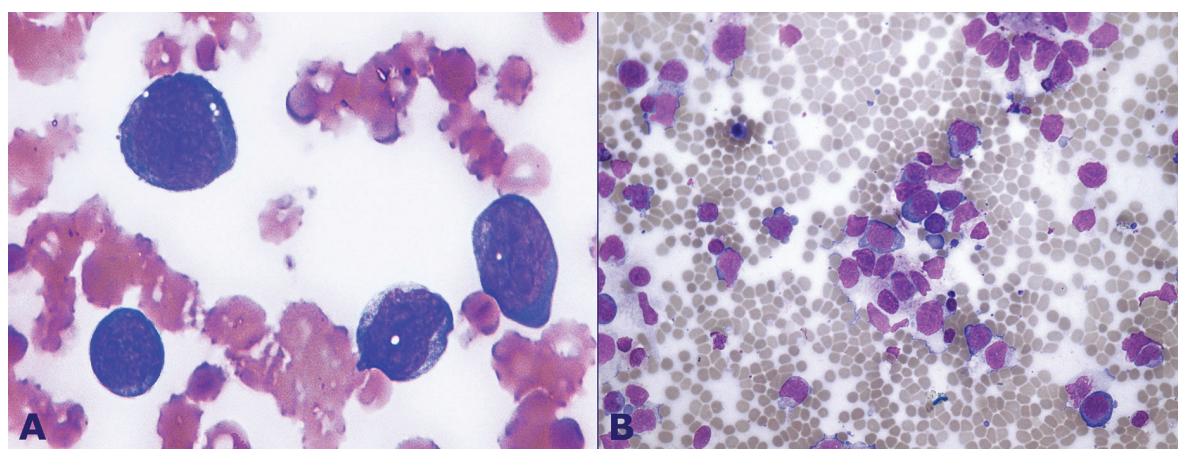**Figure 1. A** - Photomicrography of peripheral blood film showing a high magnification field with four atypical lymphocytes. (Leishman's staining, 1000X); **B** - Photomicrography of fine needle aspiration biopsy of the lymph node showing discoesive cells, irregularly folded nuclei, scant to moderate cytoplasm and cytoplasmic granules of atypical lymphoma cells (May-Grunwald stain, 400x).
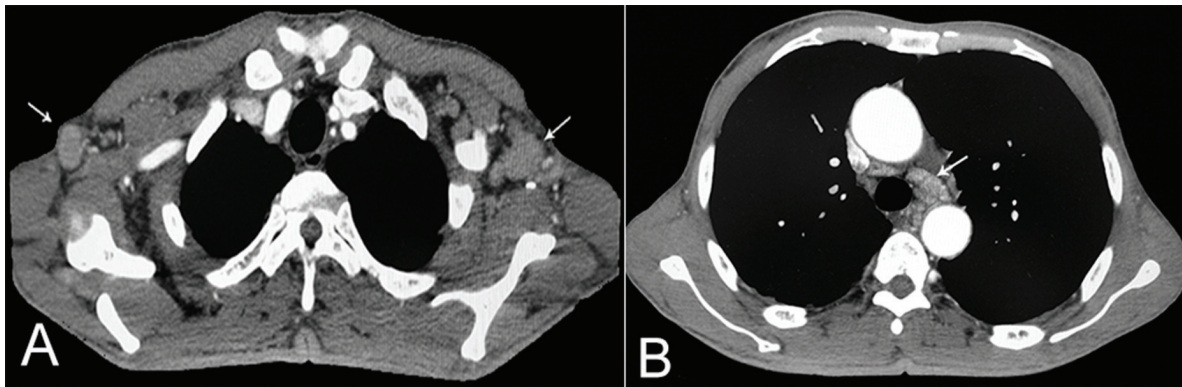
Figure 2. Axial CT of the thorax. **A** - Axillary lymphadenopathy (arrows); **B** - Mediastinal involvement of lymph nodes (arrows).
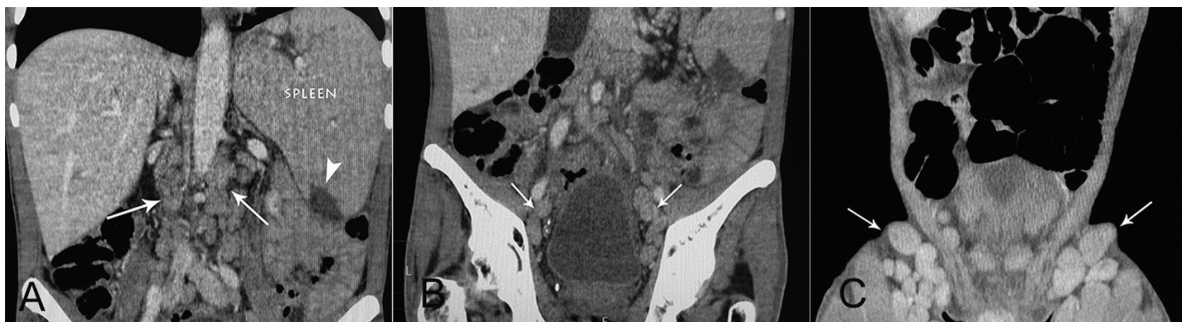

Figure 3. CT of the abdomen—coronal reformation. **A** - Splenomegaly with a hypoattenuating peripheral area (arrowhead), and periaortic lymphadenopathy; **B** - Bilateral enlarged lymph nodes in the iliac chain (arrows); **C** - Lymphadenopathy in the groin region (arrows).

inconspicuous nucleoli, and cytoplasmic granules, which were consistent with an aggressive non-Hodgkin lymphoma (Figure 1B).

The lymph node excisional biopsy showed diffuse and permeative lymphomatous growth with focal angiocentrism and areas of necrosis and apoptotic bodies. The cells were medium-sized to large, mostly monomorphic, but with some anaplastic foci, with irregularly folded nuclei, granular chromatin, and inconspicuous nucleoli. The cytoplasm was moderate-to-scant and eosinophilic. Many mitotic figures were present (Figure 4). The immunohistochemical panel is shown in Table 2. In situ hybridization for Epstein-Barr virus (EBV) was diffusely positive (Figure 5 and Figure 6). These features were consistent with an aggressive non-Hodgkin lymphoma, most likely of natural killer (NK)/T-cell phenotype and T-cell receptor gamma gene rearrangement by polymerase chain reaction (PCR) was present and clonal.

The outcome was unfavorable with extensive local lymphedema and infection of the surgical site. Blood culture isolated *Staphylococcus epidermidis* in

the blood sample (one in eight samples) treated with oxacillin. However, he remained hypoactive, obtunded, and presented multiple organ failure. He died on the tenth day of hospitalization.

AUTOPSY

An emaciated male cadaver with an abdominal paramedian incision scar was examined. Lower limbs edema was present along with multiple pigmented somewhat atrophic bilateral skin lesions. Histology showed chronic dermatitis with acanthosis, hyperkeratosis, and mild lymphomononuclear perivascular inflammation and atypical lymphomatous cells (Figure 7A). Deep venous thrombosis was identified in the right inguinal and popliteal regions. The inguinal surgical incision site drained fibrinous and purulent exudate. Microscopic examination revealed an abscess with necrotic debris and multiple Gram-positive and Gram-negative bacterial colonies. The heart was enlarged due to left ventricle hypertrophy (heart weight: 596g; mean reference value [mRV]: 327g). The
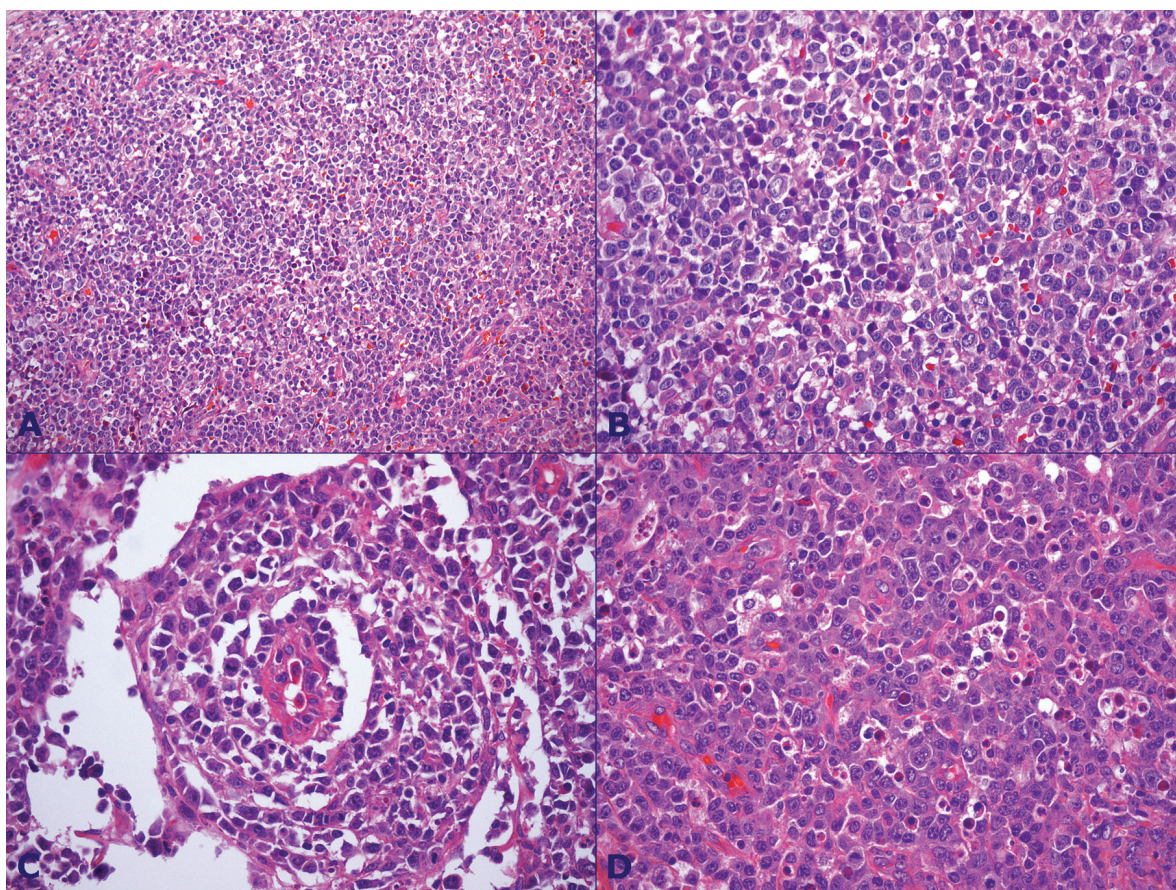
Figure 4. Photomicrography of lymph node biopsy. **A** - Diffuse solid lymphomatous growth (H&E, 100X); **B** - Monomorphic cells with irregularly folded nuclei and granular chromatin (H&E, 200X); **C** - Focal angiocentric pattern (H&E, 400X); **D** - Many apoptotic bodies and inconspicuous nucleoli (H&E, 400X).

Table 2. Immunohistochemistry panel

Antigen	Result	Antigen	Result
CD20	Negative	Bcl-2	Positive
CD3	Positive	Bcl-6	Negative
CD5	Negative	CD138	Negative
CD4	Negative	CD10	Negative
CD8	Negative	CD21	Negative
CD56	Positive	Granzyme	Positive
CD30	Positive	Perforin	Positive
EMA	Negative	TCL-1	Negative
ALK	Negative	Ki67	Positive 99%
EBV(LMP1)* (LMP1)	Negative		

*In situ hybridization for EBER was diffusely positive.

lungs were friable, reddish/purple, and heavy (right lung weighed 1244 g; mRV: 450 g; and the left lung weighed 675 g; mRV: 375 g), with multiple scattered foci of consolidation, which were confirmed as acute bronchopneumonia and acute alveolar damage upon histological examination. Focal septic emboli were detected as well. Enlarged lymph nodes measuring up to 4 cm were present in the pulmonary hila and around the carina.

Numerous enlarged lymph nodes were present mainly in the iliac bifurcation and in the groin. Lymphoma cells diffusely infiltrated the spleen and bone marrow. Intra or perivascular malignant cells were found in the lungs, skin, and liver (Figure 7B-D).

The spleen was winy-colored, enlarged (weighed 910 g: mRV: 112 g) and hardened. At the subcapsular region, friable whitish/yellowish areas were present and acute infarction was confirmed on histology (Figure 8).

The liver weighed 2314 g (mRV: 1985 g). The pancreas was slightly hardened without focal lesions. Alcoholic chronic pancreatitis was diagnosed at histology. In the digestive tract, erosions were found in the stomach, rectum, and sigmoid.

The kidneys presented subcortical cysts. Focal malignant cells could be identified in glomeruli. Acute tubular necrosis was evident. Signs of chronic
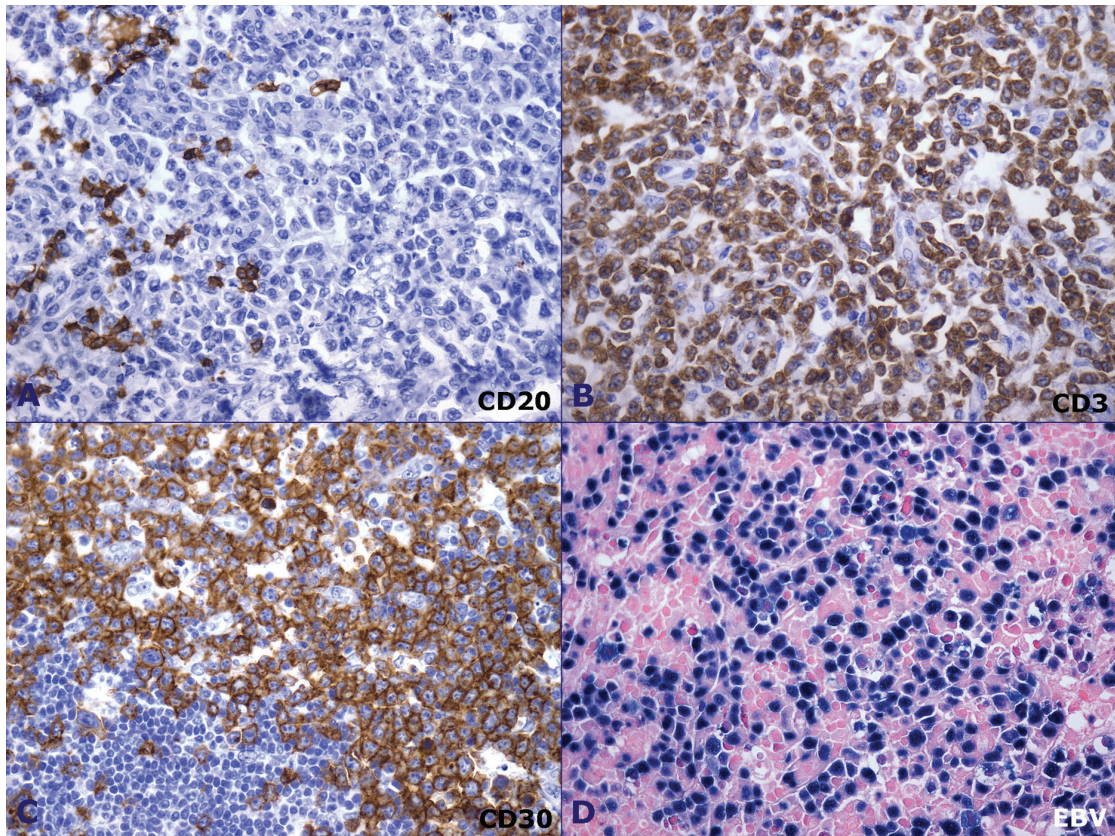
Figure 5. Photomicrography of lymph node biopsy. **A** - Negative immunohistochemistry for CD20 (400X); **B** - Positive immunostaining for CD3 (400X); **C** - Immunostaining for CD30 (400X); **D** - Diffusely positive in situ hybridization for EBV (in blue) (400X).
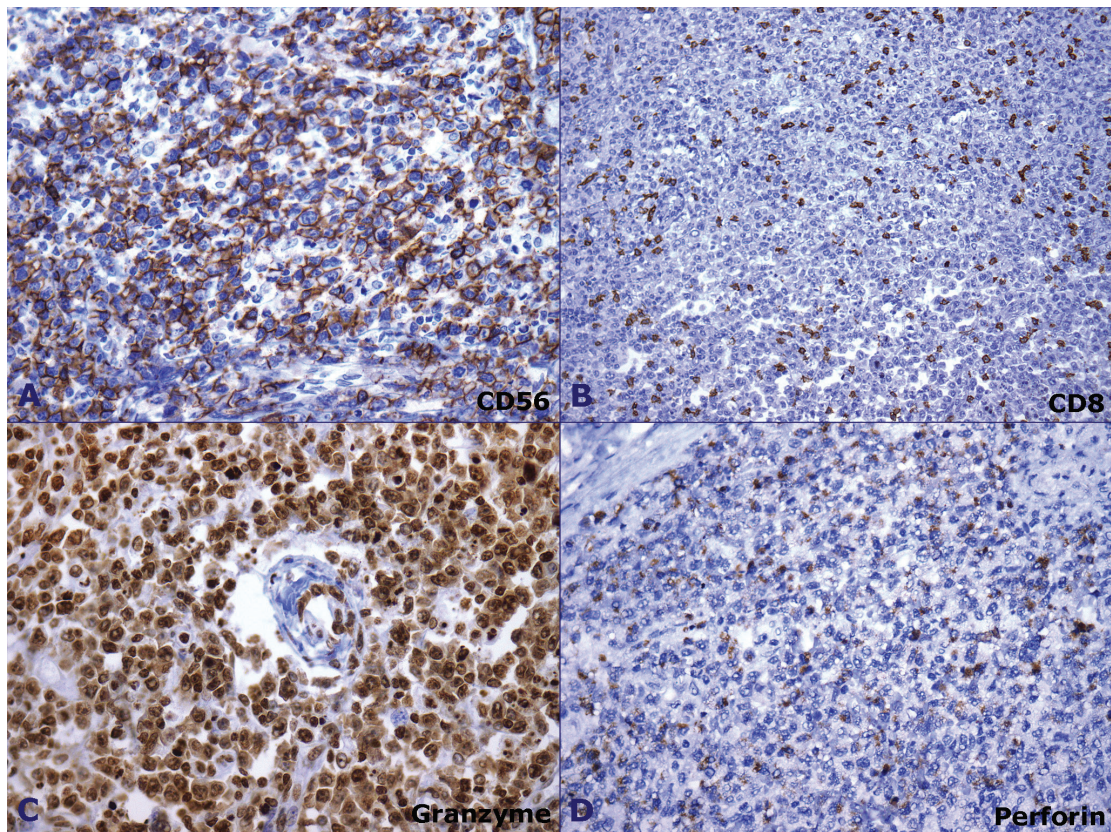
Figure 6. Photomicrography of lymph node biopsy. **A** - Positive immunostaining for CD56 (400X); **B** - Negative immunostaining for CD8 (200X); **C** - Positive immunostaining for granzyme (400X) and **D** - perforin (200X).
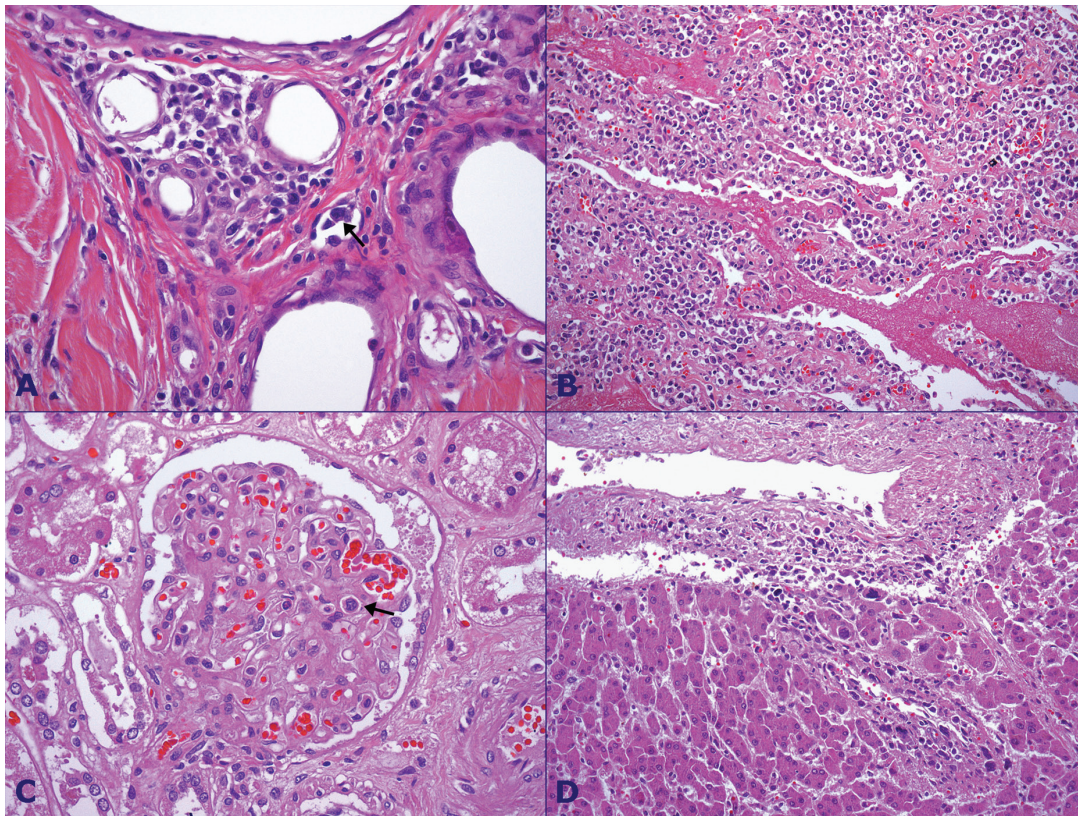
Figure 7. Systemic infiltration of organs by lymphoma cells: skin (**A** – arrow pointing to an atypical intravascular lymphoma cell; H&E, 400X); lung (**B** - H&E, 200X); kidney glomerulus (**C** – arrow pointing to an atypical intracapillary lymphoma cell; H&E, 400X); perivascular and periportal lymphomatous infiltration of the liver (**D** - H&E, 200X).
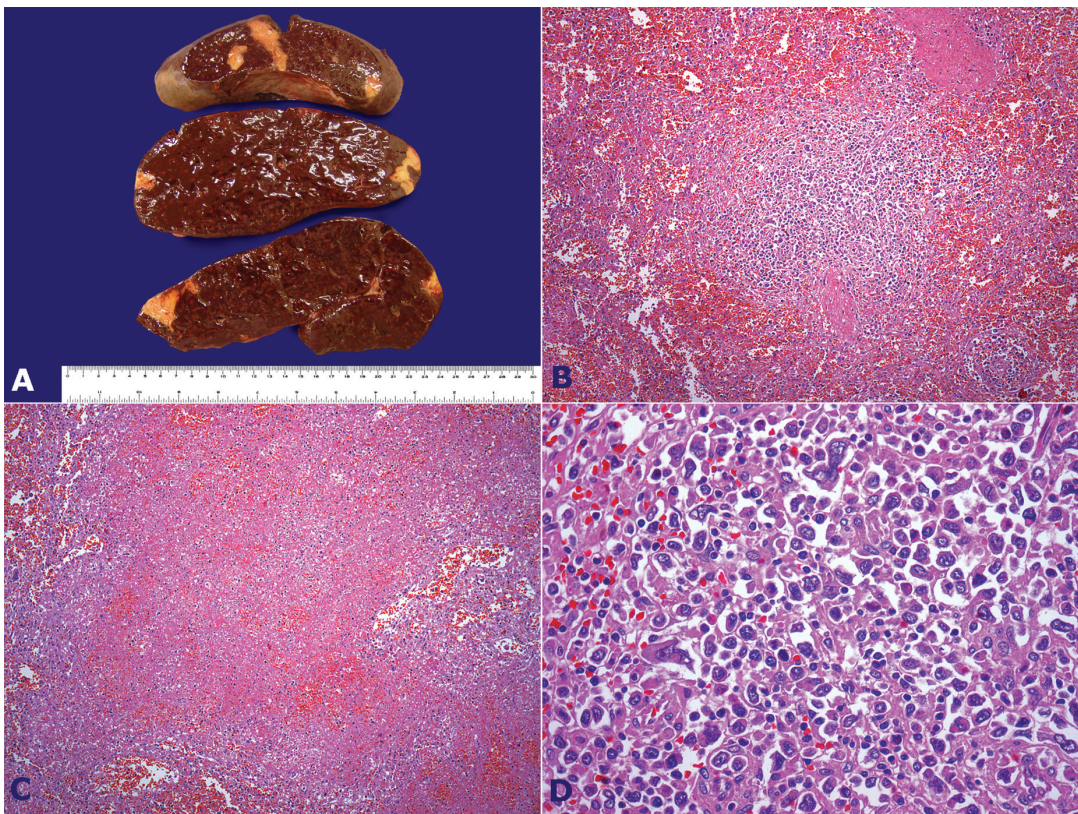
Figure 8. A - Gross aspect of the enlarged spleen with infarcts. AT microscopy: **B** - Perivascular and nodular lymphomatous infiltration (H&E, 100X); **C** - An area of infarct (H&E, 100X); **D** - Lymphoma with some anaplastic cells (H&E, 400X).

systemic hypertension were present in the kidneys and brain. Autopsy also diagnosed acute adrenalitis with cytomegalovirus inclusions confirmed by immunohistochemistry.

DISCUSSION

Historically, NK cells were described in 1975 by both the Kiessling group and the Herberman group.[1-5] Later, in 1987, a population of T-cells that shared some features with NK cells, such as cytotoxic activity and immunophenotype positivity for NK markers, was described. Recently, this subset of T-cells has been called NKT cells (also known as NK-like T-cells).[6,7] The term NK-like T-cells was initially used to refer to any T-cell that expressed cell surface antigens associated with the NK-cell lineage. NKT cells are a small population of thymus-derived T-cell that are restricted by the CD1d histocompatibility complex protein class I-like (MHC-I) molecule, expressing semi-invariant T-cell receptor (TCR) that confers a specificity for glycolipid antigens. However, the classification of NKT cells is problematic because it does not define a T-cell lineage with unique phenotypical or functional attributes, but they represent distinct lineages of T-cells that can express NK-cell antigens.[8]

NK cells and their functions are at the interface between innate and adaptive immunity. The innate immune system shows characteristics of recognition of molecular patterns and rapid response, and there is no need for clonal expansion. But, the boundaries between lymphocytes of the innate and adaptive immune system are blurred, since some innate lymphocytes can rearrange clonal antigen receptor loci and at the same time show the same characteristics of the innate immune system. Between T lymphocytes, there are $\alpha\beta$ TCR-expressing T-cells of which the TCR does not recognize MHC/peptide complexes. They are called invariant NKT cells (iNKT) and T-cells expressing $\gamma\delta$ TCRs, both of which are related to the CD1d restrict molecule and the CD56 positive immunophenotype.[8,9]

An overlap between a subpopulation of the T-cell and the NK-cell antigen expression, function, and patterns of disease does exist, probably because both arise from the same bi-potential NK/T precursors, being ontogenetically similar.[1,10] NK cells and subtypes of T-cells are considered as cytotoxic cells, which contain cytotoxic granule proteins such as TIA-1, granzyme, and perforin in their cytoplasm. Moreover, there is also a subset of cytotoxic T-cells that express NK-associated antigens (such as CD56) representing the NKT cells.[10-12]

This complex network of the immune system is reflected in the histopathologic and phenotypic heterogeneity within distinct lymphoma entities, with overlapping features between different entities, especially among T-cell and NK-cell lymphomas.[13] Most extranodal lymphomas arise from cytotoxic cells, since these cells are located mainly at extranodal sites, such as the splenic red pulp, gastrointestinal tract, skin, and other epithelial sites, with primary nodal involvement being rare.[11,12]

This case report illustrates how challenging the classification of T-cell and NK-cell lymphomas is. Herein, we report a rare case of an HIV-related T-cell/NK-cell disseminated lymphoma with prevailing nodal involvement, NK cell immunophenotype and clonal TCR gene rearrangement.

Despite the rarity of NK-cell neoplasms, the most common and well-characterized neoplasm of this cell lineage is the extranodal NK/T-cell lymphoma, nasal type (ENKTCL).[11,14] By definition, ENKTCL is a predominantly extranodal lymphoma characterized by vascular damage and destruction, prominent necrosis, cytotoxic phenotype, and is associated with EBV. It is designated "NK/T" because, while most cases appear to be genuinely NK-cell neoplasms, some show a cytotoxic T-cell phenotype and a clonal TCR rearrangement.[15] These criteria were better established in 1994 by the Hong Kong workshop sponsored by the Society of Hematopathology, later supported by the data of Emile et al.[16-19] Morphologically, the disease is characterized by a polymorphic infiltrate, consisting of atypical cells with a broad cytological spectrum, which include small, medium-sized, or large atypical cells, with a mixture of inflammatory cells, which are frequently associated with zonal pattern necrosis and admixed apoptotic bodies.[15,18]

ENKTCL is more prevalent in Asian and native populations of Mexico, Central America, and South America, whereas it is uncommon in North America and Europe. It occurs most often in adults (median age ranges from 49 to 53 years) and is more prevalent in males.[15,20-22] According to the site of origin, ENKTCL can be divided into two major subtypes: nasal and extranasal (often referred to as extranasal NK/T cell lymphomas).[15,23] The nasal subtype is the most frequent and affects the upper aerodigestive tract,

with the nasal cavity being the prototypic site of involvement. Extranasal NKTCL is frequently detected at an advanced stage, shows the same histopathology and immunophenotipic characteristics of the nasal NKTCL, but involves other extranodal sites, such as skin, soft tissue, gastrointestinal tract, and testis, usually without lymphadenopathy nor any apparent nasal involvement.[15,23] Bone marrow involvement, at the time of diagnosis, is uncommon in nasal (< 3.5%) and extranasal (< 7%) NKTCL.[20]

Until today, only a few cases of extranasal NKTCL with primary lymph node disease have been described.[21,24-27] A high frequency of monoclonal TCR gene rearrangement in the nodal NKTCL series was observed, showing that, despite the similar immunophenotype, some are derived from cytotoxic T-cells.[20,26] Nodal NKTCLs involve the cervical lymph nodes, present similar histology and phenotype of extranodal NKTCL and have a poor prognosis (less than 12 months' survival).[20]

Another NK-cell neoplasm considered in the differential diagnosis, of the case reported herein, was the aggressive NK cell leukemia/lymphoma (ANKL). Except for the higher positivity of CD16 in ANKL, NKTCL and ANKL share an identical immunophenotypic profile; namely, CD2+, CD3ε+ (cytoplasmic), CD56+, CD4-, CD5-, TIA-1+, granzyme+, perforine+, a strong association with EBV by in situ hybridization for EBER and germline configuration of the TCR gene.[15] However, ANKL shows some distinguishing features: involvement of young-aged patients, (from teenager to middle-aged: mean = 39 years), lack of gender predominance, and the presence of tumoral cells in the peripheral blood, as well as bone marrow infiltration—albeit minimal in some cases. The cutaneous involvement is uncommon and nodal disease is more frequently observed. Morphology is of monotonous-appearing; the involved tissues are usually dense, permeative, with medium-sized lymphoid cells with round nuclear contour. Prominent apoptosis and angioinvasive-angiodestructive growth pattern also can be seen.[15,24,28] ANKL presents a fatal clinical course; most patients die within days-to-weeks after presentation (median survival of 58 days). Distinguishing ANKL from advanced systemic NKTCL is not an easy task because of the discrepancy of a high number of neoplastic cells in the peripheral blood and poor bone marrow infiltration. Patients with nasal NKTCL rarely develop features of ANKL.[15,24,29-31]

The case report herein seems to be similar to the rare cases reported on the lymphoma workshop of the XVIth meeting of the European Association for Haematopathology and the Society for Hematopathology (EAHP lymphoma workshop).[32] The workshop encountered four cases of EBV-positive T-cell lymphoma that did not conform to NKTCL as classically defined. The cases were relatively monomorphic and all had lymph node involvement at presentation. Interestingly, the cases were associated with immunodeficiency, were HIV-associated, and presented a marked intravascular component (both features present in the case herein reported), and post-transplant or advanced age related. These observations confirm that not all EBV-positive T-cell lymphomas should be classified as NKTCL, but whether they represent a distinct entity remains to be determined. (The term "nodal T-cell/NK-cell lymphoma" was proposed to separate these cases.[32])

Interestingly, one of the first series of NKT cells lymphoma in literature, described by Macon et al.,[7] showed EBV-associated disease, in an advanced stage, with a median survival less than 6 months and a high frequency of chronically immunosuppressed patients (four out of six patients). The authors suggested that NK-like T-cell lymphomas should be included in the differential diagnosis of T-cell proliferations developing in immunosuppressed patients.

Our case report had many similarities with ANKL, such as monomorphic morphology, bone marrow and peripheral blood involvement, and nodal presentation. However, the patient was out of the usual age range for this neoplasia, was HIV-associated, and presented a clonal TCR rearrangement. To the best of our knowledge, there is no case of ANKL related to HIV in the English literature.

Most non-Hodgkin lymphomas that have developed in HIV patients showed B-cell phenotypes, such as Burkitt lymphoma, primary effusion lymphoma, plasmoblastic lymphoma of the oral cavity, and multicentric Castleman disease. HIV patients with lymphoma often present extranodal disease, most frequently involving the gastrointestinal tract, the central nervous system, the bone marrow, and the liver.[15] There are very few reported cases of NK/T-cell lymphoma associated with EBV in an HIV patient.[33-35] Canioni et al.[36] reported the first case of NKTCL in an HIV patient in 2001. NKTCL cases in HIV have varied

with respect to immunophenotype, sites of disease, and clinical presentation.[36] The primary sites of disease of NKTCL related to HIV patients include nasopharynx, tonsil, parotid gland, lung/mediastinum, colon, liver, and lymph node. The majority of patients were men (median age of 42 years), with low CD4 counts (< 200/dL). The prognosis of NKTCL in HIV-related patients is very poor, usually with less than 1 month of survival.[33-35]

This case report illustrates the challenging diagnosis and classification of NK-cell neoplasms, particularly in the HIV-infected patient. Moreover, the diagnosis of NK/T-cell neoplasms is complicated by the significant phenotype overlap between NK cells and cytotoxic T-cells, and the lack of a clonal marker in NK cell neoplasms. Despite the overlap of this case report between both NKTCL and ANKL, this case most probably represents the nodal T-cell/NK-cell lymphoma HIV-related proposed by the EAHP lymphoma workshop.[32]

REFERENCES

1. Bonavida B. NK cell phenotypic and functional heterogeneities and molecular mechanisms of cytotoxicity. Crit Rev Oncog. 2014;19(1-2):21-45. http://dx.doi.org/10.1615/CritRevOncog.2014010804. PMid:24941371

2. Kiessling R, Klein E, Wigzell H. "Natural" killer cells in the mouse. I. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype. Eur J Immunol. 1975;5(2):112-7. http://dx.doi.org/10.1002/eji.1830050208. PMid:1234049

3. Kiessling R, Klein E, Pross H, Wigzell H. "Natural" killer cells in the mouse. II. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Characteristics of the killer cell. Eur J Immunol. 1975;5(2):117-21. http://dx.doi.org/10.1002/eji.1830050209. PMid:1086218

4. Herberman RB, Nunn ME, Lavrin DH. Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic acid allogeneic tumors. I. Distribution of reactivity and specificity. Int J Cancer. 1975;16(2):216-29. http://dx.doi.org/10.1002/ijc.2910160204. PMid:50294

5. Herberman RB, Nunn ME, Holden HT, Lavrin DH. Natural cytotoxic reativity of mouse lymphoid cells against syngeneic acid allogeneic tumors. II. Characterization of effector cells. Int J Cancer. 1975;16(2):230-9. http://dx.doi.org/10.1002/ijc.2910160205. PMid:1080480

6. Godfrey DI, Hammond KJL, Poulton LD, Smyth MJ, Baxter AG. NKT cells: facts, functions and fallacies. Immunol Today. 2000;21(11):573-83. http://dx.doi.org/10.1016/S0167-5699(00)01735-7. PMid:11094262

7. Macon WR, Williams ME, Greer JP, et al. Natural killer-like T-cell lymphomas: aggressive lymphomas of T-large granular lymphocytes. Blood. 1996;87(4):1474-83. PMid:8608238.

8. Berzins SP, Smyth MJ, Baxter AG. Presumed guilty: natural killer T cell defects and human disease. Nat Rev Immunol. 2011;11(2):131-42. http://dx.doi.org/10.1038/nri2904. PMid:21267014

9. Vermijlen D, Prinz I. Ontogeny of innate T lymphocytes – some innate lymphocytes are more innate than others. Front Immunol. 2014;5:486. http://dx.doi.org/10.3389/fimmu.2014.00486. PMid:25346734

10. Colucci F, Caligiuri MA, Di Santo JP. What does it take to make a natural killer? Nat Rev Immunol. 2003;3(5):413-25. http://dx.doi.org/10.1038/nri1088. PMid:12766763

11. Greer JP, Kinney MC, Loughran TP Jr. T cell and NK cell lymphoproliferative disorders. Hematology (Am Soc Hematol Educ Program). 2001;2001(1):259-81. http://dx.doi.org/10.1182/asheducation-2001.1.259. PMid:11722988

12. Jaffe ES, Krenacs L, Raffeld M. Classification of cytotoxic T-cell and natural killer cell lymphomas. Semin Hematol. 2003;40(3):175-84. http://dx.doi.org/10.1016/S0037-1963(03)00132-X. PMid:12876666

13. Swerdlow SH, Jaffe ES, Brousset P, et al. Cytotoxic T-cell and NK-cell lymphomas: current questions and controversies. Am J Surg Pathol. 2014;38(10):e60-71. http://dx.doi.org/10.1097/PAS.0000000000000295. PMid:25025449

14. William BM, Armitage JO. International analysis of the frequency and outcomes of NK/T-cell lymphomas. Best Pract Res Clin Haematol. 2013;26(1):23-32. http://dx.doi.org/10.1016/j.beha.2013.04.003. PMid:23768638

15. Raphael M, Said J, Borisch B, Cesarman E, Harris NL. Lymphomas associated with HIV infections. In: Swerdlow SH, Campo E, Harris NL, et al., editors. WHO classification of tumors of haematopoietic and lymphoid tissues. IARC: Lyon; 2008. p. 340-2.

16. Jaffe ES. Classification of natural killer (NK) cell and NK-like T-cell malignancies. Blood. 1996;87(4):1207-10. PMid:8608206.

17. Emile JF, Boulland ML, Haioun C, et al. CD5-CD56+ T-cell receptor silent peripheral T-cell lymphomas are natural killer cell lymphomas. Blood. 1996;87(4):1466-73. PMid:8608237.

18. Jaffe ES, Chan JK, Su I-J, et al. Report of the Workshop on Nasal and Related Extranodal Angiocentric T/Natural Killer Cell Lymphomas. Definitions, differential diagnosis, and epidemiology. Am J Surg Pathol. 1996;20(1):103-11. http://dx.doi.org/10.1097/00000478-199601000-00012. PMid:8540601

19. Kwong YL, Chan ACL, Liang RH. Natural killer cell lymphoma/leukemia: pathology and treatment. Hematol Oncol. 1997;15(2):71-9. http://dx.doi.

org/10.1002/(SICI)1099-1069(199705)15:2<71::AID-HON601>3.0.CO;2-U. PMid:9375032

20. Lima M. Aggressive mature natural killer cell neoplasms: from epidemiology to diagnosis. Orphanet J Rare Dis. 2013;8(1):95-104. http://dx.doi.org/10.1186/1750-1172-8-95. PMid:23816348

21. Gualco G, Domeny-Duarte P, Chioato L, Barber G, Natkunam Y, Bacchi CE. Clinicopathologic and molecular features of 122 Brazilian cases of nodal and extranodal NK/T-cell lymphoma, nasal type, with EBV subtyping analysis. Am J Surg Pathol. 2011;35(8):1195-203. http://dx.doi.org/10.1097/PAS.0b013e31821ec4b5. PMid:21716086

22. Li S, Feng X, Li T, et al. Extranodal NK/T-cell lymphoma, nasal type: a report of 73 cases at MD Anderson Cancer Center. Am J Surg Pathol. 2013;37(1):14-23. http://dx.doi.org/10.1097/PAS.0b013e31826731b5. PMid:23232851

23. Au WY, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood. 2009;113(17):3931-7. http://dx.doi.org/10.1182/blood-2008-10-185256. PMid:19029440

24. Chan JKC, Sin VC, Wong KF, et al. Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood. 1997;89(12):4501-13. PMid:9192774.

25. Chim CS, Ma ESK, Loong F, Kwong YL. Diagnostic cues for natural killer cell lymphoma: primary nodal presentation and the role of in situ hybridisation for Epstein-Barr virus encoded early small RNA in detecting occult bone marrow involvement. J Clin Pathol. 2005;58(4):443-5. http://dx.doi.org/10.1136/jcp.2004.022608. PMid:15790718

26. Takahashi E, Asano N, Li C, et al. Nodal T/NK-cell lymphoma of nasal type: a clinicopathological study of six cases. Histopathology. 2008;52(5):585-96. http://dx.doi.org/10.1111/j.1365-2559.2008.02997.x. PMid:18370955

27. Chang ST, Liao YL, Lin SH, Chuang SS. NK-cell lymphoma with nodal presentation and expression of cutaneous lymphocyte-associated antigen. Pathol Res Pract. 2010;206(7):463-6. http://dx.doi.org/10.1016/j.prp.2009.07.001. PMid:19628338

28. Cheuk W, Chan JKC. NK-Cell neoplasms. In: Jaffe ES, Harris NL, Vandiman JW, Campo E, Arber DA, editors. Hematopathology. Philadelphia: Elsevier Saunders; 2011. p. 486-90.

29. Suzuki R, Suzumiya J, Nakamura S, et al. Aggressive natural killer-cell leukemia revisited: large granular lymphocyte leukemia of cytotoxic NK cells. Leukemia. 2004;18(4):763-70. http://dx.doi.org/10.1038/sj.leu.2403262. PMid:14961041

30. Ruskova A, Thula R, Chan G. Aggressive Natural Killer-Cell Leukemia: report of five cases and review of the literature. Leuk Lymphoma. 2004;45(12):2427-38. http://dx.doi.org/10.1080/10428190400004513. PMid:15621755

31. Zhang H, Meng Q, Yin W, Xu L, Lie L. Adult aggressive natural killer cell leukemia. Am J Med Sci. 2013;346(1):56-63. http://dx.doi.org/10.1097/MAJ.0b013e3182764b59. PMid:23241562

32. Attygalle AD, Cabeçadas J, Gaulard P, et al. Peripheral T-cell and NK-cell lymphomas and their mimics; taking a step forward - report on the lymphoma workshop of the XVIth meeting of the European Association for Haematopathology and the Society for Hematopathology. Histopathology. 2014;64(2):171-99. http://dx.doi.org/10.1111/his.12251. PMid:24128129

33. Oh SC, Choi CW, Kim BS, et al. NK/T-cell lymphoma associated with Epstein-Barr virus in a patient infected with human immunodeficiency virus: an autopsy case. Int J Hematol. 2004;79(5):480-3. http://dx.doi.org/10.1532/IJH97.A10316. PMid:15239400

34. Panarelli NC, Furman RR, Wang YL, Elstrom R, Cohen JA, Chadburn A. NK/T cell non-Hodgkin lymphoma in a HIV-positive patient. J Hematop. 2010;3(1):35-40. http://dx.doi.org/10.1007/s12308-010-0057-5. PMid:21373175

35. Nagahata Y, Kato A, Imai Y, Ishikawa T. HIV-related NK/T-cell lymphoma in the brain relapsed during intensive chemotherapy but regressed after chemotherapy discontinuation: the importance of maintaining cellular immunity. Int J Hematol. 2014;100(4):402-6. http://dx.doi.org/10.1007/s12185-014-1610-2. PMid:24938379

36. Canioni D, Arnulf B, Asso-Bonnet M, Raphael M, Brousse N. Nasal natural killer lymphoma associated with Epstein-Barr virus in a patient infected with human immunodeficiency virus. Arch Pathol Lab Med. 2001;125(5):660-2. PMid:11300939.

Correspondence
Serviço de Anatomia Patológica, Hospital Universitário da Universidade de São Paulo
Av. Prof. Lineu Prestes, 2565 – Cidade Universitária – São Paulo/SP – Brazil
CEP: 05508-000
Phone: +55 (11) 3091-9384
E-mail: crisrf@hu.usp.br