Case report

Kaposi sarcoma facilitates the diagnosis of Castleman disease in a patient living with HIV

Sarcoma de Kaposi favorece o diagnóstico de doença de Castleman em paciente vivendo com HIV

Fernando Oliveira e Silva[1]*
César Cilento Ponce[2]
Rosely Antunes Patzina[2]
Edgar de Bortholi Santos[3]

[1] Centro Hospitalar Universitário de São João, Doenças Infeciosas - Porto - Portugal
[2] Instituto de Infectologia Emílio Ribas, Patologia Clínica - São Paulo - Brazil
[3] Instituto de Infectologia Emílio Ribas - São Paulo - Brazil

Submitted: 21 february 2023
Accepted: 17 march 2023
Published: 12 may 2023

***Corresponding Author:**
Fernando Oliveira e Silva
E-mail: fernandofreitas_pt@hotmail.com / u014967@chsj.minsaude.pt

DOI: 10.5935/2764-734X.e20230325-en

ABSTRACT

Diseases caused by human herpesvirus 8 (HHV-8) can affect immunosuppressed patients, particularly those co-infected with the human immunodeficiency virus (HIV). Castleman disease is one such condition that is rare and challenging to diagnose, given its numerous nonspecific symptoms and multiple differential diagnoses.
This study reports a case of a patient living with HIV who was diagnosed with multicentric Castleman disease, wherein the diagnosis was facilitated by the concomitant presence of Kaposi sarcoma in the gastrointestinal tract, both of which are directly related to HHV-8 infection.

Headings: Kaposi sarcoma; Human Herpesvirus 8; HIV; Giant lymph node hyperplasia; Case report.

RESUMO

O herpesvírus humano 8 (HHV-8) é um vírus com capacidade de causar doença em pacientes imunodeprimidos, particularmente em indivíduos coinfectados pelo vírus da imunodeficiência humana (HIV). Algumas destas manifestações, como a doença de Castleman, são pouco comuns e o diagnóstico pode ser difícil pela variedade de sintomas inespecíficos e pela existência de múltiplos diagnósticos diferenciais. Reportamos o caso de um paciente vivendo com HIV cujo diagnóstico de doença de Castleman multicêntrica foi favorecido pela existência concomitante de sarcoma de Kaposi no trato gastrointestinal, lembrando que ambas entidades estão diretamente relacionadas à infecção pelo HHV-8.

Descritores: Sarcoma de Kaposi; Herpesvirus humano 8; HIV; Hiperplasia do linfonodo gigante; Relato de caso.

INTRODUCTION

Human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma (KS)-associated herpesvirus, was discovered in 1994 through molecular biology techniques. This virus has pathological potential in patients infected with human immunodeficiency virus (HIV) and can cause several other diseases, including primary sinus lymphoma[1] and Castleman disease[2], in addition to KS.[3]

Given that these diseases are rare or declining in prevalence, it is crucial to document cases of HHV-8 infection to assist clinicians in recognizing and managing these conditions, particularly in the context of immunosuppressed patient care.

CASE REPORT

A 28-year-old male hairdresser, who reported having sex with men, presented with cervical and axillary adenomegaly, accompanied by a subjective feverish sensation.

Following the advice of a client, he underwent a rapid HIV test which yielded a positive result. Upon receiving the result, he sought specialized outpatient care and was prescribed antiretroviral treatment (ART) consisting of tenofovir, lamivudine, and dolutegravir.

After a month, due to persistent symptomatic conditions, the patient was admitted to a reference hospital for cervical lymph node biopsy. On admission, chest computed tomography (CT) revealed the presence of pulmonary nodules (Figure 1), in addition to bilateral prominent mediastinal, hilar, and axillary lymph nodes (Figure 2). Furthermore, abdominal CT showed hepatosplenomegaly as well as retroperitoneal, pericecal, mesenteric, and perisplenic lymph node enlargement. Histological analysis of the right cervical lymph node biopsy revealed exuberant follicular lymphoid proliferation and moderate plasmacytosis, with negative microbiological study and culture findings, indicating the presence of HIV-associated lymphadenopathy in the follicular hyperplasia stage (Figure 3). Following this diagnosis, the patient was discharged for outpatient follow-up with continued ART.

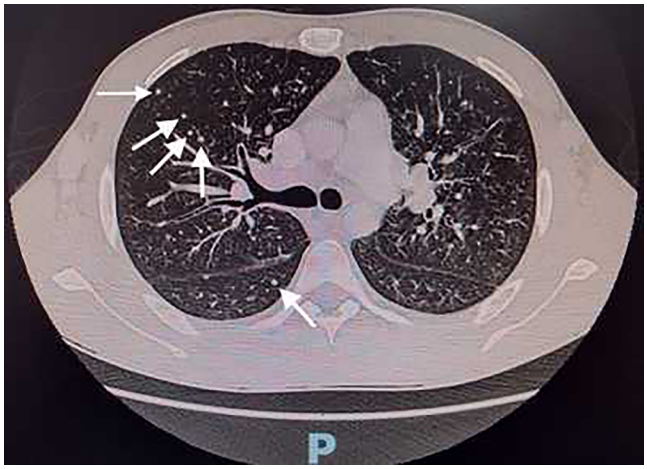

Figure 1. Chest computed tomography (CT) showing the presence of scattered small pulmonary nodules, as indicated by the arrows.

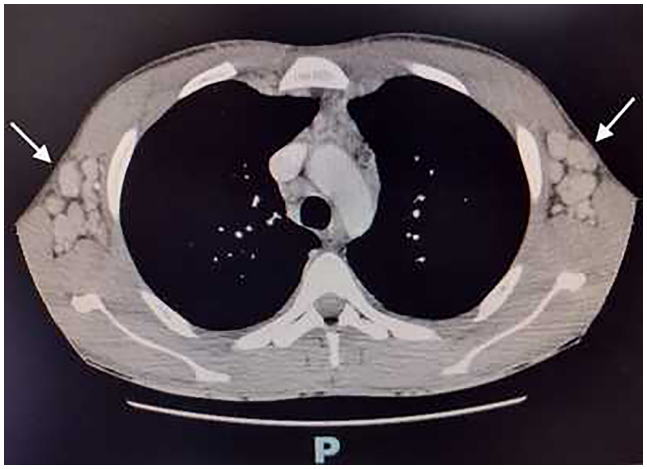

Figure 2. Chest computed tomography (CT) revealing the presence of lymph node enlargement in both axillae with measurements of up to 2.6 cm in the short axis, as indicated by the arrows.

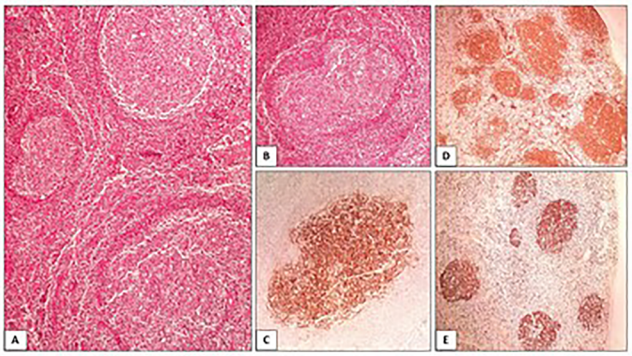

Figure 3. A. Lymphadenopathy associated with human immunodeficiency virus (HIV) infection in the phase of explosive follicular hyperplasia (H&E, 100X); B. Expanded lymphoid follicle with a "geographical" aspect and depleted mantle zone (H&E, 100X); C. Follicle center dendritic cells demarcating follicular expansion (IHC CD23, 100X); D. Cortical zone of the lymph node (IHC CD20, 40X); E. High cell proliferation rate in hyperplastic germinal centers (IHC Ki67, 40X). H&E: hematoxylin and eosin stain; IHC: immunohistochemistry.

Over the following weeks, the patient returned to the outpatient care service several times due to continuous fever and adenopathy. Subsequent chest and abdominal CT revealed superficial and deep lymphadenopathy in multiple locations. To rule out opportunistic lung diseases, the patient underwent a bronchoscopy, which only showed posterior chronic laryngitis. Microbiological bronchoalveolar lavage tests yielded negative findings, and transbronchial biopsy yielded nonspecific results (focal anthracosis and fibrosis). At the time of bronchoscopy, the HIV

viral load of the patient was 733 copies/mL and CD4 T lymphocyte count was 242 cells/μL. However, a definitive diagnosis for the patient's symptomatic condition could not be established.

Four months following the onset of the condition, the patient was hospitalized once again due to an event of syncope, accompanied by lymph node enlargement, fever, and tremors. On the 7th day of hospitalization, bone marrow aspiration was performed to exclude lymphoproliferative disease or opportunistic infection, which noted hemophagocytosis – a finding that, along with fever, splenomegaly, peripheral blood cytopenia, high blood ferritin level, and hypertriglyceridemia, allowed the diagnosis of a hemophagocytic syndrome according to the modified criteria of the Hemophagocytic Lymphohistiocytosis (HLH-2004) trial.[4] The patient was started on corticosteroid therapy with prednisone 40 mg/day and was weaned off the medication over the following week.

The patient underwent positron emission tomography (PET) during this hospitalization, revealing glycolytic hypermetabolism in multiple lymph nodes with supra- and infra-diaphragmatic conglomerates in the pharyngeal and palatine tonsils, in the focal gastric areas, and in parietal thickening areas in the cecum. These findings were classified to be of an undetermined nature. On the 12th day of hospitalization, upper digestive endoscopy was performed, which revealed multiple wine-colored lesions (Figure 4) in the esophagus, stomach, and duodenum. Mucosa biopsy samples were collected from the gastric and duodenal regions, revealing atypical vascular proliferation in the lamina propria and rare and uncharacteristic cytopathic endothelial cell changes (Figure 5). Positive immunohistochemistry finding for the HHV-8 antigen was observed. Thus the diagnosis of gastrointestinal KS was defined based on the integrated immunohistochemical profile, endoscopic, and histological reports.

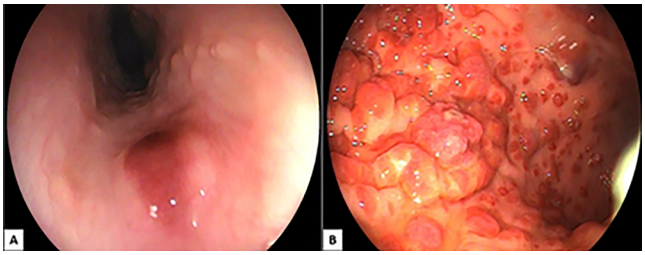

Figure 4. Upper digestive endoscopy findings. A. Small diffuse wine-colored lesions in the esophagus compatible with Kaposi sarcoma (KS); B. Gastric mucosa with mild diffuse edema and enanthema; extensive elevated, wine-colored, diffuse lesions confluent in the gastric fundus and body; and some ulcerated at the apex and covered by fibrin and hematin.

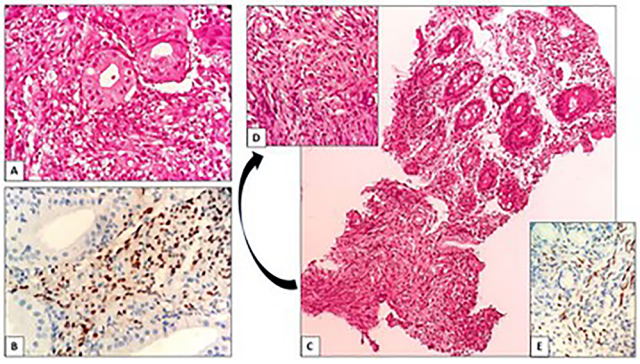

Figure 5. A. Spindle cell neoplasm delimiting vascular lacunae and characterizing KS in the gastric mucosa (H&E, 400X). B. HHV-8 infection in neoplastic cells in the stomach (IHC LANA-1, 400X). C. Duodenal mucosa with deep tissue KS (H&E, 200X). D. KS area in detail (H&E, 400X). E. HHV-8 infection in neoplastic cells in the duodenum (IHC LANA-1, 400X). H&E: hematoxylin and eosin stain; IHC: immunohistochemistry.

A new peripheral lymph node biopsy was performed to further investigate the extent of HHV-8-related infection and rule out other possible systemic conditions. The biopsy results showed that the cortical and paracortical zone had undergone involution, with marked medullary plasmacytosis, indicating HIV-associated lymphadenitis in the follicular involution stage (Figure 6). The immunohistochemical panel of this biopsy showed positive finding for HHV-8, and based on the overall clinical and histological picture, the patient was diagnosed with Castleman disease.

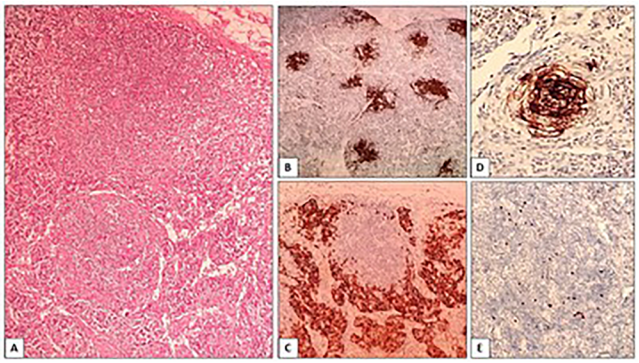

Figure 6. A. Castleman disease presenting with characteristic follicular involution (H&E, 100X); B. Involution of lymphoid follicles and of the cortical zone of the lymph node (IHC CD20, 40X); C. Dense plasma cell infiltrate extending from the medulla to the superficial lymph node cortex (IHC CD138, 40X); D. Follicle center dendritic cells characterizing follicular involution (IHC CD23, 200X); E. HHV-8 infection in B lymphocytes and plasma cells demonstrated by latency-associated nuclear antigen 1 (IHC LANA-1, 100X). H&E: hematoxylin and eosin stain; IHC: immunohistochemistry.

After receiving chemotherapy with liposomal doxorubicin, the patient experienced acute and severe

abdominal pain with gaseous distention on the first day. This was managed with analgesia and laxatives; additionally, an urgent abdominal CT did not show any significant changes. However, cervical and axillary lymphadenopathy showed clear and rapid regression after the chemotherapy. Subsequently, the fever subsided, and the patient was discharged 5 days later (on the 19th day of hospitalization). The patient was advised to continue treatment and follow-up in a day-hospital regimen.

DISCUSSION

The seroprevalence of HHV-8 varies across continents and tends to be high in South America, with some urban areas showing a prevalence of >15%.[5] The prevalence of HHV-8 in certain native indigenous communities in Brazil is >50%.[6] The transmission mode of HHV-8 is not fully understood; however, sexual transmission, particularly among men who have sex with men,[7] is one of the most frequently described routes. Transmission through vertical and saliva routes is also possible, based on the serological patterns observed in several households.[8]

The clinical syndrome associated with primary HHV-8 infection is not well-established and most infections are asymptomatic and go unnoticed. However, febrile maculopapular rash has been reported in immunocompetent children in the past.[9]

In terms of KS, this neoplasm directly related to HHV-8, can be classified into four epidemiological types: the classic, endemic, epidemic, and iatrogenic types.[10] Of these, the epidemic type corresponds to KS affecting HIV-infected patients, which has significantly reduced with the universal availability of ART.[11]

Although KS can manifest as a neoplasm in various parts of the body, the mucocutaneous and/or visceral forms are more common.[10] In the present case, there was no cutaneous involvement while the patient presented with only gastrointestinal disease, an atypical initial presentation which led to delay in diagnosis. Notably, the visceral form of KS is often asymptomatic,[10] primarily affecting the gastrointestinal tract and respiratory system - initial bronchoscopy in this case did not reveal the characteristic endobronchial violaceous lesions.

Confirmation of the diagnosis of KS should be sought through biopsy whenever feasible. The typical histological findings include spindle cells, cellular atypia, neovascularization processes with perivascular inflammatory infiltrate, and hemosiderin deposits, which are characteristic histological findings of the disease.[10]

Concerning Castleman disease, it was originally described in 1956[12] as a rare lymphoproliferative disorder that can occur in two forms: unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD). UCD is confined to a single body region and is not associated with HHV-8, whereas MCD can involve multiple body regions and can be caused by HHV-8 or have an unknown etiology (idiopathic). In HIV-infected patients, HHV-8 is often associated with the development of MCD.[3]

Notably, MCD was first reported in 1978[13] and is a systemic disease characterized by generalized lymphadenopathy and nonspecific symptoms, such as fever, fatigue, weight loss, possible respiratory symptoms, and night sweats, with an average history of approximately 3 months before diagnosis.[14] Physical examination typically reveals lymphadenopathy, hepatosplenomegaly, and peripheral edema. Laboratory tests may show cytopenia (anemia and thrombocytopenia), hypergammaglobulinemia, hypoalbuminemia, and elevated C-reactive protein (CRP) level.[14,15] Pulmonary radiology often shows reticular and/or micronodular patterns.[16]

Due to the nonspecific nature of these presentations, MCD may be confused with other conditions, such as lymphomas, autoimmune diseases, and even bacterial or viral infections.[15]

The presented case herein pertains to a patient whose clinical findings meet several clinical criteria for MCD, with a prolonged course of febrile generalized lymphadenopathy, hepatosplenomegaly, peripheral blood cytopenia, and nodular pattern on chest CT. Late diagnosis is common in MCD, particularly in patients with more advanced acquired immunodeficiency syndrome (AIDS), as opportunistic pathologies, which include lymphomas and tuberculosis, are typically the primary concern due to their higher incidence.

The diagnosis of MCD is based on clinical and pathological criteria, requiring a biopsy for confirmation. Cases of MCD associated with HHV-8 usually have preserved nodal architecture, show plasmacytosis and hypervascularity in the interfollicular region along with an increased plasmablast count in the mantle zone of B-cell follicles, besides positive immunohistochemistry for HHV-8.[17]

KS and MCD are often noted as comorbidities in individuals living with HIV due to their shared etiological agent HHV-8. Both diseases, albeit more rarely, may also co-occur with primary effusion lymphoma.[18]

The coexistence of several entities can pose significant challenges in clinical practice, as their presentations are similar, with multiple signs and symptoms that can complicate the diagnostic process and lead to inadequate therapeutic recommendations. Treatment options for KS depend on the severity and stage of the disease, either local

(topical injection of chemotherapy drugs, laser, cryotherapy, and irradiation) or systemic (liposomal anthracyclines or paclitaxel).[10] ART is crucial in the treatment of KS in HIV-infected patients, as immune recovery can lead to lesion regression. In contrast, the treatment of MCD involves rituximab, either alone or in combination with other drugs.[14] When KS and MCD coexist, combining rituximab with liposomal doxorubicin is the recommended therapeutic approach, with clinical response rates close to 90%.[19]

HHV-8 is associated not only with KS, MCD, and primary effusion lymphoma but also with a fourth entity called Kaposi sarcoma inflammatory cytokine syndrome (KICS).[20] KICS shares symptoms such as fever, fatigue, edema, neuropathy, and respiratory and gastrointestinal symptoms with MCD, but with greater severity, often requires intensive care for mechanical ventilation or renal replacement therapy.[21] Laboratory findings include anemia, thrombocytopenia, hypoalbuminemia, and elevated CRP levels. While KICS systemic inflammatory response can lead to symptoms and laboratory test results similar to those of MCD, some typical MCD characteristics, such as splenomegaly and disseminated lymphadenopathy, are absent in KICS. The diagnosis of KICS is also associated with HHV-8 and requires histopathological exclusion of MCD.

Finally, the clinical evolution here reported was also confounded by hemophagocytic syndrome, which can be triggered by infections, mainly viral infections[22]. Its clinical presentation can also lead to signs, symptoms, and changes in complementary exams that often divert the diagnostic focus from the true underlying etiology.

CONCLUSION

The diagnosis of HHV-8-related diseases can be challenging due to the several possible presentations, multiple differential diagnoses, and potential coexistence of some of these conditions, particularly in patients living with HIV.

Hence, this case highlights the importance of investigating MCD in patients with KS presenting with febrile lymphadenopathy. Alternatively, MCD cases should always be examined for the presence of associated KS, as these two conditions co-occur in more than 50% of patients with MCD.[18]

Considering the coinfection of HHV-8 and HIV, it is important to consider the possibility of these diseases even in the post-ART era. Therefore, accurate diagnostic definition plays a fundamental and strategic role in ensuring appropriate treatment and achieving better prognosis for affected individuals.

REFERENCES

1. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science. 1994 Dez;266(5192):1865-9.
2. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based
3. Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood. 1995 Ago;86(4):1276-80.
4. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011 Out;118(15):4041-52.
5. Freitas RB, Freitas MR, Linhares AC. Prevalence of human herpesvirus 8 antibodies in the population of Belém, Pará, Brazil. Rev Inst Med Trop S Paulo. 2002 Dez;44(6):309-13.
6. Biggar RJ, Whitby D, Marshall V, Linhares AC, Black F. Human herpesvirus 8 in Brazilian Amerindians: a hyperendemic population with a new subtype. J Infect Dis. 2000 Mai;181(5):1562-8.
7. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. N Engl J Med. 1998 Abr;338(14):948-54.
8. Plancoulaine S, Abel L, Van Beveren M, Tregouet DA, Joubert M, Tortevoye P, et al. Human herpesvirus 8 transmission from mother to child and between siblings in an endemic population. Lancet. 2000 Set/Out;356(9235):1062-5.
9. Andreoni M, Sarmati L, Nicastri E, El Sawaf G, El Zalabani M, Uccella I, et al. Primary human herpesvirus 8 infection in immunocompetent children. JAMA. 2002 Mar;287(10):1295-3000.
10. Hengge UR, Ruzicka T, Tyring SK, Stuschke M, Roggendorf M, Schwartz RA, et al. Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 1: epidemiology, environmental predispositions, clinical manifestations, and therapy. Lancet Infect Dis. 2002 Mai;2(5):281-92.

11. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. AIDS. 2006 Ago;20(12):1645-54.
12. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer. 1956 Jul;9(4):822-30.
13. Gaba AR, Stein RS, Sweet DL, Variakojis D. Multicentric giant lymph node hyperplasia. Am J Clin Pathol. 1978 Jan;69(1):86-90.
14. Bower M, Newsom-Davis T, Naresh K, Merchant S, Lee B, Gazzard B, et al. Clinical features and outcome in HIV-associated multicentric Castleman's disease. J Clin Oncol. 2011 Jun;29(18):2481-6.
15. Collins LS, Fowler A, Tong CY, Ruiter A. Multicentric Castleman's disease in HIV infection. Int J STD AIDS. 2006 Jan;17(1):19-24;quiz:5.
16. Guihot A, Couderc LJ, Rivaud E, Galicier L, Bossi P, Oksenhendler E, et al. Thoracic radiographic and CT findings of multicentric Castleman disease in HIV-infected patients. J Thorac Imaging. 2007 Mai;22(2):207-11.
17. Dupin N, Diss TL, Kellam P, Tulliez M, Du MQ, Sicard D, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. Blood. 2000 Fev;95(4):1406-12.
18. Ramaswami R, Lurain K, Polizzotto MN, Ekwede I, Waldon K, Steinberg SM, et al. Characteristics and outcomes of KSHV-associated multicentric Castleman disease with or without other KSHV diseases. Blood Adv. 2021 Mar;5(6):1660-70.
19. Uldrick TS, Polizzotto MN, Aleman K, Wyvill KM, Marshall V, Whitby D, et al. Rituximab plus liposomal doxorubicin in HIV-infected patients with KSHV-associated multicentric Castleman disease. Blood. 2014 Dez;124(24):3544-52.
20. Uldrick TS, Wang V, O'Mahony D, Aleman K, Wyvill KM, Marshall V, et al. An interleukin-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without Multicentric Castleman disease. Clin Infect Dis. 2010 Ago;51(3):350-8.
21. Polizzotto MN, Uldrick TS, Wyvill KM, Aleman K, Marshall V, Wang V, et al. Clinical features and outcomes of patients with symptomatic Kaposi Sarcoma Herpesvirus (KSHV)-associated inflammation: prospective characterization of KSHV Inflammatory Cytokine Syndrome (KICS). Clin Infect Dis. 2016 Mar;62(6):730-8.
22. Filipovich A, McClain K, Grom A. Histiocytic disorders: recent insights into pathophysiology and practical guidelines. Biol Blood Marrow Transplant. 2010 Jan;16(Supl 1):S82-S9.