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Castleman's Disease: Literature Review

Patrícia Virgínia Bastos de Figueiredo[1], Caio Porciúncula Teixeira Basto[2], Lívia Maria Simonek Mendes[1], Aiany Sabriny de Macedo Nunes[3],GabrielPorciúncula Teixeira Basto[1], Laís Bezerra Perrusi[1], Marinus de Moraes Lima[1]

1 – Medical Faculty, Centro Universitário Maurício de Nassau, Recife, Brazil.
2 - Service of General Surgery, Hospital dos Servidores do Estado de Pernambuco, Recife, Brazil.
3 – Service ofInternal Medicine, Hospital dos Servidores do Estado de Pernambuco, Recife, Brazil.
Correspondingauthor: Patrícia Virgínia Bastos de Figueiredo. Medical Faculty, Centro Universitário Maurício de Nassau.Address: 316 Jonathas de Vasconcelos St, 51021140, Brazil.

Abstract
Castleman's disease was first described in 1956 by Benjamin Castleman. It is characterized by being a lymph node disease and can be classified anatomically as localized (unicentric) or disseminated (multicentric). In addition to this division, it can be classified histologically into three subtypes: hyaline-vascular, plasmacytic and mixed. The main clinical manifestations in unicentric disease are derived from local compressions by ganglionic growth, while in multicentric disease there is an increase in systemic symptoms, derived from the action of inflammatory cytokines, mainly interleukin-6. After the discovery of HIV and the HHV-8 virus, there was an important relationship between the patient's serological status and the appearance of lesions and a great influence on the prognosis of patients with Castleman's disease. The diagnostic approach currently used is based on performing a biopsy of the affected lymph node, associated with the collection of the patient's serology. Another auxiliary measure is the measurement of biomarkers for monitoring and controlling the disease, the main one being the quantification of HHV-8 DNA. The "gold standard" treatment performed for the unicentric form is total surgical excision of the lesion, which can be associated with radiotherapy and chemotherapy, used in cases of therapeutic failure. The multicentric form has several therapeutic modalities, the selection is based on the differentiation of the patient's serological status. The use of Rituximab as the basis for the treatment of HIV-positive patients is well documented in the literature. Furthermore, it is a consensus that all these patients should undergo antiretroviral therapy regardless of the level of involvement of the disease and the base therapy chosen. Targeted anti-IL-6 therapies (SIltuximab) are recommended in the treatment of seronegative patients. The management of patients in remission and those considered refractory still lacks studies with greater relevance to be safely employed in daily medical practice. Patients apparently have a good prognosis. However, there is still a need for studies with longer follow-up periods, as the disease is still considered relapsing and remitting.

Keywords: *Castleman's Disease, Angiofollicular Lymphoid Hyperplasia, HHV-8, HIV.*

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I. Introduction

Castleman's Disease (CD) is described as a rare lymphoid tissue disorder of controversial origin, which presents as a morphologically atypical hyperplasia, affecting B lymphocytes.[1,2,3] It was first described in 1956 by pathologist Benjamin Castleman, who defined it as a hyperplastic disease with neoplastic aspects: identified several patients with solitary and hyperplastic mediastinal lymph nodes containing follicles with interfollicular vascular proliferation, histologically similar to a thymoma, of unknown cause.[2,4,5] Since then, several names have been referred to been employed: giant lymph node hyperplasia, lymphoid angiomatous hamartoma, angiomatous lymph node hyperplasia, follicular lymphoreticuloma and Castleman's lymphoma.[2]

There are two forms of syndromic presentation: unicentric (UCD) and multicentric (MCD). In the unicentric form, only one lymph node is involved, usually in the anterosuperior mediastinum region and more rarely in the abdomen, usually without clinical symptoms.[1,5] It is benign and is usually curable with a surgical approach. The multicentric form presents in a disseminated form, with generalized lymph node enlargement, autoimmune manifestations and recurrent infections. The symptoms of this subtype are varied, and may present anemia, fatigue, anorexia, night sweats, weight loss, fever, among other systemic manifestations and may be associated with malignancies, including the POEMS syndrome.[5,6] This form is associated with frequency to Human Herpes Virus type 8 (HHV-8) and to Human Immunodeficiency Virus (HIV). Regardless of the association with HHV-8, there is an overproduction of IL-6 and polyclonal proliferation of B lymphocytes,

stimulating the appearance of autoimmune alterations. In HIV-positive patients, the disease presents more aggressively, with more intense symptoms, higher prevalence of pulmonary symptoms and greater association with Kaposi's Sarcoma (KS).[3,5]More recently, Takai et al recognized a form of clinical presentation. severe that includes some laboratory alterations such as thrombocytopenia, ascites, reticular fibrosis, renal dysfunction and organomegaly, named TAFRO syndrome.[45]

The histopathological analysis of lymph nodes classifies CD into three types: vascular hyaline, plasmacytic and mixed variant.[3] In the unicentric form, the most common histological pattern is vascular hyaline, corresponding to about 90-95% of the localized forms.[3,5,7] In the multicenter, the predominance of the plasma cell form is more common, which may or may not be associated with HHV-8 and HIV-1, with a less favorable prognosis in infected patients.[2,3,5]

CD is a condition that, due to its clinical characteristics, has a wide differential diagnosis, the main one being lymphoma. It is a condition considered rare, with few papers of great scientific relevance published so far. Therefore, the aim of this study was to review the main characteristics of CD based on the most recent articles published in the medical literature, bringing together the various aspects of epidemiology, clinical manifestations, diagnostic criteria, therapeutic modalities and prognoses associated with this clinical condition.

II. Methodology

Searches of articles in Pubmed and Scielo databases were carried out, complemented with the works of the specialized journals The Lancet and Blood Journal, with compiled from the year 2003 until May 2021. The main search descriptors were: "Castleman's Disease (Castleman's Disease), "Angiofollicular Lymphoid Hyperplasia", "HIV", "HHV-8". Associated qualification descriptors: epidemiology, classification, diagnosis and treatment. All studies that addressed Castleman's disease as the main focus, regardless of the subtype of the disease, were used as the basis for the production of the text. Articles that presented histopathologically confirmed cases, clinical trials and review articles on the various aspects of the disease were included. Articles that addressed diseases with similar pathologies without diagnostic confirmation were excluded. Data from articles that had no basis for their construction were not used in the formulation of the text. In addition to the articles used in our database search, bibliographical references for these were reviewed, and the oldest articles of greatest importance and impact on the medical community were added.

III. Epidemiology

CD is characterized as a rare clinical disorder and its prevalence is not well established due to difficulties in epidemiological analyses. To date, more than 400 cases have been reported in the medical literature. In Brazil, few cases have been reported.[8]

In the US, the prevalence is estimated to be between 30,000 – 100,000 cases, from patients who had lymph node enlargement who were later diagnosed with CD.[8] CD can inflict any age group. The age of affected patients ranges from 8 to 69 years, with a median of 35 years at diagnosis. There does not seem to be a predominance of ethnicity or gender.[6,9] The unicentric form affects more adolescents and young adults, while the multicentric form affects more elderly and immunodeficient individuals, especially those with the Acquired Human Immunodeficiency Syndrome (AIDS). Seropositives seem to have a higher risk of developing multicentric CD associated with Kaposi's Sarcoma.[1] It is estimated that 77% of patients diagnosed with CD have it in its unicentric form, while 23% have it in the multicentric form.[10]

A study conducted in American medical centers, Mayo Clinic and The Fred Hutchinson Cancer Research Center, estimated that 61% of patients seen and diagnosed with MCD were men with a mean age of 55 years and 68% were white. Of those, 15% were HIV positive and 17% were HHV-8 positive. The most reported symptom was fatigue, corresponding to 49%. And, the main subtype identified was the plasma cell variant with 49%, while 33% was the vascular hyaline and 18% of the mixed type.[11]

IV. Pathophysiology And Clinical Manifestations

The clinical manifestations of CD are varied. The spectrum of the disease has greatly increased since its discovery in 1956. Currently, this disease encompasses different disorders in various aspects of the human body. There is an intersection of events that occur at the hematological, oncological, rheumatological and virological levels, all of which corroborate similar histopathological changes.[12]

From a histopathological point of view, there are three main subtypes identified: the hyaline-vascular, the plasma cell variant and the mixed. Alterations of the vascular hyaline subtype are found in 95% of patients with UCD, although they may affect, to a lesser extent, those with multicentric disease.[10,13,14] As it is a subtype with little production of systemic inflammatory cytokines, the patients with the unicentric form of CD present a spectrum of the disease that manifests itself asymptomatically in most cases, and its discovery is made incidentally through imaging exams. The presentation of the UCD is quite varied. Its signs and symptoms are mainly related to the compression of adjacent structures by the growth of the affected lymph node chain.

Therefore,Talat et al (2012) gathered data from 404 patients, where the main sites of disease involvement were observed. The main proven site was the chest cavity (29%). The main symptoms manifested by these patients were nonspecific symptoms, such as cough, dyspnea, chest pain, hemoptysis.15 Lymph nodes that affect the abdominal cavity (21%) can rarely generate obstructive symptoms of the gastrointestinal and urinary tract.[16]

There are, however, patients with UCD in which the histopathological diagnosis shows cells of the plasma cell variant or mixed type. These are the main histopathological findings of patients with the Multicentric form of CD, whether idiopathic or associated with the HHV-8 virus. Therefore, all affected by these subtypes will present similar clinical features, the difference being made by the number of lymph node chains affected. These histological subtypes present, among their characteristics, secretion of inflammatory cytokines: TNF-alpha, interleukin-1, and mainly, interleukin-6 (IL-6). IL-6 can originate from morphologically altered cells in the body, found in idiopathic cases of Castleman's Disease (iMCD); or produced viral IL-6, through the replication of HHV-8 in the affected plasma cell.[3,17]This exacerbated production of these cytokines generates varied systemic dysfunctions. The inflammatory status generates B symptoms, represented by fever, night sweats and weight loss.[1,3,17] These were the main symptoms described by patients with DCM in the study published by Robinson et al (2013).[11] There are also reports of patients who presented cytopenias, hepatosplenomegaly, polyclonal hypergammaglobulinemia, hepatic, pulmonary and renal dysfunction, often requiring intensive care.[1,18,19,20] Recent studies have demonstrated the importance of renal involvement in patients with CD.

A study published by Zhang et al (2012) evidenced the presence of kidney damage in 25% of patients evaluated with a histological diagnosis of CD. Of these, 63% had acute kidney injury, most of which had a good organic response after chemotherapy, with complete improvement in kidney function.[21]

The relationship of MCD with HIV and HHV-8 infection is well documented in the literature. HHV-8, also called Kaposi's Sarcoma herpes virus, was discovered in 1994, described by Chang and Moore, and was soon associated with several diseases. A case series carried out soon after this discovery showed that 75% of HIV-positive patients and 13% of HIV-negative patients with MCD would develop Kaposi's Sarcoma.[19,22] This evidence is very important for the study of the clinical manifestations of CD, because in addition to the aforementioned manifestations, when associated with HIV and HHV-8, the disease manifests itself more exuberantly.[19] HIV-positive patients are more likely to develop neurological symptoms when compared to the unicentric form of the disease. They can be associated with manifestations after polyneuropathic infiltration, leptomeningeal and central nervous system. There is a description of the association between CD and myasthenia gravis, although it is rare.[23,24] The POEMS syndrome, which consists of a set of symptoms characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes, has usually been related to CD (11-30%). [25.26]

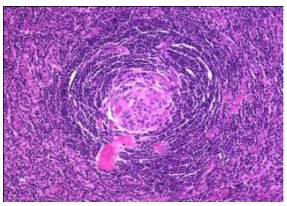
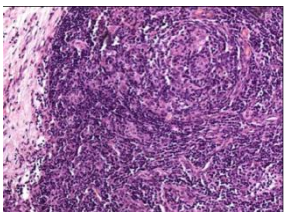
Therefore, Castleman Syndrome is characterized by a wide spectrum of disease, with different onsets and clinical presentations, and should always be considered in the differential diagnosis of various diseases in our daily lives.

V. Diagnosis

CD is usually suspected based on findings from imaging tests, including ultrasound, computed tomography, magnetic resonance imaging and/or PET-CT, being useful in detecting lymph node enlargement and in assessing the extent of the disease.[27] CD staging is important to stratify risk, determine treatment choice and prognosis. Three important points need to be addressed: extent of the disease, which can be assessed by imaging exams; histopathological classification, as it has implications for therapy; and viral etiology, determined by serology to clarify HIV status, presence of Epstein Barr virus, and immunohistochemistry to detect viral IL-6.[28]

The diagnosis must be established by excisional biopsy of the lymph node tissue, with the architecture of the entire germinal center and interfollicular zone preserved for analysis by experienced histopathologists.[29] In cases of deeper or less accessible disease, Core-Biopsy is preferred over aspiration puncture with a fine needle, as it has low sensitivity, both for the UCD and for the MCD.[27]
The histological classification of CD is shown in table 1.

Table 1: Classification according to histology (Adapted from Mendonça et al and Saeed-Abdul-Rahman et al)[3,29]

Hyaline vascular variant 	Atrophied germinal centers; Mantle zone expanded with small lymphocytes; Proliferation of follicular dendritic cells in concentric layers; Hypervascular interfollicular lymphoid tissue and penetration of the follicles by radial capillaries, surrounded by collagen or hyaline material.
Plasma cell variant 	Hyperplastic germinal centers; Accumulation of plasma cells in the interfollicular zone; Absence of capillary proliferation; There may be hyalinization of some follicles.
mixed variant	It has features of the both variants.

The hyaline-vascular form is characterized by distinct follicles, with expansion of the mantle zone and small lymphocytes forming concentric rings that surround the germinal center, which is highly vascularized. Vascular proliferation also occurs between follicles and there is often perivascular hyalinization.[30] The plasmacytic variant (PC) is found mainly in the multicentric or systemic form of the disease.[28] The histology of this form reveals diffuse proliferation of plasma cells in interfollicular tissues, without the presence of hyaline-vascular changes. When these histopathological features are found concomitantly with the proliferation of plasma cells, CD is classified as mixed or intermediate.[4]

In addition to lymph node biopsy, the initial laboratory evaluation of patients includes blood count, inflammatory markers (ESR and C-reactive protein), albumin, renal and liver functions. The evaluation of plasma cell dyscrasias, including immunoglobulins, electrophoresis and immunofixation of serum and urinary proteins, light chains, bone marrow biopsy, and 24-hour proteinuria should also be included.[31] HIV serology should be performed in all patients. In those with MCD associated with the virus, a thorough physical examination should be performed to assess the presence of lesions compatible with Kaposi's Sarcoma, given the high prevalence in the association of these entities.[27]

The diagnosis of HIV-associated MCD also requires clinical features of active disease. There are no "gold standard" criteria for establishing this diagnosis, but a French study described criteria to define a patient acutely suffering from an attack of HIV-MCD. Patients need to have fever and high C-reactive protein, in the absence of any other cause, associated with three (03) of 12 additional clinical signs or symptoms, described in Table 2.[31]

Table 2: Definition of active Castleman's Disease (Adapted from Gerard et al) [32]

Characteristics:

Fever **CRP > 20mg/l in the absence of another cause** Associated with at least 3 of the following criteria: 1) Peripheral lymphadenopathy 2) Splenomegaly 3) Edema 4) Pleural Effusion 5) Ascites	6) Cough 7) Nasal Obstruction 8) Xerostomia 9) Rash 10) CNS symptoms 11) Jaundice 12) Autoimmune Hemolytic Anemia

Plasma levels of HHV-8 DNA must be obtained, as these levels correlate with symptomatic disease and may serve as a useful biomarker, both to confirm the diagnosis of MCD and to monitor disease activity and response to therapy. In clinical studies, levels of cytokines IL-6 and IL-10 have been used as surrogate markers of disease activity. However, its routine dosage is not recommended.[27]

Computed tomography scans of the chest, abdomen, and pelvis should be performed at the time of diagnosis to assess for the presence of adenopathy, splenomegaly, or mediastinal masses. This imaging modality helps to assess the extent of disease and resectability criteria in patients with UCD. The importance of the routine use of PET-CT has not been well established in the CD scenario, even though the lymph nodes affected by the disease are quite avid for fludeoxyglucose.[27]

From a pathological point of view, CD is a diagnosis of exclusion. Its histological features are varied, giving rise to a wide spectrum of differential diagnoses, which include benign and malignant entities. it must be includedin the differential diagnosis of any heterogeneous tumor mass located in body cavities, especially in the retroperitoneum. For its differentiation, the following should be used as a basis: careful histological examination, immunohistochemistry, clinical findings, laboratory, and radiological tests.[33,34]

VI. Treatment

The therapeutic approach to CD encompasses several factors. There are several treatment modalities, primarily separated by the subtype of the disease in question. Examples of treatment are: surgical excision of affected lymph nodes; local radiotherapy; chemotherapy; and the use of specific target drugs, mainly Rituximab (anti-CD20) and Siltuximab (anti-IL6).[11,15,16,35,36]

After several studies, the majority being case reports or case series, an excellent pattern of response was obtained after surgical treatment in the Unicentric form of CD. In these cases, total resection of the primary lymph node had a survival rate greater than 90% after 5 years of follow-up. Similar results were obtained regardless of the affected site, whether in the peripheral lymph node chain (inguinal, axillary, neck) or in central areas (chest, abdomen, retroperitoneum, pelvis).[15] Therefore, surgical treatment with total resection of the lesion as the "gold standard" for UCD.[15,16] There is indication for surgery for partial resection in lymph nodes that affect regions considered to be unresectable, such as, for example, those surrounding noble structures. Due to the latent evolution of the disease, good results were also obtained with partial resections, relieving patients' symptoms and obtaining low levels of lesion recurrence. Adjuvant techniques, such as radiotherapy or chemotherapy, also used in patients with MCD, can be used, aiming to cure these patients.[16,35,37] The National Comprehensive Cancer Network (NCCN) has published an updated guideline for the treatment of the unicentric form of CD. The proposed approach consists primarily of differentiating between patients with resectable and unresectable lesions. After making this distinction, each patient will have a specific therapeutic sequence. For those with resectable lesions, the objective is the total excision of the lesion, with subsequent observation and clinical follow-up to detect signs of disease recurrence. For lesions in which it was not possible to perform a complete resection, clinical assessment of the patient becomes essential for the follow-up of therapy. For patients who are asymptomatic, the same sequence is followed, that is, clinical follow-up to detect signs of disease recurrence. For symptomatic patients, it is recommended to follow the therapeutic protocol for unresectable lesions.[38]

Patients with this type of involvement, said to be non-resectable, may be submitted to different treatment modalities. At this stage of the disease, both radiotherapy and Rituximab can be used alone. Or, combine them with prednisone and/or cyclophosphamide. Embolization of the lesion may also be considered in selected cases. After this initial approach, a new evaluation is performed, checking the possibility of resection of the remaining lesion. If resectable, it follows the pattern described above. If it remains inoperable, it is indicated to perform therapy different from that previously performed.[38]

In cases of refractory or recurrent disease, the use of some modality among all the ones already described may be considered, even if this approach has already been used. There is still the possibility, if the patient is seronegative for HIV and HHV-8, to add therapy with Siltuximab or Tocilizumab.[38]

There are also reports of good results after surgery in patients with the Multicentric form of CD. In these cases, surgery has the function of aiding in the diagnosis by performing larger biopsies. After the diagnosis is made, there is no proposal for curative surgery. Surgical interventions will be used in order to unblock compressions that cause important symptoms, such as airways, intestinal and also in cases of massive organomegaly.[15]

The definitive treatment of MCD depends on several variables, considering the enormous spectrum of the disease. After performing the biopsy, the histological subtype will be defined. Allied to this data, the following criteria are used to define the therapeutic modality: the patient's clinic and the laboratory tests presented by him. MCD can be subdivided into seronegative (HIV-1/HHV-8 negative) or seropositive (co-infection HIV/HHV-8 or HHV-8 positive / HIV negative), this subdivision being the most important for the choice of treatment .[38]

Liu et al (2016) carried out a systematic review of aspects of the disease in patients with iMCD, that is, seronegative, which obtained important information about the type of treatment performed for this subgroup of patients in the last 20 years. The use of different therapeutic modalities was observed over time, most of them with a good response rate. Of the sample of 128 patients obtained in this study, 47 were treated with steroids in monotherapy, 47 with nonspecific cytotoxic chemotherapy, 11 with monoclonal antibody anti-IL6, these being the main modalities used. All had a good response rate. However, among the therapies used, the use of Rituximab, included in the group of chemotherapy, and anti-iL6 were the ones that obtained the best response.[17]

A randomized, double-blind clinical trial published by Rhee et al (2014) compared the use of Siltuximab versus Placebo in patients with iMCD. The main outcome assessed was the duration of the tumor and the symptoms involved. Other primary outcomes assessed were complete or partial response. In all outcomes, the use of Siltuximab associated with intensive care had better results compared to intensive care alone.[39]

In seronegative patients, with active disease and without documented organ failure, the primary treatment should be started with Siltuximab or Rituximab, the latter in association or not with prednisone. After the initial treatment, the result is evaluated through imaging exams. In case of unfavorable evolution, whether initial non-response or recurrence, treatment should be changed to alternative primary therapy, before being considered as refractory.[38, 46]

For HIV-positive patients, the treatment is different. Hoffmann et al (2011) published a cohort that assessed the response to different treatments proposed for HIV associated with MCD used in the period 1998-2010. The first point considered by the study was the improvement in the prognosis of the patients studied, either through the implementation of antiretroviral drugs, through earlier diagnosis or through different approaches used in patients diagnosed with this disease. The study allowed for analysis of the response of patients who used Rituximab as the basis of treatment. When used, either as monotherapy or associated with cytostatics, Rituximab had a better rate of symptom remission and disease improvement in periods of 1 and 2 years after treatment was instituted, when compared to the use of cytostatics alone. The disease-free survival rate observed at 1 year was 95% and at 2 years, 79%.[36]

Bower et al (2011) performed a retrospective cohort comparing survival in patients with HIV-MCD before and after the institution of treatment with Rituximab. In patients diagnosed prior to the introduction of this therapy, the overall survival at 2 and 5 years was, respectively, 42 and 33%. After the introduction of Rituximab as base therapy, the survival rate in the same period was 94% and 90%.[40]

However, there are descriptions of recurrence or progression of Kaposi's Sarcoma in patients with HHV-8 associated with MCD. Uldrich et al (2014) prospectively evaluated the response to treatment with Rituximab 375mg/m2 associated with liposomal Doxorubicin 20mg/m2 in patients with HHV-8 and MCD, plus therapeutic consolidation with IFN-γor association between Zidovudine and Valganciclovir. Disease-free survival at 1 year was 81% and 69% after 2 years, with a mean follow-up of 58 months. Of the 17 patients who took part in the study, only 1 had a new onset of KS or worsening of preexisting lesions. These data, despite not being absolute and needing further studies to be consolidated.

Although Rituximab-based treatment has good results in several studies, MCD, mainly associated with HIV, remains a relapsing and relapsing disease.[42,43] The disease-free and relapse-free survival rate was 82% in 5 years, in study published in 2017. Treatment with Rituximab 375mg/m2 alone or in association with Etoposide 100mg/m2 was used as a therapeutic basis, mainly used for patients with low performance status or organ failure. Recurrence was evaluated through imaging exams, performed in patients who had reappearance of symptoms or changes in laboratory tests.[42] The use of Rituximab associated or not with Etoposide appears to be the current consensus for the treatment of HIV-MCD.[40,41 .42.43]

The use of antiviral agents needs further studies to be used as drugs that can control the disease and improve survival. However, some studies advocate its apparent benefit as maintenance therapy after disease remission.[41,43] The use of antiretroviral therapy (ART) in HIV-positive patients with MCD has shown to be promising when combined with disease control drugs. There is no evidence that the use of ART alone has good results in the treatment of MCD. Its use has shown an improvement in overall survival rates and a decrease in KS recurrence in patients who used Rituximab.[36,40,43]

The scheme currently proposed for the treatment of HIV-positive patients is based on the patient's clinic. For patients without organ failure, the initial treatment can be performed with Rituximab, which may or may not be associated with Doxorubicin or prednisone. In case of a positive response to the treatment, the patient must enter into an observation protocol and active search for disease recurrence. In case of recurrence or failure in the initial response, alternative therapy can be used with the use of Zidovudine associated with Valganciclovir. In case of new failure, the patient should be considered to have a refractory or progressive disease.[38]

HIV-positive patients with MCD who present organ failure or fulminant disease by HHV-8, the therapeutic regimen to be used is the combination of Rituximab with chemotherapy (CHOP, CVAD, CVP,

liposomaldoxorubicin). After treatment, in case of a good response, the conduct becomes observational. In cases of disease failure or recurrence, the patient should be considered as having a refractory or progressive disease.[38]

In cases of refractoriness, combined therapies (CHOP, CVAD, CVP, Liposomal Doxorubicin) associated with Rituximab, if not already used, or single agent therapy (Etoposide, Vinblastine, Liposomal Doxorubicin) in association with Valganciclovir in cases of seropositive patients. Response to treatment should be assessed through laboratory tests and imaging. In case of therapeutic failure after using these modalities, treatments less described in the literature can be used. Consider the use of Rituximab associated with Thalidomide, or Bortezomib, or Lenalidomide. Another proposal could be the use of Tocilizumab (anti-IL6) or Anakinra (anti-IL1) or high doses of Zidovudine with Valganciclovir, alone. In last case, autologous hematopoietic stem cell transplantation may be considered. Treatment for refractory patients lacks evidence in the literature.[38]

CD is an uncommon lymphoproliferative disorder that continues to pose several clinical challenges. Your prognosis is variable and difficult to predict. In the long term, patients with MCD will have a worse prognosis when compared to patients with UCD, especially if associated with the HIV and HHV-8 virus, as the disease can be aggravated by Kaposi's Sarcoma and other conditions.[27,44]

VII. Conclusion

After evaluating the main characteristics of CD, it can be concluded that it is a condition considered rare in the current medical literature. There is a bias towards verifying the scope of the disease, as its diagnosis depends on the biopsy of the lesions and subsequent histopathological reading of the fragments. It is believed that, due to the high complexity of the diagnostic approach, epidemiology still does not represent the totality of cases distributed worldwide.

In most large studies, there was a standardization of the main clinical manifestations, while case reports presented cases with varying symptoms and possible associated diseases.

The therapeutic approach, despite studies with good success rates in treatment and survival, still needs scientific proof of most drugs through well-designed, randomized, blinded clinical trials with representative samples. The groups of refractory and relapsing patients are those most in need of elucidating the ideal therapy. The prognosis of the disease, although apparently good, is still uncertain.

Therefore, it is concluded that CD is characterized by being a complex pathology, with several variables that influence its full understanding, requiring further research to elucidate its pathophysiology and definition of protocols for diagnosis and treatment.

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