Castleman disease. Histopathological and immunohistochemical analysis of 39 cases

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Abstract

Introduction: *Castleman disease (CD) is a rare lymphoproliferative that comprises two distinct clinical subtypes (unicentric and multicentric) and has two basic histopathology patterns that are hyaline-vascular (HV) and plasma-cell (PC) type. Some cases of multicentric PC disease are associated with HHV-8 infection.* **Objective:** *To present the histopathologic and immunohistochemical characteristics of 39 cases of CD.* **Methods:** *A review of cases with the diagnosis CD from the files of the Department of Pathology of the ABC Medical Centre in Mexico City was performed. Thirty-nine cases of CD were identified, and a detailed paraffin immunophenotypic study of 9 of them was completed using desmin, cytokeratin OSCAR (CO) and Epidermal growth factor receptor (EGFR), to evaluate the dendritic cell population.* **Results and Conclusions:** *Of the 39 cases of CD, 24 were HV and 15 CP. All HV cases were unicentric and only one case of CP was multicentric. The most frequent localization in both subtypes was in lymph nodes; 21/24 cases in HV and 15 cases of CP. All cases were immunostained with CD20 that was expressed in the germinal centers (CGs), CD3 in the paracortical zone, and CD21 in follicular dendritic cells (CDF) within CGs, with expansion towards the area of the hyperplastic mantle zone (only in the HV variant). One case of CD CP was positive for HHV-8. Of the nine cases (6 HV and 3 PC cases) that were detailed with IHC, we found EGFR expression in FDC in all but one of the 9 cases studied and desmin was positive in fibroblastic reticulum cells (FRC) in all, but one of the cases of CD. CO was positive FRC in 3 of 6 cases of HV type and all (3) of the PC type. Clinical, histopathological and HIV and HHV-8 status markers, allow for the classification of CD into groups with markedly different outcomes and disease associations.*

KEY WORDS: *Castleman's disease hyaline vascular type. Castleman's disease plasma cell variant. Cytokeratin positive fibroblastic reticulum cells. Desmin. Epidermal growth factor receptor.*

Introduction

Castleman disease (CD) is a heterogeneous group of non-neoplastic lymphoproliferative disorders divided in the hyaline-vascular (HV) and plasma cell (PC) variants, both with variable histology and clinical evolution[1-3]. The unicentric (localized) form of both types has a good prognosis, whereas the multicentric (systemic) presentation, which usually occurs in a scenario of immunocompromised patients, has high morbidity and mortality with few therapeutic options[1,4,5]. Although it is not considered a neoplastic lesion, the multicentric CD variant is treated as such and is associated with an increased risk for the development of diffuse large B-cell lymphoma and Kaposi's sarcoma[3,5,6].

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HV CD is commonly unicentric[7] and, although rather infrequent, it can be associated with synchronic or metachronic appearance of follicular dendritic cell sarcomas[8,9].

There are reports of epidermal growth factor receptor (EGFR) expression in follicular dendritic cells (FDCs) of both varieties, and a possible pathogenic relationship has been proposed[2,8,9]. In addition, there is an increase in the levels of FDC (CD21-positive) and fibroblastic reticular cells (FRCs) (desmin- and cytokeratin-positive) in both CD variables, with their function or diagnostic importance not being clear[8,10-13].

The purpose of this manuscript is to present the clinicopathological and immunohistochemical study of 39 CD cases analyzed in a single institution. In addition, in nine of these cases, the immunohistochemical study was complemented by assessing EGFR expression within the germinal centers, and FDC and FRC distribution in both CD subtypes.

Methods

Cases with a CD diagnosis were searched at the Centro Médico ABC (CMABC) Department of Surgical and Molecular Pathology medical records within a 15-year period (2000 to 2015), with 39 cases being found, from which data such as gender, age and localization, as well as the histopathology report, were obtained. Of the 39 cases, 30 (76.92%) corresponded to external materials received for histopathological diagnosis consultation, and 9 were from patients who arrived to CMABC presenting with adenomegalies.

For the HV-CD diagnosis, histological criteria included the presence of atrophic lymphoid follicles with variable hyalinization areas, expanded mantle zones composed of concentric rings ("onion skin" appearance) paracortical expansion with high endothelial venules increase and partial or complete absence of subcapsular sinuses.

For the PC-CD diagnosis, histological criteria included variable presence of atrophic or hyperplastic lymphoid follicles, with variable mantle layer and paracortex expansion with numerous polyclonal PCs.

For diagnosis, all 39 cases had CD20 (BioSB/L26/1:500), CD3 (BIOCARE/M/1:50), CD138 (BioSB/EP201/1:80), Kappa (BioSB/L1C1/1:400), Lambda (BioSB/lambda14/1:400), CD21 (Dako/1F8/1:30) and HHV-8 (human herpesvirus 8, BioSB/13B10/1:10) determined.

In nine cases, detection was carried out by immunohistochemistry with desmin (BioSB/EP15/1:20), OSCAR cytokeratin (BioSB/OSCAR/1:30) and EGFR (BioSB/31G7/1:100) for assessment of these antigens expression in FDCs and FRCs.

Results

Of the 39 CD cases, 24 were HV (62%) and 15 were PC (38%). Of the 24 HV-CD cases, 16 were females (67%) and 8 were males (33%), with ages ranging from 3 to 64 years (with an average of 31 years); age was not available in 5 patients. Of the 15 PC-CD cases, 4 were females (26.5%) and 11 were males (73.5%), with ages ranging from 12 to 74 years (with an average of 46 years); age was not available in 5 patients. All HV-CD cases were unicentric and only one of the PC-CD cases was multicentric.

Most common localization in the 24 HV-CD cases was the lymph nodes (21 cases: 87.5%); 2 in axillary lymph nodes, 4 in cervical lymph nodes, 2 in peripancreatic lymph nodes, 2 in mediastinal lymph nodes, 1 in one lymph node of the perirenal region, 1 in one lymph node of the suprarenal region, 1 in one jugulodigastric lymph node and other in one lymph node of the retroperitoneal region. One case occurred in the shoulder soft tissues and 2 in the lung. The remaining 7 cases were in lymph nodes, but the localization was not specified in the referral form.

Histologically, HV-CD showed round-shaped or irregular hyperplastic lymphoid follicles of similar sizes and disperse on the cortex and the medulla of the lymph node (Fig. 1 A). Some of these follicles had two or more germinal centers (twinning) (Fig. 1 B). Germinal centers were atrophic and many of them had fibrosis and scarce small lymphocytes, as well as numerous FDCs within the fibrous areas (Fig. 1 C). At the paracortex, numerous high endothelial venules with mild perivascular fibrosis were identified, with these vessels dispersedly radially penetrating the germinal centers, forming structures resembling a lollipop (Fig. 1 B and C). In some cases, within atrophic germinal centers, there were dysplastic FDCs with large nuclei of irregular contour, with granular chromatin and small nucleoli (Fig. 2 A to C). These dendritic cells spread towards the hyperplastic mantle zone cells (Fig. 2 C). These follicles' mantle zones were broad and formed concentric rings of small lymphocytes, which gave them the appearance of "onion skin". In the paracortex there were also sparse PCs, immunoblasts, small lymphocytes and eosinophils. Paracortex PC mantles, as observed in PC-CD, were absent. In most cases of the HV variant, lymph nodes

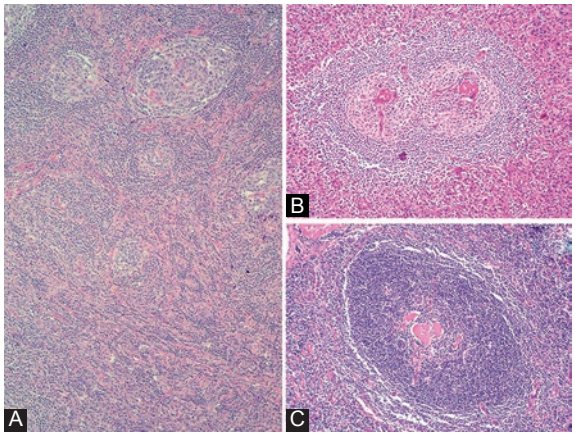

Figure 1. *Castleman disease, HV variant.* **A***: germinal centers, some of them atrophic, and paracortical vascular proliferation.* **B***: lymphoid follicles with two or more germinal centers, referred to as "twin germinal centers" (twinning): some paracortical vessels radially penetrate germinal centers, forming lesions that resemble a lollipop.* **C***: germinal center with central fibrosis, with concentric rings formation composed of small lymphocytes, which gave it an appearance of "onion skin".*

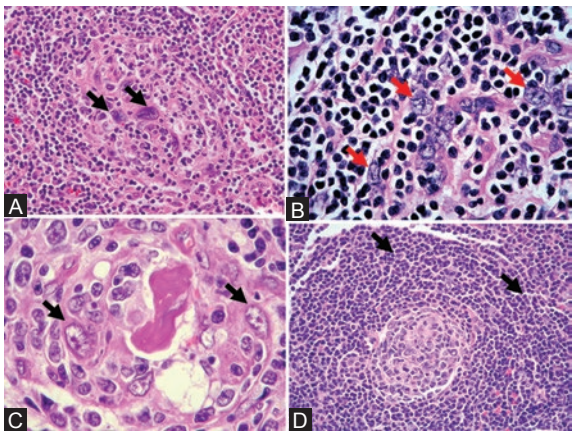

Figure 2. A, B *and* **C***: atrophic germinal centers of the HV variant contain increased FDCs, some of them with signs of dysplasia (arrows) characterized by nuclear enlargement with granular chromatin and visible nucleoli.* **D***: FDCs migrate towards the mantle zone.*

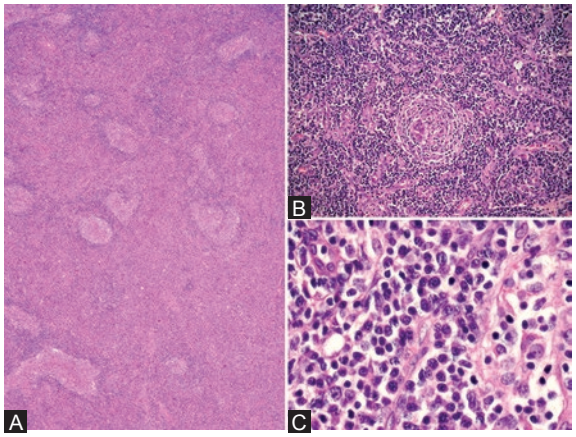

Figure 3. A*: the PC variant shows large or normal size lymphoid follicles, with germinal centers with preserved polarity.* **B** *and* **C***: there are numerous plasma cells in the interfollicular and medullary areas, with occasional binucleated forms.*

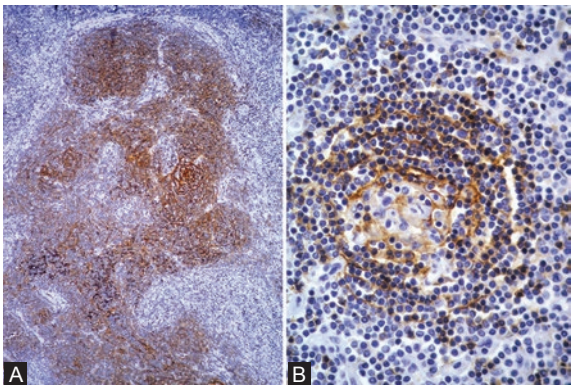

Figure 4. *With CD21, FDCs showed constant distribution within germinal centers, with intense positivity and accentuated expansion towards the hyperplastic mantle zone in the HV variant (***A***), more restricted to the germinal center and only focally towards the mantle zone in the PC variant (***B***).*

subcapsular sinusoids were obliterated. Dense sclerosis with multifocal distribution was identified in some lymph nodes.

With regard to PC-CD, localization in all 15 cases was: 4 in cervical lymph nodes, 3 in axillary lymph nodes, 1 in one supraclavicular lymph node, 1 in an inguinal lymph node, 1 in a mesenteric lymph node, 1 in a cystic lymph node and 4 in lymph nodes with no localization being referred.

Histologically, PC-CD cases showed normal or atrophic lymphoid follicles with germinal centers with preserved polarity and variable mantle zone, and characteristically numerous PCs at interfollicular and medullary areas, with occasional binucleated forms (Fig. 3 A to C). Vascular proliferation in interfollicular areas was variable. Nodal sinusoids were present, some of them slightly distended. The mantle zones were well-defined between the paracortex areas, but there was no hyperplasia as in HV-CD. In one case, there were larger cells with plasmablastic appearance predominating at the mantle zone and within the paracortex. These were the cells that tested positive by immunohistochemistry for HHV-8 (a virus associated with Kaposi's syndrome) (see below).

All 39 cases were CD20-positive, with expression predominating at germinal centers. T-lymphocytes were positive for CD3 predominantly at the paracortical zone. CD21 showed FDC constant distribution within germinal centers with intense positivity and expansion towards the hyperplastic mantle zone in the HV variant (Fig. 4). In all 15 cases with the PC variant, areas of CD20-positive germinal centers were identified, as well as CD3-positive expanded paracortical

zones. In these cases, CD21 showed no expansion towards the mantle zone. Numerous CD138-positive PCs, all of them polyclonal, were identified in paracortical zones.

All 39 cases were immunostained with HHV-8 and all HV-CD cases tested negative; only one case of all 15 with the PC variant (the multicentric case) was positive in mantle zone and paracortical region-localized plasmablasts.

Of the 9 cases where paraffin blocks were available, complementary immunohistochemistry studies were performed with desmin and OSCAR cytokeratin. Six cases (67%) were HV-CD and 3 cases (33%) were PC-CD. Of the 6 HV-CD cases, 5 were females and one was male, with ages ranging from 19 to 55 years (with an average of 36 years). Of the 3 PC-CD cases, one was female and 2 were males, with an age average of 55 years (40-56 years).

Desmin expression evaluated the presence of FRC. In the HV variant, we found diffuse cytoplasmic positivity in 3 cases, multifocal in one case and focal in one, and it was negative in one case (Fig. 5 A). In the PC variant, there was diffuse positivity in one case and multifocal positivity in two (Fig. 5 B). Morphologically, in both variants, these cells were thin, with finger-like long prolongations distributed both at the follicle mantle zone periphery and the paracortical zone, around some high endothelial venules and with subcapsular distribution (Fig. 5 A and B).

The presence of FRC was assessed with OSCAR cytokeratin as well. In the HV variant, there was multifocal positivity in two of the 6 cases (Fig. 5 C), and in the PC variant, there was multifocal positivity in all 3 cases. These cells showed finger-like morphology with long prolongations predominantly distributed on the paracortex and around high endothelial venules (Fig. 5 C and D).

EGFR expression was observed both in FDCs' germinal centers cytoplasm and membranes, and both in the HV (Fig. 6 A) and PC (Fig. 6 B) variants. EGFR expression was proportional to the degree of dysplasia shown by FDCs, i.e., the higher the EGFR expression, the higher the degree of FDC dysplasia (Fig. 6 A and B).

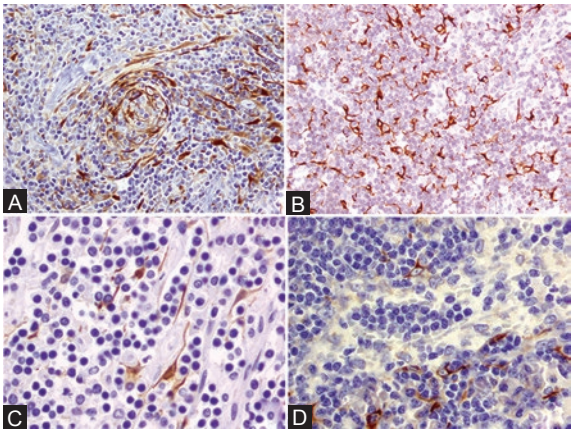

Figure 5. *Fibroblastic reticular cells were positive for desmin both in the HV variant (***A***) and the PC variant (***B***). In addition, these cells expressed OSCAR cytokeratin both in the HV variant (***C***) and the PC variant (***D***). In both cases, and with both immunostainings, these cells' distribution was predominantly in the paracortical zone.*

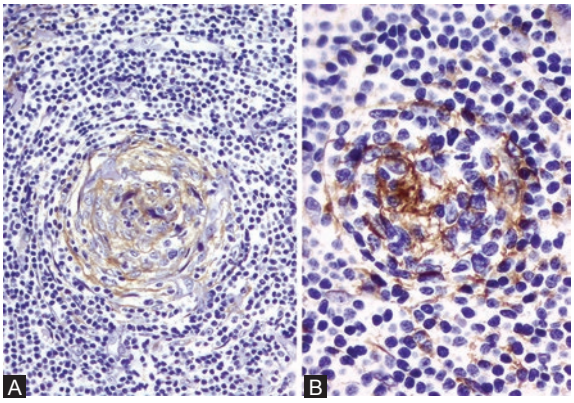

Figure 6. *EGFR expression was observed in germinal center FDCs both cytoplasm and membranes, both in the HV variety (***A***) and the PC variety (***B***).*

Discussion

CD, also known as angiofollicular hyperplasia, giant lymph node hyperplasia or angiomatous lymphoid hamartroma, is an infrequent reactive lymphadenopathy[3,13,14]. It was first described in 1954 by Benjamin Castleman (1906-1982) in a 40-year old patient who presented with high fever, sweating, fatigue and non-productive cough, with a mass in the anterior mediastinum[15]. Presumptive clinical diagnoses were teratoma, tuberculoma, thymoma and Hodgkin's lymphoma[3,15]. Histologically, Castleman identified a peculiar form of lymphoid hyperplasia, characterized by atrophic germinal centers formation with variable hyaline fibrosis, which mimicked structures similar to Hassal corpuscles in the thymus, but without central keratin. In addition, in the germinal centers peripheral portion, he observed a concentric pattern of the mantle zone lymphocytes that resembled "onion skin", while in the paracortical zone there was accentuated vascular proliferation[10,15]. Two years later, Castleman reported this case again together with other 12 more, which were mediastinal tumors that had previously been diagnosed as thymomas[16]. Based on this, he

made the description of a new disease that he indicated was neither neoplastic, nor of thymic origin, which corresponds to what we know today as the HV variant and that bears the name of Castleman disease[3,6,15,16]. In 1969, Fledring and Schillings described the PC variety, which was invariably associated with a clinical presentation with fever, lymphadenopathy, splenomegaly and anemia[17], and, in 1972, Keller, Hochholzer and Castleman defined and differentiated the HV and PC variants in a review of 81 cases[18]. In 1983, Frizzera et al.[19] reported the clinical, morphologic and immunophenotypical characteristics of 15 patients with CD of multicentric involvement (MCD), where, clinically, all patients had fever, night sweats and weight loss. Morphologically, compromised lymph nodes had preserved architecture with paracortical expansion with marked diffuse plasmacytosis and some prominent germinal centers with vascular hyalinized focal changes, i.e., they had both HV and PC variants' characteristics[19,20]. Some patients infected with the human immunodeficiency virus (HIV) have the MCD PC variant, and it was Soulier et al.[21] who identified HHV-8 an all HIV-positive patients with MDC and in 40% of those who were HIV-negative.

CD is a group of uncommon disorders the prevalence of which is not well established, but it is estimated at approximately 1 case per 100,000 population in the USA[1]. It affects predominantly lymph nodes of the trunk, neck and abdomen by 70, 15 and 15%, respectively, although there have been cases described in the lung, larynx, parotid, pancreas and meninges[22]. Clinically, it can be localized in a single lymph node or lymph node station (unicentric), or it can involve two or more lymph nodes or lymph node stations (multicentric)[2].

Histologically, it is classified in variant HV and variant PC, but CD with mixed characteristics has been occasionally reported[3,23]. However, since most PC variant cases may have some HV variant characteristics, many authors consider these cases as mixed within the PC variant spectrum[24]. CD current classification comprises: 1) the HV variant; 2) the unicentric PC variant; 3) the HHV-8-associated multicentric PC variant; and 4) the idiopatic multicentric PC variant (iMCD)[20] (Fig. 7).

The HV variant accounts for 90% of CD cases and corresponds to most unicentric CD cases[3,4]. There are few reports on multicentric HV-CD cases, and probably they correspond to the PC variant[6,9]. HV-CD occurs in a broad age range, but it is more common in young adults with a mean age within the third or fourth decades of life at diagnosis. It has no predilection for neither gender, and most patients present with a localized mass with no constitutional symptoms or laboratory abnormalities. The mediastinum is the most common localization, followed by neck and abdominal lymph nodes[20].

Numerous etiological factors have been suggested for its development, including autoimmune phenomena, immunodeficiency, low-grade chronic inflammation, response to an unknown environmental cause and Epstein-Barr virus (EBV) infection. However, its cause remains unknown[1].

Histologically, germinal centers are usually atrophic, with scarce lymphocytes, and contain an increased proportion of FDCs, some of them with signs of dysplasia, characterized by nuclear enlargement with granular chromatin and visible nucleoli. Mantle zone lymphocytes are arranged in concentric rings, giving an appearance of an "onion skinning" pattern.

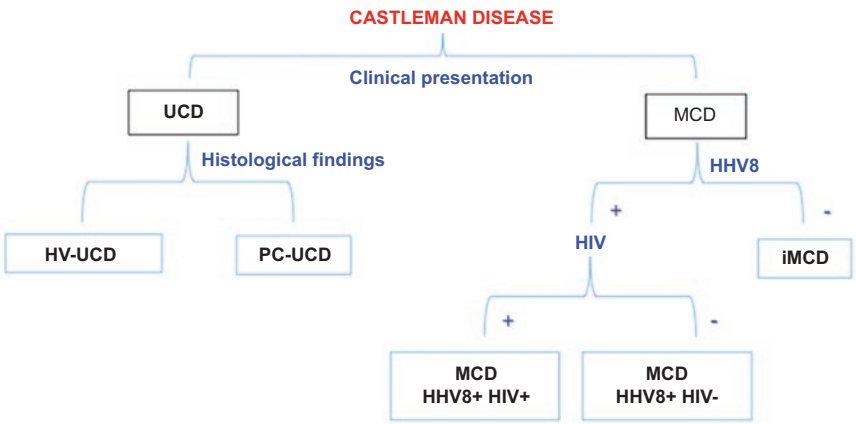

Figure 7. *Castleman disease current classification[20]. HHV: human herpesvirus; HIV: human immunodeficiency virus; HV: hyaline vascular; iMCD: idiopathic multicentric Castleman disease; MCD: multicentric Castleman disease; PC: plasma cells; UCD: unicentric Castleman disease.*

Follicles are often radially penetrated by blood vessels originating in the paracortical zone, giving an appearance of a lollipop[5]. Each follicle can contain one or more germinal centers[10,25], and the interfollicular region shows numerous high endothelial venules[2].

According to Keller et al.[10,25], HV-CD can have two varieties: 1) the "follicular type", which has numerous lymphoid follicles in more than 50% of the affected lymph node surface, with germinal center alterations that include follicular lysis, germinal centers progressive transformation, mantle cell hyperplasia and atrophic germinal centers[25]; and 2) the "stroma-rich" subtype, which is characterized by large paracortical expansion areas (interfollicular) with a complex network of high endothelium venules, and these areas must correspond to more than 50% of the affected lymph node surface[5,10,25].

Germinal center FDCs can display variable degrees of dysplasia, and CD-associated FDC sarcomas have been described[2,8,9,26]. In fact, recent molecular studies have demonstrated clonality in FDCs of the HV variant and suggest that genetic alteration on these cells may be the cause of the disease[26-28]. Interestingly, FDCs in CD cases, both HV and PC, exhibit EGFR diffuse and intense expression, which is not observed in FDCs of other diseases, such as different lymphomas and reactive lymph nodes, which is information that can be useful in the differential diagnosis with other reactive processes[8,9,26-28]. Of our 9 cases where we immunostained with EGFR, 8 tested positive at variable intensity in FDCs.

Normally, in the lymph node interfollicular zone there are FRCs, which account for 20-50% of the non-hematopoietic compartment[12,13]. These cells were described in 1987 by Franke and Moll[29], and subsequently they were confirmed by Coggi et al.[30]. These cells have an elongated cytoplasm that is in contact with other similar cells and create a tridimensional network where leukocytes migrate from and transport soluble antigens and some signaling molecules into the lymph nodes[31,32]. These FRCs provide part of the nodal structure, contribute to B and T cells compartmentalization and direct leukocyte traffic through the secretion of chemokines (IL-7 and CCL-9) that are implicated in T-lymphocyte survival[31,32]. These FRCs are positive for desmin, actin and some cytokeratin types, and are located at the paracortex, predominantly distributed around high endothelium venules and in the subcapsular region[10,12,30-32]. There are only few data on the pathophysiological role of these cells in the diagnosis of CD[10]. Danon et al.[10] have reported the presence of these cells as part of proliferation in the stroma-rich variant, without being able to specify their exact function. We found them in all varieties, expressing both desmin and cytokeratin at different proportions.

The HV variant differential diagnosis can include several conditions. Some lymph nodes might show focal changes resembling CD, which have been called Castleman-like changes and can occur in different reactive or neoplastic conditions, such as Hodgkin's lymphoma or several non-Hodgkin lymphomas, particularly mantle-cell lymphoma[33-35]. Castleman-like changes have also been reported in HIV-associated lymphadenopathy, particularly histological changes described in the "C-pattern", which represents the stage known as the burnout stage of infection. It should be emphasized that these changes are focal and not widespread as in CD[3,33].

Thymoma is another condition included in the CD HV variant differential diagnosis. As a matter of fact, as previously stated, on his original description, Castleman indicated that the disease he was describing resembled thymoma. Both thymoma and the HV variant can occur in the mediastinum, and HV-CD hyalinized atrophic germinal centers can resemble Hassall corpuscles; however, it should be remembered that the presence of Hassall corpuscles is very rare in thymoma[5,25].

The unicentric PC variant (UPC) accounts for less than 10-20% of CD cases, and it occurs in a patient population that is similar to that with the HV variant, but with a predominance of males, and some of them immunocompromised[1,20,33]. In many of the cases reported as UPC-variant CD, when studies have been made to determine the extension of disease, other compromised lymph nodes have been found and therefore these cases rather correspond to the multicentric variant[3,4,6]. UPC-CD is commonly associated with systemic manifestations such as fever, night sweats, weight loss, general malaise, hematologic alterations such as anemia, thrombocytopenia and hypergammaglobulinemia and splenomegaly[1,3,7]. In these patients there is a serum human interleukin 6 (hIL-6) increase, which is what lymphadenopathy and systemic manifestations of the disease are attributed to (see below)[1,7,33].

HHV-8 plays a predominant role in the pathogenesis of the PC variant[1,23,36]. HHV-8 is a rhadinovirus discovered in 1994 by Chang et al.[37] as "gammaherpesvirus" in a Kaposi's sarcoma of a patient with AIDS, and it

has an estimated prevalence of 25% in the USA[23,24,37]. As other herpes-type viruses, HHV-8 has two main phases of genetic expression: a latent and a lytic phase. At the latent phase, there is a release of latency genes, such as the latency-associated nuclear antigen, and in the lytic phase it is when the production of new virions takes place and viral IL-6 (vIL-6) release predominates[6,23].

Lymph node lymphovascular cells HHV-8 lytic cycle leads to the destruction of these cells, which entails the formation of a hyaline scar, while the production of vIL-6 elicits neoangiogenesis mediated by fibroblast growth factor and vascular endothelial growth factor[3,23]. This angiogenesis is represented by the numerous high endothelial venules present both at the nodular paracortex and the vessels penetrating the germinal center of patients with UPC-CD.

In addition, the increase in hIL-6 production leads to the proliferation of plasmablasts, which are predominantly localized around high epithelial venules. If these plasmablasts are found in small aggregates, then they are regarded as microlymphomas[1,2,9,38], which are defined as monoclonal proliferation of IgM- and HHV-8-expressing plasmablasts[20,38]. PC-CD main pathophysiologic process has been proposed to be B-lymphocyte hyperproliferation elicited by vIL-6 and hIL-6 paracrine and autocrine signals[3,6,23].

PC-CD is classified according to HHV-8 expression, which can be positive or negative[36] (Fig. 7). The HHV-8-postive PC variant generally has a more aggressive course than its HHV-8-negative counterpart[33]. HHV-8 infection is detected in up to 50% of PC-CD cases and in up to 100% of HIV-infected patients[3,23,24]. The hypothesis has been proposed that the association of CD and Kaposi's sarcoma in a single lymph node is due to lytic infection by lymphovascular endothelium HHV-8 and B-lymphocytes[3,23].

Histologically, UPC-CD can have "normal" lymphoid follicles or germinal centers variable hyperplasia with mantle zone inconstant expansion. Some of these follicles may show similar changes to those observed in the HV variant, i.e, germinal centers atrophy, variable fibrosis and hypervascularization; however, these changes may not be present. One characteristic of the PC variant is interfollicular expansion at the expense of numerous PCs. In approximately 50% of cases, these PCs can express restriction to light chains, predominantly to lambda chains (IgGλ/IgAλ), whereas in the other 50% PCs are polytypical[3,38].

PC-CD differential diagnosis should be with diseases characterized by marked follicular hyperplasia and interfollicular plasmacytosis, such as lymphadenopathy in patients with rheumatoid arthritis, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, plasmocytoma, angioimmunoblastic lymphoma and C-pattern HIV-associated lymphadenitis[3,33].

In 1978, the first case of HHV-8+ CD multicentric variant was published by Gaba et al.[39], who separated it from the unicentric form due to its multifocal nature[39]. This variant is an uncommon disease the incidence and prevalence of which are uncertain, with different pathogenesis and with much worse prognosis than other CD variants[6]. In 2010, Soulier et al.[21] described HHV-8+ MCD, which may or may not be associated with HIV. Virtually all MCD cases in HIV-positive patients are associated with HHV-8 infection, but MCD with HHV-8 can also occur in HIV-negative patients (Fig. 7)[1,6,33].

PC MCD occurs in an older age group (median age at the sixth decade of life). It occurs to immunodepressed subjects and HIV-positive patients, and commonly manifests itself with generalized lymphadenopathy, constitutional symptoms and hematological alterations with elevated IL-6 serum values during symptomatic episodes[6]. Patients typically present with fever, sweats, fatigue, cachexia, lymphadenopathy, splenomegaly, cytopenia and hypoalbuminemia, signs and symptoms that are often serious and can lead to patient death[6].

HHV-8+ MCD pathogenesis is attributed to a proliferation of HHV-8-infected B-lymphocytes, which produce vIL-6 and deregulate hIL-6[6,38]. Excessive production of IL-6 is a shared property with Crohn's disease and rheumatoid arthritis that stimulates C-reactive protein production by hepatocytes, which contributes to the inflammatory syndrome[6].

The HHV-8+ MCD variant has an aggressive clinical behavior, occurs commonly with systemic manifestations, entails a reported 2-year mortality of 50% and is considered to be a premalignant condition. Transformation to DLBCL, angioimmunoblastic lymphomas, plasmablastic lymphomas, classic Hodgkin's lymphomas, Kaposi's sarcoma and plasmocytoma has been reported in up to 25% of cases[6,24,38]. Patients with HHV-8+ and HIV+ MCD are 15-fold more likely to develop a lymphoma than the HIV+ population without CD[20,33,38].

Some patients show histopathological changes and clinical findings that are similar to those observed in HHV-8+ MCD, but without having HHV-8 or HIV infection; these cases are known as idiopatic MCD (iMCD)[20,40]. While HHV-8+ MCD is mainly a

lymphoproliferative disorder with risk of progression to lymphoma, iMCD remains controversial and it possibly constitutes more than one disease. Recent data have outlined at least one distinctive syndrome characterized by thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly, referred to by the TAFRO acronym or also as Castleman-Kojima disease (see below). This is a hypercytokinemic proinflammatory state that is similar to its counterpart, but of unknown origin[20].

Castleman-Kojima disease or TAFRO syndrome occurs in older adults, with a mean age of 56 years, and predominance in females (4:1). It is not associated with viral infection with HHV-8, HIV or EBV, and it is histologically similar, but with lower degree of plasmacytosis and marked vascular proliferation in the interfollicular area with atrophic and slightly hyalinized germinal centers. These patients' bone marrow biopsies generally show megakaryocyte hyperplasia with associated emperipolesis and slight myelofibrosis. These clinicopathologic features suggest that the TAFRO syndrome may represent a different iMCD subtype[20,40].

iMCD diagnosis is more difficult, since its symptoms are ill-defined. There are different theories about its pathogenesis, such as cytogenetic abnormalities or genetic polymorphism involving IL-6 receptor genes, which suggests an aberration in the germline of genes implicated in innate immune system regulation[41]. Histologically, it shows characteristics of both HV and PC variants[20], with polyclonal PCs proliferation in the interfollicular area and relatively normal germinal centers.

In summary, CD is a diagnostic challenge because: 1) pathological findings with hematoxylin and eosin are not entirely specific, since they can be seen in other reactive and neoplastic conditions; 2) its clinical presentation is heterogeneous; and 3) it can be associated with viruses such as HIV, HHV-8 and EBV, which can mimic other lymphoproliferative disorders.

In CD, there is an increase in the number of FRCs that express desmin and OSCAR cytokeratin, and there is EGFR positivity in the FDCs of lymph nodes affected by CD (at any of its variants, HV or PC), the pathophysiological meaning of which is unknown.

The presence of dysplastic FDCs in CD's atrophic germinal centers has been demonstrated both by cytological and molecular studies, with suggests that a genetic alteration in these cells may be the cause of CD. The EGFR expression that characterizes FDCs present in CD is not observed in other types of follicular hyperplasia or in lymphomas, and positive EGFR in FDCs could therefore be used to establish the CD diagnosis. In addition, the possibility has been proposed that, by EGFR being positive, anti-EGFR agents may be of use as adjuvants in systemic regimens for cases of unresectable CD[8,11].

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