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Hydroa like-lymphoma or hydroa vacciniforme-like lymphoproliferative disorder

Linfoma pseudo-hidroa o trastorno linfoproliferativo tipo hidroa-vacuniforme

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Abstract

Hydroa vacciniforme-like lymphoproliferative disorder (HV-LPD) is a cutaneous form of Epstein-Barr virus-positive T/NK cell lymphoproliferative disease described in Mexico in 1998; It was recognized as such in 2008 by the World Health Organization and in 2016 it was classified as a lymphoproliferative disorder. There are different hypotheses that attempt to explain the pathogenesis of this entity, among them: chronic Epstein-Barr virus infection and UV radiation as a trigger. The classic clinical picture is presented as edema and vesicles that heal into crusts leaving varioliform scars in photo-exposed areas, while the atypical picture presents with necrotic papules and vesicles with extensive varioliform scars in both photo-exposed and non-photo-exposed areas, in addition to systemic symptoms. There are clinical and histopathological criteria to make the diagnosis of HV-LPD, in addition, PCR is helpful to find the presence of EBV. It is characteristic the angiocentric and angiodestructive lymphoid infiltrate involving dermis and hypodermis, with the immunohistochemistry markers of cellular differentiation compatible with T and NK lymphocytes. Several lines of therapy have been studied, mainly chemotherapy and radiotherapy with poor results, as well as immunomodulatory therapy and allogeneic hematopoietic stem cell transplantation, which so far have had the best results.

In summary, HV-LPD remains a peculiar lymphoma very difficult to manage entity due to its low incidence worldwide, its pathophysiology and treatment are still under study.

KEYWORDS: Hydroa vacciniforme like lymphoproliferative disorder; Epstein-Barr virus; T/NK cells lymphoproliferative disorder; World Health Organization; UV radiation; Edema; Scar; PCR; Dermis; Hipordermis; Immunohistochenistry; Immunomodulatory therapy; Allogeneic hematopoietic stem cell transplantation; Lymphoma; Incidence.

Resumen

El trastorno linfoproliferativo tipo hidroa-vacuniforme (HV-LPD) es una variante cutánea de la enfermedad linfoproliferativa de células T-NK positivas al virus de Epstein-Barr, descrita en México en 1998. Fue reconocido en 2008 por la Organización Mundial de la Salud y clasificado en 2016 como un trastorno linfoproliferativo. Existen diferentes hipótesis que intentan explicar la patogenia de la enfermedad, por ejemplo: la infección crónica por el virus de Epstein-Barr y la radiación UV como desencadenante. El cuadro clásico aparece con edema y vesículas que forman costras y dejan cicatrices varioliformes en áreas fotoexpuestas, mientras que el cuadro atípico se manifiesta con pápulas necróticas y vesículas con cicatrices varioliformes extensas en las áreas fotoexpuestas o no, además de síntomas sistémicos. Existen criterios clínicos e histopatológicos para establecer el diagnóstico; sin embargo, es importante la PCR para identificar el virus de Epstien-Barr. Es característico el infiltrado linfoide con destrucción vascular, que afecta la dermis e hipodermis, con marcadores inmunohistoquímicos de diferenciación celular compatibles con linfocitos T y NK. El linfoproliferativo tipo hidroa-vacuniforme es una forma rara de linfoma, de difícil tratamiento; debido a su baja incidencia en todo el mundo, la fisiopatología y tratamiento permanecen en estudio.

PALABRAS CLAVE: Trastorno linfoproliferativo tipo hidroa-vacuniforme; Virus Epstein-Barr; Célula T-NK relacionadas con el trastorno linfoproliferativo tipo hidroa-vacuniforme; Organización Mundial de la Salud; radicación ultravioleta; edema; cicatriz; PCR; dermis; epidermis; inmunohistoquímica; terapia de inmunomoduclación; trasplante alogénico de células madre hematopoyéticas; linfoma; incidencia.

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BACKGROUND

Hydroa vacciniforme-like lymphoma (HVLL) was originally described in 1998 by Magaña et.al. as "angiocentric cutaneous T-cell lymphoma of childhood (ACTCLC) and the term "hydroa-like lymphoma" was coined in the literature; is a cutaneous lymphoma already known as an Epstein-Barr virus (EBV)-driven lymphoproliferative disease that involves children and young adults of Latin American and Asian descent.[2]

In the World Health Organization (WHO) – European Organization for Research and Treatment of Cancer (EORT) classification of primary cutaneous lymphomas, HVLL was considered as a variant of the extranodal NK/T-cell lymphoma nasal type.[3]

In the 2008 WHO classification of hematological neoplasms, HVLL is recognized as a distinctive clinicopathologic type of cutaneous lymphoma, included in the group of EBV+ T-cell lymphoproliferative disorders of childhood.[4]

Several studies on clinicopathologic, phenotypic, and molecular features of HVLL have been published.[5,6,7]

The classic inflammatory disease hydroa vacciniforme (HV) was first described by Ernest that evolve into crusts and consequently leave varioliform scars after exposure to the sun. No systemic symptoms are observed and the disease usually spontaneously reverts in adolescence or early adulthood.[8]

Definition

HVLL is cutaneous form of Epstein-Barr virus positive T/NK-cell lymphoproliferative disease that occurs in childhood and in childhood and frequently develops infiltration to other organs as a life-threatening disease.[9]

The most affected populations are children and and young adults in Latin America, especially in Peru, Mexico and Guatemala, as well as in Asia particularly in Korea, Japan and Taiwan, and rarely occurs in caucasian; however, isolated cases have been reported in adults and the elderly.[10,11,12] There are different hypotheses that try to explain the pathogenesis of this entity. The main ones include chronic infection by the Epstein Barr virus. After acute infection, the virus remains latent in B lymphocytes and is maintained in this way, thanks to a limited number of transcripts and viral proteins that inhibit apoptosis and promote cell proliferation; however, when the patient's immunity is compromised, cell division becomes uncontrolled and can lead to different lymphoproliferative disorders.[13]

EBV has tropism for B lymphocytes, which are infected through the surface protein CD21,[14] so that the binding to T/NK cells is not well established, however it has been described that in order to be infected, NK cells acquire CD21 through synapses with infected B lymphocytes, thus enabling EBV to attach to them.[15]

Reactivation of viral replication plays a very important role in EBV transformation to malignancy. EBV replication during an early lytic phase may facilitate an appropriate environment for tumor development by the effect of the chemotactic pathway of CCL5 to attract monocytes, which promotes the differentiation of tumor-associated macrophages (TAMs) and these in turn secrete IL-10 inhibiting the inflammatory response. In this way the lytic replication of this virus attenuates the protective action of CD8+ lymphocytes. Another way to block this response is by encoding microRNAs (miRNAs) attenuating CD8+ T lymphocyte chemotaxis and generating down-regulation of CXCL11 expression and inhibition of Major Histocompatibility Complex type I (MHC-I), thus restricting the presentation of tumor antigens. [12]

UV radiation has been described as a trigger, since it can cause DNA damage in skin cells, in which there are microbial commensals that

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generate a microenvironment that prevents colonization by other microorganisms and this is affected by UV radiation, altering the skin barrier function, which facilitates colonization by other microorganisms. This also induces the release of antimicrobial peptides from the innate immune response and the stimulation of γδ T cells and inhibition of effector T cells, thus modulating the immune response.[12]

Despite these possible theories, the pathogenesis of this entity remains entirely uncertain.

The World Health Organization (WHO) in 2008, published the classification of hematopoietic and lymphoid tissue tumors, where it recognizes this entity as "hydroa vacciniforme like lymphoma", later, in the 2016 update, changed its name from lymphoma to " hydroa vacciniforme like lymphoproliferative disorder", due to its relationship with chronic active EVB infection thus covering the entire clinical spectrum of the disease,[16,17] same that is subclassified in:

- Classic Hydroa vacciniforme
- Atypical/ Severe Hydroa vacciniforme
- Hydroa vacciniforme like lymphoma

The 2016 classification places the hydroa vacciniforme like lymphoproliferative disorder in a first large group which are the mature T/NK cell neoplasms, within which there is a subgroup of chronic active EBV infection, previously called EBV+ T/NK cell lymphoproliferative disorders of childhood, which are again subdivided into the systemic form and the cutaneous form, the latter, being where the hydroa vacciniforme like lymphoproliferative disorder and severe mosquito bite allergy are located.[14,16,17]

According to the current literature HVLL or hydroa vacciniforme-like is subclassified into classic, severe and hydroa vacciniforme-like lymphoma. The clinical presentation is the following:

Classic hydroa vacciniforme presents with papules and vesicles that heal to form crusts leaving depressed, varioliform scars in photoexposed areas. Serum EBV DNA levels are elevated, with normal antibody titles.[10]

Both severe or atypical hydroa vaccinifomre and hydroa vacciniforme like lymphoma present with necrotic papules and vesicles with extensive varioliform scarring in photoexposed and non-photoexposed areas, in addition to systemic symptoms such as fever, lymphadenopathy, increased liver enzymes, very high EBV DNA in serum with >10,000 copies/mg and antibody titles demonstrating chronic active infection.[10] It is classified as hydroa vacciniforme like lymphoma when there are extracutaneous symptoms of hepatosplenomegaly, lymphadenopathy and bone marrow infiltration in addition to hematologic abnormalities; there may also be fever, weight loss, asthenia and elevated DHL.[12]

The diagnosis of HV-LPD is often delayed for many years because the skin changes are usually nonspecific for the clinician who is not aware of this disease and is often as an inflammatory skin disease, such as rosacea or granulomatous cheilitis, sarcoidosis, dermatomyositis, and lupus erythematosus profundus.[18]

There are no specific criteria published by the WHO to make the diagnosis of HVLL/HV-LPD, however, the original papers published by us present the clinical and microscopic features to recognize it and to make a specific diagnosis.[1,2] Also in the also in the polymerase chain reaction (PCR) in situ hybridization will identify the presence of small RNA encoded by EBV, as well as its copies in serum of viral DNA.[11]

Histopathology

Histopathologically it is characterized by a perivascular and periannexal lymphoid infiltrate that may have few reactive lymphocytes.[19] The

dermis shows an extensive predominantly perivascular lymphocytic infiltrate associated with reticular degeneration, spongiosis or necrosis of the epidermis.[20] The lymphocytic infiltrate is atypical with small to medium and large-sized pleomorphic cells with an enlarged round or oval nucleus.[21] There is usually an angiocentric and angiodestructive lymphocytic infiltrate with extension into the subcutaneous fat as well as spongiotic vesicles and ulcerated lesions, but no epidermotropism. Infiltrating cells are EBV positive.[19] Perivascular infiltrating lymphocytes are moderately dense in the superficial and deep dermis with extension into the subcutaneous tissue. Patients with severe symptoms present with larger and deeper infiltrates, often involving the dermis and hypodermis. Cases with an NK phenotype should be differentiated from severe mosquito bite hypersensitivity with a prominent eosinophilic component in the infiltrate and panniculitic involvement.[19]

In immunohistochemistry it is possible to appreciate cell differentiation markers compatible with T and NK lymphocytes. Most cases of HVLL or HV-LPD present cytotoxic T cells with CD3 +, CD8 + immunophenotype and positive cytotoxic markers (TIA -1, granzyme B +). A smaller proportion have the NK cell phenotype with CD56 +.[11] A retrospective analysis of 41 patients with HV-LPD showed on immunohistochemistry all the patients involved were positive for CD3, CD5, CD7, TIA1, in 12 patients CD4, 9 patients CD8, and 18 patients with CD4 and CD8.[20] CD30 and CD56 positivity is most frequently seen in biopsies with NK cell phenotype, neoplastic cells surround individual fat cells and may histologically resemble a subcutaneous panniculitis T-cell lymphoma. Cases demonstrating a monoclonal rearrangement in the TCR-c receptor favor a T-cell lineage, which is useful in delineating the T-cell lineage from the NK-cell lineage in HVLPD cases, in addition to immunostains for TCR-cd and TCR-ab.[11]

At present there is no specific treatment regimen, however in the literature we can find a number of therapeutic measures that have been managed over time. However, it must be clear that if left the its natural evolution, this disease will progress and will kill the patient, has has been demostrated in our series[1,2] and many others.[20]

Options such as chemotherapy and radiotherapy have been used where the regimens were BFM-90/95, for pediatric non-Hodgkin's lymphoma (NHL) and gemcitabine for adult extranodal NK/T-cell lymphoma of the nasal type. The effects were transitory and did not result in sustained remission. These treatments eliminate EBV-infected cells, but could not prevent reinfection. It was therefore concluded that both therapies offer little benefit, with a transient effect without sustained remission, and that these therapeutics increase mortality from sepsis or liver failure.[9]

There are other reports in Latin America that contraindicate the use of chemotherapy as the first line of treatment due to poor results in patients who have received it. When this treatment fails to eradicate the lymphoma, it can worsen the prognosis by inducing immunosuppression and reactivation of EBV replication.[12]

Immunomodulatory therapies may offer a better first-line treatment alternative, have been shown to provide temporary remission and improve symptoms. Agents that have been used include prednisolone, interferon alpha, cyclosporine, chloroquine and thalidomide.[19]

An innovative therapy that has shown successful results, as described in a retrospective review by Ruan et al in 2020, on the clinical course of 10 patients, with the use of intravenous immunoglobulin which was used at a dose of 0.4 g/kg from 3 to 5 days per month until the disease was stabilized with less than 5 relapses in one year, then gradually reduced every month for

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three months. Subsequently, systemic glucocorticoids were used when extensive ulcers or persistent fever was present for more than three days, which were rapidly reduced in time and dose, after remission of the episodes. This study demonstrated that the mortality rate is lower than that reported with other treatments and patient hospitalization costs were reduced as no additional antibiotics or secondary therapies to chemotherapy were required.[22]

With regard to phototherapy, narrowband UVB phototherapy (NBUVB) three times a week for five weeks is most often recommended, while psoralen-UVA (PUVA) phototherapy is not recommended for younger patients.[12]

Currently allogeneic hematopoietic stem cell transplantation (HSCT) may be the only curative therapy for this disease, as it is the only therapeutic measure that has achieved long-term remission, as demonstrated in a case report by Li et al in 2018, in which a child achieved long-term remission by allogeneic hematopoietic stem cell transplantation followed by immunotherapy with donor EBV-specific cytotoxic T-lymphocytes.[23] Subsequently, a retrospective study of 19 patients described the case of a patient who received an allogeneic hematopoietic stem cell transplant and treatment with EBV-specific cytotoxic T-lymphocytes (EBV-CTL) after chemotherapy; so far reported he was alive and disease-free at last follow-up, showing an outcome consistent with those of previous reports.[9]

Despite being considered the best treatment at the moment, a conservative approach is recommended as first-line therapy in patients with HV-LPD to avoid unnecessarily aggressive treatment.[24]

CONCLUSION

conservative initial treatment is suggested for most patients, such as topical and oral corticosteroids at low doses of antibiotics when there is a concomitant bacterial infection. It is of utmost importance to identify patients at higher risk of progression to aggressive phases of this entity in order to provide them with individualized and effective treatment.[20]

At present, there are no defined prognostic factors for progression of systemic disease. It has been suggested that elevated serum EBV viral DNA titles (> 600 copies/mL) predict a worse prognosis and a progressive clinical course while patients with a normal serum EBV DNA load follow a more indolent disease course.[11] On the other hand, elevated LDH levels (318 - 1202 IU/L) have been associated with an increased risk of progression of systemic T/NK lymphoma [20]

It has been reported that the most important factor predicting poor prognosis is extracutaneous involvement; individuals with skin-only lesions have shown better outcomes. High Ki67 expression has been associated with a more aggressive clinical outcome.[24]

Regarding patients who progressed to systemic lymphoma, histologic changes were demonstrated showing dense and diffuse, atypical, medium to large-sized lymphocytes with accelerated mitoses and presence of tumor necrosis.[12]

Based on the literature review, that this condition is a rare entity that is difficult to diagnose, since other photodermatoses may present similar clinical lesions to those of the HV-LPD. Its incidence and prevalence is centered in some Latin American and Asian countries. It should be considered when presenting systemic symptomatology accompanied by dermatologic lesions. When the diagnosis is made, there is usually an advanced stage and progression of the disease, with dissemination to other organs and systems, as reported in the literature.

It is also important to consider that the development of this disease is closely linked to a chronic

stage of EBV infection and other environmental and genetic factors, which brings us closer to understanding the pathophysiology of this disease, which until now has been somewhat unknown and has allowed the development of new therapeutic strategies that promise to provide a better prognosis.

There are several therapies used, such as chemotherapy, immunoglobulin, corticosteroids, phototherapy and hematopoietic cell stem cell transplantation. Of all these therapies, only the use of immunoglobulin and hematopoietic cell transplantation showed improvement of the lesions and symptoms, and even remission of the disease, while the patients treated with chemotherapy presented disease progression and a higher mortality rate.

It is worth mentioning that HVL-PD was unknown and poorly addressed until the first reports made by Magaña et al in 1998, which gave rise to highlight the importance of this entity, and therefore new studies would be carried out to try to explain this condition, although to date the pathophysiology and the therapeutic approach remain uncertain. Further studies are required to complete the understanding of this pathology.

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