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REVIEW ARTICLE

Plasmacytoid Dendritic Cell Leukemia: Updated Review

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ABSTRACT
This review article compiles updated information on Plasmacytoid Dendritic Cell Leukemia, a type of uncommon or rare myeloid neoplasm, with typically cutaneous manifestations with or without extramedullary involvement and leukemic dissemination, which makes it difficult to differentiate from other neoplasms. This review aims to provide a brief update on key points such as its epidemiology, pathogenesis, diagnosis and treatment, in order to allow early recognition of the disease considering its rapid evolution and poor prognosis.

Keywords: Dendritic; leukemia; plasmacytoid

Introduction

Blastic plasmacytoid dendritic cell neoplasia (BPDCN) is a rare aggressive hematologic malignancy that typically affects the skin, peripheral blood/bone marrow, lymph nodes, and central nervous system (CNS).[1] This rare disease represents less than 1% of all hematological neoplasms and 0.7% of primary cutaneous malignancies. [2,3]

There are two types of dendritic cell neoplasms according to their origin: 1) mature cell proliferative neoplasia (MPDCP) associated with myeloid neoplasia and 2) blast cell neoplasia (BPDCN).[2] However, once it was determined that the disease originated from plasmacytoid dendritic cells (pDC), the World Health Organization (WHO) in 2008 reclassified it as a subtype of acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL), and later in 2016 it was reclassified again in a category related to dendritic cells, and by 2022, the WHO included it in a category called "plasmocytoid dendritic cell neoplasms." [4]

In the first instance, to ensure the diagnosis, a multidisciplinary approach is essential that involves a hemato-oncologist, a transplantologist, a dermatologist and a pathologist, preferably with subspecialization in dermatopathology and/or hematopathology.

Patients with this type of cancer have a difficult diagnosis and an extremely poor prognosis, with rapid relapses even after treatment with chemotherapy. [5]

Epidemiology

Dendritic cell leukemia is a rare disease, with an overall incidence rate of 0.04 cases per 100,000 inhabitants. It is generally a disease of adults, with a mean age of 53 to 68 years and a male:female ratio of 2.0 to 3.3:1. It was recently found to have a bimodal incidence pattern, with higher incidences in those under 20 years of age and those over 60 years of age; ethnic predilection is unclear and there are conflicting published reports. [2,6]

It constitutes 0.44% of all hematological malignancies, less than 1% of acute leukemias, and 0.7% of cutaneous lymphomas detected each year and accounts for approximately 700 to 1,000 estimated cases annually in the United States of America. (USA) and Europe. Despite the advances experienced in recent years in diagnosis, biological recognition of the disease and treatment, the average survival is 8 to 14 months after the initial diagnosis.[7]

Etiopathogenesis

Dendritic cells are usually found in lymph nodes and tonsils, being rare in the thymus, bone marrow, spleen and lymphoid tissue associated with mucosa. Dendritic cells regularly accumulate in lymph nodes after exposure to viruses or autoimmune diseases such as Kikuchi lymphadenitis, Castleman hyaline vascular disease, systemic lupus erythematosus, or psoriasis. In response to this exposure, dendritic cells secrete massive amounts of type I interferons (α and β) in addition to other proinflammatory cytokines such as IL-6, IL-8, IL-12 as well as tumor necrosis factor; However, although the non-association between Epstein Barr virus (EBV) and this neoplasia has been clarified, its true pathogenesis is still unclear, and it is hoped that in the future there will be light on its precise etiology. [2,4,6,8]

At the level of the CNS, a significant dysregulation has been identified in micro RNAs, genes such as Neuroligin-4X (NLGN4X), enzymatic markers such as Doublecortin (DCX) and Ubiquitin C-Terminal Hydrolase-L1 (UCHL-1) were expressed in tumor microenvironments, for this reason, their participation in this neoplasia is emphasized.[4]

Clinical diagnosis

Dendritic cell leukemia is a malignant and aggressive neoplasm, whose clinical manifestations are very variable, and are often misdiagnosed. Around 85 to 90% of patients affected by this type of neoplasia present dermal lesions at the time of diagnosis, which are variable in size (millimeters to 10cm), shape and color (erythematous, reddish or bluish). Three dermatological patterns of presentation are described, with isolated violaceous nodules being the most frequent with a 73% frequency, followed by disseminated lesions of a mixed type between macules and nodules in 15% and finally, with a 12% frecuency of violaceous macules similar to hematomas, which may present simultaneous or subsequent systemic dissemination, and may even become scaly over time, while between 10% to 15% usually present with overt leukemia, and up to 50% may manifest only with lesions cutaneous. [2,5-8]

The most commonly affected areas of the body are the face or scalp in 20%, lower limbs in 11%, trunk in 9% and upper limbs in 7%, however, involvement of the mucous membranes is also described in a 6%, especially in the oral mucosa.[7,8]

A key characteristic of this type of pathology is that approximately between 50% and 60% of patients present lymph node and spinal cord involvement with hematological alteration, with rapid and aggressive systemic dissemination, indolent clinical

presentation and isolated skin involvement; medullary leukemic infiltration occurs in 73%, and the most common findings in peripheral blood are thrombocytopenia, anemia and neutropenia in 78%, 65% and 34% respectively, associated with lymphadenopathy in 56% of cases. [2,5,7,8]

At the extramedullary level, extension to the tonsils, nasal cavity, paranasal cavity, tongue, breast, lungs, gallbladder, liver, spleen and eyes has been documented; In one third of patients there is CNS involvement, especially when the disease relapses. [6-8]

Pathological diagnosis

The diagnosis is established through the histopathological study of the affected tissue associated with the application of immunophenotypic markers. The histopathological organization of tumor cells has been described as heterogeneous and complex, lymphoblastic or myeloblastic type, with a small to medium-sized, agranular, sparsely abundant cytoplasm, without Auer rods, an irregular nucleus, a discrete nucleolus and fine chromatin. Its proliferation rate estimated by Ki67+ shows great variability between 20 and 80%, especially due to atypical mitoses. In the medium-sized cellular infiltrate, small and large cells are observed accompanied by an inflammatory infiltrate. [5-8]

Dermatologically, a typical medium-sized diffuse monomorphic infiltrate is evident, affecting mainly the dermis and subcutaneous cellular tissue, respecting the Grenz zone and the epidermis, characterized by irregular and eccentrically located nuclei, finely dispersed chromatin and one or more small and scattered nucleoli, some authors report nodular, perivascular and periadnexal patterns, and necrosis can rarely be found; However, sometimes an angiocentric/angiotropic infiltrate with a lichenoid appearance can be found. [5-9]

At the lymphatic level, it presents a diffuse leukemic-like pattern in interfollicular and medullary areas without affecting the B cell follicles and progresses to cortical areas, being able to completely erase the lymph node architecture; When tumor cells infiltrate the bone marrow, they are usually focal at first, in small groups or due to interstitial infiltration and subsequently become massive once the disease progresses. Histologically, they appear with blasts of variable size, of undifferentiated appearance, with round or oval nuclei, with clear chromatin with one or several nucleoli and basophilic cytoplasm without granulation, which may contain micro vacuoles along the cell membrane. [5,7,8]

Genetic diagnosis

The genetic background of BPDCN demonstrates a heterogeneity of these anomalies; The majority of patients are known to harbor chromosomal abnormalities detectable on conventional karyotyping, and a complex karyotype has been identified in up to 75% of patients. [1,7]

The most frequently affected chromosomes are 5 (5q21 or 5q32 in 72%), 6 (6q23-ter in 50%), 9 (28%), 12 (12p13), 13 (13q13–21 in 64%) and 15 (15q in 43%), in addition to others with less frequency such as 4 (q34.1 - q34.2), 9 (p13.2 - p11.2 - q12 - q34.3) and 13 (q12.11 - q31.1), and others with overexpression of the oncogenes HES6, RUNX2 and FLT3 without associated genomic amplification.[1,7]

Likewise, mutations have been detected involving multiple genes, including TET2, ASXL1, NRAS, ATM, ZRSR2, NRP1, IL3RA, DERL3, LAMP5, PTCRA and PTPRCAP, as well as a fraction of the genes SIGLEC6, LTK, FCER1A, CD59, CADM1 and TMEM14A are present in this type of leukemia. [1,7]

Immunophenotypic diagnosis

There is no specific immunophenotypic definition for this neoplasm; However, when tumor cells are found in the bone marrow and blood, the diagnosis is mainly based on the immunophenotype of samples from these tissues; Furthermore, phenotypic heretogeneity has been demonstrated. [5]

The cells of this neoplasm are positive for markers such as CD123, BDCA2 (CD303) and TCF4, while they are negative for the cytochemical stains of myeloperoxidase (MPO), butyrate esterase and naphthol-AS-Dchloroacetate esterase. A specific lectin, BDCA2 (CD303), is a specific marker, but with limited sensitivity for its use due to its frequent downregulation (30%) for this neoplasia, or its expression is very low by flow cytometry, and its interpretation is difficult.[1,5,11]

Recent research has proposed that TCF4/CD123 dual-color staining is highly sensitive and specific for the detection of dendritic cell leukemia in formalin and paraffin fixed tissues, being the first to suggest this diagnosis if this type of leukemia is diagnosed identified population of blasts with very high CD123 expression.[1,11]

Likewise, frequent expression of CD4, CD56, HLA-DR and TCL1 has been described. The neoplasm can also express other markers related to CD2, CD5,

CD7, CD33, CD38, CD45, CD64, CD68, CD117, HLA-DR, transcription factor Spi-B and TdT in a variable manner, additionally to have a high index Ki-67 proliferative. However, by definition, dendritic cells are negative for B, T, and myeloid cell lineage-specific antigens. [1,5]

Immunophenotyping by multicolor flow cytometry is essential for initial diagnosis and for the detection of residual disease after treatment. [1]

Identifying BPDCN is not difficult when the CD45-low blast population lacks all myelomonocytic, erythroid, megakaryocytic, lymphoid, and plasma cell lineage markers. Only CD4 and CD56 are expressed at a high level of HLA DR. [11]

Several authors have proposed that the coexpression of CD4, CD123, BDCA4 and/or BDCA2, with or without expression of CD56, and the lack of CD11c, CD3, CD79a and MPO are sufficient for the diagnosis of this tumor, and it has been described that, if CD123 is not expressed, or is weak, or is positive, but BDC4 or BDCA2 is not expressed, the diagnosis of BPDCN should be confirmed. [12]

As dendritic cell leukemia frequently expresses myeloid or lymphoid lineage markers (CD7, CD33, CD117, CD22, cCD79a, and cCD3), the diagnosis may not be immediately evident, so diagnosis remains a challenge. [11]

Differential diagnosis

Using histology, immunohistochemistry and flow cytometry, the differential diagnosis is made with other neoplasms, the main ones being myeloid sarcoma, acute myeloid leukemia, T-cell lymphoma/lymphoblastic leukemia, NK cell leukemia and some lymphomas/leukemias mature, T cell leukemias. [2,5,6]

Thus, the expression of markers, such as myeloperoxidase, CD34, CD117 or lysozyme and CD68 with diffuse staining is typical of myeloid sarcoma, which is negative for the markers CD56, CD123, myxovirus or TCL1. For T-cell acute lymphoblastic leukemia/cutaneous lymphoblastic lymphoma, positivity is for cytoplasmic CD3, CD2, CD5, and CD7 in addition to TdT, and is mostly double positive or double negative for CD4 and CD8. [2,5,6]

Primary or secondary cutaneous T cell lymphoma is differentiated by the expression of CD3 without CD56; while NK cell leukemia expresses CD56, often TIA-1, granzyme B and/or perforin, sometimes CD3 and does not express CD4. In this way it can be identified that it is a dendritic cell leukemia since it expresses very typical markers for them as explained above. [2,5,6] (Table 1)

Tabla 1. Diferencial diagnosis of BPDCN

	CD123	CD4	CD56	MPO	CD2	CD3	CD8	CD34	CD117	CD68	TIA-1	Granzima B
BPDCN	+	+	+	-	-	-	-	-	-	-	-	-
Myeloid sarcoma	-	-	-	+	-	-	-	+	+	+	-	-
T-cell acute lymphoblastic leukemia/cutaneous lymphoblastic lymphoma	-	+/-	-	-	+	+	+/-	-	-	-	-	-
Primary or secondary cutaneous T-cell lymphoma	-	-	-	-	-	+	-	-	-	-	-	-
NK cell leukemia	-	-	+	-	-	+/-	-	-	-	-	+	+

MPO, Miloperoxidasa, NK, Natural Killer.

Treatment

Advances in the knowledge of the pathogenesis of this neoplasia have provided new knowledge for the diagnosis and development of specific treatment strategies, immunotherapeutic options are encouraging, however, a standard treatment has not yet been established due to its variability in diagnosis and the low frequency of the disease. [6]

Therapeutic options are based on retrospective studies and case reports, and skin lesions can be treated with focal radiation, oral corticosteroids or chemotherapy, the latter option being used in high doses combined with hematopoietic stem cell transplantation, with its limitations in frail, elderly and relapsed or refractory patients.[12]

Historically, three conventional chemotherapy regimens have been used: acute myeloid leukemia (AML) regimen such as ICE (Idarubicin, Cytarabine, Etoposide) or MICE (Mitoxantrone, Cytarabine, Etoposide); acute lymphoblastic leukemia (ALL) regimen such as Hyper CVAD (Hyperfractionated Cyclophosphamide, Vincristine, Adrimycin, Adrimycin and Dexamethasone) alternating with Methotrexate and Cytarabine, or lymphoma regimen, CHOP (Cyclophosphamine, Adriamycin, Vincristine, Prednisone), with these regimens there is no a complete remission rate between 53 and 89%, with the LLA regimen being the most effective. [2,14]

In 2018, the FDA approved Tagraxofusp, a therapy targeting CD123 (interleukin 3 receptor alpha chain), a protein overexpressed on the cell surface of various hematological malignancies (AML, ALL, and BPDCN), in phase III studies they found an efficacy of 90%, a survival rate of 59% at 18 months and 52% at 24 months. [15,16,17]

According to studies, chemotherapy combined with hematopoietic stem cell transplantation (HSCT) is the traditional treatment for BPDCN, improving the patient's overall survival. With consolidation therapy (allogeneic or autologous) after a first complete remission, Allogeneic HSCT has a higher remission rate and lower relapse rate than autologous HSCT.[15] Its limitations are donor restriction, limited availability according to the health system and patient fragility.[5]

Conclusions

BPDCN is a rare disease that is likely underdiagnosed and underreported.

The patient with potential suspicion of BPDCN should undergo specific studies to reach the correct diagnosis as quickly as possible due to the aggressive natural course of the disease.

Conventional treatment has given disappointing results due to the clinical variability of this neoplasm, and intensive treatments with allogeneic stem cell transplantation are reserved only for patients with good general condition, which is a tiny group.

This leukemia has a poor short-medium term prognosis despite the various treatments used due to its aggressiveness and the difficulty of its diagnosis.

New approaches using well-tolerated targeted therapies are needed for the majority of patients who cannot receive intensive chemotherapy.

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