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Cutaneous Mastocytosis: Diagnosis and Treatment for the Physician of First Contact

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ABSTRACT

Mastocytosis is one of eight subcategories of neoplasms. Classification of Myeloproliferative Tumors of Lymphoid Tissues and hematopoietics of 2008 of the World Health Organization; is a heterogeneous group of myeloproliferative diseases that distinguished by excessive proliferation of mast cells morphologically and immunophenotypically atypical, in addition to the accumulation of these cells in one or more organs or tissues, including the skin, bone marrow bone, liver, spleen, and lymph nodes.

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INTRODUCTION

Mast cells are involved in many physiological reactions. The property of reacting to various stimuli affects different allergic diseases, such as asthma, atopic dermatitis, urticaria or anaphylaxis, as well as participating in the immune response. Mast cell mediators include histamine, proteases, heparin, proteoglycans, leukotrienes and other cytokines with different effects on cells; they are also implicated in autoimmune and inflammatory diseases and some malignant tumors.[1]

Mastocytosis is one of eight subcategories of myeloproliferative neoplasms in the 2008 World Health Organization Classification of Tumors of Lymphoid and Hematopoietic Tissues; is a heterogeneous group of myeloproliferative diseases that they are distinguished by the excessive proliferation of morphologically and immunophenotypically atypical mast cells, in addition to the accumulation of these cells in one or several organs or tissues, including skin, bone marrow, liver, spleen and lymph nodes. [2]

According to the World Organization for Health, disease can be classified as Cutaneous mastocytosis, which is limited to only the skin, or systemic mastocytosis, in which the mast cells infiltrate other organs with or without damage of the skin. Symptoms, natural history, and survival varies widely between different categories of mastocytosis. Therefore, symptoms are usually the result of mast cell-derived mediators and may range from mild symptoms to some that can be life-threatening. [2]

The main objective of the treatment of mastocytosis is the control of the symptoms, there is no curative treatment so far. The biggest part of treatment recommendations of these patients is based on the opinions of experts rather than on the evidence obtained from through clinical trials.[3]

PATHOGENESIS

Mast cells are derived from CD34 progenitors from the bone marrow and circulate as precursors in the peripheral blood to the organs where they will be differentiated by the influence of the stem cell factor. Systemic mastocytosis has been associated with mutations in the oncogene homolog v-kit Hardy-Zuckerman 4 sarcoma viral feline (KIT), which codes for a receptor transmembrane with tyrosine kinase activity type III (KIT receptor, CD117), which is expressed by mast cells, the progenitor cells hematopoietic cells, germ cells, melanocytes, and interstitial cells of Cajal in the gastrointestinal system and that, together with the factor of stem cells, is responsible for the growth of the mast cells; It is also involved in melanogenesis, hematopoiesis, gametogenesis, and the regulation of slow gastric waves. The interaction between KIT and its ligand SCF is essential for normal mast cell development from their hematopoietic progenitors. [4]

In addition, it is key in the regulation of proliferation, maturation, adhesion, chemotaxis and their survival and their mutation leads to atypical hyperproliferation of the mast cells. Two mutations are reported cause amino acid substitutions, known as Asp-816(r) Val and Val-560(r) Gly in the proto-oncogene c-kit. The D816V mutation is commonly found in adult patients with mastocytosis, it is estimated to be present in more than80% of patients, although their existence is not necessarily indicates a concomitant hematologic disease, whereas the mutation V560G is only found in a small number of patients. The D816V mutation leads to the activation of the tyrosine kinase domain, which results in constant cell proliferation. Other oncogenic mutations that have recently been identified in patients with mastocytosis include TET2 (from the oncogene family) and N-RAS. TET2 is a suppressor gene and its frequency in systemic mastocytosis is 20 to 29%; however, it does not seem to have an impact on the patient survival. [5]

These mutations are not specific for mastocytosis and their role is still unknown. KIT mutations are frequently associated with mastocytosis; however, this does not occur universally, so the question is: what other individual mutations are necessary and sufficient to cause mast cell transformation?

Histamine is one of the main enzymes released during mast cell degranulation, their normal plasma concentration is 0.3 to 1 ng/mL. Other authors found that the histamine levels are increased in mastocytosis; however, they are not related directly with the number of mast cells in the lesions. [6]

Tryptase is another of the enzymes is released from mast cells, its normal plasma concentration is less than 11.5 ng/ mL. Belhacin et al. found that tryptase concentrations are higher in atopic patients, with an average of 14.2 ng/mL, while in nonatopics the average concentrations are 4.12 ng/mL. [7]

CLASSIFICATION

The diagnosis and classification of mastocytosis is based on the identification of mast cells. by morphology, immunophenotype or genetics, using the 2008 World Health Organization criteria, which divides tumors in the following categories: 1) mastocytosis cutaneous (limited to the skin), 2) mast cell tumor extracutaneous (unifocal mast cell tumor with non-destructive features), 3) mast cell sarcoma (unifocal mast cell tumor with destructive characteristics and scarcely differentiated), 4) systemic mastocytosis that invariably affects the bone marrow, manifests with skin lesions and is more common in adults. [8]

The most common form of mastocytosis in the pediatric population is cutaneous, which is usually a benign disease most cases are transient and remit spontaneously at puberty. Mastocytosis skin is divided into three subgroups: urticaria pigmentosa, diffuse cutaneous mastocytosis, and solitary mast cell tumor. [9]

Urticaria pigmentosa is the most common type. in adults and children. Colored macules are found yellow to reddish brown and some papules may be present. They are usually seen in the upper and lower extremities and some times in the thorax and abdomen. It is rare to observe it on the palms, soles, face, and other exposed areas of the skin. It can be seen and Darier's sign (appearance of erythema and urticaria after five minutes of persistent scratching). [10]

Solitary mast cell tumor is less common tan urticaria pigmentosa, also seen in children and tends to regress. [11]

Systemic mastocytosis is divided into four subcategories: indolent (without evidence of extracutaneous organ dysfunction), aggressive (with extracutaneous organ dysfunction), associated with other clonal hematological diseases with non-mast cells and mast cell leukemia. [11]

Indolent systemic mastocytosis includes the largest subgroup (49%). Compared to the other subgroups, manifests itself at a later age early age (49 years) and has a higher prevalence (66-75%) of skin lesions and symptoms linked to mast cell mediators and gastrointestinal. Usually does not cause systemic symptoms (<20%). The Organization World Health Organization recognizes two variants of indolent systemic mastocytosis: mastocytosis latent systemic and isolated mastocytosis in the bone marrow. The first is distinguished by greater mast cell burden, defined by the existence of two or more findings B; furthermore, who the suffer have lower life expectancy (120 months) compared to mastocytosis indolent systemic of another type (301 months). [11]

In addition, these patients are older at diagnosis (64 years) and more data on attack to general state (45%) and anemia (55%). The group of patients with isolated mastocytosis in the bone marrow more often have symptoms derived from the release of mediators mast cells (86%), including anaphylaxis (78%). Pardanani et al. carried out a clinical trial in 150 patients with indolent systemic mastocytosis and found that approximately 14% belong to the group of latent systemic mastocytosis, 23% with criterio from the marrow isolated mastocytosis group bone, while 63% did not meet the parameters for any category. The risk of transformation to acute leukemia or mastocytosis aggressive systemic is low (<1 and 3%, respectively), but significantly higher in the latent systemic mastocytosis (18%). [12]

The subgroup of hematological diseases clonal cells with non-mast cells is the second most common, with a prevalence of 40% and much of its population has a neoplasia associated myeloid. 45% is of the myeloproliferative type, 29% myelomonocytic leukemia chronic and 23% myelodysplastic syndrome. A third of patients have significant eosinophilia, especially those with mastocytosis myeloproliferative systemic On average, the rate survival is 24 months, but this varies according to the associated myeloid neoplasm. [12]

The survival of patients with myeloproliferative systemic mastocytosis is 31 months, which is significantly higher than in the patients with chronic myelomonocytic leukemia (15 months) or myelodysplastic syndrome (13 months). The transformation to leukemia is more common in the latter, with a rate of 29%.[12]

Aggressive systemic mastocytosis is the third subgroup in frequency (12%). The patients show attack to the general state (60%), hepatosplenomegaly (50%), lymphadenopathy (30%), severe anemia (Hgb < 10 g/dL, 24%) leukocytosis (41%) and elevated tryptase (>200 ng/mL, 40%). The average survival rate is 41 months and transformation to leukemia occurs in 5% of patients. Lastly, leukemia mast cell disease, which is relatively rare (1%), is very aggressive and its survival rate is just two months. [13]

DIAGNOSIS

Once the clinical history and examination physics make us suspect mastocytosis, it should be carry out the diagnostic approach with the evaluation of the bone marrow, since this is the site universally implicated in mastocytosis of the adult, in addition to allowing to detect if there is a second hematologic malignancy. In the histological examination we observed infiltration of the tissues by atypical spindle shaped mast cells, as well as a high nucleus:cytoplasm ratio. The biopsy of organs other than bone marrow bone, such as the liver or spleen, is only done to demonstrate infiltration as the cause of organic deterioration. The pathognomonic finding in the biopsy are the accumulations of mast cells in the form spindle, with lymphocytes and eosinophils in several locations, frequently location perivascular, paratrabecular, or both to the medulla bone (major criteria). Mast cell hyperplasia is not pathognomonic of mastocytosis, as it is has been found in pediatric patients with other hematological diseases. In 1991, Parker found that lesions in the bone marrow of children are small perivascular areas of clusters of mast cells with a round and oval nuclei, rather than the spindle shape found in adult lesions. [14,15]

Immunohistochemical antibodies are positive, such as tryptase, CD117, CD2, and CD25. These studies can be complemented with serum tryptase concentrations and measurement of metabolites of mast cell activation, which include a 24-hour urine test to look for of N-methylhistamine and 11-beta-prostaglandin F2. Among the immunohistochemical markers, tryptase is the most sensitive, to the extent that almost all mast cells, regardless of their stage of maturation, activation or localization in the tissues, express this marker and allows detection of even small infiltrates of mast cells. [16]

In systemic mastocytosis, elevated serum tryptase concentration (>20 ng/mL) is a minor diagnostic criteria according to the classification of the World Organization of Health, which occurs in most of the patients regardless of subgroup, although there is a proportion of patients with aggressive systemic mastocytosis associated with other hematologic clone not linked to mast cell that have concentrations greater than 200 ng/ mL. These concentrations can also be elevated in other neoplastic diseases, for which is not useful if we want to make a diagnosis of a second neoplastic disease.64 Identifying KITD816V is a minor criterion according to the criteria of the World Health Organization 2008. There is a high correlation between the detection of the KIT mutation and the sample, in addition of the study method. [17]

The determination of tryptase and KIT are unable to distinguish between normal or neoplastic mast cells. Evaluation for systemic mastocytosis should include tryptase, CD 117 and CD25 and should be tested with flow cytometry to immunophenotype it. The immunohistochemical detection of the aberrant expression of CD25 on mast cells from bone marrow appears to be a reliable tool in systemic mastocytosis and can detect virtually all subtypes of mastocytosis systemic. Sotlar et al. reported that CD30 (Ki-1 antigen) is preferentially expressed on neoplastic mast cells from patients with aggressive systemic mastocytosis or leukemia mast cell (11 of 13; 85%) compared with indolent systemic mastocytosis (12 of 45, 27%), this characteristic can work as a severity marker; however, the use of this antigen is still under study. [18,19]

Neoplastic mast cells generally express CD25, CD2, or both, and abnormal expresión of at least one of these agents is a criterion lower for the diagnosis of mastocytosis according to the criteria of the World Health Organization Health. CD2 is much more variable than CD25, therefore, the latter is considered a more reliable marker. It is very important to perform skin tests, specific and total IgE to all the patients. [20]

TREATMENT

Currently there is no curative treatment. of systemic mastocytosis and treatment pharmacological does not show an increase in the survival. The current treatment recommended by the World Health Organization against systemic mastocytosis is mainly palliative and directed at the symptoms caused by degranulation of mast cells pruritus, urticaria, angioedema, erythema, nausea, vomiting, abdominal pain, diarrhoea, anaphylaxis, skin diseases (for example, hives pigmentosa) or organ dysfunction due to mast cell infiltration. [21]

Treatment options include as little as observation, measures to avoid symptoms related to the release of mediators of mast cells, supportive measures (transfusions or osteoporosis treatment) to treatment cytoreductive, oriented to the reduction of neoplastic cells, which is reserve for patients with aggressive conditions or severely affected by adverse effects. [22]

Education is the cornerstone of treating patients, because they will Benefit the information and advice of a physician well prepared and informed. The source of information for most patients are random pages on the internet and this information varies widely in quality and relevance due to the rarity and heterogeneity of the disease, which culminates in misinformation. [23]

Interferon alpha (IFN-a) is the first-line cytoreducing treatment in patients with symptomatic systemic mastocytosis. Since your first report in 1992 IFN-a was administered in small case series and has been shown to

alleviate symptoms associated with mast cell degranulation, decreasing infiltration into the bone marrow by mast cells and the frequency of cytopenias, findings on the skin and osteoporosis. [24]

Treatment is not effective evenly and the frequency of response of C findings is 20 to 30%. The duration and dose of IFN-α treatment they're clear; however, the administration of steroids can increase its effectiveness (even 40% more) and tolerability. The time to wait the best answer is about one year or more. The treatment is associated even in 50% with toxicity, including symptoms flu, bone pain, fever, cytopenias, depression and hypothyroidism. [22]

Finally, a proportion significant number of patients will experience relapses when stopping IFN-a +2-chlorodeoxyadenosine (cladribine or 2CdA) has shown in vitro and in vivo activity against neoplastic mast cells, with activity in all types of mastocytosis. The administration of 2CdA is recommended as first line in cases where rapid destruction is indicated of mast cells, or in symptomatic patients or resistant to IFN-a. The toxic effects of 2-CdA include myelosuppression and lymphopenia with increased risk of opportunistic infections. [22]

There are no controlled studies on the leukotriene receptor antagonists and mastocytosis. However, patients who do not controlled with antihistamines have been shown to respond to these antagonists. [22]

General anesthesia carries additional risk for the patient with mastocytosis due to many anesthetics are releasers of mast cells, the risk of anaphylaxis is increased perioperative Patients should be premedicated with antihistamines and steroids. In 2007, Carter et al. published the first report of a pair of patients treated with omalizumab with relief of their symptoms, specifically severe episodes of anaphylaxis. There are recent reports suggesting that omalizumab decreases the symptoms of mastocytosis. [23]

Omalizumab is indicated as treatment for patients with asthma serious, but it has shown utility in urticaria, mastocytosis and idiopathic anaphylaxis. In seriesof cases has been shown to significantly decrease attacks of anaphylaxis. Siebenhaar and employees reported significant relief from pruritus and intractable urticaria after starting treatment with omalizumab. [23]

The appropriate selection of patients to give them aggressive treatment is very important. Must consider the existence of findings B and C. [23]

Type B findings refer to the growth of organs without function problems. these don't are treated, but are closely monitored in search for findings C. The latter include organ dysfunction due to mast cell infiltration. Cytoreductive treatment necessary. Danorubicin, doxorubicin and vincristine have shown utility. [23]

In the latest research, efforts are have led to the development of targeted treatments to KIT because more than 95% of patients has the D816V mutation, which is a mutation point that substitutes valine for aspartate in codon 816 of exon 17. [24]

Imatinib is the only drug targeting KIT has received the approval of the Directorate United States Food and Drug Administration for the treatment of systemic mastocytosis aggressive. Its administration is restricted to patients without the D816V mutation because the mutation makes them resistant to drugs, which excludes most patients. [24]

Second-generation drugs, such as dasatinib and nilotinib have shown little clinical efficacy. [24]

CONCLUSION

Mastocytosis includes a group of disorders rare, distinguished by excessive proliferation and accumulation of mast cells, which may be confined to the skin or damage the bone marrow bone and other tissues. The main factor in the pathogenesis of mastocytosis is the mutation activates the KIT gene.

Children usually present with cutaneous forms of mastocytosis that decrease or are relieved. entirely for adolescence, while that adults manifest systemic forms of persistent mastocytosis.

Signs and symptoms of mastocytosis can be classified into skin findings, symptoms secondary to the release of mediators of mast cells and symptoms secondary to infiltration of other organs by mast cells. Exists wide variety of triggers that can precipitate the release of mast cell mediators and can trigger events ranging from mild reactions up to anaphylaxis.

Evaluation of the patient with suspected mastocytosis begins with history and examination of s signs and symptoms of systemic damage and evaluation of the skin for lesions suspicious. In addition, we must rely on laboratory tests, such as complete blood count, liver function tests and serum tryptase concentrations.

Patients with suspicious skin lesions should undergo a biopsy. biopsy of bone marrow is not routinely done in children with mastocytosis, unless there are findings of systemic damage. Also, adults with suspected mastocytosis should undergo a biopsy and bone marrow aspirate.

The diagnosis of systemic mastocytosis requires the existence of major criteria and a criterion minor or three minor criteria. Once the diagnosis is determined, it is important to continue the evaluation to determine the subgroup of the disease in which the patient is and if there are findings B or C.

Currently there are no curative treatments. of systemic mastocytosis and treatment is aimed at reducing the patient's symptoms. and improve her quality of life.

We must inform the patient about his her disease and make him aware of it, in addition to educating him about the multiple mast cell-releasing stimuli.

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