SYSTEMIC MASTOCYTOSIS.

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Systemic mastocytosis represents a group of disorders characterized through excessive accumulation of mast cells in tissues and organs accompanied by clinical symptoms derived from degranulation and releasing of mast cell specific mediators such as histamine, tryptase, prostaglandins . Clinical aspects are heterogeneous, according to the tumoral burden and visceral infiltration.

WHO classification describe two categories of disease:

1. Cutaneous mastocytosis- mast cell infiltration is limited to the skin, without any systemic involvement, seric tryptase level being normal;
2. Systemic mastocytosis, with large spread of clinical aspects, depending of the grade of visceral infiltration (hepatomegaly, splenomegaly, adenopathies, lung involvement), with or without skin involvement.

Systemic mastocytosis(SM) is a rare disease, with an uncertain incidence. SM affects both genders and any age. Children have frequently cutaneous form, adults the systemic one. The molecular abnormality described in SM is the somatic mutationof protooncogene c-kit, which encodes a tyrosinekinase receptor for srem cell growth factor; this mutation takes place in codon 816, with valine replaced by aspartate (Asp816Val). The result is an independent activation of c-kit receptor, with autophosphorilation and activation of STAT5, P13K,AKT paths. The final consequence is uncontrolled proliferation and resistence to apoptosis of mast cells from skin and organs. These molecular abnormalities are translated in aberrant expression on the membrane of mast cell of the receptor for interleukin5 and for c-kit. The abnormal mast cell has an aberrant coexpression of CD117, CD25, CD2 and cytoplasmic tryptase.[1,2,3]

Clinical aspects are extremely polymorphous, according to the presence and severity of skin and visceral infiltrates with mast cells and with the presence of degranulation symptoms(skin involvement- Darier'sign, café au lait spots, bullous eruptions , patchy or diffuse rash; hepatomegaly, splenomegaly, adenopathies, with or without signs of organ failure for systemic form of disease; symptoms of activation syndrome, triggered by alcohol,stress, infections, interventional measures, heat or temperature variation,etc, such as: fever, rash, diarrhea, collapse, hypotension, abdominal cramps, angioedema, more or less life threatening)[2.3.4,5]

Diagnosis can be difficult and require an experienced interdisciplinary team(allergologist, dermatologist, hematologist and hematopathologist), because of corroboration of clinical, hematological and histopathological aspects of diagnostic, in order to establish if the WHO criteria of diagnosis are fulfilled and to frame the disorder in the clinical form. The diagnosis is made in the presence of a major and a minor criteria or in the mandatory presence of 3 minor criteria.[1,3,6,7]

Major criteria :

1. Multifocal infiltration with ≥15 mast cells in bone marrow and/or extracutaneous tissue; cells are positive for blue toluidine and for the immunohistochemical test for tryptase,

Minor criteria:

1. 25% mast cells with atypical morphology(spindle shaped) in bone marrow or extracutaneous tissue;
2. Coexpression of CD25, CD117, CD2, on flowcytometry or immunohistochemistry
3. Detection of c-kit mutation (D816V) in blood or bone marrow
4. Seric tryptase level >20 ng/ml not detected if it is associated a clonal myeloid disorder)

The presence of B (burden) signs > 30% mast cells in bone marrow or serum tryptase >200 ng/ml; hypercellularity of bone marrow, organomegaly, but without signs of organ failure) does not represent an indication for treatment. C (cytoreductive) signs must be correlated with impaired visceral function due to mast cell infiltration and their presence represent a sign for starting cytoreductive therapy (cytopenias, hepatosplenomegaly accompanied by hypoalbuminemia, portal hypertension, hypersplenism, osteolytic lesions, fractures of pathological bone, cachexia, malabsorbption)[8,9]

Treatment of SM has two objectives: improving the quality of life through reducing symptoms. Degranulation syndrome can be prevented by patient education- avoid triggers for mast cell activation (alcohol, heat, emotional stress, infections). Prophylaxis of degranulation is made with H1, H2 inhibitors, corticosteroids and/or addition of mast cell membrane stabilizers (cromoglicate) . The treatment of aggressive systemic form is challenge. There is no standard of treatment. First line of treatment consist in Interferon administration, associated with corticosteroids in order to minimize degranulation syndrome. Second line treatment is represented by Cladribine reserved for interferon resistant or intolerant patients). Tyrosine kinase inhibitors (Dasatinib) is more effective than Imatinib, that does not act on D816V mutation, but it can be used in mast cell disease associated with clonal myeloproliferative disease hypereosinophilic syndrome PDGFR/FIP1L1). In clinical trials inhibitors of c-kit such as Rapamycin and analogue Geldanamicin, or anti CD25 monoclonal antibodies can be used for aggressive ,malignant forms of disease. For these aggressive forms, including mast cell leukemia, the chemotherapy followed by allotransplant could be an option.[8,9,10]

The prognosis of SM is variable, depending of clinical aspects, age and form. There is a possibility of continuum progression toward an aggressive form, so clinical observation is indicated.

It is mandatory to collaborate with other specialists for managing such a difficult and heterogeneous disease.

Bibliography:

1. Horny HP, Metcalfe DD, Bennett JM, Bain B, Akin C, Escribano L, Valent P- Mastocytosis, 54-61, in WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed, 2008, IARC, edited by Swerdlow S, Campo E, Lee Harris N, Jaffe E, Pileri S, Stein H, Thiele J, Vardiman J.
2. Worobec A, Metcalfe D, chapt 88, pag 2054-2067- Systemic Mastocytosis in Wintrobe's Clinical Hematology, 12th ed, 2009, Lippincott Williams &Wilkins.
3. Molderings G, Brettner S, HomannJ, Afrin LB- Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options, Journ of Hematology and Oncology, 2011, 4:10.
4. Scwartz LB- Clinical utility of tryptase levels in systemic mastocytosis and associated hematologic disorders, Leuk Res. 2001, 25, 553-562.
5. KudaH, MorinagaS, Shimoshata Y et al- Solitary mast cell tumour of the lung, Cancer, 1988, 61, 2089-2094.
6. Furitsu T, Tsujimura T, Tono T et al- Identification of mutations in the coding sequence of the proto-oncogene c-kit in a human mast cell leukemia line causing ligand independent activation of c-kit product.; J. Clin Invest.1993,92,1736-1744.
7. TefferiA, Lasho TL, Brockman SR,Elliott MA, Dispenzieri A, Pardanani A- A FIP1L1-PDGFRA and c-kit D816V mutation based clonality studies in systemic mast cell disease associated with eosinophilia; Haematologica,2004,89,871-873.
8. Valent P, Sperr WP, Akin C- How I treat patients with advanced systemic mastpcytosis- Blood, 2010,116,5812-5817.
9. Valent P, Akin C, Sperr WR, Horny HP, Metcalfe D-Smouldering mastocytosis with slow progression; Int Arch.Allergy Immunol.2002, 127(2),137-139.
10. Quintas-Cardama A, Aribi A, Cortes J, Giles F, Kantarjian H, Vertovsek S- Novel approaches in the treatment of systemic mastocytosis; Cancer, oct1, 2006, vol107, no7.,1429-1437.