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Mastocytosis always presents a challenge for the treating physician. Sometimes the increase in mast cells is confined only to the skin (cutaneous mastocytosis). Sometimes the increase in mast cells is found also in internal organs (systemic mastocytosis. Analysis of a patient with systemic mastocytosis inevitably leads to contacts and discussions with colleagues from many medical specialities.

Recently about 40 doctors from different medical fields met in Groningen, The Netherlands, to exchange ideas and discuss guidelines for the diagnosis and treatment of patients with mastocytosis. The participants have vast clinical experience with patients with mastocytosis and are internationally renowned researchers. The Netherlands and Sweden are the only two countries in the world where the main histamine metabolite (methylimidazole acetic acid) is determined routinely. The metabolite is an excellent indicator of the extent of a patient’s mast cell disease.

Mastocytosis is a heterogenous group of diseases. Clinical symptoms are caused by the release of mast cell mediators or by mast cell infiltration. Cutaneous mastocytosis or urticaria pigmentosa is a benign disease located only in the skin. Systemic mastocytosis starts in adult patients and is a myeloproliferative, monoclonal disease. The liver, bone marrow, skeleton, spleen, and gastrointestinal tract are infiltrated by mast cells. Clinical findings include ascites, cytopenia in the bone marrow, osteoporosis with pathological fractures and malabsorption.

The majority of patients with systemic mastocytosis exhibit a c-kit mutation (Asp-816-Val). The mutation induces a proliferation of mast cells without the influence of stem cell factor.

WHO classification

Cutaneous mastocytosis

Urticaria pigmentosa is a benign disease characterized by an increase in mast cells located only in the skin. Most patients are children (65%).

Systemic mastocytosis

This form of mastocytosis starts in adult age. Eighty-five percent of patients with systemic mastocytosis have a non-aggressive form of the disease.

1. Indolent, systemic mastocytosis. Many patients remain in this tranquil stage of disease the rest of their lives.
2. Aggressive, systemic mastocytosis with mast-cell infiltration in the bone marrow, skeleton, liver, spleen, lymph glands and gastrointestinal tract.
3. Aggressive, systemic mastocytosis with contemporaneous acute myeloic leukemia.
4. Mast cell leukemia.

From kit to clinical medicine

Genetics

Kit-mutation and mutation in the gene for platelet-derived growth factor (PDGF) leads to spontaneous mitosis of mast cells without the influence of stem cell factor. In many cases the mutation Asp-816-Val is found. Also, other kit-mutations occur. A different genetic profile in different forms of mastocytosis will predict the treatment of mastocytosis in the future.

Bone marrow

Analysis of the bone marrow is central for the diagnosis of systemic mastocytosis. Multifocal infiltration of mast cells, eosinophils and lymphocytes are characteristic of the disease. The mast cells have a myelomastocytic, CD34 positive progenitor and are oval, immature and hypogranulated.

In indolent, systemic mastocytosis, the number of mast cells in the bone marrow biopsy is less than 5%. Aggressive, systemic mastocytosis exhibits a mast cell number of more than 5% in the marrow. Patients with more than 20% of mast cells in the bone marrow also have circulating mast cells indicating mast cell leukemia. This is a very rare form of mast cell disease.

Immunohistochemistry

CD25 is found on the mast cell in systemic mastocytosis but not on normal mast cells. An investigation from Lubeck of more than 100 patients with systemic mastocytosis revealed CD25 expression on virtually all mast cells and the finding was reproducible. Eighty control patients without mast cell disease had mast cells negative for CD25.

Mediator releasing agents for the clinician to be aware of

Diet

A histamine-free diet is recommended to patients with gastrointestinal symptoms. The patient should avoid cheese, smoked food, fermented meat, canned fish, tuna fish, aubergine, soy products and alcohol.

Drugs

Acetylsalicylic acid, morphine, muscle relaxants containing curare, amphotericin B and radiographic contrast media can cause a fall in blood pressure with syncope.

Insect stings

Patients with mastocytosis who develop severe reactions in the skin or syncope after insect stings should carry an EpiPen.

Therapy for aggressive, systemic mastocytosis

Cytoreductive therapy

1. *Thyrosinekinase inhibitor (Glivec).* Patients with c-kit wilde-type or PDGF mutation are the best responders to Glivec treatment. New thyrosinekinase inhibitors are on way. Some of those also will be effective in patients with the Asp-816-Val mutation.
2. *Interferon alpha.* During treatment with interferon alpha the amount of histamine metabolite in urine is reduced indicating a decrease in mast-cell mass. Gastrointestinal symptoms are reduced and osteoporosis ceases. The duration of interferon treatment should be at least six months.
3. *2-chlorodeoxy-adenosine (Cladribine).* Cladribine is a purine analogue, which significantly reduces the mast-cell mass. It has been used only in some cases of aggressive systemic mastocytosis. Side effcts are mainly related to bone marrow suppression with pancytopenia.
4. *Glucocorticoids.* Glucocorticoids have a suppressive effect on stem-cell factor producing cells. This factor is necessary for the mitosis of the normal mast-cell. In aggressive, systemic mastocytosis, the mast cells are dividing spontaneously without any influence of the stem cell factor. Thus, the number of mast cells is not influenced to any appreciable degree by glucocorticoids. The symptoms may be reduced in patients with gastrointestinal involvement with malabsorption or in patients with hepatomegalia and ascites. Treatment with glucocorticoids reduces the number and function of osteoblasts and worsens an already existing osteoporosis.