Diagnosis and Classification of Mastocytosis – Nancy Gould

Research of mast cells and mastocytosis has made impressive progress over the past decade toward understanding what is different about mast cells in patients who have mastocytosis compared with mast cells in people who do not. A group of 23 researchers from Europe and the United States met in Vienna in September, 2000, and, after lengthy discussions, arrived at a consensus as to what criteria will accurately diagnose mastocytosis, and how to classify the various sub-types. Their conclusions are reported in a series of articles in the July, 2001, issue of Leukemia Research. This paper is a short summary of some of their discussions.

It is important to remember that mastocytosis - an abnormal accumulation of mast cells in one or more organ system - can occur secondarily to other causes, such as inflammation and some kinds of leukemia. The disease being described here is more accurately thought of as “primary” mastocytosis, meaning the increased number of mast cells occurs independently of any other cause. However, because of the increased number of mast cells in primary mastocytosis, conditions such as osteoporosis and inflammation may arise as a result of the activity of those mast cells. The manner in which primary mastocytosis can be distinguished from secondary mastocytosis and other conditions is addressed by the consensus and discussed herein.

Of note, the consensus should help make mastocytosis more understandable to the medical people we rely on to take care of us. It has been accepted by the World Health Organization (WHO) as an international standard for diagnosis of mastocytosis, and it is hoped this information will contribute to better understanding, management, and treatment of the disease.

Symptoms and other findings

Patients with mastocytosis may or may not have constitutional symptoms, including weight loss, pain, nausea, headache, malaise, or fatigue. These symptoms may be due to uncontrolled proliferation of mast cells or involvement of distinct organs, such as the stomach and intestines, or bone or bone marrow. Constitutional symptoms also can result from high levels of mast cell mediators in the bloodstream. The severity of symptoms varies from mild to life-threatening, and recurrent presence of the following symptoms may be recorded as part of the diagnosis of mastocytosis: syncope, hypotensive shock, diarrhea with abdominal pain, peptic ulcer disease, severe bone pain, severe headache, and flushing.

There may be enlarged lymph nodes or an enlarged liver and/or spleen. Biopsy of these organs is not normally indicated unless there is an aggressive progression of cell infiltration. Studies other than skin biopsy are not normally indicated in typical childhood disease confined to skin. In children whose disease is severe and progressive and in adults with suspected systemic mastocytosis, studies may include one or more of the following: X-ray of the chest, X-ray of the whole skeleton, ultrasound of the abdomen, endoscopy and biopsy of the gastrointestinal tract, MRI of bone marrow, bone scan, or CT scan. Which of these studies should be done, if any, is indicated by the individual patient’s symptoms. However, in all adults with suspected systemic mastocytosis, a bone marrow biopsy and aspirate should be performed.

The study of biopsy tissue in patients with suspected mastocytosis requires the use of appropriate stains. Tryptase is the stain of choice, as toluidine blue and Giemsa stains are more likely to be affected by tissue processing and may not always produce reliable results.

In skin, accumulation of groups of mast cells combined with the presence of urticaria pigmentosa or mastocytoma is diagnostic of cutaneous mastocytosis. In some cases, it may be difficult to establish a diagnosis. The absence of skin lesions does not rule out the diagnosis of mastocytosis.

The most common type of lesion found in bone marrow biopsy of patients with mastocytosis is multiple dense, well-defined aggregates that are typically located against the surface between bone and bone marrow, and around blood vessels. If significant percentages (more than 25%) of mast cells in these aggregates are elongated (spindle-shaped), then the diagnosis is systemic mastocytosis. However, the mast cells may be round and almost indistinguishable from normal tissue mast cells. In such cases, testing to establish the presence of other criteria is required. A few laboratories are able to test for the presence of the typical mutation of the c-kit receptor on mast cells. Measurement of serum
tryptase levels and the finding of markers called CD2 and CD25 on mast cells are other tests that can help to establish the diagnosis of systemic mastocytosis.

In many patients with systemic mastocytosis, fewer than 5% of all cells in the bone marrow smear are mast cells. The abnormalities that may be seen in mastocytosis mast cells are elongated shape, oval nuclei that are not in the center of the mast cell, and fewer than usual granules inside the mast cells, with those present being in groups rather than scattered. If two or more of these features are found, the cells are referred to as atypical mast cells. Sometimes the nucleus of atypical mast cells will have "lobes."

When the diagnosis of mastocytosis has not previously been established, specialized analyses may be required to differentiate between mastocytosis and other non-mast cell disorders of the blood-forming system, such as leukemias and myeloproliferative disorders. In some of these other disorders, the diseased cells contain and release low amounts of tryptase. Additional blood cell studies and chromosome analysis may be necessary to make a clear diagnosis in such cases.

A well-established and important marker of disease is the level of tryptase. In fact, serum levels of total mast cell tryptase may reflect the total burden of mast cells, with the normal range from less than 1 to 15 ng/mL. In patients with only skin mastocytosis, serum tryptase levels may be normal or slightly elevated. In most patients with systemic mastocytosis with diagnostic bone marrow lesions, serum tryptase levels exceed 20 ng/mL. However, elevated total tryptase levels occur temporarily after extensive mast cell mediator release and have been seen persistently in some other diseases such as non-mast cell leukemic and pre-leukemic blood disorders, so when one of these disorders is present, the level of total serum tryptase cannot be regarded as a diagnostic marker for systemic mastocytosis.

Diagnostic criteria for mastocytosis of the skin
1. Typical skin lesions - urticaria pigmentosa, diffuse cutaneous mastocytosis, or mastocytoma; and
2. Positive Biopsy of affected skin, with typical infiltrates of mast cells in a diagnostic pattern.

Diagnostic criteria for systemic mast cell disease
The presence of one major and one minor criteria or three minor criteria constitute the diagnosis of systemic mastocytosis.

Major criteria
Biopsy finding of multiple dense accumulations of mast cells in bone marrow or in other non-skin tissue.

Minor criteria
1. In bone marrow biopsy, more than 25% of the mast cells are spindle-shaped (elongated) or in bone marrow smears, more than 25% of the mast cells are atypical mast cells.
2. Detection of a point mutation at codon 816 in the kit receptor gene. This may be found in bone marrow or blood or other internal organ.
3. Mast cells in bone marrow, blood, or other internal organs are found to have on their surface the kit receptor plus molecules called CD2 and/or CD25.
4. Serum total tryptase level persistently greater than 20 ng/ml. This criterion cannot be used if the patient has a clonal non-mast cell associated hematologic disorder.

Criteria for classification and description of each category of mastocytosis
Mastocytosis of the skin in children often clears spontaneously before adulthood. Other patients may progress from one classification to another, or, more often, remain in the same classification throughout their lifetime.

The major classifications proposed by this group of specialists and researchers include: Skin mastocytosis, indolent systemic mastocytosis, systemic mastocytosis with an associated clonal hematologic non-mast cell disease, aggressive systemic mastocytosis, mast cell leukemia, mast cell sarcoma, extra cutaneous mastocytoma. These will be defined and discussed below.

Depending on the age of the patient and their signs and symptoms, after mastocytosis has been diagnosed further testing may be indicated to determine which classification accurately describes their
mastocytosis. This information may provide the patient with a realistic prognosis and will help the doctor-patient team determine the best treatment for the disease.

When aggressive disease or an associated hematological disorder is suspected, further evaluation of the patient may include:

1. X-ray or CT scan of the chest, looking for evidence of significantly enlarged lymph nodes (greater than 2 cm in diameter);
2. X-ray of the skeletal system, looking for osteoporosis (thinning of the bone), osteosclerosis (areas of thickening of the bone), or areas where calcium has been completely lost from bone;
3. CT scan or ultrasound of the abdomen, looking for enlarged liver or spleen, enlarged lymph nodes, or the collection of fluid; and
4. Endoscopy and biopsy of the GI tract, looking for evidence of mast cell infiltration, ulcers, or areas of bleeding.

Other tests may be done, as indicated, if there is a suspected hematologic disorder or to evaluate the individual patient’s symptoms. By contrast, further testing should be kept to a minimum when the disease seems to be confined to the skin, and in most pediatric cases.

**Classes of disease**

**Cutaneous (skin) mastocytosis:** These people will have typical skin lesions, biopsy evidence of mast cell infiltration in the dermis (lower layer of skin), and they do not fit the criteria for systemic mastocytosis.

**Indolent systemic mastocytosis:**
These people fit the criteria for systemic mastocytosis and may have an enlarged liver or spleen.

People whose disease has been present for many years or whose disease begins in a severe form may fit the criteria for a sub-classification of “smouldering systemic mastocytosis”. These people may advance to one of the more aggressive classifications of mastocytosis. This newly proposed sub-classification is characterized by the presence of 2 of the 3 findings below:

1. More than 30% of the bone marrow is filled with mast cells; and/or serum tryptase level is higher than 200ng/ml,
2. Some abnormal cells are seen in the bone marrow but these do not fit the diagnosis of one of the associated clonal hematologic diseases; blood counts may be normal or slightly abnormal,
3. There is an enlarged liver with normal liver function or/and enlarged over-functioning spleen or/and enlarged lymph nodes;

   and the two findings below:

   1. Mast cells represent less than 20% of the cells in smears of bone marrow aspirate; and
   2. No mast cells are identified in their circulating blood and the patient does not fit criteria for aggressive mastocytosis.

**Systemic mastocytosis with AHNMD (Associated clonal hematologic non-mast cell disease)**
These people fit the criteria for systemic mastocytosis and they fit the WHO criteria for myelodysplastic syndrome, myeloproliferative syndrome, acute myeloid leukemia, or non-Hodgkin’s lymphoma. These people often do not have urticaria pigmentosa-like skin lesions. Successful treatment of the hematologic disorder has not been shown to change or improve the systemic mastocytosis in these people.

**Aggressive systemic mastocytosis**
These people fit the criteria for systemic mastocytosis; and their bone marrow biopsy reveals abnormal blood cell formation but does not fit the WHO criteria for an AHNMD, as listed above; and bone marrow aspirate smears show less than 20% of the cells to be mast cells; and there are no mast cells identified in the circulating blood; and the presence of at least one finding below:

1. An abnormal blood count
2. There is an enlarged liver, and liver function is impaired
3. There is an enlarged spleen, and its function is abnormal
4. Malabsorption with weight loss is present and is due to mast cell infiltration in the GI tract that interferes with its normal function.
5. Bone involvement is seen, with large areas of calcium loss and/or pathologic fractures; presence of osteoporosis alone is not considered to be an “aggressive” feature.
6. Other internal organs are affected by mast cell infiltrates with impairment of organ function.

**Mast cell leukemia**
These people fit the criteria for systemic mastocytosis, and a bone marrow aspirate smear shows that 20% or more of the cells are mast cells or 10% or more mast cells are seen in circulating blood and the shape of mast cells and their nuclei have malignant features. These people do not fit the criteria for an AHNMD (as above).

**Mast cell sarcoma**
A sarcoma is a tumor made of cells from connective tissue. Mast cell sarcoma is an extremely rare tumor. In 3 cases reported so far, the tumor has been located in the larynx, in the colon, and inside the skull. Prognosis is very poor. People with a mast cell sarcoma have a single tumor made up of abnormal mast cells, and they do not fit the criteria for systemic mastocytosis, and they have no skin lesions, and pathology examination of the tumor shows it to be very malignant with an aggressive growth pattern.

**Extra cutaneous mastocytoma**
This means a single mass made up of mast cells that is in some location other than skin. It is a very rare finding, and the prognosis is good, with no progression seen in cases so far. People with extra cutaneous mastocytoma do not fit the criteria for systemic mastocytosis, and they have no skin lesions, and pathology examination of the lesion shows it to be made up of normal- or nearly normal-appearing mast cells with a non-aggressive growth pattern.

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**Reference:**
Diagnostic criteria and classification of mastocytosis: a consensus proposal; P Valent, H-P Horny, L Escribano, BJ Longley, CY Li, LB Schwartz, G Marone, R Nuñez, C Akin, K Sotlar, WR Sperr, K Wolff, RD Brunning, RM Parwaresch, KF Austen, K Lennert, DD Metcalfe, JW Vardiman and JM Bennett; *Leukemia Research* 25(7):603-626

**Definitions:**
Atypical: Not typical of the normal cells
Bone marrow aspirate: fluid removed by suction from the bone marrow
Endoscopy: direct visual inspection of the upper or lower gastrointestinal tract, using a special, flexible tube called an endoscope
Hypotensive: Involving abnormally low blood pressure
Malaise: A general feeling of not being well
Mediators: Substances that cause a response
Syncope: Loss of consciousness and muscle tone caused by decreased blood supply to the brain

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