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Multidisciplinary Approach to Making the Diagnosis of Systemic Mastocytosis

Announcer:
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Dr. Castells:
Hello, my name is Mariana Castells. I'm the director of the Mastocytosis Center here at the Brigham and Women's Hospital. And today I will be talking about the multidisciplinary approach to making the diagnosis of systemic mastocytosis. Mastocytosis is defined into mast cell activation disorders, which are primary mast cell activation disorders, which are clonal, also including secondary, which are not clonal but fulfill some of the criteria for multi-organ system symptoms and idiopathic mast cell activation syndrome with hereditary alpha-tryptasemia.

Initially, if our diagnosis requires to obtain a thorough medical history that includes symptoms and reactions to foods, to medications, to surgery, we need to have a baseline tryptase that will give us a sense of the elevation. Then screening for the kidney mutation would be mandatory and then biopsies either of skin and or bone marrow biopsy will provide us a certain diagnosis. Tryptase is the primary mast cell mediator and it's elevated in over 90% of patients with systemic mastocytosis. Patients presenting with anaphylaxis will require two measurements and a significant elevation above baseline would include a 20% increase plus two.

If that goes back to normal, then the patient should only be screened for systemic mastocytosis if symptoms of two organ systems exist. And tryptase elevations are associated with histamine and prostaglandin and leukotriene elevations in patients with mastocytosis. Secondly, the mutation, so a detection of the KIT D816 mutation is seen in over 90 to 95% of patients with mastocytosis. 10% of them will have negative KIT D816V mutation. And patients who have a high burden of the mutation as seen here are the patients in which from indolent disease may go to advancement. So it is critically important that we determine the mutation burden. And as you can see here, the KIT is the molecular marker of mastocytosis and the D816V mutation in the enzymatic activation is the most frequent, although other mutations can coexist or can be associated with systemic mastocytosis. The patients who have here in this side only mutations on the KIT.

In mast cells, the D816V here is present only on mast cells are patients who are going to remain indolent for the rest of their lives. Their lifespan is not going to be different than people without mastocytosis. And patients who have multi-lineage presence of the D816V mutation in additionally to the mast cells in other cells such as eosinophils, monocytes, neutrophil, lymphocytes, and other are patients in which the mastocytosis will or can advance to a disease that will be more aggressive and require potentially chemotherapy. Biopsy is the third criteria for the diagnosis of mastocytosis.

We have here that a patient presenting with a lesion compatible with cutaneous mastocytosis has a biopsy and then staining with CD117 which is KIT shows those brown cells that are elongated that are abnormal mast cells making the diagnosis of cutaneous mastocytosis. Here we have the another patient who has the presence of aggregates, and those aggregates contain more than 50 mast cells. And in those patients, we see here also that the patient has bone marrow mast cells, so systemic, and also the cutaneous mast

cells that you see here. And the staining of those include tryptase and CD 25.

In patients who have low mast cell burn or monoclonal mast cell activation disorder, there will be no aggregates such as the ones presenting in systemic mastocytosis. And we see here that patients with indolent systemic mastocytosis have those aggregates with more than 50 mast cells. But compared to patients with hereditary alpha-tryptasemia with duplication or triplication of tryptase genes, those have a very small aggregates and those are different.

Gastrointestinal biopsies can also be used for the diagnosis of systemic mastocytosis, and in patients, we see that not only the number of muscles have to be increased but also the aggregation and the staining for CD 25 and for tryptase such that in patients with 50 mast cells into duodenum, we will consider that to be normal. But in patients who have aggregates, we will consider that to be abnormal. And we see here, for example, normal mast cells here that are not aggregated and abnormal mast cells that are aggregated in different patients presented the aggregation of tryptase positive CD 25 positive key positive mast cells.
So gastrointestinal biopsies can actually be used from the diagnosis of mastocytosis. So the classification of mastocytosis include the cutaneous and the systemic, the indolent, the associated with the hematological disorder, the aggressive, the muscle cell leukemia, muscle sarcoma, and extra cutaneous muscle cytosis. And the diagnostic criteria include those multifocal aggregates of 15 or more mast cells that stain with CD 25 that also have spindle-shaped morphology and that the mutation is positive in the blood or in the bone marrow and the tryptase level is associated with more than 20 mast cells. According to the recent 2022 variants for mastocytosis, we have a mastocytosis that is bone marrow mastocytosis with low mast cell burden but some compact infiltrates. We have indolent systemic mastocytosis with a low mast cell burden less than 5% with compact infiltrates and KIT positive mast cells.

We have smoldering mastocytosis in which the burden is increased up to 30% and there is more diffuse compacts KIT D816V is positive and there is a high tryptase level and organomegalies can be present in the liver and the spleen with two B and no C findings and then aggressive mastocytosis is a mastocytosis in which we have the C findings as defined by the involvement of other organs with malabsorption with abandoned splenomegaly, very high tryptase levels, skin lesions may be absent and the key mutation present with multi-lineage involvement.

A systemic mastocytosis with associated hematological malignancy is also associated with other mutations and other hematological diseases in addition to the mastocytosis. So we have here that mast cell leukemia is the most aggressive of the advanced disease. There is more than 20% or 50% of mast cell burden, the KIT mutation is positive, and other KIT mutations are present, and the KIT lesions as skin lesions may be absent in those patients. Pregnancy is a special consideration of patients with the mastocytosis and its patients are not thought to have less fertility, they can become pregnant.

The pregnancy has no complications although avoidance of triggers is recommended and pre-medication for delivery is recommended and outcomes are normal for women who have mastocytosis. Other conditions that mimic mast cell disorders can actually be present in patients and can confuse such as endocrine conditions, gastrointestinal conditions, immunological conditions, and also neurological conditions. And in those patients, we have to review the tryptase level, the KIT mutation, and the biopsies of the organs.

So, thank you very much for listening to the multi approach to the diagnosis of the mastocytosis. Mastocytosis is a rare disease and sometimes the diagnosis is not initiated at the time of the onset of the symptoms. Patients who present multi-organ symptoms that are consistent with mast cell activation symptoms need to be evaluated for tryptase, for KIT mutation, and potentially with the biopsy of the bone marrow and or skin or other organs to be evaluating the infiltration of the mast cells and making the diagnosis of systemic mastocytosis. Thank you very much.

Announcer:
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