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Released: 12/21/2022
Valid until: 12/21/2023
Time needed to complete: 1h 22m

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Symptoms of Systemic Mastocytosis

Announcer:
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Dr. Castells:
Hello everybody, I am Mariana Castells. I am the Director of the Mastocytosis Center at the Brigham and Women's Hospital here in Boston. And today I will talk to you about symptoms of systemic mastocytosis. Systemic mastocytosis is a rare disease, and the presentation can actually mimic many other diseases. We have here that the mast cells are unique cells of the innate immune system. They are positioned in any of our organs, from the skin, to the gastrointestinal tract, to the lining of the blood vessels. And they actually have granules that produce mediators, as well as mediators that are derived from their membrane.

We have that the mast cells have histamine and tryptase from the granules, but can produce the mediators that we will talk today about, which are prostaglandin, leukotriene, and others. The symptoms that those mediators can produce include systemic symptoms including anaphylaxis, but also fatigue, generalized malaise, weight loss, respiratory symptoms, neurological symptoms, musculoskeletal, digestive, cutaneous, and cardiovascular. And those are related to each one of the sets of the mediators.

So as we were saying, in constitutional symptoms, we have the potential for the fatigue to be prominent. In cutaneous, the flushing, the itching, the hives. In gastrointestinal, the abdominal pain, the diarrhea, the malabsorption. In skeletal symptoms, we can actually have osteopenia, osteosclerosis, and also pathological fractures. And neuropsychiatric symptoms are very prominent, headaches, but also anxiety, depression, irritability, what we call mixed organic brain syndrome with short memory span, inability to concentrate, and also sleepiness.

In pulmonary and ENT, patients with mastocytosis may have symptoms of rhinitis and also respiratory symptoms, including shortness of breath and at times, wheezing. Atopy such as asthma and allergic rhinoconjunctivitis is present in patients with mastocytosis, but not at increased frequency as compared to the general population. And we see here that because of the mast cell mediators, those for example, such as histamine, can induce symptoms in the skin and the blood vessels, the prostaglandins in the brain and also in other organ, as tryptase in the coagulation cascade bradykinins can also be active at hypertension and swelling.

Leukotrienes in the bronchial tree, bronchospasm and swelling and platelet activating factor can also be participant to the vasodilation. So essentially the symptoms of mastocytosis relate to the release of the mediators and the impact of the mediators in the organ systems. And we can actually look at the cutaneous systems in more detail, and the flushing is the most prominent, but pruritus and hives are also, and dermatographism is very prominent. We can look at gastrointestinal symptoms and abdominal pain and bloating, but diarrhea, nausea, and also gastroesophageal reflux and vomiting are very prominent.

In respiratory symptoms, we can have symptoms of cough, and chest tightness, and shortness of breath. In skeletal symptoms, we can actually have joint and bone pain, and also like we are mentioning fractures, but osteopenia, and osteoporosis can be prominent. And neuropsychiatric symptoms including the headaches, the poor concentration, the loss of memory, and depression, anxiety, all of those

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symptoms can be present in patients with mastocytosis. And constitutional symptoms in addition to anaphylaxis can induce a lot of fatigue, and night sweats, and fever. And as we see here, mast cells can be activated through not only Ig mechanism but through KIT mechanisms and through IgG.

There is new ways to activate mast cells that are called MRGPRX to a new receptor and that general anesthetics, some antibiotics including quinolones and vancomycin can activate mast cells. So the mechanism by which mast cells release those mediators actually depends on which triggers and which receptors are activated. Importantly, mastocytosis as you see here, has been associated to a new genetic trait that is called Hereditary Alpha-Tryptasemia. And this genetic trait is present in 6% of the general population but is much more prevalent in patients with systemic mastocytosis. And what happens in those patients is there is a duplication of tryptase genes that puts them at risk for severe anaphylaxis.

So patients who have this extra tryptase gene in chromosome 16 and who have systemic anaphylaxis are more prone to have more severe muscle activation events. And those muscle activation events can actually be associated with severe anaphylaxis. So in our patients, when we make a diagnosis of mastocytosis, we have to make sure that we actually look for potential, this trait, this genetic trait. If tryptase is above eight nanograms per milliliter, so even in patients who have normal tryptase, we will be looking for that. And you see here that this is a tryptase level during anaphylaxis and tryptase level during mastocytosis. And normal tryptase may occur in 10% of patients with mastocytosis as you have here.

And we have to look at patients who have anaphylaxis with two measurements, one during the episode and one at baseline. And that would be critically important to understand which patients may only have anaphylaxis and which patients may have mastocyosis. And because tryptase range, as we can see here in patients with 60 and 70, the tryptase may actually rise over time. We have to make sure that the reference range are looked upon in an age-dependent way in our patient population.

The serum tryptase level is really important because it's associated not only with systemic mastocytosis with other malignancies. So an elevated tryptase level in the setting of symptoms of mast cell activation has to be actually looked upon to rule out other hematological and malignancies. And you see here that the source of the elevated tryptase can be the mast cells which is typically in systemic mastocytosis but in other malignancies can be basophils or can be other neoplastic cells. And the mediators of mastocytosis can actually be seen in the urine for N-methyl histamine.

You see here how elevated as compared to the control group. You see here the prostaglandins, they are also elevated as compared to the control group. Their leukotrienes are also elevated as compared to the control group. The triggers for the symptoms can be physical stimuli, frequent heat, changes in temperature, rubbing, cold, sunlight. But they can be also emotional triggers, stress, anxiety, a lack of sleep.

They can be infections, they can be also medications, non-steroidal anti-inflammatory medications, Morphine, also quinolones, cough medication. They can be dentition, vaccinations, can be surgery. So we have to pay attention to those triggers. So we essentially, at the end of the day, what is important from patients who come to see us with symptoms of mast cell activation is that we go for the cutaneous symptoms, the gastrointestinal symptoms, the neuropsychiatric symptoms, the anaphylactic symptoms, and the systemic symptoms. And we evaluate that patients with mastocytosis have typically more than two organ systems that are associated with symptoms. And in those patients it will prompt us to do tryptase level, urine mediators, and KIT mutation as we will see in the diagnostic criteria. Thank you very much.

Announcer:
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