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WHIM Syndrome and CXCR4 Variants: New Insights into Cellular Changes That Can Impact Patient Treatment Plans

Announcer:
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Dr. Bledsoe:
Hi everybody. My name is Jacob Bledsoe. I'm a Pathologist and Director of Hematopathology at Boston Children's Hospital, and an Assistant Professor of Pathology at Harvard Medical School. And today I'll be talking to you about WHIM syndrome briefly, about the diagnostic difficulties that we encounter when thinking about this and when working patients up.

So to start off, WHIM syndrome, as you likely know, is an autosomal dominant disorder that's caused by mutations in the gene CXCR4. And these mutations may either be inherited from the patient's affected parent, or actually, in a larger proportion of cases, may occur de novo as a new mutation in a patient whose parents do not carry the mutation. In fact, one study found that around 59% of WHIM syndrome mutations occurred de novo. Therefore, we cannot really rely on a family history of immunodeficiency or a family history of recurrent infections to clue us into WHIM syndrome in the majority of cases. And the same study showed that patients with a family history were diagnosed earlier and received earlier treatment, experienced less hospitalization, and had less end-organ damage than those without a family history, because they came to clinical awareness more rapidly than those without a family history.

So what clinical signs and symptoms do we use to consider a diagnosis of WHIM syndrome or to clue us in to this disorder? So the cardinal clinical features that are used to recognize and diagnose WHIM syndrome are those for which WHIM syndrome takes its name. So warts, hypogammaglobulinemia, infections, and myelokathexis. And these are the key clinical features in addition to neutropenia and lymphopenia. However, it's worth noting that these clinical features are variable in their occurrence and also in their age of onset, and this often results in a delayed diagnosis. For example, warts may only be present in 40 to 80% of patients, depending on the study, and they often don't occur until later, like in teenage years or early adulthood. So they may not be present at the time of initial patient presentation. Same thing goes for hypogammaglobulinemia, it's only seen in a subset of the patients. In contrast, recurrent infections, neutropenia, and lymphopenia are present in the vast majority of patients with WHIM syndrome.

So what are the reasons for delayed diagnosis? Patients with WHIM syndrome typically present with recurrent infections and severe neutropenia in early childhood, which prompts further workup. Unfortunately, the diagnosis of WHIM syndrome is challenging for several reasons. First of all, as I mentioned, the clinical features are variable. Secondly, WHIM syndrome is a very rare disorder, and physicians may not be familiar with the pertinent features that facilitate its recognition. And this applies both to the clinical people who are working – clinical physicians who are working the patient up, as well as to the pathologists who are looking at the bone marrow specimens themselves. The third thing is that infections result in an increase in neutrophil count that may mask neutropenia at the time that these patients really come to clinical presentation. That is when they're infected, and so it may not be apparent that these patients are neutropenic or severely neutropenic. And lastly, demonstration of myelokathexis is best accomplished by bone marrow biopsy, and the

extent of morphologic changes of myelokathexis is variable, and it's much more difficult to establish myelokathexis on a peripheral blood smear evaluation.

Just to briefly mention myelokathexis morphology. So myelokathexis refers to abnormal retention of neutrophils and leukocytes in the bone marrow in the setting of peripheral cytopenias. So in these patients, they don't have peripheral neutrophils, but when you look at their bone marrow specimen, they have plenty of neutrophils that are trapped in the bone marrow. And the neutrophils of WHIM syndrome have a very characteristic morphology with long, thin chromatin strands separating nuclear lobes of neutrophils. However, the proportion of neutrophils that are abnormal varies from case to case. So for example, in the top left figure, you can see only a few of these neutrophils have really long, thin strands, whereas in other cases, the vast majority of neutrophils will have myelokathexis morphology. And we had shown in an earlier study that looking at bone marrows from WHIM syndrome, that the variability of myelokathexis ranges from 32 to 80% depending on the patient.

So what is the importance of early diagnosis in these patients? So as I mentioned briefly earlier, that the earlier these patients are diagnosed, the earlier they can start treatment, which is usually with GCSF therapy, and that leads to a decreased risk of severe infection and decreased rates of hospitalization, as well as less end-organ damage, including bronchiectasis and hearing loss, which result from recurrent and severe pulmonary and ear infections, respectively. And lastly, once these patients get on our radar, we can increase their surveillance for tumors, because we know that patients with WHIM syndrome have an increased risk of both HPV-driven solid tumor squamous cell carcinoma, for example, of the vulva or anus, as well as EBV-driven lymphomas.

So my last slide just highlights the fact that delayed diagnosis in WHIM syndrome really needs to change. And how are we going to improve our diagnosis of WHIM syndrome in a timelier fashion to catch these patients before they get older and have more severe infections? First of all, we can increase clinician and pathologist familiarity with the disorder. We're currently working on a project that characterizes the bone marrow morphology and peripheral blood morphology for pathologists and clinicians to help improve their knowledge of the subject. Secondly, we could think about new assays to develop for – to evaluate CXCR4 expression in these leukocytes that are abnormally retained. And they're ongoing studies that we are developing looking at CXCR4 expression by flow cytometry. And lastly, these patients are increasingly being sequenced in the germline when they present with unexplained and persistent neutropenia or suspicion for other immunodeficiency. I think that will increase in the future as well.

So with that, I would like to thank you for your time, and I hope you learned something useful with this video. Thanks.

Announcer:
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