Making the Diagnosis for EDD Patients

CME Series on Epidermal Differentiation Disorders — Presented by Dr. Lara Wine Lee

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Welcome to Making the Diagnosis for EDD Patients, part of First's CME series on epidermal differentiation disorders or ichthyosis. Presenting this topic is Dr. Lara Wine Lee. Dr. Wine Lee is an associate professor of dermatology and pediatrics at the Medical University of South Carolina, where she has practiced since 2014.

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She cares for children with genetic skin disorders as part of the pediatric dermatology program.

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Thank you for having me today to discuss making the diagnosis for our EDD patients. I do have to disclose that I've received research funding related to the content of this presentation from Leo Pharmaceuticals and Mayne Pharmaceuticals. So today we hope to develop an approach to the clinical diagnosis of EDDs understand the importance of obtaining a definitive diagnosis and how we would get to a definitive diagnosis through our different diagnostic workup modalities.

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So to approach the diagnosis of epidermal differentiation disorders, we first have to understand the classification. So for non syndromic EDDs These are the ones that predominantly involve the skin. So there are not gene driven extracutaneous manifestations. While other systems besides the skin may be involved, it is related to the problems in the skin and not related to an abnormality specific to the gene.

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This includes many disorders that were historically grouped as the non syndromic ichthyosis, and the phenotype here really does help us guide that first kind of diagnostic idea that then guides our testing and further workup.

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the syndromic EDDs have skin findings plus extracutaneous features related specifically to the genotype. However, the skin still may be the earliest clues that can help you look at the other systems that may be involved and really can kind of help us get ahead of any problems that will develop by getting appropriate specialists involved to address the other extracutaneous manifestations.

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Whereas the palmoplantar EDDs have both syndromic and non syndromic forms, but predominantly have the palmoplantar involvement as the cornerstone of the condition, and with that can have associated hair, nails and teeth problems that can help guide the diagnosis. And we'll talk about the patterning and the clues from the patterning that can get us to a diagnosis.

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So there is the naming convention of how we kind of put this together, which is to name the gene followed by either nEDD for non syndromic, S for syndromic and P for palmoplantar. Oftentimes there is a descriptor that may be added giving some association with the terms that we've had for some time, such as lamellar or Harlequin or Netherton.

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So you will have the gene plus the type of EDD plus that helpful descriptor to make sure we're getting to that right category. So what are our key elements to making a first approach to kind of the diagnosis. So always start with your clinical features. This is going to be a full characterization of the type of skin findings that we're having.

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What do the palms and soles look like. What is the distribution and quality of any of the scaling. What is the presence or absence of any extracutaneous features? The inheritance pattern can be very important, understanding does it seem to have an X linked inheritance pattern, an autosomal recessive or autosomal dominant? And then kind of putting this all together and trying to correlate these findings with specific types of well characterized EDDs that we may know about. Next, we frequently will look at the importance of molecular testing.

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This comes in several forms. Usually a starting place is going to be full panels that are commercially available. And certainly if there's a family history that may be known, more targeted testing can be more efficient for the patients. And sometimes we do run into diagnostic uncertainty and thinking about the importance of ancillary types of methods to get at a diagnosis can come into our evaluation as well.

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And here, if we have specialist involvement in characterizing something such as a neurologic finding or another extracontinuous manifestation may help us hone in on that diagnosis. So let's start with making a clinical diagnosis. So here are several pictures of different types of ichthyosis and palmoplantar involvement. And you really want to look at the quality of the scaling the amount of inflammation, whether there is, currently if you're seeing an infant or a history of the collodion membrane, is there hyperkeratosis of the palms and soles, or is that absent or more mild?

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And an important part of your evaluation is also looking at any skin fragility or frank blistering, such as we see in our epidermolytic types of ichthyosis. And then when you see more hyperkeratosis deciding whether it's a true palmoplanter keratodermo, is there then the presence of ichthyosis involving larger areas of the skin or not. Here understanding, is it a fine scale?

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Is it a thicker scale? Is it distributed on certain surfaces of the body? Does it spare certain areas? So more generalized, more regional, particularly paying attention to flexural involvement, extensor involvement, the face, the scalp and the concept of transgredient, which is the line between the palmer skin or the skin of the soles of the feet, and then the dorsal surface that can tell you the type of, you know, pEDD that we may be dealing with.

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You always want to examine those epidermal appendages, the hair, the nails, the teeth that can be affected as well. And how do these clinical diagnoses kind of guide our further workup or move us towards our next diagnostic steps? And this is not a comprehensive list. This is just an example of how you kind of may put some of these findings together.

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For instance, if you're seeing fine scale with hyperlinear palms, this could be in our category of FLG-nEDDs, whereas we have an X-linked inheritance patterns mainly those maternal male relatives are affected more of that thicker polygonal scale in our X-linked ichthyosis. Whereas the Claudian membrane and history or if you're seeing an infant at the time of evaluation, leads us into kind of a group of the autosomal recessive congenital ichthyosis that has specific types of panel testing that would really want to be considered at that point. Severe atopic disease, severe erythrodema, hair shaft abnormalities in SPINK5 sEDDs,

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and then as we mentioned, the skin fragility and that blistering which is very pronounced in infancy, although later on may progress to more hyperkeratosis, gets into those keratinopathic ichthyosis. And then considering those extracutaneous findings, such as deafness along with PPK, gets us into the GJB2 types of ichthyosis and pEDDs.. So starting with our non syndromic EDDs, a little bit of a diagnostic algorithm that can help you make that clinical diagnosis.

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So first we think about looking at the patient. Is there involvement of the skin? Of the whole body or just the palmoplantar area? If we're more palmoplantar involvement we're going to go down that pathway of the pEDDs. Extracutaneous features that are very prominent might bring us into our syndromic forms. However, if those are not present in the patient, then we're thinking about our non syndromic ichthyosis.

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And there we kind of start putting together the findings that we have to guide the potential genetic findings. So the genetic ones shown in red of note here are going to be some histopathological features. I will tell you that across the types of ichthyosis there's many of the histologic features are not very specific. So here is just focusing on ones that may be more specific to the type.

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Although oftentimes histology is not necessary if you can get that appropriate genetic diagnosis. So this is a good algorithm. So if you're looking at kind of congenital involvement in a neonate or an infant or seeing an older patient that may have a history of this and kind of look at that category and get down a certain pathway of different types of genetic basis for the condition that are highlighted here, whereas non congenital or more progressive types,

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So perfect example of this would be ichthyosis vulgaris due to filaggrin mutations where the generalized scaling may actually not develop until later and sort of may progress over time. So really important to kind of get that time course. It's a really good opportunity to look potentially at pictures, If you're meeting a patient when they're a little bit older, as well as understanding the family history again.

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The next category of syndromic EDDs you start with that skin phenotype and really understanding the patterns that you're seeing, the involvement of the skin and the palmoplantar area, as well as associations such as the hair, the nails. But then really consider that full range of other types of findings. So particularly for our syndromic EDDs they oftentimes have more than one system involved.

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And again related actually to the gene, not just to the skin involvement. And these extracutaneous features can be diagnostically very, very critical. You may need help from different specialists to fully categorize them and really kind of characterize what you're seeing to lead to that level of testing. And then just some hints here about different systems that have prominent involvement that may kind of lead you down one pathway to appropriate diagnosis.

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And then the last of the three major subtypes are the palmoplantar EDDs, and here pattern again is very very important. So the extent of involvement - is this an isolated non syndromic form where we don't have extracutaneous features that are associated with just the skin or their syndromic features where they're outside of the skin involvement that you're seeing, understanding whether the full service of the palms and soles is affected, or is it more of a focal.

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And the focal ones pictured here in the lower panel are oftentimes the focal hyperkeratosis over pressure points. So that's kind of the difference of the diffuse and the focal ones. All the way to the side there showing an example of more kind of punctate types where you get the hyperkeratosis in those smaller areas. And does this involve just the palms and soles, or does it extend in that transgradient type of way beyond the palmoplantar skin, or even does it extend to other surfaces such as the elbows and the knees?

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And that would be a progradiens. Again, inheritance pattern is very important, particularly because there are several types of this that are autosomal dominant, so that you may really have a strong family history. And truthfully, if you're seeing a patient when they're very young, they may actually not have full development of their cutaneous kind of findings. So understanding what the pattern is and what the clinical manifestation in an older relative may actually really be more useful, because over time they become a little bit more clear what that clinical diagnosis may be.

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And there is a lot of overlap. So while we look at patterns and we find it important to kind of characterize the patterns which help us also with management and expecting what types of problems they're going to develop over time and get us to that correct diagnosis. You can see a lot of overlap here. So the colors will represent the different types of pEDDs that we can see based on the genetic diagnosis.

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And there's a lot of overlap for instance in the diffuse versus focal. Some of this again maybe age maybe very patient specific. But nonetheless they can kind of help us get into that category. That kind of guides further work up and treatment. So here's our diagnostic algorithm. Once we've looked at our palmoplantar patients, and separated again that extracutaneous versus the cutaneous findings.

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So if they're extracutaneous findings we're looking more at those syndromic types with one set of genetic diagnoses and understanding if they might have cardiac involvement, if they might have prominent involvement of the ears or the teeth. And it gets us into one category where, as with the cutaneous, so the non syndromic forms, that subtype really can be important.

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I want to point out the more mutilating types where they get the pseudoainhum, which are those kind of constriction bands on the fingers and the toes that can lead to auto amputation. Important to recognize those so that you can manage that before there's more severe scarring and potential sequelae of loss of those those functions. And the inheritance pattern is featured in our diagnostic algorithm because there's a very prominent different types of inheritance patterns for these patients.

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So once we've approached our clinical diagnosis, in most cases, very important to get a more definitive diagnosis by looking at genetic causes. And then this can either confirm or further refine your clinical diagnosis. So there are several steps or approaches to treatment. Many times we do start with these multi gene panels that can look at kind of a range of the type of genes that make cause the condition that we're seeing in front of us.

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This is oftentimes a first approach because they're very efficient. They're very cost effective. Oftentimes we'll have insurance coverage. Although you can work with your genetic specialists to kind of make sure that you're choosing a panel that will be very efficient and affordable for the patient. The genes may differ from laboratory to laboratory. And so it isn't really critical to have thought about your clinical diagnosis.

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Consider the things that you're looking for, and then to check your gene panel to make sure that there's no major areas that you are suspecting that would then not show up on that panel, because it would be a reason to choose a different panel. So it's not always just as simple as kind of picking that panel that's in front of you.

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Your clinical suspicions or your kind of clinical differential is really going to guide the most appropriate one. And important, just for completeness sake, that these panels include deletion and duplication analysis for some types, again, based on your clinical diagnosis. For our syndromic types, or certainly if we have atypical features where you've kind of got your constellation of symptoms, you're saying it really doesn't really fit well into one of the buckets.

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I've followed my diagnostic algorithm, and I'm feeling like I can't really kind of pin it down on one. That's where considering something like, whole exome or genome sequencing. And oftentimes this can be complex so that there are pathogenic variants that may not be shown on our conventional testing, but may show up in some of this more advanced testing.

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So again, very, very important for our genetic specialists and our genetic counselors to really be involved here, to make sure that the interpretation of the tests and also to consideration when reanalysis as we get new information or we actually discovered new mutations in the gene or actually new genes completely reconsideration of testing, if we haven't really achieved a diagnosis that fits the clinical symptoms that we're seeing in the patient, targeted testing can be really useful within families and confirming the diagnosis in that patient.

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So we may have known family variants but can consider that testing to confirm it for the patient that's sitting in front of you as

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I also wanted to mention the registry that's available through First Foundation that's housed at Yale. This is expanded genetic testing available for patients at no cost. Whether there has been lack of confirmatory diagnosis on conventional testing, or additional kind of atypical features that need to be characterized.

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Details of this can be found on the web page, and with information about how to submit information to the

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Additional special considerations for molecular testing can be very specific to the type ichtyosis or pEDD that we are faced with, and I want to point out here, this is really why it's important to have involvement from genetic specialists and genetic counselors that are versed in testing, and may have a good amount of knowledge about EDDs. Genetic counseling, in particular, is really important to provide not just information about the genetic inheritance patterns, but to consider really what the benefits and the risks and limitation of genetic testing may be, as well as to make sure that the process of genetic testing goes very smoothly.

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This is oftentimes done prior to testing. And then actually after we get those results back as well. And this provides a lot of support for the patients and their families, as well as helping to educate a variety of the health care providers about the results of the genetic testing, the

pathogenesis based testing. So, again, the clinical diagnosis and the targeted kind of gene testing is becoming increasingly important for therapeutic considerations, as well as knowing what other specialists may be involved and looking at potential extracutaneous manifestations that we really want to make sure that we're managing in our patients to maintain health long term.

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However, molecular testing does not always confirm a diagnosis, and there could still be diagnostic uncertainty. And there are situations then that we have to consider about tissue sampling, such as skin biopsies, to look at histology or electron microscopy. This could help us resolve uncertain pathogenesis when we have not been able to understand from the clinical standpoint and consistent genetic results that we have.

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While many of the EDDs they share similar histology, there are really some very specific ones and certain types. And so there is a role kind of for histologic testing in the future, but really more to kind of interpret your genotype and context, not necessarily to really define the diagnosis as a standalone test. There are, you know, particularly like for instance, our keratin associated EDDs that have some very specific findings, but you really have to consider the value of that, particularly because it is a little bit more of an invasive test.

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Similarly, there can be some biochemical testing or a microscopic evaluation of the hair when we suspect, for instance, a hair shaft abnormality with some hair abnormalities, that can kind of help us get into that right category as well, and really remember that an important part of the diagnostic workup is going to be involvement in specialists to really categorize some of those extra cutaneous findings, to help us understand how that might contribute with the skin findings to getting us to the right diagnosis.

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And thank you very much for your attention today.