Extracutaneous Manifestations of EDDs

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

---

00:00

Welcome to Extracutaneous Manifestations of EDDs, part of First's CME series on epidermal differentiation disorders or ichthyosis. Presenting this topic is Dr. Lara Wine Lee. Dr. Wine Lee is the professor of dermatology and pediatrics at the Medical University of South Carolina, where she has practiced since 2014. She cares for children with genetic skin disorders as part of the pediatric dermatology program.

00:26

Well thank you very much for having me today to discuss extracutaneous manifestation of epidermal differentiation disorders. I do have to disclose relationships with Leo Pharmaceuticals and Mayne Pharmaceuticals related to clinical trials and ichthyosis. Today, our objective is to discuss a wide range of extracutaneous manifestations with focusing on eye and ear issues, as well as understanding when co-management with other specialists is very important.

01:01

So to kind of group our extracutaneous manifestations of EDDs It's important to note that they actually occur across all subtypes. Now the syndromic types may have very prominent extracutaneous manifestations that are related to the underlying genetic basis. Whereas our non syndromic ones, the extracutaneous manifestations are oftentimes related to the epidermal findings, where the severe skin disease alone is causing most of those manifestations that we're seeing.

01:31

Whereas our palmoplantar EDDs have both syndromic and non syndromic forms, both of which can have extracutaneous manifestations as well. The systems involved are wide ranging but very prominently can have neurologic, immunologic, eye and ear problems, as well as metabolic nutrition and cardiac problems. The diagnostic clues that we get from the extracutaneous findings can actually be really central to getting our appropriate clinical diagnosis that may then guide our further workup to really get the genetic diagnosis that's going to be so important to understanding the management of the patient.

02:13

Getting the appropriate genetic diagnosis is so important then to get an appropriate care team where you get the specialists involved that can do not just management of the problem that's in front of you, but also to do preventative care and prevent some more severe sequelae that can

arise. So we're going to start with discussing ear problems in patients with EDDs because this can occur in upwards of 80% of all patients, including over half of the patients reporting hearing loss.

02:50

And I do like to group these into a few categories. So first of all, many patients, particularly with ichthyosis, have external canal disease. This has to do with the scaling of the skin leading to obstruction and conductive hearing loss. The genetics of the particular type of EDD may also specifically contribute to developmental abnormalities that lead to sensory neural hearing loss.

03:16

And in addition, there can be changes both in syndromic and non syndromic forms of the external ears, which then compound the problems that we are seeing above.

03:29

So across all types of ichthyosis having external auditory canal involvement is very common.

03:38

This is a keratinized epithelium as well. So there is scaling that is occurring within the canal. This then gets mixed with the wax and the debris leading to these recurrent obstructive plugs. This is compounded by oftentimes the small size of the canal, which can occur just because of the age of a younger child, or in some of the types of EDDs that have smaller ear canals.

04:03

That may be actually a lifelong problem as well. So over time, you have a buildup of this plug that then is obstructive or partially obstructive of the external canal, leading to oftentimes itching or a full sensation, frank pain and then reduction of hearing progressively. It also predisposes to recurrent infections. So external ear infections. But it's also important to note that the plugging of the canal can prevent us from having an appropriate diagnosis for middle ear infection or otitis media.

04:39

Over time, the conductive hearing loss can lead to problems with speech development, particularly within those critical time periods. The infection risk and the repeat need for debridements can lead to further issues of inflammation, infection, and scarring. So show a demonstration of what a keratinaceous plugging looks like. At the top picture here there is a plug which is again a mixture of that scaling and wax and is completely obscuring the tympanic membrane.

05:10

You actually cannot see the canal at all. The plug can be removed whether some techniques both used at home and in the office of specialists, such as an ENT doctor. But the canal still oftentimes has some abnormalities, some inflammation, some scaling that again predisposes to infection. This is compounded by the fact that with the scaling of ichthyosis, you can have the increased infection and the likelihood of infection and otitis externa

05:38

are recurrent infections of the external ear canal leads to potentially progressive scarring and further plugging over time. So we really oftentimes have to stay ahead of that. There are several techniques that can help manage this over time. And I do really think that a combination of in office types of procedures, as well as some home techniques under the guidance of a physician are very important.

06:04

So in your office, I really do encourage you to always examine the external auditory canal of the patient, even if they don't have any complaints. This is particularly important in our youngest patients, who are not able to tell you, and may just be having subtle problems with hearing to really kind of get ahead of any problems that would develop.

06:23

It is important to understand appropriate instrumentation of the external auditory canal, and there are several devices that can be used for this. This is one example, for instance, that has a guard so that you can't actually put it too far, but can be very, very challenging in younger kids anyway. And always consider when we need to progress to hearing testing, and to make sure that we're not having any impacts on hearing.

06:46

The use of products that kind of dissolve the wax are very central to the management of patients that are getting with these obstructive plugs and particularly were currently. So several types of peroxide drops that are available and can be very, very well tolerant, tolerated even in our youngest patients, as well as liquid colace which is a stool softener that is over-the-counter, can be helpful for earwax removal.

07:10

Oftentimes, if you're doing some type of product that loosens up and decreases the hardness of the plug, you really want to follow it by some type of irrigation to remove the debris. And these techniques can be done at home under the guidance of an appropriate doctor.

07:29

Ear malformations can be common in both syndromic and non syndromic forms of EDDs and it really can have some specificity to the actual type. And this can actually help you make a clinical diagnosis or can at least get you down the right pathway. So just some examples here of very more rudimentary ear development in a patient with harlequin type ichthyosis as well as other, you know, developmental abnormalities of the ear.

07:58

And remember this often translates to a smaller external auditory canal. Compounding the issue with plugging over time.

08:08

In addition to the conductive hearing loss, there are subset of patients with EDDs that actually have sensorineural hearing loss as well. The really prototypical type here is going to be KID syndrome, keratitis, ichthyosis and deafness, which has that classic triad. And the hearing loss can be very, very profound and quite progressive, with the average age of onset of more severe hearing loss, actually, in those toddler years.

08:32

And if you think about it, those toddler ages are really when language development is so important. And so having the right diagnosis and understanding that the patient really needs regular and expected manage of this progressive hearing loss can be important to maintaining appropriate developmental over time. There's actually a variety of types of EDDs that are related to the GJB2 gene mutation, and all of them do share in common the sensory neural hearing loss.

09:00

So important, though, to note that in addition to the sensory neural issues that in this type of EDDs You can also have still the obstructive plugging. So all of the techniques that we talked about previously are very, very important. So they're not compounding the sensory neural hearing loss with a conductive hearing loss as well.

09:24

Moving on to discuss eye complications, which is another one of the most prominent extracutaneous manifestations, particularly in our ichthyosis patients. This can again be both specific to the genotype and shared across different types. So most prominently is going to be scaling of the eyelids. What this leads to over time is the ectropian, so the turning out of the eyelids that can lead to scarring and inflammation and the inability to close the eyes.

09:55

So the picture here is a patient actually that is trying to have full eye closure and has the corneas then that are exposed even at the point of full. This is the fullest eye closure for them. Over time, this can lead to what we call exposure keratopathy, leads to a thinning of the corneas. Infection can be very prominent with the downstream sequelae of scarring, perforation, and vision loss.

10:20

The inflammation along these island margins also leads to loss of the eyelashes. Again, not then with another loss of a protective layer from the corneas. And oftentimes the extent of this can be related to the severity of the ichthyosis. But it can also be independent of that. So as an important consideration across all types. In addition, some patients also have meibomian gland dysfunctions, the meibomian glands are the glands that secrete the protective film of the eye.

10:51

They occur right there at the eyelid margin, as pictured here, and leading to a lot of those dry eye symptoms chronic inflammation and scarring over time. This type of scarring actually turns the eyelids in, which then is another point of irritation, inflammation and scarring, leading to potentially photophobia and erosions, which can be very prominent in certain types. It's also important to note this can be more severe, again, specifically on the type of of ichthyosis, and particularly with our patients with IFAP and KIDs syndrome having probably additional types of meibomian gland dysfunction, making these eye symptoms to be a very, very prominent part of their condition.

11:36

There are also types of EDDs that are very, very specific, just related to that specific genotype. Many of these may not actually have severe vision manifestations over time. What would be important for patients to understand and also to counsel their providers. So, for instance, if their ophthalmologist doesn't see a large cohort of patients with EDDs They may not be familiar with that.

12:01

So really perfect example here is going to be STS-sEDD, or X-linked ichthyosis where you get these small corneal opacities that can be noted on eye exam. They do not have vision sequelae over time, but if noticed and not attributed correctly to the type of ichthyosis, it could be misinterpreted to having another cause that then would lead to unnecessary workup.

12:26

We've already talked about IFAP and KID syndrome, where there's very progressive ocular discomfort, ulceration and scarring, and then in the KID patients, in addition, so poorly understood type of vascularizing keratopahy that compounds the photophobia irritation and

leading further to that reduced vision that can also be related to the meibomian gland dysfunction.

12:52

If the eye changes are progressive, you can have vision effects. And the exposure care topic should really be addressed and managed from early on so that we're not having the ulcerations, the perforations, the opacity and the scarring and the scarring, particularly in our more severe types, can happen in a quarter of patients or more.

13:15

Showing here just some examples of really kind of late stage type of disease. And we really want to get ahead of that scarring with some management techniques prior to that, because then we're dealing with changes that can be irreversible. But it's important to note that the severity of the eyelid findings are not always related to type. So these patients in the first two panels are showing lamellar ichthyosis in a patient with harlequin ichthyosis.

13:43

But even when we have less severe scarring such as this patient in the third panel, still very, very significant, ectropian, madarosis, loss of eyelashes and inflammation of those eyelid margins. So what do we do? Good news is that we do have some very easy to do types of interventions that can help prevent the more permanent changes over time.

14:10

First of all, very important to have regular eye exams with an ophthalmologist because it's difficult to see some of the sort of micro-scarring or the early changes, to be able to get ahead of them before they cause more of a problem. Very liberal use of the eye lubricants that are recommended by the eye doctors can be important, particularly during sleep, as well as lubrication of the eyelids as well to keep that skin in the best shape as possible.

14:39

And then a lot of opportunity with the use of topical or systemic retinoids to loosen up the scale and decrease the scarring that can happen over time. And this is a good example that's just published in the literature. Looking at the use of topical tazarotene for reversal of some of the ectropian and the eyelid changes that had developed in this patient.

15:00

And then unfortunately, if we're unable to prevent that over time, surgical correction could be really important to protect the eyes and prevent more long term vision loss.

15:12
All patients with EDDs should be followed for the growth and nutrition. So there are several reasons for this. First of all, particularly with more severe types where you have a lot of skin turnover and inflammation, there's an increased caloric need and the potential for higher fluid losses. This is particularly important in the neonatal period and in our infants.

15:35
And so good management, making sure we're preventing undernutrition and considering micronutrient deficiencies that have been documented in many of the cohorts of ichthyosis can be important again from birth and on. So nutritionists and gastrointestinal specialists can really help us with this. There's certain types, particularly syndromic, EDDs, such as Netherton syndrome, where there's even a more severe skin barrier, dysfunction, failure to thrive,

16:06
that's compounded by atopic disease that may lead to problems with particular types of foods. So across all physicians do recommend that we're trending weights. We're looking at linear growth. We're considering whether growth philosophy is appropriate over time and thinking about when is appropriate time to have a more formal nutritional assessment. But it's important that poor growth really does warrant the need for a dietary assessment and review of feeding difficulties, whether they're related to the EDD,

16:36
for instance, if you know that you have a lot of tightness around the mouth that can lead to problems, particularly in the infantile period with appropriate kind of sucking on the bottle and tiring out before, because we can't make a good suck and getting that appropriate amount of nutrition in. So thinking about that early on and not kind of waiting to get behind if we're seeing falling off of the growth curves, there are also all some guidelines that show the types of micronutrients that we should follow, which is common to actually many of our types of skin disease, to make sure that if supplementation, or just kind of management of the types of food, particularly

17:14
in the infantile period when we're looking at formula changes to kind of stay ahead of those micronutrient deficiencies, these are all very important for the skin and for healing of the skin as well. There's a variety of musculoskeletal and neurologic kind of issues that arise both in syndromic and non syndromic forms of EDDs. So important for like palmoplantar hyperkeratosis, whether it is more of the palmoplantar EDDs or whether our ichthyosis types, if you get a lot of restriction of the scaling of the palms and the soles, there can be a limitation of activity over time that then can have a reduction in function and particularly loss of fine motor function that can be

17:57

treated both with releasing sort of medical techniques to soften up the skin, release some of those contractures, but also physical therapy and exercises. So we don't really get to a point of irreversible restrictions of movement. There are certain types, particularly of more mutilating types of palmoplantar keratodermis, though, that this can even happen within the neonatal period, and such as Vohwinkel syndrome, where we really would want to involve hand specialists quite early to preserve as much function as possible. All of your visits, you should consider assessing range of motion, gait, hand function and footwear needs.

18:35

So we don't really think about it, but particularly if we're having a lot of pains, limitation of walking with more hyperkeratosis of the soles of the feet, changes in the footwear, appropriate footwear, and potentially actually speaking with people that specialize in this area to get devices that kind of help to relieve pressure on those areas can improve gate and it can improve pain.

18:57

So I really do like to have good relationships with my physical and occupational therapists with experience in these patients, and then in extreme circumstances, to consider whether surgical correction for selected patients may be important. However, when you're assessing the kind of the gate and the functional aspects, it's important to know that there are certain types of EDDs are syndromic forms that actually can have neurologic involvement as well.

19:24

And so that there might be things like spasticity, peripheral neuropathy, ataxia that are separate from the the skin manifestations related to more of that genotype of the syndrome X. And so really kind of a comprehensive evaluation here in terms of development and neurological involvement, can help you separate out whether there is an additional neurologic or developmental issue that really needs to be addressed for these patients.

19:54

So, you know, in the clinic, when you're considering these different phenotypes, you really have to have a holistic approach to the patient and really consider all of the systems because it's a good opportunity if you get the appropriate specialists involved, whether it's a genotype specific extracutaneous manifestation or whether it has to do with the severity of the skin problems, getting the right specialists involved to get ahead of any problems before they develop more severely, can really help kind of long term management of the patient and also really can help guide our testing.

20:33

So we can help using these different findings to get a correct clinical diagnosis, but then kind of use the guides as further testing to make sure that we're getting that appropriate diagnosis to take the best care of the patient. So putting this all together is how do we approach extracutaneous manifestation screening in clinic. So first of all, always think about the eyes, assess eye lid movement,

20:57

ask about vision, ask about eye pain. Talk about hearing. Examine the ears to see if obstruction is a problem. Understand language development and whether that is being affected. Look at the growth trajectory. Think about feeding and hydration. Make sure we're staying ahead of that. That can vary. Also different stages of life. So important to kind of always address that.

21:20

Think about those micronutrient deficiencies. Consider mobility. Consider pain and heat tolerance so that we can, you know, have enough full ability to participate in different activities and certainly understand when neurologic or metabolic evaluation may be important. And the bottom line here is there's lots of help out there to really get a good care team for patients to address all of the the issues that you may be seeing in your clinic, to make sure that the patient is getting a complete and kind of holistic care then, that stays ahead of any problems before they develop into any irreversible problems.

21:58

And thank you for your attention today.