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### Exploring Xeroderma Pigmentosum

Dr. Greenberg:

Xeroderma pigmentosum, or XP as it's known as, is a rare genetic condition that can lead to defective DNA repair, a side effect that has sparked an interest in understanding the clinical characteristics of this condition, as well as the mechanisms behind UV damage and repair.

Welcome to *DermConsult* on ReachMD. I'm Dr. Michael Greenberg, and joining me today to discuss patients with xeroderma pigmentosum is Dr. Kenneth Kraemer. He's the Senior Investigator at the Laboratory of Cancer Biology and Genetics at the National Cancer Institute in Bethesda, Maryland. He is also the corresponding author of the study we'll be reviewing. Ken, thanks for being here today.

Dr. Kraemer:

Oh, thank you for inviting me. I'm glad to be able to talk to you about our studies with XP.

Dr. Greenberg:

Good. So, starting off, tell our listeners a little bit about yourself and your training and how you became interested in xeroderma pigmentosum.

Dr. Kraemer:

I'm a dermatologist. I work at the National Institutes of Health. Initially I did a training in internal medicine. I went to Brown undergraduate and Tufts Medical School, and then spent three years at Harlem Hospital being trained in internal medicine, and during the Vietnam War, I was fortunate to be able to get into the public health service. I was assigned to do research at the National Institutes of Health, where I've been ever since, except for a couple years when I went to Miami with Harvey Blank and did a dermatology residency.

Dr. Greenberg:

So how did you get interested in xeroderma pigmentosum? Was that handed to you or did you suddenly go, "Wow I think this is fascinating, I wanna look at this?"

Dr. Kraemer:

Well, when I came to the NIH, I was assigned to work in the dermatology branch, and in those days, they had patients who were very ill with mycosis fungoides, and other life-threatening diseases in an inpatient service, and with my experience in internal medicine at Harlem, they needed somebody to take care of them. I started working with Dr. Jay Robbins at the dermatology branch, and he was working with xeroderma pigmentosum. And again, we had an inpatient who was actually dying of metastatic melanoma and I started taking care of him. And that actually whetted my interest in this disease. It was very unusual, very rare, but patients developed skin cancer at a very early age. These included melanoma and non-melanoma cancers, and they have an average age of less than 10 years when they develop these cancers.

Dr. Greenberg:

Okay, thank you. So listen, I'm a practicing suburban dermatologist, and I honestly can't recall the last case of xeroderma pigmentosum that I've seen in my office – probably was 30 years ago. Can you give us a really quick overview of XP, including its symptoms and how serious this disease is?

Dr. Kraemer:

About half of the patients have marked severe burning on minimal sun exposure. Usually early in childhood, they will develop very pigmented freckle-like lesions. In fact, if you see a child under two years old that has extensive freckling, that may alert you to the fact

they may have xeroderma pigmentosum. About half of the patients develop this early onset of freckling, and the other half don't. They get severe blistering on minimal sun exposure. And all of them go onto develop skin cancers at an early age, if they are not protected from the sun. And so the main goal is early diagnosis and sun protection, and then keep looking for possible tumors during later in life. It turns out that those patients that have the burning on sun exposure also may develop a progressive neurological abnormality.

Dr. Greenberg:

It seems from your review, of a couple years ago, the one that sparked our interest in talking to you, that xeroderma pigmentosum cell cultures are really valuable in understanding DNA repair. Can you elaborate on this?

Dr. Kraemer:

Xeroderma is a genetic disease. It's recessive, they're inherited from each parent. And the parents are clinically normal, but the parents have a one-in-four chance of having an affected child and the inherited defect in the ability to repair DNA that's damaged by sunlight. The sunlight causes photo products of the DNA and there is a whole mechanism called the DNA repair pathway that is used to remove this damaged DNA. If the damage is not removed when the cells try to replicate, either the cells die or alternatively, they put the wrong base in place, and in certain cases, if that's in the wrong gene, this may lead to cancer. So by studying the cells in the laboratory from patients with xeroderma, we learn a lot about the mechanism of sunlight-induced skin cancer.

Dr. Greenberg:

You also wrote that the accelerated development of cancers in XP has been used as a model to discover new cancer chemo preventative agents. Can you tell us a little bit more about this?

Dr. Kraemer:

That is true. There's a very long process that goes from the original damage of the DNA via the cells of the DNA by the sunlight to cells proliferating and then ultimately progressing and then developing cancer. We did a study a number of years ago, with an oral retinoid Accutane – the same drug that's used for acne treatment, and we found that that drug will interrupt the progression of these initiated tumor cells to go on to develop cancer. We were able to use a small number of xeroderma patients to show how effective the Accutane was, because each patient had multiple primary skin cancers. And we could dramatically reduce the frequency of new skin cancers in these patients by giving them oral Accutane and it showed that Accutane was a very effective in chemo prevention of skin cancer, and that was probably the first demonstration in humans of effective chemo prevention. Unfortunately, as dermatologists know, the Accutane itself has many side effects, and it's a limited number of patients that we would want to treat with this because of the side effects.

Dr. Greenberg:

For those of you just tuning in, you're listening to *DermConsult* on ReachMD. I'm Dr. Michael Greenberg, and today I'm speaking with Dr. Kenneth Kraemer about his research on xeroderma pigmentosum

So Dr. Kraemer, you've been studying this disease as part of Forty Years of Research on Xeroderma Pigmentosum at the US National Institutes of Health. Why is this research so vital for patients with xeroderma pigmentosum right now? Can you tell us a bit more about your process?"

Dr. Kraemer:

We're one of the few places in the world that is actually studying this disease. It's very rare, so the patients can come to the National Institutes of Health, where we are, in Bethesda. But this is your tax dollars at work. We have a large hospital in Bethesda. We can fly patients in. We get very intensive, extensive, evaluations for a three-to-five day visit. We bring the patients and their whole family, and they get seen by dermatologists, ophthalmologists, they get audiology testing. If they have neurologic problems, we can do physical therapy. We have neurologists go over them. We do extensive blood tests and radiologic examinations. As we follow the patients along, we're discovering new features of the disease that we didn't know before. We can diagnose the patients earlier. They're protected from sunlight and so they are living longer, and we're finding other things. For instance, we found women in their 20s who have this disease are getting premature menopause, and that's telling us that the DNA repair is playing a role in the normal maturation of the female endocrine system. Some of the patients are developing thyroid nodules at an early age. We're finding an increase in thyroid cancer, especially in patients in other parts of the world. Recently we found one of the forms of the disease is associated with an early onset of leukemia, and we're finding unusual forms of leukemia. Up until the past, initially we knew that patients had a higher frequency of skin cancer, and of central nervous system cancers. We don't really know the mechanism for these internal tumors. We suspect it may be related to oxidative damage in cells.

Dr. Greenberg:

Just in case a practitioner wants to know, are all expenses included – airfare, hotel – everything, so these people don't have to put anything out of their pocket?

Dr. Kraemer:

Virtually everything is covered. Everything in the hospital, all the medical examinations are covered. The airfare is covered for the patient and family members. Actually we study the whole family, so the parents and any siblings we would bring in, as well. And they have a Children's Inn on the campus, which is like a Ronald McDonald House. And so they have minimal expenses for some of the meals and things like that, but overall, most everything is covered.

Dr. Greenberg:

Okay, so where do you see your future research heading?

Dr. Kraemer:

Well we are looking at this and also another rare disease called TTD – trichothiodystrophy, and it similarly is rare, but these patients don't get increased skin cancer. They have developmental issues. Their brains don't develop properly, their bones don't, they have immune problems. During the mother's pregnancies, they have problems. But amazingly, they have mutations in the exact same genes as the xeroderma patients do. They have different mutations in those genes, and we're trying to figure out why it is that one mutation of the gene will give you 10,000-fold increased risk of skin cancer, but another will not do that, but only give you a lot of developmental delays. And if we can understand more of that, we may be able to get inside symptom mechanisms of not just skin cancer, but of human development.

Dr. Greenberg:

So, what's the take home message for our listeners?

Dr. Kraemer:

We are actually discovering more and more patients with xeroderma who are not so profoundly affected as children, but they are later in life. And the other thing is that we're finding as more and more people are getting hold of exome sequencing, that they're carrying mutations that are of the same type that we see in the xeroderma patients. And so, there may be minor effects of these mutations in the general population, and they may be, for instance, the type of person who has multiple skin cancers. Without overt features of xeroderma might have mildly defective DNA repair.

Dr. Greenberg:

Thank you. Well, that's a great way to end our discussion today on such a rare and interesting disease. I want to thank Dr. Kenneth Kraemer for joining me to discuss the current research, as well as his study on patients with xeroderma pigmentosum. Ken, it was great speaking with you today. Thank you.

Dr. Kraemer:

Thank you very much, and I would like to point out that I don't do any of this in isolation. We have a large team of people that work with me. I mentioned John DiGiovanna is a dermatologist, Deborah Tamura is a research nurse, and Sikandar Kahn works in the laboratory side of these studies, and we have tremendous collaborations with many other specialists in their line.

Dr. Greenberg:

That was great. Thank you. For ReachMD, I'm Dr. Michael Greenberg. To access this episode and others from *DermConsult*, visit [reachmd.com/dermconsult](https://reachmd.com/dermconsult), where you can Be Part of the Knowledge, and thank you for listening.