



Hematology

Advances in the Treatment of Cutaneous T-Cell Lymphoma (CTCL)

Hosted by: Steven Gore, MD

Guest: Michael Girardi, MD, FAAD,
Professor of Dermatology, Yale School of
Medicine

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Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists, who are on the forefront of the battle to fight cancer. This week it is a conversation about cutaneous T-cell lymphoma or CTCL with Dr. Michael Girardi. Dr. Girardi is Professor and Vice Chair of Dermatology at Yale School of Medicine and Dr. Gore is a Professor of Internal Medicine and Hematology at Yale and Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore I think that probably most of our listeners have never heard of cutaneous T-cell lymphoma which I guess we sometimes abbreviate as CTCL, but I have to say that I have been personally interested in it a little bit since I first heard about it in medical school where they used to call it mycosis fungoides which I think translates to fungating fungus, is that right?

Girardi That is the literal translation and there is confusion with the terminology for sure, even among medical professionals. Cutaneous T-cell lymphoma is kind of the umbrella catchall term that is used for all of the different subtypes of lymphoma that can go to the skin that is derived from a white blood cell, a lymphocyte called T-cells.

Gore But don't lymphomas cause swollen glands and things like that, we think of lymphomas as being masses in lymph nodes?

Girardi They do, they do indeed. So lymphomas are any cancer of lymphocytes that can arise in any tissue, very commonly they will arise in lymph nodes or if they arise in another tissue like the skin, they can involve the lymph nodes and of course they involve the blood, then we can have the leukemic manifestation of the lymphoma and in CTCL, we often see all 3 go together, the skin involved, the blood involved, and lymph nodes involved. So technically it is a non-Hodgkin's lymphoma that starts manifests in the skin, but can also involve the lymph nodes in the blood.

Gore Why would a lymphoma arise in the skin, why should there even be these lymphocytes there in the first place?

Girardi Lymphocytes are everywhere in the body and in the skin, in particular. In fact, a study was done to calculate the number of lymphocytes in the skin, white blood cells in the skin, and there were more in the skin than in the circulation in the blood. So, if we think about the skin, what is the function of the skin, a major function is to defend the rest of the body against any external insults including infectious agents and so we

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certainly want our immune system for which lymphocytes are the primary surveyors of to protect us and to be they are a part of the defense mechanism and so lymphocytes populate the skin but they also regularly and efficiently help defend us.

Gore Now in this particular kind of cancer, the lymphocytes are of the T-cell variety, right? What does that mean exactly?

Girardi There are 2 major types of lymphocytes, there are T-cells and B-cells and they kind of work in coordinated ways, hand-in-hand; B-cells are largely responsible for making antibodies.

Gore Like if you get a tetanus shot?

Girardi Yes, you will manifest production of specific antibodies that can attack, bacteria for example in the external space. T-cells have evolved more to protect us against viruses and also to protect us against some cancers as they can develop. So they are both important components. T-cells in particular will hone to the skin more regularly than B-cells, but B-cells can also.

Gore Do we know why that is?

Girardi I think it is primarily the function. B-cells can release antibodies out of certain factories like in lymph nodes and the spleen that get into circulation and those can permeate everywhere including the skin; whereas T-cells, we need their cellular function, we need the cells to carry out their function for defense purposes.

Gore So they are the sentries on guard at the location, is that right?

Girardi Yes, that is a very important component of their function.

Gore Do we have any idea why these T-cells in the skin go bad?

Girardi I get asked that a lot and so I can tell you that we have studied the genetics of CTCL and have seen a huge variety of genetic alterations, mutations, and also gene copy numbers that change, additions to certain genes and deletions of certain genes, it is a huge spectrum and so that does not really tell us why that is happening, but we know that T-cells, like other cells in the body where there is a lot of increased risk of cancer over a person's lifetime are a highly proliferative-type of cell.

Gore They grow a lot.

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Girardi Yeah, they need to make a lot of themselves and particularly against infections and so when you have that capacity as a cell, errors can happen and mutations in the DNA that guide the cell cycle, how cells turnover, how they proliferate, how they make more of themselves, can go awry and if they harbor these mutations, if they stick, if they stay with the population of cells just like in any other cancer, then the growth becomes uncontrolled and so it happens to skin T-cell, then the growth becomes uncontrolled in the skin and patients will wear their lymphoma, they will have lymphoma right there on their skin and you think that may make it easy to diagnose both for the patient and the doctor, but it is often very confusing because it can manifest so many different patterns and because there can be so many different subtypes.

Gore And I remember that I was taught during my fellowship that this particular lymphoma often went undiagnosed often for many years, and people were told they had psoriasis or pseudo-psoriasis or other more common and benign skin disorders. Is that still happening?

Girardi That is very much still a common phenomenon and it is understandable in a lot of ways because again the patterns that are seen on the skin do not always follow the textbooks, so there are some classic presentations for cutaneous T-cell lymphoma and the subtype you referred to as mycosis fungoides where we have these patches or flat round to oval pink to red lesions that like to present in sun-protected areas, so that would be what we call the bathing trunk areas, on the buttocks, on the inner thighs, on the breasts, under the arms, these are sun-protected areas which gives you a clue as to why we use ultraviolet light to often treat these early stages of CTCL that is they are very sensitive to certain wavelengths of ultraviolet light, but it is also a clue to diagnosis. It presents in these areas, and it tends to get lighter in the summer on patients and in the winter, it seems to be more pronounced but sometimes it looks like psoriasis, sometimes it looks like eczema, sometimes it looks like a ringworm, like a fungal infection of the skin. It can take on different morphologies, not just necessarily the classic round and oval, it can become more ring-shape, it could become even more polygonal sometimes and that can be very confusing to patients, and to doctors and there is another element of delay in diagnosis and that other element is this is not a histologic diagnosis like melanoma might be.

Gore Histologic meaning how it looks under the microscope?

Girardi Yes, if a doctor performs a biopsy.

Gore Skin biopsy?

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- Girardi Skin biopsy, takes a piece of skin, say 3 mm, sends it to the pathologist and says, hey what is going on here? It is not always a black and white reading when it comes to CTCL.
- Gore It is not a slam dunk.
- Girardi No. There is often a lot of dependence on the experience of the pathologist in seeing a lot of cases of CTCL. It is a relatively rare form of lymphoma, about 4% of non-Hodgkin's lymphomas are of the CTCL type, but in the skin, the affected cells, the abnormal T-cells that might be present can be few and far between, they are often a minority of the T-cells that are in the skin on the biopsy and so knowing exactly what to look for, looking for changes in the nuclei, the shape of the center of the cells, looking for where they are, how they line up and how they interact with other cells becomes a very important component for an experienced pathologist to make that diagnosis. Sometimes we get back from the pathologist, suggestive of CTCL or consistent with CTCL and these are kind of the gray areas of the diagnosis, so we need to turn to often some more high tech state-of-the-art molecular studies to help us with the diagnosis.
- Gore Before we get to some of that cool stuff, I would like to see if we can clarify, a lot of listeners may have psoriasis or eczema, but this is not a common problem compared to those, right? Most people who have psoriasis and eczema, that is really what they have.
- Girardi Absolutely Steve. Psoriasis and atopic dermatitis or eczema are much more common than CTCL and so we do not want to insinuate that people who are walking around with common skin conditions have CTCL. However, if a patient develops eczema in their 50s and didn't have it as a child, CTCL likes to come on as we get older. It is really a condition that can occur at any age, however, it is much more common in patients in their 50s and 60s if they didn't have a history of eczema or they did not have a history of psoriasis and it is atypical.
- Gore Atypical, not typical.
- Girardi Not typical. So say it is occurring in a distribution that is not consistent where psoriasis typically occurs which is on extensor surfaces, elbows, knees.
- Gore And the doctors, the dermatologists know about that?
- Girardi They do, yeah, and they should pick up on that. It is coming on later in life without a history in the younger years.

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- Gore That should get their attention.
- Girardi That should be a clue to maybe I need to do a biopsy and see if there is something that might be a little different than what I thought it was in the first place. Another clue is lack of response to treatments. So someone who has a later onset or has what they think is eczema, what the doctor thinks is the eczema, but it is not responding well to treatments, then this might be a nudge to see a specialist, see a dermatologist, get a biopsy, get a full expert clinical opinion as well as a full pathologic, histologic vantage on what is going on.
- Gore Like if I had psoriasis nowadays that was not responding, there is some stuff in the commercials that they are pushing, some high-tech stuff that is curing all these people's psoriasis or making them go out in public in those commercials.
- Girardi There are plenty of those, yes.
- Gore So I would just say, give me one of those expensive high-tech things. I am saying this because I would think this is how it is being promoted to us as consumers.
- Girardi Sure, and being sure of the diagnosis in the first place.
- Gore Absolutely and of course, as patients we should never be making our own diagnosis and our own treatment recommendations without having an expert.
- Girardi Absolutely not, however, it is important for patients to feel empowered to ask.
- Gore The other thing I wanted to convey before you get into some of the more sophisticated diagnostic things is, dermatologists are always telling us to stay out of the sun and use the number 30 sunscreen and all that stuff, and it is sounding like you are telling me that unless you are sunbathing in the Caribbean or the South of France, I am putting myself at risk for T-cell lymphoma if I don't do some sunbathing, that is not the right take home message, correct?
- Girardi That is not, no Steve. It is critically important for people to protect themselves from sun exposure and the harmful effects of UV rays that come with that, in particular because the risk of skin cancer, and when I say skin cancer, I mean, melanoma, squamous cell carcinoma, basal cell carcinoma, is very real.
- Gore Very much more common than this.

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Girardi Much more common and they in particular like to affect people as they get older, people with fair skin, people that have had outdoor exposure, or sun lamp exposure and indoor tanning is a major risk factor for that. That is not the same as when we say we use medicinal ultraviolet light to protect against CTCL. It does not prevent CTCL, it is used to treat. It is done in a very measured way, stepwise way, in an office we have a treatment center here, there are treatment centers across the country. We use a specific wave length of light. In one case, we use a very narrow band of ultraviolet B light and this can really be used effectively and safely, it does not increase the risk of skin cancer to a substantial level over your natural exposure and can really be a tremendously effective first line treatment, skin-directed treatment for a lot of forms of cutaneous T-cell lymphoma.

Gore This is a very fascinating subject and I think one that most of our listening audience probably has never heard about, but right now, we are going to take a short break for a medical minute. Please stay tuned to learn more information about cutaneous T-cell lymphoma.

Medical Minute

Support for Yale Cancer Answers is provided by AstraZeneca, dedicated to providing innovative treatment options for people living with cancer. Learn more at astrazeneca-us.com.

This is a medical minute about head and neck cancers. Although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancers and their treatment. Clinical trials are currently underway to test innovative new treatments for head and neck cancers and in many cancers less radical surgeries are able to preserve nerves, arteries, and muscles in the neck enabling patients to move, speak, breathe, and eat normally after surgery. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore and I am joined tonight by my guest, Dr. Michael Girardi, who is Professor of Dermatology and Vice Chair of Dermatology at Yale School of Medicine. We have been talking about a very rare form of lymphoma which presents in the skin known as cutaneous T-cell lymphoma. Mike, before I started getting you off topic, intentionally, you had mentioned that oftentimes it is really difficult to make a diagnosis on the way the cells look in skin biopsies for this particular sort of disorder and you need to do some genetic testing or things like that. What can you tell us about that?

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Girardi What we know about T-cells is normally they will rearrange some of their genes and we have evolved to have this process happen because it gives diversity to our immune system.

Gore Oh that is so complicated, I don't really understand, tell me in a little easier terminology.

Girardi There are surface proteins, proteins on the cells, on T-cells that can recognize a great variety of infectious agents.

Gore So they are like the radar looking for their target, right?

Girardi Yep and there are different specificities that are attributed to different T-cells and so we can take advantage of this diversity of T-cells by looking at the genes that have shuffled to make these receptors and so in CTCL as in any cancer, there is a clonal expansion, there is a signal that gives rise to the other cancer cells.

Gore So every cell is related to every cell, they are basically identical copies?

Girardi Yes and so we can look at the genetics in specific to the receptors, these T-cell receptors.

Gore The radar protein?

Girardi Right and then we can zoom in and say, has there been a clonal expansion of these T-cells?

Gore So are they all carbon copy of each other?

Girardi That is right. So that molecular level of testing can be very sensitive and can give us a tremendous clue beyond just the pathology as to whether we might be looking at CTCL.

Gore But you told me you have only got a 3 mm piece of tissue, how can you do these DNA tests in such a small amount of tissue?

Girardi There is a special molecular test and process where we can amplify the gene, so we can make more copies of them and then we can do the sequencing analysis, so we will actually have the machines go in one by one and look at each of the coded bases to identify sequence in the DNA.

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- Gore That is fascinating. Before we go on, for the patients who have an underlying diagnosis, I guess as you said, if they are not responding well to treatments, these are the people who should be more worried about whether there is something else going on right?
- Girardi Yes, so we talked about some of the clues to presentation and we were talking about early stages of mycosis fungoides where we have these patches, these flat areas of involvement, but sometimes we see these plaques.
- Gore Plaques?
- Girardi Yeah, a plaque is a thickened lesion of skin, it has raised to it. You can run your finger over it and you see that it is above the level of the surface of the skin.
- Gore It kind of bumps up.
- Girardi Yeah, and so this is a more concerning form of CTCL and mycosis fungoides and that subtype. We can also see an evolution to actual tumors on the skin.
- Gore Those are the mushrooms, right?
- Girardi This is what led to, in France in the 1800s, to coin the term mycosis fungoides with these fungating mushroom-like tumors that can occur on the skin. This is what we are trying to prevent when we treat these lesions early. So early diagnosis, early treatment decreases the number of abnormal cells in the skin that have a chance to go on and give rise to other sub clones that might behave differently.
- Gore But wait a minute Mike, let's say I've got this early stage mycosis fungoides presentation in one or two places on my skin, you tell me you want to put me under some ultraviolet lights and that is going to help prevent progression and that is fine, I'm cool with that, but you're telling me this is cancer, I want to cure this thing, I don't want to have to worry about not curing and just having some ultraviolet lights to shrink the lesion, I am not happy with that.
- Girardi I understand and patients often express that sentiment also, there is a dictum here with CTCL. Early disease tends to be extremely slow growing. We have plenty of time to treat it with safe, easy treatments including ultraviolet light, but not limited to. We have other topical creams, ointments, that can also be used and we can use the very superficial form of electron beam therapy, our therapeutic radiologists can employ in the care of patients and really eliminate lesions but ultimately cure for early

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disease is not something we talk about, it is overkill. The toxicity level that we would need to take on as a risk to try to cure patients of this in early disease is just too great. It is too great a risk and the chance of curing early disease that way is incredibly small.

Gore When you say that the thing is incredibly slow growing, that may be easy for you to say, but does that mean like 5 months, does that mean 2 years, does that mean a decade?

Girardi We are talking about years to decades when it presents in its earlier stages. However, not everyone presents with the earlier stages. Some of them tend to present with more aggressive disease.

Gore Without having had that precursor?

Girardi And you know we have to respect the fact that this is indeed cancer. It is cancer of white blood cells, but early disease can be managed more conservatively and in later disease, that is if we start to get thick plaques, more widespread lesions or if we actually get tumors, if we get blood involvement, if we get frank lymph node involvement, then we need to bring out the armamentarium and in the last 10 years we have had tremendous advancement in the treatment of these more aggressive forms of cutaneous T-cell lymphoma, that is later stage disease but also more aggressive subtypes.

Gore And what do those treatments look like?

Girardi For patients with extensive skin involvement, for patients with lymph node involvement, we really will turn to more systemic administered treatments that is intravenous or oral pills.

Gore Chemotherapy, really?

Girardi So chemotherapy is something that we really try to stay away from, even with more advanced disease with CTCL that tends to not be as much of a durable response with this condition, but we are seeing a lot more response to certain categories of agents. One major category is called retinoid and it works on receptors that are inside the cells, not on the surface.

Gore So that is like the stuff that teenagers put on their skin for acne, right?

Girardi It is related to that, very good Steve, but not the same thing.

Gore Ok, but similar.

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Girardi A derivative, and years of research that have evolved to help with treatment of CTCL along that particular class of agents, yes. Another one that is really exciting is the class of agents that are monoclonal antibodies. So they get infused into the circulation and they target certain proteins that are on the surface of these cells and there are several that have been identified specific to CTCL and a lot of times these monoclonal antibodies are attached to certain toxins that can kill the CTCL, so a seek and destroy approach to finding the cells wherever they may be in the body, not just in the skin. Another treatment that we do is called photopheresis and this is very commonly used for patients with blood involvement who have leukemic-type of CTCL, often those under the name of Sèzary syndrome, again for another French doctor who named it.

Gore Not Hungarian? It is always a Hungarian, looks like a Hungarian name to me?

Girardi Those countries are next to each other.

Gore No, not exactly.

Girardi Sèzary syndrome usually presents more with what we call erythroderma and that is fancy for red skin and so red skin patients who have CTCL are much more likely to have blood involvement with their CTCL.

Gore You mean, like their whole body is red?

Girardi Yes, so the definition formally is 80% or more, but I think patients with 30%, 40%, and 50% red involved in their skin have blood involvement.

Gore And we are not talking about normal complexion, right, they are not really pink people in the first place?

Girardi No, these aren't ruddy fair-skinned individuals who have little bit of redness.

Gore This is some change for them.

Girardi So it is the triad that we talk about with Sèzary syndrome, red skin, intense red skin, usually itchy, flaking, and then lymph node swelling.

Gore Oh, ok.

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Girardi And so we know this is going to lymph nodes too and then leukemic involvement and so blood tests where we can profile all of the T-cells becomes a standard part of the way we workup patients with CTCL because we want to keep tabs on whether their blood is involved because the treatment dynamics change. We want to get into the blood with other treatments and attack those cells. So one of the ways that we do that is with photopheresis.

Gore What is that?

Girardi Photopheresis is a treatment that was originally developed by Dr. Richard Edelson who is the chair of dermatology at Yale that has numerous centers across the country and the world, now about 200 centers in this country alone and it is a treatment on the blood where some of the patients blood is temporarily taken out and processed by a machine to separate the white blood cells from the red blood cells, then the white blood cells are treated in a way with a naturally found chemical called Psoralen, in combination with again ultraviolet light, in this case ultraviolet A light and so this combination of the Psoralen and the ultraviolet A light has a profound effect on cancerous T-cells. It allows them to undergo a slow death. This has a name for it called apoptosis, but this slow death is in particular good to empower the immune system when these cells are infused back into the body to attack not just the slowly dying cancer cells but to ignite a new response against the living malignant T-cells.

Gore Wow, that is amazing. I always wondered, it does not seem to me like even remotely imaginable that you can be taking out enough T-cells in that machine to treat them all, I mean you just told me there are a gazillion T-cells, right.

Girardi Yeah, so you are not taking them all out, you are taking this portion and in this portion, a patient may have 10% or 20% of their peripheral blood circulating T-cells actually be malignant CTCL cells and so, yes you may damage some of your normal T-cells in this process, but the key-part of it is the clone that has expanded is damaged in a way that you can ignite an immune response against those malignant cells, it is almost like a vaccination against a cancer.

Dr. Michael Girardi is Professor and Vice Chair of Dermatology at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against the cancer. You are on Connecticut Public Radio.