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answers

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Hosts

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**What's New in
Dermatopathology**

Guest Expert:

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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at the Yale Cancer Center and she is an internationally recognized clinician and clinical researcher. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of The Breast Center at Smilow Cancer Hospital at Yale-New Haven. Yale Cancer Center Answers features weekly conversations about the most recent advances in the research diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about dermatopathology with Dr. Rossitza Lazova. Dr. Lazova is Associate Professor of Dermatology and of Pathology at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar Dermatopathology is not something that everybody talks about, why don't you start by telling us a little bit about what it is exactly that you do?

Lazova Dermatopathology is a specialty behind the scenes, so to speak. We train in either pathology or dermatology and then we do additional training in dermatopathology as a fellowship. Dermatopathology is a skin pathology. We have to examine skin biopsies and make a diagnosis.

Chagpar What kinds of things do you look at, I would think it is moles and things like that?

Lazova When a patient goes to see a dermatologist for any particular problem, either a rash or a mole or any other lesion on the body, the dermatologist most of the time knows what they are dealing with, but sometimes they are not sure and they biopsy these lesions, they send the piece of tissue to our Yale Dermatopathology laboratory or another dermatopathology laboratory for histologic examination. The tissue is prepared, very thin sections are placed and a stained slice and we, the dermatopathologists, examine the tissue and make a specific diagnosis. We tell the dermatologist what the patient's condition is, what type of rash they have, whether they have a benign mole or the deadliest cancer, malignant melanoma.

Chagpar How exactly do you do that, is it all just looking under a microscope and pattern recognition or are there fancy-schmancy tools that you use as well?

Lazova The gold standard in pathology, including dermatopathology, is the examination of hematoxylin and eosin stained tissue sections. We do use pattern recognition and specific criteria to make the diagnosis, however, in the modern age we have additional tools that are at our disposal, this includes immunohistochemical stains that we use to recognize the origin of the tissue cell and additional studies such as molecular studies, genetic studies and others.

Chagpar Tell me more about that, how those studies help you to tell the difference between skin lesions because I mean for a lot of us, and the audience who is listening to us tonight, they may have a mole, it looks like a mole, and we really cannot tell the difference between one kind of mole and another kind of mole, but you can?

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- Lazova That is correct. There are different kinds of moles and there is the cancerous counterpart malignant melanoma, so it is very important for patients to regularly examine their skin and to go to a dermatologist for a full body examination if they have problems or if they have a family history of melanoma, that is extremely important. By examining the lesions on the skin of the patient's the dermatologist may be absolutely certain that they are benign moles and in this case they do not biopsy them, they can follow them clinically for changes, but they are reassured they are benign and nothing needs to be done, but sometimes they look atypical. They have different colors, the border is not smooth, they are large, they are irregular, and then they would biopsy the lesions and send them to us. Many patients do not even know that when a biopsy is taken from their skin it goes to a dermatopathology laboratory and we as dermatopathologists making the diagnosis, we determine whether the lesion is benign or cancerous, in other words our diagnosis can change a patient's life. If we make a diagnosis of malignant melanoma, malignant melanoma is the deadliest cancer in humans because gram a patient can die from a gram of cancer, that little, from just a few cells, even less than a millimeter deep in the dermis, a patient can die.
- Chagpar Clearly everybody should make sure that they are getting skin checks and if there is something that is of concern it should be biopsied and examined by a dermatopathologist. Tell us about the spectrum of things that you see and a bit more about your own research interests?
- Lazova Most of the time it is very clear by applying the histopathologic criteria whether a lesion is benign or cancerous and it is very easy to make the diagnosis of course after years of training and years of practice. I have been practicing dermatopathology for 17 years now at Yale University; not counting my fellowship with Dr. Bernard Ackerman, who is the greatest dermatopathologist of all times. We have different tools as I mentioned, immunohistochemical staining, we can make sure that the lesion is melanocytic, in other words composed of melanocytes, by using specific melanocytic markers and we can use a marker for proliferative activity, it is usually low in benign lesions and very high in malignant melanomas, in cancerous lesions, because cancerous cells tend to proliferate at a much higher rate.
- Chagpar Tell us more about your particular area of interest and expertise?
- Lazova As I mentioned there are different types of moles and one of these types is the so called Spitz nevus, it is a benign mole that usually occurs in children and young adults near the knee and on the face most commonly, and grows very rapidly. These lesions are pink, reddish or different shades of brown when they are biopsied and we examine them, they are composed of very large cells, we call them epithelioid because they resemble keratinocytes, so large epithelioid cells that are arranged in large nests. When this type of nevus was described originally by Sophie Spitz in 1948 she actually thought that these were juvenile melanomas because these cells looked so atypical and so cancerous to her that she believed that these were melanomas, however, later it became apparent that no patients die of this cancer, so the pathologists realized that in fact that this is a type of a benign nevus and in honor of Dr. Sophie Spitz it is called Spitz nevus. At the other end of the spectrum is Spitzoid melanoma, this is a cancerous lesion, malignant melanoma, that resembles

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under the microscope a Spitz nevus. Then in the middle of the spectrum, these atypical Spitzoid neoplasms or atypical Spitzoid lesions that are very difficult to study and to make a definitive diagnosis. Experts in the field disagree, although we apply the available histopathologic criteria many of these lesions have conflicting criteria, some are benign and some are malignant lesions so therefore it is basically impossible in some cases to make a definitive diagnosis of whether the patient has a mole or melanoma and this is the area that I most interested in, spitzoid neoplasms, Spitz nevi, Spitz with melanoma, and the lesions in the grey area, the atypical Spitz with neoplasms.

- Chagpar That is concerning, especially given what you had said earlier about the value of the pathologist being able to say to the dermatologist, this is benign versus this is melanoma, because as you said it is a very malignant disease that can be lethal, and to hear that there is a fuzzy area in the middle, is really quite shocking. Tell us what you do exactly, how do you communicate that to the physician and perhaps more importantly, to the patient, who is then left in a quandary of, is this benign, or is this malignant?
- Lazova This is very frustrating, as you mentioned. It is frustrating for us and it is frustrating for the clinicians and for the patients. When we get a lesion like that which is very difficult to study extensively we show it in conferences to our colleagues. We are a group of 8 dermatopathologists, so all difficult cases are shown in conference and then we can send the cases to other expert dermatopathologists in the field who have studied spitzoid neoplasms, but regardless, as I mentioned, there is a lot of variation and different opinions with difficult neoplasms and no matter who the expert it does not really tell you exactly whether the lesion is benign or malignant, so this could be very frustrating. Of course the clinician wants to know what they should do, do they treat it as melanoma or do they do nothing which is dangerous to under diagnose a lesion, if it is malignant to call it benign, or to over diagnose it and have the patient subjected to unnecessary surgery. So of course we scratch our heads, we pull our hair out and we use all possible ancillary studies to give us an answer and there are ancillary studies that might be helpful, comparative genomic hybridization, FISH and something that I have been doing for a few years now, mass spectrometry analysis. Studying melanocytic lesions by mass spectrometry basically studies the protein composition of the cells, it is objective, and it does not involve the interpretation of histopathologic criteria because regardless of the objectivity of this criteria, we are all humans and we use our subjective application of these criteria when we study a lesion. So I have been very satisfied with the results of mass spectrometry and I can tell you more about it.
- Chagpar Please do. Tell us more about how you use that and how that helps you to give a diagnosis to a patient, and how accurate is that?
- Lazova This is a method that has been recently introduced and is not yet used for clinical application, it is still in research, however, I am right now finishing a large study that is involving numerous institutions from the United States and there is international involvement.

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Chagpar I want to hear more about that study and I want to hear more about how you are using mass spectrometry to give patients and clinicians an answer to, is this cancer? Is this not cancer? First we need to take a short break for a medical minute. Please stay tuned to learn more information about Spitz nevi, dermatopathology and mass spectrometry with my guest Dr. Lazova.

*Medical
Minute*

Breast cancer is the most common cancer in women and in Connecticut alone approximately 3000 women will be diagnosed with breast cancer this year. There is new hope though, earlier detection, noninvasive treatments and novel therapies provide more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with the disease. With screening, early detection and a healthy lifestyle breast cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center to make innovative new treatments available to patients. A potential breakthrough in treating chemotherapy resistant breast cancer is now being studied at Yale combining BSI-101, a PARP inhibitor with the chemotherapy drug irinotecan. This has been a medical minute brought to as a public service by the Yale Cancer Center and more information is available at yalecancercenter.org. You are listening to the WNPR, Connecticut Public media source for new and ideas.

Chagpar Welcome back to Yale Cancer Center Answers, this is Dr. Anees Chagpar, I am joined today by my guest Dr. Rossitza Lazova. Right before the break we were talking about dermatopathology and this is an interesting area looking at Spitz nevi. Spitz nevi being this benign lesion occurring in kids, as I understand, but that has a counterpart that is not so benign called Spitz melanoma, and all of that is well and good, except that there is this grey area in between where our pathologists who are the people who help us to decide whether something is benign or malignant are in a bit of a quandary, Rossitza you were telling us right before the break how you are using fancy tools and advanced technologies to help patients get those answers?

Lazova Yes, this is the most difficult area in dermatopathology, differentiating benign from malignant melanocytic lesions and particularly in the area of Spitzoid neoplasm. Many people are interested in studying this area and I became interested in studying it years ago in 2008 and I started the Yale Spitzoid Neoplasm Repository, which is a compilation of tissue samples that are stored at the Yale Dermatopathology Laboratory. It contains about 3000 tissue samples and these tissue samples are used for different types of research studies including mass spectrometry. Again, about that time, 2008 and 2009, I was talking to a friend of mine and he said, why don't you study Spitz lesions with mass spectrometry, and I said, I cannot because these are formalin fixed paraffin embedded tissue sections and you need fresh tissue to use mass spectrometry. He said, no, no, no, there is Dr. Richard Caprioli at Vanderbilt University who created a new method and it is called MALDI, or Matrix-assisted laser desorption/ionization imaging mass spectrometry, that studies 5 micron thick tissue sections from formal and fixed paraffin-embedded tissue and he can do that for you, so I immediately called Dr. Caprioli and he said, of course I will do that and I was very fortunate to receive a Pilot Grant from the SPORE in skin at Yale to do mass spectrometry on subsets of Spitz

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nevi and Spitz with melanomas. We discovered proteomic differences in two groups that were able to differentiate between the benign and the malignant counterpart in the Spitzoid neoplasms. This study was published about two years ago and for the last two years I have been collecting samples and I have been very fortunate that my colleagues were so wonderful in contributing to this study, 11 institutions within the United States and 11 countries throughout the world, so I have more than 100 samples of lesions in the grey area of the atypical Spitzoid neoplasms to be studied by mass spectrometry applying the algorithm the we already discovered, the proteins that were differentially expressed in the two groups, and the results are very promising, in fact, this week and next week I am writing up the manuscript to be submitted for publication with the results from mass spectrometry that correlate better with the clinical behavior of a lesion than the histopathologic gold standard examination. This is very fascinating because again we can look at cancer on the molecular level and see whether they are really benign or malignant and I can tell you very interesting stories about that.

Chagpar That is fascinating because one of the things that I think is so critical is that mass spectrometry is objective, granted that there are guidelines that have objective criteria, but as you say, a lot of the guidelines are based on subjective pattern recognition and here you have an objective technology that can say, if you have got protein X, you are malignant, if you have got protein Y, you are benign and it separates things out but is it really that clean or in that middle grey area are there some proteins that are a little bit expressed, but not completely expressed or mixes of the proteins that were found in the benign nevi as well as in the malignant nevi?

Lazova That is an interesting question. Most of the time, I would say more than maybe 95% of the time, the results for mass spectrometry are clear-cut for benign or malignant. Rarely, the mass spectra are in the middle, they are numbers that are very close to each other so I cannot make a distinction but then I always repeat the sample and usually the repeat result helps me in making the distinction, but as with everything else there are very rare cases in which results are unclear.

Chagpar Yeah.

Lazova But most of the time, definitely I would say more than 95% of the time, the results are clear and the sensitivity and specificity for this method is in the mid 90%.

Chagpar Wow, I think that is just tremendous that you take this group of patients who were wondering whether or not this was benign or malignant and for 95/100 you can give them a clear-cut diagnosis.

Lazova Absolutely, and patients find me through my publications through the Yale Spitzoid Neoplasm Repository, they email me, they would like to participate in the repository, they send me their tissue samples, it is amazing, and these poor patients struggle because they are diagnosed with these lesions in the grey area and I help them define their lesions better and give them hope that it is not really a cancer and they will live.

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- Chagpar It is so interesting that you say that, because it goes back to how you opened our conversation tonight which was really that dermatopathology is one of these hidden specialties in the back room, you do not really see them upfront, but they are the ones in the back room doing all the work while you are visiting with your dermatologist and it really is quite telling that you actually do have a connection with patients because you do make such a big difference. Is this technology available everywhere or is this something that is of critical expertise that you can only find in a few pockets?
- Lazova As of now, I am basically the only one doing it in the world.
- Chagpar You are kidding, really.
- Lazova Yes, and I have collaborated with a colleague from Harvard University, and with him we studied benign nevi, conventional benign nevi and conventional melanomas, not the Spitzoid type, so this will help in difficult lesions that are not Spitzoid, any difficult melanocytic lesions in which making a histopathologic diagnosis is challenging, we can subject it to mass spectrometry and a diagnosis can be rendered with bigger certainty.
- Chagpar But for those patients who have Spitz nevi, you are really the world's expert, that is phenomenal, how common are Spitz nevi and Spitz melanocyte lesions?
- Lazova Spitz nevi are not very common, as I mentioned they are usually present in children, they develop in children and young adults, but sometimes middle aged adults present with these lesions and usually these are the difficult lesions. Let me tell you a story, I am discovering very interesting stuff with the mass spectrometry. For example, there was a patient who was a 50-year-old and a new lesion on the thigh developed for a year and a half. It was biopsied by the dermatologist, we examined it at the Yale Dermatopathology Laboratory, and we diagnosed it as Spitzoid malignant melanoma because applying all the criteria, the lesion was very large, there was no maturation of the melanocytes with their descent into the dermis, multiple mitotic figures, all of these features are for malignancy. We sent it out, we all looked at it at a conference, and everybody agreed it was Spitzoid melanoma, so we then sent it out to other experts, they agreed that it was Spitzoid melanoma and this was our diagnosis. The patient even had the micrometastasis in the sentinel lymph node. Then, of course, I included this patient as a Spitzoid melanoma in my initial study and this was one of the two cases that did not classify correctly. It was classified as Spitz nevus, so I said okay, the method is not perfect. It misclassifies this lesion as benign when it is malignant. However, I also received a Pilot Grant from the Gilead Foundation to sequence Spitz nevi and Spitzoid melanomas and this Spitzoid melanoma was included in the Gilead's study and it was sequenced and 11p amplification was found in this Spitzoid melanoma. Well 11p amplification is a genetic abnormality that has been only seen in Spitz nevi. Therefore, with two molecular studies, we have found that this particular case is not a Spitzoid melanoma but it is a Spitz nevus and it is behaving as a Spitz nevus, because the patient has been free of disease and well for years now with very thick 4.75 mm diagnosed at the time as melanoma.

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- Chagpar How interesting, how do you explain the micrometastasis in the sentinel node? I mean for me that was kind of a clincher.
- Lazova I agree, because we are not used to that. However, there have been multiple publications in the last 10 years or more of atypical Spitzoid neoplasms often metastasizing to the original lymph nodes, to sentinel lymph nodes mainly, and the patient being well for many years and nothing happens to the patient. It is a very interesting observation and it is difficult to explain. We have to call them by definition metastases, but they could basically be nevic rests because many years ago with breast cancer when lymph nodes were taken out from a patient with breast cancer, melanocytes from benign nevi are sometimes found in the lymph nodes and Spitz nevus is only one type of benign nevi. Why not rest small groups of these melanocytes from the Spitz nevus, it is okay for them to go to the lymph nodes if now the nevi can have melanocytes in the original lymph nodes. So there are a lot of questions that we have to answer and we are all studying that and many, many people in the field are studying that, but it becomes evident that these Spitzoid neoplasms often metastasize to sentinel lymph nodes, to original lymph nodes, but do not go beyond them and do not kill the patient.
- Chagpar Interesting, so in our last 30 seconds, I have one final question for you. Do you see a day when mass spectrometry and genomic sequencing will take the place of using the microscope to make these diagnoses?
- Lazova I do not think so, as much as I am optimistic about the results of the study, the dermatopathologists eyes and the pathologists eyes will still be the gold standard for many years, but the ancillary studies will be incorporated in the final diagnosis.

Dr. Rossitza Lazova is Associate Professor of Dermatology and of Pathology at Yale School of Medicine. We invite you to share your questions and comments with doctors Foss and Chagpar. You can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. As an additional resource archived programs from 2006 through the present are available in both audio and written versions at yalecancercenter.org. We would like to thank the Yale Cancer Center for providing production support as part of the connecting our communities initiative from Connecticut Public Broadcasting. I am Bruce Barber hoping you will join us again next Sunday evening at 6 for another edition of Yale Cancer Center Answers here at WNPR Connecticut's Public Media Source for news and ideas.