New Approaches to Diagnosis of Early Mycosis Fungoides
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Roberto Novoa, MD, FAAD, interviewed by Olayemi Sokumbi, MD, FAAD

OLAYEMI SOKUMBI, MD, FAAD: Hello, everyone. I am Yemi Sokumbi, Professor of Dermatology and Laboratory Medicine and Pathology at the Mayo Clinic, in Jacksonville. I have the pleasure of discussing with my colleague today, Dr. Rob Novoa, who is Clinical Professor of Dermatology and Pathology at Stanford University. Dr. Novoa and myself will discuss some of the challenges with diagnosing early mycosis fungoides and discussing opportunities and the new approaches to making early diagnosis. Thank you so much for joining me, Rob.

ROBERTO NOVOA, MD, FAAD: Thank you for having me.

OLAYEMI SOKUMBI, MD, FAAD: Perhaps to set the stage for our audience, we both know that making a diagnosis or an early diagnosis of mycosis fungoides can be challenging, particularly as we compare it to making the diagnosis of benign inflammatory dermatosis. When you think about this challenge as it pertains to your practice, what do you think our current limitations are in being able to make an early diagnosis of MF?

ROBERTO NOVOA, MD, FAAD: First of all, mycosis fungoides is a very heterogeneous disease, so that if you biopsy an area that's more heavily or less heavily involved, there might be more cancer cells or fewer cancer cells, so it can be sometimes hard to tell. Additionally, a lot of the treatments that we use for benign inflammatory diseases like corticosteroids can mask the lymphoma and can actually chase away the neoplastic lymphocytes from the epidermis, making a diagnosis much more difficult.—

--And it's clinically variable in appearance. It's one of those diseases that we should always keep in the back of our minds clinically, because it can be so varied in its appearance. While there are kind of classic presentations of those kind of patches and plaques on photo protected

areas, it can be quite varied in its appearance and so it can throw all of us for a loop, dermatologists and pathologists together.

OLAYEMI SOKUMBI, MD, FAAD: You're right. And you mentioned a few things that certainly ring true when we think about benign inflammatory dermatosis. We think about patches, plaques, certainly that falls in the realm of atopic dermatitis, psoriasis, a lot of our common dermatoses. And then, of course, depending on the stage and the timing of the biopsies, and most of our patients are on topical treatments so the histopathology also becomes quite challenging. We have our diagnostic criteria on histopathology. I wonder, what's your feature that you would like to see that you consider to be the most helpful when you're thinking through early MF versus some of the benign inflammatory dermatoses?

ROBERTO NOVOA, MD, FAAD: I can't tell you that there's one feature that dominates over all others. I wish it were that easy. I always kind of think of a circle that I'm kind of running through. I'm always double-checking myself at every point within this circle. So I start with the clinical, a history, and that clinical presentation. That's always, as we all know, really that clinical history is paramount for coming up with these answers. Next, I look at the histomorphology. So I'm going to be looking for the things that we all kind of classically learned in residency.—

--So that's the lymphocytes, those T-cells going up and into the epidermis. So that epidermotropism, perhaps some tagging of lymphocytes at the dermoepidermal junction. And then papillary dermal fibrosis. When it's present, that can be really, really helpful, especially in cases like Sézary syndrome, where there might not be quite as much epidermotropism, or in cases where the patient might have received topical steroids and so that might obscure some of the findings.—

--Then I will often use things like immunohistochemical stains to further figure out what's going on, so that CD4:CD8 ratio is a common tool that we will use. We have CD3, CD4, and CD8 and

compare that ratio. And then finally, do we need any additional ancillary studies, things like high-throughput sequencing can be helpful. If at any point in that cycle things don't make sense, I kind of run that equation over again, because I feel like there can be false positives and false negatives at basically every point in that cycle.—

--So from the clinical history, the histomorphology, the immunohistochemistry, and those ancillary studies, we can be led astray at any point of that cycle. Running it through in a circle always kind of helps to make sure that I'm coming up with the right diagnosis. If I had one feature that I had to pick that would be especially helpful, hmm, perhaps it would be the tagging of atypical lymphocytes at the dermoepidermal junction with maybe some (s/l Pautrier microabscesses), but nothing is perfect.

OLAYEMI SOKUMBI, MD, FAAD: I think I pushed you to make those comments because I do think, exactly what you mentioned, we love textbook diagnoses but if it was textbook, we wouldn't be having this discussion. So it's helpful to understand some of the features that maybe might be more reliable, maybe more common than others. Are you team shave biopsy or team punch biopsy for MF?

ROBERTO NOVOA, MD, FAAD: I am team multiple punch biopsies. I think that the sampling of different lesions from different parts of the body kind of gives us the most information. I would rather have that than a shave. I think it might be interesting actually now in the era of clonality to compare the yield when doing high-throughput sequencing for punch biopsies versus shave biopsies. If anyone out there is interested, we can chat, because I think it might be an interesting thing that if you are just doing a shave and you're limiting the amount of dermis and subcutis, that perhaps that would increase the yield by sampling more of the lymphocytes and maybe that would make a test like high-throughput sequencing more sensitive.—

--But as far as on pure histopathology, I really do like the punch biopsy. I think it gives me information about the hair follicle, about the adnexal structures, to make sure that there's no adnexotropism, and also making sure that there's no involvement of the subcutis, I know I have seen cases. So I'm getting skewed by being at a referral center for lymphoma, and so we see those aggressive cytotoxic lymphomas with angiotropism, with subcutaneous involvement. So I will admit that my sample is skewed and biased but my mind always goes to those kind of unusual cases where getting that full thickness punch biopsy was really helpful. How about you, what team are you on?

OLAYEMI SOKUMBI, MD, FAAD: That's a very good point you made, by the way. So same as you, the referral bias does impact my decision making. But for exactly the reasons what you mentioned, you see those scary cases where you have adnexotropism and you might have missed the eccrine glands. You might have missed the deeper involvement because you had a superficial shave. But for the folks who are in the community seeing true patches, a broad shave can be helpful. The caveat is to make sure that you are very familiar with the morphology of MF, because I have seen clinical cases that they look like thin plaques but on a punch, the adnexotropism doesn't represent what I'm seeing clinically.—

--So I think to be safe, particularly because you don't know the type of lymphoma you are dealing with, that a punch does give me that peace of mind that I have all the information necessary that allows you to be predictive about the type of lymphoma you are dealing with.

ROBERTO NOVOA, MD, FAAD: There's a case I've never forgotten during my first year as an attending of a young woman in her 20s who had undergone two heart transplantations and she developed this very refractory scarring alopecia all over her body and it had been called lichen planopilaris, like a lichen planopilaris universalis. And any time you hear an unusual disease like

this that you've never heard of, you always have to be a little alarmed. She had papules, plaques, and a lot of comedone and cystic lesions.—

--On the biopsy, I understand why it had been biopsied multiple times. There was this kind of dense lichenoid infiltrate but only focally. Some of the few hair follicles that had not been destroyed and really around the sweat glands could you see these (INAUDIBLE)tropism and adnexotropism that led us to make the diagnosis. Unfortunately, this woman passed away from her disease. So I think the adnexal structures can make a big difference in making the diagnosis.

OLAYEMI SOKUMBI, MD, FAAD: While you were talking, I noted that you mentioned briefly, you talked about immunohistochemical stains and you talked about we'll get into details about opportunities for clonality but we were talking about shave versus punch. Do you mind just sharing your perspective, because some could argue clinically MF is a clinical suspect, on biopsy you see all of the findings we talked about: Pautrier microabscess, tagging, you see papillary dermal fibrosis, all of the key features of mycosis fungoides, atypical lymphocytes that are epidermotropic.—

--IHCs follow the rules, CD4 greater than CD8, perhaps slight loss of CD5, perhaps loss of CD7. So a perfect picture, if you will. In that scenario, do you consider clonality testing? If you do, why? And make an argument for one versus the other in terms of the role of clonality in making this diagnosis.

ROBERTO NOVOA, MD, FAAD: I think that's another great question, especially in an era where we're trying to be conscious about the costs of care. I would say that in any patient who has kind of T1B or greater, so if they have an increased burden of disease, if they have more of a body surface area, certainly if they have any kind of nodules, I do think that it can be helpful to

do clonality in those cases, because when you find the neoplastic clone, that tumoral clone frequency, it seems to be helpful in prognosis.—

--So a TCF of greater than 25 percent has been independently associated with a worse prognosis. I think those patients who may go on to require stem cell transplantation, it can be helpful to have that clonality in order to monitor them over time and look for minimal residual disease. I think also there are some rashes that we get as a result of the treatment that we're doing for patients, so things like mogamulizumab, where the diagnosis can be incredibly difficult.—

--Where you get epidermotropic lymphocytes and you get skewing and there's already papillary dermal fibrosis from their old disease, so it can really be tricky. In those cases, clonality can be a lifesaver. But overall, do I think it's necessary every single time? Not necessarily. I do think if there is a clinical doubt about the diagnosis or if they have anything that might suggest more aggressive disease, then I think clonality can be helpful. But I think if everything is classic and they seem to have very limited disease, I think clinical discretion is a reasonable choice.

OLAYEMI SOKUMBI, MD, FAAD: You made the point that sometimes it can be challenging to emphasize to which is that clonality goes beyond diagnosis. People often think about the clonality testing as you need it to make the diagnosis of MF but, like you mentioned, if the clinical, the path, the IHC stain line up very okay, calling it what it is. But there is a role for clonality beyond the diagnosis as we sort of track disease, particularly more aggressive disease post stem cell transplantation.—

--And then the moga story, we can talk about it for days because that is one that really can look like MF and present and look like residual MF. And so you're left feeling and wondering is it recurrent disease, is this due to the drug. And so having that clonality tested is very beneficial in that arena. What are you doing these days?

ROBERTO NOVOA, MD, FAAD: I was just going to mention that our center was involved in some of the early descriptions of the moga-associated drug eruptions. There are a lot of these early cases where I was really worried about MF and where I told our clinicians, “Oh, my gosh, I think it’s undergone a phenotypic switch. It’s now a CD8-positive MF.” So just to give a little bit of perspective to the practicing dermatologist, mogamulizumab is an antibody to CCR4.—

--CCR4 is one of these chemokines that helps T-cells home to the epidermis. So when you treat somebody with this antibody, you’re wiping out the T-cells that are homing into the epidermis. So cells that express that include MF. But also some of the T-regulatory cells that live in the epidermis, these CD4-positive T-regulatory cells that live in the epidermis, those are also CCR4-positive. So some have hypothesized that by wiping out the CCR4-positive T-regulatory cells, you’re then getting an influx of CD8-positive cells in some of these kind of autoreactive rashes.—

--You get epidermotropism of these CD8-positive cells and it can look very confusing to us. So I’m glad that we figured it out to some degree. I was definitely wrong in those early phases and the clonality has been very helpful with figuring that out.

OLAYEMI SOKUMBI, MD, FAAD: So when you’re doing clonality testing, what approach do you use at Stanford?

ROBERTO NOVOA, MD, FAAD: We like to send specimens from two sites. I do think it’s helpful to get evidence of a shared clone between two different sites, just like with traditional PCR. And we will do HTS at this point pretty much for all of our patients. Instead of doing regular PCR, we don’t really do traditional PCR. If we’re going to get clonality, we’ll usually get HTS. We have an in-house platform that we use sometimes. We also will sometimes send to Adaptive, as well.

OLAYEMI SOKUMBI, MD, FAAD: Before you switched to HTS, were you previously doing PCR? How does that compare? What's your experience with both?

ROBERTO NOVOA, MD, FAAD: This has been something that's been in a bit of flux but the traditional sensitivity for PCR was quoted at being around 70 to 80 percent, with some studies suggesting it was as low as 44 percent in the cases (s/l of growing) mycosis fungoides. High-throughput sequencing seems to be more sensitive, exactly how much more sensitive, it's not yet clear.—

--It also just varies on how severe the disease is and what the definitions people use for mycosis fungoides. But it does appear to be somewhat more sensitive. There was an early study citing that it was 100 percent sensitive, I know it's not. I know it's not 100 percent sensitive. I've seen cases that were definitely cutaneous lymphoma that had negative HTS, so I know that's not the case. But I think it can be helpful. It's more sensitive in general. Also, it can give you, just as we mentioned earlier, information about the neoplastic clone, which can then be very helpful if you want to track disease over time.

OLAYEMI SOKUMBI, MD, FAAD: You did mention the extraordinarily, I guess maybe rare scenarios where PCR is negative, HTS is negative. What are some approaches that might be available for us to pursue a search for clonality, especially if your suspicion is high.

ROBERTO NOVOA, MD, FAAD: I do think it can be, again if we're talking about advanced disease, we're talking about pretty significant interventions. We're not just talking about clobetasol and PUVA or narrowband UVB. We're talking about stem cell transplantation or electron beam radiation deliverable to skin. At that point, it's comforting to have some kind of molecular evidence of disease.—

--One thing that has been helpful is using some of these kind of somatic panels to do sequencing to look for mutations. So that could be things like Foundation. That can be some of these in-house tests that we have. We have one here at Stanford, that's the Stanford Actionable Mutation Panel. UCSF and a lot of academic institutions have their own. Tempus has a good one, as well. So essentially you're looking for some of these typical mutations in MF (s/l to) these pathogenic mutations, and that has been helpful in a few of these cases.—

--They're unusual and uncommon, but if a patient has really significant disease that is going to require a significant intervention and you can't find a clone, that can sometimes be a helpful way of proceeding.

OLAYEMI SOKUMBI, MD, FAAD: You've taken us on a whirlwind, if you will. So early mycosis fungoides clinically mimicking benign inflammatory dermatoses. Key histopathologic features that we as dermatopathologists look for. We use immunohistochemical stains to help us out. Clonality testing can be helpful, particularly if it's not as perfect under the microscope and with our stains. PCR, an option readily available but of course, HTS now even more we're starting to see really increased adoption of that for clonality in early mycosis fungoides. Any key points that you think our audience needs to understand, clearly take away from this in terms of improving their yield of diagnosis?

ROBERTO NOVOA, MD, FAAD: As a clinician, if you're going to biopsy for mycosis fungoides, really try your best to have the patient off of topical steroids for I prefer three weeks from the areas that you're going to be biopsying. So I think that, first and foremost, really helpful. Secondly, make sure you include mycosis fungoides on your differential diagnosis to the pathologist, so that it crosses their mind. Because sometimes if they don't think of it, they won't look. And if they don't look, they won't make the diagnosis.—

--Third, I would say that if you're going to get high-throughput sequencing, sometimes some insurances might not cover this, so try to double-check to see if it's covered. Adaptive does have programs to help people pay for this test. Finally, when you do order these tests, they can be a little bit confusing to interpret. So there can sometimes be, they'll tell you two TCR-beta dominant sequences have been identified and then one dominant TCR-gamma sequence has been identified.—

--That is normal, that might just mean that there's just one neoplastic clone at that point. Because a neoplastic clone might have two rearranged TCR-beta alleles and just one rearranged TCR-gamma allele. So that doesn't mean that there's two clones. But patients can develop some intratumoral different new clones. So they can have point mutations or (s/l strain ship) mutations within that hypervariable region that we're testing.—

--So patients can develop multiple clones over time, so it can be really helpful to check between different clones and to look for that exact sequence. Finally, I will say the other reason I really like to have multiple biopsies is that there might be one biopsy that has the clearly dominant sequence. And then in the other biopsy, it might come out as polyclonal but when you look, the top clone in that quote, unquote polyclonal distribution is actually shared with it and is the same clone as the dominant one in the other biopsy. So I think getting multiple biopsies just increases the likelihood that you will find that top dominant sequence.

OLAYEMI SOKUMBI, MD, FAAD: So key points: holding on the topical steroids a few weeks, usually about three weeks. Doing the multiple biopsies certainly helps even with interpretation of the HTS testing, if you were to pursue that. And if you are doing the HTS testing, make sure that you look for insurance approval to minimize some of the complications we unfortunately have to deal with these days. Thank you so much, Dr. Novoa, for taking the time and discussing "New Approaches to Early Diagnosis of Mycosis Fungoides.: I enjoyed the discussion.

ROBERTO NOVOA, MD, FAAD: Thank you so much for having me, it was a real pleasure.