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Interstitial Pneumonia with Autoimmune Features (IPAF): A Research Classification

Dr. Johnson: This is CME on ReachMD. I'm Dr. Shira Johnson and joining me to discuss Interstitial Pneumonia with Autoimmune Features are our faculty from National Jewish Health in Denver, Colorado: Dr. Amy Olson, who is a Professor in the Division of Pulmonary, Critical Care & Sleep Medicine. Dr. Jeffrey James Swigris, who is an Associate Professor in the Division of Pulmonary, Critical Care & Sleep Medicine, and, Katherine Rosen, a nurse practitioner in the Division of Pulmonary, Critical Care and Sleep Medicine.

Welcome to the show today.

Dr. Swigris: Thank you.

Dr. Olson: Thank you.

Ms. Rosen: Thank you.

Dr. Johnson: Could you give us some background information on the IPAF classification?

Dr. Swigris:

I P A F, or IPAF, which stands for interstitial pneumonia with autoimmune features, is a classification, and I think what I would like our listeners to take away from this discussion today is just that. IPAF is a research classification, and the reason that IPAF came into existence is because what we were finding was that a number of groups from various academic centers were publishing case series on patients with similar clinical features, and those are features that make us all think about systemic autoimmunity and the possibility that a systemic autoimmune condition was driving the patient's interstitial pneumonia. And a number of groups put out these papers and each group seemed to use different criteria. And so, to get a better handle on what we were actually seeing and to provide some unity to classification criteria, a working group was formed, predominantly through the efforts of Dr. Aryeh Fischer, and so a multidisciplinary, multinational group was formed to come up with consensus classification criteria. And we could use these criteria to define this group of patients who seem to have certain features of systemic autoimmunity but who do not fulfill criteria for a diagnosable connective tissue disease, such as rheumatoid arthritis or systemic sclerosis, dermatomyositis, et cetera. So, in order to move the field forward in an attempt to study these patients, the thrust was really to develop classification criteria that we could all use in the research paradigm.

Dr. Johnson: Good background. So, what are the classification criteria for IPAF?

Dr. Olson: The presence of interstitial pneumonia by HRCT or surgical lung biopsy, the exclusion of alternative etiologies, and the patient does not meet criteria for a defined connective tissue disease and has to have at least one feature from the domains of Clinical, Serologic, or Morphologic perspective.

Dr. Swigris: Those domains, those Clinical, Serological, and Morphological domains – again, these were really made up and agreed upon by this working group. So, in the Clinical domain, you have things like mechanic's hands, edema of the fingers, and arthralgias. Again, things that would not meet other classification criteria for a defined connective tissue disease. So, we're not talking about bilateral, symmetric wrist and small joint stiffness, lasting greater than an hour that would meet criteria for rheumatoid arthritis. So, it's a bit more nebulous. It's, quite frankly, a bit more subjective. The Serological domain contains various autoantibodies, including ANA, Sjogren's antibodies, CCP antibodies, myositis-associated and myositis-specific antibodies, et cetera. And then the Morphologic domain consisted of interstitial pneumonia in a particular pattern. And a key point here is that if you meet criteria in a domain, you would be given a certain number of points. And what is sometimes misconstrued is that the presence of usual interstitial pneumonia or UIP, either on HRCT or surgical lung biopsy, does not allow one to meet classification criteria for IPAF, and that is not true. A patient can meet IPAF

classifications even though they have a UIP pattern. It's simply that the UIP pattern does not confer any points toward meeting the classification criteria. So, the Morphologic domain consists of interstitial pneumonia in various patterns, like NSIP or LIP, and that's either on CT scan or in a biopsy, or what we call multicompartment disease. So, lung docs and often rheumatologists think of the lung in various compartments. So, you have the airways compartment, the vascular compartment, the parenchymal compartment, the pleural compartment, et cetera. And when we see a patient who has multicompartment lung disease, that would be pleural and parenchymal disease, or pleural and airways disease, that is otherwise unexplained, you may – it would meet this Morphologic domain. So, you need to have findings – at least one finding in each of two domains in a patient with interstitial pneumonia who does not meet criteria for a classifiable connective tissue disease.

Dr. Johnson: A few years ago, Dr. Swigris, you published a single center experience on features and natural history of patients with IPAF. Could you summarize some of the study for us and tell us what you learned about these patients?

Dr. Swigris: Sure, and maybe I'll take this opportunity to expand on that because, like you mentioned, this was a single center, retrospective case series, 56 patients, the majority of them were women, never smokers, and they looked a lot like cases that were published by other groups. And I want to mention the so-called "Chicago series" or the "Oldham cohort"; this was by Justin Oldham and his colleagues at the University of Chicago. It is really cited much more frequently than our case series, but the members in each cohort were very similar – women, never smokers, a lot of circulating autoantibodies including ANAs and anti-synthetase antibodies, and nonspecific interstitial pneumonia was the most common HRCT pattern in our group. And I want to highlight some of Dr. Oldham's findings. And the one that I think is really interesting is that when Oldham and colleagues looked at their patients who met IPAF classification criteria and divided their cohorts in to those folks who had a UIP pattern versus an NSIP – a nonspecific interstitial pneumonia pattern – and they compared their IPAF subgroup with UIP to patients with IPF, so idiopathic pulmonary fibrosis, they found the survival no different between those two groups. And they compared their patients who met IPAF with an NSIP pattern to patients with CTD-related, so bona fide connective tissue disease-related NSIP, and it turned out that those patients with IPAF had a survival experience that was no different from patients with CTD-related NSIP. This suggests that maybe the IPAF criteria don't have a whole lot of benefit in terms of predicting disease behavior, and maybe it is the underlying histological or radiological pattern that drives survival and natural history of these folks. An important point, though, is that all of these studies that deal with IPAF are retrospective, and we have yet to do the studies that are needed that are the prospective studies to really determine if defining patients with IPAF or classifying patients with IPAF, if it really matters. We don't know that yet.

Dr. Johnson: What is the treatment approach for patients who meet IPAF criteria?

Dr. Olson: We think it's very important to realize that IPAF is a research classification and not a diagnostic classification. Within IPAF, there is a very heterogeneous mix of patients, and one treatment strategy is unlikely to fit them all. So, for now, as of September 2019, without additional data to inform decision-making, our recommendations are to treat the patient in the clinical summary diagnosis, not the research classification.

Dr. Johnson: Katie, Can you share with us some cases of patients who meet IPAF criteria?

Ms. Rosen: Sure. So, one – a 48-year-old woman who on CT has an NSIP pattern without organized pneumonia. She has a history of Raynaud's symptoms and has, on her serologies, a positive anti-CCP. Thus far, her imaging has not shown that she has any erosive joint disease, and she has no outward manifestations of a defined rheumatological disease.

Dr. Swigris: Let me comment, if I may, Katie, on that, patient. So, if we go back to the IPAF criteria, this is a woman with an interstitial pneumonia. She has an NSIP pattern on HRCT and that would meet a criterion in the Morphological domain. She has Raynaud's phenomenon which would meet one of the criteria in the Clinical domain, and she has an anti-CCP antibody, which would meet the criterion in the Serological domain. So, she actually has one criterion for each of the three domains. She could be classified as having IPAF. An interesting nugget of information, when anti-CCP antibodies were first discovered – when they first came out, Dr. Olson and I used to, used to tell these patients, you have rheumatoid arthritis. And because these were touted as being so highly specific for rheumatoid arthritis, and now we're finding they're not quite as specific as we once thought. About 30% of our patients with idiopathic pulmonary fibrosis have anti-CCP antibodies, and a small subset of those patients will go on to develop rheumatoid arthritis, but most will not. Regardless of that, this woman clearly meets criteria for IPAF.

Another example would be take a 65-year-old woman with longstanding Raynaud's phenomenon and anti-CCP antibody, but a UIP pattern on HRCT. Again, the UIP pattern does not give her a point, so to speak, in that Morphological domain, but she has Raynaud's phenomenon, which would meet a criterion in the Clinical domain and an anti-CCP antibody, which would meet the Serological domain. So, by definition, she has or meets IPAF classification criteria. One of the things that I like to bring up to people when I speak to them about IPAF is this lady, in my mind, has idiopathic pulmonary fibrosis. So, her clinical summary diagnosis is idiopathic pulmonary fibrosis. Her research classification is IPAF. We have no idea whether the presence of the anti-CCP antibody and the Raynaud's will

predict that she will develop a bona fide classifiable connective tissue disease, nor do we know whether those confer a different prognosis. So, we don't know whether she should be treated any differently than treating her as a patient with IPF. She certainly meets those criteria diagnostically, and that's how I would treat her. So, I would treat the lady with an antifibrotic and recognize that she has IPAF, she falls into this category that we need to study further to better understand whether we should be doing anything different for her.

Ms. Rosen: It's important for the patient to also be very well educated about these terms, especially if we're going to include IPAF in their note and the patient gets record of that, because I think it can be misleading and potentially misleading to whoever sees her out in the community. She needs to understand that her working diagnosis is IPF because we found that immunosuppression was, in fact, harmful to these patients before the advent of antifibrotic therapy.

Dr. Johnson: What can be expected in the future related to IPAF? Will this become a clinical diagnosis or what's the implication for clinical practice?

Dr. Olson: Well, we definitely need prospective research to determine if the classification system matters, to determine if the natural histories of different subgroups meeting IPAF criteria behave differently, and to sort out whether the criteria should be changed. For example, people have raised the question about whether esophageal dysmotility should be included in the clinical criteria, and how to assess it. What are the cutoffs? Mild, moderate, or severe? So, I still think we have prospective research to do to determine more meaningful information from the criteria that we have developed.

Dr. Johnson: Of course. That's a great way to round out our discussion on Interstitial Pneumonia with Autoimmune Features, IPAF, A Research Classification. I want to thank my guests for helping us better understand interstitial pneumonia with autoimmune features, IPAF.

Dr. Olson: Thank you.

Katie: Thank you.

Dr. Swigris: Thank you.