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Idiopathic Pulmonary Fibrosis: The Role of Radiology in Accurate and Timely Diagnosis

Announcer Open:
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Dr. Chung:
Welcome to today's continuing medical education webinar, Idiopathic Pulmonary Fibrosis; The Role of Radiology in Accurate and Timely Diagnosis. My name is Jonathan Chung. I'm Professor of Radiology, formerly at University of Chicago, and I will be the Incumbent Divisional Chief at University of California, San Diego. And I want to introduce Dr. Seth Kligerman, who will be giving this talk with me, who's Professor and Chair of the Department of Radiology at National Jewish Health.

These are disclosures. I have no relevant financial disclosures, and Dr. Kligman has these disclosures. So, he's a consultant advisor and speaker for Beringer Ingelheim and an independent contractor for Bayer.

So, these are learning objectives and so if you can integrate the current guideline-based high resolution CT patterns when making the diagnosis of IPF, idiopathic pulmonary fibrosis, you can identify clinical and imaging conditions that mimic the UIP pattern in HRCT scans, and you can also discuss how multidisciplinary discussions improves accuracy and confidence in making the diagnosis of idiopathic pulmonary fibrosis after this talk, I feel like we would have been successful.

Alright, so now we'll be getting to the meat of the talk. And so those pre intervention questions are important, right? So, I think they will sort of guide you on what we think is our important points within this talk. But let's go ahead and first start with the current guideline-based CT patterns and the diagnosis of IPS. So, before we really talk about the patterns in our HRCT interpretation, we probably should talk about idiopathic pulmonary fibrosis. Just to get everyone on the same page. So, idiopathic pulmonary fibrosis, which I will just call IPF from now on, given how long it is, how difficult it is to say that, because it's a very winded, diagnosis here. IPF, it's a chronic progressive pulmonary fibrotic condition, and as you can infer from the name, it's of unknown cause. It's a relatively rare condition, but the incidence is increasing more recently, probably with the increased use of CT scans in modern day medicine. The previous data suggests that the median survival of patients with IPF is around 2 to 3 years, though I think most people agree that's probably a little bit longer than that.

But that being said, the prognosis is still very poor. We now do have antifibrotic agents which have been shown to decrease the rate of worsening in patients with idiopathic pulmonary fibrosis, and likely also helps in terms of survival. The UIP pattern, also known as the usual interstitial pneumonia pattern, is the imaging and histological correlate for idiopathic pulmonary fibrosis, though obviously, the UIP pattern can be due to other causes as well. But most cases of UIP really are going to be due to idiopathic pulmonary fibrosis. And as we all know, HRCT really is the gold standard in terms of imaging every pattern of pulmonary fibrosis, including idiopathic pulmonary fibrosis.

In terms of demographics, idiopathic pulmonary fibrosis more commonly effects men. It's a disease of older people, so it would be very,

very uncommon to get idiopathic pulmonary fibrosis in say, some in their 40s or even someone in – in their lower 50s. These patients tend to be older. Also, there is an association with smoking, but not a one-to-one-type association, like with emphysema. We just know there is a strong link between the two.

In terms of clinical presentation, unlikely to really make a diagnosis based purely on physical exam. But very often patients with significant pulmonary fibrosis, even aside from idiopathic pulmonary fibrosis, you're going to hear crackles on auscultation. But these other things, these are common to other pulmonary conditions as well, things like chronic dyspnea, dry cough, digital clubbing. These are not specific findings, which often leads to a delay in diagnosis of patients with idiopathic pulmonary fibrosis. Every once in a while, a patient will actually present acutely with like, an acute exacerbation of their underlying idiopathic pulmonary fibrosis, but that's actually a rarity. Most of the time, they're going to present in the chronic setting.

Alright, so we mentioned HRCT being the gold standard way to image these patients. And so really, what is an HRCT? What differentiates an HRCT from a regular chest CT? Well, number one, we don't give contrast for HRCT. We're really looking to lung parenchyma, and we don't need contrast in the lungs, really, to bring out that. A purist would actually say that if you gave contrast, you might actually cloud mild central lobular findings within lung parenchyma. That might be a little bit too strict in my mind, but really, you don't need to give contrast. If you don't need to give contrast, you don't give it, because, obviously, anytime you administer anything to patients through their intravenously, you risk them having an adverse reaction to it.

Also, with modern DA scanners, we're going to do a volume metric acquisition. So, we're going to be able to get that data and we're going to be able to reconstruct it in any plane and any slice thickness that we want up to a certain level. Because these are HRCTs high resolution chest CT scans, we're going to reconstruct the chest CT very thin. So, we reconstruct typically around 1 mm, but I've seen other people do sub millimeter, but anything less than 1.5 mm or at 1.5 mm or less is acceptable.

In terms of the number of acquisitions in addition to the regular supine inspiratory scan, we can also do the expiratory scans, and we can also do supine scanning. And so, why do we do expiratory scanning? The one real reason to do it is to look for significant air trapping. If you have significant air trapping, it actually draws you away from diagnosis of UIP, and more toward alternative considerations. Specifically, the most common thing we think about is hypersensitivity pneumonitis.

And then, in terms of the pro imaging, why we do that? Well, the lungs, even though they're mostly filled with gas, they do have some weight to them. So, along the posterior aspect of the lungs, when you're supine, you can get a little bit of atelectasis, and that can obscure some mild underlying fibrosis or other mild interstitial changes. And so, to open those areas up, we put the patient over onto their belly, and we'd scan through the at least through the lung base, but some people actually do through the whole thorax to make sure we're not missing something within those posterior aspects of the lungs.

You obviously can reduce radiation dose, though I say that you should actually be a little bit cautious of doing this. I've seen some people be maybe a little bit too aggressive in terms of using reduced radiation exposure or using a very heavy, yeah,construction filter because this can sometimes mask some mild interstitial lung disease, or make it just look different where the eye won't be able to discern things in the same way that you would if you were using normal filter with the normal amount of radiation photons. So, be a little bit careful the radiation and reducing radiation dose but certainly we want to follow that LR principle.

OK. So, in terms of reporting HRCT, you want to use standard terminology, you can't just make up your own words. You got to use what's described in the Fleischner Lexicon. When you have the HR – when you have the HRCT in front of you and you're trying to describe what's going on, also want to talk about the distribution and the severity. And we'll talk about the distributions in just a bit, a few slides from now. There are multi-society guidelines out there. There's A – the ATS multi-sided guidelines, and then there's a Fleischner Society Guidelines for categorization of the UIP pattern on imaging. And so, you should follow those guidelines, and Dr. Kligman will go into detail in just a few slides from now.

If it doesn't look like UIP. So, we talked about UIP. UIP is a very important pattern and remember, UIP is the imaging histological correlate of idiopathic pulmonary fibrosis. But it doesn't look like, that actually looks like something else, we can invoke these other categories. And again, Dr. Kligerman will go into this. But things like, the other categories are, indeterminate for UIP and the alternative diagnosis. If it doesn't look like UIP, you should try to create a differential diagnosis or, in some cases, a specific diagnosis, if it's a classic for some sort of alternative condition, like hypersensitive pneumonitis, or certain types of connective tissue disease, or some other phenotype.

UIP, as I alluded to before, it is an imaging histological pattern, but it, in and of itself, is not diagnostic of idiopathic pulmonary fibrosis. Most cases, again, of UIP will be due to idiopathic pulmonary fibrosis, but not all cases. So, here we have our differential diagnosis for pathologic UIP pattern. IPF is the first thing there, but other things can cause as well, including collagen vascular disease, specifically rheumatoid arthritis, more than systemic sclerosis. I've all seen mixed connective tissue disease giving you a UIP pattern of pulmonary

fibrosis. Chronic fibrotic hypersensitivity pneumonitis can certainly give a UIP pattern. But a bunch of other things can give you this pattern as well.

Once you have an HRCT, it can be pretty overwhelming. So, probably were 1,000 images in that HRCT scan, depending on how you reconstruct things. It could be almost for someone who is a relative neophyte to HRCT like, so daunting that you maybe we just want to put it back on the list, right? And just click off it because we don't know how to approach it. This is a very simplified way of how to approach HRCT in a sort of, an algorithm. And this is what I teach my residents, this is what I teach my fellows, and I think it's tried and true. I think it works pretty well.

So, first of all, you want to figure out the main patterns are. So, what are the findings? Is there reticulation, ground-glass opacity, consolidation, air trapping. You want to get all these findings. What are the major findings? And we're not saying you have skipped every – you don't have to, like, calculate every single finding because most HRCTs are going to have a little bit of ground-glass here, a little bit of reticulation there. We're talking like, what's the main findings, the main handful of findings there.

Once you have those, you kind of put that in your back pocket and you figure out the distribution of disease. And so, where is the disease most preponderant? Where is it – where is it affect – where is the majority of disease? And there are really two planes that we worry about in HRCT. There's the axial plane, so the axial plane is where we're cutting through the C – the patient while they're getting that CT scan, and everyone's familiar with that. But then, also, there's zonal plane. Really that – that's the superior inferior plane. So, in the axial plane, we want to determine is it peripheral, is it central, is it diffuse? That kind of idea. Is it peripheral with subpleural sparing, which we diagnostically usually will consider, like central and preponderant. And in the superior interplane, or the zonal plane, we want to know, is it upper, mid, lower, or diffuse in terms of the preponderance of disease? And then, you can integrate the other imaging findings or clinical data. So, it's not just about looking at the lung parenchyma, you also look at other things like the esophagus, the chest wall. Obviously, if you have someone with pulmonary fibrosis at the lung basis, and they have a really dilated esophagus, and you could tell that based on the spine they're actually young patient as well, you're already thinking, ah, this patient may have connective tissue disease, specifically systemic sclerosis, because we know these patients oftentimes will have associative esophageal dysmotility, which on CT manifests as diffuse esophageal dilation. So, things like that. Just being a detective and getting all the information available to try to reach the most accurate diagnosis for the patient.

In terms of the fibrotic patterns, what are we talking about? So, you got to use the lexicon, right? So, I'm sure you guys are aware of these – of these specific findings, but this is the language that you want to use in your HRCT report, and this is the one that you probably want to create for yourself in your mind. Because all of these different patterns that we'll talk about later, are based on these fibrotic patterns combined with distribution. So, you need to use a lexicon. the first pattern most common is the earliest finding of pulmonary fibrosis is reticulation. For those of you guys who took Latin, you guys know that the root retae means lattice-like, or net-like pattern, and what it is referring to is these tiny little lines superimposed on each other, which is the earliest finding of pulmonary fibrosis. When you have associated traction bronchiectasis and bronchial, or bronchiolectasis, which will manifest as, essentially, irreversible airway dilation or tiny little cysts in the peripheral area of lung, superimposed in reticulation, you can be pretty sure you're dealing with a case of real pulmonary fibrosis.

The next thing we look for, is honeycombing. So, honeycombing really is end-stage pulmonary fibrosis. So, these are going to manifest as these subpleural regions of fibrotic cyst, usually smaller than a centimeter lining up in rows or stacking upon each other. And we're going to see a zillion examples of honeycombing, so don't worry about that if you're confused about what I'm saying.

And then other important non-fibrotic findings we want to look for, because these oftentimes will draw us away from a diagnosis of UIP and more to our alternative diagnosis, include ground-glass opacity, mosaic attenuation and consolidation. For those of you guys who need a little refresher, remember, ground-glass opacity just means white stuff in the lungs that's translucent, so you can still see it through the underlying through the the white stuff to see the underlying pulmonary architecture. You can still see the vessels through the white stuff, so it's just this hazy whiteness. And consolidation is really just the same side of the coin – or the different side of the coin, where it's white stuff in the lungs, but it's so dense you can't see through it anymore. So, essentially, it's opaque. So, the underlying architecture is obscured by the consolidation.

I talked about these distributions already, but I'll mention them again. So, remember, in the there's two planes that we worry about. The the axial plane and the zonal plane. In the axial plane, where you want to see is the lung disease peripheral, is it central, or with – peripheral with subpleural sparing, or diffuse? And in the zonal plane, is it upper, mid, lower, or diffuse? So, you get the findings, the main patterns, combine it with the distribution, and then once you have done these two steps and you've done it accurately, you should be able to figure out what the pattern is.

And so, here's a nice example. So, on the left-hand side, we have the prone image, on the right-hand side we have a sagittal image, and clearly, we have areas of fibrosis reticulation with subpleural honeycombing and traction bronchiectasis and bronchiolectasis at the lung

bases. The honeycombing are these areas of subpleural cysts which are lining up in rows and stacking upon each other. There's also a little bit of emphysema within the lungs as well. These are actually examples of MinIPs, so, not MIPS, MinIPs, minimum intensity projected images, which bring out these low-density areas. So, we're trying to highlight these areas of honeycombing and some areas of traction, bronchiectasis and bronchiolectasis. So, a nice example here of honeycombing. I'll tell you; this is a UIP pattern of pulmonary fibrosis, but again, this is just a little teaser because very soon Dr. Kligman is going to go into a more comprehensive description of these different patterns of fibrosis.

And with that, I will throw it to Dr. Klingerman.

Dr. Kligerman:
Thank you, Jonathan. So, I'm going to be following up and talking about, basically the categories of IPF, or UIP pattern, and then talk about clinics – uh – clinical mimics of the UIP pattern.

So there are two main criteria. As a radiologist, I tend to use the Fleischer Society but using the ATS criteria works as well. And as you can see with the case on the left, there's lower lobe predominant, it's subpleural, there's honeycombing, there's traction bronchiectasis. Like 75% of these patients, a good chunk, this patient's a smoker. And one thing that people always ask is, at what point – you know, a lot of these smokers with IPF tend to have paraseptal emphysema, and the question is, when does honeycombing, as it's creeping up, become paraseptal emphysema? And the answer is who knows? I mean, it's very hard to tell. If the cysts are quite larger in the upper lobes, thinking more paraseptal emphysema, but at some point, they're going to meld together and be quite difficult.

So as Jonathan was saying, the distribution and the categorization is very similar between the two criteria. Both are basilar and subpleural predominant. Heterogeneous, but it could be diffuse. Basically meaning, that it could be asymmetric sometimes could be, you know, a lot of mid-lung predominance, but it usually is symmetric. Honeycombing is what really differentiates the definite UIP pattern from the probable UIP pattern, which we'll talk about. And then, peripheral traction bronchiectasis/bronchiolectasis, i.e., permanent airway dilation due to the alveolar collapse in this condition.

Now, one thing that's important in the Fleischner Society, they add reticulation something that's not in the ATS criteria of articulation, as we know, and is the first finding that we see in fibrosis. And then very importantly, absent features to suggest an alternative diagnosis lots of ground-glass, extensive mosaicism, dilated esophagus, so on and so forth, which we'll talk about a little bit later.

So, this is our typical beautiful UIP pattern. Uh, lower lobe predominant. You can see the stacks of pleural cysts. If we could follow out these airways, we can see in the left upper lobe, this dilated airway. And one thing that Dr. David Lynch points out, which is actually very helpful, is that even – even though this disease is a lower lobe, subpleural predominant, you often get, or should get, quite pronounced involvement of the anterior aspects of the upper lobe. So, if you don't have anterior involvement of the anterior aspects of the upper lobes, and just dependent abnormality in the bases, you know, something may be a little bit odd. But usually, in almost all condition – all instances with a typical UIP pattern, it really is going to be lower lobe predominant. But you will see that anterior upper lobe disease as well.

So, what are some of the pathologic hallmarks of someone with UIP? Here isa nice just coronal image of someone with kind of large honeycombs something we'll talk about a little bit later, but lower low predominance. We can see that the airways are dilated, there's traction bronchiectasis/bronchiolectasis. It does extend into the upper lobes. But what I want to point out here is what the patients explant looks like. So, you can see more centrally, kind of more around the central portion around the peribranchiovascular interstitium centrally, the lung it's going to be abnormal pathologically, but it appears slightly more normal. As we get to the marked periphery of the lung, along the inferior surface, posterior surface, as well as the anterior surface, we see this very yellow-grayish stuff, and this is end-stage fibrosis on gross imaging. It's really destroyed lung. When you zoom in on it, you can see all of these little cystic areas, and these cystic areas are what makes up the combination of both traction bronchiectasis and honeycombing that we see in traction bronchiolectasis, and honeycombing that we see on imaging. And it's important to remember that honeycombing pathologically: what the pathologist sees in honeycombing: what we see, even though they correlate very well, they are not the exact same thing. So, we see these large cysts. And when the pathologist is looking under microscope, he's seeing these very small, you know, cystic areas, which we'll talk. So, on a slide or two coming up.

So, the pathologic hallmarks of UIP – again, I'm not a pathologist. I've worked with many over the years – is something called spatial heterogeneity. So, with diseases, or I don't want to say disease, but with fibrotic patterns like NSIP, you see a spatially homogeneous pattern. So, the fibrosis looks very similar throughout the lungs. You don't see these, really, areas of end-stage fibrosis with extensive secondary lobular collapse like you see here. But anyways, you see this really extensive area of alveolar collapse, secondary lobular collapse, here, and then right next to it, you see an area that isn't normal, but is much less involved. You can see the normal or some alveolar walls a little thickened, but you can make out the normal architecture. You're not going to see that in someone with an NSIP pattern of fibrosis.

And then, here is the honeycomb cyst, which they see pathologically. And we know that pathologic honeycomb cysts actually represent these pinched off terminal bronchioles. That was something that was kind of debated for many years, but this – not only did some gross pictures like this, where you can see an airway extending into the honeycomb cyst, the honeycomb cyst will be lined by epithelium that has undergone some changes, but usually there's some hint of some respiratory epithelium along the edges. But importantly, when people do certain genetic analysis of the wall, they realize that the makeup of the wall is actually respiratory epithelium that you would see in a terminal bronchial. Surrounding that are these areas of these kind of band-like purplish area of that look like organizing pneumonia. Now, if we put this in the middle of the alveolar - alveoli, we would call it organizing pneumonia, but if you put it in the interstitium, we then call that a fibroblast – against the honeycomb space, we then call that a fibroblastic focus.

So, other things, again, this is a condition secondary to extensive alveolar collapse. So, instead of seeing big open lobules with thousands of alveolar walls, it has all collapsed down. So, you can see the makeup here is an artery in the middle here's another artery in the middle and next to that is a collapsed airway and all this secondary lobular collapse. Something that you really tend not to see in other patterns of fibrosis.

So, volume loss is, again, a big thing that you see. Now, we all know that the lower lobes should be your largest lobe. I mean, that's where most of your air flow goes. Um, in this case, yeah, this patient does have some emphysema, but you can see the dramatic volume loss in the right lower lobe, right? So, the right lower lobe should be the biggest, and here it's by far smallest. It's basically the same size as the right middle lobe, and that's because that's where the majority of alveolar collapse is, and so we see this pronounced volume loss in the lower lobes, which is what we see on imaging. Now another thing I'm going to point out here, this isn't in the Fleischer criteria or the ATS criteria, it's just something I want to point out. There's been a couple of nice radiologic pathologic papers that have come out in radiology that have shown, when you see these areas of nodular what look like calcification within the areas of fibrosis that are very fine nodules, these are actually areas of nodular ossification. This is actually metaplastic bone formation. And the pathologists and radiologists at UCSF did a very nice study where they looked at a bunch of these cases with this dendriform – well, it doesn't have to be dendriform ossification. That's one pattern of ossification. But with these patterns of ossification, if you see this within the fibrosis, it is much more likely to be a UIP pattern of fibrosis than any other pattern of fibrosis. So, if you're kind of debating and you see extensive nodular ossification, something that may kind of push you towards one side or the other.

And then the question about honeycombing, you know, and this is something that came out a while ago – how good are we for distinguishing honeycombing? And you know, the study came out showing that radiologists, the agreement value wasn't that great. You would think that our kappas would be fantastic, that we'd have excellent agreement and in a lot of cases we do, and in some cases we don't. I think the case on the – on the right here under B, these are very large areas of, I wouldn't even call them cysts, they almost look like bullish changes. There actually is architecture inside of these areas. This is going to be something we often see with airspace enlargement of fibrosis, something often we see with smoking. It's really not honeycombing. But what about the case on the right? I mean, we clearly have traction bronchiectasis. There's some subpleural cystic change. Some people called this honeycombing, others did not. So, it's not always easy, especially when it's intermixed with smoking-related lung disease. And when we get these bizarre looking cystic structures, a lot of people say, oh, it's cystic, it's sub plural in the lower lobes, it has to be honeycombing. But we know that's not true. Look for other signs. Look for the traction bronchiectasis, look for your volume loss, look for your reticulation, so on and so forth.

Here's just an example of something that was called honeycombing, and you can see that here is this cystic area. But one thing that you often will see with these areas of airspace enlargement with fibrosis, which is a smoking-related process, which basically means you get pronounced fibrosis in the alveolar walls, so the emphysema looks more cystic. It looks like it has walls to the emphysematous spaces. In a lot of cases it will appear to almost spare the subpleural portion of the lung here. But here you can see, on the sagittal image, that we actually have sparing of the inferior lung, the costophrenic sulci are actually normal. And this is something that is in the upper lobes in mid lung, and there's also no fibrotic changes with this. There's no traction bronchiectasis and this is something we're recognizing to be secondary to smoking, which this patient has, and not actually honeycombing. But again, it could be really difficult. You got to spend time, look at this, realize that these actually are not cysts, that these are actually just dilated secondary lobules. You can see the pulmonary arterial in the middle of them. It's not a cyst that you see in honeycombing.

So, you know, here is more examples. You know, the right, patient's a smoker. Now in this case, there's clearly traction bronchiectasis, there's clearly fibrosis here. There is subpleural reticulation. There's volume loss. The fissure is pulled down. But I'm not calling this stuff on the right, or at least on this image, I'm not calling these large areas with internal structures honeycombing. Now on the left, you know, is this honeycomb? Is this a honeycomb? Um, I, you know, it's hard to tell. I don't know on this one. This would be an interesting one to ask a bunch of colleagues on this one slice. You know, as you scroll through, there may be other areas that are more consistent with honeycombing.

There's definitely fibrosis. It is definitely lower lobe predominant. I'm going to call it either a probable UIP pattern, if not a definite. It depends if there are areas I can definitely say is honeycombing. You know, this one on the mid portion on the right, again, these areas of cystic change. There is some bronchiectasis, some volume loss. But, you know, I would not call this honeycombing. These are very funny, bizarre-shaped lobulated cysts. There's a lot of emphysema. It looks like the paraseptal emphysema we see in the upper lobes. But again, you're going to see some debate over this.

Dr. Chung:
Yeah, I'm with Dr. Kligerman, there. That's a hard one, like on left side. On the right side, though, not. We would just call that emphysema with maybe a little bit of, you know, scarring. You know, or airspace enlargement with fibrosis, you know, that kind of morphology up on the left probably maybe. I mean it's hard.

Dr. Kligerman:
It's hard.

Dr. Chung:
But well, I'd probably call it some honeycombing on the left, but again, there's going to be a lot of inter-reader variation with this.

Dr. Kligerman:
And this is one image. I could tell you, if you scroll down, there was areas of clear honeycombing so, it did. But, on this one image it's tricky, right? So, and –and there are cases where it's just, this is all you see throughout and you're wondering. And yeah, people will go back and forth.

Now here's a 60-year-old woman with dyspnea. And this is something that Jonathan wrote up, which actually has changed a lot of our perceptions and things we see with relation of primary causes of UIP i.e., the idiopathic form, meaning we haven't figured out what the causes yet, and secondary causes, most notably connective tissue disease. So, you can see here this is a kind of a curved sagittal. Let's try to show the lower lobes and try to show how straight this demarcation is between this area of very pronounced honeycombing and the lung right next to it, which almost looks normal. I mean, yeah, right next to it maybe not, but you go a couple of millimeters above it and, you know, there's no honeycombing. And this is something Jonathan described with the straight edge sign. but the other thing which we noticed – so, there's clear honeycombing. I think everyone who's a chest radiologist can call this honeycombing. Um, but one thing I've noticed in a lot of these cases, just as in anecdotally, is that even though there's such extensive honeycombing, and a lot of these cases that turn out to be secondary causes, connective tissue disease, like this case, which we'll talk about, you would expect exuberant traction bronchiectasis and bronchiolectasis with this degree of honeycombing, but these airways are mildly dilated at best.

You could see even out here, these little airways, these little bronchi and bronchioles, if you follow these up, they do connect. They're not the severe bronchio – like the last case I showed you that had, you know, no, honey – these airways are dope – totally pulled apart. And here, it's not. So, that's something else. But then there is, So, anyways, this patient, if you look at it, and this is where it gets confusing because we would look at this in imaging and say this is a UIP pattern. I mean, it's UIP. There's honeycombing, it's lower lobe predominant, it's subpleural. But this is just going to show you that not just because we say it's UIP doesn't mean that that's where it ends. Their findings here the straight-edge sign exuberant honeycombing that point towards a secondary cause. But this is where the multidisciplinary diagnosis discussion comes in. Because, you know, you would look at this say it's UIP. But again, UIP is not always synonymous with IPF. And here's the patient's, you know, labs and they're positive for everything. They had a mixed connective tissue disease.

So, here you can see the straight-edge sign very nicely. You can see the apical anterior involvement, which is also – you often they are connected and – but often – which is also interesting. The UIP fibrosis, the ones that are IPF, the fibrosis that I was talking about anteriorly tends to be more here, where it's a little bit different distribution than that honeycombing, we tend to see in people with secondary causes of UIP the – with connect tissue disease. But you can see these very large honeycombs cysts, straight-edge sign, and anterior upper lobe honeycombing. This stuff up here. So, a very important paper written by Jonathan.

So, what about ground-glass? Right? We see ground-glass in UIP. We see it. Fibrosis – fine fibrosis can appear as ground-glass. And the question is, when is too much too much? And that is something that you'll get a lot of disagreement with. This case looks like a lot of ground-glass to me. I see a lot of ground-glass in the fibrosis. Exuberant traction bronchiectasis and bronchiolectasis, clear honeycombing. But there's a lot of ground-glass. So, is this just a case of UIP/IPF with ground-glass? Is this a secondary cause like someone with a connective tissue disease, or is this patient having an acute exacerbation? Is this their early onset of their acute lung injury? And it's really hard to tell, and this is where, you know, I have to give a differential diagnosis. You know, we're not perfect. I say, geez, a lot of ground-glass. It's UIP pathologically, I'm sure about that, but I'm not 100% sure it's IPF. You know, you need to do a full

work up.

So, let's talk about the cases of probable. So, everything is pretty much the same between ATS and Fleischer. They show the same thing. But the only difference is we have no honeycombing. We still see that lower lobe subpleural predominance. We see the reticulation. So, here if you see the ground-glass is all within the fibrotic areas. The areas that are less fibrotic, don't have the ground-glass. You see the – still see the traction bronchiectasis and bronchiolectasis, so it basically looks like what we saw before, just no honeycombing.

And here are more cases with probable UIP pattern. You know, this one, it's asymmetric. We can see asymmetric disease. Unilateral disease, I've never seen. Asymmetric disease, we will see. This one, you know, lower lobes, subpleural predominant. There's anterior fibrosis. There's honey - paraseptal emphysema in the upper lobes, there's central lobular emphysema. There's no honeycombing. But what Jonathan has shown in some of his very important chess papers is that even though there's not honeycombing in the appropriate clinical context, i.e., all the markers for tissue – connective tissue disease are negative, there's no evidence that there is any findings of hypersensitivity pneumonitis clinically that you probably don't need a biopsy because the vast majority of these are going to be UIP pathologically. Even if you had positive serologic markers, still a fair amount of these that you biopsy are still going to be UIP with this pattern.

So, why not biopsy them? I always say, like, I love RAV PAF correlation, so I'm like, dude, just biopsy them. It's not innocuous. Um, bad things happen to people that have undergo lung biopsies, especially older people who have UIP. So, those are the patients who have the worst complications. Smoke – older male smokers with UIP/IPF. Those are the ones who do worse. So you know, as much as I would love that path on everybody, it's not an innocuous procedure. In some cases, you need it. Some cases it's – you're not sure the imaging is unclear, and you have to do it, but that – that's really the reason. It is – it is a major thing. And then, people talk about well, what about, um – uh, cryo biopsies. We did cryo biopsies at UCSD. I have to say, the amount of good samples that were diagnostic were very limited. Um, they do bronchoscopic biopsies – same thing. You need a large amount of tissue to make this diagnosis. You can't have this little fleck of stuff.

So, what about this? And we see this, and if this and it's kind of weird because if the patient is symptomatic and they're coming in with a cough and shortness of breath, you know, we're supposed to call it one thing, and if the patient is asymptomatic and there's no findings, then we would call this interstitial lung abnormality. I don't want to get into that. But let's say you saw a case like this where there is mild fibrosis. You can see there's – this airway is a little dilated, there's some subpleural reticulation. It's super mild. It's very mild. You know, here – right here it's a little dilated. I mean, it's not bad. So, what do you do with this? Right? So, there's really two things that I call indeterminant that, if someone who comes in is symptomatic, where it's just too early to tell. There's just something there, it's mildly fibrotic, and I don't know. It could be this patient could live another 20 years and have CT's every year and it's not going to change, and then other times it will. And then there's other ones that are, they have findings that kind of look like UIP, but there's things that are weird about it. I had a case today that I'm – that my second-to-last case to today that I use the indeterminate pattern on. So, and this case kind of looks similar-ish to it, although mine was a little bit less – more bizarre-looking.

So, there's subpleural cystic change. Is it honeycombing? I don't know, maybe. I don't know. I, again – how – there's – this patient's a smoker, there's this stuff, it's small cystic stuff. A lot of people call this honeycombing. I actually did call this honeycombing. But there's sparing of the costophrenic sulci. You don't see spare – UIP/IPF needs to involve This is where – the first part that's involved is the inferior costophrenic sulci. This shouldn't be spared. This big area has is basically hyperlucent, there's a lot of ground-glass. So, there's a lot here that says I'm pretty sure, pathologically, this is going to be UIP, but I'm not really sure that it's going to be IPF. Now, this patient underwent an extensive workup. Everything was negative. No history of any exposure, no connective tissue disease. They weren't sure, and it was progressing, so this patient did undergo a biopsy, and the biopsy said it was UIP. So, this was – eventually came out to there was no signs of peribronchiolar granulomas or things to suggest hypersensitivity, and it was just said UIP.

So, we just labeled this a bizarre, atypical pattern of IPF and that's what was used to diagnose with. So, these are ones where you're just not sure, something is weird. And I had a case like this that did have some lower lobe honeycombing, but there was a lot of ground-glass and there was a lot of just, a – a couple of weird things, a couple of nodules. It just was odd. There were things about it that I didn't want to say, you know, I think this is going to be a probable or definite UIP pattern. It was just a little bit off. So, you know, if you're not sure and it's a little bit bizarre, don't be afraid to use the indeterminate pattern.

And here was that case I showed you before. So, here's 2007 with that little bit of schmutz at the base, and here the patient is in 2019 with the classic UIP pattern. A hundred – you know, this is typical UIP lower lobe subpleural honeycombing. And now if this patient came in incidentally and we saw this, let's say on an abdominal pelvis CT, or patient came in with a mild cough, we would now call this interstitial lung abnormality, and we know that a fair amount of these patients will progress to this fibrosis. And this also shows us there's a lot of lead-time bias between when we initially make the diagnosis. I always akin UIP/IPF to almost, like, renal failure. It takes a big

whack for, you know, you have to lose a fair amount of your lung before you really become symptomatic, just like with renal failure. You could go on for years and it's on until you have a creatinine of 3 or 4 before you become really symptomatic.

So, these patients kept smoldering fibrosis for years and it's only after they get it to, you know, a significant amount that they become symptomatic. So, by the time we see them, they already have extensive fibrosis. From – so, from that point on there's that where that 2 to 3-year survival came on. But if you tracked them back, the majority of them had fibrosis for a really long time. Although there are some rapid progressors, I will say that.

And this just shows where it is at start. Here's another one with, I mean, very mild subpleural reticulation. I would call this, you know, if the patient came in asymptomatic, you know, I would say ILA with a probable UIP pattern. But I know for a fact, because Lynch and I were arguing about – not arguing, but discussing this the other day, he would not. He would just say it's – it's just fibrotic ILA because there is fibrosis, interstitial lung abnormality plus fibrotic or non-fibrotic. You can see there's subtraction bronchiectasis. To me, there's the anterior stuff, there's the lower lobe costophrenic sulci. Anyways, this was a military case, and they biopsy everyone in the military. And you could see with just this little amount of reticulation, this patient underwent open lung biopsy, and it is just classic UIP. Alveolar collapse, there's honeycomb cysts throughout here, there's fibroblastic foci. These are the septae that are being pulled apart and are fibrotic. So, even with this little amount – amount of fibrosis, this is typical, classic UIP pathologically.

So, what about an alternative diagnosis? So, peribranchiovascular or peribronchiolar ground-glass and fibrosis extending to the periphery with subpleural sparing, that's classic for NSIP. We're not going to want to call that. Sometimes the peribranchiovascular fibrosis extends to the periphery and there's no subpleural sparing. Um, and it could be difficult, especially if there's no honeycombing. Um, but things we look for, marked mosaic attenuation with lobular air trapping. We're thinking of hypersensitivity pneumonitis. Parenchymal cysts, meh, you know, honeycomb or cysts, I'm not – you know, I think they're talking about in the parenchyma, not subpleural stacked cysts. A lot of ground-glass or consolidation, we're thinking of organizing pneumonia. Centrilobular nodules or micro nodules, you don't really see in people with UIP. And then, the atypical distribution, really upper lobe predominant, really peribranchiovascular with subpleural sparing. And very importantly, other findings to suggest connective tissue disease. This is a patient having, you know, destroyed shoulders because they have rheumatoid. Do they have a huge esophagus? And spend, I know everyone's busy; I know we're super busy. Spend a second to look in the chart and just see if the patient has any history of a connective tissue disease. It will really help you out.

Other things they talk about in the ATS diagnosis, you know, dilated esoph – a lot of these are signs of a connective tissue disease. Plural effusions, I don't like, personally. They're talking about, like lupus-like thickened rind of plural thickening. But all these people are older males with heart failure, and they can have plural effusion. So, that itself is not one. Pleural, you know – and extensive lymph node enlargement, they're talking about sarcoid. But we know that people with IPF get big lymph nodes. People with fibrosis get big lymph nodes. So, just because you see big lymph nodes, don't exclude IPF. You know, they're talking about that classic symmetric mediastinal hilar adenopathy as bulky and calcified, OK with that. But, you know, just don't say, oh, I heard they say lymphadenopathy and therefore this patient has some big nodes so it can't be a UIP pattern. that's not true at all.

So, here you can see upper lobe fibrosis with some plural thickening that's extending along the fissures, kind of creeping along, and some with pleural parenchymal fiber elastosis. Here the conglomerate lymphadenopathy in the mediastinal hilum. This is perihilar fibrosis rope extending out. This is a non-smoker. This is cicatricial emphysema. This is the lung actually being pulled apart by the fibrosis. This is in a non-smoking patient. And then, same thing here in this patient with silicosis. Never-smoker, and it looks like they have emphysema in the lower lobes, and that's literally because the lung is tethered down here, and it's literally being pulled open by this confluent upper lobe fibrosis in the silicosis patient. So, not everyone who's a smoker has fibrosis.

Classic. This is one thing, one thing only. Perihilar fibrosis extending to the upper lobes. I don't care if you want to call this honeycombing or not. I don't care if you say there's, you know, traction bronchiectasis. There is. This degree of mosaicism, this degree of perihilar fibrosis. There nothing else. This is fibrotic hypersensitivity pneumonitis. That's all there is.

So, here, you know, a lot of patients with connective tissue diseases will have some bizarre patterns of fibrosis. Now, rheumatoid arthritis, even though it's often weird-looking. So, here you see a lot of upper lobe fibrosis, there's some ground-glass. These almost always are UIP pathologically. Look at the destroyed shoulder. Scleroderma, you can get UIP pattern, both pathologically and on imaging in scleroderma, but look at this patient. There's a lot of ground-glass, the PA is big, this patient has raging pulmonary hypertension. It's a young woman. And they have the big esophagus. So, if I'm seeing a UIP pattern in a 30- or 40-year-old, something else is going on. It could be familial pulmonary fibrosis, but it's not – it's not going to be your typical IPF. And then, asbestosis, pleural plaques, I have yet to see. I think I have one case of asbestosis. Remember, that's the fibrosis-associated with asbestos. I think I've yet to see one case of asbestosis where there's, like, honeycombing. But pathologic, I mean, I think I have one. But pathologically, if you biopsy the subpleural ground-glass, and try its UIP.

Dr. Chung:
Just one case of the honeycomb cysts in asbestosis.

Dr. Kligerman:
Yeah, I and I think I have one and it might have been when I did residency at Nashville Jewish like, you know, 20 years ago. But I doubt – probably the same case. Yeah. I mean, you just don't see it.

And then you get some weird causes of UIP pathologically, and a lot of these don't look like IPF. So, Hermandsky-Pudlak albinism, oculocutaneous blindness. You have seen in Puerto Rican populations. Weird parenchymal cystic stuff. But no one is going to look at this and say, oh, this is a UIP pattern, but pathologically, it is. Now, even those with familial pulmonary fibrosis, some of them will have – now, I should have – have a low scroll-down here, this patient did have some lower lobe honeycombing here. Some patients will have a classic UIP pattern, but a lot of patients don't. This patient has a telomerase mutation. They also had PPFE, pleural parenchymal fibroelastosis, associated with their UIP, nonetheless, which is not uncommon in general. You can see this long here is very ground-glassy. It's very granular-looking, it looks nodular. Yeah, you could call that honeycombing. I don't know. But no one's going to look at this and say, oh, this is classic UIP pattern. But nonetheless, all these underwent open-lung biopsy or transplant, and these were these were all UIP.

And then, this is something a peri lobular pattern, or there may be another name for it. It's these areas of lobular sparing. Very common in organizing pneumonia or other acute lung injuries. So, if you see that something to think of as not being something you see with UIP.

Dr. Chung:
Alright, now let's talk about multidisciplinary discussion in the diagnosis of idiopathic pulmonary fibrosis. So, what is MDT good for? So, really MDT is the gold standard way to establish a diagnosis in, really, any type of interstitial lung disease, idiopathic pulmonary fibrosis being the paramount diagnosis, the most important one. And so, this will increase diagnostic confidence. You can also use it to decide whether or not you need to approach the surgeon for surgical lung biopsy to maybe get some pathological specimens. And also you can use MDT to help guide management. For example, maybe the clinician doesn't know that they should start steroids in a patient, they can talk to the radiologist, look for areas of ground-glass opacity, like inflammatory-type ground-glass opacity to look for any sort of signs of inflammation. And certainly, in the setting of MDT, it can help establish prognosis as well. People have asked me, well, who should be on the MDT team? Well, pulmonologists definitely you need, radiologists you definitely need. Pathologists are necessary as well, though I think most medical centers are moving away from pathological specimens in the setting of pulmonary fibrosis. And then you could also have a rheumatologist. At the University of Chicago, we have a rheumatologist. Just invaluable to have that. And geneticists and other individuals, as well, as part of the healthcare team.

So, what's the role of radiologists in the setting of MDT? Well, obviously we are looking at the HRCT, that's our main tool. So, we want to assess the quality of the HRCT scan and then provide the interpretation of the HRCT scan using the two-pronged approach that we described previously.

We also want to identify for other comorbidities. Remember, especially in patients with idiopathic pulmonary fibrosis, these patients are older, so very often they have comorbidities, like heart disease and sometimes lung cancer.

Here's an example. We have a 64-year-old woman with shortness of breath and so here, we see diffuse ground-glass opacity and reticulation throughout the lungs. A little bit of mosaic attenuation as well. And then on pathology, and so I am not the pathological expert that Dr. Kligerman is. My skills are pretty rudimentary compared to his, so I'm actually going to punt to Dr. Kligerman and ask him what he thinks. So, the question really would be about is, is it UIP or is it not UIP, but I'm going to punt the comment here.

Dr. Kligerman:
So, this was called UIP by the pathologist, and it is. It's temporally spatially – or heterogenous. There's so – but the imaging was weird, so we said, is – are you sure? Are there something that's – you and so they – you know, there's a lot of slides, there's a lot imaging, let me go back and take a second look. And they went back, and they said, oh, you know what, you're right there is some airway center fibrosis in a lot of areas and there are some granulomas. You know, because initially this patient was being called IPF and we're like, eh, the imaging is a little odd. It could be. But, you know, and then it turns out she had this mold exposure and by this – having the pathologist go back and the MDT, her diagnosis changed to fibrotic HP.

Dr. Chung:
Wow, that's great. That's, like, a wonderful example. There's another patient here. So, we have a patient with alternative diagnostic category. This is nice and pretty. So, we have the axial and the coronal here. So, definitely looks like this is a central lung preponderant pattern. We see reticulation, some mild ground-glass opacity, and some areas of traction bronchiectasis and bronchiolectasis. And then,

in the coronal plane, it looks like in it's probably a diffuse pattern as well in the superior interplane, and maybe someone argue that there are some areas of subpleural honeycombing in the left lung apex. And then these random kind of biggish cyst in the mid and lower lung zone. So, this is a complex weird pattern. I think that for many reasons, we might invoke the alternative diagnostic category, but spe – specifically for here, I would say the home run here, the slam dunk, is the axial distribution. Really, it's central and preponderant and not peripheral lung preponderant.

And so, this patient, on pathology, what do we have here? We have, evidence of pneumonectomy on the left and the right. So, it looks like that – this was taken from a so, after a transplant, and we see no evidence of end-stage lung honeycomb in the lung, but no evidence of malignancy. Dr. Kligerman, would you like to speak more?

Dr. Kligerman:
Yeah. So, they basically said it looks like UIP, it looks like NSIP, you know, it's end-stage lung, blah blah blah. And the point being is that, even though they said that this is UIP, it's – with some areas of NSIP, this is not UIP, right? There's no – so, pathology, if they see end-stage fibrosis, a lot of time they just say oh, it's UIP because everything's collapsed and destroyed. But, you know, the imaging here is – is not UIP. Um, so, the pathologist isn't the gold standard basically.

Dr. Chung:
Yup, yup. I think if you actually look at the data the data suggests that about 20% of the time the pathologist will change his/her diagnosis based on MDT.

Dr. Kligerman:
So, this is just showing that same patient back in 2005 where, you know, you would just call this NIP back in 2005. And this is how she progressed all those years later.

Dr. Chung:
Hmm. Yeah, that's a nice example as well. And like all pulmonary fibrosis, as it becomes more and more advanced, starts to start looking like UIP on histology, and then also on imaging. So, if we were to let this go to maybe 2020, if the patient were still alive at that point, given this progression disease, they may start looking like running into a UIP pattern.

Dr. Kligerman:
Yeah, it does. And it's just funny because this patient, if you looked at her history, it says she had IPF because the pathologist called it UIP. And you're – you're like, dude, this is not IPF.

Dr. Chung:
Excellent.

All right, so we talked about this a little bit. So, there is unfortunately a lot of inter-observer agreement issues between radiologists and then, also between pathologists, and even amongst healthcare professionals, like pulmonologists. And so, the value of the most disparate team is that you achieve a more accurate diagnosis and a more confident diagnosis. MDT really is the gold standard. I really, I mean, Seth, I don't know about you, but I don't know of any other condition where pathology is not the gold standard.

Dr. Kligerman:
I don't. Unless they've taken the clue from this, I don't think there is. I mean, I don't know if other boards have done this in terms of other diagnoses. I haven't heard of them.

Dr. Chung:
Yeah, I mean, that's why I love interstitial lung disease. It's really a team effort. It's like a puzzle putting things together.

Dr. Kligerman:
Absolutely.

Dr. Chung:
And so, how do you do MDTs? I know we're all busy, it's hard to get everyone in the same room at the same time. And so, you can do MDTs in asynchronous ways. So, you can actually do it through written reports. You can do it through electronic communications, HIPAA-compliant electronic communications through Epic, – even via text, as long as it's HIPAA-compliant. And obviously face-to-face would be the, I think, the most desirable way to do it. But again, it's hard to get people all at the same place at the same time. Even zoom calls I think are becoming increasingly difficult because of how busy people are.

So, the way that most places, most places who do a lot of interstitial lung disease will approach the MDT is that they'll have some sort of regular scheduled MDT. But again, it doesn't have to be this way. It can use other technologies, other methodologies, as long as

everyone gets a say, and there isn't someone who's dominating the conversation. Obviously, you want to document the MDT discussion in some way into the EMR. And then also, you want to be able to addend those reports or add on to reports some way in the EMR if diagnostic test results become available.

Here's some wonderful patient resources that you can look at. So, depending on your background, you can look at the pulmonary fibrosis foundation. They have all sorts of levels of information, education material for patients, but above the patient level as well. Like, I refer to this a lot. American Lung Association is a good place to look, as well as the Chest Foundation.

Seth, do you want to take it from here?

Dr. Kligerman:
Yeah, sure. So this is just talking about complications of IPF. One of the ones we have to be really careful about is lung cancer. This is a patient who had two biopsy-proven cancers, a squam in the left upper lobe, and the adeno in the right upper lobe. These patients are often smokers, just having fibrosis also increases your risk for malignancy. And it can be really hard to differentiate between some things we'll talk about.

So, here's this 61-year-old patient with idiopathic pulmonary fibrosis, who came in short-of-breath, a lot of ground-glass. You're like, that's not good. This patient is going to start to crump. And then you see, he's intubated a couple of days later, he's on ECMO. He's not looking good. And we have his lungs, which usually means bad things, but he actually managed to get a lung transplant. And what you can see here is this is a classic acute exacerbation. So, down in the lower portions, you see typical alveolar collapse, secondary lobular collapse with pathologic UIP, and then the upper lungthe upper slides, you see all this pink material, and these are all hyaline membranes. So, these are findings of diffuse alveolar damage superimposed on UIP, which is what, you know, the pathology saw. So, acute exacerbations are called the accelerated phase. Basically, people coming in with an acute lung injury, just like we saw COVID causing acute lung injury. It's a bad acute lung injury and a lot of patients with IPF that develop this can die. It's radiologic diffuse cellular damage and if they survive, you will see that the fibrosis that's afterwards is much worse than it was when they before the acute exacerbation.

Lung cancer, I talked about. You know, here's another case. Clear lung cancer on the right. What about this? You'll see a lot of these areas of confident fibrosis. The answer is I don't know, you've got to follow them. Everyone – you know, a lot of people want to PET them. That's fine, but I think following in something like on the left is fine. Clearly, the one on the right is a very nasty looking lesion. And if you're not sure, these require very short-term follow up, you know, a 3-month follow up.

So, in summary, you know the ATS and Fleischer Guidelines are slightly different, but these are guidelines. They're not set in stone; they're just supposed to help you out. And there will be cases – there's cases every day that I see and I'm like, I have no idea what this is. I mean, at least I could say, it's not going to be UIP, at least on imaging, but I have no clue what the diagnosis is. Bizarre things. So, it really is, you know, and the experts disagree, I mean, there are cases where if I'm sitting next to Lynch and I'll say, yeah, I think this is indetermined. He's like, no, I call that probable. You know, or vice versa. Just disagree. So, that's fine. You can be wrong. And the disagreements are part of what makes it fun. It's a multi-disciplinary process. no one's right all the time. Although Lynch is pretty close.

Dr. Chung:
He is. I want to thank our learners for coming to this program, or listening to this program. To claim CME or CE credit, please click on the claim credit link in the resource section to complete the online evaluation.

Thank you all for being part of this program. Enjoy the rest of your evening.

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