Idiopathic Pulmonary Fibrosis: Real World Application of Diagnostic and Therapeutic Advances

Josh: Good afternoon and thank you for joining us. If you could both please introduce yourselves and tell us where you're from.

Ahmed: I am Ahmed El-Bershawi. I am one of the pulmonary and critical care doctors in private practice in Southern California, in Riverside.

Hassan: My name is Hassan Bencheqroun. I'm also a community practice physician in Riverside, Southern California.

Josh: Okay. Thank you for joining us. If you could please tell us about the case we'll be discussing today.

Hassan: We are presented with a 57-year-old gentleman. The ethnicity is not specified, but he presents with an abnormal chest x-ray for 3 months. Apparently, the chest x-ray was normal about 5 years ago. His symptoms are just mild dyspnea on exertion without any cough. His medical history is mainly for reflux for 30 years for which he is taking omeprazole 40 mg daily. We are also told about our gentleman, that he is a lifetime nonsmoker. He works as a pharmacist. He also describes some mold in the home, but there is no history of interstitial lung disease in his family. So far, we have just nondescript, very benign symptoms. The chest x-ray just says "abnormal."

Physical examination shows normal blood pressure of 114/73 and a heart rate of 70. The respiratory rate is normal at 16. His oxygen saturation is 96% on room air, which is normal, but drops to about 93% when he is walking, which is an interesting thing to keep in mind. His auscultation according to the case reveals that he has some crackles on the inspiratory phase at both bases, which are described as dry crackles, but the cardiac examination is normal. There seems to be no clubbing and no joint deformities or rashes.

We proceed with some pulmonary function tests, but at this time, I just want to pause and think of someone like this presenting to our clinic. It's quite normal and common to find these. They have a broad range of differentials so far, mainly anything from an adult onset asthma, which the dry crackles would not go with it, but at least we keep the common things common in our mind. He is a nonsmoker, but it doesn't say whether he grew up in a home of second-hand smoking. There is no exposure occupationally that is relayed. However, we do not know if he has ever had any silica or asbestos exposure. We will assume that they were not presented, therefore, they are nonexistent.

His normal cardiac examination probably shies away from anything cardiac that would explain his dyspnea. Typically for someone with interstitial lung disease, they are sent to a cardiologist first, to try to find out if there is any substrates that are dyspnea, prior to arriving at the pulmonologist's office, which is one of the notorious reasons for delay of diagnosis.

Hassan: Continuing with the tests that are presented, we have an FEV1 of 4.42 liters or 90% predicted and a forced vital capacity of 5.1 liters or 83% predicted resulting in a ratio of 0.87. This is essentially a normal spirometry. The total lung capacity is 7.40 liters or 88% predicted, also normal. Does not show any restriction or obstruction. It is interesting, though, to see that the transfer factor of carbon monoxide is 23.41 milliliters per millimeters of mercury per minute. That would give us a 57% predicted. That shows an isolated decrease in the transfer factor of carbon monoxide.

The change that happens to the DLCO, as compared to the DLCO corrected for alveolar ventilation, is not parallel. There is always that controversy of wanting to know the other number. I tend to trust if there is a diffusion capacity or transfer factor capacity that is low, isolated, with dry crackles and dyspnea on exertion, as well as a slight desaturation on exertion, those are elements that are sufficient to raise our suspicion for some interstitial lung disease, especially with the Velcro crackles although a vascular abnormality could also be considered at this time.

Dr. El-Bershawi, any other contradictions or questions?

Ahmed: No. This pulmonary function looks decent except for the diffusing capacity, I agree.

Hassan: Would you like to look at the x-ray and comment on it?

Ahmed: Sure. Essentially, it's not that impressive. It does have nice size of the heart, good lung volume. Vascularity seems to be decent. Maybe there is, just because of the topic of the discussion, maybe we can see there might be findings in the interstitium, but if this was an abdomen x-ray, it can pass as normal in my eye.

Hassan: I completely agree with that. It's when we are prompted, with biased sensitivity of the interstitial lung disease topic, that we could say there *might* be some prominence of interstitial markings in the right base and maybe the left base. Again, I agree with you. It would pass as normal if it wasn't for this.

The discussion question before us is based on this patient's presentation, "What conditions would you consider in the differential diagnosis?" At this time, the differential could be indeed broad. I guess we can summarize it in big categories

of infectious, inflammatory, neoplastic, and miscellaneous. With infectious being any fungal infection, he had some exposure to mold at the home so I would probably want to know more about that and more specifics. Asthmatics tend to have the Aspergillus component so that could also contribute to these symptoms that we've seen. However, what doesn't go with that, perhaps, is just the dry Velcro crackles on auscultation seems to be a leading physical finding.

He has reflux, so aspiration also comes to mind, which more goes toward the inflammatory, although some infectious component can be considered as well. Perhaps some pulmonary edema although he doesn't seem to have anything cardiac-wise, but I would be curious to know what the finding of his echocardiogram may be and rule out anything cardiac or even pulmonary vascular. I would probably also want to know if there is another differential of pulmonary eosinophilia. All of these are within the infectious and inflammatory, probably other things such as any sarcoidosis could also give this the fibrotic portion of it would present with such a thing.

Dr. El-Bershawi, anything else I'm missing that we could put into this category?

Ahmed: My thought is pulmonary vascular disorder. Thromboembolic disease, because of the poor diffusion. Interstitial lung disease, because of the crackles on the physical exam. Maybe consider ruling out infection because of the environmental history of the mold. That's about it. Could be left-sided heart as well, but doesn't look like that from the x-ray or from the presentation. Dyspnea on exertion is broad.

Hassan: Another thing which is not mentioned there, but one could think about drug-induced pulmonary toxicity, but he only has omeprazole which I know has not been reported to have any of these symptoms that are described in him. We also would like to know if he has any pets or birds or he had any exotic travel recently. Hypersensitivity, pneumonitis could come to mind in that setting. He doesn't have any hemoptysis, but intra-alveolar hemorrhage, or what we would call diffuse alveolar hemorrhage although sometimes it can be more localized. We would look into that.

Those are some of the things that come to mind at this time. Connective tissue disorder—they made a point to say that he didn't have any symptoms that can make one think about that, including joint deformities or rashes. We are left mainly with interstitial lung disease and rule out any infections is what is at the top of the list.

Josh: Based on that, what would you do next? What tests would you order?

Hassan: I would probably want to get, first of all, some blood work. In my clinic, what I have is a template of sending for an autoimmune workup, preliminary. Some of these people could present with a nonspecific either rheumatoid factor or anti-nucleic acid antibody, which if they are the only ones isolatedly increased, they usually are moderately increased, and they do not necessarily show an autoimmune. But if they are high in addition to others such as either anti-Sjögren antibodies or anti-scleroderma antibodies or some of these, then it would lead our diagnosis.

I would probably want some blood work to see if there is any peripheral eosinophilia. I've had a couple of patients which not necessarily would say that this is an eosinophilic, but we live in the belt of coccidioidomycosis, which could give also some ground glass or miliary or peripheral eosinophilia so the infectious part could come into play. Antibodies against Aspergillus maybe, as well as some beta galactomannan, those are things that I would either at once if my index of suspicion is high. In this case, I'd probably go with some screening tests at first, blood work-wise, and because we want to know, this has been going on for 3 months, I'd probably want to get high-resolution computed tomography (CT) along with the blood work. With these 2 things, we would have a better idea of what to tell our patient.

Dr. El-Bershawi?

Ahmed: I would get an echo and a high-resolution CT. I probably would not order any blood work at this point.

Hassan: Okay. You echo is mainly to . . .

Ahmed: Rule out pulmonary artery hypertension, check the left-sided function just to get it out of the way. Both things stay in the back of my mind. If this is out of the picture, then I can focus on the lung. Then the high-resolution CT, because of the physical exam and the diffusion of course.

Hassan: The other additional tests that are presented in the question are bronchoalveolar lavage (BAL). I would not bronch this patient at this point.

Ahmed: You're right.

Hassan: I probably would want to get the CT. You're right, I would get an echo as well but the blood work as well.

It asks about thoracoscopy or surgical biopsy. Again, it's too early to proceed with those. What do you think?

Ahmed: I agree.

Hassan: I think we are in agreement. As far as serology, I think it goes well with the blood work. I would probably want to proceed with serology first, as I mentioned, for autoimmune workup.

Ahmed: Yes. I think there is a room for it, I might order maybe 1 or 2 as screening. Might not be as extensive as you, but more or less it has room, of course.

Hassan: The other thing that I probably would want to know, in the screening blood work, is a sedimentation rate, as well as a CRP, even though they are nonspecific at least they give me an idea of whether we are in the ballpark of inflammatory versus something more interstitial. I would probably get these two.

Josh: Okay. Let's pause for a moment and take a look at the second part of the case and see what tests were actually ordered and what the results are.

Hassan: Our patient had, in fact, a high-resolution CT, a bronchoscopy, a serology, and surgical biopsy. In that order, they are presented. On the CAT scan, the high-resolution CAT scan, we are starting to see very subtle findings that are indeed interstitial and peripheral in the subpleural distribution. I would say there is a thickening of some of the interlobular septae in a subpleural fashion. Some micro nodules although the thickening of the septae seems to be a bit more pronounced. They are in a rim bilaterally. They tend to distribute mostly in the lower, rather than the upper, although they can still be found in the upper as you cruise through the CAT scan.

We do not have mediastinal window so I'm unable to comment whether there is a lymphadenopathy. The esophagus seems to be somewhat thickened toward the bottom, which goes along with his reflux history. Again, this contributes to our discussion about interstitial lung disease. Sometimes, if it was a hypersensitivity pneumonitis, for example, it would be mostly in the upper lobes. It doesn't appear to be typical of any sarcoid or other. There does not seem to be emphysematous changes. There seems to be a little bit of a bowing of the fissures perhaps pointing to a subtle air trapping, but the total lung capacity was described as normal although it might have been hyperinflated and high, and the interstitial lung disease might have brought it down a bit.

Proceeding with the results, the BAL is described with normal appearance. The cell count differential is mainly 70% macrophages, about 4% lymphocytes, and 5% eosinophils. If there was any lymphocytic predominance, we would be mostly . . . Actually, it is seen in idiopathic pulmonary fibrosis (IPF) as well as hypersensitivity pneumonitis. It would have pointed us toward that, but at this time, it seems to be a fairly bland composition of the BAL.

What are your thoughts so far, Dr. El-Bershawi?

Ahmed: I cannot make any extra comments on the CT scan. You said it perfectly. This CT scan would not strike me as ultimate or aggressive or genuine, I guess. That's my opinion. It doesn't look like the BAL is any impressive. There is no eosinophilia.

You mentioned couple of comments about the microphages. Can you state them again, Dr. B?

Hassan: I was mainly saying that this looks bland. This is what I would expect from a BAL. There is no increased lymphocyte composition. There is no eosinophilic component. This is pretty standard.

Ahmed: I'm assuming from this that there is no infection. This is something that was not commented on. I'll leave it as if there is no infection. Then the serology indicating there is no connective tissue disease so to speak. The surgical biopsy, I stopped reading pathology for a long time so I cannot give any opinion about that.

Hassan: I agree with you. I'm not necessarily the best in reading those, but I would actually just pick up on in terms of the pathologies that there are some foci that you can see. There's a lot of fibroblasts along with some areas of normal alveoli. You can see distinctly that there are areas of normal and areas of abnormal lung. I'm not seeing a lot of inflammation although I'm not the best at reading that. There is some inflammation. All it says to me is that there are two types of lesions and not a whole lot in between. I don't see granulomas, for example. It doesn't look like it's sarcoid. I don't see any infiltration of the alveoli such as for pulmonary hemorrhage. I think the last slide does show a fibroblast focus if I remember correctly.

This is in line with what I would pick up to be a usual interstitial pneumonitis although I would be curious to read the pathologist's report because I'm not the best expert at this.

Hassan: At least from what we would pick up, and I completely agree with you, the CAT scan findings are more subtle. I don't see honeycombing. All I see is just there is a clear abnormality that seems to be a very fine interstitial component that is subpleural, mostly basilar predominance. There are no cystic changes. There is no septations that looks fibrotic.

If it is IPF, then it is at the very, very beginning, but it could be a number of other components. The pathology is what leads us toward the usual interstitial pneumonia (UIP). There is many conditions that would have UIP, but in this particular case, in the clinical context and the occupational and mold exposure

which did not pan out to be something significant and in the PFT that we saw as well as the symptoms, I would probably err towards a diagnosis of IPF in this particular patient, idiopathic part being that we didn't find anything to explain it.

Dr. El-Bershawi?

Ahmed: No, I would not tell the patient he has IPF if I don't have a pathology report. If I have a pathology report, I need to know why there is a UIP. What is the cause? I think the workup is not complete. I need to make sure the recurrent aspiration is dealt with. I want to make sure the rest of the serology as well as the echo. I think from the symptoms, from the pulmonary functions, from the age, I don't have a complete picture. I will have to wait for something official from the pathology.

Hassan: I agree. Assuming that the pathology report comes back with UIP, would you still not tell the patient that he has IPF until you obtain the echo?

Ahmed: Yeah. It is small area of the lung. Even UIP is a pathological diagnosis. It's not IPF per se. You can have UIP coming from different backgrounds. The age maybe younger, maybe not. Recurrent aspiration can give you the same CT scan. If that is indeed UIP, could be early. Hopefully, maybe aggressive treatment will be needed. I think in my practice, what I do is I don't have a good cause for the IPF, so to speak, and I ruled out everything else, I don't think the patient does well. My best chance to help that patient is if I can find out a cause that contributes to his pathological picture.

Hassan: Very good. Do you think that in the aspiration pneumonitis, we would have a UIP pattern?

Ahmed: Probably not. You're right. Probably not, but that pattern on the CAT scan could be because of the aspiration pneumonitis.

Hassan: I agree, imaging wise. Regardless, even if I were to give him the diagnosis right now or not, all pulmonary fibrosis patients would have to be evaluated and treated aggressively for reflux because it is such a prevalence.

Ahmed: You're right. I agree.

Hassan: Micro aspirations are extremely prevalent in this population so I would probably . . . Whether to say that it is a cause or to treat it as a comorbidity of it, then either way, we will probably proceed with the same.

Ahmed: I agree.

Hassan: What type of test would you send to find out if perhaps he does have reflux . . . ??

Ahmed: No. I would try to improve his treatment. I would double the dose of the Protonix, and I would add an H2 blocker, as well, at the highest dose. I will give him maybe 6 weeks. I would not wait for this long. I would want to know more about the pathology and pursue that as well. The problem is, if this is genuine IBF, meaning there is no infection, no connective tissue disorder, no cardiac issues, no thromboembolic disease, no autoimmune disease. The next questions say, "Would you consider treatment?" Well, from his symptoms, I would rule out nocturnal hypoxemia. He desats during the day. He might need oxygen at night. Personally, I would not start him on the treatment on pirfenidone or the other medicine.

Maybe 2 or 3 causes, one, maybe the patient is doing better or still doing good, still functional. Maybe you can argue saying that if you intervene now, that's a better chance for that patient, but I would not. Number two, is the cost. Then number three, the number you need to treat to improve. There is not even an FEV1 reduction yet. When I reach that level that I know there is no connective tissue disorder, cardiovascular, pulmonary vascular infection, autoimmune inflammation, eosinophilia, sarcoidosis, granuloma, when I know that and I know that it's purely IPF, depends on the stage, if I can watch the patient with a series of pulmonary functions, I would do that. I will keep a close eye on him.

I would treat other things, post nasal drip, gastric reflux. If I reach the diagnosis of IPF, I usually would not provide further treatment because of the cost and the number to treatment. I usually would refer the patient. I used to deal with a physician. She was excellent. She will send me the report. I will talk to her over the phone. Now, Dr. Bencheqroun is my partner in practice, and I know he knows more about that so I just send those patients to him. I'm not sure I'm sold yet on the treatment. At least that's my opinion.

Hassan: Very interesting, and I hear your argument for this. Here is my thought process.

When it comes to pulmonary fibrosis—as far as the diagnostic criteria—they have already been posted by the ATS and ERS—major and minor criteria in the absence of a surgical lung biopsy, which is why I would not have gotten a biopsy in the beginning, the major criteria being the exclusion of other known causes. We've gone through that in addition to an impaired gas exchange, which we've seen, especially also the desaturation on walking. Bibasilar reticular abnormalities with minimal ground glass on high resolution, which we have seen in this patient. In his particular case, the transbronchial lung biopsy or his biopsy right now or even a BAL show no features to support an alternative diagnosis.

As far as the major criteria, we're set for him. The minor criteria is the age—more than 50 years—and the insidious onset of otherwise unexplained dyspnea on exertion, the duration of the illness being over 3 months, and bibasilar inspiratory crackles, so you'd have to have all major criteria and 3 out of the 4 minor criteria. Actually, he fulfills all of them. Based on the imaging, I'd probably give him the diagnosis of IPF regardless of the lung biopsy. We are fortunate that he has a lung biopsy.

Regarding pathology, one of the conferences I went to explained it beautifully to me: with UIP pattern, in the same slide, same specimen, you would see 2 or 3 different stages of the same disease, which is one is normal lung, second is interstitial inflammation, and the third is fibrosis and fibroblastic foci. This is quite striking in this particular slide that you can see one of them, the alveoli that are normal alveoli, and then next to them there are alveoli that are actually the architecture of the lung is distorted right next to a lot of fibrotic areas. Then there is the slide which shows the fibroblastic foci.

In my opinion, I would probably be much more aggressive in revealing to this patient that this is probably IPF although much of the finding of the causes of pulmonary fibrosis or interstitial lung disease still remains based on some labs with sensitivity and specificity may be sometimes questionable and a recall of the patient as to whether he had any exposure that could explain it. I always leave some room that this may be revealed 5 or 10 years down the line. It's not idiopathic. It's something else. We will continue to look for the reasons including aspirational reflux, whether they are comorbidity or actually causal.

I agree with you in terms of continuance to find a reason, but I would definitely be much more aggressive. In my view, if this is UIP, I see that there are already 3 stages, so it is an active disease for me. Anything that already is established as a fibrosis, we will not recover. I probably would want to start him on either pirfenidone or nintedanib. In my view, that would actually slow down the progress of the disease. There is no study right now for the combination so I've never combined them because we don't know if they actually inhibit each other or potentiate each other or have nothing to do with each other. I think recently, there has been a small study that came out with N-acetylcysteine on top of pirfenidone. I think the methodology of that study was just suggestive but not necessarily something that was practice changing.

Pulmonary rehab, I don't think I would send them to pulmonary rehab because he seems to be a fairly active patient, has no restrictive or obstructive disease. He seems to have a mild dyspnea on exertion, but his functionality is still okay. I would encourage him to continue going to the gym or at least work out 3 times a week. Those are my arguments with the questions presented.

Ahmed: Okay, a few things. You agree with me that you can find UIP in the pathology that's not IPF, correct?

Hassan: Agreed.

Ahmed: You agree with me that this CT scan is not typical of IPF?

Hassan: Agreed.

Ahmed: You agree with me that the presentation can be due to other causes?

Hassan: Agreed.

Ahmed: It's a judgment call. I agree with you. I trust your experience. You have much better experience than me. That's probably what it is, but as far as I practice, I want to be honest in my presentation to what I do. I would probably shy away from calling it IPF. I think the workup need to be more complete. I would not start on treatment. I think that's part of the reason why we're having this discussion.

Hassan: Yeah. So far that's, I think, the purpose of the educational program, the differences in practice. How would you disclose the diagnosis to the patient who has been through a biopsy and . . .

Ahmed: I would tell him that he does have interstitial lung disease. I usually tell the patient that interstitial lung disease is like a car. He might have a BMW, he might have a Mercedes, I don't know yet. I have some suspicion, and it's important to watch this closely. We don't want it to get bad. Part of this umbrella can be really bad disease or terminal. It's a significant diagnosis. Once I disclose to the patient IPF, and they look it up on the Internet, again, survival is worse than cancer.

I would present it this way, I will finish my workup. If I indeed reach the same diagnosis, I still would refer the patient either to you or back to San Francisco just for the fact that I don't have any experience with these medications. I think it's cost-ineffective, in my opinion.

Hassan: Fair point. Cost of medication?

Ahmed: The cost of medication given the number of patients you need to treat. If I want to put them on, I just need somebody to hold my hand. As I practice now, I don't start the patient on.

Hassan: Okay. As far as disclosing, that's always a tricky thing. I completely agree with you. I also too use the word interstitial lung disease, but the biopsy itself does show fibrosis so I cannot shy away from saying pulmonary fibrosis. I would probably say idiopathic is a very specific term. I would say it's almost like I'm using a legal term, so I would not necessarily use it unless I signed on the dotted line, which I'm not ready to sign yet.

I would call it pulmonary fibrosis. I would probably say I'm going to give you information on all of them. I'm going to tell you that there is a strong probability that you may have IPF. I would use that term. I would probably give them information about the treatment and say, "My recommendation is such," and offer them a second opinion. I think we have here—close to us in Los Angeles—Joseph Lynch III, MD, whose interstitial lung disease program is well known.

Ahmed: I think you are right. I send you all my stuff so we're good.

Hassan: If we wanted a second opinion, I would probably say that. In this day and age, it is probably more regimented or regulated by the insurance rather than anything else. It's always a challenging, challenging conversation so I usually ask the patient to bring their family. Then I would usually ask them to visit later and meet with them and answer any questions that they may have.

I had one patient who took the second pulmonary opinion and went to it and I never saw them again. Most people go to "Dr. Google" and find out that this disease will kill you within 3 to 5 years, so they come in the second time with their family with a long list of questions that usually boils down to one: "Am I going to die?" It's a tricky question to answer, but truly, if I hand them printouts of pulmonary fibrosis and reputable websites where to go and look for themselves, it makes them feel that they actually did something instead of just staying idle and hearing from one source. I caution them from giving it a mortality.

Unfortunately, the onset of cough has been linked to be a prognostic factor in addition to a drop of FVC, usually vital capacity by 10% within 6 months, that has been traditionally a prognostic factor. It is one of the elements that were used in the recent pirfenidone trials and nintedanib trials. I would ask them to be followed symptomatically as well as with pulmonary function tests, just as you mentioned yourself earlier. If it is an active disease, then I disclose to them that this is indeed active disease and, whether it idiopathic or not, it's still pulmonary fibrosis that's active and that's robbing them of their breath.

They should probably start thinking about advance directives. I give them a questionnaire about that to bring them the next time in talks about the advance

directives. It moves away from just the medical portion of it to also the social part.

Ahmed: You're right.

Josh: Any closing remarks?

Hassan: I believe it's a relevant issue. You've touched on a very sensitive topic for all pulmonologists. We do have some disagreements in terms of when to start things, but ultimately, I think, we all arrive to the same conclusion.

Ahmed: As community doctors, I think we need to do more, catch it early, and be more aggressive. I'm not sure that there is a sense of optimism about it, hence, the lack of enthusiasm. That's my opinion. Somebody who is in a younger generation, like Dr. Bencheqroun, might have a different mood to it. For me, being in practice for maybe 12 or 13 years, I try to watch early for maybe early referral for a transplant. I'm willing to change, but it will need a good amount of maybe education, re-education, and more experience.

Hassan: The only thing I would add to that is there is always a component at that time, especially if I catch them early, to refer them to a clinical trial. Some of them are more comfortable to do diagnostic clinical trials. There is one that is looking into biomolecular markers in the BAL, for example, to see if we can avoid the need for a biopsy. There are others that are therapeutic, which is now the combinations of medications or future generations of those same classes of medications. I think that thinking about sending them to clinical trials would be important.

However, as a community doctor, I think I would love to know one place where I can go find all of those by zip code. That way, it's easier for us within the flow of our day. I don't believe that there is good communication between the big centers and the small communities in terms of referring these patients.

Ahmed: I agree.

Josh: Thank you both for speaking with us today.