INTRODUCTION

Hello, this is Harold Collard, associate professor of medicine, Division of Pulmonary and Critical Care Medicine, and director of the Interstitial Lung Disease Program at the University of California, San Francisco. I would like to welcome you to "Peer Perspectives, Idiopathic Pulmonary Fibrosis, Real World Application of Diagnostic and Therapeutic Advances."

IPF is a chronic, progressive, ultimately fatal form of interstitial lung disease. Although recent years have witnessed the introduction of new IPF-specific therapies, the recognition and diagnosis of IPF remain clinical challenges.

Diagnosis requires an extensive process, excluding possible causes of these non-specific, relatively non-specific respiratory symptoms. Imaging and histology are common components of the evaluation. Importantly, an interdisciplinary team of clinicians, pathologists, and radiologists experienced with interstitial lung disease is a critical part of the evaluation. There are many questions about how and when to best use these therapies that are newly introduced.

Today, using a case study of suspected IPF, we will look at the challenges inherent in the diagnosis and management of this disease, from the perspective of two community-based pulmonologists. First, you will have an opportunity to review the case presentation with the community physicians, listen to their methodology and approach to assessing and diagnosing a patient, presenting as the case does. After, I will comment on the case study, discuss evidence-based practices and guideline recommendations for IPF diagnosis and treatment and review some of the challenges that community physicians face in dealing with this disease.

CHALLENGES: RARITY, NIHILISM, AND EXPERIENCE

You have just finished listening to two community pulmonologists, discussing this relatively typical case of IPF. I think it illustrates a number of the challenges that face clinicians, particularly community clinicians, when confronting a possible IPF diagnosis. I have a number of questions I want to address around diagnosis and treatment and will try to relate that back to this case discussion.

As is sometimes the case, in this patient, the presentation was quite non-specific. In fact, the original reason for evaluation was due to an abnormal chest x-ray. It was not a particularly compelling symptom complex. When there is, it is usually often non-specific, shortness of breath or cough, and it is commonly considered, at least initially, to be something like asthma or COPD, reflux, sinus disease, things that are much more common in general practice than idiopathic pulmonary fibrosis.

I think that there are a couple of key challenges to the community providers that I want to mention upfront, and then I have some more specific questions I want to address. I think that the first is that IPF is, as we say, a zebra. It is an unusual condition. It is not the most common presentation of shortness of breath or cough. In fact, probably more common than IPF are uncommon presentations of common things, like heart failure, asthma and so on. It is only to be expected that community physicians, when faced with a patient with these symptoms, think of those other conditions, first, and we know that it often takes over a year for the patient and physician to come around to a diagnosis of IPF.

That is a major issue for this disease because in that year or more of time that passes between presentation and eventual diagnosis, this disease progresses. In general, patients who finally present to at least a tertiary care center, so to referral centers, with IPF, have often moderate, sometimes even advanced, disease. In a disease that is primarily characterized by scar, that is irreversible. A key to IPF is early diagnosis, and it is a real challenge because of its rarity, and therefore not being on the top of the list for community clinicians.

So I think that is something that we need to try to educate the community about, but in the end it is always going to be an issue because uncommon things don't make the top of the list to begin with.

A second issue that this case raises, particularly in discussion, is the sense of nihilism around this diagnosis. For years, there was nothing we thought that we really could do for patients with pulmonary fibrosis. The diagnosis was essentially a non-urgent one because there was really no action to be taken, so often it was noted in the chart as a comorbidity. Radiologists, when they noticed it, in their reports, didn't call for emergent or urgent evaluation. It was a side note.

Again, I think that a lot of that stemmed from the fact that we didn't know what to do about it, and it was an unfortunate and hard condition because it would progress without really any chance of intervention. That is no longer the case, as we will talk about.

In fact, it has never been the case, universally. There are many cases of pulmonary fibrosis, non-IPF cases or causes, that are actually treatable, so I think there are two issues around this nihilism. One is the recognition that all fibrotic lung disease is not IPF. The second is that now, even for IPF, we have interventions that can make a difference in patients' lives, so this nihilism is a really important issue, though, and it is still quite prevalent in the community, I think, particularly among pulmonologists and practitioners who have been in practice for a longer period of time. Actually, one of the discussants in the case mentions that.

This is a hard thing to change because experience is working against us there, but, again, education here, in terms of reaching out to the community and trying to re-educate them around the things we can do for these patients, is really critical.

Lastly, I want to point out the general challenge is the lack of expertise in diagnosis and management. The diagnosis of IPF is a real challenge because it requires knowledge, in fact, colleagues with expert knowledge, interpretation of high-resolution CT scan, and, in some cases, surgical lung biopsies. In most places in the United States, CT scans are read by general radiologists. Again, this is an experience thing. General radiologists, in most cases, do not have the expertise and experience with high-resolution CT scan to pull out reliably a pattern that is diagnostic of IPF.

We see this all the time in our practice where patients come in, with a CT interpretation that says, "Usual interstitial pneumonia pattern," which is the pattern seen in IPF, and it is not. This is, again, an issue of expertise and experience. It has nothing to do with the ability of the radiologist, but it highlights the challenge in the community because, when you are pressed for time and you are working in a busy office, it is not easy to, number one, identify, and, number two, have time to discuss a CT scan and the case with a radiologist and/or pathologist.

That is a third challenge that we face, moving forward. How do we take this model of multidisciplinary diagnosis, access to experts in radiology and pathology, and implement it in a practical way for the community physician? I look at it a lot like tumor board where patients with IPF, as do patients with cancer, who should have, at the beginning of their evaluation, a multidisciplinary discussion and management planning conference. We need to have that infrastructure, in the US, to allow that. That may, hopefully, in the end, be the answer to helping community physicians to improve their comfort level and education and experience around IPF.

SUSPECTING & DIAGNOSING

I want to address a few specific questions about diagnosis and treatment. The first is, when should IPF be suspected? As I mentioned a little bit earlier, that is a tough one because it should probably always be suspected in a patient who has progressive, or chronic or progressive, dyspnea, but of course dyspnea is non-specific, so I think that the things that really should key the clinician into the possibility of IPF are two things.

Number one, crackles on exam. I think that many times careful auscultation of the chest will reveal crackles that are dry, inspiratory, bilateral and those need to be evaluated. Those should not be ascribed to atelectasis or heart failure. They need to be evaluated as possible ILD. That should prompt a high-resolution CT scan in almost all cases. Then you can move on from there.

Number one is crackles. Number two is the incidental radiograph, either chest x-ray or CT scan, that is done in an unsuspecting patient, that notices evidence of interstitial lung disease. As I mentioned earlier, often these reports are non-urgent. The scarring is mentioned, but not highlighted.

When a radiologist sees a nodule or a mass in the lung, there is a very specific action plan dictated in the impression and recommendation. That needs to happen for fibrotic lung disease, and I don't see that happening. I think that those are the two conditions where specifically IPF should be suspected. Again, in patients who have progressive dyspnea, particularly those who are older, IPF should be on your radar.

Remember, IPF is a disease of aging, and as you go from the 50s to the 60s to the 70s, the incidence increases dramatically, to the point where people in their 70s, the risk is somewhere on the order of 1 in 200. It is remarkably high, so it becomes a relatively common disease when you get into the older age populations. This is something to remember in your clinical evaluation.

Then, when you suspect it, what tests are needed, to diagnose IPF? The key diagnostic test for IPF is high-resolution CT scan, so you need to have, number one, a good protocol for high-resolution CT scanning. That should include supine and prone images, and it should include expiratory images, ideally dynamic expiratory images, which image the patient as they are breathing out. The combination of these three different views gives you a nice comprehensive assessment of the interstitium and the presence of interstitial changes, such as reticulation, traction bronchiectasis, honeycombing, ground glass, nodules, etc, so high-resolution CT scanning, done properly. Then, as I mentioned earlier, it needs to be interpreted by an expert radiologist.

I think that most clinicians are familiar with the concept of sending surgical lung biopsy out for review by expert pathologists. We should have the same approach with high-resolution CT scans in patients in whom we suspect IPF. Again, the infrastructure for that doesn't exist, the same as it does for

pathologists, but we need to have that because, again, general radiologists are not accurate in identifying IPF from among other interstitial lung diseases.

If high-resolution CT scan is not diagnostic, which about half the time it won't be, so it will show you fibrosis, but it is not a specific pattern, then surgical lung biopsy is still the additional diagnostic test. Surgical lung biopsy is done videoscopically. It has gotten a lot of attention or discussion, recently, around potential risk for acute exacerbation of lung disease or other surgical complications.

My experience, in my review of the published literature, in stable outpatients, as is usually the case, is that surgical lung biopsy is quite safe. The complication rate is very low, less than 5% for lung pneumothorax and probably even lower for exacerbation of disease, but there is morbidity associated with it in terms of pain, prolonged either nerve pain or a discomfort at the site. It is not something to be done, of course, lightly. At the same time, if it is going to make the difference between diagnosing IPF and a non-IPF condition, which makes a difference from a treatment perspective, then I usually come down on the side that has more benefit than risk.

Those are the two key tests for the diagnosis of IPF. Then, critically, as I mentioned earlier, these have to be discussed in a multidisciplinary context. That is a real challenge in the community. It is probably not practical, but it makes a huge difference in the diagnosis. I can tell you, many times, I have reviewed a case, I think that I know what it is, I sit down with my radiologist and pathologist, and it changes my mind. I am used to looking at these cases all the time, so it is really important to do, as much as you can, to have a multidisciplinary discussion.

A final question around diagnosis is when should patients be referred to a specialist? As I mentioned before, I think that there should, in every case, be a specialty evaluation of patients with IPF. Now that specialty can be either local or at a tertiary center, depending on the interest and expertise of those involved. What I would like to see, and there are efforts to try and make this happen, is the development of regional IPF centers of excellence across the country so that most general pulmonologists and most patients have, within reasonable distance, a center that can see them, reasonably quickly, and evaluate the diagnosis, and then help that referring physician with information about that and how to manage the patient.

The management doesn't go to the specialists, but the specialists really are a diagnostic and oversight of management, consultant. I think the community physicians should, in general, refer all patients that they think have IPF to specialists for accurate diagnosis, and also because this field is rapidly changing. There are lots of clinical trials of therapies and ongoing modifications to what is recommended, so it is important for patients and their referring docs to have updates on that, regularly.

PHARMACOLOGIC TREATMENT

Once you have made a diagnosis of IPF, when should you treat, and what drugs should you use? The first comment is to say that IPF is no longer a disease that should be treated with steroids or other immunosuppressant drugs. There was a landmark trial, published in 2012, that looked at the treatment of patients with IPF, with prednisone combined with azathioprine and N-acetylcysteine. As many listeners may know, that was the standard therapy for decades when you take N-acetylcysteine out, and then, more recently, the combination of all three.

Many patients got this combination of therapies. It turns out, in a randomized controlled trial, that these therapies increase the short-term risk of morbidity, and perhaps mortality. In the trial, there was an increased rate of death in the treatment group compared to placebo, and clearly an increased rate of hospitalization, generally for respiratory causes.

The mechanism for this is unknown. It may be that it is infection-related. It may be that these drugs are somehow toxic to the normal aveolar epithelium of the IPF lung. Regardless of mechanism, the best data we have on these therapies show that they are harmful. The patients with IPF should not be prescribed prednisone or azathioprine. N-acetylcysteine on its own appears to be harmless but also appears to make no difference—in another trial that compared monotherapy with N-acetylcysteine—to placebo.

An important negative, in terms of treatment, is not to use those drugs. This is another thing in the community that has taken some time to penetrate because, for years, those were the go-to therapies. It also highlights the importance of accurate diagnosis because non-IPF interstitial lung diseases are still treated with those drugs. Historically, if you couldn't tease out IPF from these other diseases, it didn't make as much of a difference in terms of your management. You still used the same medications. That is no longer the case, so accurate diagnosis is even more important now because, if you use those traditional therapies in IPF patients, you may well be harming them, and you are certainly not helping them.

What about new therapies, pirfenidone and nintedanib? Pirfenidone and nintedanib were both approved by the FDA last year. Pirfenidone has been available outside of the US for a years, in many countries, so both of these are antifibrotic therapies, specifically for patients with IPF. The new guidelines, which were just released a few weeks ago at the American Thoracic Society meeting, comment on the use of these two drugs and give a provisional recommendation to use them in patients with IPF. In the view of this expert panel, the benefits of these drugs, in general, for IPF patients, outweigh the risks, so they are recommended therapies according to guidelines for the treatment of IPF.

As I mentioned, they are also both FDA-approved and available now. Who to use them in is, I guess, open for some debate. The label is broad, saying that they can be used in patients with IPF. The clinical trials studied patients with what we have called "mild to moderate disease" that has been defined by their physiology, by their lung physiology, mainly their forced vital capacity and diffusion capacity, with most trials only enrolling people who are above 50% of FVC and 30% DLCO. I would say, to give you my opinion on it, I think that those thresholds were arbitrary. They were designed for clinical trial purposes, not because they are thought to represent a biologically distinct group of patients that would respond particularly to these drugs.

So I extend the range of patients that I treat beyond those limits, and really, I would say, in most cases, in thinking about using these drugs, it is primarily in patients who are really ill, either transplant-ready or in the realm of symptom management and the tide of care where I think that it is unlikely that these drugs, which are antifibrotic, are going to have a big impact, so I generally don't recommend them there, but my practice, at least, is to use them relatively broadly.

Why do we do this? What do the trials tell us? Essentially, both drugs slow the progression of disease as defined by change in forced vital capacity. That has been the primary measure of disease progression in IPF, for many years, change in forced vital capacity over time. In particular, there has been a 10%

threshold where it is felt that if you change more than 10%, in six to 12 months, that is a clinically meaningful progression. Both drugs have been studied and shown to reduce the rate of decline by about 50% and to reduce the number of patients who have a 10% decline by approximately the same number, a third to 50%.

Importantly, these drugs are not cures. These drugs slow disease, significantly, but it is to be expected that patients who are treated with these drugs still will have progression of their disease. That is a really important point to convey to patients.

What are the differences between these two drugs? Efficacy is similar. I don't see a difference in efficacy. There are discussions about one drug perhaps having a mortality signal that is stronger than the other. When I look at the data, I think that they are quite similar. There are different secondary endpoints that were looked at in these trials. One drug appears to have an impact on rate of exacerbation of disease. The other one, it is unclear. Again, I don't see those as meaningful differences. I think that the efficacy, as best I can tell, is similar.

The differences are really mainly in tolerability. Both drugs are safe in terms of risk of LFT abnormalities, for example. It is about 3% in both. It is mainly a tolerability issue, so pirfenidone has two main side effects. One is gastrointestinal, the upset stomach, dyspepsia, nausea, occasionally diarrhea and photosensitivity rash. Pirfenidone is basically stomach and rash. Again, the rash is photosensitivity. Nintedanib's main effect is diarrhea. For pirfenidone, about a third of patients in the trials got either GI side effect or photosensitivity rash, so it is really important to counsel your patients about both of those.

Taking the drug with food is really important for both of those because the side effects are related to peak dose, circulating dose, which food reduces. Particularly the photosensitivity, patients need to protect themselves with UVA/UVB protection and clothing.

For nintedanib, the diarrhea is managed symptomatically. Loperamide or other antidiarrheals can and should be used, and it is about 60% of patients on nintedanib who have some degree of diarrhea.

In all cases, most patients were able to stay on both of these drugs with effective management of these side effects or active management of these side effects. It doesn't mean they didn't have persistent side effects, but they were able to tolerate them and stay on therapy, but it highlights an important issue with both of these drugs, which is that we are not sure of the impact of therapy, with these, on quality of life.

Quality of life was looked at, in the nintedanib study, and the best sense is that there is a signal that maybe quality of life is preserved a little bit better in the nintedanib group than in the placebo group, but I think that it is quite clear that, for some patients—particularly those that have real side effects from these drugs—their quality of life is worse, so the balance of that against this benefit of slowing disease is important to assess with each patient and the answer is different, depending on their goals and expectations.

Finally, I think one other question that is asked a lot is, which drug should you use? The answer sometimes is driven by the side effect profile. There is a difference in dosing. Nintedanib is twice a day. Pirfenidone is three times a day. That is important for some patients. There is more experience globally

with pirfenidone than with nintedanib, so in some cases the safety experience there is relevant, and more important.

I think that it is a very individualized decision. I can tell you, in my practice, it is split, and I think that it is likely because these differences in side effects and dosing, for different patients have different levels of importance, and it ends up that both of them are used, quite frequently.

BEYOND PHARMACOLOGIC THERAPY

The final point for discussion is about other treatment beyond pharmacologic therapy. I think, as was mentioned in the case discussion, pulmonary rehabilitation is a critical component, and in early cases sometimes it doesn't make sense, but in most cases, referral for pulmonary rehabilitation, if possible, is really valuable. If there isn't a pulmonary rehab center nearby, then structured exercise and education about their disease is probably a good replacement for that.

Management, active management of comorbidities is important, particularly reflux disease, which was also mentioned in the discussion. I think that it is unclear how reflex plays into IPF, but there is a lot of interest and potential for an interaction there. That is an area of active study now. Comorbidities like COPD, pulmonary hypertension, diabetes, these are all comorbities, and it makes sense to the clinicians listening, that would have an impact, but some of them may actually impact the primary disease progression, so actively managing evident comorbidities is critical.

I think that the last thing to mention is lung transplantation. It is the minority of patients with IPF who will be candidates for lung transplant either because of their age or comorbidity or resources. For the right patient or patients that you think might be good candidates, early referral for lung transplant is critical because many patients with IPF will have unpredictable courses. They will be stable for a period of time and then have an acute worsening where they have dramatic decline in their function. Early assessment—so that both medically and socially, essentially, patients can be prepared and ready; transplant centers can be prepared and ready, for this possible intervention—is really important.

Then, of course, in patients who are transplant candidates, having early discussion about expectations, about the fact that this disease is a fatal disease, that staying active, involved in clinical trials, taking their therapy, staying healthy, definitely has an impact on disease course, but also being realistic, that it is likely that most patients who have this disease will still die from it, and planning for that, through advanced care planning and making sure palliative measures are in place, is essential.

That is probably the thing that when patients come to see me in referral, is most commonly asked about, and most commonly had not been discussed previously. Again, it is completely understandable. It is a difficult conversation. It is a busy clinic. You have other things that you are dealing with, but we all recognize that that is the fundamentally most important issue for a lot of patients, particularly as they advance and get to more critical disease. I think that highlighting that is a key thing to deal with, and in treatment is essential.

Thank you all for joining us today. I hope this case was interesting and brought up a number of important issues around diagnosis and treatment. I hope you recognize that IPF is an evolving area and that there really is a lot of hope and new information here, and that in the years to come we will hopefully turn this from a progressive disease into a manageable disease. Thank you very much.