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Clinical Reflections®: Reflecting on Missed Opportunities in Nontuberculous Mycobacteria Lung Disease

Dr. O'Donnel:
Hello, I'm Dr. Anne O'Donnell, Professor of Medicine and the Nehemiah and Naomi Cohen Chair in Pulmonary Disease Research at Georgetown University in Washington, D.C. In this interactive clinical reflections CME activity I'll be discussing the management of nontuberculous mycobacterial disease with my colleague, Dr. Patrick Flume. Dr. Flume is Professor of Medicine and Pediatrics at the Medical University of South Carolina in Charleston, South Carolina. Dr. Flume and I will be highlighting the challenging management of nontuberculous mycobacterial lung disease by presenting two interesting cases.

The first case is a patient named Carol, who's a 61 year old life-long nonsmoker with a one year history of persistent and occasionally productive cough. She was diagnosed with gastroesophageal reflux disease by her family physician and was advised to take an over-the-counter anti-reflux medication. No further evaluation was done at that time and her cough has persisted now for at least a year.

The patient's only medication is over-the-counter omeprazole. Her past medical history is significant for a severe pneumonia at age 10, a history of a positive PPD skin test at age 17 for which she received a year of isoniazid treatments for latent tuberculous, and hip surgery four years ago. Of note, the patient was told at the time of her hip surgery that her preoperative chest X-ray was abnormal, but no further work-up was done at that time.

On physical exam now the patient's coughing in the exam room. She's a thin female. She has a mildly elevated temperature at 37.5 degrees Celsius. Her physical exam on auscultation of the lungs, she has a little bit of wheezing bilaterally with some bibasal or crackles, and auscultation of her heart reveals a mid-systolic click, consistent with mitral valve prolapse.

Now she has a CT scan at this time when I'm evaluating her and the CT scan shows bilateral right greater than left tree-in-bud bronchiolitis with some nodular changes consistent with plugging up the small airways.

So, given Carol's presentation, our first challenge question would be how would you have managed her case differently? And, the possible answers are I would have, A, obtained a repeat PPD test prior to hip surgery; B, acquired a sputum sample for AFB smear and culture at the onset of her cough; C, ordered a chest CT before the hip surgery; or D, ordered endoscopy.

Now, with this challenge question I would say the best answer is C, which would have been to obtain a chest CT before the hip surgery in light of the clinical presentation of chronic cough, as well as the abnormal regular plain chest radiograph. This was somewhat of a missed opportunity to diagnose her, what ultimately proved to be nodular bronchiectasis earlier in her course. And a teaching point here is that a lingering cough in a middle-aged nonsmoking woman may represent the diagnosis of nodular bronchiectasis and raises the possibility that the patient might be infected with nontuberculous mycobacterium.

The radiographic testing in conjunction with obtaining sputum cultures, particularly for acid fast bacteria would have been helpful at that time.

Simply attributing Carol's cough to gastroesophageal reflux, especially in light of having an abnormal chest radiograph was not the right choice at that time.

So this case represents a fairly common scenario that we see, which is a delay in the diagnosis of bronchiectasis and nontuberculous mycobacterial infection.

So the prevalence of nontuberculous mycobacterial lung disease is rising in the United States and worldwide. There's approximately, roughly 100,000 U.S. residents infected with these organisms. And most cases result in lung disease, although nontuberculous

mycobacterial infections also occur in other organs like the skin.

About three-fourths of the cases occur in coastline and gulf states in the United States and Hawaii actually has the highest incidence in the United States. But MAC infection, mycobacterium avium complex is very common. Although we see it a lot in the United States, it is a worldwide infection and mycobacterium avium complex particularly is responsible for between 64 and 85% of the cases in the United States. So, it's noteworthy that the prevalence of nontuberculous mycobacterial lung disease has increased by 8.2% per year between 1997 and 2007, with roughly 20 to 47 cases per 100,000 persons in the epidemiologic study that was performed in 2012. And overall there's a definite increase in the number of laboratory specimens positive for nontuberculous mycobacterial disease with 149% increase in positivity for MAC in the timeframe between 1994 and 2014, and this was published in a paper from Adjemian in 2012.

What about the burden of this disease on the patient? Clearly the case that we presented shows the problem of chronic cough, which is more than just an annoying problem, but something that contributes to generalized problems for the patient. This includes worse physical functioning, worse general health, worse social functioning with the embarrassment of chronic cough in a social situation. Occasionally the patient has chest pain and chest discomfort and shortness of breath. And a key feature of this disease, although it's a common complaint, is poor energy or fatigue. Patients often complain that their energy levels are low, that they're mildly short of breath with exertion and that the cough is extremely bothersome and intrusive into their lives.

What about the mortality associated with NTM lung disease? Fortunately this is not generally a mortal disease, although there is information in the literature about a 4.3-fold higher chance of respiratory failure in patients with nontuberculous mycobacterial lung disease. And, some data from the literature shows that the average life expectancy's approximately 16 years and the 5-year all-cause mortality is greater than 25%. So clearly this is a disease that causes a significant burden on the patient and also can become a progressive disease that contributes to morbidity and sometimes mortality increase for an individual patient.

Moving on to treating this disease, there are significant burdens that the patient and the physician, the treating physician has to deal with in treating patients with nontuberculous mycobacterial lung disease. If the patient requires an antibiotic treatment, that antibiotic course is generally lengthy, generally 15 to 18 months.There is a high risk of adverse drug reactions. We're using generally at least three antibiotics in the treatment regimen and so, the chance of having an adverse reaction to one of the drugs or several of the drugs is high. And there are also drug-drug interactions that have to be considered in these patients, many of whom are on other chronic medications as well.

The treatment failure rate is quite considerable, depending upon how we define treatment success or treatment failure. Only about 50% of patients permanently clear their sputum culture to negative and remain negative over extended followup.

So now let's talk about what you know in light of this patient's presentation. I'm going to ask Dr. Flume to join the conversation here and address the question, what raises your index of suspicion in an individual patient for nontuberculous mycobacterial lung disease?

Dr. Flume:
We've learned a great deal over the last several years evaluating the patients that have been diagnosed with NTM lung disease, and there are certain features that stand out such that we feel that we kind of know what the risk factors are. Certainly as Dr. O'Donnell's already stated, that this prevalence increases with age, that we see the diagnosis in older patients. There's a predominance of women who have the diagnosis.

There are patients who have underlying lung disease or who have other immunodeficiency aspects either because of their underlying autoimmune disease or medications, do have an increased risk of NTM infection. For example, bronchiectasis, the risk is thought to be almost 190-fold greater in patients who don't have underlying lung disease. And in COPD, is 16-times the risk factor. So those patients who have underlying lung disease. But a classic presentation of our patients is very much like the patient described here, being very thin and older with the persistent symptoms.

Dr. O'Donnell:
So Dr. Flume, would you comment on what are the current diagnostic criteria for nontuberculous mycobacterial lung disease?

Dr. Flume:
Sure. Once one has a suspicion that NTM might be the culprit to account for the symptoms, then one needs to engage in diagnostic testing to try to confirm that diagnosis. Years ago the American Thoracic Society and the Infectious Diseases Society of America came together to establish guidelines to define NTM lung disease. And, it's been a pretty useful definition, even though it may seem a bit dated. But essentially there's a triad of features. One has to have symptoms and signs that are consistent with the diagnosis of NTM infection. These typically include pulmonary symptoms like cough. And not just a new cough, but a chronic, persistent cough. Oftentimes productive of sputum. Occasionally productive of hemoptysis and there may be some chest pain. But the other symptoms that one might describe, or as much as Dr. O'Donnell has defined, they're nonspecific constitutional symptoms such as a low grade

fever or night sweats. There might be weight loss associated with a poor appetite, and fatigue is a real common symptom. And they're nonspecific for that.

So in that patient you then would proceed to getting imaging. There should be imaging features that are consistent with the diagnosis. And chest X-ray may not be sufficient and high resolution chest CT would be very useful to not only give you information about whether this is compatible with that diagnosis, but potentially demonstrating areas of target if they can't produce sputum.

And so the features include nodules, there may be bronchiectasis, and then some patients will have actual cavities.

As can be shown in these images they're examples of both nodular densities, but also cavitary disease, and so we use the term fibronodular or fibrocavitary appearance to describe what we see. So on the left panel, what we can see in the right lung is just small nodules, both centrally and peripherally, predominantly in the right lung compared to the left lung, but the left lung is not completely absent of these features. And on the right panel you can see the development of a cavitary lesion in the left posterior and there's volume loss of that left lung. That cavity is pretty typical, in that it looks to be thick-walled. And these are features that definitely demonstrate evidence of progression. You can also see some mild features of bronchiectasis in this image.

That alone again is still not diagnostic of NTM lung disease. You need to have evidence of the bug and which bug that you've got and so you need to have microbiologic evidence. In many patients the best approach is just to get a sputum. Some will produce it spontaneously while others may need to be induced, using hypertonic saline. In patients in whom they're unable to expectorate sputum, or we can't make the diagnosis and you're still suspicious, then it may be necessary to perform bronchoscopy to try and identify the sample.

And typically we send these for culture and a smear will be performed. We have to tell patients to be patient with us because these bugs don't necessarily grow that quickly and we may need time.

We want to be certain that the organism is coming from the lung and so if you obtain it by bronchoscopy you can be quite satisfied that that organism was present in the lung. But in those samples which are obtained from sputum, there is still some concern there could be contamination from the mouth, which may not represent lower airways infection. And so the ATS/IDSA guidelines typically would like to see at least two positive sputum samples or if you get something through bronchoscopic measures, either by wash or lavage, or even considering a biopsy and demonstrating granulomatous inflammation that would be compatible with NTM infection.

Now a key caveat to the diagnosis is even if you have someone that has symptoms, radiographic features compatible with NTM lung disease, and you have an organism, you still want to make sure there is not some other etiology accounting for their symptoms, to make sure that you are in fact treating the right thing.

So why is it important to make the diagnosis?Number one is your patient can become frustrated if things take a long time before an answer is determined. As I mentioned, you want to make sure there's not some other cause of their symptoms, so we don't treat just because they have NTM present in the airways. And some patients are not necessarily going to benefit from treatment, so we want to make very certain that the reason we're treating is because of the infection and that they are likely to benefit from antibiotic therapy.

But even if we are not certain that they need to be treated, there are patients who are going to progress. You see the patient who has cavitary lung disease, that is a clear example of progression of treatment, and we would like to be able to intervene earlier to try and prevent further decline. So it's very important in patients who you do have some suspicion to make the diagnosis because that does give you an opportunity to be able to monitor them for any signs of progression to intervene appropriately.

Dr. O'Donnell:
So our next case is a patient named Jara, who's a 63 year old woman who was diagnosed with nontuberculous mycobacterial lung disease approximately three years ago when she experienced a chronic cough and mild, persistent fatigue. A CT scan at that time showed mild bronchiectasis and tree-in-bud nodularity, and two sputums then were positive for MAC.

Her past medical history was essentially unremarkable. She moved to the United States from India, approximately 20 years before this diagnosis, but had no history of tuberculosis. And she is otherwise healthy.

So appropriately, three years ago the patient underwent a three drug regimen of azithromycin, rifampin and ethambutol, which were given three times per week. The treatment was continued for 12 months. She had one sputum culture done during the course of the treatment, at approximately six months into the therapy, and that culture was positive for Mycobacterium gordonae.

Her symptoms resolved on the treatment and she completed the treatment as noted in 12 months. And then three years later she presents again with recurrent cough and came to me for a second opinion.

On her physical exam she was a well-appearing female, tall, thin, with normal temperature and normal vital signs, and auscultation of

her lungs revealed bilateral rhonchi, crackles and scattered expiratory wheezes.

Her CT scan at this point, now three years after initial diagnosis, showed worsening changes with cavitation and scattered pulmonary nodules, as well as bronchiectasis with mucous plugging. And this was a change from her prior scan.

So the second challenge question about Jara's presentation is how would you have managed her case differently? And I want you to select the best answer. I would have A) added liposomal amikacin to her initial pharmacologic regimen; B) obtained routine AFB cultures every month during therapy, or at least every three months; C) continued her initial pharmacologic regimen for six months after conversion of sputum cultures to negative; or D) ordered sensitivity testing on the cultured Mycobacterium gordonae.

Now in my opinion the best answer here is B, obtain routine AFB cultures every one to three months during therapy. And the reason for that is that it's very important to document that the treatment is working, number one, and two, the treatment duration is dependent upon the time of sputum conversion.

So, the recommendation from the ATS/IDSA guidelines is that patients be treated for 12 months with the antibiotic regimen after the sputum converts to negative. So it's very important to monitor the sputum AFB cultures while on treatment.

I would not have added liposomal amikacin to her initial pharmacologic regimen. We'll get into that in a minute. As mentioned, I said that 12 months is the appropriate timeframe for continuing antibiotics after sputum conversion. And I think it's interesting to note that many times patients who are on treatment for MAC do culture a different organism and in this case the patient cultured Mycobacterium gordonae while she was on treatment. Mycobacterium gordonae is not a pathogen and so would not have prompted any change of therapy.

So, moving on to what the recommended pharmacologic regimen is for nontuberculous mycobacterial lung disease due to MAC. If the patient has nodular bronchiectatic disease, the recommendation is three drugs, macrolide, ethambutol and a rifamycin, given three times per week. If the patient has fibrocavitary disease, the recommendation is those three oral drugs plus an injectable aminoglycoside and the treatment should be given daily and a cavitary patient potentially may need surgery after receiving antibiotic treatment.

One new thing that we have in our armamentarium now is the liposomal amikacin for refractory nontuberculous mycobacterial lung disease. This drug was approved in 2018, specifically for patients who remain culture-positive, despite receiving the guideline-based antibiotic therapy as mentioned before.

This study was an open-label randomized trial of 336 patients, who were already on a background regimen for their MAC lung disease, and then liposomal amikacin was added to the regimen because of continuing positive sputum cultures. And what happened in the study was that 29% of patients who received a liposomal amikacin as the add-on therapy versus 9% on the background regimen converted their sputum culture to negative.

What are the adverse effects of liposomal amikacin? These include dysphonia occasionally severe voice problems. Additionally many of these patients did develop cough, bronchospasm, and a smaller number had hemoptysis, and a very low number of patients had ototoxicity from the liposomal amikacin. Some other less common adverse effects were upper airway irritation, musculoskeletal pain, fatigue or asthenia, exacerbation of the underlying pulmonary disease, and rarely GI side effects such as diarrhea and nausea.

So to conclude, the general principles for treating nontuberculous mycobacterial lung disease, number one, the patient should be evaluated for an underlying treatable disorder, such as cystic fibrosis or an immune disorder, and that underlying disorder should be addressed. Two, it's very important to monitor sputum cultures for mycobacterium while the patient is on treatment. The goal of therapy, per the ATS/IDSA guidelines is to get conversion of the sputum culture from positive to negative. And patients should remain on treatment for 12 months after converting to negative.

The adjunctive therapies are very important in this disease, as Dr. Flume mentioned, treating the underlying bronchiectasis is a vital part of the care of these patients. Airway clearance, smoking cessation if the patient is a smoker, and, optimization of nutritional status and cardiovascular fitness are also key components of treating these patients in a holistic fashion.

So, the problem in this disease is that true microbiologic cure is quite allusive. Approximately 70% of patients do convert to negative while on initial therapy, but 40 to 50% of these patients either relapse or get infected with another strain of mycobacterium avium complex or another nontuberculous mycobacterial organism after therapy is completed.

The other problem is this treatment is complex as we've noted, and adherence and side effect problems can be quite difficult.

So what are the adverse effects of the standard treatments? So as, as we've said, the standard treatment for nontuberculous mycobacterial lung disease includes four classes of antibiotics, the macrolides, the ethambutol, the rifamycins, and potentially aminoglycoside by injection.

And some of the noteworthy things in these patients that need to be monitored for are GI toxicity from the macrolides, particularly optic neuritis from ethambutol, and liver function abnormality or, bone marrow suppression from rifampin. And of course the injectable aminoglycosides have their own toxicities including vestibular/auditory issues and renal dysfunction.

So patients on treatment need to be monitored closely by the treating physician, both for any kind of adverse clinical complaints related to the antibiotics, and they need monitoring for their eye abnormalities, and for lab testing abnormalities.

So a question that comes up frequently is what is the role of drug susceptibility testing in nontuberculous mycobacterial lung disease management. And I'm going to ask Dr. Flume to address this question.

Dr. Flume:
So in-vitro susceptibility testing is actually highly controversial. There are papers that have found no association with antibiotic susceptibility and outcomes and then there is a more recent publication that suggests that actually it is highly relevant. And the challenge in assessing in-vitro susceptibility testing in that manner is you have multiple drugs that you're using to treat the patient and focusing on a single concentration may not be the most effective means of knowing that relationship.

Nonetheless, patients whose organisms are resistant to some of our key drugs, especially the macrolides and aminoglycosides, generally have worse outcomes than others. And so it's my belief that we should have some knowledge to guide our therapy, to try and pick a course of regimen of antibiotics that's likely to result in benefit, assuming you can get adequate dosing.

And so it is our practice that when we get newly isolated specimens, that we send it off for testing and you can see an example of a result that we get from our testing. We are not performing that testing at our facility. We are using a reference laboratory for that purpose because we feel that it is has been much more consistent with the results.

So the keys here are the susceptibility to the macrolide, particularly for MAC and for abscessus because this is a very, very important drug in the treatment of these patients that has been shown time and again. And the aminoglycosides, particularly amikacin, is a key drug that we also use to assess it.

Dr. O'Donnell:
Dr. Flume, would you comment on compounds or regimens that are in mid or late phase clinical studies, drugs on the horizon for treating this complicated infection?

Dr. Flume:
Sure. The challenge for physicians working in this space all this time is that there weren't any novel therapies available for their use. And so, we are primarily using drugs for an alternate purpose to treat these infections, based upon *in-vitro* activity in the laboratory.

The good news is that as people have begun to appreciate that this is a much bigger condition than previously realized, and it's a much more challenging condition to treat, there's a lot of activity, a lot of new compounds that are in pre-clinical. As for those that have moved forward into the clinical space, into Phase 2 and Phase 3 trials, some of those are still geared towards using existing therapies, but really beginning to look at the regimen to try to define what is really the best regimen, acknowledging the comments that Dr. O'Donnell's already raised in terms of the challenges of taking these therapies. And so some of those include using a macrolide, such as azithromycin or clarithromycin, as part of a two or a three drug regimen. And so in combination with ethambutol and rifampins or with comparing moxifloxacin to a macrolide.

In terms of other agents which are being repurposed, clofazimine is a therapy which has been approved for the treatment of another mycobacterial infection, that being leprosy, but has known activity with both MAC and with abscessus, and so has been made available to us through special programs as an orphan anti-mycobacterial therapy. And so has been made available through a research model to treat them.

And then there are some other novel therapies which take a different approach to usual antibiotic therapy. So one that has gotten a lot of attention is inhaled nitric oxide after demonstration that nitric oxide, given at high concentrations, can be effective at killing mycobacteria in the laboratory setting. Then defining regimens that allow for the drug therapy to be used safely in humans, because nitric oxide is also toxic to people typically causing methemoglobinemia. And so some very creative minds have found regimens that show promise, and so in early phase studies, exposing patients to high concentrations of inhaled nitric oxide are currently in Phase 2 studies.

And then an alternate approach is trying to amplify the normal host defenses in combating mycobacterial infections. And so recombinant human granulocyte macrophage colony stimulating factor, GCSF, has been used to try to activate the macrophages to do a better job of managing. And, built on the support of some early clinical experience, this has been moved into clinical trials and is currently under investigation.

Dr. O'Donnell:
Alright, well, thank you, Dr. Flume. That wraps up our presentation. Thank you for participating in this CME activity, and please do not forget to take the post-test and complete the evaluation in order to receive your CME credit.