

Medical Update: Pitfalls in the Diagnosis and Management of Tuberculosis
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Archive Transcript

Rajita Bhavaraju: Good afternoon, and welcome to the second medical update of this year. Today's web-based seminar is called Pitfalls in the Diagnosis and Management of Tuberculosis.

My name is Rajita Bhavaraju, and I'm a Training and Consultation Specialist at the Rutgers Global Tuberculosis Institute at the TB Regional and Training Consultation Center for the Northeast United States.

Today's program is sponsored by the institute.

The objective for today's presentation are on this slide. This web-based seminar for clinicians will move beyond the basics of TB management and focus on some of the challenging characteristics of TB presentations and manifestation which may complicate, and at times delay the diagnosis and treatment.

Case examples will be included to illustrate these complexities. In addition, speakers will share experiences on how to manage such cases using existing resources.

Our faculty today are Dr. Katherine McGowan from the Shattuck Hospital in Massachusetts, Dr. Ameer Patrawalla from here at Rutgers University, Dr. Elizabeth Talbot from Dartmouth, and Dr. Marie Turner, also from the Shattuck Hospital. All of our faculty today share a wealth of knowledge and expertise in today's topic.

The seminar today will consist of several parts. After this introduction and some brief housekeeping details, Dr. Patrawalla will start us off with some background and overview of some of the challenges that can occur when diagnosing TB. Then, Dr. Talbot will illustrate some of these challenges with an interesting case of TB meningitis. We'll then hear from Doctors McGowan

and Turner with some additional interesting cases to further address the important issues in the management of TB.

Now, I'd like to turn the program over to Dr. Ameer Patrawalla. Dr. Ameer Patrawalla will be presenting the first talk on the pitfalls in the diagnosis and management of tuberculosis. Dr. Patrawalla?

Ameer Patrawalla: Thank you, Rajita, and thank you for inviting me to speak today and welcome to all of the attendees.

So, I'm going to start generally by reviewing some of the potential challenges you might encounter in diagnosis and management of tuberculosis, and then going to some more specific scenarios with some cases interjected that hopefully will be helpful to you.

OK. So, in terms of diagnosis of TB or tuberculosis disease, I think number one, we all have to realize that, especially in the U.S., as the number of cases are falling, we have to continue to maintain a very high index of suspicion. Currently, I think all of us pay a lot of attention to those patients who fall into our usual risk group, so, patients who are coming from outside the country where the risk of tuberculosis is much higher, patients who have HIV, and other such risk groups. However, one thing to realize is that other risk categories are growing in prevalence and becoming groups where we see a fair amount of tuberculosis.

So, some of these diseases, which are quite common, are things like diabetes where the risk of TB maybe as high as three times that of a person who's not diabetic. Certain autoimmune diseases especially because we're using a lot of biologic agents to treat those diseases such as TNF blockers or tumor necrosis factor blockers that may increase your risk of tuberculosis, certainly patients both who are pre and post transplantation are at high risk for TB, and we're certainly seeing more of those patients as well in this country, and also chronic kidney disease which is a very large group of patients in this country and a growing group, and those that we see less frequently but we do still see those that are malnourished.

And along with maintaining this high index of suspicion, we'll talk a little bit more about this, but we also have to realize that just because the sputum smear or acid fast bacilli is negative that by no means rules out tuberculosis disease. And, in fact, as we'll see later, up to 50 percent of patient with pulmonary TB will be smear negative.

Extrapolating on this, we're going a little bit further with this. So, certainly settings where diagnostic delays in terms of tuberculosis are much more common, and that certainly in populations with HIV, also in extrapulmonary tuberculosis, which we'll talk about more, and then in this larger category of patients who have smear negative disease. And I think these are settings where we have to particularly vigilant.

So, you know, one thing to consider when you're trying to diagnose somebody with tuberculosis, and often this is an afterthought, but we really have to do a very thorough microbiologic workup in those cases, especially if the case appears atypical or unusual. This may actually require multiple or even repeated diagnostic procedures, often invasive procedures if we're talking about extrapulmonary disease. And often, when we're doing invasive procedures, we don't routinely send cultures on those specimens, and so that's something to consider when you're planning your diagnostic workout.

And of course there many resources available, your local as well as regional public health authorities as well as TB experts can help quite a bit in assisting with TB diagnosis in these less usual circumstances.

So, putting it all together, TB diagnosis really rests on multiple different evaluation tools. So, our microbiologic tools are clearly one part of that, but again, by no means, are going to be a 100 percent useful to you all the time. And you certainly need to know the limitations of the tests that you're using, especially some of the more rapid tests.

Imaging can certainly help, and I'll show you some examples of that, especially when we're talking about extrapulmonary TB. But, I think, you know, your diagnosis is really going to rest primarily on the patient's risk factors, their epidemiologic risk factors, the local epidemiology in your

community, and knowing who is at highest risk in your community, and ultimately, your clinical suspicion for TB disease. And if you have very high clinical suspicion but no culture, there are no positive microbiologic assays, that certainly doesn't mean that they can't still have TB, and that's something you should consider.

So, what about TB management once you've already made the diagnosis? So, number one, multidrug therapy is certainly the cornerstone of TB management. And if the patient cannot be on a reliable multidrug regimen, you really have to consider that all medication should be held until you can come up with an appropriate regimen for that patient. We certainly use directly observed therapy in pulmonary TB, but there are certainly more complicated cases involving extrapulmonary TB or patients with significant other comorbidities like HIV, where DOT maybe especially useful and improve the outcome in those patients as well. So, if it's feasible for you, I would highly consider that.

We stress very highly that you should closely follow patients with TB disease. You have to pay very detailed attention to their symptoms, imaging, their microbiology, their drug susceptibility as well as laboratory monitoring, if that's appropriate for your patient. And one way that you could feasibly do this is with what's called a drug-o-gram where you can actually – see if I can point this out – where you can actually enter the drugs that the patient's on, the durations that they're on and off the drug. You can also enter their smears and their culture results as well as their sensitivities. And this can certainly help you track the patient and help monitor - monitor the patient to see if they're receiving appropriate therapy and if it matches up with improvement in their microbiology.

So that's just one example, I'm sure many of the people listening have different systems for monitoring their patients. And I think as long it's a comprehensive system and it works for you, then I think that that's fine. We should be aware of adverse effects and drug-drug interactions. Patients are on multiple other medications often times, and have multiple other comorbidities that can be impacted by TB treatment, and so, we certainly need to know what's to expect when we put people on these regimens.

I mentioned comorbidities. I think most of the patients I see these days with tuberculosis have multiple other medical problems that are also potentially unstable. And their TB treatment may impact their glycemic control, for their diabetes. Their TB treatment may impact their blood pressure control if they're hypertensive. And certainly, if they have HIV, we know that the rifamycins will interfere and interact with many of the HIV medications, many of the drugs that we use these days for transplant patients. And so all of these really needs to be discussed with the patient and needs to be followed.

And I think to that end, open communication with the patient's other healthcare providers, as well as the public health authorities and any hospitals that may be involved is also really key.

And I think most important on this entire slide is education in terms of the patient and caregiver can understand repeated attempts at education in multiple different forms by multiple different healthcare providers is really important. I think, if the patient understands what to expect as a result of some of these medications and some of the side effects they may have, their care will be much smoother and they'll be much less likely to default.

OK, so I'm going to move on now to talk a little bit more specifically about some of the things that I've already mentioned and I'm going to use some cases that I've seen in the past few years to hopefully try and highlight some of those points.

So this is the first case and this is a gentleman I saw a couple of years ago. This 29-year-old Indian man who presented with right leg pain which he had complained of for about four years. He noted right ankle swelling in addition to the pain about a year ago and had been evaluated by our orthopedic clinic. He denied any other systemic symptoms. A little prior history, about five years previously, he had developed a cough and fever and weight loss while visiting Denmark from India. And he had been treated for pneumonia but did not have any improvement. He recalls that he was tuberculin skin test positive. He then returned to India and his physicians there felt that he most likely had pulmonary TB and he was started on a fixed-drug combination pill including

isoniazid, rifampin and ethambutol, and he states that he took all of these medications for six months and he had significant clinical improvement.

A year later, he then moved to the U.S. and several years later is when he developed his right ankle swelling and presented to us. So, this is a plain film of his right ankle. And I think you hopefully can see here at the distal end of the fibula, there is an osteolytic region here in the lateral malleolus from the distal part of the fibula, as well as a little bit more subtle but some soft tissue swelling around it as well.

And then he had a CT scan as well of the same area and what you'll notice here again, this is the distal fibula, this is the distal tibia, and there is this sort of punched out area in the bone here with a large soft tissue mass surrounding it, and then you can also see some punctate areas of calcification here.

So, the concern at the time was that he had a malignancy, that he had a soft issue and bony malignancy. So, he underwent partial excision of his fibula and a deep biopsy of the soft tissue and the bone. And the findings during surgery were consistent with that. However, his final pathology revealed necrotizing granulomas. So, if we look at the micro, the initial specimens were smear negative for acid fast bacilli, and as we'll see, that's not really uncommon with extrapulmonary TB.

When we asked the pathologist to look back at the specimen, they were able to find in the tissue one solitary bacilli here, right in the middle.

We requested a PCR on the tissue and the MTB PCR was positive. And ultimately, several weeks later, all of the specimens grew as tuberculosis, grew *M. tuberculosis*.

So, I think this is an example and a relatively typical example of how long it can take to recognize somebody with an unusual presentation of tuberculosis. Even though this gentleman had many risk factors and had clearly had pulmonary TB in the past which clearly, you know, increased his risk for having subsequent episodes of tuberculosis, it can still be very challenging to make a diagnosis, and often requires invasive procedures and collaboration between multiple different specialties.

So, extrapulmonary TB, I think, is one of those situations like I mentioned earlier that we really have to focus in on because in the U.S., extrapulmonary TB accounts for about a fifth of all TB cases that we're seeing. And this quite consistent across other developed countries as well. Overall in the U.S., the rates of TB are actually declining, but the proportion of extrapulmonary TB is actually increasing. In several studies that I've listed at the bottom of the slide, we see an association between extrapulmonary TB more frequently with women, slightly more common in individuals who are foreign born, certainly in individuals of African or Asian descent, and certainly in populations that are more immunocompromised than others, including patients with HIV who actually have a higher risk to go on and develop disseminated TB, both pulmonary and extrapulmonary TB.

Interestingly, extrapulmonary TB seems to not be associated with some of the risk factors that we would consider more usual or more traditional. So it does not seem to be associated with incarceration, alcoholism or homelessness, at least not in the United States. And of course, extrapulmonary TB encompasses a large number of different organ systems. So, meningeal and lymph node TB is seen frequently in children, whereas genitourinary and bone or joint TB is generally seen more frequently in older adults.

In U.S.-born patients, meningeal and pleural TB seems to be more common, whereas lymph node TB seems to be more common in those that are foreign born. And it seems that there are certain sub-populations that have a higher predilection for certain organ systems, and that's not really clear why, but – for example, South Asians seem to present more frequently with lymph node TB.

So, this is a graph, a bar graph from a paper in the U.S. that looked at all cases of extrapulmonary TB that were reported between 1993 and 2006. The open circle here are the number of – sorry – the proportion of pulmonary TB cases. The white bars are the number of pulmonary cases. And as you can see, the number of pulmonary cases has been decreasing and the proportion of all TB that's pulmonary has also been slightly decreasing.

These are the extrapulmonary cases and they have been relatively steady, maybe a slight decline. But as you can see, the proportion of extrapulmonary TB cases has actually slightly risen over the past 15 years or so.

And a further breakdown of where we see extrapulmonary TB and the sites of disease show you that about 40 percent of all extrapulmonary TB is lymphatic, certainly, with most of that about a quarter being cervical. The next largest category is pleural TB, and then after that, you see a smaller proportion of bone and joint, and even less frequently, meningeal, genitourinary and peritoneal. So, our patient fits into this category with bone and joint disease which accounts for about 11 percent of all extrapulmonary TB in the last 13 years or so, certainly more frequent outside of the U.S., where upto 15 percent or even higher of all extrapulmonary TB maybe musculoskeletal.

So this is an even further breakdown of what our patient had which was musculoskeletal TB. And this is actually a study from the U.K. looking at all the musculoskeletal cases in one region over about six years. And I think this data holds true for what we see in the U.S. as well with the majority of musculoskeletal TB being focused on the spine, and then your larger joints are most prevalent, after that was the small joints, your wrist, fingers and ankle really contributing very small proportions of disease. And so, I think what this tells us is that, again, we have to be really vigilant in these cases because we may only see one or two cases in the U.S.

So, why is diagnosis of extrapulmonary TB so difficult? Well, one, it tends to be paucibacillary and much more difficult to detect on smear and even on culture. Again, diagnosis may require invasive procedures and may require repeated procedures. And this involves a lot of collaboration across sub-specialties.

Some of the rapid test that we use that you may be hearing about more recently maybe quite useful in this group of patients and I think you're going to hear a little bit more about GeneXpert later on. But in a large cohort of patients in New York City, they actually looked at all of the nucleic acid amplification tests that they had done and found that the sensitivity in extrapulmonary disease was quite good, as high as 80 or 90 percent, certainly

higher if the culture ended up being positive – I'm sorry – the smear ended up being positive.

So, your nucleic acid amplification test may certainly be useful in this group of patients. It's certainly easier to get the test done on a fresh specimen rather than waiting until the specimen has already been fixed and sent to pathology. So, clearly, something that if you can think about it while the patient is having the procedure and send it right away.

And GeneXpert also seems to have good sensitivity and very good specificity in extrapulmonary TB, certainly in tissue and in certain body fluids. And I'm sure we'll hear a little bit more about that later on.

In terms of treatment of extrapulmonary TB, it's really similar to treatment for pulmonary TB, except that you – most people would extend the duration of treatment up to usually around 12 months in meningeal TB or in CNS disease. And most of us would also extend treatment in bone and joint disease usually to nine months. And a lot of this has to do with theories about drug penetration into these areas, as well as the fact that it's really difficult to monitor these patients. Again, you're not going to be able to get repeated samples from somebody's bone. And so, you may need to use other tools, certainly clinical symptoms as well as imaging can be very useful.

So, just to summarize why there are so many challenges in diagnosing extrapulmonary disease, certainly, fewer TB cases, especially in the U.S., has led to lower suspicion overall for tuberculosis. Our public health focus is primarily on pulmonary TB because of the transmissibility. And so, that may be part of the reason why we see more delays in extrapulmonary disease. As we've seen and we've discussed, the risk factors differ between patients with pulmonary and extrapulmonary TB and we may need to use different tools to identify those patients. The diagnosis as we have discussed is clearly more difficult and often takes much longer, sometimes months to years. And patients tend to present in a more indolent fashion, and so that definitely makes it more difficult as well. Treatment efficacy and culture conversion can be difficult to detect.

And although this is a challenge, I think it's, you know, also a necessity that we really need to have a multidisciplinary approach involving multiple different specialties.

So, I'll move on to the next case and I'm running short on time so I may not get to my last few slides. So, this is a 29-year-old physician from Pakistan with a dry cough for two months. She had no fever, no night sweats, no weight loss and she reported that she was TST-negative six months previously.

This was her chest x-ray which shows bilateral upper lobe infiltrates, here and here, with a sort of interstitial quality to it and with some volume loss in the right upper lobe. So her induced sputum was smear-negative, her QFT – sorry. Her QFT or QuantiFERON Gold was positive. Because of our high suspicion for a TB disease in this patient, given her x-ray and given her risk factors, she was started on multi-drug therapy for tuberculosis and her cultures were positive about four weeks later.

So I think this case illustrates what we were talking about with smear-negative TB and that it can sometimes lead to more diagnostic delays and treatment delays and so you have to have a really high index of suspicion in these patients because if you had, you know, felt that she was smear-negative and therefore did not have tuberculosis, we would have delayed her treatment by about four weeks until her cultures came back.

So little bit on smear-negative TB. So sputum smear microscopy sensitivity is about 50 percent, so again if we rely on smears alone, we'll miss about 50 percent of cases. If your lab uses fluorescence, you may take up a few more cases but remember that it takes about 5,000 organisms per milliliter of sputum to be picked up by smear alone. And your smear sensitivity will be even lower in patients with HIV and in children. So smear negative TB can certainly lead to that both diagnostic and treatment delays. We see smear negative TB increasing especially in settings with high HIV prevalence. And up to about 40 percent of cases in the U.S. that are reported are smear negative. And I think even more importantly to recognize is that smear negative TB in several studies now accounts for about 10 to 20 percent of all TB transmission. So smear negative TB can clearly be transmissible and so just because

somebody is smear negative certainly does not mean that they're not infectious. And again in multiple studies, this number has been quite consistent that a patient with smear negative TB results in about one quarter the numbers of secondary cases that somebody was smear positive TB. So clearly it's not as transmissible as somebody with smear positive disease but can clearly lead to quite a number of cases.

And so again in our case, had we waited four weeks to start her on TB treatment, we would have allowed not only four weeks for her disease to get worse and for her to develop symptoms but also an additional four weeks that she may have transmitted disease and I don't know if you remember but she was a physician, she was actually an obstetrics resident. And the outcome, you know, could have been very serious in that situation.

So again, smear negative TB is common and it is transmissible. So infection control measures are certainly necessary. We talked a lot about the treatment delays, contact tracing is essential but again because of the diagnostic delays, it too, can be delayed and lead to more transmission. Rapid diagnostic tests are moderately sensitive in smear negative disease and may help mitigate some of the above, so both a nucleic acid amplification test as well GeneXpert can be useful in this setting and treatment is, of course, similar to patients with smear positive TB.

So I will probably finish with this last case, unless we have few more minutes for the very end, but this is a 45-year-old woman who's currently incarcerated with the history of injection drug use and she complained of cough, fevers, sweats and weight loss for two months. This is her chest x-ray which shows bilateral upper lobe volume loss as well some nodules here and here and some pleural thickening and scarring here. And unfortunately we did not have an old chest x-ray to compare this to. She was smear negative multiple times because of her symptoms, because of her chest x-ray and because of the fact that she was in a high-risk congregate setting, she was started on antitubercular therapy. Her cultures actually remained negative even at the end of the two-month period and she had minimal improvement on her chest x-ray but she really had resolution of her symptoms.

So I'm going to speak quickly about culture negative pulmonary tuberculosis which I think is something we almost never talk about. The clinical and radiologic picture is quite similar to active TB, however, your cultures remain negative and this maybe for several different reasons. The patient may have very few organisms and they just don't grow in culture. The specimen processing may have had some problems with it and there's an idea that there maybe some temporal variation in bacterial shedding. So you may just not be picking it up at the right time.

We should certainly at least get three good quality sputum that might require an induced sputum. You can consider other diagnostics such as bronchoscopy, although, in several studies, a BAL is not really any better than a good induced sputum. And in the U.S., of all the reported cases, it accounts for about 15 to 20 percent of reported cases in the U.S. And this is a treatment algorithm from the American Thoracic Society, CDC, IDSA joint statement from 2003.

And if you look here, this is your at-risk patient with an abnormal chest x-ray, whose smears are negative and you're highly suspicious for tuberculosis. In that case, you would start them on a multi-drug regimen. And at two months, if your cultures remain negative, you would repeat their imaging at that point and assess any change in their symptomatology and if those had improved, then you would consider that that patient has culture negative tuberculosis and you would go on and treat them probably for an additional two months with isoniazid and rifampin. So you could stop the pyrazinamide and ethambutol at that point and you would treat them for a total of four months.

If, on the other hand, their chest x-ray has not changed and their symptoms have not improved, you really need to at that point consider alternative diagnoses, however, if you finish and you stopped their treatment at that point, you have also treated them for latent TB infection because they've been on both rifampin and pyrazinamide for two months. And although that's not a recommended regimen for LTBI, it's certainly one that's efficacious.

So in summary with culture negative TB, a four-month regimen of isoniazid and rifampin especially with pyrazinamide and ethambutol for the first two

months as well has been shown to have a very low relapse rate. And there's really not much data on this. Maybe Dr. Talbot can tell us a little bit more but GeneXpert may have some utility here as well.

I have a couple of slides left to sort of give you a flavor of some atypical radiographic presentations that you may encounter. So lower lobe infiltrates, again, generally with TB disease we talked about upper lobe and cavitory infiltrates, however, sometimes we see lower lobe disease and sometimes along with those lower lobe infiltrates or independent you may have a lot of mediastinal adenopathy. This clearly is seen commonly in children with primary TB but you could also see it in some adult population especially in HIV.

Miliary or disseminated TB also is another presentation of tuberculosis that can sometime be missed or under recognized. Pleural effusions accounts for a fair number of the extrapulmonary TB cases that we see as we saw before. Rarely you can see masses although this is really unusual. And then actually quite frequently in the older literature, cavitory TB would present with a pneumothorax. We certainly don't see that often anymore but it's still a possibility.

So this is sort of a classic picture, a classic radiograph of somebody with cavitory tuberculosis. This is a 31-year-old man from Ecuador with cough, night sweats, fevers and weight loss and as you can see, he's got bilateral upper lobe dense infiltrates as well as multiple cavities here, here, and here. So this is one that would most likely not be missed. This is again that 29-year-old physician with with a dry cough for two months and we already went over her chest x-ray but this is what you may see in somebody with non-cavitory tuberculosis. Again, pretty distinctive, pretty suggestive of tuberculosis but certainly not as clear cut as the x-ray before this.

So this is a patient who had a left lower lobe infiltrates here with, on CT scan, also a left-sided pleural effusion. And her story was that she had a cough and fever for one week. She had a history of advanced HIV. She was originally treated for left lower lobe pneumonia and a parapneumonic effusion but didn't have any improvement. Her QuantiFERON was negative. Her sputum

smears were negative but ultimately her sputum, pleural fluid and her blood cultures even grew tuberculosis. And so in HIV, we can clearly see very atypical presentations of disease and it needs to absolutely be on our radar screen. So this was somebody with disseminated TB as a complication of their HIV.

OK. This is a chest x-ray of a 59-year-old woman with dermatomyositis who was on corticosteroids. She presented to us with shoulder pain and an ulcerated tongue mass and I'm not sure how it's projecting but on my screen, the x-ray here shows a lot of small nodules throughout the lung field a little bit more on the right than on the left. Her tongue lesion was biopsied and that was acid-fast positive on smear and her culture also grew *M. tuberculosis*. It was her CT where I think you can appreciate the very small nodules much better. And so this is a miliary pattern on both x-ray and CT scan and this was somebody with miliary or disseminated tuberculosis as a complication of her autoimmune disease and her therapy for her autoimmune disease.

I believe this is my last slide but here you see upper lobe cavities surrounded by infiltrates and a large left-sided pneumothorax actually pushing the mediastinum to the right, so probably a tension pneumothorax. And this is the second x-rays after his chest tube was placed showing resolution of a pneumothorax and, again, a lot of left upper lobe disease as well and this was the young man with sort of classic active tuberculosis with upper lobe cavities who developed a pneumothorax probably as a complication of one of those cavities.

So my take-home points are that TB disease can obviously present in many different ways and we have to be suspicious at all time especially in certain risk groups. We should utilize infection control measures appropriately and I'm not sure if I emphasized this but certainly for patients suspected of having TB in the hospital even if they're smear negative, if TB is highly suspected, that person should be kept in airborne isolation until you make a diagnosis and treat them. You should become familiar with the rapid tests that are offered in your region and recognize what are their limitations may be. And then, of course, collaborate closely with primary care sub-specialists, microbiologists, public health authorities and TB experts.

And thank you.

Rajita Bhavaraju: Thank you so much Dr. Patrawalla for really setting the stage for us so well.

I'd like to now turn the program over to Dr. Elizabeth Talbot from Dartmouth Medical School and she is actually going to do a case presentation for us and we'll get into some of the points that Dr. Patrawalla had set up for us so well.

Dr. Talbot?

Elizabeth Talbot: Hello everyone. I do think the stage has been set well but Dr. Patrawalla for the difficulty in diagnosing and managing extrapulmonary disease. I have several hats and the one that this case came to my attention, while I was wearing was that of the Deputy State Epi and also TB medical advisor. So I may not have every last clinical detail that the clinicians out there may want, but I think that there's still a useful illustration from these as a vignette.

So we received in the capacity of the health department, a routine report of a suspected bacterial meningitis, so an Infection Control Prevention had called us on February 27th to appropriately report that they were suspicious. They were managing a case of bacterial meningitis. We received the broad strokes of the case and probed a little deeper with some unexpected findings.

So this patient with a 19-year-old male from China with headache, weakness, photophobia and nausea and vomiting, and a suggestive CSF. The patient was a student at UNH and the targeted questions to us was, would we provide prophylaxis for this patient's girlfriend and put more broadly through the school system. We obtained a history from the reporter that this patient also had within their medical history two months prior to admission a hospitalization at the same institution for a right lower lobe pneumonia which was also associated with an effusion.

Diagnostics at that time did not disclose a bacterial pathogen, and an AFB smear was done on the pleural fluid, and that was negative. HIV test was also done and negative, although he did not endorse HIV risk factors. He received

two weeks of a fluoroquinolone antibiotic and was discharged with the report that his cough had improved.

He then went on Christmas vacation to his home in China. And during that time, he apparently relapsed. So this is now one month prior to the current report, he was hospitalized for several weeks again. He reported that he had been, at that time, investigated for tuberculosis. The only mechanism – method that was used for that, that we're aware of, is TST. He wasn't able to report anymore detail, but his TST was reportedly negative at that time.

He then received a routine antibiotic and his cough improved. And he was discharged to return back to New Hampshire for continuation of school.

So details around this episode include that approximately 10 days prior to admission. So following those two episodes of pneumonia, he reported to the ED with non-specific symptoms.

He was not able to report fever, night sweats, anything to suggest that something was wrong. He again came back to the ED, the same ED, on the 18th and again the 20th, saying he just didn't feel well. He was given a azithromycin. On February 24th, he now presented for the third time with headache, fever, weakness and photophobia.

So his syndrome has now declared itself as consistent with meningitis. He was admitted. He had a head CT that showed no acute intracranial abnormality without contrast. This was done in order to safely perform the lumbar puncture which showed a very low glucose, a very high protein, a moderate WBC count of 370 that were 70 percent PMNs. There was no bacterial growth, and an AFB was not done on that specimen.

He was started on IV Cipro, and I am not sure why that drug was chosen, and he was reported to be promptly improving on that regimen. And hence the report came to us as a suspect case. I want to show you those three slides again with this big obnoxious triangle with the exclamation point to say that – excuse me – we had some red flags so to speak. So this is the same slide that you saw at the beginning.

So this suspect reports the patient was from China and we were asked about prophylaxis. We saw the demographic of his birth in a high TB incident setting to be a red flag. Also, of course, the history of having had two recent pneumonias that defied routine bacterial identification seem to us a red flag also, atypical for a presentation in a healthy person for bacterial meningitis.

And then, as I imagined you've identified as well, the LT results where a red flag for the potential that this could have been *Microbacterium tuberculosis*, bacterial meningitis, because classically it does present with low glucose, high protein, a moderate WBC, and usually a low lymphocytic predominance. But in this case, a predominance of PMNs.

So we asked the question of the reporting clinicians, could this TB meningitis? And because we could not exclude, based on this history, we as the health department became involved to assist navigating that first CSF sample to MTB complex probe and AFB investigation.

The patient did poorly in the hospital. He became confused. He was noted to be asymmetrically weak and he developed seizures. His sodium was normal throughout, his serum sodium, but he required transfer to the ICU for control of his seizures.

Days later, they obtained a second CSF, and in this case, the AFB was smear positive. This isolate was sent to the CDC for prompt sensitivity testing through molecular methods, because China does have a considerable rate of drug resistant TB.

March 6th, that first CSF specimen that was diverted shows positive by Gen-Probe for MTB complex, and that specimen was smear and to date culture negative. And these were the events that prompted the clinicians to start revamping isoniazid, pyrazinamide and ethambutol.

They also started steroids and have to use antiepileptic drugs as well. Because he continued to deteriorate with regards to his mental status, he was transferred to Man's Greatest Hospital in Boston.

Note that the initiation of antituberculosis therapy was 17 days after his presentation to the emergency room and 11 days after the admission. So it seemed as though a considerable time had elapsed. This is an MRI that illustrates his findings which were somewhat classic in terms of pathology in the basilar region of the brain and also hydrocephalus.

They was diffuse leptomeningeal enhancement which is pretty consistent for having a meningitis.

So going forward I'm going to include this little New Hampshire symbol as we come back to our case during the general comments about TB meningitis, but let me say his course was complicated, so much so that – essentially two weeks into his right therapy, the clinicians elected to moxifloxacin and amikacin. They conducted a third lumbar puncture which was again smear positive.

In the meantime we got results back regarding the isolate being pansensitive so this was a great relief. He developed, three weeks into therapy, new cranial nerve deficits which resulted in a debilitating double-vision and balance problems. And because his course being complicated and not going in the right direction, his family came from China and returned him with them. Of note the clinician who had agreed to received him in China requested that the U.S. clinician sends enough medication with him to complete his course because they did not trust the quality of their local medication incidentally.

I did some investigation for the purpose of this presentation and had several confirmations that he has returned to an apparently normal neurologic function after this time, but it certainly wasn't – certainly not the direction he was heading.

So in clinical summary, he had – this is two unexplained pneumonias in an otherwise healthy young adult from China. He presented with non-specific but perceived urgent symptoms over 10 days ahead of a presentation that suggested strongly tuberculous-meningitis, anti-tuberculosis therapy was started more than two weeks after presentation and then two weeks later,

additional meds were added and his diagnosis was confirmed by probe smear and eventually culture.

So I'm going to restrain concluding comments to the diagnosis of TB-meningitis, and as tempting as it is to talk about epidemiology and treatment and others, that's what we'll talk about because that's often that we're confronted with.

So the pathogenesis helps us to understand better the approach to diagnosis. So a TB bacteremia can occur either in primary or reactivation tuberculosis disease, and during that bacteremia subependymal tubercles, which are also called Rich foci, establish. These rupture after some amount of time into the subarachnoid space and lead to meningitis.

The pathology associated with this pathogenesis is mostly localized to the base of the brain where this dense gelatinous exudate develops, surrounding the arteries and the cranial nerves. And this can result in hydrocephalus, vasculitis which then goes onto infarction and hemi- or quadriplegia. There's a very nice review of the tuberculous meningitis in the "New England Journal" several years back that might come into your reading.

I want to talk about TB meningitis outcomes because they compel us toward making an efficient diagnosis. So using the same reference and many others, TB meningitis is thought of in three clinical stages of presentation. You could present lucid with true meningismus or in a paralytic phase. And depending on what stage the patient presents, this predicts mortality not surprisingly higher with advancing stage of disease.

Our patient by the way was rather classic with regards to having had a two to three week lucid phase that was non-localizing, and then a classic meningitic stage progressing very rapidly to seizure and pareses.

There are many studies of outcome where a third to a half of patients have a complete neurologic recovery, and about a third with – who do survive it have residual severe neurologic defects such as hemiparesis, blindness and seizure disorders. So again, we're really compelled to try to make this diagnosis as efficiently as possible.

One prognosis studies that brings us back – prognosis study that brings us back to our patient is one done in Taiwan. They observed 41 adults, some of whom were more immunocompromised and had a fairly lower mortality with a very high morbidity, and they were able to identify that those who had AFB positive CSF appeared to have a worse prognosis, suggesting more multibacillary disease. And the reason I like this study is that it helped me to understand that it's not unusual for patients to get worse during therapy.

So fully half of the patients in this study got worse within the two to four weeks after having started effective therapy, so that reminds me of our case.

In another prognosis study, about 50 adults and children with TB meningitis, they look at predictors of outcomes. And unfortunately our patient had several bad markers of outcome here. So stage of disease was advanced. He had focal weakness, cranial nerve palsy, hydrocephalus and he had a delayed treatment defined as two weeks or more.

So let's make the diagnosis quickly. I'm sure you're familiar with sending CSF for AFB smear and culture and examining with an eye toward identifying a lymphocytic pleocytosis, elevated protein, depressed glucose. We all struggle with a low sensitivity for an AFB stain, and this is a pretty big range, recording 10 to 60 percent sensitive for a single CSF specimen. In studies looking at, well, what – how did you get to be on the 60 percent side of things? You let your laboratorian know that you are curious about this potential diagnosis because the longer they look the more likely they are to see in those who go onto eventually have culture-confirmed disease.

TB culture have a sensitivity, again, a big range, 25 to 75 percent, but it's delayed out two to six weeks as you're all familiar. It appears that culture is likely to be more sensitive with increased volume, but although that's intuitive, I was happy to see one study that looked and said that your yield on culture doesn't increase substantially after 6 ml. So you're not asking clinicians to just, you know, draw as much as possible that really to increase the volume to a reasonable amount, not necessarily more than 6 ml.

There are few other methods of examining CSF that I'd like to talk about just briefly, and that's GeneXpert MTB/RIF which is a Cepheid product driven to availability through the activities of FIND in Geneva and also CDC here in the U.S.

This is automated real-time PCR. This is a major breakthrough with regards to our ability to diagnose tuberculosis right at about 90 minutes. It also detects rifampin resistance within 90 minutes. So this is really a game changer for us in global TB control.

The comment I would make about that is that the jury is still out. So there had been many small studies around the use of GeneXpert on extrapulmonary specimens. This has been developed for sputum.

So what about if you use it here, and what about if you use CSF and pleural fluid and pericardial fluid, etc.? So in a metaanalysis looking at many different sample types, sensitivity appeared to be about 80 percent, but a pretty big range. A more recent study since some upgrades in the technology in fact, looked at more than 10,000 mixed population, pulmonary and extrapulmonary patients. Again the sensitivity is not perfect, maybe in their 77 percent median, specificity, however, is excellent and pretty tight. The range are 98 to 99 percent.

The variation is seen between populations, how the patients are selected, the type of extrapulmonary TB, how the samples are processed and what the researchers consider as a reference standard whether it's smear or culture, etc.

So I pulled out some selected studies that I thought might be relevant to this conversation. It is the last three that included CSF, but pretty robust numbers of patients who are examined with regards to extrapulmonary detection using Xpert. Sensitivity was variable but specificity excellent. So I propose – but we're waiting for more data, but we're considering Xpert may wind up being a rule-in test, that is if it's positive, you've made your diagnosis. So more to follow on the story of the use of the GeneXpert for extrapulmonary TB diagnosis.

One comment really around adenosine deaminase which comes up in diagnosis of extrapulmonary disease including pleural fluid, pericardial fluid and certainly CSF. So ADA adenosine deaminase simply reflects immune cell activity. There are several different kinds of ADA and macrophages produce it when they're trying to stimulate the immune system to battle pathogens like TB, but not only TB.

So in metaanalyses looking at the utility of ADA for extrapulmonary TB diagnosis, most studies chose sensitivity maybe around 90 percent, but specificity is less than 90 percent. So it's hard to know how to use such a thing and incidentally, our patient didn't have this done, so I'm not sure how that would've helped us.

Imaging of course is often used. Chest x-ray can be useful if it shows old TB, and that's going to certainly raise your suspicion for TB meningitis if you found an abnormal chest x-ray. Our patient had a normal chest x-ray. CT/MRI of the head can demonstrate hydrocephalus, basilar exudates and inflammation. Our patient had all three. There were no tuberculomas noted on our patient's imaging and no infarctions.

So TWAITS – I hope I am saying that correctly, TWAITES score had been developed to take together risk factor studies and diagnostic studies to try to establish by multivariable analysis predictive features for TB meningitis. So this had been published in the Lancet in about 2002, and was conducted, it was developed in Vietnam in adults. So in select populations using the features shown this table, age, younger being a lower value. The white blood cell count, lower being the lower value, duration of illness, lower, lower, et cetera.

The researchers were able to determine that if the score was less than or equal to four, TB meningitis should be strongly suspected, greater than four might be bacterial. Sensitivity and specificity in this first effort was 97 and 91 percent. So the specificity starts to be a bit of a bit of problem for giving false positive depending on the population you apply it to. I wanted to let you know, our case who used this scoring system, had a score of minus five, so clearly in the range that they would consider likely for TB meningitis.

The same team validated their algorithm in this clinical walk down way which was pretty are ready to use, they identified 205 inpatients in Vietnam and found a sensitivity of 99 percent. However, when other groups have tried to use this in different settings and different populations with and without CNS radiology available, they may have had different findings. So in the study in Morocco where radiology was not routinely available, they came up with a different number that was clinically relevant and extended it to include serum sodium since TB meningitis can result in an SIADH leading to hyponatremia. Our patient on this algorithm would have wound up with a prediction for bacterial meningitis by the way.

This Lancet consensus group took many of the evolving clinical predicting scoring systems and came up with this one, which is more complicated. There are 20 parameters and four categories which include clinical, such as the duration of symptoms before presentation, the CSF criteria, the imaging results, and then whether the patient has evidence of TB elsewhere, the maximum score that can be achieved on this scoring system is 20.

And based on whether imaging was used to come up with that score or not, you come up with a diagnosis of definite, probable or possible. Definite can only be achieved by microbiologic or nucleic acid amplification tests. And then otherwise you fall into a category of probable or possible. Our case fell into the range of 15 which because imaging was available would have been categorized as probable using this method.

So in summary, diagnosing TB meningitis requires high clinical suspicion especially because poor prognosis is linked to delays in the diagnosis and treatment. In this case, I think you'll note that it was the health department who raised the specter of TB here and in fact I think the health departments retain good TB diagnostic vigilance and can facilitate expeditious diagnosis. Clinical scores and algorithms are available and in general we still have to rely on presentation of risk factors, imaging, routine CSF exams, all look to the potential that GeneXpert offers us as a potential rule-in test.

So I think those are all the comments I had, and I also thank those who invited me to present here our case from New Hampshire.

Rajita Bhavaraju: Thank you so much Dr. Talbot for that very interesting presentation. I'd like to now turn the last presentation over to Dr. Marie Turner and Dr. Katherine McGowan from Massachusetts, and they also will be presenting some very interesting cases about how some of the challenges and the pitfalls can relate to a delay in diagnosis.

So, Dr. McGowan and Dr. Turner, I'd liked to turn the program over to you.

Marie Turner: OK, great. So this is Dr. Turner. We're presenting two cases that actually are currently under therapy that we felt were interesting, both have a delay in diagnosis although for slightly different reasons.

Katherine McGowan: This is Dr. McGowan. Our first case is that of a 25-year-old American-born Cambodian male whose father had tuberculous approximately one year previously. His parents were Cambodian, but lived for many, many years in Vietnam and traveled back and forth to Vietnam quite frequently.

Now, after his father was diagnosed with tuberculosis there was a contact investigation accomplished by public health. But this patient was not screened because he was unavailable. He was going to college, he had a night time job catering on the side. However, all other family members were indeed negative for tuberculin skin tests.

And like many young men, even though he had symptoms for a number of months, he ignored them until he had a cosmetic symptom. So in January of 2013, he had flu-like symptom and a dry cough. He didn't lose weight but he did develop fever, drenching night sweats and cough, but it wasn't until May, four months later, when his sister said to him, you know, "You have a great big lump on your head which looks really odd. I think you need to have that taken care of."

So that was seen in the emergency room and a very large scalp mass was indeed palpated. And the physician who evaluated him ordered plain x-rays

of the skull. And here we see a large defect in the skull with large defect in the calvarium in the skull, and then this very large scalp mass.

This is a CT scan that was accomplished, which also shows this very large scalp mass eroding through his skull, the table of his skull, the calvarium. This is an MRI film of the same issue and you can see again that he has this very large collection here with dural enhancement.

And actually this is a fantastic film. It is a sagittal view, and you can see here that he has the cold abscess here. You can see it's going through the skull. This is an MRI, so the cortex of the skull is this black line here. The marrow is represented by the white. The other side of the cortex, black. So you can see this goes straight through. And then you can see that the dural line is actually thickened here and the dura is quite irritated by this cold abscess which appears to be going through the skull.

This next MRI is just a different view, an axial view, which shows this large mass and a collection, and again erosion through the table of the skull with enhancement of the dura. Now here we see that there actually three different soft tissue masses and bony masses with enhancement of the dura in multiple different areas. Now, this is a coronal view, and here we have a soft tissue mass, below the left orbit.

Here's a sagittal view of where we have a soft tissue mass below the right orbit. And now we're back to CT, and you can see that the zygomatic arch here is eroded as is the anterior wall of the maxillary sinus. You can see here, this is the inferior orbital ridge. You can see there's destruction of this bone as well.

And what we saved for last is the chest x-ray. So what is the chest x-ray of this gentleman look like? And first of all you can see he's quite a corpulent young man, and he has this pleural process here. He's got this perihilar infiltrate here. And if you look carefully and count ribs on this side, you notice that there's a rib – that part of his rib is missing here. So we have a gentleman with a large infiltrate, a pleural process, and something is chewing on his ribs, in addition.

Here's a CT which doesn't add much, but you see the pleural process and you see the infiltrate with the suggestion of air bronchogram there.

Next we move to his – we move to his neck, plain films of the neck. And these vertebral bodies look OK, but C6 is totally destroyed, this area of C6. This vertebral body is totally destroyed. This is an MRI of the neck areas to see even though it looked normal on plain film, C3 is involved. There's enhancement. And C6, the one that is totally destroyed actually impinges on the cord.

Katherine McGowan: OK. Patient was then started on TB therapy. He was started in conventional TB therapy in an outside hospital with INH, rifampin, PZA. He transferred to our service and we add moxifloxacin, amikacin/capreomycin and cycloserine. He ultimately did grow pansensitive TB. And actually I should add that just as able to secure the correlation between his dad's TB and his. And in fact this is the same organism as his dad had a couple of years ago.

He, over the course of the next two months of IV Capreomycin, we went from amikacin to capreo. Capreo is our preferred drug here. He had partial or almost complete resolution of the cold abscess of the head. His thoracic and cervical pain improved. His headache however continued, so at that point we dc'd the cycloserine and his headache resolved.

Here's his chest X-ray. We just saw him last week. And you can see he did not yet grow his rib back but his infiltrate looks much better. And on his left-visit again was on 11/8. He had – the visit before, he'd been quite depressed and crying. We started on Zoloft.

By 11/8 the mass on the head was entirely gone. He had no side effects from the meds. He was on a somewhat unconventional dosage and a number of drugs which is something again we like to do when there's a lot of disease. He was on boosted INH, boosted rifampin, ethambutol and PZA, off cycloserine, capreomycin and moxifloxacin.

I should add that the diagnosis here was made both by sputum and rib biopsy, and that the boosted doses are based on serum drug levels and that this gentleman is HIV negative. And his only risk factor is exposure to his dad.

Marie Turner: We'll move on to our next case, that of a 21-year-old female who was born in China. She came to the United States in 2009 to attend college at UMass.

She had a positive tuberculosis skin test of 16 millimeters upon entry to college. Her chest x-ray was negative and she declined TB therapy, latent TB therapy. She felt well, and went about her business until December of 2012, at which time she develops a cough, a nagging cough. She went to student health. They did not obtain a chest x-ray but treated her with a Z-Pak, or azithromycin on two occasions.

She said perhaps she was slightly improved. She felt improved enough to leave during Christmas break to go visit her family in China. While she was in China, her parents noticed she was coughing all the time. They brought her to a local hospital, and at the local hospital a chest x-ray and CT scan were both accomplished, and you'll see those in just a moment.

They were both abnormal. She did produce sputum, her AFB smear was negative. She was told she likely had a conventional pneumonia. She was placed on an unknown type of antibiotic, but was told she did not have TB and that it was fine for her to return to the United States.

So we just recently were able to secure the films from China, and you can see that she has what looks like a middle lobe infiltrate here, diaphragm appears to be clear. We were able to get a couple of cuts of the CAT scan, and you can appreciate here that this area seems to be clear, this lung, the left lung has never really had an issue. You start to see some little nodularity in the area of the right middle lobe. As we go down this becomes more pronounced but it does appear to be limited to that area of the lung, and again looking at her lower lobe that seems to be uninvolved.

Katherine McGowan: OK. All right yes. All right OK. She returns to Boston. She continues to cough incessantly over the next five months. She had multiple visits with the mid level healthcare provider at her PCP's office. And multiple chest x-rays as well as multiple CT scans were obtained.

She was also given multiple courses of antibiotics including fluoroquinolones such as moxifloxacin and levofloxacin, augmentin and azithromycin. She was placed on inhaled corticosteroids.

This is her chest x-ray in April, and I think you can again see this – what appears to be right middle lobe involvement. We can see it clearly on the lateral. Then it's a right middle lung field involvement. And there is a chest CT. Again we see the middle lung involvement but we're beginning to see involvement in other areas that were previously not involved, the lower lobe here appears to be involved, the mid lung field, again continues to be involved.

And here we see again more involvement lower lobe, continued involvement mid-lung field. The opposite lung appears fairly spared, and here we see more extensive disease in the lower lobe and continued involvement of the mid lung.

In several pictures here, we just wanted to show you the extent and the evolving involvement of the lower lung that was not present on the previous CT scan that Dr. Turner showed you.

Marie Turner: So by June the patient was no better. She actually personally noted that there was a pulmonary physician across the hallway from her PCP, and she asked her doctor and her healthcare worker, "Gee, do you think I can go see the pulmonary physician?"

They were told it was not a good idea. Nonetheless, being a college kid, she did go to the pulmonary office, asked if she could be seen, they said yes, the appropriate consultation request was obtained. And two weeks later she saw the pulmonary physician.

He repeated the CT scan which now is worse again, but he did the one thing that the earlier caregivers did not do, and that is they did an AFB smear which was positive. And I'd like to point out at this point going back to our first speaker, that the fact the she was AFB negative in China certainly did not mean she didn't have TB. And we see lots of TB which is smear negative.

So that was the first opportunity missed in this individual. The pulmonologist makes a presumptive diagnosis of TB. She's immediately started at the end of

June on INH, RIF, ethambutol, PZA. But over the ensuing months, for a full month she remained smear positive, moxifloxacin then is started 8/8/2013.

So what we should point at this point is that most of the TB providers in the audience know that when you have a failing regimen you never add one drug. Moreover, this is a drug that this woman had seen before because she had multiple courses of antibiotics.

So here's her June 2013 chest CT and you'd see already here, this looks like superior segment of lower lobe developed disease, she has more disease, still has disease in the middle lobe. She also has some bronchiectasis here which is quite evident. And, as I'm just going to go down these slices, as you can see she has more and more involvement of that lower lobe. So this is a very significant departure from her earliest films.

So, two weeks after initiation of the moxifloxacin, her AFB smears do indeed become negative. However, her cultures are growing both *Mycobacterium avium* complex as well as *Mycobacterium tuberculosis*. And we had great difficulty obtaining sensitivity because of the MAC overgrowth.

However, her chest x-ray is evolving and worsening. She had documented low serum drug levels of rifampin and ethambutol. And she was then referred to Lemuel Shattuck Hospital for evaluation in September.

And we were faced with several very difficult questions. Should we seek for MAC? Should we add additional drugs or should we await the sensitivities? The sensitivities we knew were going to be coming along fairly soon. We just decided to continue the INH, rifampin, ethambutol and PZA as well as moxifloxacin, and await the sensitivities which returned about nine or 10 days later.

And what we found was that there was resistance to INH at all levels. There was resistance to rifampin, ethambutol, and ethionomide. The PZA susceptibility is still pending. However, she was sensitive to some second line drug, cycloserine, capreomycin, and ciprofloxacin.

So we're again left with more questions as to how do we treat at this point? We advised the patient and convinced her to be admitted to Lemuel Shattuck Hospital where we initiated intravenous capreomycin to which we knew she was sensitive. We continued the moxifloxacin, and she was sensitive to this initially but we were hesitant about this. We were not convinced that remained sensitive.

We continued the PZA ending the susceptibility testing. We added cycloserine as well as linezolid. And actually the patient did seem to improve while she was hospitalized with us at our institution. She's tolerated the medications very well. She was only in for about a week. And then we discharged her to home, arranged for an IV infusion company to administer the capreomycin Monday through Friday for the next several weeks.

And because we were anxious about her, we did repeat another x-ray two weeks into TB treatment which probably is much too short period of time to see any real changes, and in fact it was unchanged. However, at that visit, we also have the additional information that now her initial sputum was also PZA resistant.

So what that meant, we get the point that the moxi was added, she essentially for six weeks was on moxi as monotherapy. And now, we will discontinue her PZA. So the changes we made at that point where we stopped the PZA obviously since she appeared to be resistant. And we thought about another drug to add, there weren't many at this point, so we decided to start Paser.

Now, in Massachusetts, I don't think we – certainly not on her specimen. We didn't have any first line testing for Paser so this was pure face.

But in the mean time, we've sent out the linezolid to see if that was sensitive, and in fact it was. We sent it to an outside lab. So at that point we knew she was on drugs, capreomycin, cycloserine and linezolid that she was sensitive to. We didn't know about Paser, and in terms of moxi, we think she was sensitive initially but we were concerned that she may not still be.

AFB culture for 9/9/2013 was growing so we asked the lab to repeat the sensitivities, and we're awaiting moxi sensitivity from that. But they

continued to have the same issues and that is that MAC and MTB are growing at the same time. So they literally are picking out the colonies of MTB for sensitivity.

So, one thing which became apparent – or one thing which came to light in the course of our treating her for that month was that the public healthcare she was going out to there said, you know, her apartment is kind of moldy. So we asked her in great detail was this a subterranean basement apartment, first floor apartment. I never got a good take on that, but I said, well, she has so MAC growing, she does have bronchiectasis, maybe there's a source within the house.

So we had her culture, her shower head, and cultured the kitchen faucet, both grew MAC after seven days, so after a relatively short interval. And the question then came out, again, how do we treat the MAC? Do we simply change her shower head, change the filter on her faucet in case MAC is a real pathogen and in case there's an environmental source? Or do we actually go ahead and treat her for *Mycobacterium avium intracellulare*?

And, you know, if we do, do we do MAC sensitivities which would be send-out for our lab? So, far what we've opted to do is just change that shower head and the filter on the faucet. And we are re-culturing the water sources in her house.

The last problem we've head with her is that her platelets fell to 110,000. They've previously been about 150 to 175. And we thought this might be a marker of linezolid since we know linezolid goes to the marrow and platelets are often the first thing affected.

I'll tell you what we opted to do, is we opted to just sit on it since we were concerned about the extent of her disease and the progression, and so far her platelets have not fallen further, so we seem to be OK. So I think in terms of this case and with respect to delay, one could ask the question, would it have made a difference if back, when she started school as a freshman, if she'd actually received LTBI therapy?

And I think that, you know, that's very debatable. Certainly the delay from December to almost July was really inexcusable, and somebody should have thought that this young woman who was born in China who had recurrent pneumonia that TB was certainly very high on the differential.

The first patient in terms of delay, I believe that a lot of that was the level of the patient. He just did not think it was worthwhile going to see a physician until he had a big lump on his head and his sister kind of laughed at him. It is interesting that the he matches his dad. So, in retrospect, although – I think public health did a great job trying to assess all the contacts. It is unfortunate he was missed in that first contact investigation.

So I think I'm done. We're done.

Rajita Bhavaraju: Thank you so much. I'd like to finally post Dr. Patrawalla's final take home point slide. Once again to remind people about the keeping of a high index suspicion particularly in high risk groups and about the approach that she had mentioned at the beginning to kind of look at the entire picture when considering your diagnosis of tuberculosis.

And that, I'd like to thank all the speakers for really illustrating those points extremely well with the cases that they demonstrated today.

Just a reminder, that the Global Tuberculosis Institute provides a medical consultation to members of the Northeast Region, so you can call 1-800-4TB-DOCS if you have questions. And for those of you that are outside of our region, certainly consult with your appropriate regional training and medical consultation center, as well as your state or regional TB program.

Thank you very, very much for your participation and for rich presentations today and have a good afternoon. Goodbye.