Hello. Welcome to today's Morbidity and Mortality Review webinar sponsored by the Southeastern National TB Center. I am Stefani Nixon, training coordinator at SNTC. Before we start today's event I have a few housekeeping items to go over. Today's event is scheduled for one-and-a-half hours, including the question-and-answer period at the end of the presentation.

To verify your participation in this event, please provide your email in the email pod, which is on the screen within Adobe Connect. If you provide us with your email address we will send you an email with a link to the online evaluation following today's presentation. If you're watching the event as a group, provide us with one email and you can forward the email to the rest of your group. Please be aware that you must complete the online evaluation by 5:00 PM Eastern Standard Time on Tuesday, June 30th, if you want to receive nursing or physician credit. If you submit an evaluation you should receive your certificate within eight weeks. If you do not receive your certificate, please check your junk or spam folders. You may submit questions for the speakers at any time during the presentation by typing your question in the Q&A pod. Thank you for joining SNTC today. Now I'll turn this over to today's moderator and co-presenter, Dr. Dave Ashkin.

Stefani, thank you so, so much. Hey, a lot of fun. I'm, like, looking at all the chatting and what's going on. This is really cool. I wonder if 20 years ago when they were putting all of this together, did they ever think that we'd be using this technology to get together in the afternoon to talk about TB. So, really cool stuff. I'm so, so happy to have you all together. And we have two cases to discuss. Just like Stefani said, if you have any questions, we'll be monitoring the chat. Also, in between, I may open it up and, you know, ask you guys to comment. And, at that time, if you just push "*7" that will unmute you. And, please, I'd love to hear from you guys if you have any questions. Or "*6" to put yourselves back on mute.

So today we have two cases, unfortunately, I hate to say this, both were mortalities. And they were both complex cases. I think there is a lot to learn. And I'd really like to get started. So, with that, what I'd really like to do is I'd like to present and I'd like to introduce Megan Ninneman. Megan is our physician assistant down at Jackson Memorial Hospital. We're really so happy to have Megan. And, Megan, why don't you start the case if that's okay. We have a lot to go over today.

Okay. Hi, Dave. Can you hear me?

I can hear you.

Perfect. So the first case we're going to start off with today is a 45-year-old African American female who was admitted to a Miami hospital on May 11th of 2014. At that time, she was complaining of a two-month history of nausea, vomiting, saying she could not keep food down. She also had abdominal pain with distension and she had lost about 150 pounds over the last year. She also gave a history of gastric bypass in April 2007, with a revision in April 2013. She also gave a history of a DVT to the left lower extremity three months prior, and had been maintaining on warfarin. She denied any alcohol, illicit drugs, or tobacco use. Next slide.

She was followed by her primary care provider previously, who did a CT of her abdomen and pelvis in April 2013. It showed that she had colilithiasis, ascites, and a possible dermoid mass on the right ovary. The patient was advised to be admitted to the hospital for further workup but she did not comply.

So this is -- just for a second, this is an X-ray, interestingly enough, that she had in March. I guess at this time she was being seen by her private physician. She started to have some symptoms. And I think, as we all can see here, she has this very large left pleural effusion. The way we can pretty much say it's an effusion by the meniscus side. It's almost like water on the side of your glass as it tracks up.

You could also see -- you really don't see the diaphragm at all. You really don't see the heart. So there may also be an infiltrate behind it, but definitely an effusion. And on lateral, normally as you come down the spine it should be getting darker and darker, but as you come down here you can see it actually gets whiter, and that's, again, the effusion, the fluid. And you can only see one diaphragm here, and that's
because the left diaphragm is being obscured by the fluid. So you only see the right diaphragm here. So she definitely has this left large pleural effusion.

And on CAT scan, as Megan pointed out, she had this ovarian mass here with stranding. And when they see the stranding, it's usually a fatty indication, which is suggestive that there may be a dermoid cyst. And, as you remember, dermoid cysts are actually cysts that have different parts of our epidermis, meaning, like, hair, fat, you know, so that's the hint that it may be a dermoid.

You can see here, though, one of the most interesting findings -- and we'll be talking a lot about this today -- but notice this, this is the spleen right here. And we see how white it is? This is the liver. The liver should be the exact same density as the spleen, but we can see here it clearly is not. It's darker, meaning that, actually, it has a different density. It's actually less dense than the spleen, which makes you start to think about that this may be a fatty liver, and a very, very fatty liver because it's so large and it's much, much darker or less dense than the spleen. So, Megan, what happened?

So she was, as we said before, she was admitted to the Miami Hospital on May 11th of 2014.

This is the CAT scan that they showed and that we got from the Miami hospital. You can see, this is the gallbladder here. And she has this thickened gallbladder right here. She also, again, has that density difference. Look here, this is the spleen here. And you can see how dark the liver is, again, suggesting that this is a fatty liver, a very diffuse, large, fatty liver.

And the other thing that they're seeing here, and this is ascites, right in the middle here in the lower abdomen pelvis is ascites. So she has fluid in her belly, too. And then the last thing you can see is, again, this mass here, this is actually different in density here, again, suggesting that this may be a dermoid. And then, lastly, you can see again, this is actually the bowel wall. And you can see this is a segment of bowel that's actually filled with fluid and the wall is thickened. So she had a couple different abnormal findings, Megan, huh? So what was the official reading there?

So, just like you said, Dave, they saw the coliiethiasis, that small bowel wall thickening with inflammation, the fatty liver with increased amount of ascites, and bilateral pleural fusions, and, again, that right ovary dermoid mass. They also found on her labs that she was anemic. Although her liver studies were within normal limits, they were very concerned about that elevated CA-125 of 416 concerning for a possible ovarian cancer.

Right, exactly. And what happened then?

So she developed a slow grade temperature. They did a chest X-ray. There was a question whether there was a left lower lobe infiltrate versus a bilateral pleural effusion with atelectatic changes, which they did confirm by chest CT. And then also the chest CT revealed a left axillary lymph adenopathy.

This is the X-ray here, and I think we'd agree. I mean, it's looking like it's gotten worse. Now bilateral pleural effusion. You can't see the diaphragm again, so there may be something here like an infiltrate. And, again, you can't see the left costophrenic angle, again suggesting bilateral pleural effusion. You can even see the air bronchogram here that suggests there's either atelectasis behind there or infiltrate.

This is the CAT scan here which, again, shows the bilateral pleural effusion. Here's the fluid here. And she also has, as we were discussing, atelectasis right here. So that's what we're seeing in the air bronchogram. And then, interestingly enough, when we reviewed it, and I don't know if you guys can see this, but there's a very, very tiny nodule right there. And obviously you can't see it if I keep sticking the pointer over that. Sorry about that. And as importantly, or as interestingly, she had a huge left lymph node there in the left axilla. So you can really see that that's quite big. So what happened there, Megan? What went on next?

So they decided at that time that the patient would undergo a cholecystectomy, hysterectomy, and salpingo-oophorectomy, as well as a resection of that left axillary lymph node. And what they found on
pathology was that pretty much everything was consistent with caseating granulomas, no signs or evidence of malignancy. And in the left axillary lymph node they found purulent material, which was AFB-negative, but subsequently cultured positive for TB and the MICs were reported as pan-susceptible. And probably more importantly for her at that time, they were able to rule out ovarian cancer, as both of those ovaries came back with caseating granulomas and no evidence of malignancy.

Interestingly enough, they found, as you talked about, some evidence of gray hair, you know, in the ovary, suggestive of a dermoid. But I think you'd agree, it really, really, really kind of, I think, surprised them that she had disseminated TB throughout the abdominal and peritoneal area, something I don't think they were suspecting at all. And, again, just as an aside, remember she had a very, very high CA-125. And I know in this country we don't too much TB of the abdomen, but in countries like India and Pakistan, where they see more TB, you know, that is one of the findings or at least in patients who have abdominal TB is that their CA-125 will be elevated. So kind of interesting. So what happened then?

Well they collected sputum on her. Everything was smear and culture negative. She was QuantiFERON-positive and HIV-negative.

Again, I think going along with this diagnosis of at least disseminated TB, but really no evidence, at least in the lungs. It looks like those pleural effusions are probably more likely to have been related to the process that's going on in her abdomen.

So they went ahead and started her on four drugs on May 23rd, and discharged her to do DOT at home three days later. She was able to complete eight weeks of PZA, which was discontinued after eight weeks, and continued on INH and rifampin twice a week.

So this is a chest X-ray now and this is on June -- sorry about that -- this is on June 6th, so about a month after she stopped therapy. And you see those pleural effusions have clearly gotten better. Now you can see the diaphragm. Now you can see the heart. And she still has blunting of the left costophrenic angle, and she also has blunting of the right costophrenic angle. But, again, I think you'd agree, it looks for the most part better.

So she showed up in clinic in the middle of August for routine labs. You can see here that her albumin is kind of on the low side, 2.3. Her bilirubin was within normal limits. Her AST/ALT are mildly elevated but she's not complaining of any symptoms at that time.

All right.

Unfortunately, the patient became non-adherent in August. They had to file an emergency hold order. The patient was then found in November and she was restarted on court-ordered DOT. And for the most part, she was adherent to her therapy.

This is her X-ray when they found her in November. And now you really can see a remarkable improvement. I mean, now you can see the right costophrenic angle. You can see the left costophrenic angle. You can clearly see here that the diaphragm -- I mean, and now you can see those vessels through the heart, what we want to particularly see. She's had a really nice response.

So, prior to restarting her on meds, on November 14th they repeated her labs, and you can see here that the total bilirubin now was twice what it was in August, but she has no evidence of transaminitis. So they went ahead and started her back on three drugs on November 17th. She was seen again in clinic on December 5th. She said that she was feeling much better. She had gained weight. She wasn't complaining of any other symptoms. At that time, she was switched to twice weekly therapy with INH and rifampin. And they were able to repeat her labs so that her bilirubin at least was maintaining or maybe slightly lower than it was previously, and her AST and ALT remained within the normal limits.

So, one second here. I just want to make a comment. And I think you'd agree with me that one thing that's frightening is how low her albumin is. And, on the other hand, her AST and ALT are relatively normal. And
looking at her liver, looking at that albumin, you'd really be concerned that she was having problems with her liver function. And I think that's kind of one of the comments I'd like to make, you know, we always call the AST and ALT liver function tests, but they're really not. They really have no indication of how well the liver is functioning. And for those kinds of things, as we'll talk about in a little while, you want to look at things the liver produces, things like albumin, you know, proteins that are involved in coagulation, so we follow the PT/PTT, things like glucose, you know.

So, you know, one of the things that I think is important to talk about is when we talk about LFTs, they're really not AST or ALTs. Those are really usually more like a transaminase involved in cellular injury, like in hepatitis. But what are things that would really bother you, I think you'd agree, is that it looks like here her albumin is very, very low, and the question is why.

Yeah, I would agree with that comment, especially because she seems to be gaining weight. You would expect her albumin to also be going up.

Yeah, definitely.

So the patient was seen again a month later in January. Again, she continued to gain weight and feeling good, but her labs -- repeat labs this time show an elevated bilirubin of 2.9. And, meanwhile, like you said, Dave, the liver enzymes are remaining within normal.

Interestingly enough, if you see here, her [inaudible], which is a sign of her biliary tree, is actually normal, but her -- I'm sorry, now I did it -- her transaminase, the AST and ALT, are normal, but what's very concerning is the total bilirubin now has remarkably gone up. And, again, her albumin is continuing to go down, which is very, very concerning. So I guess, you know, at this point, where was she, Megan, in her treatment?

So she had gotten 20 out of the 26 weeks of therapy that she needed. She had been culture-negative since July 16th, including a repeat sputum culture in November prior to restarting her meds. So, at this point, you know, we need to ask what we would do next.

Yeah, I agree. So let's go down to our first question here. These are always fun. So, again, there's not necessarily any right answer, I do mean this, but what would you do? I mean, what would you do now? You know, would you continue meds or repeat the ALTs in one week? Maybe hold the meds and do an ultrasound of right upper quadrant and maybe some serology to make sure she's not hepatitis-positive, you know, or viral hepatitis, like A, B, or C, switch rifabutin for rifampin and follow LFTs or stop the INH and rifampin, and start her on what we call a “liver sparing” regimen like ethambutol, Levaquin, and streptomycin? What do you guys think?

So, you know, what you see here right now, for the most part -- first of all, thanks, guys, for doing it. These are meant for discussions and everything else. We really appreciate it. So if you look here real quick and you look and you see the vast majority of people would continue meds and repeat LFTs. And I have to say that, you know, I don't think that's necessarily wrong. My only concern would be, and I think just when I'm making these kinds of decisions, is I'm thinking about things like where we are in treatment. And that's why we kind of asked that, because I think you'd agree, early on when a person is sick and they're still having positive sputum and cultures, you may want to continue the person on meds, maybe meds that don't affect their liver, like ethambutol and fluoroquinolones and streptomycin.

But, you know, now that she's 20 weeks into therapy, she is culture-negative, you know, I think I understand also maybe the idea of, like, holding the meds and doing the ultrasound because there's not the same pressure. And one of the things we will talk about is sometimes the worst thing you can do is continue the meds while the liver enzymes are elevated, mainly because it is -- you know, the whole idea of drug-induced liver damage is that your best chance of recovery is if you pick it up and stop it early. So I think these are the kinds of things that you need to look at is where you are in therapy and what are the risks.
And the other thing, I have to be honest with you, Megan, and I wonder how you feel, is that, you know, my biggest concern actually is when the total bilirubin goes up. You know, we see a lot of patients who AST and ALT go up, and they do fine, we stop them. But when the total bilirubin is going up, that's what really concerns me. I think some of the worst cases we've seen, Megan, together are those cases where the total bilirubin goes up. Do you agree?

Yeah. No, I totally agree.

Yeah, I mean that's kind of called Hy's law. Hy's law always talks about when you have an elevated, you know, bilirubin in patients who get TB meds, or any kind of drug induced, that's the one we really worry about. So let's see what happened? So what happened, Megan?

So, unfortunately, the provider was not notified of the abnormal lab value and the patient was continued on the medication.

And, you know, just a quick thing. I think all of us have been in that situation. That's why it's so important, you know, in our clinics, in our offices, that, you know, having a system that when something comes back abnormal, that it gets back to the provider. And, you know, all of us know that sometimes, unfortunately, things fall through the cracks. And, you know, I think we all appreciate that it happens, but it can actually have sometimes untoward effects. So what happened next, Megan?

So she was then admitted on January 23rd to a Miami hospital. She, at that time, had a two-day history of fever, nausea, vomiting, anorexia, diarrhea, weakness, abdominal pain, and increased thirst.

And this is a chest X-ray. And, again, I think you'd agree that her X-ray looks not bad. It looks okay. It's an AP film, that's why her heart looks a little bigger. But you can see her diaphragm, everything looks good over here. But what's happening in her labs?

Yeah, so on admission you can see that her total bilirubin continues to go up. Her albumin is about the same. Interesting, her CA-125 has now come down quite dramatically from 416 to 84, but she has that kind of disturbing CEA, which is elevated at 13.1, although the alpha-fetoprotein is within the normal limits. We can also see she continues with anemia. Her platelets are borderline low. She has an elevated PT. So going back to those liver functions, that's one thing you can also look at. Her alcohol level was ten, and normal is less than ten, so I'm not too sure what to make of that.

As a sidebar, you know, she had started taking some kind of herbal tonic, a triple S iron supplement that did have a small amount of alcohol, so I don't know if that was contributing. And then you can see her Tylenol level was 15, so she obviously had ingested Tylenol at some point in time. How much time had lapsed between her taking the Tylenol and this test or how much, we don't know. But at that time, they did check her hepatitis virologies, which were negative.

I mean, very, very interesting. A couple statements, if I may. First of all, I think you'd agree, the total bilirubin keeps going up, despite the AST and ALT being lower. That's why one of the things I really would emphasize to you guys, I know the recommendations are to follow AST in patients with TB, but I think many of us also with total bilirubin, with the understanding that there's two components and that they don't always go up together, that you can get what we call a cholestatic picture or a picture consistent with either a disease in the biliary tract or of the liver, and also rifampin can cause this, versus a hepatitis, a transaminitis, where the AST and ALT go up. And, again, like I stated before, though this is a rarer picture with an elevation of bilirubin, it's more concerning. The albumin continues to go down.

We had a great question before. Greg, how's it going? It's good seeing you, hearing you on the conference here. Greg asked us before, and I agreed, can you use a CA-125 to monitor the progress of patients who have abdominal TB? And the answer is yes. You know, and we do. And you can see in the case like this as we treat it the CA-125 actually goes down. The only problem is that if it starts going up you really can't just say it's the failure of TB, you got to make sure there wasn't an underlying other process. But the answer is yes, Greg. Thanks for asking that question.
And then, you know, what I want to show you, the other thing, is that the haptoglobin is going down, again, another protein made by the liver, suggesting that this person is having synthetic function problems. The other thing is that the PT is going up, and I want to make a statement about that. Remember, she did have a, you know, in the past, a history of pulmonary emboli and had been on warfarin, but it was not on this side.

And then, you know, as Megan said, a couple things that bothered her. Her ethanol level was not zero, it was ten, and that bothered her. Was she drinking? At that time, she denied it. The other thing was her Tylenol levels were high and, as Megan said, you really can't just take a spot of Tylenol. It really depends when she ingested it compared to where she is. And then what Megan said, which is very interesting, that she was taking this herbal tea. And, as we talked about, remember that, you know, one of the things that we saw was a fatty liver. And we'll talk about fatty livers. But one of the things that can cause fatty livers is herbal tea. So it's one of the drugs that actually are associated with it, so it was very interesting. Otherwise her serologies were negative. So kind of an interesting pattern here. So, Megan, what happened now?

So, because of the cholestasis picture they did an MRI with an MRCP, which, again, confirmed the severe fatty liver disease with evidence of anasarca, but didn't show any signs of stones or obstructions, masses. So basically there was no evidence for this cholestasis picture. They also did a paracentesis at that time, which was consistent with a transudate, and all the cultures that they did at that time for bacteria, fungus, and AFB were all negative.

So, again, I want to show you the -- this is the MRI done of her abdomen. Again, a huge difference in density. You know, and Mark Lavato is one of my favorite people in the world. Mark is on the call, and Mark is asking, like, it looks like a rifampin-related -- and that was definitely what we think about when we see a pure [indiscernible]. The only thing that bothered me is that -- and, Mark, if you want to comment, just do "7." It's always fun to hear you.

But, you know, what the question comes down to is that you shouldn't get this fatty liver. Remember, she had this fatty liver prior to being on the rifampin, you know, all the drugs. But it's kind of weird. But I do agree with you, you know, that it's elevated. And the other thing is, you know, the question of that the [indiscernible] is so normal, which is also a little bizarre when it comes to rifampin. So what happened, Megan? What did we do? Go back to -- everybody's asking what kind of herbal teas? So I just want to say that I really think the reason is -- you know, it's about 1:30 here on the East Coast. You guys on the West Coast, a little earlier. But it is about that time that, you know, we have our afternoon tea. So, Megan, what kind of tea was it?

It was -- it had some kind of an iron supplement with alcohol in it.

Right. Actually, Megan, I remember when you had it, you actually sent us the label, and it was never a tea that I had ever heard about or a supplement that I had ever heard about. It was -- I don't know where she picked it up. It wasn't a common one, if I'm correct.

Yeah, she started going to an herbal spa at some point in time, which was concerning -- you know, I think she was concerned about some of the weight she was gaining. You know, how she had had the history of the gastric bypass. So I think she had started going to this herbal spa and they had given her some herbs. And we don't know everything that she was given, unfortunately.

Right. Right. Exactly. You know, Janet is asking, you know, if the [indiscernible] does that mean it's cholestatic? And I agree, it's probably not. It's probably more directly the liver itself that's actually releasing it. So what happened then, Megan? She, what do you call it, she got transferred to Jackson, huh?

Yeah, she was transferred here to Jackson for further management and consideration of liver transplant here at our transplant institute.
So what did she look like?

So, on admission, she was hypothermic. Otherwise, her other vital signs were within the normal range. She was not in any acute distress. She had very poor hygiene. She had a newly placed central line. Also noted to have fine rales to the left posterior lung base. Her abdomen was severely distended, with hypoactive bowel stones. She had three-plus bilateral lower extremity edema. She had multiple skin wounds. And overall, the patient was a poor historian, but cooperative and able to follow simple commands.

This is never good when your slide is mainly all red values when you're looking at it. So, real quick, Megan, what did you see?

So these were her labs from admission. You can see that she's coagulopathic. She has a slightly elevated creatinine. That albumin is still hanging around, too. Her total bilirubin at this point is 13.5, despite being off of all medications. The direct bilirubin was 12. And then you can see that she has an ammonia level of 230, and her platelets now have dropped from the previous level of 134 down to 27,000. And you can see also that she has a little bit of hypothyroid and the ceruloplasmin was low, which we'll talk about in a little while. And the anti-smooth muscle antibody was elevated.

Yeah, so real quickly, I mean, I think we'd all agree, she's in liver failure. I mean, she is not producing, her ammonia is high, and she's coagulopathic. And, you know, the question is why? And Mark is saying, and I agree, that it looks like it's chronic and acute, and I totally agree with him. I think we're looking at somebody who's had some sort of liver issue that obviously was made worse; you know? The interesting parts here, real quickly, is, you know, the ceruloplasmin in part of the workup here, you're always thinking about the possibility of Wilson's disease, and hers was low, so it is possible and, you know, it's definitely in the -- you don't usually get a fatty liver with Wilson's disease. And, again, her anti-smooth muscle antibody was high, which suggests an autoimmune hepatitis, but, again, not a typical picture with a fatty liver. Things are just not making total sense.

Here's her chest X-ray again. Now, again, you don't see the diaphragm. You have this white density. I don't see the left costophrenic angle. Again, I think that there may be an infiltrate there with bilateral pleural effusion. And, Megan, what's going on?

So, unfortunately, within three hours of arriving in our unit, she became hypothermic and hypotensive. We had to give her IV fluids and start her on empiric antibiotics. And she was transferred within a couple hours to the ICU, where they had to start her immediately on pressors.

Right.

So the following day in the ICU, the patient was noted to become increasing lethargic, responsive to painful stimuli only. She developed respiratory failure, requiring intubation. And also -- so they thought, given this overall picture, they thought that she was probably in septic shock due to either an intra-abdominal infection or an ammonia. Her WBC had shot up to 21,000. Again, those chest X-rays showed opacity. ID was consulted, they recommended to continue her on empiric antibiotics. She was given lactulose and rifaximin for the hepatic encephalopathy.

Sorry about that.

They did request a hepatology consult for her acute liver failure. She was given vitamin K for her coagulopathy, along with fresh frozen plasma as needed for bleeding. They had her on synthroid for the hypothyroidism, and heavy fluids for developing this acute kidney injury. So the chest X-ray follow-up on February 11th basically showed that the opacity and the bilateral pleural effusions were improving, but otherwise no significant change.
And this is the X-ray here. And, again, now you can see the diaphragm through the heart. So, again, they thought the left lower lobe infiltrate may be getting better, but she still has a bilateral pleural effusion. And this is a comparison real quick. I mean, again, you can see the diaphragm here. And actually, to be honest, I'm not even so sure this is really diaphragm. I think this is a subpulmonic effusion. It doesn't matter you can really see through it. So the infiltrate got better, but she still has bilateral pleural effusions. So, Megan, a hepatology consult, huh?

So hepatology saw her, they didn't think that she was a candidate for liver biopsy, given the severity of her illness. They did recommend getting a copper level to rule out Wilson's disease, which they did, and it turned out that it was low and not consistent with Wilson's disease. They also recommended getting an ultrasound and doing paracentesis, but, otherwise, continuing the supportive care.

So just for a second, when you talk about Budd-Chiari, and we'll just talk about it in a second, but just for everybody out there, what Budd-Chiari is, Budd-Chiari is in patients usually who are in a hypercoagulable state. They actually get a clot in their venous outflow from the liver and it actually can cause an obstruction. And you can get cirrhosis and failure, matter of fact, it can be quite bad. And the reason I'm just bringing it up here, you know, everybody always thinks Budd-Chiari, you know, metabolic hypercoagulable disease, they also think about some of the parasites, you know, in other parts of our world, but TB, which is a hypercoagulable state, which we'll talk about later, can also cause Budd-Chiari; you know? So it's something to always be thinking about. Obviously, you know, you want to do an ultrasound with Doppler to see what the flow is. So what happened there, Megan? What did they get?

So they found that, you know, the patient obviously had medical renal disease, and, again, confirming the fatty liver infiltration with ascites, but they found no evidence of a post-hepatic venous obstruction to suggest Budd-Chiari was causing this.

All right, so this is actually the MRI of her lower spine. And I just want to show you that, as Megan has pointed out, this patient, unfortunately, was quite sick, and when she came in she had a sacral ulcer. This is the ulcer actually coming through, that's actually getting to the rectum. So they actually thought that maybe a fistula between the sacral ulcer and the rectum. Also, what they could see is massive, massive ascites. Her belly is just now filled with fluid. And then she has, again, had some thickened small bowel here throughout. You can see the thickened wall. So what was the official reading there, Megan?

So, again, the radiologists say that she had a large amount of free fluid in her abdomen. She had that sacral ulcer, suggestive of a fistula formation; the diffuse small bowel thickening; and then some atelectasis and consolidation, again, with these bilateral small pleural effusions, and that one solitary right pulmonary nodule.

Which they didn't capture, right, because all that fluid, make sure she doesn't have a subacute bacterial peritonitis. What did they find?

They found that, again, this confirmed that she had a transudate and not an exudate, suggestive -- or not suggestive of an infection.

And her labs?

So they did the follow-up labs on February 12th. Again, her creatinine continues to go up at this point, now 1.4. Albumin still hanging around the same level. Her bilirubin continues to go up. It's now 14.7. AST is mildly elevated this time but nothing significant. And her ammonia, again, is elevated at 283, despite the use of lactulose and rifaximin. Her white blood count, despite empiric antibiotics, remains high. And her platelets continue to drop.

What's going on with her culture?
So the culture workup, pretty much everything was negative. C. diff was negative. And her blood cultures were negative to-date. But they did find that on a bronchial aspirate she had a heavy growth of yeast, and that was collected on February 10th.

So February 13th she had five to six rounds of nonsustained v. tach. They had to transfuse her platelets and FFP. She had a ureteral catheter placed for continuous dialysis to try to remove some of the fluid from the body and the abdomen, but the problem that they were having was that she was still hypotensive. So they were trying to find a balance between removing some of the fluids without making her hypotension worse. They tried to do a brain CT but they were unable to do it because as they were trying to move the patient she would become unstable. But they were, at some point during that day, able to discontinue the propofol and Levophed.

So the follow-up hepatology now basically, again, confirmed multi organ system failure. The main thing to point out is that they also thought that this presentation was not consistent with a drug-induced liver injury due to the TB treatment, but everything else that they had ordered had basically come back negative.

Sorry about that.

Unfortunately, on February 14th, the patient developed some facial twitching. They thought that she may be having a seizure but they were unable to do the EEG because of the patient's wig, which was tightly glued to her scalp. They started her empirically on keppra for seizure prophylaxis, as well as restarting her on the propofol drip. The patient still remained responsive to painful stimuli, and, again, that bronchial aspirate, which had grown a yeast on February 10th, ID then recommended starting her on mycamine as a treatment.

Yeah, I mean, I think you'd agree, at this point it's becoming important where they're just doing -- so they know she's really, really immunosuppressed from her condition, they're trying to cover everything. So what happened now?

So they were finally able to get the brain CT on February 15th. It showed -- it was worrisome for the cerebral edema, unfortunately.

And this is the ultimate what you're really worried about when it comes to, you know, hepatic failure is cerebral edema. As you can see here, you can hardly see any sulci. You see that the ventricles are now being compressed, meaning she has diffuse cerebral edema. This is another view of it, you know, and you can see that you really are not seeing the typical sulci and gyrI. I mean, it's all being compressed. Also, you know, diffuse cerebral edema is all probably related to the, you know, hepatic encephalopathy. So what happened next?

So the patient's overall condition was unchanged, except for now she was no longer responsive to painful stimuli. She was continued on the current course of treatment. Her bilirubin still continued to go up, now at 15.3, and her lactic acid and white blood cell count are consistent with a septic picture. But, otherwise, her ammonia has come down nicely, from 283 now to 88.

I mean, on the other hand, that could be just that the liver is really giving out. I think you'd agree it's just not able to produce. And the last thing is, like you said, the lactic acid is really showing an inability to continue perfusion peripherally. Again, it's elevated, not horrible, but you're right, it could either be sepsis or from shunting now from hepatocellular failure. So what happened now? What was in her labs? They don't look like they're getting any better.

So five days later, the patient was severely coagulopathic, with an aPTT now 170. Her bilirubin was pretty much stabilized at that point at 15.6. Her AST now more elevated than previously. Also, the ALT was starting to go up. And her white blood cell count maintained at 21,000, 22,000, remaining anemic, but her platelet count continues to drop.
Yeah, and, again, I think someone pointed out, the AST is out of proportion to the ALT. Whenever you see that, you think about things that could do that. You know, in our normal practice, you know, one of the most common reasons we see is that somebody is drinking alcohol. But the other thing we have to worry about is things like muscle break, which I suspect was happening with her, and also, like, hemolysis. But, you know, again, I'm not so sure the AST is really out of proportion because of liver reasons. I think there was probably something else going on. Though you are starting to see that the [inaudible] is starting to go up, but, again, not horribly significant.

So, because of this, on February 21st, palliative care was consulted. Everyone agreed that despite aggressive treatment, that the patient's condition continued to decline and that her prognosis was gray, without any chance of meaningful medical recovery. They spoke with the patient's health care proxy, who agreed with the primary care team to withdraw life support. And the patient expired on that afternoon. And the family refused an autopsy.

So, I guess -- and this is where I'd like to -- so, you know, from our perspective, you know, we thought that this was probably, if we're looking at causes of death and related conditions, that it may have been a nonalcoholic steatohepatitis with hepatic failure, which we'll go through. And, you know, the question was why did she have it? And, remember, she did have a history of morbid obesity, and that's why she had the gastric bypass in the first place. She also had evidence of metabolic syndrome, but was really never diabetic.

But, you know, and the question is, as I think Mark was pointing out, and I agree, could this have been exacerbated by the TB meds? Then obviously I think that, you know, ultimately what did her in was, you know, obviously with the liver failure, cerebral edema, and, you know, she may have had sepsis, but obviously underlying it all was disseminated TB. And I think we'd all agree, a question that, you know, whenever you see disseminated TB, it's why. You know, and I think she was immunosuppressed right from the beginning. To have disseminated TB, especially of the abdomen, and diffusely like she did, she had it of the abdomen, the lymph nodes, everywhere they looked she had caseating granulomas, we really think that she must have been immunosuppressed somewhat right from the beginning, which I think was related to her liver disease.

So I guess for a second what I'd like to do is ask any comments? I mean, I think one of the comments, you know, that I saw before that I really agree with is, you know, the whole concept that sometimes we forget, you know, that the herbal products are not necessarily harmless, you know. And, again, I don't think it really had much to do with this case, but it's one of my, you know, pet peeves actually that a lot of our TB patients, they'll see somebody will develop a hepatitis, so we ask them are you taking any meds. And they'll say, "No, no, no, no drugs, no drugs," and then you find out they've been taking an herbal product, especially among many of our patients who come from parts of the world where herbal products are a very commonly used medicinal agent. So I do agree, and I think it's something we always have to remember to ask. So I don't think it really played a major part. And I think it's a great point to stop and ask. So, Elizabeth, thank you very much for that.

Before we go forward, if you couldn't mind, I'd really like to hear, Mark, why don't we put you on the spot, if you're on the phone. Push "*7". So, Mark, do you agree, disagree, what do you think?

No, I totally agree David. I think that her obesity, and we don't know whether she had diabetes at all, but that can certainly lead to a fatty liver. And, you know, we don't know her long-term course without the TB, but I think she was already heading towards the road of liver failure eventually.

Mark, I totally agree. And that's why -- anyone on -- thanks, first of all, Mark, thank you, thank you, thank you.

Sure. Sure.

Any other comments or questions, and then I'd like to do a brief overview, and then we'll go. But, you know, I think many of us see patients with fatty liver, but I don't think we totally appreciate the full
spectrum, so that's what I'd like to go over. But, before we do, anything you think that should have been done differently? I mean, I guess the biggest question I have, and, you know, if I had to have a comment, would be, you know, the whole idea that when the patient's liver enzymes were elevated, you know, I do think personally that it should have been stopped or at least switched. But I would have probably just stopped just because of the timing. Mark, while you're on, or anybody else, your comments on that? Like, what you would normally do. Mark, if you -- and I'm catching you off guard here, I'm sorry, and if I was you this is a good time, if you don't want to answer that, your phone goes dead.

I'm used to it.

But what do you do if somebody like this, with the total bilirubin being up, and they're otherwise find, what do you think how you would handle it?

No, I agree that early on, definitely, she should have had her meds stopped. And I think it's different approaches. But I would have done more extensive workup at that time. You know, I think the combination of INH, rifampin, perhaps her herbal drugs, with Tylenol and alcohol, all that may have just had a cumulative effect and tipped her over. So was it preventable, I think that's what you're ultimately asking, if there was something we could have done to prevent this ultimate outcome. And it's hard to say, but it would have been nice to have her off the drugs, at least the hepatotoxic drugs, while we were sorting all this out.

Yeah, I agree. And, on the other hand, you know, as sad as it is, I think we'd all agree, the reality is sometimes these kinds of things happen. And I think the stress is -- you know, one of the things to stress is the importance of getting results that are abnormal back to the clinician as soon as possible.

Hey, a couple things real quick. I know Greg, again, I know has asked this great question which is, you know, when you're looking at the bilirubin being elevated, what was the -- you know, how do you look at the bilirubin and what's the significance, especially direct or indirect? And in this case, and in most cases where there's direct damage to the liver, what you'll see is an elevated direct bilirubin, mainly direct. And, again, that usually shows you a pretty much more direct insult to the liver.

But from time to time you'll see the elevated total bilirubin and the indirect will be much, much higher than the direct, and the most common scenario for that, especially in TB patients, is actually a condition called Gilbert's disease. And Gilbert's disease is just a problem -- it's an inherited problem of conjugating bilirubin. It's absolutely benign. And it is quite common in certain populations, I know the Caucasian population. And, interestingly enough, the way you test for it is you give 900 milligrams of rifampin to somebody and their bilirubin will go up, and it's mainly indirect. And, again, that's because the hemoglobin that's being broken down, it will bind and become indirect bilirubin. And, again, you'll see that. But in those cases normally you'll see a drop in the -- what do you call it -- in the hematocrit, and that becomes the key -- there's usually something else going on.

If you look at on the other side, one of the most common reasons why you have an elevated indirect in a patient who is not doing so well, it's usually hemolysis. And, again, that's because the hemoglobin that's being broken down, it will bind and become indirect bilirubin. And, again, you'll see that. But in those cases normally you'll see a drop in the -- what do you call it -- in the hematocrit, and that becomes the key -- there's usually something else going on.

And then, lastly, obviously you see it in patients with really bad, sometimes, you know, myoglobin, where you're getting a rhabdomyolysis. But you are right, and Greg, I totally agree, and we've discussed this before, that when you do have somebody with an elevated total bilirubin, it's very, very helpful to do a direct and indirect to get an idea where it's coming from. You're totally right. Thanks for the question, Greg. As always, you can also, please, unmute, that's "7," if you'd like.
Let's quickly, if it's okay, talk about fatty liver real quickly. And, you know, let's be honest, it's something we see quite often. In fatty liver I'll see a steatosis, it's a fatty liver. And, again, it's usually caused -- what's most common is too much alcohol, but other reasons is obesity, insulin resistance, and alteration in triglyceride metabolism. But when you look at drugs, the drugs that cause it mainly are ethanol, steroids, and highly active antiretroviral therapy, in particular AZT, and other drugs that affect the mitochondria, you know. And the key here is, though, that usually the liver is functioning fine. It's something you'll see on ultrasounds, something you'll see on CT, but the liver is otherwise fine, you know.

And almost -- when it is caused by drugs, it's usually reversible. If you stop it, it gets better. But here's the thing, if you continue to have injury in these cases, as Mark was pointing out, these patients may progress to a hepatitis. Notice the difference. This is no longer just steatosis, this is no longer just fat in the liver. Now the liver is becoming inflamed. There is evidence of inflammation and cellular involvement. And these patients are getting sick and they're at an increased risk of cirrhosis.

And if you look at nonalcoholic steatohepatitis, this is actually now being more and more recognized. As a matter of fact, it was first recognized by our colleague up at the Mayo Clinic. And they were the first to really start describing cases of patients who were developing cirrhosis without any real sphere of etiology, normal etiology, no hepatitis C, no alcohol, no autoimmune. And, again, it was mainly seen in patients who were alcoholics, but it also could be seen in patients with diabetes, obesity, metabolic syndrome. And when it's not associated with alcohol, it's called NASH, or nonalcoholic steatohepatitis. And it's a progressive form of the benign steatosis.

You know, these cases can progress to cirrhosis. As a matter of fact, in the Western world, it is thought to be -- you know, outside of alcohol and hepatitis C, it is one of the leading -- it's the third most common cause of cirrhosis outside of those two agents. So we're seeing it more and more, especially in our patients who are having problems with the metabolic syndrome. And obviously, as the metabolic syndrome is becoming more and more common in the United States, we're seeing more of this. And, as they've stated -- or we've state, we think that what this is just a progression of the steatosis with inflammation, and it's the chronic inflammation with the reactive oxygen species that actually causes the inflammation.