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TRANSCRIPT - GR 04 18 25 **"Clinical Pathology Conference"** guest speakers Amy Mathers, MD and Adam Carlson, MD from the University of Virginia

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Internal Medicine Grand Rounds

- Welcome to medical grand rounds. We will be doing a much loved clinical teaching format today called Clinical Pathology Conference. So I'll introduce the format and our Cme. Slides, and after we talked about the details of the case, Chief Resident, Dr. Shaina Hassan, will introduce our 2 literal discussants. Dr. Adam Carlson from the division of rheumatology, general medicine inpatient attending Dr. Amy Mathers from infectious disease, also general medicine Attendant. So take us through our slides. Our Speakers presentation objectives for some of the clinical teaching that they're going to be doing as they hackers just in case all right, and following disclosures from Dr. Mathers. That will not be addressed in this teaching activity Cme. Credit for faculty, your email to Tony Brinkman during the middle of the conference, and then let's get down to the the teaching of the case the case of fever, of unknown origin, bone and lung lesions. But 1st we got to back up and talk about just the concept of the Cpc. Which is in a traditional teaching format in medicine. So realize, so what a Cpc actually is. So this is an exercise in clinical reasoning and integration of medical knowledge and decision making. And really, what we're here for is to see some faculty lay out their clinical reasoning or approach to the case, how they're bringing their medical knowledge into it, what they, what they think, they know, what they think they don't know and need more assistance in so getting them to really lay out that clinical reasoning and to put out that differential diagnosis, and of course, try to put the nickel down on your highest suspicion. Of course, that's what we're really focused on. In fact, discussants are often focused on getting the right answer reports. But other typical features of the format is just sowing some seeds of doubt to avoid anchoring as well as to maybe all right. So the concepts, practically speaking, so in thinking about what kind of cases we might go through at a Cpc. So a former faculty member here really introduced this 2 by 2 table life is a 2 by 3 tables. So we're often thinking about common conditions and less common conditions and typical presentations and atypical presentations. So the typical presentation of a common condition. Maybe it feels kind of boring.
- It could be pretty anxiety. Provoking, too. Right? Oh, my gosh, yeah, am I missing something here?
- Maybe a atypical presentation of a less common condition. Right? So, you know, I think, as a discussion you're often trying to think about in your approach to the Cpc. Is this typical presentation of a less common condition that feels pretty good, or maybe an atypical presentation of a common condition. So we're talking.
- But of course this is a theoretical model only, and it really is not that helpful? So again, just remind us of principles of diagnostic reasoning. So, thinking about the approach to the case, you know, at some point we have to start generating some hypothesis about our approach to what we think is going on with the patient,

integrating the data, so organizing and manipulating the facts. To think about, what do we think is really central, important, reliable data here.

- And then we're using that and both our both our system, one and 2, thinking to try to generate some problem presentation. I just refining this hypothesis with the rest of the data, maybe getting other consultant input in the literature and then finally getting down to that working diagnosis.
- Alright. So I'm gonna introduce Dran to come through and talk about our discussants. Case.
- Okay? Awesome. So we got a good one for you all to start with. This is a 42 year old male. He has a history of chronic Hep. C. As well as remote ivy he presents to an outside hospital. He has a ten-day history of cough and several days of fever, pretty high fever up to 104 degrees. State of health. Again.
- Highlighting his review of systems, fever, cough. He had this right sided chest, pain, non radiating quality. But it's not as well as some body.
- And throughout interviews with the patient he denies having any offices, urinary symptoms, abdominal pain had any weight loss, no edema that he describes, and no rash as far as a little bit more background on him again. Chronic hepatitis C. Chronic low back pain some family history of lung cancer. He's a 1 pack per day smoker as far as Iv drug use last time he was a year prior and of note. He was incarcerated from May to December of last year 2024. Currently this case is early January of this year, as far as medications. He's just on walnutrin and Saba.
- So for his initial presentation he presented to the outside hospital in early January again, having cough fevers, malaise at that workup. There was some mild leukocytosis. It was a chest X-ray performed, otherwise known. He did perform a Ctpa, no evidence of there, but there was commentary on multiple pulmonary molecules.
- There was a large nodule on the right upper lobe of the lung that was concerning by the radiologist at the outside hospital for metastatic disease in a small location. So on this presentation, he was treated with Augmentin for a presumed cath, because of the concern of topical metastatic disease, he was told to follow up when he was connected.
- Oncology However, 24 h later he presents again to the outside.
- There isn't anything in the glass and at this point in time. He's admitted with concern in the hospital, and we started on as far as the initial labs that were going on him. As you can see he has some anemia leukocytosis. His chemistries aren't really that remarkable other than a low album. His coagulation studies are normal.
- He does have some elevated Esr. And Crp. And, as anticipated, his Hep C. Antibody was reactive. They did during this admission, do some more broader infectious workup on him, including 2 fever. Brucella, Bartonella, as well as and other micro studies on him, including urine culture, blood pressures, respiratory pathogen, panel, cryptococcus, as well as spedum cultures were negative highlighting the imaging that he had done during his admission. So he had a repeat chest X-ray. There was evidence of that right upper lobe nodule, maybe concern for developing pneumonia because he was admitted for concern for endocarditis. He had an echo done. Echo showed overall normal ventricular function without any significant valvular abnormalities that would be concerning for an endocarditis.
- He had a Ctpa repeated, and again, no PE. But, interestingly, or he had enlarging pulmonary nodules compared to about 2448 h prior, when he had had that initial Ctpa. And there's evidence of destructive lesions in the right 8th rib and T. 3

vertebral body, he lost enlarging pleural appointments and the admin call has also demonstrated some scattered lytic lesions throughout, including the left iliac bone and nodular opacities throughout the lung patient.

- So at this point in time. The outside hospital has some concern for possibly a metastatic disease process, and they opt to try and target the left iliac bone for a biopsy.
- So the results of the left iliac crest biopsy. Interestingly, our pathologists comment and say that evidence of acute and chronic osteomyelitis the pathologists also comment on final review. There's no overt evidence of a neoplastic process. They also comment that the plasma cells are positive for CD 100 ratio polytypic by Rna. They also sent micro studies on this negative for Ebv. HIV. Cfp, as well as fungal Afb. And bacterial vultures.
- So at this point in time, the outside hospital requests to transfer this patient to Nda, because the patient continues to have ongoing fevers, despite broad spectrum antibiotic therapy, and they feel that the patient needs tertiary care at this point.
- So the patient arrives to Uva and is admitted by the overnight general Medicine resident in terms of the initial vital signs and exam. You can see on the left. This is overnight. When the patient was admitted.
- Stable and nothing really notable. On exam the comments, on no evidence of no raptures that they could know. The patient ended up having a neck call overnight, had a temperature up to 40°C, and to the 120 s. And in the morning, when the patient was handed off to the primary general medicine team, they commented in their physical exam at this point. In time he was ill, and started hearing Tachycardia, and they did note a small lanching erythema dispatch on his right test, but on their exam they also did not notice any significant rashes or one bad knowledge.
- These were his labs on his initial admission to Uk. So again, you can see evidence of that anemia, some rhetocytosis. Again, the coagulation studies are normal. Chemistry is also pretty standard with, again, not evidence of hypoal anemia. His Hcv viral load was in the 2 thousands. Again, elevated Esr. Crp. And an elevated Ferritin micro studies were repeated on this patient that were overall negative with blood cultures in process at the time of admission. They also obtained a histoblasto antigen that were negative, and this the general medicine team opted to get a repeat Ct test by contrast and again there was compared to the Ctpa. That was done by the outside hospital. At this point, maybe one prior. There was an increase in the number and size of diffuse solid pulmonary nodules. The right upper lobe mass is now 4.5 cm in size from the 1.5 cm that was noted on the chest. X-ray maybe about a week and a half prior. There's a new lytic lesion in that right 3rd rib with an associated pathologic fracture. And there's again more lytic lesions now involving the T 3 vertebral body.
- So to give you guys all a quick timeline summary. So our patient on day 0 has a cough, fevers and chest pain. On day 10 he presents to the outside hospital er he has a dppa that knows multiple pulmonary nodules. He's treated with augmention for presumed CAD.
- On day 11 he presents again, and he's admitted with concern for possible endocarditis, and during the admission at the outside hospital. He's treated with vancomycin, cepizolin, and docin for a total of about 5 days on day 16 at the outside hospital. He has a left iliac crest biopsy that shows concern for chronic

ultimaelitis. His infectious workup is negative, and on day 24 he's transferred to Uva.

- Day 26, he remains febrile and a repeat, Ct. Test at that time shows increase in the number and size of pulmonary nodules, as well as an increasing number of lytic lesions and rib.
- So, handing off to our faculty, we are asking them, What's your working differential at this point? And what would be your next step to make this diagnosis? And why so? I have the pleasure of formally introducing our discussants today. Dr. Adam Carlson and Dr. Ian Mathers.
- So, starting with Dr. Carlson, he obtained his medical degree here at Uva School of Medicine, and went on to complete both his Internal Medicine Residency and Rheumatology fellowship at Ucsf. He returned here to Uva in 2014, and he is now an associate professor of rheumatology and currently serves as a rheumatology fellowship director.
- He has particular expertise in musculoskeletal ultrasound for the diagnosis and treatment of rheumatic musculoskeletal conditions, and has a very strong interest in medical education of residents. Next, we have Dr. Mathers, who obtained a medical degree at the Loyola Strips School of Medicine, and competed for internal medicine.
- She has been at Eba since completing her infectious infectious disease fellowship in 2,009, and is the Bayer Mandel, Professor of Internal Medicine and a professor of pathology.
- Additionally, she's the associate director of Clinical Microbiology, and the former director of the antimicrobial stewardship program. She directs the clinical microbiology sequencing lab and has an active research program focused on antimicrobial resistance and genomic applications in public health with active funding to the Cdc.
- So we're very excited to have them come, discuss this case with us, so please join me in welcoming.
- We're going to start off with Dr. Carlson. Right? Thank you.
- Alright. So you know, one of the things that was interesting when I was 1st reading this case was initially just looking at some of the trends, and I think it can be useful at some point when it comes to making diagnosis and so forth. But there are some concerns that we have about how frequently we're ordering some of these tests and how to interpret them and those sorts of things.
- And so I thought this would be a good opportunity to kind of provide some background so that we can now develop a framework for ordering and interpreting our. So I'm going to do a little tangent first, st we're going to talk about that. That's first, st and then we'll come back to my differential and so forth.
- After that in the context, actually of talking about my differential and with the acute phase reactant, I'm going to spend a little bit of time talking about the difference between autoinflammatory disease and autoimmune disease and and I'll say, just at the outset. So I'm gonna show you. The this is was recently published in the New England Journal, and a really helpful kind of time course, of what happens with acute phase proteins in response to some sort of exciting. Now, before I go on, though I wanted to explain a little bit about the difference, or what drives, what drives these processes like, what drives the kinetics of these proteins, and so forth, so harkening back to for many of us, probably medical school and immunology. Just remember that, poised at interfaces in our body, we have cells of the innate

immune system. So things like that. And when this part of the immune system comes in contact with molecular patterns of pathogens or damaged cells, they begin to secrete cytokines and a whole host of other signaling molecules that then in turn one, they ramp up their, you know, they recruit more immune cells. So we ramp up the immune system.

- And a lot of these are in response to some of those cytokines that are secreted in those early phases of the immune response. Now the na immune system will then go on and serve as a bridge to activate the adaptive immune system which is comprised of things like B cells and T cells. And like, I said, we're going to talk about autoinflammatory diseases and autoimmune diseases. So autoinflammatory conditions arise when there are problems and with innate immune cells and auto inflammatory. Or, excuse me, autoimmune condition arise. And we have problems with T cells. Right? Our adaptive.
- All right. So back to the kinetics here. So one of the things to know. So let's talk about this. So I would argue that the most useful acuphase protein that we look at in clinical practice is the crp.
- And the reason is because it's primarily because of its kinetics and the degree of its change. So within hours of a syndrop you will see the crp rise over a hundredfold within hours, and so it responds quickly to that, and not only that it declines quickly once that send us.
- So there's a whole bunch of other things up here, and one of the things you don't see up here is the segmentation rate and the sedimentation rate is a very actually, it's very complex, and a lot of things influence it so. But the primary driver of an elevation in your sedimentation rate, which, by the way, for those of you who aren't familiar, the way that we do that is, you draw some blood. You put it in a 10 cm blast tube. You start a stopwatch. You wait an hour, you come back, and you see how far the meniscus of red cells has fallen and it's measured in millimeters.
- But it's primarily influenced by fragranogen. And you'll notice that fragranogen takes time to come up and reach its peak. So your segmentation rate, if it's just in response to an inflammatory condition, really takes time to ride over the course of days, and it stays elevated for longer and has a slower deadline. So just keep those things in mind. So in this particular case, remember, when the patient came in, he had a set rate of 24, which, I would argue is pretty darn close to normal and a crp of 20. You're like holy smokes. And then, several days later. Well, what happens? Well, his crp is 16. Well, that's still really stinking high, but the said rate is now 79. So just keep those things in mind in terms of now the rise in your crp, and a lot of these things are all primarily driven in the context of il. 6.
- And what happens is Il-six works on the liver, and it's the liver that's producing a lot of these. Now, c-reactive protein is a complement protein that is there to kind of sop up bacteria.
- So one other thing I just want to point out here is there are inverse acute phase reactants or negative acute phase reactants, and the albumin is a good example of that. So you'll often see there's your prp go up and your albumin go down in the context of acute inflammation.
- But one final point that I wanted to make is for us as rheumatologists. We really want a more robust, acute phase reactant to measure inflammation in the setting of things like
- Ginsal arteritis, and one of the reasons so temporal arteries and large vessel vasculitis, and one of the reasons is because we like to use therapies that target. Il

6. So when we give Actemro or Tocilizumab, you can't look at your crp anymore. It's no good. And your said rate will be normal.

- But it can be falsely normal, because there's other pathways of inflammation that are wrong. And so ideally, what we want is we want some type of vendor of inflammation that doesn't track with Il-six. And so there are things like procalcitonin, or this molecule contractin, 3 which are made by non immune cells cells in the periphery that give us more information about inflammation, maybe in response to bacterial pathogens or other pathogens, and so they may have also some some utility it when it comes to tracking, how severe an infection is. Okay, moving on. Finally one of the reasons why the sed rate is a real challenge is because there are so many physiologic and pathologic variables that influence the sed rate.
- So things like anemia. So anemia changes the rheological properties of blood cells as does polycythemia. So if you're anemic, it elevates your set rate, and if you're polycythemic, it's the reverse. If you have a gammopathy of any cause. It could be a polyclonal gammopathy like you would see in Lupus or Sjogren's, or it could be a monoclonal process in things like myeloma that will elevate your set rate. And so the reason that I mentioned this is sometimes you'll see. So we're often we have to explain a discrepancy between the set rate and the server.
- So with the said rate, if the set rate is high and the crp is normal, we have to go looking for these other things, and that's the reality of what happens in things like lupus and so forth, is that these patients, their set rates are always high, but they're actually, their disease is pretty well controlled. Well, that's because they have a polyclonal gammatopy.
- Another another in the other situation is, what about when the crp is really high, but the set rate is like 0.
- Well, that's a special. That's a special situation where you should be wondering. I wonder if this person has a macrophage activation syndrome, because those patients by definition their fibreration is in the basement. And so they're separate is normal. But they're profoundly in a way.
- And that's where the Ferritin will come in. So that's kind of one that this is another acute based protein, as it turns out, that can be incredibly beneficial, at least in the world of rheumatology, because there are these hyperferricinemic syndromes that we talked about, so stills disease or adult stills is one example of that, and another that we may see in some of our patients is Hlh, and that's usually associated mostly with cancer followed by infections followed by okay. So
- I kind of came at this 1st sort of thinking about it from the perspective of a rheumatologist, and then we'll kind of transition over to as an internist about it. But when a rheumatologist, when I'm thinking about fevers, I often make this. This is something that I developed recently is, I really start to think, separate these things of autoinflammatory diseases and autoimmune diseases.
- A lot of autoinflammatory diseases have really profound fevers, and a subset of auto-inflammatory conditions includes the periodic fever syndrome. So things like familiar fever trash, which is, don't worry about all these things. But the point being trash is a Tnf receptor associated. But the point here is that the type of fever the duration of the fever, really helps us in terms of thinking about these sorts of conditions. Now, many of these conditions are Derma mediated. So they're typically inherent.
- But what we have learned recently is that there's actually now some things that develop as somatic. You guys have heard about. Maybe you've heard about vexus

which is associated with nds, and it's this overlap of stills and medium vessel vasculitis. So these are all in this auto-inflammatory bucket, and we treat it a very specific way now with the autoimmune conditions, it's a pretty short list of things that cause fears that I carry around with me. So, as a general rule, rheumatology always on your differential to diagnoses, is sarcoid, and Bichette's, because Bichettes can just as much as sarcoid do whatever it wants so those are always. And then certain manifestations of lupus can be associated with fevers because they tend to be more inflammatory. So a patient has arthritis or servicitis, and Ra. Again, this is much lower on our differential, but it's up there along with some of the other in this particular situation, and this is one of the ways that I approach. My kind of clinical reasoning in these cases is that try to find one thing, not to anchor on right. But to use as a foundation that I then build around and it's the thing that I feel like has the fewest. I mean, it's the smallest in isolation kind of the fewest possibilities, and then I'll fit in some of the other things and see where there's overlap. In this case it's the lytic bone lesions right? Those really kind of gave me some pause. And there's a really fun mnemonic. If you can look on radio gear we use it occasionally. It's called fog machines, but that the differential for Linux donations is not that long as it turns out so, this is kind of how I was approaching this. And again, this is kind of more of my rheumatology band, because I wanted to talk about this, because the remember that we have lytic lesions.

- We have fevers, and we have lung lesions. That's kind of and-. And this is where all those the things kind of the only thing that I can think of in our in our world that would explain everything. Assuming there's 1 unifying diagnosis as a rheumatologist.
- This condition, chronic, recurrent, multifocal osteomyelitis is an auto inflammatory condition.
- It causes sterile oculitis. It typically affects the long bones. It has a predilection of clavicle. The problem here is that it's the wrong demographic. It's usually kids.
- And because it's germline based, generally speaking, so we typically pick this up sooner, it responds really robustly to Nsaids. Typically, occasionally we'll have to use some other drs. all these other things in the rheumatology world are like metabolic bone diseases. Right? They're not. Gonna they're not gonna be associated with fevers or lung conditions. That's like, it's that short in my view.
- Okay, so here's my internal medicine differential. And I'm realizing now in retrospect, as I'm up here, I didn't really explain my reason here, sort of because sarcoid's up there right. But I didn't explain all the other stuff so well. Myeloma and lymphoma are really high on my differential in this particular situation. Mostly, again, it's the bone lesions are really giving cause. And I would say that this differential kind of has that has that lytic bone lesion as sort of my central theme, if you will. So metastatic, solid tumors so it could be a lung cancer that's metastasized to the bone with all this other stuff that's going on, and to the lung multiple nodules, melanoma is less likely than Rcc, because I feel like we would have seen that on imaging. But melanoma is one of those things that can do lytic lesions that you just can't see, and then a bone seeking infection. So anyway, my next step, my next step, is actually probably to call my colleagues over here, maybe for a bronch or a navigational biopsy. I don't know if that would be needed with this type of lung mass there, but we need tissue. And so I would say, that's probably where I think we need to go to next.

- The either, taking a fresh look at the existing histology can be beneficial if we can get it, although sometimes you just have to start afresh and just do another bone biopsy or something along those lines in the right context. And then, finally, you know, you're going to consult. So with that I will.
- And then what else?
- So I'm going to talk. So we know this patient has infectious disease. They have hepatitis. C, so I'm here. So again, the rules of the Cpc. Were laid out nicely by Dr. However, there's some additional rules they asked me here as a rheumatologist, I'm like, okay, is this some sort of room id trick, or what is it? But I was thinking, you know, this patient does have an infectious disease.
- And so I wanted to talk a little bit about Pepsi and what that puts people at risk for, and then just kind of walking through, and how you take in pathology results, and put it the context with interpretation of microbiologic results. So this is generally my approach to the world of infectious disease. You know you take the pathogen, which is like what I love to think about. And then the host vulnerability which I'm not. People know me. I'm not really an immunologist, but it's really really critical, because what kind of infectious diseases can this person get based on their immune status?
- And so for me, as an infectious disease, doctor. Timing is everything. The pace at which an infection unfolds gives me tons of clues about what that is that obviously can change in different hosts. You've got somebody who's neutropenic and bacteremic. They're not going to do so well in a matter of hours. And so, you know, you have to kind of put all that into context. But then, where is the symptomatology going, and what kind of organisms go to that location?
- And really, for this particular case which I'll talk about. It's pretty diffuse, although bone, lung brain as well. What kind of exposure? So is this the type of pathogen we should think about that everybody's exposed to. We assume everybody's sort of exposed to E. Coli and staph aureus, and maybe less so. Brucella or tuberculosis do they have unusual disease?
- You know things that they put themselves at risk for. And so with the history of Ibd, you do have to think about, there might be injection or inhalational if there's still substance, use dependencies. And so you have to take that kind of in context, age is always helpful. What kind of infections do people get? What comorbidities they have? And are they on any immunosuppressing medications?
- And then what type of immunocompromised so is their skin intact? Is their innate immune system working right do they have T cell, B cell deficiencies? Neutrophils are always helpful. And then, of course, here we are at Cpc. Do they have something that we don't know about. Right? So is this patient presenting a new and has some immunocompromising condition that we didn't know about at diagnoses, and that's presenting as an infectious disease.
- So for this particular case, this thing is rocking and rolling like this patient is rapidly evolving for that nodule to go from that size to the next size that does make me think of aggressive, infectious disease. Actually, things like Staph Aureus. Or there's not that many organisms actually, that could do that. He's got, you know, pleuritic chest pain, but but also nodules in the lung, and then lytic bone lesions and lytic bone lesions. I also anchor to, and I'll talk a little bit about. But then we've got a diagnosis on path of osteomyelitis.
- There's actually not that many non-infectious things that can look like osteomyelitis under a microscope.

- His risk factors incarcerated in Virginia actually being in jail for that short period of time is not that big of a risk factor for TV honestly and in the State, the number one risk factor is not actually being born in Virginia. And so I'm not sure he's that high risk for TV, but you definitely have to put it on your differential with this particular case.
- I already talked about the injection and hhalational exposure. He does not have unusual exposures that they haven't told us about, and hopefully they won't try to trick us. It turns out he's a raw milk farmer. Hcv. So we've got to think about hepatitis C as a chronic condition. But also, how does it change your immune? What does it put you at risk for? And how does that impact your ability to fight off other infections? Actually the albumin malnourished was my last Cpc. That they tricked me on, which was candle pneumonia, just for the record, which is terrible to do to a stewardship director. Malnourishment albumin 2.7 usually isn't in the range. It's so acute. I don't think that's what's playing a role. It's probably acutely dropping. And then this concern for malignancy that put them at risk for immunocompromised. And then I'm going to talk specifically a little bit about hepatitis C, and like, I said, could he already have something that we don't? So this is my original sort of fuo approach to this case. There's several things that we've already sort of ruled out, and I will kind of talk through some of them.
- I'm not going to go through this long list. But this is the list I came up with, and
- I think the diagnosis might be on here and talking to Dr. So, and then, you know, Dr. Carlson nicely went through all the autoimmune, but hepatitis c vasculitis, I thought, was another one that I was going to talk a little bit more about and non-infectious issues.
- So again, talking, I think it's important that we talk about the fact that this patient does have an infectious disease. And I just wanted to highlight this. So there's a lot of product infectious diseases that we all carry around. And we don't think that much about as acute infectious diseases that can then reactivate. So herpes viruses. Of course we do think about that, but that's something that this patient might not have acquired. But now that is immunocompromised is roaring to the front. It's none of these. But I just think it's important to think about these viruses that we might chronically carry. That, then, can reactivate at inconvenient times retroviruses. So if he's got HIV. Htlv 1, 2, those can cause immunocompromise and have an impact on immune. Cell function. He doesn't really have risk factors for those. And they ruled out HIV. So it's not that hepatitis. So we know he has hepatitis C. And what does that do? Well, chronic. You know, hepatocyte inflammation causes T cells, B cells to be highly activated. And it actually wears on your immune system in really interesting ways that I've learned about in putting this case together and then reactivation of sort of some of the other chronic viruses like Bk or Jc. Virus in the very immunocompromised. But that's not what this patient has. I don't think so. Extrahepatic manifestations of Hep C, so 70% of untreated hepatitis C patients will have a complication. These are some of the lists. There's some really nice studies done of meta-analysis looking at people that have Hep C, and looking with control groups of people that don't have hep C, and for me my brain goes to cryoglobulin vasculitis, and you know, cryoglobulinemia mixed cryoglobulinemia being the immune system is activated and producing all these, you know mixed new complex is basically 12 times higher in patients with hepatitis C than the average public mixed cryoglobulinemia vasculitis which can potentially cause diffuse pulmonary issues and get into the bones. If I saw some case, reports

is 4.9%. But I don't think that's what this is, because I think for this patient to be presenting that way.

- He would have some other findings by now, and so he just doesn't have a lot of the other symptoms or a lot of skin conditions. And so this could be a rare presentation of a common thing. So I'm not completely discounting it. But I don't think that's what he has lymphoma. So I did not realize how dramatic the risk for non-hodgkin's lymphoma is in the hepatitis C population. But it is pretty dramatic. So risk of lymphoma is 60% higher in patients with Hep Cv compared to non controls. So then, lastly, I just want to finish out with, how do I think about sensitivity and specificity? As a microbiologist, we're taught sort of back in med school sensitivity and specificity is how well does the test detect the disease? And how well does the negative? You know a negative test? Say, you don't have the disease? And we walk around with that. But actually, it's never really that that's sort of population based. It's in your patient. What's your pretest probability? And what I'm going to say, is for patients in infectious disease. If this was
- Mrsa bacteremia and endocarditis causing these bone lesions, we would have grown it so. Organisms that grow well, those kind of come off of my list right out of the gate, we've already you know, for you know, turns the earth over for that fastidious organism. So this is a picture of Nocardia. Nocardia is on my list, but he's not immunocompromised, and I will stand by the fact that this cannot be nocardia moving this fast but lung bone. Those all could be targets for nocardia, but it just cannot move that fast in the lab or in the patient, and they cultures will cultures from Culpeper. Maybe not for opercardia, but culturestoplasmosis again. I just don't think it could move this fast. It could be histo except again, I'm going to get to number of organisms. If this patient had disseminated histone moving this fast, we would have seen it on Antigen.
- So the Antigen test is not perfect, and if you look up the sensitivity and specificity of urine histaminogen, it's not perfect, it's far from that. But in this particular patient I would think there would be enough Antigen to turn the Antigen antibody test positive. And that's true for Brucella and Coxiella. So I took kind of all of those that can cause fever of unknown origin and bone lesions off of my list. Antimicrobial effects this patient was on vancom.
- It is old Dr. Mathers. We got to keep them on bank of Piptazo because we didn't take the cultures until they gave that. Well, anything causing this disease we would have found by now, so I don't think it's antibiotic effect. So it's kind of my thesis statement. So this is my refined differential from what I started with. So I left Tb. On there, because Tb. Tests are not perfect, but I still think, based on pretest probability and the rate at which this is moving. It's unlikely to be. Tb, you know that's just blossoming unless he's super immunocompromised. And again, that would be, I just don't think that's what this is. So, my internal medicine best guessis actually my internal medicine, slash pathology best guess I go to the osteomyelitis. So we have pathology that a pathologist in this state read out as acute and on chronic osteomyelitis, and that doesn't really match with lytic bone lesions. Honestly because lytic bone lesions are things that are rapidly sort of destructive seen on, and we know they're evolving quickly. And osteomyelitis from an infectious etiology just cannot evolve that quickly. And so it pushes me to. You know we've got bone lesions and inflammation has been nicely outlined. We've got leukocytosis monocytosis which always perks my ears up for something's wrong with your heme system solid appearance on the Ct. Could it be a primary cancer? Lymphoma is a

little unusual there, but could be. And then I told you why I didn't think so. I think it's lymphoma and I think it's Non Hodgkin's lymphoma of some kind, and I'm going to put my nickel down on anaplasmic large cell because it's the most number of case reports where I can say it was erroneously called acute osteomyelitis, because it has so many neutrophils infiltrating in the lytic bone lesions that they find, and it's also just rocking and rolling. But non-hodgkin's diffuse, diffuse, large cell B lymphoma is actually the most common in hepatitis. C so that's probably maybe what it did.

- Multiple myeloma usually cause high fevers recurrent. You've already talked about it. He's the wrong patient for the chronic, recurrent, multifocal osteovasculitis, Sarcoid and Tb. And again, hopefully, it's on this list. There you go. And then I would also talk to Dr. Carlson. I would actually get that Osteomyelitis slide here, have our pathologist review it. I would have it sent down. We can easily do that. Know that that we can get path here and have everybody re-review it.
- Cryoglobulins I would want, anyway, because, having cryaglobule anemia sets you up for lymphoma actually as pep-up just to rule out multiple myeloma with all those rib lesions. I think it'd be like awkward not to, even though it's unlikely that. And then I would discuss with pathology pulmonary, and try to figure out in surgery, actually go to path 1st and say, Do you have to do an excisional?
- Or is an fna from pulmonary good enough, and going to make the diagnosis? Or should we go after one of these liver lesions? And then maybe a phone that was fantastic. So let's talk about the next diagnostic step, final diagnosis and clinical course of this case presented to our general medicine service. So thank you for that team for bringing this case onto our radar and the general medicine team's working diagnoses just lifted right out of that initial H. And P. So they were also concerned about malignancy, atypical limbal representation. Leukemia, or primary solid tumor, again brought up some of the other infectious potential causes, and again, that team's rapid guess was autoimmune rheumatic. Herologic mediology felt to be less likely and talking through the pathology tissue options. It was settled on body radiology for biopsy of the lung lesion and the biopsy was performed without complication. There were a couple of other tests that were ordered and resulted while pathology is pending. Just to give everybody in the room just kind of the sense of how things resulted with that patient. So an MRI brain was also done which showed an enhancing osseous lesion, the right occipital bone, as well as a soft tissue enhancing lesion, and then some diffuse smooth enhancement, and then T cell or circulating plaques. So next I'm going to ask Dr. Nate Roberts from hematology to talk with us about the pathology slides in the patient's course.
- Someone say, wow! I'm very impressed by our panelists here. I learned a lot about this case. And this is my patients. Discuss the case. Reminded how much I used to, how much I miss the workup aspect of these things.
- So joining faculty here as a hemock specialist, we don't really do a lot of the workup. And typically patients only see us once we know what the diagnosis is. So it's really refreshing to see how people think about cases like this before they actually know what the answer is. But I'll just make a few comments about the path here again, full disclosure. I'm not a pathologist, but back here it's always a top one there's not focusing there you go red dot. Okay,
- So this is the H and E, 4. Dx magnification. And really, what we see here is large atypical cells. Just these sheets of these very large, ugly looking sites, and there's some atypical mitotic figures, and I would have to probably look at this very closely

to see the mitotic figures. But the main finding here is that there are very large looking cells, and there's no real appreciable architecture here, and if if I'm remembering correctly. This is from a lung, the lung biopsy. Okay, So we don't really see a lot of lung architecture, either. So it doesn't look like a lung cancer.

- CD, 45. That's a universal hallmark of hematologic cells, and tells us that this is probably a hematologic Neoplasm and then the 2 sort of most important stains. CD, 30 and Alk staining so CD. 30 is in the Tnf. Family of signaling molecules. It's a surface protein. There are a handful of hematologic cancers that will express. CD, 30. The 2 that come to my mind is the most common are hodgkin, lymphoma, and anaplastic large cell lymphoma. These large B cell. Lymphoma can also have some CD 30 expression.
- But when we look at the other stain the alk on the right here, there really is only one, maybe 2 lymphomas that will express alk, and that includes anaplastic, large cell lymphoma, and sometimes diffused large B cell lymphoma can also have alk positivity as well, but so in this case the final diagnosis wasn't that our campus, or thinking about this diagnosis without obviously knowing what the answer was ahead of time just by looking at the imaging that was available. The clinical course. It truly is remarkable that we were able to think about this ahead of time, because this is a very rare lymphoma. So when someone comes in with destructive bone lesions and a big pulmonary nodule, I certainly, as a phone specialist, would not be thinking so. I'll just make a few comments about Alcl as we discussed most of these. This is a T-cell lymphoma, so most of the cases are positive for one or more T-cell antigens, including CD. 3, 43, 45. Most will have a clonal T-cell receptor gene rearrangement. We often see periphertical involvement of lymph nodes with this intrasinusoidal dissemination. And then the hallmark cells are these very large acceptable cells that often have this horseshoes horseshoe shaped nucleus and if you all have been to Dr. Enrique Markey's grand rounds, you might recall that the peripheral T cell lymphomas are a very rare and heterogeneous group of lymphoid neoplasms in the United States. There's probably around 80,000 cases of non-hodgkin lymphoma diagnosed per year. And among the non-hodgkin lymphomas around 10% are t-cell lymphomas. So I typically quote the patients, there's around 5 to 10,000 cases of T-cell lymphomas in the Us. Per year and among the T-cell lymphomas there's 4 umbrella categories, which include the cutaneous lymphomas, the most common being mycosis, fungoides, leukemic lymphomas, including atll, which is associated with htl one the nodal t-cell lymphomas under which Alcl is included, and then the extranodal T-cell lymphomas, of which extra nodal and T cell lymphomas are the most common.
- There is some geographic variation in which of these subtypes are more common, depending upon the area that you are in right now, there's probably around 30 to 35 subtypes recognized in the most recent who and Icc classification, and this number continues to grow as we get better at identifying this wastebasket category of other T-cell non-hostin lymphomas that we don't quite think fit into the other categories.
- And you can see here that Alcl, there's Alp positive and Alp negative, that is, around the 3rd or 4, th most common type of T cell lymphoma overall.
- And in the case of Alcl. Ap positive Alcl, it's clinically associated with this 2 5 translocation fusion fuses the Npm. One gene which most of us are probably familiar and acute myeloukemia to the out gene, and you get this Npm. One out fusion product, which is an ondo gene. I love these diagrams that remind me of the conspiracy meme from Philadelphia. But long story short, this fusion product drives

cell growth and cell division in various growth pathways in cells a couple more key points, CD, 30 is universally expressed in Alcl, both positive and Alpha negative types, and, as I mentioned earlier. Alcl comprises around 10% of all cases of peripheral T cell lymphoma.

- You can see here that in the case of Alp positive Alcl, it is more frequently seen in younger patients, which again, that might have been a tip off to someone thinking about this, this patient was in his early forties, whereas the other T-cell lymphomas are more commonly seen in older patients with regards to alk positive versus alk negative disease. We know that alk positive patients have a much better prognosis than alk negative patients. However, the prognosis for Alcl in general is much better than the other types of T cell lymphomas. But importantly, we can see that in the case of Alk, positive disease, the average survival is actually measured in decades. And that's often what I emphasize and quote to patients, because when they hear a diagnosis of T cell lymphoma there's a lot of appropriately bad press online. But fortunately for this patient, he has a quite good prognosis. And then, recently, within the last 5 years, there's been a significant change in the approach to Alp. Positive echelon. True was a randomized study that compared this new drug called Rintuximabin with chp chemotherapy to chop. And essentially what this trial showed was that in the case of CD. 30 positive lymphomas. The addition of Rintuximab significantly improves progression-free survival and actually overall survival which I didn't show the OS curve.
- But again, this study, the echelon 2 study was comprised primarily of patients with anaplastic, large cell lymphoma they made up around 70% of the patients on the study. So my practice and Dr. Markey's practice is, we really reserve the usage of prentuximab for patients who have Alcl.
- Whereas for patients who have non-alcl subtypes, you can see here on the forest plot that there really wasn't that much difference. Comparing Bbchp with chop the study obviously wasn't designed to identify a statistically significant benefit. But I think the fact that this hazard ratio is basically sitting on. One tells me that Alcl really is driving most of the benefit that we'll see in this study and just a few more trivia things for you guys. Rituximab Medotin is an antibody drug conjugate. So the antibody targets. CD, 30, there is a cleevable linker that is linked to this payload of monomethyl arstatin E, so the dotan is not the payload, but once this antibody is internalized in the cell the linker is cleaned, and then the chemotherapy is released, which then goes on to damage the microtubule system and preventing cell division and leading to cell death.
- Bv. For those of us who might be going into general internal medicine or family medicine or outpatient internal medicine. This drug causes a lot of nausea, neuropathy, neutopenia, and diarrhea.
- So for primary care, physicians who are seeing patients who are getting this particular drug. These are the most common side effects to be aware of and then just to close it out as I expected and hoped for. This patient has had a really impressive and robust response to chemotherapy. Thus far
- I've included a few representative, a representative image here, from his initial Cp. Stand showing the dominant pulmonary mass in the right upper lobe. And then this is his test scan after 4 cycles of chemotherapy essentially showing a complete response to treatment this far and clinically, he's doing much better. He's gained 30 pounds back. Some of that could be steroids, but I think he also had significant weight loss leading up to his original diagnosis. And, interestingly, I'm glad that one

of our rheumatology colleagues is here, after the second cycle of chemotherapy, he presented with this diffuse, macular, erythematous, rash as well as diffuse hand leg swelling and I initially thought he was experiencing a hypersensitivity reaction to the Rintuximab, which we can sometimes see with these antibody products. So I treated him with a course of steroids. Those symptoms got better. And then we did this kind of desensitization protocol with the Rintuximab. But he's continued to have this rash and swelling. So I ended up sending the cryolobulins. Actually they were negative, because in clinic I was wondering if he was experiencing some sort of autoimmune issue related to his hepatitis C, but I think the jury is still sort of out on what's going on with his rash and the swelling. I learned that there is something called puppy hand syndrome, which I think he may have, but he's also in pretty high doses of Gabapentin for neuropathic pain which may be causing his edema. So I still do wonder if he may have some underlying autoimmune issue, particularly now that the lymphoma appears to be in remission.

- But I agree completely with the comments that were made earlier about the association of hepatitis C with lymphoma. We definitely see that in multiple other non-hodgkin lymphomas in this patient's case, it does make you wonder if there could have been potentially a causal relationship behind. Why, he might have developed this T cell. But that's kind of where we are now.
- He's doing really well, and I emphasize that the goal is cure, and that there's a really reasonable chance that he will achieve cure.
- Thank you, Dr. Roberts, for being here, and for some of the teaching around the underlying diagnosis and real thanks to Carlson, Dr. Mathers for reigniting this teaching format, I honestly, I was just hoping to get to lymphoma there, and as in all respects, with both of you, your clinical in teaching acumen, you've only exceeded expectations, so many. Thank you.
- Questions from the from the audience, I think, is everyone probably noted from the last slide. The iliac lesion looks to have resolved on, pet. I don't think that there was formal diagnostics done on the inpatient side to sort of further Dr. Mathers conclusion, which was definitely something I was not sure. Aggressive lymphomas being mistaken for Osteo. Yes, Sarah, it sounded like you had a pretty high hep, c viral load during all of this is that treated before after during so well, it has. I don't know. But there's evidence that treatment actually helps lymphoma, and you can actually treat Hep C in the lymphoma regresses. It usually comes back and requires chemo. But it is recommended that you actually treat that hep, c, yeah, this was a point of conversation that we had, and
- I think the the main concern that was raised was the potential that the Hep. C treatment could cause side effects, and then it would be difficult to discern if the side effects were from the hepatitis C treatment, and then also the concern that with chemotherapy the patient might experience nausea and vomiting which could compromise his ability to comply or adhere to hep. C directed therapy. So we're not treating his hepatitis C right now. We're preserving that for the end of treatment. It's almost there but certainly, once he's finished he will definitely need hepatitis. C directed therapy. So far his liver numbers have. He's not shown evidence of forcing acute hepatitis. He does have abnormal findings on his imaging of an enlarged liver. I don't believe he has evidence of cirrhosis at this point, but he definitely needs to be treated for Hep, C.
- The other comment that I might make is, think this patient also had a culture that was positive, for I don't know if the in putting this case together, remember seeing

that. But I do believe that you did have something else that should have worked there. There was Mac, and was discussed with ideas of potential contaminant.

- Thank you again. We're a little bit over time.