Episode 190: SLS w/ Emma, Dan & Jack

Sharmin Shekarchian:

Hey folks, just a quick reminder that this episode is not meant to be used for medical advice, just good old fashioned education. All patient information has been modified to protect their identity, and the views expressed in our podcast do not necessarily reflect the opinion of our employers.

Dan Minter:

Hey. Welcome back, Clinical Problem Solvers. Thanks for joining us for another installment of SLS or Spaced Learning Series, in which we revisit schemas previously discussed on the podcast. My name is Dan Minter. Today, I'm here with my fellow co-hosts and good friends, Jack Penner and Emma Levine. How are both of you doing? It's been so long since we hung out.

Jack Penner:

Doing good. We have successfully conquered numerous technological challenges. It's actually the second time we are recording this episode and probably the fifth set of microphones and headphones that we have cycled through in trying to prep for it. So, we're feeling good. We are very well prepared and excited to talk about some medicine.

Dan Minter:

I swear we've done this before, Jack. [crosstalk 00:01:02]. Emma, how are you doing?

Emma Levine:

I'm good, technologically competent, clearly. Glad I'm finally learning how to use Zoom.

Jack Penner:

I will say I do feel like as time has gone on, I feel like my Zoom hiccups are less and less excusable. I'm like, "Oh, I forgot to record the meeting for the fifth time." It's been a year and a half of doing this. So I appreciate the mutual support from this group.

Emma Levine:

And I appreciate Dan's incredible diagnostic reasoning and figuring out what was wrong with my technology.

Jack Penner:

That is true. There is a schema for everything, including a broken headphones. Well, before we get started with the case, hey, just a quick reminder that this podcast is not meant to be used for medical advice, just good old fashion education. All patient information has been modified to protect their identity. The views expressed in our podcast do not necessarily reflect the opinions of our employers. It sounds like Emma has an awesome case for us today, so Dan and I will get to try to slog our way through what is bound to be some interesting clinical data here. Emma, do you want to take us away?

Emma Levine:

Absolutely. Let's get into the case. You're called to see a 25-year-old woman who presented with fatigue and swelling in her bilateral ankles. Symptoms have been present for the past two weeks and have been

worsening over that time. She's previously been healthy and takes no medication. Her family history is notable for a diagnosis of lupus in her maternal aunt.

Jack Penner:

All right. So, I would say it sounds like the two features that we have jumping out here, at least in this first output of information is on the one hand we have fatigue, and on the other hand, we have lower extremity swelling. I think one of the challenges that we have whenever we reason through a case is to answer the question where should we invest our cognitive energy from the start? From a reasoning perspective, we want to invest our mental efforts into the symptoms or the problems that are going to have a more limited differential because that's going to give us a more efficient reasoning path, right?

So in this case, fatigue can be caused by anything from a cold to cancer. It has an incredibly broad differential that can oftentimes be difficult to sift through when you're grappling with fatigue alone, while lower extremity swelling can help us hone in on a few specific organ systems. So at this point in the case, we're likely better off saying, "Let's figure out what the cause of the patient's lower extremity swelling is," that will also likely be a contributing factor to her fatigue.

Dan Minter:

Well, Jack, that is going to be tough to follow. Well, if we are going to approach the lower extremity swelling, I think of this as like a tiered series of schemas. My first schema really focuses on what are the most common causes of lower extremity swelling, and for that I think heart, liver, kidney. So, is it heart failure? Is it end-stage liver disease, like cirrhosis, or is there the nephritic or nephrotic syndrome that's leading to lower extremity edema? I've also heard this referred to as cardiosis, hepatosis, and nephrosis. So with that first pass of our big checklist, how can you distinguish between edema that's related to heart failure, chronic liver disease or kidney pathology?

When are you going to examine the patient and you're looking at their ankles, first look up at their neck, see if the JVP is clearly elevated or not. If it is, that will be a signal that there's maybe something going on with the heart, and you're seeing the manifestation for elevated right atrial pressure. In terms of diagnosing a chronic liver disease, we try and see the stigmata of chronic liver disease. You can divide those into evidence of portal hypertension, like you might see with ascites, with a big spleen with esophageal varices, if that's reported, or caput medusae. Alternatively, you can see evidence of hyperestrogenism with the development of spider angiomata. In terms of finding evidence of kidney disease, this is much more laboratory-based so you're going to look for proteinuria on the UA and you're going to look at the creatinine on the basic metabolic panel.

If it's not one of those big three buckets of heart disease, liver disease or kidney disease, then I take a pause and step back and start thinking about what else could cause lower extremity edema, and then I moved to something more of a pathophysiologic approach saying, "Is this due to increased hydrostatic pressure or is it due to decreased oncotic pressure?" And then you can think of regional variations. Is this there's something blocking the lymphatic drainage or the venous drainage? Or you can think of just sort of like diffuse anasarca from a patient who has advanced disease of any sort leading to hypoalbuminemia. But again, just to recap, I'm going to do my first pass, is that heart, liver, kidney, before moving on to a more nuanced analytic approach.

Emma Levine:

That was incredible teaching. I could listen to the two of you talk all day. I really loved, Jack, how you focus on the diagnostic energy, where we focus that energy, and then, Dan, how you had a well-worn approach to common problem as bilateral lower extremity edema.

On exam, our patient is afebrile, heart rate 95, blood pressure 145 over 85, oxygen saturation 98% on room air. She was noted to have conjunctival pallor and bilateral lower extremity pitting edema to the shins. Her JVP is not elevated and there's no evidence of ascites, spider angiomata, jaundice or telangiectasia. Exam is otherwise unremarkable. Basic lab is notable for white count of five, hemoglobin of 6.8, and platelets of 240. For her BMP, sodium of 140, potassium of 4.5, chloride 102, bicarb of 20, BUN of 40, creatinine of 2.5, and glucose of 125. Her prior baseline was presumed to be normal.

Jack Penner:

All right. So building off of Dan's discussion of an initial approach to bilateral lower extremity edema, we can prioritize the most likely cause of her lower extremity swelling based off of what we don't see here, right? As Dan shared with us, we can think about a cardiac disease as a cause of lower extremity edema, particularly when it's accompanied by other exam findings of heart failure. In this case, the patient doesn't have an elevated jugular venous pulse, which has a pretty good diagnostic utility in decreasing the probability of heart failure, likewise, we don't see signs of decompensated liver disease related to portal hypertension or elevated amounts of estrogen levels, which can further decrease the probability of liver disease. We don't see that this patient has ascites and we're not seeing things like spider angiomas or telangiectasias or jaundice as Emma shared with us, right?

And so, while we may oftentimes say heart, liver, kidney, in that order, in this case, we can reprioritize that DDx and move renal disease up to the top of our differential, just based off of the exam alone. Then, when we moved to the labs, that is further validated when we see that this patient has an acute kidney injury, suggesting that there is renal disease present. I will say, all of the causes of lower extremity swelling that Dan listed can be accompanied by an acute kidney injury. But in this case, again, the absence of the elevated JVP and the absence of signs of decompensated liver disease help us prioritize that it actually is the kidneys that are the primary problem, both in terms of the acute kidney injury, but also in terms of this patient's lower extremity swelling.

So, where do we go now in terms of thinking about the patients acute kidney injury, right? We've talked multiple times on the Clinical Problem Solvers before that our broad approach to an AKI would include a prerenal process, an intrarenal process, or a postrenal process. In reality, when somebody comes into the hospital, the pre-test probability in a hospitalized patient is always going to be highest for a prerenal etiology, whether that's related to hypovolemia, like low PO intake or over-diuresis, hypervolemia, like acute decompensated heart failure, right? We've talked about patients who may have liver disease and present with lower extremity swelling. Those individuals can also develop acute renal insufficiency, like hepatorenal syndrome as a complication of their decompensated cirrhosis, or we can sometimes see medications contribute to a prerenal AKI, things like ACEs or ARBs, as well as NSAIDs.

Right after we think about a prerenal etiology, the next most likely diagnosis is going to be a postrenal etiology, whether that's related to renal obstruction at the level of the urethra, like we see in BPH, or renal obstruction at the level of the ureter, which could come from something like urethral compression from a retroperitoneal process. In those situations, our workhorse diagnostic tests are going to be a PVR, if we're thinking about urethral obstruction, or thinking about a renal ultrasound if we're thinking about ureteral obstruction. If both of those diagnostic schemas aren't returning with helpful findings, we don't have a clear culprit for a prerenal cause, our PVR is negative and our renal ultrasound doesn't show hydronephrosis, that's when we will oftentimes then look at the intrarenal causes of an acute kidney injury.

However, there is one clinical circumstance where an intrarenal AKI can ratchet right up to the top. It's not the only one, but it's one that's worth remembering. And that's when the urinalysis shows a

very specific constellation of findings that makes us think about there potentially being an intrarenal process, and specifically a glomerular process, particularly when we see things like proteinuria, hematuria, and potentially findings like dysmorphic RBCs or RBC cast on the urinalysis, because those things all greatly increase the probability of an intrarenal process. So, to summarize, when we think about AKI, we'll say prerenal first, then postrenal, then intrarenal. But if the UA is full of all kinds of pizzazz, like proteinuria, hematuria, or RBC cast, then we'll say, "Intrarenal, you win from the get go. We're going to think about you first."

Dan Minter:

I wish my urine was full of pizazz. That was a master class discussion. So, where do we go from here? The other main clinical finding on the labs so far is this pretty dramatic anemia, severe anemia with a hemoglobin of 6.8. So when we have two pretty dramatic findings, like this AKI and the severe anemia, one way that we can advance in this case is to see where the schemas for those two findings overlap. So I know Jack just had a master class discussion of an approach to acute kidney injury. What if we were to think about anemia and filter or further thought process through the schema of anemia and where that could overlap with AKI. There's a whole bunch of different ways to approach anemia. Some people will start with the MCV.

From a more pathophysiologic perspective and one that might be a little bit more helpful for our overlap schema right now you could think also just of what's physiologically going on. That could be anemia related to production issues, anemia related to blood loss issues, or anemia related to peripheral destruction, so like a hemolysis sort of picture. If we could post it that the anemia is hyperproliferative or a production problem, how then could we have renal dysfunction? It's pretty commonly taught that folks with end-stage renal disease or chronic kidney disease can have anemia because EPO, erythropoietin, is produced by the kidneys. So it's very common that you'll get anemia in the setting of renal failure. So that's certainly one possibility.

What if the issue is not production, but rather blood loss, like you might have with a GI bleed or some other source of bleeding? Certainly, blood loss, if it's hemodynamically significant, could give you a prerenal acute kidney injury. Also, you may have blood loss in patients with cirrhosis, as we alluded to earlier, whether that's overt clinical bleeding or something a little bit more insidious. Cirrhosis, as Jack said, could be predisposing to the hepatorenal syndrome, which could affect your kidneys. But certainly, if you're losing blood, you'd have to think either, is it a shared pathophysiologic mechanisms that's also affecting the kidneys or is the blood loss going to directly lead to a prerenal physiology of the AKI? So lastly, are peripheral destruction of blood cells, if that's causing our anemia, how can that be related to renal dysfunction?

If you have destruction of blood cells, I think of this in one of the former program directors of UCSF, Harry Hollander would say, "Is it a bad red blood cell or red blood cell in a bad world?" So if it's a red blood cell in a bad world, which were deferred to something in the extracellular environment destroying the blood cells, one of the more typical examples of that would be an autoimmune hemolytic anemia. What's going to cause autoimmune hemolytic anemia? Frequently, that'll be part of some shared autoimmune syndrome like lupus, which could also affect the kidneys. If the bad world is not immunologic in nature and is instead causing peripheral non-immune mediated destruction of the red blood cells like you might see in a MAHA or thrombotic microangiopathy, such as TTP or atypical HUS, those can also as systemic disorders affect the kidneys.

Lastly, if it's not something going on in the extracellular environment to the blood cell, but it's instead having to do with the blood cell itself, meaning that you may have some abnormal membrane or enzymopathy, you could say, is there a manifestation of that that affects the kidneys? A classic example

might be sickle cell disease, where renal involvement is relatively common. There's probably other areas of overlap between our anemia schema and our acute kidney injury schema, but these are just some initial thoughts where you could see evidence of overlap.

Emma Levine:

Amazing discussion, team. Ready for more info?

Dan Minter:

Let's do it.

Emma Levine:

Smear with microspherocytes no schistocytes, LDH 600, reticulocytosis count elevated at 6.2%, urinalysis with 3+ albumin, 10 to 20 RBCs, and zero to five WBCs.

Dan Minter:

Okay. I'm going to be an... Well, I guess I am an ID fellow now, but I love non-malignant hematology. It's one of the few loves of my life, so I'm really excited to see this pattern on the labs already. So basically, as we go back to our schema for anemia, is it a production issue, blood loss, or destruction of the blood cells? We have a very important clue here. The LDH or lactate dehydrogenase is pretty elevated in this case. What does that suggest? So lactate dehydrogenase is expressed throughout the body and is an intracellular enzyme. So when you have cellular destruction, you can see that the elevated in the peripheral blood. One of the hematology fellows actually told me was the most sensitive marker of hemolysis that we have.

So, I'm already thinking that this anemia could be a hemolytic anemia. We see further supporting evidence in that the reticulocyte count is elevated, suggesting that the body recognizes that it's lost some blood and it's trying to compensate. So again, our schema for hemolytic anemia can go back to, is it some problem with the blood cell itself, a bad red blood cell, or is it a problem in the exterior world, so a blood cell on a bad world? If it is a problem with the blood cell, you can think, is it in the membrane? Is it in the enzymes, or is it in the hemoglobin? If it's a normal blood cell existing in a hostile environment, then you can think, is it immune-mediated or non-immune mediated? We do have additional clues here with the blood smear. So the blood smear is one of the most important tools we have for evaluating different hemolytic anemias.

What we're told is that there's no schistocytes, but instead we see microspherocytes. So the absence of schistocytes may push us away from a toxic non-immune mediated environment to the blood cell, like you might see in thrombotic thrombocytopenic purpura or hemolytic uremic syndrome or DIC. The microspherocytes can suggest that there may be an autoimmune component to the hemolytic anemia. The way that I conceptualize that is you get an antibody or some antibody or complement binding to the red blood cell membrane as the red blood cell passes through the spleen macrophages. Take a little chunk out of the membrane, and that deforms the otherwise biconcave morphology of the red blood cell and it becomes a small spherocyte. So this is something that would be seen typically in an autoimmune hemolytic anemia. What do we need next to further corroborate this? It will be really important to have a Coombs test, and that's going to tell us if there's IgG or complement bound to the membrane mediating the process of hemolysis.

Jack Penner:

Thanks so much for that, Dan. So now after that approach to thinking about hemolytic anemia, let's take some time to dive a little bit deeper into this patient's acute kidney injury. We talked a little bit about how sometimes the urinalysis can have some pizazz with it. I would say that UA with three-plus albumin, 10 to 20 reds, and some white cells has a pretty good dose of pizzazz on there, right? And so, in this case, we're ratcheting intrarenal AKI up to the top of our differential, not only because the probability of an intrarenal process goes up with those UA findings, but the specific types of intrarenal disease that we're thinking about can be quite morbid, and so they warrant a fairly urgent diagnostic evaluation.

So then what exactly is it that makes us think about the intrarenal acute kidney injury here? Again, we can use some of these findings localize where within the kidney this kidney injury is coming, right? Some of you may have heard the term before active urine sediment. While that is sometimes a term that's thrown around when we're thinking about something like a glomerulonephritis, I find that it can actually cause more confusion than clarification because there's actually a number of diseases that can cause these types of findings of albuminuria and hematuria together. Those can be things like Alport syndrome, thin basement membrane disease, or Coumadin-induced hematuria. So it's important when you see those diagnostic findings on the UA. Well, think about an intrarenal process, but those should not necessarily be synonymous with a glomerulonephritis, unless you have findings like RBC casts or dysmorphic RBCs.

Now, if we think about where these findings help us localize to, we know that when the glomerulus gets damaged, it can start to fail at its normal job. One of its normal jobs is to keep protein in the bloodstream and outside of the urinary filtering system. And so, when we have a problem with the blood vessels of the glomerulus, we can get protein leaking into the urine. In this case, the three-plus albuminuria helps us think about the glomerulus as a potential site of the lesion here, right? So now if we're going to think about a glomerulopathy as the potential cause here, let's take a second to then work back through the other potential areas of the kidney that can be affected by an intrarenal acute kidney injury, right?

We can have tubular problems, which could be things like ATN or obstruction. We could have vascular problems, many of which Dan already mentioned, things like TTP, HUS, as well problems related to the vasculature, like an acute hypertensive episode, and then also something like scleroderma renal crisis? All of those processes can cause an acute kidney injury via a vascular mechanism. Then, the other area of the kidneys that can be effected is actually the renal interstitium, and that is usually going to be caused by things like drugs, antibiotics, PPIs or NSAIDs, as well some infections. Common ones that we might see would be something like pyelonephritis, and then there's a host of rarer organisms, like leptospirosis or TB that can do it. And then, lastly, autoimmune diseases, which can cause vascular causes can also cause an interstitial nephritis, particularly things like Sjogren's syndrome, sarcoid, or lupus, right? But in this case, our cognitive energy should be invested within the glomerulus based off of these UA findings and particularly thinking about a glomerulonephritis.

Now, there's a few different categories that we can think about of glomerulonephrititis, try to say that five times fast. You could think about an immune complex-mediated glomerulonephritis, which can be things like lupus, or a post-infectious GN, or endocarditis. We can use the complement levels to help stratify that, or we can think about things like IgA nephropathy or IgA vasculitis, which will oftentimes have normal complement levels. Moving away from the immune complex category, there's also Pauci-immune glomerulonephritis, which can have positive ANCA serologies, things like GPA, MPA, or eosinophilic GPA. And then, lastly, we can have the anti-GBM category of glomerulonephritis, something like anti-GBM disease.

Now, again, these classifications or categories are based off of histopathologic findings that we might see. The reason that this histopathologic classification is helpful is because oftentimes patients

who have a suspected GN, we get a renal biopsy in these patients to help us make a definitive diagnosis. There is serologic testing that can help us here. But when we see that pattern of the UA and this degree of acute renal injury, it's worth asking ourselves, does this patient need a biopsy to assist with making a fairly rapid diagnosis of the underlying cause of this significant acute kidney injury?

Emma Levine:

That was incredible. Thank you both so much. All right. Back to the labs, direct antiglobulin testing positive, ANA one to 640, double-stranded DNA elevated, C3, C4, low.

Jack Penner:

Awesome. So as we just talked about, we have complement levels here, which, again, help us further narrow this patient into potentially having an immune complex-mediated GN. In addition, we have this profoundly positive ANA at one to 640, as well as a positive double-stranded DNA, and we have the positive DAT or direct Coombs testing, which makes us think about an autoimmune hemolytic anemia here, right? So now we have a combination of an autoimmune hemolytic anemia, a suspected immune complex-mediated GN, as well as positive antibody titers, which are consistent with antibodies that we may see in somebody who has a diagnosis of lupus. This is all laid on top of the background information that we have, which is this patient's family history, right? So I think that this constellation of findings between the background family history and the foreground findings of the autoimmune hemolytic anemia and the suspected immune complex-mediated GN help us think about lupus as a very likely unifying diagnosis in this case.

Dan Minter:

So if we do have a diagnosis of lupus and we're trying to explain the kidney injury with this, as Jack said, that could be explained by the glomerular pathology, tubular and interstitial pathology of vascular lesions. The thing that probably that the top of our mind is going to be whether or not this is a glomerular pathology in the form of lupus nephritis. I was lucky enough to spend some time on the rheumatology service here at UCSF a couple months back, and I learned so much from the rheumatologists. One of the things that had been a very large source of confusion for me during residency was how do you further classify this nephritis, and what do the different classes actually signify? One of the things that I learned was that the class of lupus nephritis really refers to histopathology. You may see written in the chart basically class one through six. It's not necessarily that the classes, as they get higher, corresponds with extensive disease or anything like I may have assumed early on, but really that these different classes corresponded different histopathologic findings.

So, the way that I've been able to remember this more or less is that one and two go together and those refer to mesangial nephritis, with one being minimal mesangial and two being mesangial proliferative. Three and four go together with the broader pathology referring to glomerulonephritis. So three is focal nephritis, whereas four is diffuse nephritis, so it's more sensitive than class three. Class five is membranous nephropathy, so that will present more as nephrotic syndrome. Class six is advanced sclerosing nephropathy. This is something that's a little bit more akin to end-stage kidney disease. So, I'll be really interested to see what is found on renal biopsy because that determination of the classification is going to be very important in terms of determining what sort of treatment this patient will ultimately receive.

Emma Levine:

The patient then underwent a renal biopsy that demonstrated areas of class three and class five lupus nephritis. She was started on pulse steroids and transition to further treatment with mycophenolate mofetil and steroids with plan to follow up in renal and rheumatology clinics. She was evaluated by hematology as well for her warm autoimmune hemolytic anemia, and it was found that the current immunosuppressive regimen would adequately treat her autoimmune hemolytic anemia as well. Six months later, her creatinine had returned to normal levels and she was not exhibiting further evidence of autoimmune hemolytic anemia.

Jack Penner:

Thank you so much, Emma. What a fantastic case to get to think through. I'm feeling very relieved that this patient had what seems to be at least a positive initial clinical trajectory, acknowledging that these initial presentations of lupus with a substantial renal injury can be a devastating initial clinical course with some of these patients ending up on renal replacement therapy. And so, I'm very, very happy to be able to learn from this case, and also very, very happy that the patient was able to have a good recovery. Dan, reflections on the case or anything as we wrap up here?

Dan Minter:

Yeah. Just to thank you again, Emma, for presenting this. I don't think it's necessarily an obscure presentation for lupus since both of these are pretty well-described manifestations, but it's certainly good for us to go through the exercise of trying to see going from symptom to laboratory finding, to ultimately histopathology to trace that diagnostic arc for a patient like this. And then one of the things that I reflect on in terms of how can we reason better through this is really what can you hang your hat on the findings in this case that initially tipped us off to something potentially autoimmune going on where the presumably hemolytic anemia and also the glomerular pathology, and then trying to see where those two schemes overlap. So, that's a good exercise that I try and take forward as I think through different cases.

Jack Penner:

Meanwhile, I'm just over here thinking about pee and pizazz, so thank you all for milking as much education as possible out of this case with my potty mouth over here.

Dan Minter:

Awesome. Well, thanks everybody. It was a blast.

Emma Levine:

Couldn't agree more.

Jack Penner:

We want to talk to you for the next installment of the Spaced Learning Series.

Dan Minter:

That's a wrap, folks. Whoo!

Jack Penner:

Whoo!