A Case of Lupus Nephritis

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SHARON G. ADLER, MD: Good afternoon. I have the honor of moderating this session today because I stood in Jerry Appel’s shoes last year. Each year the American Society of Nephrology invites a clinical nephrologist to test that person’s mettle, usually an outstanding clinician, against the explicatory prowess of a renal pathologist. This year, Dr. Gerald Appel will be our clinician. Some of you in the audience may know that Jerry is an inveterate White Sox fan, and this year, after decades of doing not so well, they hit the ball out of the park, so, Jerry, you have to do as well as your team. I am going to present the case, and then Dr. Appel will discuss it.

The patient is a 23-yr-old Hispanic female who presented 1 mo previously to her private physician with a headache. She was treating her headache with a magnesium-containing herbal medication. A neurologic evaluation, including an MRI, was negative. At that time the serum creatinine was 1 mg/dl, and her BP was 120/80 mmHg.

One month later, she again presented with continued headache, 12 d of diarrhea, new-onset hypertension with a BP of 180/120 mmHg, and a fever of 104°F. Gross hematuria and a lower extremity rash had been noted for the past week. She was given nifedipine, which she did not take.

She returned the next day for reevaluation of her BP and was found to have worsening hypertension. Her serum creatinine rose to 1.6 mg/dl; her temperature had risen to 104°F; her urinalysis showed 3+ blood and 3+ protein, and the urinary sediment revealed several red blood cell casts. Over the next 2 d, her serum creatinine rose sequentially to 1.8 and 3.2 mg/dl, and oligoanuria developed.

Her past medical history was notable for her having had two first-trimester spontaneous abortions. The family history was unknown, as the patient was an adopted child. Her medications included only the unknown herbal medication. Her review of symptoms was essentially negative except for the information already provided. On physical examination, the BP was 220/120 mmHg, pulse was 55 beats/min, and weight was 183 lb (83.2 kg). The examination of the head, ears, eyes, nose, and throat showed mild periorbital puffiness and grade 2 hypertensive changes. Her lungs were clear to percussion and auscultation; her heart demonstrated a regular rhythm without murmurs or gallops. There was a three-component friction rub present. The abdomen was soft and nontender, with no masses or organomegaly. There were normal bowel sounds. There was no evidence of clubbing, cyanosis, or edema. The lower extremities demonstrated a few petechiae and a blotchy erythematous, blanching, nonpruritic rash. The neurologic exam was essentially normal.

Diagnostic studies were performed. One of two blood cultures grew *Staphylococcus epidermidis*. Chest x-ray showed mild cardiomegaly. An abdominal CT scan showed a small amount of pelvic fluid and mild pericardial and bilateral pleural effusions. The sodium was 133 mEq/L, potassium 7.5 mg/dl, and magnesium 2.2. The white count was normal at 7.9 × 103/μL, hemoglobin was 11.7 g/dl, and hematocrit was 36%. The platelet count was 100,000 103/μL. Hepatitis B and C serologies were negative. Rheumatoid factor was weakly positive. C3 was low. Antinuclear antibody (ANA) was positive at 1:320. Anti–double-stranded DNA and anti–SCL-70 studies were pending. The stool was negative for leukocytes and blood. Stool cultures for *Clostridium difficile* were negative, and ova and parasite exams were pending. A renal biopsy was performed. Dr. Appel, good luck.

GERALD B. APPEL, MD: We are ready for the biopsy. In the tradition of a true baseball fan of the White Sox, some of you have come here to see me pitch a no-hitter, but most of you have come here to see me strike out, so we will find out.

Challenging case. In this 1-h session, I am going to go through the case, emphasizing what I think is important, in terms of the history and physical and laboratory evaluation. Then I’m going to go through a differential diagnosis. I will then try to synthesize a diagnosis, and finally we’ll find out if I’m right or wrong.

The history of the patient usually provides much crucial information in arriving at a diagnosis. To start, this is a 23-yr-old Hispanic female without any prior history until 1 mo ago, when she presented with headaches. She had no renal findings. This is important that her presentation is part of a systemic disease, not a disease isolated to the kidney. Fortunately, we have baseline laboratory data, as well. Often we don’t get the baseline data, and that makes judgments of acute versus chronic renal disease much more difficult. We know she had a normal BP, her baseline creatinine was 1 mg/dl, which may or may not have indicated a normal GFR for her. Unfortunately, we do not have a baseline urinalysis.
She comes in with her headache and she has had a negative MRI of her head. Moreover, there is no diagnosis of the cause of her abnormal urinalysis. They didn’t make any diagnosis. This sounds like a typical medical evaluation: “You don’t have this, and you don’t have that, so go home.” So, despite a negative MRI, we have no diagnosis or prescribed therapy. The only medication she’s taking is an herbal magnesium preparation. While some might think this is irrelevant, a few of you are saying, “glomerulonephritis due to the magnesium herbal preparation.” I doubt this.

She returned 1 mo later with a headache again and 12 d of diarrhea. Now her BP is markedly elevated to 180/120 mmHg, and she has a fever. She also has a history of 1 wk of gross hematuria and a rash, which is very helpful in terms of the differential diagnosis. She is treated with a dihydropyridine calcium channel blocker, presumably bringing her BP under control.

When she returns the next day for reevaluation of her BP, it is actually worse and her creatinine is now up to 1.6 mg/dl. She is febrile to 104°F. Again, this all points to a systemic disease. Urinalysis shows 3+ blood, 3+ protein, and red cell casts. This is very helpful since it narrows the differential. It points to the value of doing your own urinalyses.

Over 2 d, she develops oligoanuria, with creatinine rising up to 3.2 mg/dl. The patient is developing acute renal failure. There is no family history available. We do have a past history of two spontaneous abortions, a negative review of systems, and the fact that her only medicine, aside from the recently given nifedipine, was this herbal magnesium preparation. That is all the history we have.

On physical examination, we have a BP now of 220/120 mmHg and a pulse of 55. Some would think about those diseases that give you a fever with disproportionate bradycardia. Perhaps typhoid fever. There is such a list of those diseases, but I don’t know what they are. When I see people who are bradycardic and they’re febrile, they’re usually trained athletes, such as a basketball player, who are relatively bradycardic all of the time. She has mild periorbital puffiness, not frank periorbital edema. Mild puffiness may be due to makeup and cosmetics. Don’t overread diagnoses into this. She does have a pericardial friction rub, but she does not have a murmur. Her lungs are clear, her abdomen is negative, and she has no peripheral edema. Neurologic exam is entirely negative despite all of her headaches.

There is one other finding on physical, which is very helpful to me. She has a few petechiae and a blotchy, blanching, non-pruritic, erythematous rash. Without needing to be dermatologists, what is most helpful to me is that it’s a blanching rash. Things that are ecchymotic, hemorrhagic, petechiae, those things are clearly rashes that would not blanch; this is a blanching rash, and, therefore, it tells me something else.

We have more laboratory data. The blood urea nitrogen and creatinine are way up there, 56 and 4.4 mg/dl. The white blood cell count is normal, and she is not very anemic (her hematocrit is 36; her hemoglobin is 11.7). This is very important in the differential since there are many etiologies of acute renal failure that are associated with a significant degree of anemia. The platelet count is 100,000. Although decreased, this unfortunately fits a lot of different diagnostic possibilities. One blood culture comes out positive for S. epidermidis. At many centers, I sometimes think one out of every four blood cultures is positive for S. epidermidis. It is just contamination as if you took a skin culture. Thus, although I note it, I don’t put a lot of stock in one positive culture alone. Stool is negative for white cells and C. difficile. Chest x-ray shows mild cardiomegaly but no infiltrates. This is not a case of pulmonary renal syndrome. CAT scan shows some fluid in the pelvic, pericardial, and pleural areas, nothing that’s really distinguishing and specific.

Note the serologic test, which is very important here. There is a positive ANA at a titer of 1 to 320. Even if this lady were 84 yr old and the ANA was positive at 1 to 320, it’s still probably positive. In an elderly person with an ANA at 1 to 40 or 1 to 80, I wouldn’t care about it. Here in a young lady, a very strongly positive ANA is most helpful. The fact that her C3 is low is even more helpful because we have a limited differential of what gives you a low complement. If the patient has a low complement, I immediately focus on certain diseases, which I will cover in a few minutes. We have a borderline rheumatoid factor, which is helpful.

Then we send out our tests. Now, they sent out an anti-DNA double-stranded antibody. That makes a lot of sense. We sent out an anti-SCL-70, looking for scleroderma. Now, this could be important. This person has very bad hypertension, but clearly her rash is not a skin finding of scleroderma. She doesn’t have sclerodactyly. I would also order ANCA titers and anti-glomerular basement membrane (anti-GBM) antibody. While we might want some other laboratory tests, they did not get them. Fortunately, we don’t need more tests because we get the biopsy anyway.

What are the key points here? This is a systemic disease. It’s not an isolated renal disease. Actually, if you take diseases in which the biopsy is valuable, systemic disease is always in the category where renal biopsies make the biggest difference. When you look retrospectively at where the biopsy has changed a diagnosis, systemic diseases and diseases with heavy proteinuria are at the top of the list.

The patient has headache, fever, rash, hypertension, and acute renal failure. She’s oligoanuric. This is very helpful in the differential, and, as we will see, the urinalysis is extremely helpful. Those are the things that will help me make a decision as to what the diagnosis will be.

First, let’s think of our differential of acute renal failure. We know this patient has acute renal failure. We have a baseline creatinine. It’s risen up right in front of our noses. In our differential diagnosis, we can throw out prerenal azotemia and postrenal azotemia right away in this case. This is a biopsy conference. This is a “CPC.” There is no one that’s going to present postrenal azotemia at a biopsy conference. Half of our biopsy conference CPC at Columbia University is trying to guess what Vivette D’Agati and Glen Markowitz are trying to trick you with. We always say, “Oh, it can’t be that diagnosis. It’s too simple and straightforward, they would never do that.” And then they throw it in and fool us. However, here at the ASN CPC, it will not be pre- or postrenal azotemia.
Acute tubular necrosis in someone who is febrile is possible, but the BP is not low and the patient still has a progressive course. We also have some things that would suggest acute interstitial nephritis (AIN), acute glomerulonephritis (GN), and vascular acute renal failure.

Could this be AIN? AIN, acute or allergic interstitial nephritis, is certainly a pattern of acute renal failure that’s usually medication related. You have interstitial inflammation, interstitial edema, and only patchy tubular damage. Glomerular lesions are usually uncommon. In a biopsy from a normal kidney as clearly seen by silver stain, the tubules are all back to back. The interstitium is this potential space between them. If you look at a biopsied case of AIN due to a penicillin, there would be a dense inflammatory interstitial infiltrate. You can’t even make out the tubular architecture in places. At high power, there are lymphs, some monocytes, and lots of binucleated eosinophils. They are all over the place.

If you take penicillin-related AIN, which is the prototype for β-lactam, penicillin, and cephalosporin AIN, what clinical picture do you usually see? Rash, fever, eosinophilia. This person has a rash. This person has fever. We don’t know anything about eosinophilia. We can say that even with penicillins, the hypersensitivity triad of all three of these findings (rash, fever, eosinophilia) is found in <30% of patients. Most, however, do have some combination of these features. This patient has two of them, rash and fever.

However, nonoliguric acute renal failure is the typical presentation of AIN. This person is oligoanuric, but, of course, that doesn’t mean an AIN diagnosis is excluded.

The classic rash for AIN looks like a typical allergic drug reaction: A maculopapular rash on the trunk, upper extremities. Here the rash is more on the lower extremities. It is blanching, as it can be in AIN.

Next, let’s look at the urinary findings in AIN cases: Mild proteinuria, sterile pyuria, hematuria in >90% of the cases, and gross hematuria in about 30% of the cases. These data came from a review that I did on 178 cases of β lactam–related AIN, but nevertheless, if you look at the gross hematuria, it was mostly in the kids, and especially in the old days with methicillin interstitial nephritis.

The classic and most helpful finding is that of eosinophils in the urine, eosinophiluria. For those of you who don’t do the specific Hansel stain, the Wright stains work pretty well. In this case, we could do a Wright stain if we do it correctly to check for eosinophiluria.

Could this person have medication-related AIN? Most AIN in modern times is medication related. To start, she’s not taking any “medicines,” only magnesium herbal preparation. We don’t know what that is, and therefore I’m putting it to the side until I’ve got clarification of what it is. If you can look at the list here, there is one thing on the list though that should rise up in your minds—nonsteroidal agents—and the reason I say this is this lady is complaining of chronic headaches, and, remember, people don’t consider this a medication. If you’re taking Advil, Motrin, or whatever, you’re just taking it all of the time, it’s not a medicine, and you’ll miss that in the history. So, could this be medication-related AIN and acute renal failure?

Well, as you all know, most nephrotoxicity with the nonsteroids is due to prostaglandin inhibition and renal blood flow changes. It’s not due to AIN. You’ll see a thousand cases of people who drop their GFR and raise their serum creatinine because they’ve had changes in blood flow, for every one with true AIN. On the other hand, AIN has been reported with all nonsteroids, including COX-2 inhibitors. We’ve had some of the reports of Vioxx, when it was available, and Celebrex causing AIN. It is often in older patients and with prolonged use. You rarely get rash, fever, and eosinophilia with nonsteroidal-induced AIN, perhaps because nonsteroidal anti-inflammatory drugs (NSAID) are antipyretic drugs, so they block the fever, and they’re anti-inflammatory, so they block the reaction outside of the sequestered organ of the kidney. In any case, you often see red cell casts in AIN, even though you have an eosinophilia on the kidney biopsy, with nonsteroidal AIN with NSAID.

Usually it’s nonoliguric renal failure. Of course, NSAID AIN is also associated with certain glomerular lesions. The two most commonly are minimal-change disease and membranous nephropathy. Neither would necessarily give this picture, but you could get a glomerular disease here.

So, what favors AIN? We have a systemic disease with acute renal failure. We have a rash, fever, an episode of gross hematuria, and then hematuria. What’s against AIN? Severe hypertension. The hypertension is way out of proportion for what I might expect for an interstitial disease. There is clear inciting medication. Most AIN is nonoliguric; she’s oliguric. The rash is atypical. It’s only on the lower extremities. In fact, there are certain rashes that I think of on the lower extremities: Petechial rashes and vasculitides, like Henoch-Schönlein purpura. I also think of a variety of others that I’ll come to but usually not AIN.

Moreover, the urine here has red cell casts. Now I can’t remember which conference at the ASN it was, where a great pathologist, Dr. Helmut Rennke, said, “Don’t be so surprised if you see red cell casts in AIN.” Helmut happens to have one of the only papers on AIN with red cell casts in a case of amoxicillin interstitial nephritis. Of the 158 cases of β lactam AIN in our Columbia manuscript, only nine patients had red cell casts. Almost every one of those patients had another disease that could do it—diabetes, subacute bacterial endocarditis (SBE)—something they were getting the antibiotic for. It’s very rare to see red cell casts in AIN. It is possible. I admit there are a couple of reports in the literature, but it certainly is not a typical urinary finding. Hematuria, yes, but red cell casts, no.

Overall, I don’t think this is AIN. Do we have signs of glomerular disease? Three sure signs of glomerular disease are red cell casts, deformed or crenated urinary red blood cells, and large amounts of albuminuria. We don’t know how much the 24-h urine is here. If we looked at her urine sediment, it can be very helpful in some cases. If we saw lots of red cells and they are crenated or deformed red cells, that’s much more likely to be glomerular disease. Of course, you could look at the urine under phase contrast microscopy. It turns out the deformed erythrocytes that are most likely to indicate glomerular disease are the acanthocytes, the ones with the little Mickey Mouse ears coming off them. If you don’t see them, I would say all bets are
off. Likewise, if we see red cell casts, it’s a glomerular disease, until proven otherwise. Here we do see red cell casts. That’s good enough to make me lean toward a glomerular disease.

Now we’ve got a systemic disease, acute renal failure, and evidence of glomerular disease. When you have a glomerular disease, usually the next step is to look at the “serologic tests.” Which serologic tests are most helpful? This is always controversial even among really good, solid clinicians. When I was in charge of the Renal Section of MKSAP 12 and 13 for the American College of Physicians, the area that gave us the most dissension among five or six very good clinicians was what serologic tests to obtain in somebody with heavy proteinuria, with a clear glomerular disease, who you were going to biopsy. My colleagues’ opinions ranged from Paul Kimmel, who said, “I’d get bing bing bing” (including ANCA, anti-GBM, hepatitis B, hepatitis C, etc.), to John Harrington, who said, “I wouldn’t get anything. If I’m going to biopsy the person, I do the kidney biopsy, and then the next day, after I see the biopsy, I’ll get all of the tests I need to present the case at rounds.” John Harrington’s been around nephrology a long time, and I’m beginning to think he may be right, but I have got to go with Paul Kimmel for at least a few tests in every case like this.

I think the two things that are most helpful are the ANA and the serum complement. These are just the two tests they give us here. The ANA is a broad screen not just for lupus but also for all collagen vascular diseases and some other diseases. For example, some HIV-positive patients are now having lupus-like syndromes. The complement value is extremely helpful because there are very few renal diseases with a low complement, and it really divides them nicely. If we consider low complement in glomerular disease, we have lupus and collagen diseases, SBE and postinfectious GN, cryoglobulinemia, with or without hepatitis C, and idiopathic membranoproliferative GN. There are a number of other rare diseases that can give a low serum complement, for example, heavy-chain deposition disease. If you happen to have a large production of heavy chain, an IgG subtype that binds the complement, it will be associated with a low complement level. Cholesterol emboli have been reported with low complement levels. The hereditary complement deficiencies such as C2 deficiency will be associated with a low serum complement level. Sometimes the pattern of lowered complement can be helpful. If you look at C3 and C4 in lupus, they go down hand in hand. In SBE and most postinfectious GN, you are more likely to have a lower C3. In cryoglobulinemia and hepatitis C, you are more likely to have a low C4. We are only given the C3, but it is reduced.

Going a little further on the differential diagnosis in this case, could she have a thrombotic thrombocytopenic purpura/hepaticolic-uremic syndrome (TTP/HUS) syndrome? She had a diarrheal illness. Maybe she had a bad contaminated hamburger or vegetable taco a week before. These patients have hypertension, their platelets are often low, and they have acute oliguric renal failure. Her story is not a bad background for a TTP/HUS-like picture; however, the platelets are really only borderline low, and her hematocrit and hemoglobin are well preserved, both of which are really unusual in severe TTP/HUS renal failure. Maybe at an early stage of TTP/HUS, but here she already has a creatinine of over 4 mg/dl. She has fulminant renal failure with a platelet count that is only a little low, with a hemoglobin that is well preserved, and there’s no mention of a microangiopathic hemolytic anemia. Certainly, if TTP/HUS were the diagnosis, someone would check the peripheral blood smear to look for the classic microangiopathic picture. Moreover, there are no neurologic symptoms to support a diagnosis of TTP/HUS, the ANA is positive, and the complement C3 is low. TTP/HUS just doesn’t fit.

Another possibility is HIV-related GN. Why would I possibly think of that? If your grandparent was a doctor, they thought of syphilis as the great imitator and they always thought of checking for syphilis. In our generation, we always have to think of HIV, especially if the case doesn’t fit together. You should always check an HIV titer because some of those cases turn out to be HIV positive.

This is not classic HIV-associated nephropathy with collapsing focal sclerosis; however, HIV has been associated with a whole variety of other glomerular diseases, including TTP/HUS, immune complex GN, and, not uncommonly, a lupus-like syndrome, and this patient has a low C3 and positive ANA. Could she be HIV positive? Certainly. It’s certainly one serologic test to obtain. If this is an HIV-related disease, it’s not collapsing focal sclerosis.

Could this patient have SBE? This is somebody who has a fever, and she’s coming in with a positive blood culture. The blood culture happens to be positive for S. epidermidis. Maybe she has an abscess someplace. This person has fever, rash, a positive blood culture, and a low complement. All of those things go along as well, and she actually has a urinalysis with red blood cell casts, so that fits also; however, she doesn’t have a murmur. There’s a rub, but there’s no murmur. You can say, “They could have missed the murmur,” but they listened closely enough to find a cardiac rub and they couldn’t hear a murmur. Surprising. In fact, here’s somebody who comes in with a temperature of 104°F and doesn’t have a murmur, and it is only S. epidermidis in one blood culture, a common contaminant. The illness is relatively short; she’s not significantly anemic, and she’s got the positive ANA, which I can’t explain with a postinfectious etiology.

Could she have two diseases together? It’s always possible. At my institution, Columbia University Medical Center, that’s just the kind of renal biopsy the pathologists like to present. Something with a big twist or a double diagnosis, two disease processes going on at the same time. I do not think that’s the case here.

What about lupus? How many people think she has active lupus nephritis? That’s a lot of people here. Okay. I think you’re saying that because you knew I’m doing the CPC.

She is a young, female with systemic illness and with a glomerular disease causing acute renal failure. She has a urinalysis with active sediment, with red cells and red cell casts. She has a positive ANA and a low complement. That’s all certainly in favor, but this is fulminate acute renal failure in a very short time. She doesn’t have any joint systems, or malar rash, or other symptoms, except for the headache, and all of a sudden she develops fulminate acute renal failure.
Can lupus do this? Absolutely. There are certainly many cases in the literature of simultaneous onset of systemic lupus erythematosus with acute renal failure due to lupus GN; however, it’s not the typical finding. The patient also had an episode of gross hematuria, which is not a typical finding in lupus nephritis. She has no edema to suggest the nephrotic syndrome. Many patients with severe proliferative lupus GN are nephrotic. If the anti-DNA were strongly positive, I’d be betting on an active lupus GN.

One more potential diagnosis. Could this lady have antiphospholipid syndrome or anticardiolipin syndrome? She’s a young female with a systemic disease and fever. Antiphospholipid syndrome certainly can present with a catastrophic syndrome and catastrophic renal disease. There are many cases in the literature. She had two prior first-trimester miscarriages. In the history, that makes me think of antiphospholipid syndrome. In fact, if she had three and I got a negative antiphospholipid or anticardiolipin, I’d repeat it. Two? One negative would be enough; but, nevertheless, that’s the only thing strongly in the history that helps you in diagnosing antiphospholipid syndrome.

She had an episode of gross hematuria. She could be having thromboses and medullary infarcts, giving her the gross hematuria. She has a rash. It is a blanching rash here on the lower extremities. Could this be a network-like pattern of livido reticularis? That’s the only consistent thing, if found on physical examination, that helps support a diagnosis of antiphospholipid syndrome. If I see a young lady with unexplained renal disease and she has livido reticularis, I always get an anticardiolipin and a lupus anticoagulant to check for antiphospholipid syndrome. She has lowish platelets. Again, something that consistent, around that range of 100; if you look at lupus patients with antiphospholipid syndrome, they have lowish platelets. ANA is positive; it goes along. The C3 may be normal or low, again, if it’s a lupus-like case.

Of course you would check a prothrombin time and partial thromboplastin time (PTT) before doing a kidney biopsy. If the PTT is elevated, then I check the anticardiolipin antibody titer. A high PTT would be suggestive that this is an antiphospholipid syndrome.

Livido is a network-like pattern that can be seen on the upper extremities but is more common on the lower extremities. Often the finding is not clearcut. It’s a very vague network-like pattern, and in my office, like a lot of you, I have fluorescence lighting, and sometimes I look at my own hands and I think I have livido myself.

If this is GN related to an antiphospholipid antibody, the renal biopsy might show change in the small vessels with marked narrowing due to a combination of hypertension and antiphospholipid antibody. The lumen will be markedly narrowed. Often in antiphospholipid syndrome GN, there are findings in the GBM, by electron microscopy, but not necessarily a lot of deposits. If we had a lot of immune complex deposits, we’d be talking about active lupus, and if her anti-DNA antibody came back positive, yes, she should have subendothelial deposits and probably deposits elsewhere along the basement membrane, but she might have widening of the subendothelial space by the so-called fluffy flocculent material, which is fibrin or fibrin-like products suggestive of a coagulopathy. This is not specific for anticardiolipin syndrome but could support the diagnosis if found on this patient’s biopsy. Another common finding in thrombotic microangiopathies is “mesangial interposition,” “reduplication” of the GBM and widening of the subendothelial space.

I’m pretty sure she’ll have mesangial deposits. Now whether she’ll have a lot of lupus-like findings and diffuse proliferative disease as well, I don’t know. If her anti-DNA is negative, then I’d guess against it. If her anti-DNA is positive, then I’d guess in terms of both coagulation and an active lupus biopsy.

So, what about antiphospholipid syndrome? It can be primary or secondary, primary or idiopathic and secondary in association with lupus or other collagen-like diseases. It’s associated with thromboses, venous thromboses, deep vein thrombosis, pulmonary emboli. Arterial thromboses can give you CNS disease, strokes, migraines, etc. Coronary arteries, renal arteries can be involved. You could get microinfarcts or large infarcts due to the anticardiolipin syndrome. Recurrent fetal loss; she has two miscarriages. Livido reticularis, thrombocytopenia. She should have hemolytic anemia, but she’s not very anemic. The renal disease certainly fits, and she has a lot of these findings.

If you look at what happens in antiphospholipid syndrome, there are some antiphospholipid antibodies that bind directly to the lipid membrane, but most of these are IgM and aren’t associated with thromboses. If you take the most common IgG, anticardiolipin antibodies, most of these antibodies bind to β-2 glycoprotein-1. It’s the β-2 glycoprotein-1 that binds to the lipid surfaces, and then the antibody binds on top of that. β-2 Glycoprotein-1 is a plasma protein. It serves as a natural anticoagulant. It binds to anionic phospholipids and inhibits the prothrombin to thrombin conversion. Most of the anticardiolipin antibodies we recognize in serum bind to a domain on β-2 glycoprotein-1, and then the complex inhibits the action of β-2 glycoprotein-1, leading to increased thromboses.

For clinicians, every time you think of antiphospholipid syndrome, check both a lupus anticoagulant and an anticardiolipin antibody. Do them both, because, again, in some labs, one’s better; in some labs, another is better. You don’t have to have both positives here, but again, they’re different tests. They do confirm that you have this thrombotic tendency due to the antiphospholipid antibody.

Now, the assays for the anticardiolipin antibodies are now very well standardized. Some of you know that a few years back you would get positives on somebody; then it would be negative, then it would be positive. It turns out it depended on what cardiolipin they were using in the ELISA assay. If the cardiolipin was oxidized in the bottom of these little wells of the assay plate, it gave good results. If it was not oxidized cardiolipin, it gave negative results, even in someone with anticardiolipin antibody. This test has now all been standardized. You can check for anticardiolipin antibodies, lupus anticoagulant, and anti-β-2 glycoprotein antibodies as well.

Now, what about the renal manifestations? Do they fit in here? Thromboses, at any location within the renal vascula-
ture—could be renal artery, renal branches, or you could have renal vein thrombosis—that would do this. You can also have intraparenchymal arterioles being involved and the glomerular capillaries being involved, by thromboses. Any of these are possible.

Acute renal failure has been reported, due to renal infarcts, renal vein thrombosis, thrombotic microangiopathy (TMA) in the glomeruli, and renal cortical necrosis. More commonly, clinically you get a chronic presentation here with a clinically silent illness for a certain amount of time where they have hypertension, renal insufficiency, proteinuria hematuria, and some have the nephrotic syndrome.

I think this lady has a systemic illness, acute renal failure, due to a glomerular disease. She has a lupus-like syndrome. I think she’s going to be anticardiolipin positive or antiphospholipid positive, with some coagulation in the kidney. We may see it in the small vessels and in the glomeruli as well. Could she have diffuse proliferative lupus as well? Certainly. If her anti-DNA antibody titer came back really high, I’d say yes, okay, it’s certainly a possibility. Could she have a postinfectious superimposed? No way of knowing without the biopsy. That’s the reason we do the renal biopsy.

So, at this point I’m ready to turn this over to Sharon and then to the pathologist.

SHARON G. ADLER, MD: Thank you, Dr. Appel. I think it’s always a privilege to watch the workings of an astute clinician as he meets a clinical challenge, and that’s what actually each of us does every day; however, the pathologist always gets the last word and is always right. So, I’d like to introduce Dr. Cynthia Nast, Professor of Pathology at the David Geffen School of Medicine and Renal Pathologist at the Cedars Sinai School of Medicine, again, who is always right. Cindy.

DR. CYNTHIA NAST: The renal biopsy has 15 glomeruli by light microscopy and is an adequate biopsy. All of the glomeruli are abnormal and are more or less similar to one another. The urinary spaces are open in all of the glomeruli within the biopsy. There are no crescents and no segments of sclerosis. Glomeruli are hypercellular, and the hypercellularity involves most of the glomerular profiles. There is a small segment in this glomerulus that does not show significant hypercellularity, but the remainder of the glomerular tufts have a considerable increase in cells with mesangial widening and hypercellularity. The capillary lumina often are occluded, primarily due to circulating leukocytes. Ninety to 95% of this glomerulus shows hypercellularity, and this process is present in more than half the tufts of all glomeruli, indicating a diffuse and global process (Figure 1).

In addition to hypercellularity, two or three glomeruli have capillary lumina that are completely occluded with fuchsinophilic deposits forming hyaline thrombi. In the glomeruli with hyaline thrombi, there often is less extensive hypercellularity. In this glomerulus, few segments have mesangial hypercellularity, and leukocytes are within capillary lumina (Figure 2); however, including the areas with hyaline thrombi and those with increased cells, the majority of glomerular tufts are involved, indicating a global process. Segmentally, the large immune complex deposits occluding the capillaries extend into adjacent mesangial regions. There also are glomeruli with capillary wall double contours.

Many mononuclear leukocytes are within mesangial regions and capillary lumina, with a number of neutrophils also present, resulting in a mixed infiltrate of inflammatory cells. In some foci with extensive neutrophil infiltration, there is karyorrhexis with breakdown of cells and fragmentation of nuclei. On the hematoxylin and eosin stain, in areas of karyorrhexis and nuclear breakdown, there are smudgy, purplish, amorphous globular structures (Figure 3). These are hematoxylin
bodies, which were used in the past to diagnose lupus nephritis but now are just fun to find.

In addition to hypercellularity, fuchsinophilic deposits, hyaline thrombi, and karyorrhexis, there are two glomeruli with abnormal arterioles. There is one arteriole with fibrin almost completely occluding the lumen with swollen endothelial cells, a small area of lumen remaining patent, and fibrin in the arteriolar wall (Figure 4). Another glomerulus at the edge of the biopsy has an intraglomerular arteriole with extensive fibrin throughout the wall, incorporated fragmenting leukocytes, and luminal fibrin with virtually complete occlusion of the lumen. So there is, in addition, a TMA, as Dr. Appel so astutely predicted.

The interstitium has edema but no inflammation, so Dr. Appel was correct in that there is no acute interstitial nephritis. However, tubular cells are flattened with marked dilation of the lumina, and there is focal denudation where the tubular basement membrane is devoid of overlying epithelial cells. Cellular debris is in the tubular lumen admixed with Tamm-Horsfall protein, and proximal tubules have loss of brush border staining, all indicative of acute tubular necrosis.

By immunofluorescence, the glomeruli are positive for full-house immunofluorescence including IgG, IgA, IgM, C1q, C3, and κ and λ light chains. The immune reactants are in a granular pattern in mesangial regions and also in capillary walls in a granular and confluent granular pattern, which corresponds to large subendothelial deposits (Figure 5). There are focal granular deposits of IgG, C1q, and C3 within some tubular basement membranes, but no immune complex deposits are in the walls of any arteries or arterioles.

Ultrastructurally, there are large subendothelial electron-dense deposits, so-called wire loop lesions, corresponding to the findings on immunofluorescence of confluent capillary wall deposits. The overlying capillary basement membrane is of the normal width and electron density, with partial foot process effacement but no significant subepithelial deposits. Other glomeruli show capillaries with subendothelial deposits and swollen endothelial cell cytoplasm as well as leukocytes within capillary lumina. This inset shows a subendothelial deposit and endothelial cell cytoplasm containing a tubuloreticular structure (Figure 6). Few capillary walls lack deposits, although endothelial cell cytoplasm is swollen. There are electron-dense

Figure 2. This glomerulus has several capillary lumina occluded with large subendothelial deposits in the form of hyaline thrombi (arrows) with only two segments demonstrating significant hypercellularity (Masson’s trichrome). Magnification, ×120.

Figure 3. Glomeruli with leukocytic infiltrates and karyorrhexis. (A) Nuclear fragmentation is present in a segmental distribution (thick arrow). There is one area with extensive immune complex deposition and associated reduced cellularity (thin arrow). (B) A hematoxylin body is present, appearing as a purple amorphous structure (arrow; hematoxylin and eosin). Magnification, ×160.
deposits scattered throughout mesangial regions. There are no significant subendothelial lucent zones, in spite of the TMA. Therefore, the diagnoses are diffuse proliferative lupus nephritis, TMA, and acute tubular necrosis. The lupus nephritis shows both diffuse and global hypercellularity where >50% of the glomeruli are involved (in fact, all glomeruli), with each glomerulus having more than half of the profile involved. There are infiltrating leukocytes with karyorrhexis as well as

**Figure 4.** Glomerulus with adjacent thrombosed arteriole. (A) The arteriolar lumen is almost completely occluded by fibrin (Masson’s trichrome). (B) The arteriole has swollen endothelial cells and luminal fibrin that extends into the tangentially sectioned vascular wall (periodic acid methenamine silver). Magnifications: ×80 in A; ×160 in B.

**Figure 5.** Glomerulus stained for C1q demonstrating granular mesangial and capillary wall staining. There is segmental confluent granular capillary wall staining (arrow) corresponding to large subendothelial deposits (wire loop lesions). Magnification, ×120.

**Figure 6.** Electron micrograph of a capillary wall demonstrating subendothelial electron-dense deposits and swollen endothelial cell cytoplasm containing a tubuloreticular structure (arrow). Magnification, ×10,000.
subendothelial deposits in the form of hyaline thrombi and wire loop lesions, and these immune deposits stain with full-house immunofluorescence, all features of diffuse proliferative lupus nephritis. Using the International Society of Nephrology/Renal Pathology Society classification of lupus proliferative nephritis, this is a class III-G (A) lesion; class IV is diffuse lupus nephritis, G is global involvement, and A indicates an active lesion. There were no significant chronic changes.

Thrombotic microangiopathy already has been discussed in part by Dr. Appel. In the setting of lupus, it can be considered a lupus vasculopathy and may be due to antiphospholipid antibodies or antiphospholipid syndrome, as has been discussed. It also can be found in patients who have immune complex deposition within vascular walls. A recent article in Kidney International by Dr. Sesin from NYU discussed endothelial protein C receptor alterations and shedding in patients with lupus and lupus vasculopathy. This may be one factor involved among many others that are not yet well understand in patients who develop lupus vasculopathy and do not have antiphospholipid syndrome or immune complex deposition; we certainly do find vasculopathy without either of these. Thrombotic microangiopathy also may be a manifestation of malignant hypertension, HUS, or TTP and can be seen in scleroderma.

Additional clinical information obtained after the biopsy included SCL-70, anti-Ro (SSA), anti-La (SSB), anti-Smith (Sm), anti-ribonucleoprotein (RNP), ANCA, and anti-GBM antibodies, all of which were negative. The anti–double-stranded DNA was positive. The kidney biopsy results were available long before you got the serologies back. The anticardiolipin antibody was negative; however, antiphospholipid and anti-β-2-glycoprotein-1 antibodies were not tested, so antiphospholipid syndrome or immune complex deposition; we certainly do find vasculopathy without either of these. Thrombotic microangiopathy also may be a manifestation of malignant hypertension, HUS, or TTP and can be seen in scleroderma.

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So what happened to this patient? She was treated with steroids and cyclophosphamide, antihypertensive agents were continued, and she was anticoagulated. She was on dialysis for 5 d, at which time her creatinine started to come down. Now, 4 mo later, her creatinine is 1.5 ml/dl and she is doing well. Her hypertension is well controlled, the headache is gone, and the platelet count has normalized.

SHARON G. ADLER, MD: Thank you. I think our contestant did very well with a very difficult case, and, Jerry, I think I want to take you on, on the usefulness of a positive ANA. I think in this patient, an ANA was very, very useful, and I think it is more useful in patients who have a clinical syndrome that is consistent with lupus, but I think if you get an ANA in a person with a low likelihood of having lupus, then you are more likely to see a false-positive than a true-positive, and so I actually err with the ANA on this side of John Harrington and not order it unless the clinical syndrome is consistent because otherwise it may lead me down the garden path, whereas I will get complements as a surrogate for ANA. What do you think?

GERALD B. APPEL, MD: Okay, well, you know medicine is not a democracy but let’s vote. How many people, if you have somebody with glomerular disease, routinely get an ANA? Overwhelmingly for getting the ANA. I am not going to say anything more after the landslide for the ANA!

SHARON G. ADLER, MD: You’re wasting your money. You’re wasting our money.

GERALD B. APPEL, MD: I just want to comment about the course of the patient, which is obviously very gratifying that this person did so well. You know, the big issue here is not how you treat the severe lupus nephritis. You can argue to use cyclophosphamide or mycophenolate mofetil (MMF), both with pulse steroids. Some big-league therapy was needed for the diffuse proliferative with the subendothelial deposits. The big question is do you anticoagulate the patient? Do you keep the patient on long-term anticoagulation? Are you going to say that, yes, she has part of a coagulation syndrome and therefore she is going to have to stay on Coumadin long term, especially since it is a young female? What happens when she gets pregnant? Then you have to use heparin and aspirin. It would be much easier if there were a clearcut antiphospholipid antibody and you would say it goes with the thromboses. Another question is whether I would have used cyclophosphamide or MMF because there are no crescents and very little necrosis. I might have used MMF, but I certainly would have given pulse Solu-Medrol and I would have anticoagulated as well. Of course, I do not know if I would have done as well as you did. You can’t argue with success.

SHARON G. ADLER, MD: Just for fun, if there are questions from the audience, there are two microphones in the aisles and I think Dr. Appel would very happy to answer questions related to this case but not cases that you have that you want him to help you with.

GERALD B. APPEL, MD: But I only want to do multiple choice questions.

QUESTION: That was excellent, wonderful presentation. The question I have as far as using MMF; most of the studies, the one from Hong Kong and one recently from here, when they use MMF as induction therapy, the creatinine on average was 1.6 mg/dl or less, and most of it was really for proteinuria. Do you feel comfortable based on these studies that in such an acute presentation, where the patient went to acute renal failure and required dialysis, that MMF would be as good as cyclophosphamide?

GERALD B. APPEL, MD: I think that is a great point. No, I don’t feel as comfortable. The two situations I don’t feel at ease with mycophenolate yet are (1) when the creatinine is much higher than most of the patients in the studies and (2) if we have a lot of crescents and necrosis; we just don’t know how well the mycophenolate will work. In our recent study of 140 patients with a 3-yr follow up, patients were mostly diffuse proliferative, some must have had crescents but we don’t know the details of those data yet. So, I share your concern 100% until more data are available.
AGNES FOGO: Agnes Fogo from Vanderbilt. First of all, Jerry, congratulations on the White Sox and on a wonderful discussion by both. My question is a bit philosophical. I’m looking at this history and the biopsy findings; I thought about cryoglobulinemia, and I thought about cryoglobulinemia when I saw the morphology also, particularly with those polymorphonuclear leukocytes mixed in and the substructure of the deposits by electron microscopy, and I wonder practically is that something one could consider in lupus cases with substructure deposits, about a quarter of them will have a positive cryocrit and if so does it really matter how you approach them?

GERALD B. APPEL, MD: Okay, well I leaned over when I saw the biopsy, leaned over and asked Sharon, “Does this patient have cryos?”

AGNES FOGO: Well, did she tell you yes or no, or did she let you sweat?

GERALD B. APPEL, MD: She said no. The person did not have cryos, but cryoglobulins are our least reliable test. They all precipitate out on the way to the laboratory, so you have to send them two or three times or carry the tube under your arm or something to keep it warm, but the biopsy is very suggestive of cryos. Here is a very terrible lupus nephritis with no crescents. It is an adequate sample; if it were crescentic, I would have said fine, but I also thought exactly the same thing with those big glob-like deposits and everything that it was a cryo-type case. Now, the one thing we can say is we could always ask, “Well what about the C4 level?: If the C3 were low and the total were low and the C4 was not as low, I would think a little less likely for cryos, but even so, the only therapeutic thing you could argue for would be plasmapheresis, which would have been very reasonable except again it is hard to argue with success. This person got better and did not have cryos.

AGNES FOGO: I don’t think we know that. I don’t think there was a cryo test done, and I would like Cindy’s perspective on the morphology in general in lupus cases with substructure of how you approach or think about that possibility.

DR. CYNTHIA NAST: Actually, the substructure is artificially induced by the digitization and enlargement of the slides. When I actually examined the specimen ultrastructurally, it did not have the particular cryoglobulin substructure under the electron microscope. In addition, the immunofluorescence is classic for lupus with 4+ IgG, 4+ C1q, and only 2+ M and 3+ C3. To have cryo with 4+ C1q and lesser amounts of IgM and C3 is unusual, and this was against the presence of cryoglobulins. They did test for cryo, and it was negative. The patient had no other clinical evidence of cryo, but I think it is a very good point.

QUESTION: The lower extremity rash?

DR. CYNTHIA NAST: I think it may have been related to the TMA.

GERALD B. APPEL, MD: The lower extremity rash, I can say for cryos is usually petechial hemorrhagic. It is not blanching. I put a lot on a dermatological finding here, but I will tell you, that biopsy, when I looked at it, the first thing that went through my mind was, “Oh, wait a minute, I missed this thing.” This is cryo, so it is a good thing the cryos are negative.

QUESTION: So, this rash is a blanching rash, it is not a vasculitic rash, so what is the rash in this case?

GERALD B. APPEL, MD: I think it was livido reticularis. That is my guess. I don’t know, I didn’t see the patient. Trying to diagnose a rash without seeing it is difficult; even dermatologists have to see the rash. It was a blanching rash on the lower extremities, and my guess it was a livido-type picture. Now, you can argue we didn’t have a positive anticardiolipin, but we didn’t test for lupus anticoagulant or antiphospholipid, and certainly they were anticoagulating based on the fact of a TMA. In somebody with two miscarriages, that would be my guess.

SHARON G. ADLER, MD: Thank you very much for your enthusiastic participation.