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## Hypertension and its complications in a young man with autoimmune disease

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## Case Introduction

A 30 year-old man, who had moved to the UK from South Asia, was referred to the renal clinic with nephrotic syndrome. He had recently been diagnosed with systemic lupus erythematosus (SLE) after presenting to the rheumatology clinic with joint pain, skin rash, and pleuritic chest pain and fulfilling 8/17 SLICC diagnostic criteria.<sup>1</sup> His immunology was in keeping with active SLE: his complement levels were low and he had antibodies against double-stranded DNA and extractable nuclear antigens (ENA) (**Table S1, A**).

Our patient had heavy proteinuria (3.9g/day) and a low serum albumin (25g/L) in keeping with the nephrotic syndrome. Although his excretory renal function was normal he had microhematuria (3+) on urinalysis. An urgent renal tract ultrasound with Doppler revealed he had a pre-existent renal vein thrombosis for which he was anticoagulated. In the absence of any serological evidence of antiphospholipid syndrome, this was attributed to his nephrotic syndrome. He went on to have a renal biopsy. This demonstrated classes III (focal proliferative) and V (membranous) lupus nephritis (**Figure 1**).

At presentation, his blood pressure (BP) was 126/88mmHg in the absence of antihypertensive treatment. Although this lay within both UK and US recommended guidelines, we recognize that given this man's age and heavy proteinuria a lower BP target may have been beneficial.<sup>2,3</sup>

## Management of Lupus Nephritis

Our patient started standard induction immunosuppressive treatment for lupus nephritis comprising of glucocorticoids and pulsed intravenous cyclophosphamide.<sup>4</sup> However, his disease proved difficult to manage over the next two years. He tolerated only a short course of cyclophosphamide due to an anaphylactoid reaction, subsequently attributed to the mesna component (given to protect the bladder epithelium). Alternative induction therapy with mycophenolate was not tolerated due to gastrointestinal side effects. Switching this to an enteric preparation of mycophenolate (Myfortic) made little impact on disease activity after six months. Similarly, three months of azathioprine had little effect. He was finally treated with the anti-CD20 B-cell depleting monoclonal antibody, rituximab.

Over these two years our patient's lupus nephritis failed to enter remission and his renal function gradually deteriorated (**Figure 2**). He remained nephrotic with up to 10g/day of proteinuria and a serum albumin of <20g/L (2.0g/dL). Given his increased thrombotic risk he remained anticoagulated with warfarin, although his INR fluctuated considerably and was difficult to maintain within the therapeutic range.

## Worsening hypertension

During the first six months following presentation, and in the context of ongoing nephrotic syndrome and fluid overload, our patient's BP rose rapidly to ~175/110mmHg, on no medications. Over this time he retained normal excretory renal function and serum electrolytes. Inflammatory markers were consistent with active SLE. Serum albumin was depressed at 17g/L (1.7g/dL) and he was hyperlipidemic (cholesterol 6.6mmol/L, triglycerides 8.9mmol/L), in keeping with nephrotic syndrome. A number of factors were likely to have contributed to his hypertension, which would require different therapeutic strategies (**Table S2**).

## Discussion: managing the hypertension

**Dr. Neeraj Dhaun:** Given the likely pathophysiology for our patient's hypertension, would anyone like to suggest some management strategies?

**Dr. Suzanne Oparil:** Blockers of the renin-angiotensin-aldosterone system (RAAS).

**Dr. Dhaun:** A good start! Would you like to give our patient an angiotensin-converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker?

**Dr. Suzanne Oparil:** I would probably start with an ACE inhibitor. Thirty years ago, that was used for lupus. And then if that didn't work, I would probably add an endothelin-blocker. I wouldn't combine ACEs and ARBs, at least at first.

**Dr. Dhaun:** Okay, so we have the option of an ACE inhibitor followed by an endothelin (ET)-blocker. ET blockers are only currently licensed for pulmonary arterial hypertension and scleroderma ulceration, so we would be using them off-license. Any other suggestions of how we manage this patient's hypertension - any non-pharmacological strategy?

**Dr. Daniel Battle:** We talk a lot about the RAAS, but rarely try to measure its activity. You could start by measuring plasma renin activity, which is significantly elevated in a scleroderma renal crisis, for instance. We learned from one of the presentations yesterday that urine angiotensinogen, which is easily measurable, can be decreased by mycophenolate. So you could potentially measure urine angiotensinogen and circulating angiotensin II.

**Dr. Dhaun:** Absolutely. One thing I'd like to draw your attention to is that this case is from some years ago. Urinary angiotensinogen would not have been available to us then, nor is it, to my knowledge, used in the clinical setting. Certainly, plasma renin and plasma/urine catecholamines might have been available. I'm not sure how interpretable these would be in the context of renal impairment, proteinuria, fluid overload and the combination of various therapies such as corticosteroids and other immunosuppressive agents.

**Dr. Fernando Eljovich:** Given the level of BP, most guidelines would support the use of two different antihypertensive agents. I would consider ACE inhibitors, dihydropyridine calcium channel blockers and a diuretic as the main options here. However, I am unclear as to the benefits of calcium channel blockers in those with kidney impairment.

**Dr. Dhaun:** Sir, before you sit down may I ask you, which class of calcium channel blockers you would choose? The ones whose hemodynamic effects are predominantly on the afferent renal arterioles such as nifedipine, or those that predominantly affect the efferent renal arterioles such as amlodipine?

**Dr. Eljovich:** I was surprised recently by the fact that impairment of renal auto-regulation is applicable to both dihydropyridine and non-dihydropyridine calcium channel blockers. The effect of non-dihydropyridines is similar in direction but less powerful than that of dihydropyridines, consistent with the less potent vasodilator effects of the non-dihydropyridine agents.

**Dr. Dhaun:** Fair enough. So I'm going to take the opportunity to ask you one other question. What would you be trying to achieve here by controlling BP in this patient? What is your target and what are your goals longer-term?

**Dr. Fernando Eljovich:** My main concern is the contribution of his high BP to the progression of renal disease.

## Progress

As discussed, management of this patient's BP required a holistic approach. Most importantly, we had still not managed to achieve remission of his SLE. General lifestyle measures were encouraged, namely salt and fluid restriction. Pharmacologically, a combination of diuretics and RAAS blockade was initiated - Furosemide 80mg daily and Valsartan 160mg daily; he was intolerant of Ramipril due to headaches. Given the lack of BP improvement, two further agents, a calcium channel blocker and an alpha blocker, were added. However, these provided little added benefit - average BP remained ~170/90mmHg (**Figure 3**).

Our aims here were to reduce our patient's proteinuria (and so preserve renal function) as well as lowering his cardiovascular risk. This risk is disproportionately high in SLE with an up to a ~50-fold increased risk of myocardial infarction.<sup>5,6</sup> Given his renal impairment and genetic background, his cardiovascular risk was likely to be significant, even at this young age.

At this point, our patient continued to have 5-10g/day of proteinuria with deteriorating renal function. Thus, achieving BP control was critical. He was also anemic (Hb 84g/L), in keeping with his level of renal dysfunction and hyperkalemic ( $K^+$  5.8mmol/L). Continued lymphopenia, hypocomplementemia and prolonged erythrocyte sedimentation rate were all consistent with ongoing active SLE.

**Dr. Dhaun:** So our patient's BP and renal function are deteriorating. What factors might be contributing?

**Prof. Anna Dominiczak:** One problem is that you haven't managed to control his lupus. He still has an active immune disease that is destroying his kidneys, whatever you do. And even if his BP had been perfect, which is unlikely under the circumstances, you would still have progression of the disease because the kidneys are being destroyed.

**Dr. Dhaun:** Absolutely. As Prof Dominiczak correctly points out, the active SLE will not only be driving the renal disease but as it is a systemic disease, it will also be contributing to the hypertension directly. So one mechanism to reduce the BP has to be targeting the underlying SLE. However, the SLE treatment will also be contributing to the hypertension, as our patient continues on reasonably high doses of corticosteroids alongside other immunosuppression.

**Dr. Jan Basile:** Can you go back to the drugs again? Okay, so od means once a day?

**Dr. Dhaun:** Yes, od means once daily.

**Dr. Basile:** What was the potassium?

**Dr. Eve Miller-Hodges:** 5.8mmol/L

**Dr. Basile:** I appreciate that the  $K^+$  is a concern and I don't know if you have access to the new drugs available to manage hyperkalemia. However, using once daily furosemide in the management of hypertension is a big mistake in my opinion as this will lead to paroxysmal sodium retention. If you are going to use furosemide I would suggest at least a twice daily dosing regimen.

Valsartan 160mg once a day also concerns me. It's as if there is a fire going on in your house and you are trying to use a straw to try to put the fire out while the fire is still raging. The patient's BP is elevated. If the patient is on mycophenolate why not use diltiazem to reduce its dose and so save some money with the added benefit of better BP control.

The biggest problem I see with diltiazem is under-dosing; with verapamil it is the constipation. Using an inadequate dose is common; diltiazem is available in 180, 240 and 300mg tablets and you need a good-sized dose for it to be effective as a blood-pressure lowering agent.

And then as a fourth drug, I'm not sure why you would use an alpha blocker before a beta-alpha blocker. I know the K+'s a concern, and that might be a reason to use a lower dose of the valsartan but would you consider spironolactone? I think this patient has a lot of salt-volume induced hypertension.

Finally, do we have any idea of nighttime BP? Would you consider giving some of these medicines at night instead of just in the morning to achieve better 24-hour BP control? In general, I would have approached BP control differently.

**Dr. Dhaun:** Thank you, those are all excellent points. Broadly in response, this patient was managed in the nephrology unit and so we often tend to focus on the kidney and the SLE before BP. For example, our patient is nephrotic and so the valsartan is an attempt to reduce proteinuria. The rationale for the once daily furosemide will become apparent later. However, this was more directed towards managing fluid overload than the hypertension. Finally, there will be a US/European divide here; we tend not to use diltiazem for hypertension. We tend to use alpha blockers as third- or fourth-line agents for treatment of hypertension.

### **Hypertension in nephrotic syndrome**

Thus, the major factors contributing to his hypertension were worsening renal impairment, ongoing proteinuria, salt- and water-retention, and ongoing SLE disease activity. We also had some concerns about adherence to treatment, suggested by his erratic warfarin control, although this was never confirmed.

There are two main theories for the etiology of hypertension in nephrotic syndrome. The 'underfill' hypothesis suggests that the significant loss of proteins in the urine leads to a fall in plasma oncotic pressure which leads to extracellular volume expansion and resultant intravascular volume depletion, reviewed in.<sup>7</sup> This then promotes salt and water retention via activation of the RAAS. By contrast, the 'overfill' hypothesis advocates that the urinary protein loss itself causes proteolytic activation of the epithelial sodium channel (ENaC), directly leading to renal sodium retention. Plasminogen is lost in the urine and activated to plasmin in the urinary space by the urokinase-type plasminogen activator. This is thought to directly and indirectly activate ENaC, as reviewed in.<sup>8</sup> Both these mechanisms may be active in this case.

### **Further investigations & progress**

Our patient had little evidence of hypertensive end-organ damage outside the kidney. He had a normal transthoracic ECHO and normal funduscopy. 24-hour ambulatory BP measurements were not available to us. Dual RAAS blockade was attempted with the re-introduction of ramipril, but this had to be withdrawn due to hyperkalemia, even with correction of his acidosis. The diuretic dose was then increased. A repeat renal biopsy was performed to clarify the extent of lupus nephritis and to exclude additional causes. This showed progression of his underlying disease (**Figure S1**).



In an attempt to control our patient's SLE, we opted for a further trial of oral (low dose) cyclophosphamide but without the Mesna component. By this point, he was suffering from the burden of heavy immunosuppression and had had a number of hospital admissions with infections. His renal function continued to deteriorate and he was now unable to tolerate any form of RAAS blockade because of hyperkalemia. He was maintained on a combination of loop and thiazide diuretics, a calcium channel blocker and an alpha blocker.

Use of spironolactone in this gentleman, as was previously suggested, would have been difficult. He had deteriorating renal function and a tendency towards hyperkalemia even on suboptimal doses of valsartan. From a nephrology perspective, spironolactone was best avoided, particularly given a significant dietary K<sup>+</sup> intake.

The disease progression evident on the repeat renal biopsy suggested that there was compromised renal blood flow. Therefore, we felt that a major component of our patient's hypertension was driven by the renal inflammation, so the focus of management should be on controlling his underlying SLE.

#### **Discussion: Additional Therapies?**

**Dr. Dhaun:** So what would you do next in this gentleman?

**Dr. Battle:** I like this comment about plasmin activating the sodium channel; this is a novel concept. In the nephrotic syndrome, independent of proximal nephron sites that retain sodium, a site of sodium retention is the cortical collecting duct where plasmin might activate ENaC. So focusing on downregulating this with either spironolactone or amiloride may work for hypertension control. However, as a consequence you might worsen the hyperkalemia. This is a situation where the new potassium binders might aid us. We have patiomer, which is already approved in the United States and Z-S9 is pending FDA approval. Either these two, or even the old-fashion kayexalate, could be used to facilitate the treatment of hyperkalemia. I also couldn't agree more with the comment that once daily furosemide is not appropriate but common practice in the United States. I see that sadly this also happens in the UK.

**Dr. Dhaun:** Thank you. Unfortunately, the potassium binders weren't available to us at that time or indeed now. Our general maneuver to offset the potassium retention associated with RAAS blockade was to add a loop or thiazide diuretic to increase kaliuresis. So what would you do next in this patient?

**Dr. Eljovich:** I'm going to suggest something else thinking more of a few steps further down the road. Although SLE is primarily an antibody-mediated disease you cannot really exclude a participation of T-cell mediated inflammation. This might be contributing to the hypertension. Then if I would have failed with more therapies in this patient and even at the risk of going to jail...

**Dr. Dhaun:** Are you hinting at renal nerve ablation here?

**Dr. Eljovich:** Not at all! For renal nerve ablation we have the clearly negative results of a randomized clinical trial. I won't go to jail for that. But I would go to jail for abatacept; this would inhibit the co-stimulation of T-cells. I don't know what it would do to the lupus because you have a very active process in terms of autoantibodies, but it might well reduce the BP. Who knows?

**Dr. Dhaun:** Yes, abatacept is an interesting idea. The trials of abatacept in renal disease and hypertension were not there at the time this patient was being managed. However, I would come back to you and suggest that whilst there is indeed a T-cell component to SLE, it is primarily driven by B-cells and plasma cells so perhaps a B-cell depletion strategy or an inhibitor of B-cell activating factor might be more appropriate here. So, any other ideas?

**Dr. Basile:** What was his heart rate?

**Dr. Dhaun:** Ah, good question.

**Dr. Miller-Hodges:** 90bpm.

**Dr. Basile:** A lot of the drugs you are currently using to control BP work on volume, and to me you have little effective blockade of the RAAS. I think we must work on that. If I couldn't because of the potassium, which is really tying my hands, it would be nice if you had patiromer available.

**Dr. Dhaun:** Sadly we do not.

**Dr. Basile:** Okay. I would at least want to use a beta-alpha blocker if you feel strongly about the alpha blocker. Or even a beta blocker alone. I would also consider, because of the renal function, another loop diuretic. I don't know how bad the renal function or the GFR is now. I would consider adding diltiazem to the nifedipine. Is that a once-a-day, long-acting nifedipine?

**Dr. Dhaun:** That is correct.

**Dr. Basile:** In these kinds of complicated cases, adding diltiazem to the dihydropyridine, calcium channel blocker can get you some additional BP reduction. Of note, the higher the salt intake, the more these agents will lower BP as they work on volume as one of the mechanisms of action. One of the reasons why we don't have verapamil + diuretic or diltiazaretic (diltiazem + diuretic) is because when those studies were done, sodium was not controlled for. So it was hard to see an additional effect of those two agents together unless sodium was controlled for.

**Dr. Dhaun:** Two comments in passing. We attempted the addition of the direct renin inhibitor, aliskiren, to valsartan. However, this had to be stopped due to unacceptable hyperkalemia. Second, we also tried short-acting nifedipine given three times a day. Although this provided a better BP-lowering effect than the longer acting drug it resulted in severe headaches so had to be stopped.

### **Acute Deterioration**

With limited therapeutic options, the patient's BP remained high. Soon afterwards he presented acutely to the Accident and Emergency Department with headaches, seizures, confusion and agitation. He was very unwell. BP was 240/140mmHg, pulse 157bpm, temperature 36.6°C (97.8°F), blood glucose 10.2mmol/L (184mg/dL). He was intubated and ventilated, and his seizures were controlled with intravenous phenytoin. Investigations at this time are shown in **Table S1, B**. He was still anemic; his CRP was now high, and he had stable renal impairment. Serum electrolytes were normal; there was systemic lactic acidosis in keeping with sustained seizure activity.

**Dr. Dhaun:** So what is the differential diagnosis here?

**Dr. Laffer:** You basically are questioning whether he has lupus encephalopathy versus what we used to call hypertensive encephalopathy, or now PRES (*Posterior Reversible Encephalopathy Syndrome*).



**Dr. Dhaun:** Correct! Another possibility is that this could be a complication of his lupus, particularly infection secondary to his immunosuppression, or, as you suggest a complication of the hypertension such as a stroke.

**Dr. Miller-Hodges:** Our key message is that, given the significant immunosuppressive burden, infection is an important differential here. Given the acute change in neurological state we should attempt to discriminate between this being a primarily vascular event or a primarily autoimmune event. How might we do that?

**Audience Member:** You need an MRI.

**Dr. Miller-Hodges:** Anything else?

**Dr. Dhaun:** Yes, I've just got to say, we're in the UK, not the US.

**Prof. Jennings:** You might look at his retina.

**Prof. Dominiczak:** Look at his retina and if okay, do lumbar puncture maybe?

**Dr. Dhaun:** These are our choices in the UK.

**Prof. Dominiczak:** Yes, a graded approach to investigation.

**Dr. Miller-Hodges:** He was neurologically altered with a GCS of 11.

**Audience Member:** So back in the old days, if you didn't have papilledema, one might want to do an LP.

### Investigations and Progress

In the UK, the first imaging performed was a CT head. The initial non-contrast scan showed some areas of low attenuation in the posterior occipital regions and excluded a major bleed or space-occupying lesion (**Figure 4, A**). A lumbar puncture was performed and the cerebrospinal fluid was acellular and had glucose and protein levels within normal limits. All microbiology and virology was negative. A subsequent MRI brain scan demonstrated areas of hyperintense white matter changes in the posterior occipital regions (**Figure 4, B**). The working diagnosis was PRES so the clinical priority was BP control.

**Dr. Dhaun:** Now, the question here is how are you going to reduce the BP acutely? Again, there might be a UK/US divide here.

**Dr. Basile:** To me, when the brain is involved in an encephalopathic presentation, nitroprusside is the first drug to consider.

**Dr. Dhaun:** Okay, so sodium nitroprusside. Anything else?

**Prof. Dominiczak:** Nitrates?

**Dr. Dhaun:** Yes, intravenous nitrates. Any other class of antihypertensive agent that you might use?

**Prof. Dominiczak:** Some people also use IV labetalol.

**Prof. Friedrich Luft:** Perhaps even earlier in this course, we used to give people minoxidil and their renal function occasionally got substantially better. I realize it might cause fluid retention but particularly if you're only giving furosemide 80 mg once a day, but that might be an option.

**Dr. Dhaun:** Thank you. I think minoxidil is used more in the US than in the UK? We rarely use it.

**Dr. Eljovich:** I wanted to remind you that the improvement in GFR with minoxidil is like the early improvement in GFR with amlodipine in AASK. In the amlodipine arm of AASK, the GFR initially goes up, and I believe you, as nephrologists, shouldn't like it.

**Dr. Dhaun:** Thank you for that. Okay, so intravenous nitrates and beta-blockers are both options here. Could I ask how much you would want to reduce the BP by?

**Prof. Jennings:** We want to go to safe levels, not normal levels.

**Prof. Dominiczak:** And slowly, not too fast.

### **Acute management.**

An acute reduction in BP was attempted using intravenous glyceryl trinitrate (titrated to 250mcg/min). Nitroprusside was contraindicated due to the presence of significant renal impairment and thus increased risk of toxicity. We aimed for a target BP reduction of ~10-20% within the first hour and <25% within the first 24 hours to avoid precipitating further vascular injury via cerebral hypoperfusion.

BP fell by ~20% over the first 24 hours using intravenous nitrates and our patient's consciousness level improved, although he remained confused. However, despite the addition of his usual and additional oral antihypertensive agents (Metoprolol 100mg bd, Ramipril 10mg od, Metolazone 2.5mg od, Doxazosin 8mg bd, Nifedipine 20mg tid, Candesartan 8mg bd), as well as intravenous furosemide (120mg bd) and intravenous adrenergic blockade (labetalol 2mg/min) his BP remained ~200/100mmHg without a return to normal neurologic function (**Figure 5, A**). His renal function deteriorated (creatinine 205µmol/L (2.32mg/dL)) and he had now developed both hyponatremia (Na<sup>+</sup> 132mM (normal range 135 – 145)) and hypokalemia (3.0mM (normal 3.6 – 5.0)).

### **Discussion: Next Steps**

To summarize, despite alpha blockade, beta blockade, calcium channel blockade, RAAS blockade and addition of both loop and thiazide diuretics, our patient's BP remains dangerously high. So what further information would you like here and what would you do next?

**Dr. Eljovich:** His mean arterial pressure went from 200 to 133 on the fourth data point. That's about a 33% reduction, is that right? So he may be confused because you may have gone below 75% of his starting pressure.

**Dr. Miller-Hodges:** The lowest BP in the first 24 hours was actually 194/84mmHg, so actually only a 20% reduction from the starting pressure.

**Dr. Eljovich:** The safety point, and actually it's a relative safety point, because you don't even know whether that BP is the usual BP that determines the range of the auto-regulatory curve, is about 75% of your starting BP, after which you start having hypoperfusion. The brain can increase extraction of oxygen below this point, therefore you have a little more of a safety range, but one has to be very careful with that initial reduction nonetheless.

**Dr. Miller-Hodges:** Our achieved BP reduction within the first 24 hours was within the recommended 25% threshold. This also coincided with an improvement in his neurologic status. BP did not fall much further over the next three days so cerebral hypoperfusion is unlikely to explain his ongoing confusion. Would anyone like any further information at this point?

**Prof. Jennings:** What's happened to his creatinine and kidney function?

**Dr. Miller-Hodges:** His renal function has deteriorated somewhat and he has also now developed both hyponatremia and hypokalemia. There is also evidence of ongoing systemic inflammation. He isn't behaving quite as we'd expect.

**Dr. Laffer:** At least in our ICU, nicardipine confers a large volume load when you give it intravenously. So he's becoming overly diluted or volume-expanded. I can't tell you as a

nephrologist what to do about that, but that seems to be part of the problem. Also, is he still on cyclophosphamide?

**Dr. Miller-Hodges:** Yes, he was still prescribed oral cyclophosphamide, although this had been temporarily withheld. He is still on corticosteroids and was in fact prescribed hydrocortisone in the first few days of this admission to avoid a hypoadrenal crisis.

**Dr. Laffer:** In terms of blood-brain barrier and SIADH, that's now going to be a problem as well (i.e. cyclophosphamide may be directly contributing).

**Dr. Miller-Hodges:** Yes, indeed it is, thank you. Would anyone else like to suggest anything?

**Dr. Basile:** I would like to get a handle on his volume status. You have him on dual RAAS blockade. His renal function has deteriorated from 1.9 to 2.32, while all of this is going on. Would a plasma renin and a plasma aldosterone help in any way, or a non-invasive evaluation of cardiac output to peripheral vascular resistance, just to get a better handle on his volume status as it is often difficult to determine by clinical examination. I presume the urine output is good?

**Dr. Miller-Hodges:** Urine output was adequate rather than good.

**Dr. Basile:** So, you need to know which way to go when adding additional antihypertensive agents. I also remain concerned that he is on ramipril and valsartan (dual RAAS blockade) with renal deterioration at this point.

**Dr. Dhaun:** May I make a couple of comments at this point. At presentation, our patient had evidence of an acute fall in hemoglobin level. This was on a background of uncontrolled SLE. While the relative anemia might be a feature of accelerated phase hypertension, my worry was that it might represent the development of another autoimmune complication involving the neurological system. So perhaps we should be considering additional treatments for the autoimmune disease, such as plasmapheresis.

The other discussion we had at the time was whether we should give up on his kidneys and accept dialysis as the best option. We had already given our patient a lot of immunosuppression over a long period of time. He had suffered a number of infective complications and so perhaps sacrificing the kidneys was not the worst-case scenario. Indeed, it was likely that despite everything our patient was going to reach end-stage kidney failure in a relatively short time. At that point, or even before, we would have to consider the option of a kidney transplant. Given that this would be associated with a significant long-term immunosuppressive burden it might be better for our patient in the short term that we cut our losses, gradually withdraw the current immunosuppression and prepare for end-stage kidney failure.

**Dr. Basile:** In my practice, while I believe that measuring plasma renin and plasma aldosterone has a place when you are three drugs in and you are looking at what to do next, you could blindly add spironolactone as a fourth drug. While it may be difficult to interpret these levels in the setting of RAAS blockade, especially dual RAAS blockade, in my practice I think it still can be helpful. We did a study in Charleston published a number of years ago with Dr. Laragh. The group we found where knowing the plasma renin and plasma aldosterone levels was most helpful were those uncontrolled on three or more drugs. While Dr Laragh was a proponent of using the plasma renin as a deciding factor for the first drug chosen, we found it best in those with resistant hypertension.<sup>9</sup>

**Dr. Anna Oliveras:** For sure in this patient we must think of his uncontrolled autoimmune disease as the leading cause of hypertension. However, it should be interesting to

perform a renal Doppler-ultrasound, just to rule out a renovascular disease in this patient with such high and difficult-to-treat hypertension.

**Dr. Dhaun:** An excellent point, thank you.

### **Case Resolution**

Thank you for the suggestions. Renin and aldosterone levels were not checked given the confounding effect of dual RAAS blockade and fluid overload. Urinary catecholamines were normal and an MRI of his abdomen showed no adrenal masses and excluded renal artery stenosis.

With no evidence of infection, the posterior white matter changes evident on imaging, and neurologic findings that corresponded to the BP, we felt the diagnosis remained consistent with PRES. However, our patient's BP was unusually difficult to manage and he had ongoing evidence of active SLE. Both needed to be addressed. As has been suggested, we were now in a position to aggressively offload his salt and water excess using an aldosterone antagonist (spironolactone 100mg daily).

The SLE was treated with high-dose prednisone (40mg daily), plasmapheresis and full dose MMF. His BP improved rapidly, in the context of an 8L diuresis. He was discharged from hospital two weeks later with normal a neurologic examination but still requiring multiple antihypertensive agents (**Figure 5, A**). This requirement was transient, as his SLE rapidly went into remission over the next 6 weeks. He had complete resolution of his nephrotic syndrome, with proteinuria falling to <0.5g/day, and stabilization of renal function (**Figure 5, B and C**). Immunological markers of SLE activity also improved.

He was maintained on long-term dual RAAS blockade, a beta blocker and twice daily furosemide, with a clinic BP of 135/75mmHg. A repeat MRI at six months showed complete resolution of the previous changes.

### **PRES in SLE**

PRES describes a clinical neurological syndrome characterized by headache, seizures, altered mental status and typical radiological findings (white matter edema particularly affecting the posterior circulation). It is thought to arise from a failure of cerebral autoregulation in the context of an abrupt rise in BP. This leads to hyperperfusion and vasogenic edema. Patients with SLE are at increased risk of developing PRES due to a number of mechanisms outlined in **Table 1**.

### **Summary**

We present a case of hypertension and a hypertensive emergency in the context of active SLE. BP control was achieved with diuresis, RAAS blockade and aldosterone antagonism, as well as by aggressive management of the underlying SLE.

### **Sources of Funding**

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### Figure Legends

**Figure 1:** Initial glomerular histology. A, normal glomerulus. B, Class III (focal proliferative) and Class V (membranous) lupus nephritis. Single arrow: thickened capillary wall. Double arrow: focal proliferation.

**Figure 2:** Progression of lupus nephritis. A, renal function and immunosuppression, showing deteriorating renal function despite treatment. B, urinary protein loss and immunosuppression, showing heavy proteinuria.

**Figure 3:** BP and antihypertensive agents

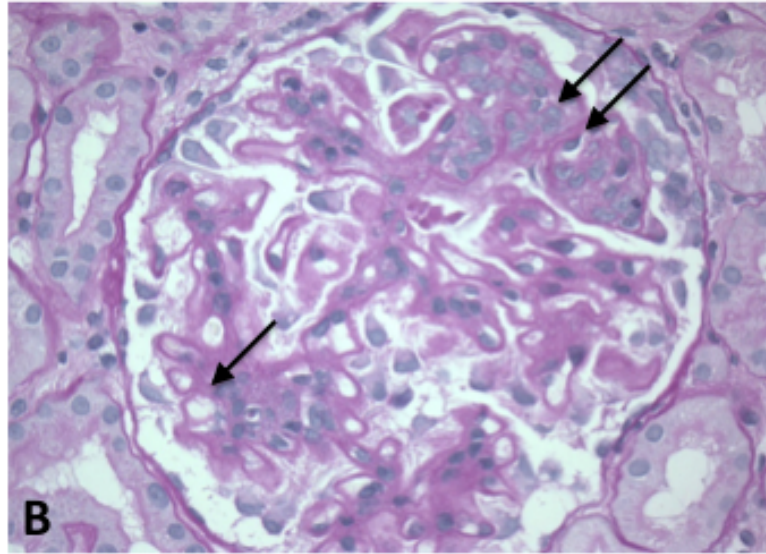
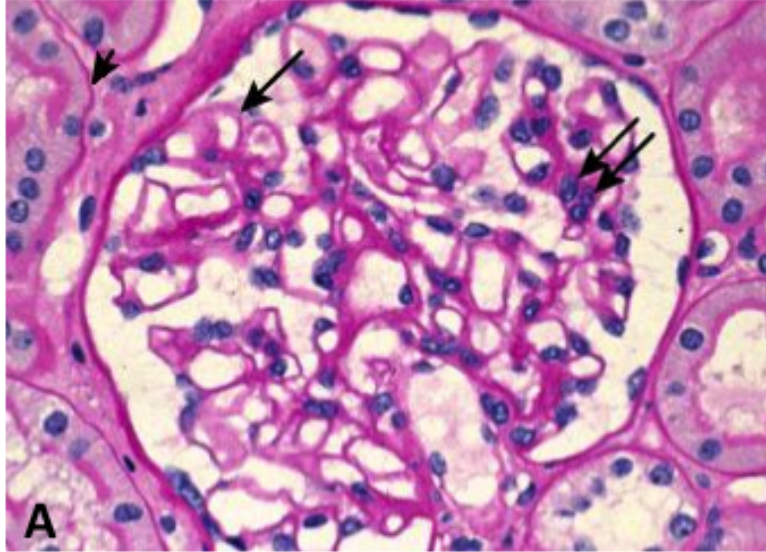
**Figure 4:** Brain imaging. A, Non-contrast CT Brain, showing areas of low attenuation in the posterior occipital regions. B, MRI brain scan, showing areas of hyperintense white matter changes in the posterior occipital regions.

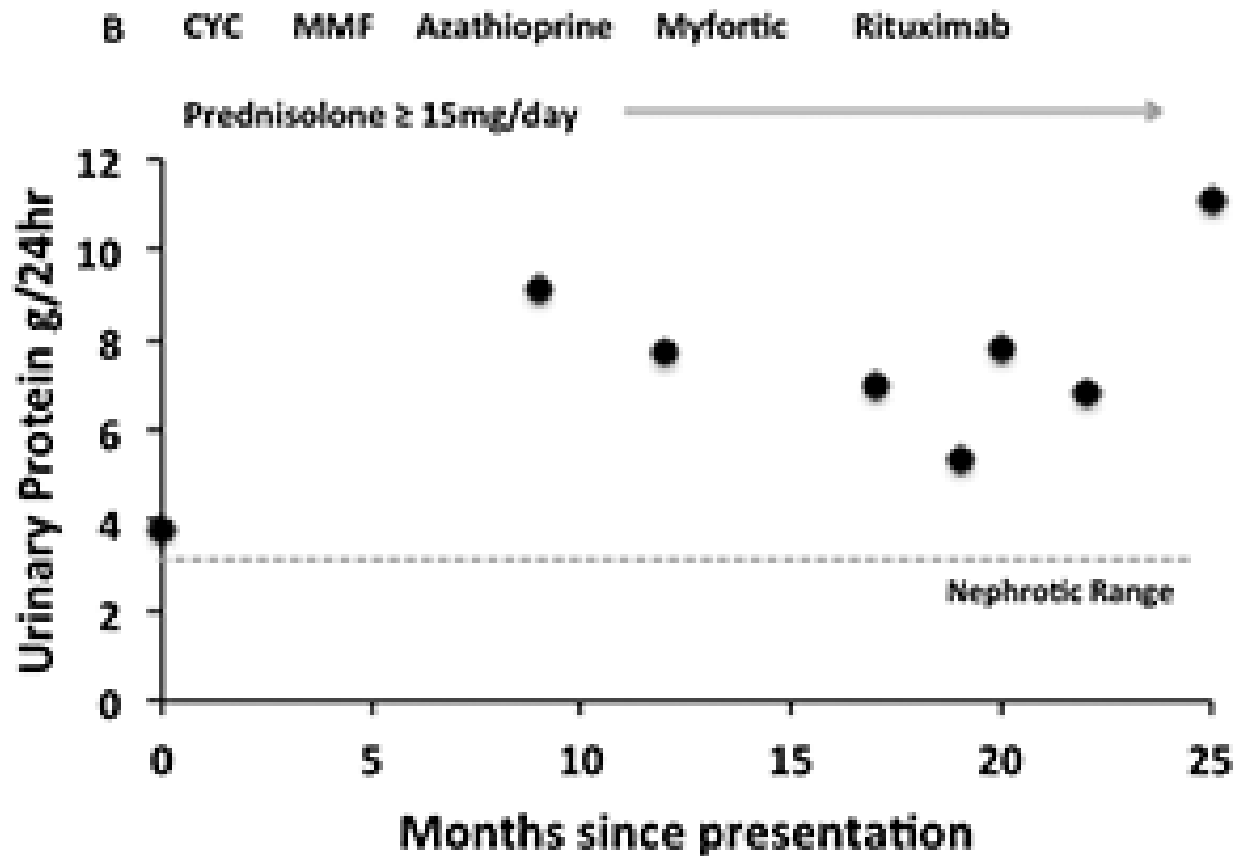
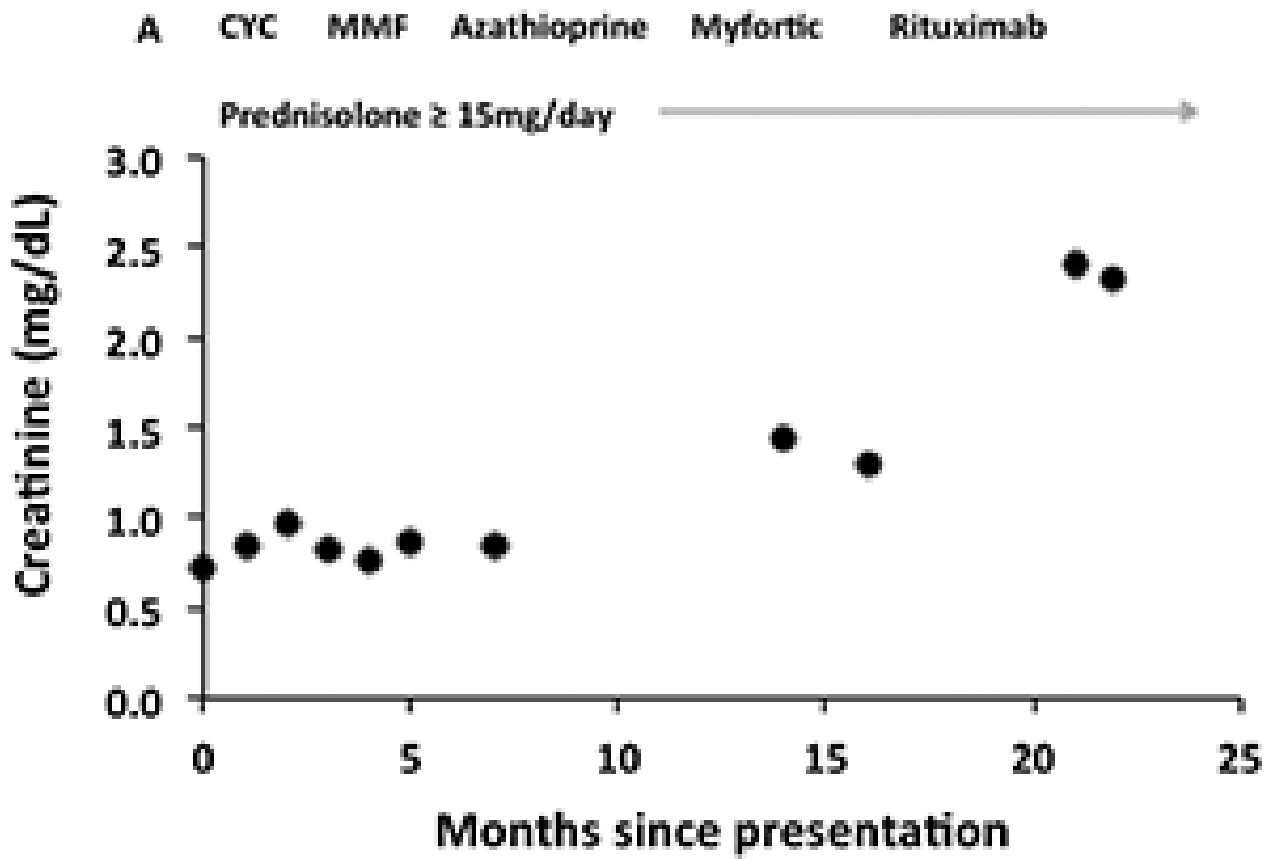
**Figure 5:** BP and proteinuria during acute presentation with seizures, and during recovery. A, BP and treatment during acute phase. B, BP and treatment during recovery. C, Proteinuria during recovery (g/24hrs).

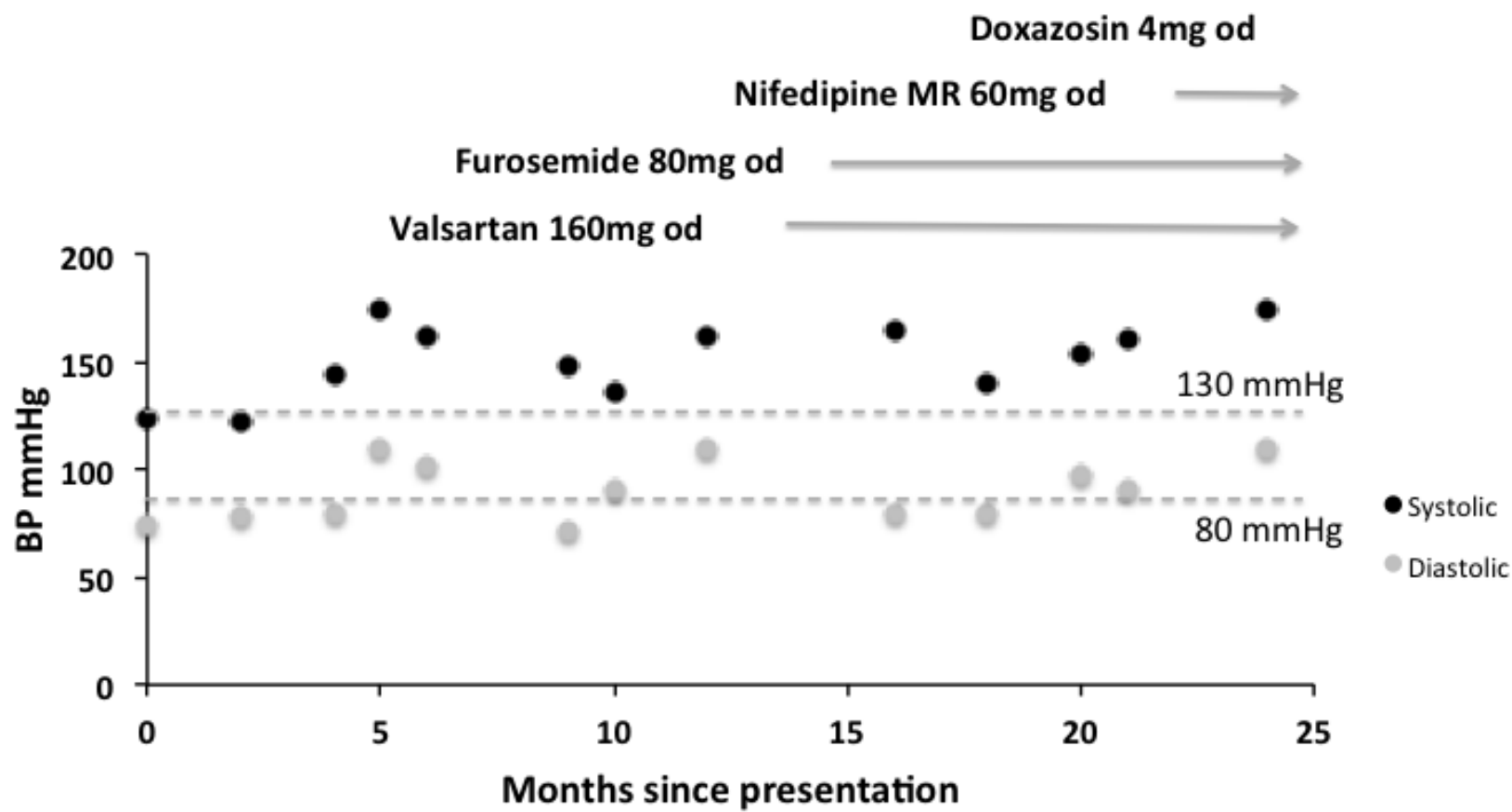


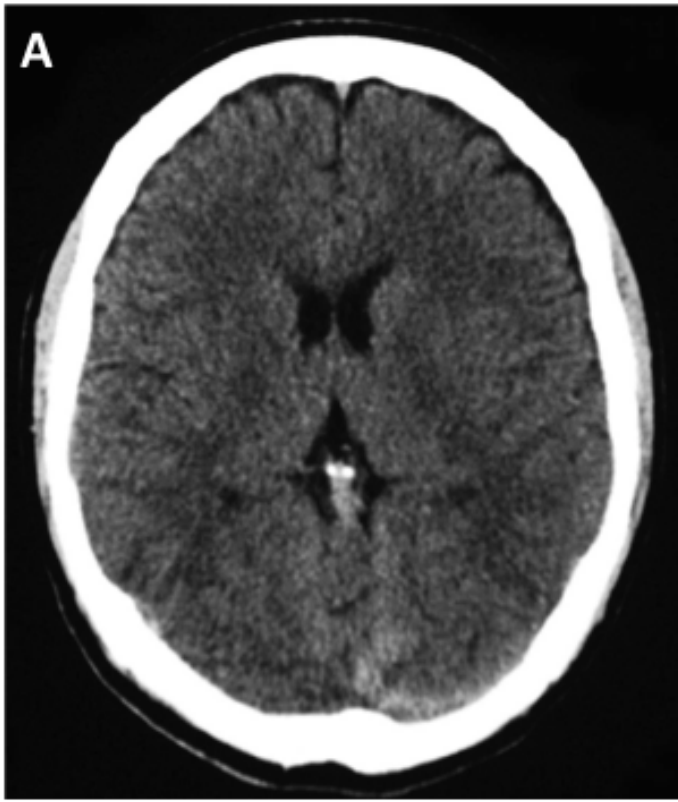
**Table 1: Risk Factors for PRES in SLE**

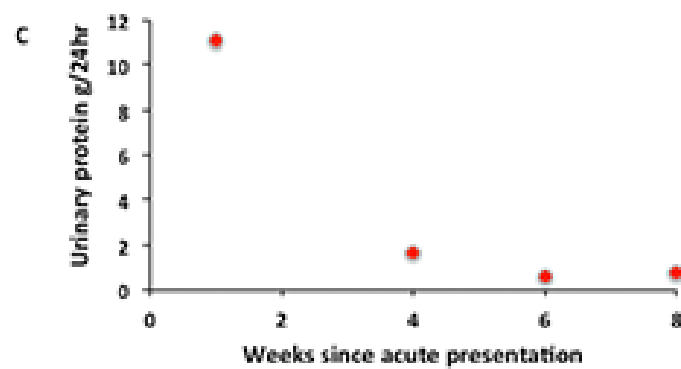
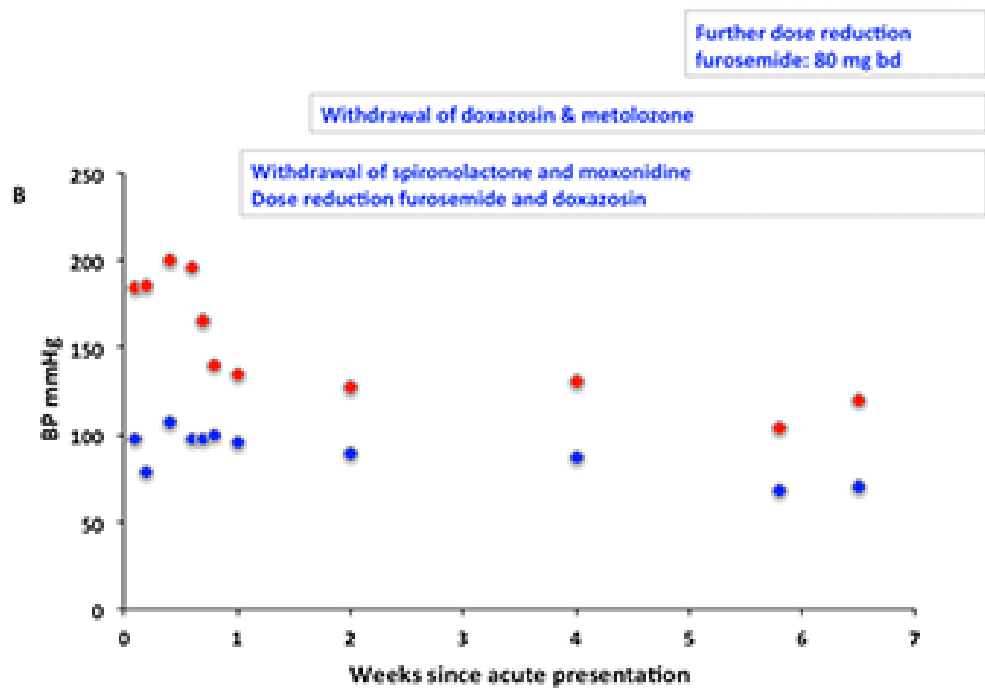
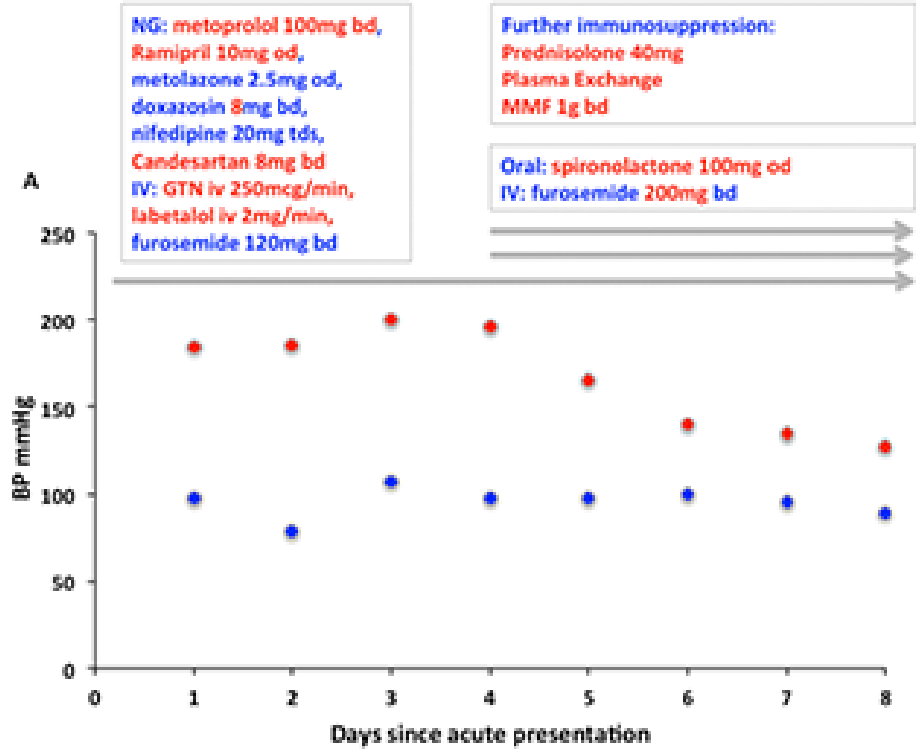
<b>Risk factor</b>	<b>Mechanism</b>	<b>Effect</b>
Immune-complex mediated endothelial damage <sup>10</sup> Endothelin-1 activation <sup>11</sup> RAAS activation <sup>12,13</sup> Pro-inflammatory cytokines <sup>14,15</sup> Cytotoxic drugs <sup>16</sup>	Endothelial Dysfunction <sup>17</sup>	Compromise integrity of blood-brain-barrier Compromise cerebrovascular autoregulatory mechanisms
Renal impairment <sup>18</sup> Hypertension <sup>19</sup> Fluid retention <sup>16</sup>	Endothelial dysfunction Cerebral hypertension	Compromise cerebrovascular autoregulatory mechanisms
Young age <sup>20</sup> Lymphopenia <sup>20</sup> Dyslipidemia <sup>20</sup>	Associations (mechanism unknown)	













## Supplement

### Hypertension and its complications in a young man with autoimmune disease

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**Table S1: Laboratory Investigations. Abnormal results indicated by \*.**

<b>Test</b>	<b>Result</b>	<b>Reference Range</b>
<b>A Initial Investigations</b>		
Creatinine, mg/dL	0.80	(0.67 - 1.36)
Creatinine, $\mu$ mol/L	69	(60-120)
Albumin, g/L	25*	(35 - 50)
Urinalysis	Blood <sup>++</sup> , protein <sup>++++</sup>	
Urinary protein, g/24hours	3.90*	(<100mg)
C3, g/L	0.49*	(0.75 - 1.65)
C4, g/L	0.09*	(0.14 - 0.54)
Anti dsDNA, U/L	>200*	(0 - 10)
Anti Ro, U/L	>100*	(0 - 25)
Anti La, U/L	>100*	(0 - 25)
Anticardiolipin IgG, GPLU/ml	4	(0 - 10)
Anticardiolipin IgM, MPL	1.50	(0 - 9.8)
Lupus anticoagulant	Negative	
Platelets, x 10 <sup>9</sup> /L	284	(150 - 350)
Lymphocytes, x 10 <sup>9</sup> /L	0.48*	(1.5 - 4.0)
CRP, mg/L	13	(1 - 5)
ESR, mm/hr	102*	(0 - 10)
Cholesterol, mmol/L	6.6*	
Urate, mmol/L	0.28	(0.12 - 0.36)
Echocardiogram	Normal LV size Good systolic function	
Fundoscopy	Normal	

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**B Investigations at acute presentation with seizures**

Hemoglobin, g/L	79*	(135 - 180)
WCC, × 10 <sup>9</sup> /L	9.6	(4.0 - 11.0)
Platelets, × 10 <sup>9</sup> /L	261	(150 - 450)
CRP, mg/L	139*	(0 - 5)
BUN, mg/dL	35.9*	(7 - 18.5)
Urea, mmol/L	12.8*	(2.5 - 6.6)
Creatinine, mg/dL	1.98*	(0.67 - 1.36)
Creatinine, μmol/L	175*	(60 - 120)
Sodium, mM	132*	(135 - 145)
Potassium, mM	4.4	(3.6 - 5.0)
H <sup>+</sup> , nM	81.3*	(35 - 45)
Lactate, mM	12.0*	(0.5 - 2.2)
Urinary metanephrine, μmol/24hr	1.3	(0.4 - 3.4)
Urinary normetanephrine, μmol/24hr	0.5	(0.3 - 1.7)

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**Table S2: Factors contributing to hypertension**

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<b><i>Traditional Risk Factors</i></b>
• Race
• Renal disease
• High dietary salt intake
<b><i>Lupus-related / specific risk factors</i></b>
• Systemic inflammation
• Glucocorticoids
• Nephrotic syndrome
• Endothelial dysfunction: <ul style="list-style-type: none"><li>○ Immune-complex mediated endothelial damage</li><li>○ Endothelin-1 activation</li></ul>
• Renin-angiotensin-aldosterone system (RAAS) activation

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**Figure S1: later glomerular histology**

Biopsy 2: Class IV (proliferative) & Class V (membranous) lupus nephritis. Single arrow: gross thickening of the capillary basement membranes; double arrow: proliferation throughout the glomerulus

