Resistant Hypertension in a Dialysis Patient

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The following case was presented on 23 June 2019 as part of the Clinical-Pathological conference chaired by Anna F. Dominiczak and Rhian M Touyz at the European Meeting on Hypertension and Cardiovascular Protection in Milan, Italy. Peter Gallacher and Neeraj Dhaun presented the case.

Case Introduction

We present a case of resistant hypertension in a patient with chronic kidney disease (CKD). The patient is a 41-year-old woman who first presented to her general practitioner (GP), almost 20 years ago, with peripheral edema and lethargy. She is a lifelong smoker and is obese. Her past medical history includes asthma and cervical spondylosis. The reason for referral to the renal team was dipstick-positive proteinuria in the context of low-serum albumin.

As this case is from Scotland, the majority of results will be reported in SI units. In the context of a 24-hour urinary protein excretion of almost 4 grams per 24 hours, hypoalbuminemia of 25 grams per liter, and clinical evidence of peripheral edema bilaterally to her knees, a diagnosis of nephrotic syndrome was made. The patient's renal function and blood pressure (BP) were normal at this stage.

Some of her initial blood results are shown in Table 1. She was not anemic and had normal white cell count and inflammatory markers. However, her serum cholesterol and triglycerides were markedly elevated. An immunology screen was negative, as was blood-borne virus serology.

Pictures of the patient's renal biopsy, from which she was diagnosed with primary membranous nephropathy are shown in Figure 1. On the left there is evidence of glomerular basement thickening; on the right, there is evidence of granular IgG deposition, which is typical for this disease. Membranous nephropathy is a cause of nephrotic syndrome in adults, and over four-fifths of cases are associated with increased levels of phospholipase A2 receptor antibodies. Hypertension is present in up to half of patients with membranous nephropathy at the time of diagnosis.

At the time of presentation, 20 years ago, management of membranous nephropathy largely revolved around the treatment of BP and proteinuria. In keeping with this, the patient was commenced on an angiotensin-converting enzyme (ACE) inhibitor and loop diuretic.

The patient's BP readings over the first 12 months are shown in Figure 2A.

The patient's BP increased over the first six months after diagnosis, despite a doubling in doses of both the ACE inhibitor and loop diuretic. Although no longer routinely practiced in the United Kingdom, the patient also received an angiotensin receptor blocker (ARB) at four months to provide dual blockade of the renin-angiotensin system (RAS). The patient's excretory function remained within the reference range for the first six months (Figure 2B). Despite this treatment, the patient remained heavily proteinuric and hypoalbuminemic (Figures 2C and D).

In summary, the patient had clinical features of ongoing nephrotic syndrome, with increasing clinic BP readings. For discussion, is there any additional information you would like to know at this stage? What are the key factors driving this patient's hypertension? Are there any suggestions for ways in which we can manage this patient's BP at this stage?

Discussion

> **Prof. Dominiczak:** Why would you combine ACE inhibitor and ARB? All guidelines say no, in red, in very big letters.

Dr. Dhaun: That is an excellent question, thank you. This case is from around 20 years ago and it was managed by nephrology. At that time, most management of nephrotic syndrome was targeted at reducing proteinuria. The drugs with the best evidence to do this in CKD are ACE inhibitors or ARBs. Either drug alone will reduce proteinuria by around 30-50%. The effect of adding in the second agent is to give an additional reduction in proteinuria of around 10-20%. This is due to additive blocking of the RAS, with combination treatment giving up to about 90% RAS blockade. In current times, we would try and avoid dual RAS blockade.

What other information would you like? We have a lady in her early 40s with nephrotic syndrome.

Dr. Nademi: I'm Dr. Nademi from Iran, intervention cardiologist. I want to know about kidney imaging data: sonographies, CT, angiography.

Dr. Dhaun: Thank you for your question. As this lady underwent a kidney biopsy, she had an ultrasound scan of the kidneys at the same time. This was unremarkable.

Dr. Nademi: What about renal arteries? Was there any evaluation, including scan or angiography?

Dr. Dhaun: We did perform doppler ultrasonography and this demonstrated no compromise of renal blood flow. At that time, we did not proceed to a CT scan or formal angiography.

Dr. Adamczak: I've got one remark. Do you use furosemide? The patient has normal kidney function at this stage of CKD.

Dr. Dhaun: Yes, the patient was already prescribed a loop diuretic.

Dr. Adamczak: Taking into account anti-hypertensive properties, first of all, you should use a thiazide or thiazide-like diuretic. The antihypertensive properties of these agents are more potent than loop diuretics. Therefore, if the patient has good kidney function, you should start with the thiazide or thiazide-like diuretic. Second question, what is the treatment of underlying diseases? Were steroids, cyclosporine A, or tacrolimus used, or were you just waiting?

Dr. Dhaun: In response to your first question about the choice of antihypertensive, this patient had nephrotic syndrome, and, in the renal community, we would probably choose an RAS blocker first-line, probably an ACE inhibitor. In terms of managing fluid overload alongside this in context of nephrotic syndrome, we would probably choose a loop diuretic first. We may then add in a thiazide diuretic. In response to your question about the treatment of underlying membranous nephropathy, this case is from 20 years ago and, at that time, perhaps even now, standard of care is conservative management, that is, BP and proteinuria control, for six months. In this case, we are still within that 6-month window.

Dr. Mallamaci: First, I'd like to have a 24-hour profile of the patient, then maybe a calcium channel blocker.

Dr. Dhaun: I think those are excellent suggestions.

Prof. Touyz: It was interesting that, as you added more drugs, the BP went up. I'm going to ask you about the doses of the drugs you used, particularly with respect to candesartan and patients with proteinuria. Around 10-12 years ago, there was the notion that doses that were being used were suboptimal. In fact in 2009, a study by Ellen Burgess and her colleagues in Calgary showed that supramaximal doses of candesartan had some benefit in patients with hypertension and proteinuric kidney disease. I'd be curious to know if you would have considered that at this point?

Dr. Dhaun: Indeed, supra-therapeutic doses of ARB were in vogue at that time. In the U.K., the maximum licensed dose of candesartan is 32 mg daily. In this patient we went as high as 64 mg daily. There was some data at that time suggesting that doses as high as 128 mg might be beneficial for maximum proteinuria reduction. There may be worries about combining an ACE and an ARB in patients with CKD, especially in those with nephrotic syndrome, which is characterized by a state of intravascular volume depletion. With dual RAS blockade in this context, a renal 'hit', such as diarrhea or vomiting, may precipitate acute kidney injury.

Dr. M. Barigou: We didn't discuss the risk factors contributing to hypertension in this case. This patient is obese, and she has a renal disease with a massive proteinuria, which are three major risk factors contributing to her hypertension. To improve her blood pressure, we should appropriately treat every one of these identified risk factors. Moreover, concerning hypertension management, we have data comparing sequential RAAS blockade versus nephron blockade in CKD patients, and we know that the latter is probably more efficient by inducing a large and well-tolerated reduction in blood pressure via a progressive increase in sodium depletion (ref: Bobrie G, Frank M, Azizi M, et al. J Hypertens. 2012;30(8):1656–1664).

Dr. Dhaun: These are all important points that we will cover as the patient's journey continues.

Prof. Touyz: Perhaps we'll address the case, and then we can bring up more discussion in a little while.

Case Progression

Twenty-four-hour BP monitoring was performed and confirmed that the patient did indeed have sustained hypertension throughout the 24-hour period, without the expected 10% dip in overnight readings (Table 1). The patient's 24-hour urinary sodium excretion also suggested that her dietary salt intake was very high.

Both electrocardiogram (ECG) and echocardiogram were normal at this stage, and there were no abnormalities on fundoscopy. Serum and urinary cortisol were also normal, as were urinary metabolites. Broadly, general factors contributing to this patient's hypertension include underlying essential hypertension and her adherence to medications (Table 2). Lifestyle, as has been pointed out, is also very relevant, especially given we are from Scotland. For example, we know the patient was overweight, did not exercise, and consumed a diet relatively high in salt.

In terms of factors specific to the underlying membranous nephropathy, her persisting nephrotic syndrome will also lead to ongoing salt and fluid retention through activation of the RAS. There are also the effects of inflammation and autoimmunity, and all of these factors combine to contribute to vascular stiffening, accelerated atherosclerosis, and therefore worsened hypertension (Table 2).

There were also some excellent suggestions regarding a treatment strategy. What we did in the first instance was maximize the ARB, and thereafter attempted to introduce a fourth agent, namely amlodipine. Unfortunately, this was not tolerated by the patient, due to worsening of her leg swelling, whilst atenolol was contraindicated due to the history of asthma.

Consequently, the patient was commenced on the rate-limiting calcium channel antagonist, verapamil. However, as can be appreciated from Figure 3, it made little impact on the patient's clinic BP readings, which continued to average between 160 and 170 mmHg for systolic BP, and 90 to 100 mmHg for diastolic BP.

The patient's renal excretory function also started to decline about six months after her initial diagnosis, with estimated glomerular filtration rate (eGFR) dropping from around 45 to 25 ml/min/1.73 m^2 over a period of 12 months (Figure 3). Perhaps unsurprisingly, the patient continued to have heavy proteinuria, and remained hypoalbuminemic, with an albumin mostly in the range of 15 to 20 g/L.

One year following initial presentation, blood results demonstrated a new anemia, most likely as a consequence of the declining renal function. Supplementary Table 1 is a summary of the patient's investigations at 12 months. Are there any suggestions regarding a management strategy for the patient's hypertension at this stage?

Discussion

Dr. Zoghby: You mentioned in your earlier slide about the salt intake, which is a very important factor here. If a patient is on a high-salt diet, you're not going to accomplish much progress in controlling the hypertension without limiting the salt intake. In addition, the patient has severe nephrotic syndrome with volume overload, so maybe the diuretic dose is not optimal. If she is volume overloaded, you can add six or seven antihypertensives without improvement unless her volume status is controlled.

Dr. Dhaun: I agree with your comments, and, as I'm sure this audience is aware, reducing salt intake *per se* reduces both BP and proteinuria. I agree that trying to target these general lifestyle factors is very important. In terms of the diuretic dose, we are not scared as nephrologists to give doses of furosemide up to 500 mg a day. It is usually once the loop diuretic dose is optimized that we consider adding in additional classes of diuretics.

Dr. Mallamaci: Did you say you were sure she was non-dipper?

Dr. Dhaun: She was a non-dipper. That's right, yes.

Dr. Mallamaci: What about sleep apnea?

Dr. Dhaun: That's a good question. I remember this patient well and her physical characteristics supported a diagnosis of sleep apnea She snored at night and complained of daytime somnolence but had not received an official diagnosis of sleep apnea.

Dr. Adamczak: The patient’s CKD is still progressing. The first issue is reduction of salt intake. What kind of advice was given to the patient?

Dr. Dhaun: In the renal clinic, we advise limiting dietary salt intake and suggest ways to do this: salt alternatives, not adding salt to cooked food, avoiding foods such as processed meats and white bread that contain a lot of salt. Unfortunately, many patients will not adhere to the diets prescribed.

Dr. Adamczak: It is not enough to say to a patient, "Eat less salt." But it's necessary to advise to avoid processed food, which is the most important source of sodium in the diet; 85% of sodium in the diet comes from processed food. That is why these instructions should be more complex, not just, “don't use salt.” Patients should be advised to reduce processed food intake and replace them with fresh food products. This is the first point. Second, the progression of CKD in this patient is still ongoing. Therefore, it's urgently necessary to reduce BP. What can we do? First of all, we can give a calcium channel blocker, but maybe another one, lercandipine, which doesn't give peripheral edema. We can start the treatment with doxazosin. It would be perfect, especially in this case, in a non-dipper, because we can start this treatment with the dose of doxazosin in the evening. It helps to mimic the physiological blood pressure dipping pattern. Therefore, my suggestions are: on every visit, discuss salt intake, start treatment with doxazosin with small doses, and then escalate the dose and maybe try another calcium channel blocker.

Dr. Dhaun: Those are all excellent suggestions. Doxazosin is a good antihypertensive to choose. As this case was from around 20 years ago, the importance of diurnal BP variation and its links to outcome were not as well understood as they are now. Additionally, the concept of chronotherapy, that is, giving some antihypertensive medications at night, to exaggerate the nocturnal dip in BP in order to improve patient outcomes, did not really exist, at least not in renal circles. In terms of reinforcing the avoidance of processed food, this was difficult as the patient’s clinic attendance was sporadic.

Dr. Krekels: Mariella Krekels from The Netherlands. Maybe I missed it because everybody talks very fast, but what did happen to her weight when you installed the furosemide? Because I think if she didn't lose weight, the first thing I should do is advise the loop diuretic.

Dr. Dhaun: An excellent point, as weight provides a good measure of fluid balance, provided it is done on the same set of scales, at the same time of day, with the same clothing. The patient came to the same renal clinic, so weight assessments were probably reliable. Weight was rising, alongside the clinical assessment of increasing peripheral edema. This, alongside the declining renal function, prompted us to increase the dose of furosemide. You'll see what happens in just a bit.

Prof. Dominiczak: You’re now giving her lots of drugs. Lots of everything, and you're not having an effect. Have we checked the adherence? Because if the patient is not coming to the clinic and takes so much salt, despite your advice, I am getting suspicious. That's number one. Secondarily, the six months, the magic six months of nephrology have now passed. Is the process in the kidney getting very, very severe? Are we now not just idle membranous nephritis, does that become some rapidly progressive story?

Dr. Dhaun: In response to the adherence issue, we did consider this being an issue, reflected by the poor clinic attendance, and that weight was increasing with a combination of drugs that work in the majority of people. The patient did have one or two admissions to receive intravenous diuretics and, during these, with observed dosing, that is, us making sure she was taking her tablets, BP remained high. Then, in response to whether we are now reaching the point where the decline in renal function

reflects underlying worsening of renal disease, in this case, membranous nephropathy, absolutely, and we shall see what happens in a second.

Dr. Barigou: Concerning the management, my colleagues suggested to increase furosemide. But I think that we should add an effective long-acting thiazide diuretic (chlortalidone or indapamide) just to optimize nephron blockade at different sites, which would induce a higher natriuretic effect. Moreover, I would propose to add a GLP-1 receptor agonist which will have at least four benefits: improving her obesity, lowering her blood pressure, improving her renal disease, and decreasing her cardiovascular risk (ref : Pi-Sunyer X, Astrup A, et al. N Engl J Med. 2015;373(1):11–22). This would be the ideal strategy for me.

Dr. Dhaun: I think if we were treating this lady now I would agree that management would probably be different.

Dr. Zoghby: I agree with some of the suggestions. However, this patient has been on a lot of medications, but we are not addressing the primary underlying process. We know that she has a severe nephrotic syndrome, right? She has significant proteinuria. Therefore, by definition, her BP is driven by heavy salt intake and volume overload. So really, the first step is to control the volume. The second step is controlling the underlying disease (membranous nephropathy). I also failed to mention another observation. As a nephrologist, I note that the kidney function declined very quickly and, in the setting of severe nephrotic syndrome, one should consider the possibility of renal vein thrombosis contributing to her picture as well.

Dr. Dhaun: Those are all excellent points. The one I'll comment on, in the interest of time, is the last one about renal vein thrombosis. At that time, we didn't generally anticoagulate patients with membranous nephropathy, which I think we would do now. The clinical picture associated with a renal vein thrombosis tends to be an acute decline in renal function, often with a sudden increase in peripheral edema. The decline in renal function here was quite gradual. I agree with you about treating the underlying disease. It is noteworthy that this case is before the era of screening for antibodies against the phospholipase-A_2 receptor.

Dr. Kirpalani: Is it possible that she was taking some other medications? I missed the age, but certainly end-stage and contraceptive.

Dr. Dhaun: She's 41.

Dr. Kirpalani: Oh no, unlikely. But are there additional medications which she might have been taking?

Dr. Dhaun: Actually, you make a very good point. She was 41, but there were no hormonal treatments that she was taking. Additionally, given the diuretic-resistant edema, one might consider non-steroidal anti-inflammatory agents, but there was no suggestion of these.

Prof. Touyz: Perfect. I think we'll move on in the interest of time. We'll have time in the next little series to ask further questions, but let's see how the patient progresses.

Case Progression

First of all, and as has been suggested, we increased the dose of the loop diuretic. That was predominately due to issues with persistent peripheral edema. An attempt was also made to introduce a fifth antihypertensive agent, an alpha blocker. Unfortunately, the patient failed to tolerate this due to headache. As a result, the centrally acting antihypertensive moxonidine was introduced around 12 months after the diagnosis.

Additionally, we thought the blood pressure was being driven by the underlying active renal disease. As nephrologists, we love to give immunosuppression and so we started the patient on immunosuppression during this period. At that time, around 20 years ago, there was no consensus on the optimal immunosuppressive regimen for primary membranous nephropathy, meaning the patient received numerous different agents during the course of her treatment (Figure 3). Despite the immunosuppression, the patient's excretory function declined further before stabilizing around a GFR-15, and the patient continued to have nephrotic range proteinuria and an albumin of less than 20.

Just over two years after her diagnosis, the patient was admitted to hospital with a fluctuating Glasgow Coma Scale (GCS) score and brief observed episodes of left-lateral gaze deviation, involuntary eyelid twitching, and nystagmus. The patient was markedly hypertensive on admission, with a BP of 225/130 mmHg. In addition to the antihypertensives listed, the patient was prescribed erythropoietin and oral glucocorticoid.

There were some changes secondary to long-standing hypertension evident in both ECG and echocardiogram, although fundoscopy was normal. The patient's computed tomography (CT) and magnetic resonance imaging (MRI) brain scans were also normal. Given the patient's presenting features and marked hypertension, a diagnosis of hypertensive encephalopathy was considered most likely. This diagnosis will not be covered any further during this presentation, as it has been discussed previously during a Clinico-Pathologic Conference in 2015 (see weblink).

Following this admission, we elected to stop all immunosuppression. Our team also reviewed the patient's lifestyle and adherence to treatment before commencing the thiazide-like diuretic metolazone. Over the subsequent years, the patient's BP remained problematic (Figure 4). The patient's admission with hypertensive encephalopathy unfortunately precipitated a significant deterioration in the patient's excretory function (Figure 4). She therefore received a pre-emptive renal transplant six years after her initial diagnosis. The patient's renal function improved modestly during the four years following the transplant. However, her residual function was still relatively poor, with an eGFR of around 20 ml/min/1.73 m^2.

She remained hypertensive, and at one year, some further investigations were conducted. The patient underwent repeat 24-hour BP measurement and, alongside this, we assessed 24-hour pulse wave velocity as a measure of arterial stiffness (Supplementary Table 2). Again, the patient was hypertensive, without the expected nocturnal dip in either blood pressure or arterial stiffness. Supplementary Table 2 is a summary of the patient's medication at this time, including her immunosuppressive regimen at one-year post-transplant. Why do you think the patient's blood pressure is proving so difficult to control post-transplant?

Discussion

Prof. Touyz: We have seen for the past 20 years since she first presented, that the BP medication has slowly increased in dosage, and we've added a number of new antihypertensive drugs. All of them seem to be at maximal or super-maximal concentrations. At what point do you think we should say, hang on a minute, how can we rationalize this and actually start removing some of these antihypertensive drugs? Because it seems, most likely, that all these extra drugs are probably not doing anything beneficial and maybe even some harm.

Dr. Dhaun: That is a very good point. I suspect we lost focus on the antihypertensives used as we probably paid more attention to the immunosuppression we had prescribed and the side effects of this. After this, given the patient had received a renal transplant, our focus would have shifted to potential immunological problems, such as rejection. I guess we might not have been as on the ball as we might have been at managing the hypertension and rationalizing its treatment.

Dr. Zoghby: I have a couple comments—one comment and one question. My comment: Obviously, it's not the case here, but one thing to exclude and discuss with a woman of reproductive age is pregnancy, as it can worsen an underlying hypertension or kidney disease. My question: Do we know whether her underlying membranous nephropathy is primary or secondary? We assumed it is primary, but do you think she could have, for example, lupus with a membranous presentation?

Dr. Dhaun: Very fair points.

Dr. Zoghby: And that's something we didn't talk about. Did she have systemic symptoms, such as a rash or joint swelling? Did she have any immunologic serology done, such as double-stranded DNA? Maybe you mentioned and I missed it.

Dr. Dhaun: Again, fair points. The patient was not pregnant, and this was confirmed via testing prior to giving any immunosuppression. In terms of your question about whether this could be a secondary membranous nephropathy, her renal biopsy showed positive immunofluorescence for IgG_4, supporting primary membranous nephropathy. Additionally, immunology showed no antibodies against double-stranded DNA and there was no clinical syndrome in keeping with systemic lupus erythematosus. As membranous nephropathy may be secondary to malignancy, some centers may perform CT scanning looking for evidence of this; we did not do this in this case as we felt that the histological features and the patient's progression was in keeping with primary membranous nephropathy.

Dr. Hiremath: Swapnil Hiremath from Ottawa. A couple of comments, which don't address the overall course but relate to the fact that she's on tacrolimus and erythropoietin beta. We think the hypertension caused by tacrolimus is due to vasoconstriction, which could be antagonized by calcium channel blockers, as she's on verapamil but she's not on the dihydropyridine calcium channel blockers throughout the course. The second one is that they (calcineurin inhibitors) also act on the thiazide-sensitive sodium channel, so she's not on a thiazide diuretic—those agents would be helpful.[1] The second comment, of course, is the role of erythropoietin (EPO) in hypertension.

Dr. Dhaun: Excellent. As you eloquently describe, one of the contributors to this lady's hypertension is likely to be the tacrolimus. Calcineurin inhibitors cause preferential afferent arteriolar constriction and

this may be countermanded by giving a calcium channel blocker that acts primarily to vasodilate the arteries. An example would be nifedipine, which is recognized, through the same mechanism, to improve eGFR in the post-transplant period. With regards to your comment on tacrolimus activating the thiazide-sensitive sodium channels, I hadn't thought of that! Finally, as you say, EPO, especially with its chronic use, contributes to hypertension.

Dr. Adamczak: First, what was the tacrolimus blood concentration? This is crucial, not the tacrolimus dose, but blood tacrolimus concentration. Tacrolimus dose should be adjusted to its current blood concentration. Tacrolimus blood concentration that is too high leads to calcineurin nephrotoxicity and blood pressure increase. Second, it's necessary to check renal artery stenosis of the transplanted kidney. The doppler ultrasound of the transplanted kidney renal artery should be done.

Dr. Dhaun: Thank you. You have made a lot of good points there. First, your question about tacrolimus trough levels. The patient had received a well-matched, donation after cardiac death, kidney transplant. In this setting, we tend to keep tacrolimus trough levels at 8-10 ng/L in the first six months post-transplant. Second, renal artery stenosis in a transplanted kidney is relatively common, but we excluded this on the basis of doppler ultrasound, which showed appropriate resistive indices. Additionally, this lady was on an ACE inhibitor, and in the setting of significant renal artery stenosis, one might expect this to be associated with an unacceptable and progressive decline in renal function.

Dr. Nademi: I want to know about the inflammatory parameters of this patient. For example,is the patient's C-reactive protein (CRP) concentration elevated? and NA. And also, in these years, does she develop something more in other organs like the lung, eye, and others?

Dr. Dhaun: This patient did have evidence of hypertensive end-organ damage. We described a trans-thoracic ECHO that demonstrated concentric left ventricular hypertrophy, and her proteinuria might well have contributed, in small part, to her hypertension.

Dr. Nademi: What about lung? Were there any new problems in the lung?

Dr. Dhaun: In the lung?

Dr. Nademi: Something like sarcoidosis?

Dr. Dhaun: No.

Dr. Nademi: New problem?

Dr. Dhaun: No. There were no obvious new problems that required us to investigate or image the lungs. In terms of the other question about immunology and inflammatory cascade, the problem with CRP in these patients is you often will see a low-grade CRP response post-transplant, with levels of 10-20 mg/L. However, immunology remained negative, and this is about to become relevant!

Dr. Kirpalani: The general dictum is usually one disease, but did you look at renin and aldosterone levels? I mean there might have been primary, which might be hiding in a micro-nodule or something.

Dr. Dhaun: That is a very fair point. When she was admitted with hypertensive encephalopathy, she underwent CT scanning. That didn't show any obvious macro-nodules. The patient had also had 24-hour urinary metanephrines done at presentation and these had been normal.

Case Progress

So, in addition to the factors contributing to this patient's hypertension that we have discussed previously, we have the immediate effects of immunosuppression, including calcineurin inhibitors, as well as the autoimmune response toward the transplanted kidney. There are changes in vascular structure and function that predate the transplant. They improved somewhat following transplantation, but nevertheless remain significant. Finally, chronic EPO administration is associated with increases in arterial BP. This may be related to changes in the production or sensitivity of endogenous vasopressors, or as a direct result of basal constrictive effects of EPO itself (Table 2).

Unfortunately, around four years after she received her transplant, the patient experienced recurrence of membranous nephropathy in her graft, confirmed by repeat renal biopsy. This occurs in around one-third of such patients. Within 24 months, she'd reached end-stage renal failure, and had commenced hemodialysis.

BP remained as much of a problem for this patient, even after commencing hemodialysis, with readings averaging around 150 systolic and 90 diastolic (Figure 4). Metolazone was stopped shortly after commencing hemodialysis because the patient had started to lose her native urine output.

For our next discussion point, why does this patient remain hypertensive? And how would you manage her hypertension at this stage?

This woman is now on hemodialysis and in her early 50s.

Discussion

Dr. Hiremath: I don't know why she is hypertensive now; I think we have never managed to control her hypertension. In hemodialysis, especially given the data, which have come out recently. There was the Italian study a few years ago on carvedilol,[2] but then the small Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL)[3] from Dr Agarwal's group. She's not on a beta blocker. I often use beta blockers as first-line or second-line on hemodialysis patients.

Dr. Dhaun: Absolutely.

Dr. Hiremath: And there are some observational studies showing that, for end-organ damage, beta blockers are perhaps superior to other agents in hemodialysis patients.[4,5]

Dr. Dhaun: That is an excellent point. Beta blockers are perhaps the first-line antihypertensive agent in dialysis patients, partly because dialysis is arrhythmogenic. In this patient, we had previously tried atenolol but had had to stop this as it exacerbated her pre-existing asthma. You could argue we should have tried a cardio-specific beta blocker, and that's a fair point.

Dr. Adamczak: Indeed, during dialysis, the most important cause of the hypertension is overhydration. You should intensify fluid removal during dialysis to achieve so-called dry weight. The second important

point is sodium concentration in dialysis fluid. What was the current sodium plasma concentration in this patient? If sodium plasma concentration in this patient is higher than the sodium concentration in dialysis fluid and sodium is transferred to the patient according to concentration gradient, it leads to overhydration and to blood pressure increase. Therefore, it is important to make individual decisions concerning the sodium concentration in dialysis fluid. The sodium concentration in dialysis fluid should be slightly lower than that in the plasma of the patient.

Dr. Dhaun: Again, very good points. As you say, in dialysis patients, especially in those who have lost their native urine output, hypertension is largely dictated by dry weight. That is the fluid weight gain in between dialysis sessions. This is managed by asking the patient to limit their fluid intake and maximize the tolerated fluid removal on dialysis. As perhaps is evident, this was not the most adherent of patients, and trying to restrict fluid, especially when they take a lot of salt in their diet, is challenging. Regarding the second thing you pointed out about sodium, we had optimized the technicalities of her dialysis through sodium profiling.

Dr. Naumnik: My question is about what has happened to this graft? Could you perform a kidney biopsy? Maybe this patient had a relapse of the membranous nephropathy, or maybe it was a rejection? The second question is: what about immunosuppressive therapy? Was it withdrawn immediately?

Dr. Dhaun: That's a very good question. She lost her transplant due to recurrence of membranous nephropathy and we performed a biopsy to show that. The biopsy didn't show any evidence of rejection. When the patient started hemodialysis, the graft was left in situ. In such patients, we leave some immunosuppression in place in order to prevent formation of new antibodies, which might make a future transplant difficult.

Prof. Touyz: Can I ask one question regarding the diuretics that you've used. You've used quite a number. I haven't seen any mineralocorticoid receptor blockers, such as spironolactone, and I'm just curious, in terms of the accelerated vascular aging and target organ damage. Any thoughts about spironolactone?

Dr. Dhaun: That's an excellent point. In relation to spironolactone, we all appreciate that this is helpful for its cardiovascular benefits, especially in those with CKD. The issue in this patient was that we had somebody with gradually worsening renal impairment who's already on an ACE inhibitor, and her potassium was running at the upper end of what is deemed acceptable. Thus, any episode of acute kidney injury might precipitate a hyperkalemic crisis for us; for example, if she took an NSAID for a headache, or if she had an episode of volume depletion due to diarrhea. From the diuretic side of things, this patient had now lost her urine output by the time she was established on hemodialysis.

Prof. Dominiczak: A quick additional point. If we assume she took every tablet you ever prescribed, and this is an assumption, was there, as our colleagues said before, another condition somewhere? Some tubular defect, something very rare, that was reabsorbing sodium that shouldn't be reabsorbed? Maybe some syndrome we don't know yet? Help us.

Dr. Dhaun: I think that's a very fair point. I think the problem in this setting is that you have a known underlying glomerular disease (membranous nephropathy), so trying to segregate tubular function,

which is affected by glomerular function, is very difficult. Nowadays we might be helped by genetic profiling, but this was not widely available to us then.

In Conclusion

Excellent suggestions have come from the audience, and certainly an important factor at this stage, which we've covered briefly, is dialysis adequacy. The patient was troubled by persistent uremia, volume overload, and difficulties in removing fluid during dialysis, all of which will have contributed to her high BP readings. There will also be contributory effects from her previous transplant, as well as renal vascular changes and disordered bone metabolism, as already highlighted. Finally, two factors that have been relevant throughout this patient's journey are her adherence to antihypertensive medication and her excessive dietary salt consumption.

In the first instance, we increased the amount of fluid removed during each dialysis session. We also optimized dialysis efficacy through a combination of longer sessions, greater use of biocompatible membranes, and a trial of hemodiafiltration to remove more middle-sized molecules.

Summary

In summary, resistant hypertension is an important diagnosis, especially in patients with CKD, and is a problem that is attracting increasing recognition. Indeed, observational studies report a highly variable prevalence for resistant hypertension, ranging between 2 and 30%,[6] depending partly on how it is defined. It is therefore important to consider terminology used in this area. For example, resistant hypertension is defined as sub-optimal BP control despite treatment with three or more antihypertensive agents of different classes, often including a calcium channel antagonist, an ACE inhibitor or ARB, and a diuretic.[7] Refractory hypertension is the term used to describe patients whose BP remains uncontrolled despite maximal antihypertensive treatment.[8] Another important concept is that of pseudo-resistant hypertension, which is resistant hypertension caused by something else, such as the white-coat effect, other medications, or inaccurate BP measurements.[7]

Regardless, resistant hypertension is significantly more common in patients with CKD and in patients with cardiovascular disease.[9,10] Perhaps unsurprisingly, resistant hypertension is also associated with an increased risk of cardiovascular events, with an approximately threefold higher risk of cardiovascular events, compared to patients with treated hypertension.[11]

Resistant hypertension is also associated with poorer renal outcomes. A sub-analysis of the ALLHAT trial demonstrated that progression to end-stage renal disease is almost two-fold higher in patients with resistant hypertension compared to normotensive patients.[12]

Finally, a word regarding our patient. There was no improvement in her BP over the following years. She remained on hemodialysis, but unfortunately suffered a fatal stroke at age 56, just 15 years after her initial diagnosis.

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Figure legends

Figure 1: Images of the patient's renal biopsy, from which the patient was diagnosed with membranous nephropathy. On the left panel is an image of a glomerulus, with red arrows indicating evidence of marked thickening of the glomerular basement membrane. On the right panel is an immunofluorescent image of a glomerulus with evidence of granular IgG deposition, which is typical for membranous nephropathy.

Figure 2: Graphs of the patient's clinic blood pressure readings (A), serum creatinine (B), urinary protein excretion (C) and serum albumin (D) results during the first 12 months following the patient's initial presentation and diagnosis.

Figure 3: Graph detailing the patient's clinic blood pressure readings, changes in antihypertensive medications and immunosuppressive regimen during the first two years after her initial diagnosis.

Figure 4: Graph illustrating the patient's clinic blood pressure readings throughout the fourteen years following her initial diagnosis, including changes in anti-hypertensive medications during this period. Lines with filled circle rather than an arrowhead indicate approximately when that antihypertensive medication was stopped

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Table 1. Results of initial investigations.

	Results	Reference Ranges
Results of initial blood tests		
Creatinine, mg/dL	0.77	(0.67-1.36)
BUN, mg/dL	8.4	(7.0-18.5)
Sodium, mmol/L	137	(135-145)
Potassium, mmol/L	4.2	(3.5-5.0)
Albumin, g/L	24*	(35-50)
Hemoglobin, g/dL	140	(135-180)
WCC, $\times 10^9$/L	10.6	(4.0-11.0)
Platelets, $\times 10^9$/L	201	(150-450)
CRP, mg/L	8*	(0-5)
Cholesterol, mmol/L	6.2*	
Triglycerides, mmol/L	7.4*	(0.8-2.1)
Bilirubin, µmol/L	16	(3-21)
ALT, IU/L	22	(10-50)
ALP, IU/L	84	(40-125)
Autoantibody screen (ANA, ENA screen, PR3, MPO, anti-GBM, anti-CCP)	negative	
HBV/HCV/HIV	negative	
Early morning serum cortisol, nmol/L	400	
Results of urine tests		

Protein excretion, g/24h		3.9*	(<0.15)
Sodium excretion, g/24h		3.9*	(<2.3 [AHA]/<2.0 [WHO])
Salt excretion, g/24h		10*	(<6.0 [AHA]/<5.0 [WHO])
Cortisol, nmol/24h		146	(20-180)
Metanephrine, µmol/24h		0.4	(0.3-1.7)
Normetanephrine, µmol/24h		0.9	(0.4-3.4)
Results of other tests			
ECG		sinus rhythm, no abnormalities	
Echocardiogram		normal left ventricular size, good LVSF	
Fundoscopy		normal	
24h ABPM			
Systolic BP, mmHg	Day	164*	
	Night	160*	
Diastolic BP, mmHg	Day	104*	
	Night	98*	

Reference ranges are shown in brackets. Abbreviations: ALT, alanine transferase; ALP, alkaline phosphatase; ABPM, ambulatory blood pressure monitoring; AHA, American Heart Association; ANA, anti-nuclear antibodies; BP, blood pressure; BUN, blood urea nitrogen; CRP, C-reactive protein; CCP, anti-cyclic citrullinated antibodies; ECG, electrocardiogram; ENA, extractable nuclear antigen antibodies; GBM, glomerular basement membrane antibodies; LVSF, left ventricular systolic function; MPO, myeloperoxidase antibodies; PR3, proteinase-3 antibodies; WCC, white cell count; and WHO, World Health Organization. *Indicates value outside the reference range.

Table 2. Summary of factors contributing to patient's hypertension.

General Factors
Essential hypertension
Patient adherence
Lifestyle
Salt intake
Weight
Physical exertion
Factors associated with underlying primary membranous nephropathy
Nephrotic syndrome
Activation of renin angiotensin system
Systemic inflammation
Auto-antibodies: immune-complex mediated endothelial damage
Endothelin-1 activation
Factors associated with advanced kidney disease
Premature arterial ageing and renovascular disease
Accelerated arteriosclerosis, atherosclerosis and endothelial dysfunction
Vascular calcification (secondary hyperparathyroidism)
Increased arterial stiffness, impaired baroreflex sensitivity and autonomic dysfunction
Erythropoietin administration
Associated changes in the production or sensitivity of endogenous vasopressors
Direct vasoconstrictive effect of erythropoietin

Adequacy of dialysis

Persistent uremia, volume overload and inadequate fluid removal

Factors associated with renal transplantation

Immunosuppressive medication, e.g. calcineurin inhibitors

Immunological role of transplanted kidney