Case report

Chronic thrombotic microangiopathy secondary to antiphospholipid syndrome, presenting with severe hypertension and chronic renal impairment

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SUMMARY

A 42-year-old woman was referred from a primary care centre for severe hypertension, stage 3A chronic kidney disease and proteinuria. This was associated with a significant obstetric history of pre-eclampsia during her previous two pregnancies. Secondary hypertension was suspected and autoimmune workup was positive for anticardiolipin IgG and lupus anticoagulant. A renal biopsy showed evidence of chronic thrombotic microangiopathy, with electron microscopy features suggestive of fibrillar glomerulonephritis. The diagnosis of antiphospholipid syndrome with antiphospholipid-associated nephropathy was made. She was started on anticoagulation with warfarin, and her hypertension was controlled with lisinopril and amlodipine with subsequent improvement in proteinuria. She remains on regular follow-up to monitor for possible development of malignancy or connective tissue disease.

and enhanced sympathetic nervous system activity.⁶ In this case, the presence of significant obstetric history in a young woman with hypertension and CKD directed further workup which revealed an uncommon aetiology of her presentation, allowing for treatment which will modify her long-term prognosis.

CASE PRESENTATION

Our patient is a 42-year-old woman who works in a church bookstore. She is married and stays with her husband and two children, aged 8 and 12 years old. She does not smoke, drink alcohol or consume recreational drugs and is not on any regular medication. She reports a medical history of hypertension diagnosed at age 40 years but defaulted medications and follow-up, and pre-eclampsia during her previous two pregnancies.

She attended the polyclinic in October 2017 complaining of bitemporal headache for the last few days. Her blood pressure was markedly elevated at 214/129 mm Hg, and a routine hypertensive panel showed a serum creatinine of 136 µmol/L (estimated glomerular filtration rate by Modification of Diet in Renal Disease equation: 39.3 mL/min/1.73 m²) and urinary microalbumin/creatinine ratio of 92.9 mg/mmol (normal 0.2–3.3 mg/mmol). She was urgently referred to an acute tertiary hospital to rule out hypertensive crisis, and was admitted for blood pressure monitoring and control.

Her blood pressure responded well to oral amlodipine, coming down to 160/90 mm Hg with resolution of headache. Her renal function remained stable, with no microscopic haematuria and a spot urine protein/creatinine ratio (UPCR) of 1.71. There was no evidence of other end-organ damage. She was discharged the next day with oral amlodipine 10 mg every morning and an outpatient appointment to evaluate for secondary causes of hypertension.

A detailed history was retaken during the clinic consult. Obstetric history was significant for pre-eclampsia during her first pregnancy (at age 30 years) and hypertension diagnosed during the first trimester of her second pregnancy (at age 34 years), with subsequent pre-eclampsia. It was unclear whether any further evaluation was performed, but she was told by her obstetrician to have 'pregnancy induced lupus' and started on methyldopa and aspirin. These were stopped after the delivery of

BACKGROUND

Hypertension is defined as a blood pressure of 140/90 mm Hg or higher at the doctor's clinic and an ambulatory blood pressure monitoring (daytime average) or home blood pressure monitoring average of 135/85 mm Hg or higher. It is a significant global health burden affecting one in four adults worldwide, and a major risk factor for many diseases including myocardial infarction, stroke, chronic kidney disease (CKD) and dementia.¹

Only 5%–10% of hypertension in adults have a secondary aetiology. However, this proportion increases to 30% in adults below 40 years old.² Identifying secondary hypertension is important as the underlying aetiology can then be addressed, arresting its progression and preventing disease-associated morbidity. Treating the underlying cause may also potentially cure the hypertension. As causes of secondary hypertension are myriad and span across multiple organ systems, indiscriminate workup can be time-consuming and costly. A targeted evaluation based on patient demographics and presence of suggestive clinical features is a more cost-effective approach.^{3,4}

CKD and hypertension are closely intertwined. It is well established that hypertension is a major risk factor for development of CKD.⁵ However, CKD also predisposes to hypertension through a variety of mechanisms including sodium retention, increased activity of the renin–angiotensin system

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Table 1 Baseline investigations

Investigation	Value	Abnormal indicator	Reference range	Remarks
Haemoglobin	132		(120–160 g/L)	
White blood cell count	10.2	H	(4.0–10.0×10 ⁹ /L)	
Platelet count	235		(140–440×10 ⁹ /L)	
Urea	9.5	H	(2.7–6.9 mmol/L)	
Sodium	139		(136–146 mmol/L)	
Potassium	3.9		(3.6–5.0 mmol/L)	
Chloride	104		(100–107 mmol/L)	
Bicarbonate	25.0		(19.0–29.0 mmol/L)	
Glucose (fasting)	4.9		(3.9–11.0 mmol/L)	
Creatinine	124	H	(37–75 µmol/L)	
Prothrombin time	11.7		(9.9–11.4 s)	
Activated thromboplastin time	49.8	H	(25.7–32.9 s)	
Total protein	73		(68–85 g/L)	
Albumin	42		(40–51 g/L)	
Total bilirubin	7		(7–32 µmol/L)	
Alkaline phosphatase	47		(39–99 U/L)	
Alanine transaminase	14		(6–66 U/L)	
Aspartate transaminase	18		(12–42 U/L)	
Calcium	2.29		(2.09–2.46 mmol/L)	
Phosphate	1.31		(0.94–1.50 mmol/L)	
Free thyroxine (T4)	11.2		(8.8–14.4 pmol/L)	
Thyroid-stimulating hormone	1.84		(0.65–3.70 mU/L)	
Red blood cells, urine	0		(0–3 /µL)	
White blood cells, urine	28	H	(0–6 /µL)	
Epithelial cells, urine	8	H	(0–4 /µL)	
Casts, urine	Nil			
Protein/creatinine ratio, urine	1.71	H	(<0.2)	
Chest X-ray				Normal
12-Lead ECG				Normal sinus rhythm, no left ventricular hypertrophy

her second child and she was not followed up. Both her children were delivered at term via normal vaginal delivery, with weights appropriate for gestational age. There was no history of unexplained miscarriages, premature births, unexplained intrauterine foetal deaths, arterial or venous thromboses. She was not previously known to have impaired renal function. Her father had hypertension and passed away at 41 years old from intracranial bleeding. There was no family history of autoimmune diseases.

Table 3 Autoimmune investigations

Investigation	Value	Abnormal indicator	Reference range	Remarks
Erythrocyte sedimentation rate	48	H	3–15 mm/hour	Westergren method
C3 complement	0.75		(0.45–0.83 g/L)	
C4 complement	0.07	L	(0.11–0.41 g/L)	
Lupus anticoagulant	Positive	H		Positive on repeat testing
Anticardiolipin IgG	>120	H	(<10 GPL-U/mL)	Positive on repeat testing
Anticardiolipin IgM	6.3		(<7 IgM Phospholipid Units/ml (MPL-U/mL))	
Anti-MPO	6.0	H	(<5 U/mL)	
Anti-Proteinase 3 (PR3)	1.8		(<10 U/mL)	
Antinuclear antibody	1/400 (nucleolar pattern)	H	1/100: trace 1/200: borderline 1/400: weak positive 1/800 or higher: positive	
Anti-double stranded DNA antibody	14.3		(<25 IU)	
Extractable nuclear antigens (anti-Smith, RNP, Ro, La, Scl 70, Jo-1)	Negative			

Since starting amlodipine, her home blood pressure was better controlled at systolic 130–140 mm Hg, diastolic 90–100 mm Hg.

Physical examination was unyielding. She was overweight (Body Mass Index 27.3 kg/m²) but did not have features suggestive of obstructive sleep apnoea. There was no rash, alopecia, oral ulcers, synovitis or other features of connective tissue disease.

In view of her previous medical history, a targeted workup for secondary hypertension was performed, including an evaluation for autoimmune disease and screen for secondary causes of CKD (tables 1–3). Significantly, the autoimmune workup was positive for antinuclear antibody (ANA) at 1/400 dilution (nucleolar pattern), anti-myeloperoxidase (MPO) antibodies at 6 U/mL, anticardiolipin IgG antibodies at >120 IgG Phospholipid Units/ml (GPL-U/mL) and lupus anticoagulant. Serum C4 complement level was also slightly low. Antiphospholipid syndrome (APS) was suspected, and she was referred to the rheumatologist and nephrologist for further evaluation.

Eventually, she underwent a renal biopsy which revealed marked arterial and arteriolar nephrosclerosis with changes

Table 2 Secondary hypertension/chronic kidney disease (CKD) investigations

Investigation	Value	Abnormal indicator	Reference range	Remarks
Active renin, serum	27.9		Upright: (1.8–59.4 pg/mL) Supine: (1.1–20.2 pg/mL)	Reference range is based on patient's age group.
Aldosterone, serum	685.2		(97.3–834.0 pmol/L)	
Aldosterone/renin ratio	0.89		(<3.8)	Ratio is derived from (aldosterone)/(active renin)/27.7
Hepatitis B surface antigen	Negative			
Hepatitis C antibody screen	Non-reactive			
HIV screen	Non-reactive			
Renal ultrasound with Doppler sonography				Kidneys normal in size, isoechoic echo pattern likely due to early changes of renal impairment. Normal renal Doppler study with no raised resistive index of intrarenal vasculature and no evidence of renal artery stenosis. Renal veins are also patent.

Figure 1 Renal biopsy, periodic acid-Schiff stain, shows marked arterial intimal fibrosis with narrowing of the lumen. A glomerulus present reveals ischaemic wrinkling of capillary walls, with an adjacent arteriole displaying complete luminal occlusion (arrow).

consistent with chronic thrombotic microangiopathy (TMA), the latter featuring double contouring and ischaemic wrinkling of glomerular capillary walls with luminal occlusion of occasional arterioles (figures 1,2). No fresh fibrin thrombi, crescents or necrotising vasculitis were identified. Two glomeruli displayed perihilar segmental sclerosis. Moderate tubular atrophy and interstitial fibrosis were present. No convincing immune complex deposits were found on light and immunofluorescence microscopy. Ultrastructural evaluation revealed subendothelial widening of the glomerular capillaries with a few small subendothelial densities. No electron dense deposits or tubuloreticular structures were found. Interestingly, several fibrils mostly measuring from 15 to 28 nm and averaging about 20 nm wide, were noted in the widened subendothelial region, raising the possibility of fibrillar glomerulonephritis (figures 3,4).

In summary, her renal biopsy demonstrating chronic TMA, presence of lupus anticoagulant and high titres of anticardiolipin

Figure 2 High magnification of a glomerulus, Masson-silver stain, shows double contouring of the capillary walls (arrows point to some double contours). The adjacent arteriole shows medial hypertrophy with effacement of its lumen.

Figure 3 Electron microscopy shows subendothelial widening with interposed cytoplasmic fragments as well as fibrils (arrows). Corrugation of the glomerular basement membrane is seen.

IgG suggested the diagnosis of APS with non-classification criteria manifestation of antiphospholipid-associated nephropathy.

DIFFERENTIAL DIAGNOSIS

A judgement call had to be made whether her hypertension was due to essential hypertension or secondary causes. Features suggestive of secondary hypertension include severity of hypertension at onset and association with CKD. It is unusual to develop pre-eclampsia before 20 weeks of gestation,⁷ thus the hypertension noted during the first trimester of her second pregnancy at age 34 years likely represents the first manifestation of underlying young hypertension, which is more commonly associated with a secondary aetiology.

In this case, CKD can be either a complication of long-standing uncontrolled hypertension or the aetiology of the hypertension. The extent of CKD in the context of at least 8 years of uncontrolled hypertension, coupled with the lack of active urinary sediment can be consistent with hypertensive nephrosclerosis. However, hypertensive nephrosclerosis may be over-diagnosed in CKD patients, resulting in missed opportunities to treat the primary renal pathology and arrest further CKD progression.⁸⁻¹⁰

Figure 4 High ultrastructural magnification of the fibrils which measure about 20 nm wide.

In addition, the patient's young age of CKD onset and history of pre-eclampsia during her two pregnancies raised the concern of underlying autoimmune disease, thus prompting further workup.

TREATMENT

She was started on warfarin for her APS nephropathy, with target international normalised ratio (INR) between 2 and 3. Her anti-hypertensives were adjusted to optimise the antiproteinuric effect of ACE inhibitors, with adequate blood pressure control on oral lisinopril 10 mg and amlodipine 5 mg every morning.

Due to the association of fibrillar glomerulonephritis with certain autoimmune conditions and malignancies, a myeloma panel and age-appropriate malignancy screening with mammogram and Pap smear were done and yielded negative results.

OUTCOME AND FOLLOW-UP

As of last review in May 2019, the patient was well. Her creatinine clearance was stable with marked reduction in proteinuria (last UPCr 0.26), INR was within therapeutic range and she was compliant with her prescribed medications. She continues to be monitored for development of symptoms suggestive of evolving connective tissue diseases during regular clinic review with the rheumatologist.

DISCUSSION

APS is a systemic autoimmune disorder characterised by a hypercoagulable state and the presence of antiphospholipid antibodies. Manifestations of disease include arterial or venous thrombosis and pregnancy-related morbidity, including miscarriage, stillbirth and premature birth due to pre-eclampsia, eclampsia or placental insufficiency.¹¹ It can present as a primary disorder, or associated with other autoimmune disorders such as systemic lupus erythematosus. The revised Sapporo criteria¹² requires the presence of both clinical (vascular thrombosis or pregnancy morbidity) and laboratory (positive lupus anticoagulant, anticardiolipin antibody or anti- β_2 glycoprotein-I antibody detected in at least two tests taken at least 12 weeks apart) criteria to make the diagnosis of APS.

Renal involvement of APS ranges from thrombosis of the renal arteries and veins, to APS nephropathy caused by acute or chronic vaso-occlusive lesions in small vessels, to glomerulonephritis. This results in post-thrombotic lesions in arterioles and glomeruli, as well as focal cortical atrophy with interstitial fibrosis on renal biopsy. The severity of APS nephropathy can range from mild chronic renal impairment with variable degrees of proteinuria and haematuria to acute renal failure with associated multiorgan involvement.^{13 14} Hypertension is highly prevalent in APS nephropathy and has been described as the hallmark feature of the disease. In a case series of 16 patients with primary APS and biopsy-proven renal involvement, 15 (93%) had systemic hypertension with severely elevated diastolic blood pressure (>110 mm Hg) in 5 (31%) patients and malignant hypertension in 2 (12%).¹⁵

In our patient, anticardiolipin IgG and lupus anticoagulant were positive and remained positive on repeat testing, thus fulfilling the laboratory criteria of APS. Although her history of pre-eclampsia during both her pregnancies was suggestive, it did not fulfil clinical criteria of obstetrical APS as there was no foetal losses at or beyond the 10th week of gestation, or preterm delivery before the 34th week of gestation. However, subsequent evidence of chronic TMA on renal biopsy would fulfil the requirement to diagnose APS with renal involvement.

The insidious onset of renal impairment differentiates it from acute TMA, which typically presents dramatically with acute kidney injury and evidence of microangiopathic haemolysis such as anaemia, thrombocytopenia, red blood cell fragments and positive biomarkers for intravascular haemolysis. The absence of fibrin thrombi within glomerular capillary and arteriolar lumens in the renal biopsy also makes the diagnosis of acute TMA less likely.¹⁶

Fibrillar glomerulonephritis is an uncommon form of glomerulonephritis characterised by fibrillar deposits in the mesangium and glomerular capillary walls. A recent case series of 66 patients showed that it presents similar to other forms of glomerulonephritis, with proteinuria, hypertension, renal insufficiency and haematuria being prominent features. Almost one-quarter of those cases were associated with malignancy and 15% associated with autoimmune disease; in particular Crohn's disease, systemic lupus erythematosus, Grave's disease and idiopathic thrombocytopenic purpura.¹⁷ An isolated case of fibrillar glomerulonephritis in a patient with APS has been reported,¹⁸ but it is uncertain whether there is a true association between these conditions. The positive ANA and anti-MPO, low C4 complement level and subendothelial fibrils seen on ultrastructural evaluation of the renal biopsy raise the possibility of an evolving connective tissue disease, which she would need to be closely monitored for.

Learning points

- Obstetric history is an essential component of history taking in all females: a history of complicated pregnancies may suggest underlying systemic pathology.
- Recognising clinical features suggestive of secondary hypertension is important in selecting patients to evaluate for secondary aetiologies, to maximise the cost-effectiveness of investigations ordered.
- Do not dismiss chronic renal impairment as merely a consequence of long-standing hypertension: a misdiagnosis of hypertensive nephrosclerosis will result in a missed opportunity to address the underlying renal pathology.
- Renal biopsy plays an important role in confirming underlying aetiology, and may reveal additional pathology guiding further investigation and management.

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