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A Pregnant Woman With New-Onset Hypertension and Acute Kidney Injury

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INTRODUCTION

Acute kidney injury (AKI) during pregnancy can be caused by any of the disorders that occur in the general population. One of the main pregnancy-specific causes of AKI is hypertensive pregnancy disorders, in particular preeclampsia. Preeclampsia is a systemic disorder, characterized by the new onset of hypertension and proteinuria after 20 weeks of gestation.[1,2] Nevertheless, the presentation of preeclampsia can be heterogeneous and there are times when proteinuria may not be present.[3,4] Delivery is currently the only treatment for preeclampsia, which raises the stakes of making a correct and timely diagnosis. We report a case of preeclampsia-associated AKI in a woman with a dichorionic diamniotic twin gestation without proteinuria or persistent blood pressure (BP) elevation. We highlight that a high index of suspicion for preeclampsia is needed when AKI occurs in the latter half of pregnancy and that kidney biopsy remains an essential tool for the diagnosis of preeclampsia in certain cases.

CASE PRESENTATION

A 30-year-old G2P1 woman with a dichorionic diamniotic twin gestation was admitted at 28 weeks 5 days gestation for severe abdominal pain and was found to have new-onset hypertension with elevated serum creatinine level. Her medical history included type 1 diabetes mellitus, anxiety generalized disorder, and previous cesarean delivery. There were no complications in her first pregnancy (delivered at term on July 31, 2012). Her type 1 diabetes was diagnosed at the age of 8 years. Her median glycated hemoglobin level was 10.1% (interquartile range 8.2%–11.5%, $n = 19$) from 2012 to 2019. She had a history of multiple episodes of diabetic ketoacidosis. The last diabetic ketoacidosis episode occurred 2 years ago. Her most recent glycated hemoglobin level was 5.9% and 5.2% at 5 and 1 month before admission, respectively.

She did not take any pain medications and denied leaking of fluid, vaginal bleeding, or decreased fetal movement. Home medications included an insulin pump. She had recently started taking 8 to 10 tablets of calcium carbonate daily for acid reflux. She had no history of kidney disease and had a serum creatinine level of 0.7 mg/dl a month before, which was consistent with her prepregnancy creatinine values. There was no family history of preeclampsia.

Physical examination revealed hypertension (134/63 mm Hg) and mild bilateral lower extremity edema. Abdomen was nontender to palpation, and moderate contractions were noted. Tocodynamometer revealed contractions every 1 to 2 minutes. Fetal heart rates were normal at 141 to 148 beats per minute. Twin B had known congenital pulmonary airway malformation and polyhydramnios with maximum vertical pocket of 13.2 cm. She was administered i.m. betamethasone (12 mg once a day) for 3 doses before admission and underwent amnioreduction twice (4 days before admission and 1 day after admission, respectively) for polyhydramnios.

Investigation revealed AKI with a serum creatinine level of 1.12 mg/dl, serum albumin level of 2.6 g/dl, and serum calcium level of 11.2 mg/dl (corrected calcium 12.3 mg/dl). All relevant laboratory results are presented in Table 1. Dynamic changes of serum creatinine and calcium levels are found in Figure 1. Renal ultrasound with arterial Doppler did not reveal renal artery stenosis or hydronephrosis.

Table 1. Relevant laboratory data

Parameters	Results			Reference range
	1 mo before admission	On admission	3 or 5 d after admission	
CBC				
White blood cell count, /μl	9900	10,700	8700	3400–9600
Hemoglobin, g/dl	12.2	12.3	10.6	11.6–15.0
Hematocrit, %	36.6	37.5	32.8	35.5–44.9
Platelet count, /μl	239,000	201,000	161,000	157,000–371,000
Peripheral smear			Negative	
Chemistry				
Sodium, mmol/l	141	135	139	135–145
Potassium, mmol/l	3.9	4.3	4	3.6–5.2
Chloride, mmol/l	102	99	105	98–107
Bicarbonate, mmol/l	22	22	25	22–29
Anion gap, mmol/l	17	14	9	7–15
BUN, mg/dl	7	11	13	6–21
Serum creatinine, mg/dl[a]	0.7	1.12	1.2	0.59–1.04
eGFR, ml/min per 1.73 m^2		66		≥60
Serum calcium, mg/dl[a]		11.2	8.5	8.6–10.0
Ionized calcium, mg/dl			5.57	4.4–5.2
Glucose, mg/dl	166	119	67	70–140
Total bilirubin, mg/dl		0.6		<1.2
Alanine aminotransferase, U/l		28		7–45
Aspartate aminotransferase, U/l		41	38	8–43
Alkaline phosphatase, U/l		220		35–104
Albumin, g/dl		2.6	2	3.5–5.0
Uric acid, mg/dl		6.7		2.7–6.1
Beta-hydroxybutyrate, mmol/l		1.4		<0.4
Bone mineral metabolism				
Parathyroid hormone, pg/ml			12	15–65
1,25 dihydroxy D2, pg/ml			36	18–78
25-hydroxy D3, ng/ml			50	
Immune serologies				
Total complement, U/ml			49	30–75
Alternative complement path function, %			34	≥46
Factor B, mg/dl			36.4	15.2–42.3
Factor H, mg/dl			32.1	18.5–40.8
C4d, mcg/ml			<1.4	<9.9
CBb, mcg/ml			1.4	<1.7
SC5b-9, ng/ml			275	<251
C3, mg/dl			122	75–175
C4, mg/dl			13	14–40
Infectious workup				
HBs antigen	Negative			
HCV antibody	Negative			
HIV	Negative			
Blood culture		Negative	Negative	
Coagulation				
Prothrombin time, s			8.9	9.4–12.5
INR			0.8	0.9–1.1
Activated partial thromboplastin time, s			26	25–37
DRVVT screen ratio			0.8	<1.2
Urinary analysis				
pH	5.0	5.0		5.0–9.0
Gravity	>1.035	>1.035		1.001–1.035
Glucose	≥1000	Negative		Negative
Ketone	Trace	Trace		Negative

(Continued on following page)

Table 1. (Continued) Relevant laboratory data

Parameters	Results			Reference range
	1 mo before admission	On admission	3 or 5 d after admission	
Bilirubin	Negative	Moderate		Negative
Urobilinogen, mg/dl	0.2	1		0.2–1.0
Blood	Negative	Negative		Negative
Leukocyte esterase	Negative	Small		Negative
Nitrite	Negative	Negative		Negative
RBC, /hpf		3–10		0–2
WBC, /hpf		4–10		0–10
Casts		Negative		
Epithelial, squamous		1–3		
24-h urine protein, mg	116	106		
Sodium, mmol/l			<10	
Calcium, mg/dl			37	
Calcium-to-creatine ratio, mg/mg			0.17	
Urinary protein-to-creatinine ratio, mg/mg	0.11	0.09		<0.18
Urine culture		Negative		Negative

BUN, blood urea nitrogen; CBC, complete blood cell count; DRVVT, diluted Russell viper venom time; eGFR, estimated glomerular filtration rate; HBs, hepatitis B surface; HCV, hepatitis C virus; hpf, high power field; INR, international normalized ratio; RBC, red blood cell; WBC, white blood cell.
[a]Dynamic changes of serum creatinine and calcium levels are found in Figure 1.

Her serum calcium and ionized calcium level were elevated, with normal 25-hydroxy D3 and 1,25 dihydroxy D2 but low parathyroid hormone (12 pg/ml) level, indicative of suppression owing to exogenous calcium. Her vitamin D and calcium carbonate supplements were discontinued and her serum calcium decreased with normal saline infusion. Her BP also improved with improved serum calcium concentration, and she did not require any antihypertensive medication. Nevertheless, her creatinine level was persistently elevated despite these other improvements. Results of additional workup including lupus anticoagulation profile, serum complement, urine and blood culture, and viral tests were unremarkable.

Though she did not have sustained hypertension or proteinuria, preeclampsia remained high on the differential, given the absence of another explanation for her AKI and her risk factors, including twin gestation and type 1 diabetes. To rule out preeclampsia, an ultrasound-guided kidney biopsy was performed by experienced operators. Biopsy revealed endotheliosis, mesangiolysis, and segmental duplication of the glomerular basement membranes consistent with preeclampsia-associated glomerular endotheliosis/thrombotic microangiopathy (Figure 2a–d). There were no complications from her kidney biopsy. She underwent emergency cesarean section. She received magnesium sulfate (6 g bolus with 1 g/h maintenance) for 24 hours postpartum. Her systolic BP rose to 140 to 165 mm Hg on the second day, requiring oral labetalol (200 mg 3 times daily) but normalized at the time of discharge. Her creatinine level returned to normal range (serum creatinine at 0.88 mg/dl 1-week postdischarge), though this was above her previous baseline. Twin B did not survive the first 24 hours, whereas twin A spent several weeks in the neonatal intensive care unit and is currently doing well.

DISCUSSION

This case highlights the importance of considering preeclampsia in cases of AKI late in pregnancy. The presentation of this patient was particularly complicated, as she did initially have alternative explanations for her AKI. Hypercalcemia is known to cause AKI and hypertension.[5] Hypercalcemia-caused AKI is usually reversible with volume expansion and lowering of serum calcium concentration.[6] The kidney function of our patient did not improve despite normalization of her serum calcium, leading us to consider alternative explanations for her AKI. We also considered abdominal compartment syndrome given her low urine output and low urine sodium. She had a twin gestation and 1 fetus had polyhydramnios, which could lead to increased intra-abdominal pressures. She underwent amnioreduction twice, once during her hospitalization, and there was no change in her kidney function. Given her long history of type 1 diabetes, we also considered that she may have "undiagnosed" chronic kidney disease owing to diabetic nephropathy. Though her serum creatinine level was in the normal range before pregnancy, she should have a physiological decrease during pregnancy.[7] As her creatinine level was unchanged during pregnancy, this could have indicated early AKI up to a month before presentation. Other causes of AKI in pregnancy, including ureteral

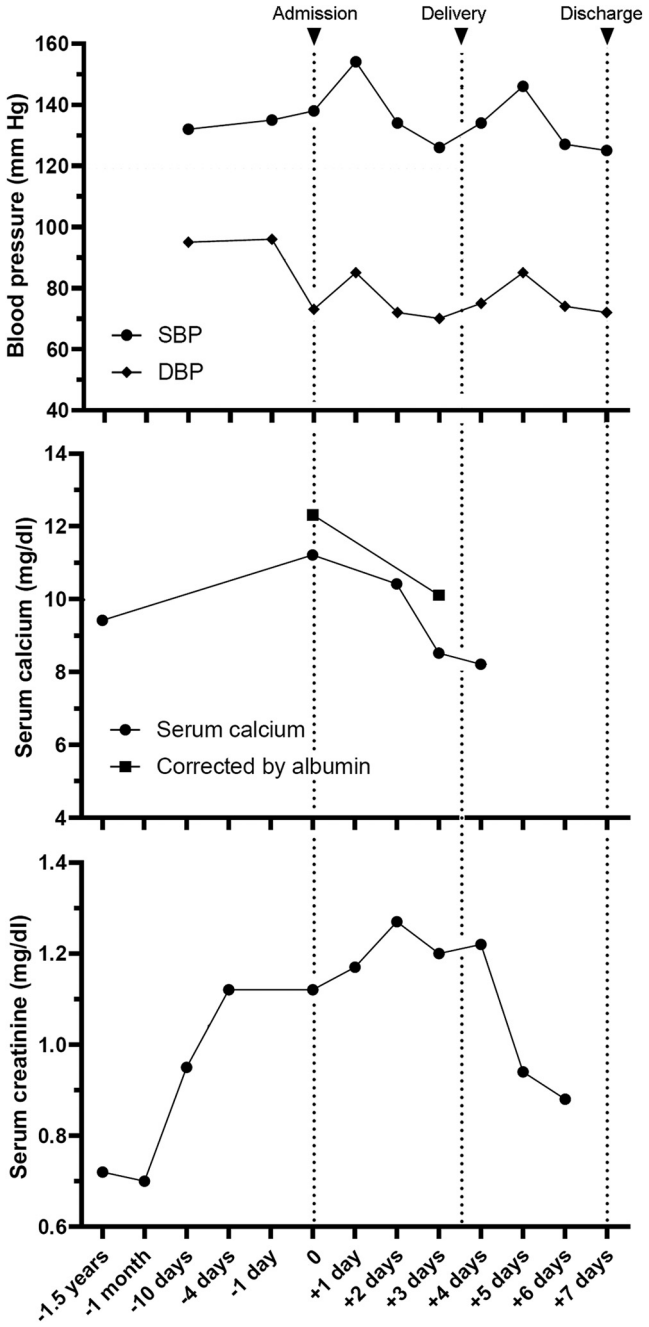

Figure 1. Time course of serum creatinine, serum calcium, and blood pressure. DBP, diastolic blood pressure; SBP, systolic blood pressure.

obstruction, acute cortical necrosis, acute fatty liver of pregnancy, and autoimmune diseases such as lupus nephritis, were excluded by additional workup and renal ultrasound. In addition, she did not have thrombocytopenia or abnormalities on liver function tests initially, and peripheral smear did not reveal schistocytes or other signs of microangiopathic hemolytic anemia.

We continued to be suspicious for preeclampsia, in particular owing to her recent changes in BP. Her BP had begun rising 10 days before admission, which was when serum creatinine level started to increase as well from 0.7 to 0.9 mg/dl. The first sign of preeclampsia is most often a rise in BP, and this is not always accompanied by proteinuria.[1] Recent guidelines for the diagnosis of hypertensive disorders of pregnancy removed proteinuria as a requirement for the diagnosis of preeclampsia, recognizing the presentation can be heterogenous.[3] This patient had severe abdominal pain, which can be a sign of preeclampsia, though these symptoms did seem to improve when calcium decreased. Though her urine protein-to-creatinine ratio was 0.09 mg/mg, 24-hour urine protein was 106 mg, and her BP level was not consistently elevated, preeclampsia moved higher in our differential, particularly as type 1 diabetes is a risk factor for preeclampsia.[8]

Knowing that preterm delivery would be very high risk, in particular for twin B, we felt a kidney biopsy was the most appropriate next diagnostic test to make diagnosis of preeclampsia. The recommended treatment for severe preeclampsia is delivery of the baby to prevent the disease from progressing.[1] The largest meta-analysis revealed that relative to postpartum biopsy, kidney biopsy during pregnancy is a morbid procedure, with a significantly higher risk of severe complications, such as major bleeding, with large perirenal hematoma, placental abruption, and preterm delivery.[9] Generally, kidney biopsy, particularly in the third trimester, is not recommended and it should be limited to women in whom a diagnosis is needed for urgent therapy. It has been found that kidney biopsy performed for the diagnosis of glomerulonephritis or preeclampsia led to therapeutic changes in 66% of cases.[9]

In this case, the biopsy results of the patient revealed signs of thrombotic microangiopathy and endotheliosis, consistent with preeclampsia. Interestingly, she had protein reabsorption droplets on her biopsy, despite the absence of proteinuria. If she had remained pregnant for longer, we may have observed proteinuria as tubular reabsorption mechanisms became overwhelmed. Hypercalcemia and volume depletion could have triggered the acute onset of preeclampsia, though she also had significant preexisting risk factors.

CONCLUSION

In conclusion, preeclampsia-associated AKI during third trimester was diagnosed in this patient. Our case illustrates how preeclampsia can be challenging to diagnose in the absence of proteinuria, and therefore clinicians need to maintain a high index of suspicion. In the absence of reliable and easily accessible

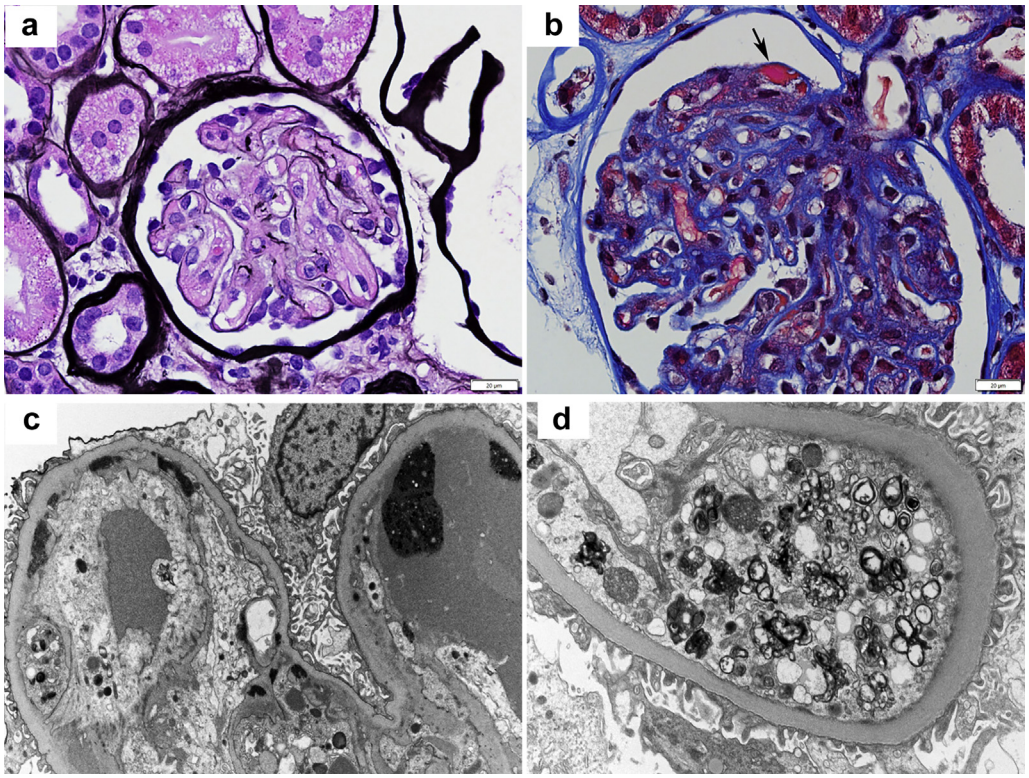

Figure 2. Kidney biopsy findings. (a) Image of the depicted glomerulus reveals global mesangiolysis, loss of endothelial cells, and global widening of subendothelial zone by entrapped plasma proteins (Jones methenamine silver, ×600). (b) Image of another glomerulus reveals a small intraluminal fibrin thrombus that stains dark red on trichrome stain (arrow) (×600). (c) An electron microscopy image revealing marked endothelial cell swelling leading to marked narrowing of the capillary lumen (capillary on the left). The glomerular capillary on the right exhibits loss of endothelial cells and subendothelial and intraluminal electron-dense deposits (likely representing entrapped IgM and other plasma proteins) (×8000). (d) Image of a glomerular capillary revealing an injured, swollen endothelial cell with loss of fenestrations and intracytoplasmic electron-dense lipid particles and lysosomes (electron microscopy, ×12,000).

biomarkers, kidney biopsy remains essential for the diagnosis of preeclampsia in certain cases where a decision is needed for immediate treatment (Table 2).

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patients discussed in the report.

Table 2. Teaching points

Preeclampsia should be considered in cases of AKI late in pregnancy.
Preeclampsia should be suspected in pregnant women with AKI even in the absence of proteinuria and/or persistent blood pressure elevation, particularly if the patient has risk factors for preeclampsia, alternative causes cannot be identified, and the timing in gestation is consistent.
Kidney biopsy should be considered for AKI in pregnancy when there is a significant chance it would change therapy and dictate timing of delivery.
Delivery is currently the only treatment for preeclampsia, which raises the stakes of making a correct and timely diagnosis. In the absence of reliable and easily accessible biomarkers, kidney biopsy would remain essential for the diagnosis of preeclampsia in certain cases where a decision is needed for immediate treatment.

AKI, acute kidney injury.

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