

Postpartum Renal Cortical Necrosis Is Associated With Atypical Hemolytic Uremic Syndrome in Developing Countries



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Introduction: Pregnancy-related acute kidney injury is the most common cause of renal cortical necrosis (RCN). Atypical hemolytic uremic syndrome (aHUS) as a cause of RCN in pregnant/postpartum is underevaluated. In the current article, we describe a series of cases of pregnancy-related RCN.

Methods: All cases with acute kidney injury (AKI) in the setting of pregnancy and postpartum state were included. Diagnosis of RCN was made by contrast-enhanced computerized tomography (nonenhancing renal cortex, enhancing medulla, and no excretion of contrast medium) or on a renal biopsy. aHUS was diagnosed in the presence of microangiopathic hemolytic anemia (thrombocytopenia, elevated lactate dehydrogenase with schistocytes on peripheral smear examination, or low haptoglobin).

Results: A total of 21 (17.5%) patients presented with RCN during pregnancy, all in the postpartum state. Twenty patients (95.2%) showed microangiopathic hemolytic anemia consistent with HUS and 1 (4.8%) patient had biopsy-proven thrombotic microangiopathy. Low complement 3 or activation of an alternate complement pathway was seen in 9 of 15 patients in which it was done. At the end of 6 months, only 2 (9.5%) patients had partial recovery of renal functions, 5 (23.8%) patients died, and 14 remained (66.7%) on hemodialysis.

Conclusion: The clinical and laboratory features are highly suggestive of aHUS in more than three-fourths of cases with postpartum RCN. Investigations are needed to look for genetic abnormalities in the complement pathway.

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KEYWORDS: AKI; HUS; pregnancy; renal cortical necrosis

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RCN is the most catastrophic form of AKI.¹ Thought to be as a result of severe renal ischemia secondary to hemorrhage or microvascular thrombosis, RCN is encountered in the developing world as a complication of pregnancy.¹ The exact pathogenesis of RCN in the obstetric setting has remained unsolved.^{2–4} Hemolysis and microangiopathy have been reported, but were ascribed to disseminated intravascular coagulation, perhaps secondary to sepsis or amniotic fluid embolism. aHUS, the commonest cause of RCN in the nonobstetric setting,¹ has recently been identified in developed countries as a distinct cause of AKI in the late pregnancy

or postpartum period.^{5,6} In recent years, we have increasingly identified clinical findings consistent with aHUS in patients presenting with obstetric AKI. In this present report, we describe the contemporary clinico-epidemiological profile and outcome of obstetric RCN from a developing country and highlight the possible contribution of aHUS to this condition.

MATERIAL AND METHODS

The current report is a part of the prospective study evaluating economic consequences of patients with obstetric AKI referred to the Postgraduate Institute of Medical Education and Research, Chandigarh, between August 2015 and November 2017. Patients with known chronic kidney disease and organ transplant recipients were excluded. The Institute Ethics Committee approved the study protocol and all patients provided informed consent.

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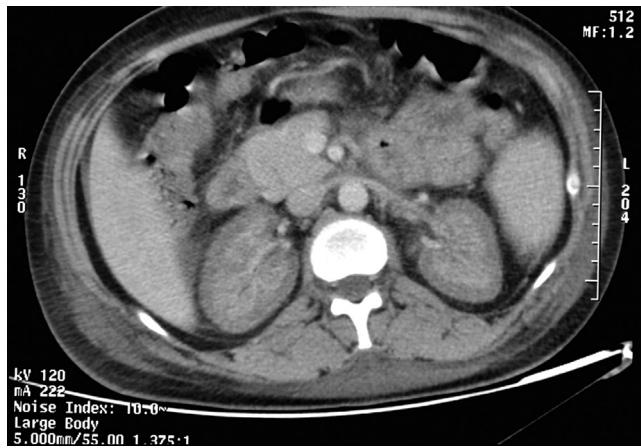


Figure 1. Both the kidneys show thin rim of enhancement in the subcapsular area with lack of enhancement in the cortical area, consistent with renal cortical necrosis.

All patients were managed as per standard of care, including dialysis and other supportive therapy. Investigations included complete blood count, peripheral smear examination, serum lactate dehydrogenase, serum haptoglobin, liver function tests, and renal function tests. We performed complement 3 and alternate pathway functional assay in 15 patients.

aHUS was diagnosed in the presence of microangiopathic hemolytic anemia (thrombocytopenia, elevated lactate dehydrogenase with schistocytes on peripheral smear examination, or low haptoglobin).⁷ Preeclampsia was diagnosed on the basis of standard clinical criteria. A diagnosis of definite sepsis was made when the patient had fever, leukocytosis, and growth of microorganisms on blood culture, whereas probable sepsis was diagnosed when the patient had fever, leukocytosis, and elevated procalcitonin but without microbiological proof.

Patients who failed to show improvement in urine output after 2 weeks underwent contrast-enhanced computerized tomography. RCN was diagnosed on the basis of characteristic imaging findings (nonenhancing renal cortex, enhancing medulla, and no excretion of contrast medium),⁸ or kidney biopsy when contrast-enhanced computerized tomography was inconclusive. All patients were followed for at least 6 months.

RESULTS

Of 120 patients with obstetric AKI referred to our hospital during the study period, 21 (17.5%) were diagnosed with RCN. The diagnosis was confirmed by demonstration of classical findings on contrast-enhanced computerized tomography (Figure 1) in 20 cases, and in 1 on kidney biopsy. Table 1 depicts the demographic and clinical details of all patients. In all cases, clinical manifestations appeared in the intra- or

postpartum period. The mean age of the patients was 26.38 ± 4.33 (range 20–38) years. Fifteen patients (71.42%) had received regular antenatal care. Seven (33.3%) patients had preeclampsia. A total of 9 (42.8%) cases had postpartum hemorrhage preceding AKI. All cases received initial management in other health facilities and were referred to our hospital after a mean interval of 4.3 days following delivery. Three cases had received dialysis before referral. Three (14.2%) patients showed bacteremia in cultures drawn within 48 hours of arrival, and another 9 (42.8%) were treated for presumed sepsis during the hospital stay.

As shown in Table 1, 20 (95.2%) patients exhibited classical microangiopathic hemolytic anemia consistent with HUS. In 1 patient, the kidney biopsy showed thrombotic microangiopathy. A total of 9 of 15 cases showed low complement 3 and/or alternate pathway functional assay, suggesting activation of the alternative pathway of the complement system. Nine (42.8%) patients had evidence of HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome.⁹ None of the patients were treated with plasma exchange either because of financial reasons ($n = 15$) or because disease was considered irreversible and hence treatment was deemed to be futile ($n = 6$). Two (9.5%) patients had spontaneous recovery of urine output with improvement in glomerular filtration rate and were able to come off dialysis. Five (23.8%) patients died in hospital, all due to health care-associated infections. The remaining 14 remained dialysis-dependent at discharge.

DISCUSSION

Through this report, we raise the possibility of postpartum aHUS as an important contributor to RCN, one of the most devastating complications of pregnancy in the developing world.

In recent years, postpartum aHUS secondary to abnormalities in complement pathway has been described in reports from the developed world.^{5,6} However, this entity is not well-recognized in the developing world, where obstetric AKI is far more common.^{10,11} In the study by Sahay *et al.*¹² 39% of RCN cases were due to obstetric AKI, but HUS was reported only in 7.3%.

We believe aHUS is underrecognized in this setting in developing countries. The timing of referral and availability of investigations could have a bearing on the detection of diagnostic findings: the classical findings of microangiopathic hemolytic anemia could have disappeared in the case of late presentation and workup. Frimat *et al.*³ reported 18 instances of RCN in patients with pregnancy-related AKI due to postpartum hemorrhage; all the patients had thrombocytopenia, and more than one-half of them had evidence

Table 1. Clinical, laboratory parameters, and outcome of all the patients

Patient no.	Age, yr	Gestational age, wk	Preeclampsia	History of blood loss	Sepsis	Hemoglobin, g/dl	Platelet count ($\times 10^9/l$)	LDH (U/l)
01	29	38	No	Yes	No	4.9	8	3687
02	23	38	No	No	Definite	8.6	30	3054
03	25	38	No	No	Probable	9.5	16	1177
04	23	30	Yes	Yes	No	4.5	58	2045
05	27	38	Yes	No	No	8.1	94	5046
06	26	38	No	Yes	No	7.1	101	2912
07	29	38	No	No	Probable	9.3	42	3219
08	29	38	Yes	Yes	No	8.7	77	3752
09	38	35	Yes	Yes	No	6.9	48	4031
10	30	38	No	No	No	8.4	295	1044
11	20	38	No	No	Probable	9.2	40	4071
12	22	38	No	Yes	Probable	7.4	91	3816
13	24	38	Yes	No	Definite	8.5	12	1026
14	32	38	No	No	Probable	8.2	21	4420
15	29	38	Yes	Yes	No	6.4	23	2046
16	24	38	No	Yes	Probable	5.2	35	8390
17	21	36	No	Yes	Probable	6.5	22	1282
18	32	37	No	No	Probable	7.9	88	1778
19	26	38	No	No	Definite	8.7	25	1617
20	23	37	No	No	No	9.2	19	3850
21	24	34	Yes	No	Probable	6.0	47	2347

ALT, alanine aminotransferase; APFA, alternative pathway functional assay; AST, aspartate aminotransferase; C3, complement 3; CECT, contrast-enhanced computerized tomography; LDH, lactate dehydrogenase; NA, not available; ND, not done.

*Died at 5 months due to infection on dialysis.

of hemolysis. A high prevalence of RCN has indeed been shown in primary HUS.¹³

In the past, RCN was attributed to massive hemorrhage or sepsis, without full understanding of the mechanism. We identified bleeding, preeclampsia, and possible sepsis in 43%, 33%, and 57% cases, respectively. Sixty percent of the patients in the present report had evidence of activated alternative pathway of the complement cascade (hypocomplementemia and/or low alternate pathway functional assay), which strongly supports the possibility of aHUS.

What could have led to the development of aHUS and RCN? We speculate that these patients might have inherited defects of the complement pathway that are unmasked in the peripartum period, especially in the presence of complications, which acted as triggers for complement activation. Confirmation of this hypothesis requires studies to evaluate variations in genes regulating the complement pathway. Genetic abnormalities have been shown in 41% to 86% of the previously reported cases of postpartum aHUS.^{5,6,14}

Forty-two percent of the patients had HELLP syndrome. Presence of HELLP is not inconsistent with coexistent aHUS; the features overlap considerably and may not be mutually exclusive. Recent reports have hinted at dysregulation of the alternative complement

pathway in patients with preeclampsia/HELLP syndrome.^{15–17}

All patients in the current study were referred from rural hospitals, and 40% of patients had not received adequate antenatal care despite the existence of government programs to improve access to medical care for pregnant women. We were unable to ascertain the quality of immediate postpartum care these patients received. In contrast, none of the patients who were followed up in the antenatal clinic of our hospital developed AKI, suggesting that inappropriate management in the early postpartum period might have triggered the cascade of events that culminate in aHUS and RCN.

The message from these cases carries important diagnostic and therapeutic implications. The constellation of findings in these cases strongly suggest a diagnosis of aHUS. In the western countries, identification of hematological abnormalities suggestive of microangiopathic hemolytic anemia in the appropriate clinical context, such as postpartum AKI, triggers the diagnosis of aHUS and institution of therapy with plasma exchange or complement inhibitors, most commonly eculizumab. Presence of advanced AKI practically rules out thrombotic thrombocytopenic purpura, the other possible cause of thrombotic

Table 1. (Continued)

Schistocytes on peripheral smear	Plasma haptoglobin, mg/dl	Serum creatinine at presentation, mg/dl	Total bilirubin, mg/dl	AST, U/l	ALT, U/l	C3, g/l	APFA	RCN diagnosed by	Outcome at 6 mo
Yes	4.07	3.6	1	103	143	104.56	51.76	CECT	Died
NA	7.3	4.9	5.8	1640	560	78.24	-0.11	CECT	On dialysis
Yes	20.89	7.0	5.5	71	21	84.24	64.64	CECT	Died ^q
Yes	8.02	5.1	0.5	106	120	58.32	27.68	CECT	On dialysis
Yes	7.52	1.8	1.78	1031	322	163.84	8.90	CECT	On dialysis
Yes	5.47	1.9	0.7	50	28	105.6	68.73	CECT	Serum creatinine 3.2 mg/dl
NA	5.85	1.5	7.2	396	242	94.16	26.10	CECT	On dialysis
Yes	12.36	4.7	0.9	51	95	37.12	64.12	CECT	On dialysis
Yes	17.47	2.6	0.5	37	35	41.76	45.51	CECT	On dialysis
No	40.43	6.0	1.74	1335	1457	106.0	29.34	Biopsy	On dialysis
Yes	20.39	3.7	1.6	205	180	54.24	8.53	CECT	On dialysis
Yes	37.76	3.1	0.6	24	5	81.28	35.15	CECT	On dialysis
Yes	9.69	2.7	5.3	409	98	179	75.35	CECT	Died
Yes	8.14	2.6	3.9	93	92	32.15	13.23	CECT	Serum creatinine 3 mg/dl
No	4.17	1.3	1	108	67	18.23	3.058	CECT	On dialysis
Yes	6.97	5.0	0.86	240	120	ND	ND	CECT	Died
Yes	36.26	10	5.9	102	46	ND	ND	CECT	On dialysis
Yes	17	6.0	6.3	6020	1763	ND	ND	CECT	On dialysis
NA	9	8.0	0.83	1636	244	ND	ND	CECT	Died
Yes	15.7	2.8	1.3	420	245	ND	ND	CECT	Died
Yes	21	6.0	1	23	44	ND	ND	CECT	On dialysis

microangiopathy. Case series have shown dramatically improved prognosis with the complement inhibition.¹⁸ However, eculizumab is not available in large parts of the developing world, including India, and even if it was available, it would be extremely expensive and hence unaffordable for these patients.

To conclude, aHUS should be considered strongly in the setting of oliguric postobstetric AKI. Early diagnosis could allow timely intervention with plasmapheresis and thereby prevent the development of catastrophic RCN. Studies are needed to identify abnormalities in complement pathway genes.

DISCLOSURE

All the authors declared no competing interests.

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