CASE REPORT

Unmasking and successful management of light chain deposition disease of kidney in pregnancy: a complex case, mirroring the complex needs of pregnancy with kidney disease in India

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Received: 15 March 2018 / Accepted: 22 August 2018 / Published online: 5 September 2018 © Italian Society of Nephrology 2018

Abstract
Pregnancy offers a precious window of opportunity to diagnose previously undetected or new onset kidney diseases in emerging countries like India, where access to medical, educational and health care facilities are not equitably distributed across varied sections of society. We report a case of a 33 year-old primi gravida who had a successful pregnancy following what was initially considered to represent preeclampsia at 38 weeks of gestation, in whom a subsequent kidney biopsy for persistence of pregnancy-related acute kidney injury (Pr-AKI) revealed light chain deposition disease (LCDD). The etiological evaluation of LCDD led to the detection of an underlying plasma cell dyscrasia which was treated effectively with chemotherapy and autologous stem cell transplant. In this report, we explore the hitherto uncharted pathophysiological relationship between LCDD and pregnancy-related kidney injury by transmission electron microscopic (TEM) studies of endothelial injury in this setting, and underscore the benefits of medical care in a multidisciplinary environment which yielded gratifying results in preservation of maternal kidney health and fetal outcome.

Keywords Pregnancy · Acute kidney injury · Preeclampsia · Light chain deposition disease

Introduction
Pregnancy-related acute kidney injury (Pr-AKI) remains a serious public health challenge contributing to significant maternal and fetal morbidity and mortality in emerging economies like India, with uneven access to prenatal care in rural populations, compounded by gender biases in equitable distribution of available health care facilities [1, 2]. While an overall sharp decline in incidence of Pr-AKI from 15% in 1980s to 1.5% in 2010 has been reported recently from India, mainly due to reduction in septic abortions, 30% of hospitalized Pr-AKI patients in a recent study had kidney injury of severity requiring dialysis [3]. Preeclampsia (PE) and hypertensive disorders of pregnancy have emerged as the principal causes of Pr-AKI, occurring in 3–10% of all pregnancies [1]. In tandem with this shift in epidemiology, pregnancy serves as a precious opportunity in rural India to detect previously unrecognized kidney diseases in women because it offers a rare window of access to medical care combined with possible symptomatic manifestations of underlying/new-onset kidney diseases. We report a 33 year-old primi gravida who presented with clinical symptoms mimicking PE which was successfully managed at our tertiary care center in India and led to the unmasking of an underlying plasma cell dyscrasia causing light chain deposition disease (LCDD) in the kidney which was treated effectively with chemotherapy and autologous peripheral blood stem cell transplant, highlighting the role of multidisciplinary care in such scenarios.
Case report

A 33 year-old Indian woman, primi gravida, presented at 38 weeks of gestation with proteinuric hypertension raising clinical suspicion of PE. Her antenatal period had been uneventful with no untoward event recorded during 8 hospital visits over 6 months except for a urine dipstick measurement of 1+ proteinuria at 34 weeks of gestation. A history of primary infertility and obesity with a calculated body mass index (BMI) of 30.49 were the only identifiable risk factors at this stage for development of hypertensive disorder of pregnancy. When she presented to us at 38 weeks of gestation, she had generalized edema, her blood pressure recording was 140/90 mmHg and urine dipstick measurement showed 2+ proteinuria. She underwent an emergency lower segment cesarean section (LCS) and delivered a healthy male infant weighing 3.12 kg with APGAR score of 9/9. Her clinical symptoms of hypertension and edema resolved following delivery and she was on regular postpartum follow-up with the Department of Nephrology for persistent proteinuria of 2+ dipstick measurement with serum creatinine at referral being 1.34 mg/dl (normal 0.5–1.4 mg/dl). At 6 months post delivery, her serum creatinine was 4.9 mg/dl with 24-h urinary protein excretion of 7.1 g. Serological tests for HIV and hepatitis viral infections were negative; serum C3 76.4 mg/dl (90–180 mg/dl) and serum C4 26.4 mg/dl (10–40 mg/dl); urine microscopic analysis; protein 3+, blood 2+, 15 RBCs, 37 WBCs and 2–3 epithelial casts per high power field; ASO and ADNB titers normal; lupus work up (ANA and dsDNA) negative. An ultrasound-guided renal biopsy was performed at this juncture.

Light microscopy (LM) showed 21 glomeruli exhibiting mesangial proliferation and nodular condensation of mesangial matrix in 7/21 glomeruli. There was focal irregular thickening of capillary walls which was PAS positive along with the mesangial nodules (Fig. 1a, b). Congo Red and Masson Trichrome stains were negative. Immunofluorescence (IF) yielded negative results for IgG, IgA, IgM, C3, C1q and C4. There was strong staining for kappa (3+) with negative lambda staining in the mesangial nodules, focal capillary walls and tubular basement membranes which was corroborated by immunohistochemistry (IHC) showing kappa restriction.

Transmission electron microscopic (TEM) study confirmed nodular glomerulosclerosis with abundant pod ery to vaguely organized electron dense deposits in the expanded and condensed mesangium (Fig. 1c, d). The capillary walls showed diffuse subendothelial linear punctate to powdery deposits (Fig. 2a, b) with mostly preserved podocyte foot processes and similar deposits along tubular basement membranes (Fig. 2c, d). Features of severe endothelial injury with swollen endothelial bodies occluding glomerular capillary lumina resembling ‘endotheliosis’ were noted in close proximity to subendothelial deposits (Figs. 2b, 3a, b). Lamina rara interna rarefaction with entrapped fibrin tactoids and platelets indicative of thrombotic microangiopathy (TMA) was observed focally (Fig. 3c, d). A final diagnosis of LCDD with kappa monoclonal deposits and evidence of TMA was rendered, based on these findings.

A serum free light chain assay showed kappa 430 and lambda 30 with K:L ratio of 14.3. Immunofixation electrophoresis (IFE) was normal and serum electrophoresis showed a decrease in total proteins, albumin and gamma globulins. Urine Bence Jones proteins was negative. Bone marrow biopsy showed mildly hypercellular marrow with 30% lymphocytosis and 12% plasma cells staining positive for CD138 on IHC and exhibiting kappa light chain restriction. Serum calcium level was normal (8.4 mg %, normal range 8.3–10.4 mg %); skeletal survey with X-ray of skull, chest, spine (thoracic, lumbosacral) and pelvis did not show any lytic lesions. Although presence of serum M protein could not be demonstrated on electrophoresis or IFE, clonality of small B cell clone on bone marrow biopsy was established on IHC and was determined to be the same in the kidney deposits and in the circulation. Hence, the final diagnosis was plasma cell dyscrasia resulting in LCDD of the kidney.

The patient was treated initially with a triplet regimen—CyBorD i.e. cyclophosphamide 300 mg/m²/week orally, bortezomib 1.3 mg/m²/week subcutaneous and dexamethasone 40 mg once a week orally. Following 4 cycles of CyBorD, she attained only a partial response, so therapy was changed to VLD i.e. bortezomib 1.3 mg/m²/week subcutaneous, lenalidomide 10 mg orally for 14 days and oral dexamethasone 40 mg once a week. Response assessment after 3 cycles of VLD revealed her still to be in partial response as observed by a reduction in serum free light chain assay levels (kappa 138, lambda 39.60 and K:L ratio of 3.5), improvement in renal function with serum creatinine lowering to 2.17 mg/dl and 24-h urinary protein excretion decreasing to 2.9 g. She then underwent an autologous stem cell transplant (ASCT) with high dose melphalan (dose adjusted to 140 mg/m² for renal failure) with a stem cell dose of 3 × 10⁹/kg of CD34 positive cells. Neutrophil and platelet engraftment was achieved on day +16 and day +20 following the transplantation. On follow-up after 1 year, the patient remains in clinical remission with normal serum electrophoresis results, serum free light chain assay (kappa 125.01, lambda 108.7 and K:L ratio of 1.15) and follow-up bone marrow biopsy showing only 3% plasma cells without any light chain restriction. Renal parameters showed concurrent improvement with serum creatinine decreasing to 1.60 mg/dl.
Discussion

The kidneys play a crucial adaptive physiological role in maternal accommodation to pregnancy, which makes kidney diseases and pregnancy an unfavorable combination contributing to adverse maternal and fetal outcomes [4]. With recent advancements in obstetric nephrology, the previously bleak outlook for pregnancy-related acute and chronic kidney diseases has been mitigated to some extent, although much remains to be understood and achieved in this rapidly evolving frontier of nephrology [5]. The situation is grimmer in emerging countries like India which lack socio-economic and gender equity in availability of health care and knowledge resources. More often than not, pregnancy serves as an occasion for diagnosis of kidney disease, as in our patient, being one of the lifetime opportunities for a woman to have access to quality health care in certain regions. In addition, pregnancy may stretch the renal reserves and facilitate manifestation of kidney diseases with profound consequences on child bearing and women’s health. Pregnancy and LCDD being extremely rare bedfellows [6], there is paucity of knowledge on the effect of one condition on the other, resulting in lack of clarity concerning treatment issues.

LCDD is a rare complication of plasma cell disorders, included under the disease classification of monoclonal immunoglobulin deposition disease of Randall type (MIDD) wherein a proliferating clone of B cells/plasma cells secrete monoclonal immunoglobulins which deposit consistently in the kidneys and less commonly in the liver and heart [7]. MIDD can occur in association with overt myeloma (serum M protein > 3 g/dl or > 10% bone marrow involvement by clonal plasma cells with evidence of end organ damage) or monoclonal gammopathy of renal significance (MGRS) characterized by monoclonal gammopathy.

![Fig. 1 a Nodular condensation of mesangial matrix with palisading of nodules (arrow) by proliferating cells (H&E, ×200). b Nodular glomerulosclerosis with irregularly thickened capillary walls and tubular basement membranes (arrows) exhibiting PAS positivity (PAS, ×200). c Abundant electron dense deposits in expanded mesangium (M) and subendothelial location with enlarged endothelial cells (E) and narrowed lumen (L) (TEM, ×6000). d Mesangial nodule (M) with abundant powdery deposits exhibiting an ill-defined organized substructure (TEM, ×8200).](image)
producing nephritogenic immunoglobulins causing exclusive renal toxicity (serum M protein < 3 g/dl or < 10% bone marrow involvement by plasma cell clone) [8]. Demonstration of clonal characteristics of bone marrow plasma cells and establishing identical clonality in circulating paraproteins and kidney deposits is essential for diagnosis of MGRS [9]. While the findings in this case fulfilled these criteria, given that plasma cell population was 12% and serum M protein was not demonstrable on electrophoresis and IFE, we refrained from a definite label of MGRS or multiple myeloma in this case. However, an overview of all relevant findings in this case indicate that this can be accommodated within the evolving pathologic spectrum of MGRS. Renal manifestations of LCDD include high-grade proteinuria, hematuria, hypertension, and renal insufficiency [10, 11]. Thrombotic risk increases with nephrotic syndrome in addition to contributions from diffuse glomerular endothelial injury related to hypertension as well as subendothelial deposition of monoclonal light chains. The risk for TMA is further accentuated in pregnancy which in itself is a prothrombotic state [12]. Pregnancy in a patient with early or as yet undetected LCDD is, therefore, a fertile background for the development of PE or hypertensive disorders of pregnancy.

Fig. 2  a Linear subendothelial punctate to powdery deposits characteristic of LCDD (arrows). Note features of injury in adjacent endothelial cells (E) with narrowed capillary lumen (L) and relatively preserved podocyte foot processes (P) (TEM, ×4200).  b Endotheliosis in close proximity to linear subendothelial powdery deposits (E-endothelial cells) with near total capillary lumen occlusion (TEM, ×16,500).  c Linear powdery tubular basement membrane deposits (arrow) typical of LCDD (TEM, x6000).  d Thickened tubular basement membranes due to massive deposits (arrow) of LCDD along the outer aspect (TEM, x6000)
PE is a protean syndrome classically defined by new onset hypertension and proteinuria (> 300 mg/24 h) after the 20th gestational week, with full recovery from hypertension and proteinuria 1–3 months after delivery [13]. Etiologies of PE are varied, with both placental and maternal causative factors identified. Piccoli et al. in their position paper have elegantly described their observations on differences in manifestations of PE due to placental and maternal causes. PE due to maternal causes has been observed to manifest usually in later stages of pregnancy with a less severe effect on fetal growth, whereas PE due to predominantly placental causes is seen to manifest earlier in pregnancy and likely compromises fetal growth [13]. In our patient, onset of symptoms was in the last month of pregnancy with no clinically obvious effect on fetal growth as evidenced by birth weight of 3.12 kg, which points in the direction of maternal kidney disease being the primary pathology. Moreover, placental PE is expected to resolve clinically 1 month postpartum, while maternal PE causes exacerbation of underlying maternal kidney disease and requires intervention by an obstetric nephrologist, as seen in our case.

The pathogenesis of PE involves disruption of utero-placental blood flow and release of angiogenic and anti-angiogenic substances by ischemic placental vasculature in unbalanced proportions, which can cause severe endothelial injury [13], observed on TEM as extreme swelling of endothelial cells occluding glomerular capillary lumina termed ‘endotheliosis’ which commonly disappears within 1 month of delivery. In this context, it is of significance that TEM demonstrated changes similar to endotheliosis in the...
biopsy performed 6 months after delivery, in our patient. Although the relative pathogenetic contributions of LCDD and pregnancy-induced hypertension (PIH) to the persisting endotheliosis-like injury in this case is difficult to assess, it seems obvious that the endothelium has taken multiple hits from LCDD and PIH during this pregnancy. Prolongation of recovery postpartum can be attributed to underlying LCDD continuing the endothelial insults to the kidney.

Diagnosis of LCDD, TMA and endotheliosis on kidney biopsy requires IF and TEM facilities at the pathologist’s disposal. It was apparent from TEM analysis that, even with the high degree of proteinuria in this patient, the primary victim of LCDD in the glomerulus was the endothelium and not podocytes. This could be a reflection of the predominant subendothelial localization of light chain deposits and the resultant complex interplay between ischemic/hypertensive endothelial injury and other chemical mediators of endothelial injury in the patient susceptible to PE. While it is too early in the day to label LCDD as one of the diseases which can manifest with a ‘pregnancy flare’, the notion still begs for a hearing in this case. The clinical course of renal disease in this patient, manifesting first as mild proteinuria at 34 weeks of gestation progressing to a clinical mimicry of PE at 38 weeks of gestation and full blown LCDD diagnosed on renal biopsy performed 6 months after delivery, further augments this hypothesis.

Whereas the commonest condition associated with proteinuric hypertension occurring for the first time in pregnancy is PE, many a case of maternal kidney disease gets masked by this diagnosis due to similarities in clinical presentation [14]. Kidney disease in pregnancy remains a challenge since clinical and laboratory findings compatible with PE do not always preclude an underlying kidney pathology. This case highlights the need for close monitoring of such patients and performing renal biopsy when indicated to unravel the confounders.

There is a deficiency of controlled studies regarding therapy of LCDD [15] and the present consensus is to monitor hematological response, the quality of which determines the renal prognosis [16]. In conclusion, this case increases our understanding of the pathophysiological processes which come into play when pregnancy and LCDD share the limelight together, while illustrating the value of a multidisciplinary team involved in the care of Pr-AKI at different stages of the disease, translating to positive mother and child health outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human rights This article is a retrospective report of a single case. For this type of article, formal consent is not required.

Statement on the welfare of animals This article does not contain any studies with animals performed by any of the authors (Since this article is a case report, it does not contain any studies or experiments with human participants or animals performed by any of the authors.).

Informed consent Informed consent was obtained from the individual patient whose medical findings are reported in this article.

Data availability Data sharing not applicable to this article as no datasets were generated or analysed during the current study. All data regarding this case is included in the submitted manuscript. The corresponding author is happy to provide any further requirements on request.

References