

## Glomerular Herniation in Toxemia of Pregnancy before 18 Weeks Gestation

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### Abstract

Presentation of preeclampsia before 18 weeks is rare. We present a case of severe preeclampsia manifesting at 18 weeks gestation, notable with concurrent renal and optic changes. Beyond the typical kidney histological features of toxemia of pregnancy, the kidney biopsy revealed a distinctive histopathological finding-herniation of the glomerular tuft into the proximal tubule. This finding is rare with only a few cases reported in the literature. We present our findings for the early identification of preeclampsia. Additionally, our case exhibited severe retinal edema on funduscopy, also offering a potential avenue for improving early detection. These insights are crucial for further exploration and understanding of these unique aspects of early preeclampsia just prior to retinal detachment.

### Introduction

Pre-eclampsia is a common disorder that affects 2-8% of pregnancies worldwide [1]. It usually follows a predictable course of events, generally beginning with the onset of hypertension, or worsening of pre-existing hypertension, after 20 weeks of gestation. This is followed by proteinuria and pitting edema, and then any of a range of end-organ complications can occur, including acute kidney injury, acute liver injury, thrombocytopenia, cerebral edema, and/or seizures. If a patient develops seizures, the disorder is now considered eclampsia. The pathophysiology is not completely understood but thought to be due to abnormal placental perfusion [2]. Many pathologic changes are seen in the affected organs, including glomerular endotheliosis in the kidneys and increased central corneal thickness and corneal curvature, decreased corneal sensitivity, and intraocular pressure [3-7]. Many risk factors have been identified for preeclampsia including nulliparity, multifetal gestations, history of preeclampsia in prior pregnancies, chronic hypertension, both pregestational and gestational diabetes, thrombophilia, systemic lupus erythematosus, pre-pregnancy

body mass index greater than thirty, antiphospholipid syndrome, advanced maternal age, kidney disease, assisted reproductive technologies, and obstructive sleep apnea [8]. Preeclampsia also commonly occurs in healthy, nulliparous pregnancies with no obvious risk factors.

By definition, preeclampsia presents after 20 weeks gestation, and anything presenting before 20 weeks is likely due to either underlying renal disease, autoimmune disease, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, triploidy, molar pregnancy or antiphospholipid syndrome [3]. Few cases have been reported in the absence of these pathologies, with a recent review identifying 37 published cases worldwide with changes in the kidney, but very few with herniation of the glomerular tuft into the proximal tubular lumen. Glomerular endotheliosis on renal biopsy can help to confirm the diagnosis [3, 4].

Many with peri-viable gestations would consider attempting expectant management to reach a viable gestational age.

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Expectant management can be considered in preeclampsia with severe features in the absence of uncontrolled severe range blood pressures, persistent headaches, epigastric or right upper quadrant pain refractory to treatment, vision changes, stroke, myocardial infarction, HELLP Syndrome, new or worsening renal issues (as evidenced by serum creatinine greater than 1.1mg/dL or twice the baseline), pulmonary edema, eclampsia, suspected acute placental abruption, or fetal death [2].

Management typically includes delivery and seizure prophylaxis with magnesium sulfate. However, at periviable gestations this would mean termination of pregnancy.

Based on the literature of preeclampsia before 20 weeks gestation, kidney biopsy has shown glomerular capillary endotheliosis. Such literature has failed to observe glomerular tuft herniation into the proximal tubules, as observed in our case presentation [3].

### Case Presentation

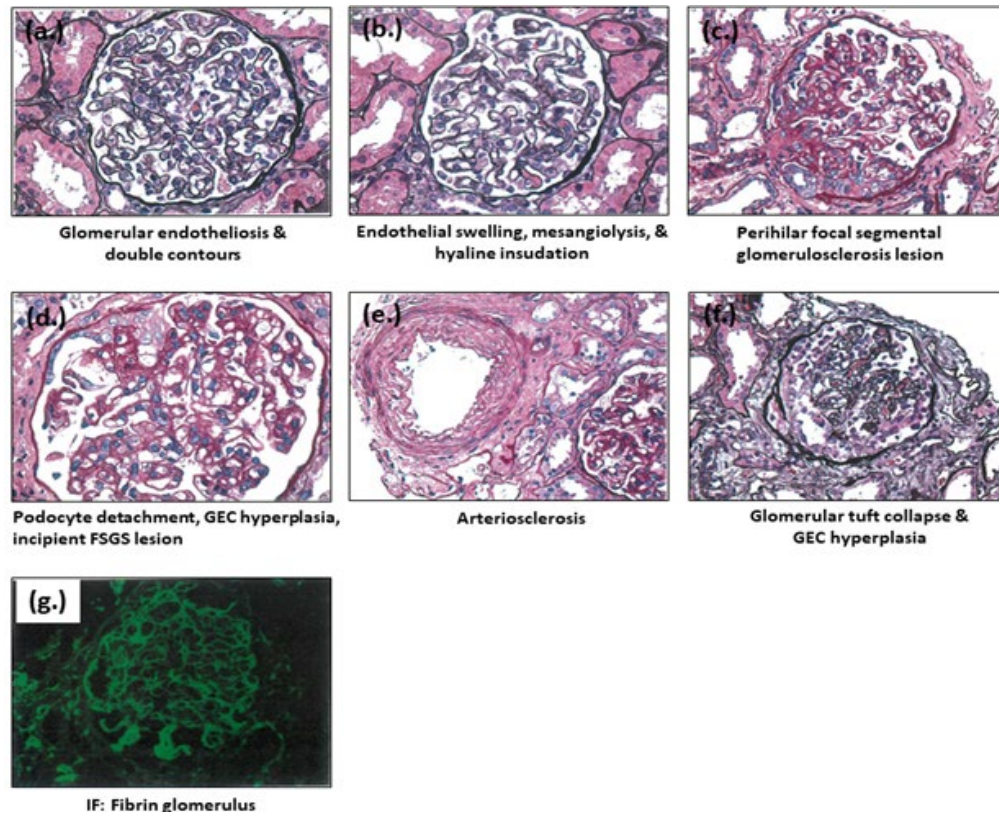
A married, previously healthy 46-year old woman, gravida two, para zero, (G2P0010) underwent successful in-vitro fertilization with a donor oocyte from a frozen assisted reproduction treatment cycle. Patient's body mass index was 31.0 kg/m<sup>2</sup>, medical history free of smoking, autoimmune illness, diabetes, kidney disease, and chronic hypertension. Routine antenatal testing revealed gestational diabetes, an elevated maternal serum alpha fetoprotein, fetal echogenic bowel.

When she presented at 18 weeks gestation for routine prenatal care, she had elevated pressures (BP 167/61mmHg). She presented to the hospital at the recommendation of her Maternal Fetal Medicine office after a visit where she was diagnosed with severe fetal growth restriction at 18.0 weeks gestation and continued to

have elevated blood pressures. She presented to labor and delivery reporting blurry vision, two weeks of shortness of breath and persistent elevated blood pressures (BP 216/120 mmHg). Standard intravenous antihypertensive treatments were administered. Blurry vision persisted, fundoscopic exam revealed severe retinal edema with pending detachment. Labs revealed creatinine 0.99mg/dL, 24-hour urine protein 5.8g.

After extensive counseling regarding recommendation of termination of pregnancy due to early onset preeclampsia with severe features, the patient initially wanted time to discuss with family and manage expectantly. Over the next two days, the patient's blurry vision persisted and it was difficult to titrate medications to maintain blood pressures in the range of 140/90. The patient's blood pressure regimen was uptitrated to Procardia XL 30mg every 12 hours and Labetalol 200 mg every 8 hours. Creatinine worsened to 1.23mg/dL with inadequate and worsening urine output. CXR revealed a right pleural effusion.

Patient ultimately chose to terminate the pregnancy via dilation and evacuation. Two days following the procedure, the patient underwent a kidney biopsy which showed glomerular thrombotic microangiopathy with endotheliosis, double contours, mesangiolytic, focal segmental sclerosing and glomerular tuft herniation into the proximal tubular lumen, features consistent with preeclampsia (Figure 1). Patient's symptoms, blood pressures, urine output, and labs improved and she was deemed stable for discharge after one week. Patient followed up outpatient with control of blood pressure with two antihypertensives and blood urea < 100 mg/ 24 hours, and serum creatinine 0.9mg/dL. Blurry vision improved 5-6 weeks after discharge from the hospital. Optic funduscopy changes reversed to normal.



**Figure 1:** Biopsy results showing herniation of glomerular tuft, image (C).

## Discussion

Early identification and treatment of preeclampsia is key to preventing further complications.

Our case showed end organ damage in both kidneys and eyes as evidenced by biopsy and exam respectively.

The renal involvement of preeclampsia is explained by “excess placental soluble fms like tyrosin kinase-1 (sFlt-1) that binds circulating vascular endothelial growth factor (VEGF) and placenta growth factor (PlGF) and prevents their interaction with endothelial cell-surface receptors. sFlt-1 is also known as soluble VEGF receptor-1” [4]. VEGF regulates endothelial cell function by the induction of nitric oxide that induces vasodilation and angiogenesis. In preeclampsia, there is an increase in sFlt-1 produced by the placenta that blocked the VEGF pathway. “The abnormal placenta, known to play a central role in the pathogenesis of preeclampsia, secretes excessive sFlt-1 into the maternal blood. This heightened level of sFlt-1 binds PlGF and vascular endothelial growth factor (VEGF), prevents their interaction with endothelial cell-surface receptors, and results in endothelial cell dysfunction. Increased levels of sFlt-1 and decreased free PlGF have been reported in women with preeclampsia as compared with healthy pregnant women” [3]. A decrease in VEGF will lead to hypertension by the decrease in baroreceptor response, causing increased vascular tone and by the increase in density of

the microvessels leading to an increase in vascular permeability. A low level of VEGF will also cause a decrease in nitric oxide, an increase in endothelin and apoptosis in the glomerular cells causes endotheliosis and renal thrombotic microangiopathy. In the podocytes, a decrease in VEGF will cause a decrease in synaptopodin, nephrin, podocyte detachment, proteinuria and podocyturia [4].

In our case presentation, the kidney biopsy showed glomerular thrombotic microangiopathy with glomerular capillary endotheliosis and glomerular thrombotic microangiopathy. These renal changes can be explained by the reduction in VEGF as seen in preeclamptic patients. “In rats, the reduction in VEGF-A dosage reduces the activation of endothelial nitric oxide synthase (eNOS) and blocks the vasodilation. This contributes to the development of systemic endotheliosis” [4]. Glomerular thrombotic microangiopathy can be explained by the “induction of apoptosis of endothelial cells due to the blockade of the VEGF pathway. The lack of endothelial cell renewal would in consequence lead to exposure of the basement membrane to the circulating blood and result in platelet activation” [4]. Our patient also had glomerular tuft herniation into the proximal convoluted tubule, which has only been reported in preeclampsia a few times [6]. and only once before 20 weeks gestation [3]. This finding suggests more unknown pathogenesis in the kidneys and prompts further research. The utilization of kidney biopsy in diagnosis

and research of preeclampsia could further elucidate this disease process and potentially help improve treatment strategy, especially in early-onset preeclampsia where the diagnosis can be difficult to make since traditionally diagnostic criteria includes gestations greater than 20 weeks.

In addition to the findings on kidney biopsy, our patient also presented with optic changes on fundoscopy. These findings on fundoscopy can also be explained by the excess of sFlt-1 produced by the diseased placenta. A high level of sFlt-1 has been associated with vasoconstriction and endothelial damage in the eye. "In normotensive pregnancy, the sFlt-1 levels are stable until the middle stage of gestation, and they increase steadily at 33–36 weeks, corresponding to the late decrease in PIGF levels. sFlt-1 acts by adhering to the receptor-binding domains of PIGF and vascular endothelial growth factor (VEGF), preventing interaction with endothelial receptors on the cell surface. Thus, placental vascular growth is tempered by an increase in anti-angiogenic sFlt-1 and a decrease in angiogenic VEGF and PIGF levels. However, in women with preeclampsia, sFlt-1 increases earlier in gestation and reaches a higher concentration than in normal pregnancy" [7]. Increasing levels of sFlt-1 will cause vasoconstriction in the choroid and reduced choroidal vessel permeability, causing the optic changes we saw on fundoscopy. Blurred vision presentation was thought to be secondary to severe retinal edema papilledema, no papilledema was seen in this patient.

### Conclusion

We report a rare case of severe preeclampsia presenting before 18 weeks gestation in a 46-year old woman who conceived through in-vitro fertilization with a donor oocyte. This case was characterized by concurrent renal and optic changes, with a distinctive histopathological finding of herniation of the glomerulus into the proximal tubule on kidney biopsy, a novel observation rarely reported in the literature. Additionally, severe retinal edema, just prior to retinal detachment, was seen on fundoscopy, suggesting a potential avenue for early detection. The challenges faced in managing this patient emphasize the complexities associated with severe preeclampsia and the importance of interdisciplinary care in optimizing maternal outcomes.

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