The Glomerular Injury of Preeclampsia

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ABSTRACT

Preeclampsia is a pregnancy-specific disorder that complicates approximately 5% of all pregnancies, making it perhaps the most common glomerular disease in the world. It is characterized by new-onset hypertension and proteinuria, in association with a characteristic glomerular lesion, endotheliosis. “Glomerular endotheliosis” represents a specific variant of thrombotic microangiopathy that is characterized by glomerular endothelial swelling with loss of endothelial fenestrae and occlusion of the capillary lumens. Associated thrombosis is unusual. Recent evidence suggests that this unusual glomerular lesion is mediated by a soluble vascular endothelial growth factor receptor that deprives glomerular endothelial cells of the vascular endothelial growth factor that they require, leading to cellular injury and disruption of the filtration apparatus with subsequent proteinuria. This review summarizes the histologic changes and the pathogenesis of the glomerular lesions of preeclampsia.


RENA L BIOPSY CASE

PRESENTATION

A 30-yr-old pregnant woman (G1P0), at 15 wk gestation, presented with new-onset hypertension (160/100) and nephrotic-range proteinuria (3.7 g/d). Her medical history was significant for polycystic ovary syndrome. This pregnancy was the result of in vitro fertilization, which was followed by fetal reduction, leaving her with twins. Her hypertension was unresponsive to labetalol, and she was admitted to the hospital for treatment. Complement levels were normal, and serologies, including a thrombophilia workup, were negative. Renal biopsy revealed 11 glomeruli, all of which showed “endotheliosis,” the characteristic finding seen in preeclampsia (see discussion that follows and Figure 1, A and B). These findings were confirmed by electron microscopy (Figure 1C). Immunofluorescence studies were significant for scattered deposits of IgM, κ and λ light chains, and fibrin along the peripheral capillary loop. Attempts to control her BP using nifedipine and Aldomet were partially successful, but her proteinuria continued to rise (peak urine protein/creatinine ratio 9). After much counseling, the patient, considering the severity of the disease and the relatively early gestational age, elected to terminate the pregnancy. Cytogenetic analysis revealed normal fetuses, and there was no evidence of a molar pregnancy. Her renal function returned to normal during the subsequent weeks and a second pregnancy, approximately 2 yr later, successfully went to term without the development of preeclampsia.

RE NA L INJURY OF PREECLAMPSIA

Preeclampsia, the most frequently encountered renal complication of pregnancy, is characterized by new-onset hypertension, proteinuria, and edema, usually developing after 20 wk of gestation. When seizures develop, it is known as eclampsia, a disease familiar to the pre-Hippocratic ancients. The presence of a placenta, with or without a fetus (hydatidiform mole), is necessary for its development. Consequently, definitive treatment is by delivery of the placenta, which, depending on gestational age, can involve significant fetal morbidity and mortality. Preeclampsia complicates approximately 5% of all pregnancies and thus may be the most common glomerular disease in the world.

The development of preeclampsia is believed to be a two-stage process: The first, asymptomatic stage is marked by abnormal placentation, possibly related to ischemia. Placental elaboration of soluble factors that enter the maternal circulation follows, leading to endothelial dysfunction and the clinical syndrome(s). Recent work has identified circulating antiangiogenic substances, which seem to cause the disease by depriving the glomerular endothelium (and possibly other fenestrated endothelium) of essential growth factors. Although preeclampsia is a multisystem process that affects vasculature throughout the body, this article focuses on its hallmark: Glomerular injury.

There is a tendency among caregivers...
to ascribe all new-onset renal disease in pregnancy to preeclampsia, in part because of reluctance to perform a biopsy. However, many studies have documented the inaccuracy of clinical diagnosis alone. One found that when diagnosed clinically, before 37 wk, 67% of women who underwent biopsy had a renal disease other than preeclampsia. Therefore, biopsy remains the most reliable way of making the diagnosis and is particularly helpful in multiparas or early in the pregnancy, to exclude other entities for which effective therapies are available.

The renal biopsy findings of preeclampsia are best appreciated in the context of the pathologic patterns seen in thrombotic microangiopathies (TMA). TMA is a term used to describe a group of clinically diverse entities, such as hemolytic uremic syndrome and malignant hypertension, among others, that are defined by a primary locus of injury—the endothelium—and the ensuing thrombosis and vascular injury. Their similar pathologic expression has led nephropathologists to adopt the term TMA to describe them all. The lesions of preeclampsia share some similarities with and intriguing differences from those of nonpreeclamptic TMA, likely owing to their differing pathogenesis.

**LIGHT MICROSCOPY**

Although the central role of the kidney was first recognized in 1918, it took several decades, in particular, the application of ultrastructural analysis to renal biopsy material, to elucidate the characteristic lesions, which are similar for both preeclampsia and eclampsia. Preeclampsia is associated with a distinctive glomerular appearance: “Glomerular endotheliosis,” a term coined by Spargo et al. The glomeruli are enlarged and solidified (“bloodless”), as a result of narrowed or occluded capillary lumens that are the result of swelling of the native endothelial cells and, to a lesser extent, mesangial cells (Figure 1). Glomerular volume is increased and correlates with the severity of the disease. The degree of endotheliosis can vary between glomeruli, although most show at least some involvement. Glomerular cellularity is not significantly increased. It is interesting that the endothelial changes are limited to the glomerular capillaries; arterioles are typically unaffected. Thrombosis by light microscopy is decidedly unusual, although fibrin can be detected by immunofluorescence in glomeruli. In marked contrast, in nonpreeclamptic TMA, thrombosis of vessels and/or glomeruli is a central finding. Cases of severe preeclampsia with accompanying vascular thrombosis often have clinical signs suggesting a superimposed nonpreeclamptic TMA. Coexistent diseases that are associated with endothelial dysfunction, such as diabetes and antiphospholipid antibodies, are also known to increase the risk for preeclampsia. These observations underscore the variable and site-specific phenotype of endothelial cells and suggest multiple and possibly overlapping pathways leading to endothelial injury in both preeclampsia and nonpreeclamptic TMA. As detailed next, the acute endothelial swelling seen in preeclampsia is due to vascular endothelial growth factor (VEGF) deprivation. In contrast, the endothelial injury noted in nonpreeclamptic TMA, although poorly understood and probably multifactorial, is likely related to impairment of VEGF signaling. Free VEGF levels are higher in patients with hemolytic uremic syndrome/thrombotic thrombocytopenic purpura.

In severe cases of preeclampsia, in particular as the lesions evolve/resolve, mesangial interposition can be seen, a finding shared with other entities resulting from chronic endothelial insult, such as “chronic” TMA or transplant glomerulopathy. Other changes, such as

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**Figure 1.** Renal biopsy findings in a 30-yr-old with preeclampsia. The patient had twin pregnancy after in vitro fertilization. Biopsy was done at 15 wk gestational after new onset of hypertension and nephrotic-range proteinuria. Glomerular endotheliosis: (A) Glomeruli showing occlusion of capillary lumens by swelling of endocapillary cells. There is no appreciable increase in cellularity. Note nearby arterioles (arrows), which are unremarkable. No glomerular or arteriolar thrombosis is seen. (B) Arrow points to the only open capillary loop in this glomerular tuft with otherwise severe capillary occlusion. Note prominent epithelial cells (podocytes) that show protein reabsorption granules (arrowheads). (C) Marked cellular swelling involving mesangium and endothelial cells leading to loss of endothelial fenestrations and capillary lumen occlusion is seen. The lamina densa of the basement membrane is intact. Only focal electron lucent expansion of rara interna was seen (data not shown). Immunofluorescence studies showed no significant Ig deposition. Electron-dense material noted (arrows) is likely fibrin related. Podocytes, despite their protein reabsorption droplets, show relatively well-preserved foot processes. Magnifications: ×40 in A (Masson Trichrome) and B (Giemsa-stained Epon-embedded section); ×3200 in C (transmission electron microscopy).
prominent podocytes with protein resorption droplets and endocapillary foam cells, are probably secondary to the proteinuria. The presence of arteriosclerosis suggests a coexisting process, such as “essential” hypertension. Whether preeclampsia leads to chronic vascular injury over ensuing years is not yet clear.

**IMMUNOFUORESCENCE MICROSCOPY**

The immunofluorescence findings are somewhat variable with fibrin deposition often being a prominent feature. The low-level glomerular Ig deposition in severe preeclampsia, reported by some, probably represents nonimmunologic insudation. This conclusion is supported by the ultrastructural observation that electron-dense deposits are inconspicuous. Its chief diagnostic role lies in excluding an immune complex glomerulonephritis, such as lupus nephritis, which often flares during pregnancy. The pathogenetic role that fibrin and its related products play has not been resolved. Although the degree of deposition has been reported to vary widely, it seems to be more common in renal biopsies obtained from patients with premature and severe preeclampsia.

**ELECTRON MICROSCOPY**

Ultrastructural analysis is the definitive way to demonstrate endotheliosis and, in some cases, may be required to make the diagnosis. Endothelial cells demonstrate loss of fenestrations with cytoplasmic swelling, owing to fluid and lipid accumulation and capillary occlusion (Figure 1C).7 Mesangial cells may show similar changes. In contrast to most other TMA, electron lucent expansion of the subendothelial zone, when present, is usually not prominent. It is interesting that despite significant proteinuria, podocytes show limited foot process effacement, a phenomenon that may also be seen with other TMA, particularly in the acute phase.9 Indeed, when quantified, the filtration slit frequency is not significantly reduced in preeclampsia below controls.7 This finding has significant implications for the investigation of mechanisms of proteinuria in general because it suggests that nephrotic-range proteinuria can occur without significant fusion of podocyte foot processes.9

**SIGNIFICANCE OF ENDOTHELIOSIS**

Endotheliosis seems to be responsible for the decreased GFR noted in preeclampsia, primarily through reduction in the ultrafiltration coefficient as opposed to diminished plasma flow. When focal, endotheliosis can be difficult to identify, and its specificity for preeclampsia may then be limited. Mild forms have been seen in up to 30% of patients with pregnancy-induced hypertension without proteinuria.10,11 Furthermore, a recent study found five of 12 control subjects (nonhypertensive third-trimester women) with trace endotheliosis.10,11 As noted by its authors, this study suggests a continuum between healthy pregnant women and the extreme of preeclampsia. Recent work, as discussed next, provides a rationale for this phenomenon. Limited endotheliosis has also been reported occasionally in association with other disorders.12 Nevertheless, when endotheliosis is present in a diffuse manner, in the appropriate clinical setting, it is virtually pathognomonic for preeclampsia.

**NATURAL HISTORY AND PROGNOSIS**

After delivery, the glomerular changes usually reverse rapidly, coinciding with resolution of the hypertension and proteinuria. However, the relationship among preeclampsia, underlying renal and other conditions, and future disease, including hypertension, is complex and controversial. For example, FSGS (a nonspecific form of glomerular scarring that can be seen in association with “essential” hypertension, as well as in primary glomerular disease) is said to accompany endotheliosis in a significant percentage of cases, but it is not necessarily predictive of current or future renal failure, as might otherwise be expected.13 Indeed, there is evidence that the segmental sclerosis of preeclampsia may be reversible. Nevertheless, considerable evidence suggests that preeclampsia predisposes women to late cardiovascular diseases.14 The increased risk for hypertension is not seen in their siblings, suggesting that it is related to preeclampsia and pointing to the role of subtle endothelial injury leading to the development of chronic hypertension.15

**PREECLAMPSIA FACTOR AND ANTIANGIOGENIC STATE**

The search for a circulating factor that causes the hypertension and proteinuria of preeclampsia has been an area of intense investigation. It is believed that excess circulating antiangiogenic substances such as soluble fms-like tyrosine kinase (sFlt1, also referred to as sVEGFR1) play a prominent role in the development of preeclampsia. VEGF, synthesized constitutively in the glomerulus by podocytes, is a critical factor for the maintenance of endothelial health, including the induction of fenestrae. Indeed, genetic glomerular VEGF deficiency has been shown to result in endotheliosis with loss of fenestrae.16 sFlt1 is a secreted protein that lacks the transmembrane and cytoplasmic domain of the membrane-bound VEGF receptor and acts as an endogenous inhibitor of VEGF signaling. Circulating levels of sFlt1, made predominantly by the placenta, are greatly increased in women with established preeclampsia, even before onset of clinical symptoms.17 That study also found a steady increase in serum sFlt1 levels in normotensive near-term women, a finding that suggests that preeclampsia represents an early and exaggerated form of normal pregnancy and helps to explain the mild endotheliosis occasionally seen in near-term normotensive biopsies. When administered to rats, sFlt1 produces a clinical syndrome and glomerular lesions resembling human preeclampsia.2 Similar observations have been noted...
when other VEGF inhibitors such as neutralizing antibodies have been used in rodents or humans.18-20

How VEGF-deficient states such as preeclampsia produce proteinuria is still unknown. Some have suggested that loss of podocyte nephrin expression may be responsible.19,21 However, whether the diminished nephrin expression is the cause or the consequence of proteinuria is unknown. Others have suggested that all three layers of the glomerular wall—endothelium, basement membrane, and slit diaphragm—may jointly constitute the barrier against proteinuria. Deen et al.22 argued that proteinuria can occur with endothelial disruption alone, which may explain the significant proteinuria noted with endotheliosis. More recently, yet another antiangiogenic protein, soluble endoglin, was reported to play a pathogenic role in preeclampsia.23 It is interesting that animals that were exposed to high levels of soluble endoglin had focal endotheliosis without significant proteinuria, whereas those that were exposed to both soluble endoglin and sFlt1 developed massive proteinuria and severe endotheliosis. Future work is necessary to clarify the mechanisms of the endotheliosis and proteinuria mediated by these circulating antiangiogenic substances.

NOTE ADDED IN PROOF
Recent case reports describe the development of proteinuria and TMA in patients receiving anti-VEGF therapy for cancer.24,25

ACKNOWLEDGMENTS
This work is supported by R01 grants from the NIDDK (DK 065997) and the NHLBI (HL079594).

We thank Drs. Frank Epstein and Seymour Rosen for helpful discussions.

DISCLOSURES
S.A.K. is listed as a co-inventor on multiple patents filed by the Beth Israel Deaconess Medical Center for the use of angiogenic proteins for the diagnosis and therapy of preeclampsia and is a consultant to Johnson & Johnson, Beckman Coulter, and Abbott Diagnostics.

REFERENCES