hemorrhage. Endoaneurysmorrhph and plication remain viable treat-
ment modalities to preserve a functional arteriovenous fistula, although this does require a period of temporary dialysis catheter use. We favor this approach over ligation in the appropriate clinical setting.

**SUPPLEMENTAL ONLINE MATERIAL**

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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Complement C5 Inhibition as a Novel Therapeutic Approach in Severe Pre-eclampsia

*To the Editor:* Determining the clinical diagnosis underlying thrombotic microangiopathy (TMA), a pathologic entity, may be challenging, as is its effective management. This is especially true when TMA occurs in pregnancy. We report a case of a woman presenting in mid-pregnancy with severe pre-eclampsia and acute TMA who was successfully managed with eculizumab.

The patient is a woman in her late 20s with gravidity G2P0010, prior end-stage kidney disease due to autosomal dominant tubulointerstitial disease, and a mutation in the uromodulin gene (UMOD). She received a living-related-donor kidney transplant 6 years previously. Her post-transplantation course was notable for urinary tract infections; however, there were no rejection episodes and no donor-specific antibodies. She was immunosuppressed with tacrolimus, prednisone, and azathioprine, because of her desire to become pregnant 5 years post-transplantation; graft function was stable (iothalamate filtration rate of 68 mL/min per 1.73 m²). She successfully conceived, but during an episode of urosepsis, she miscarried.

Her second pregnancy was initially uneventful, with a baseline serum creatinine (sCr) of 1.0 mg/dL, urinary protein 76 mg/24 h, and a normal blood pressure. At 13 weeks of gestation, she tested positive for coronavirus disease 2019, with mild upper respiratory symptoms. At 17 weeks of gestation, she presented with an acutely elevated sCr to 1.9 mg/dL, increased 24-hour urine protein (247 mg/24 h), and hypertension (139/91 mm Hg). One day later, she was admitted because of an additional rise in sCr (2.4 mg/dL); she was without systemic symptoms. Workup for acute allograft dysfunction was pursued (Table). ADAMTS13 activity was normal, her tacrolimus level was in the therapeutic range, and no new donor-specific antibodies were identified. The only positive serologic finding was a mildly elevated anti-phospholipid immunoglobulin M (IgM). A kidney biopsy was performed at 17 weeks and 6 days of gestation, which was diagnostic for TMA (Figure 1). Immunofluorescence studies revealed 1-2+ mesangial C1q positivity (not considered clinically relevant), arteriolar C3 positivity, and C4d negativity in peritubular capillaries, with trace to 1+ in the mesangium and arterioles.

In establishing a diagnosis, the following considerations were germane. Soluble membrane attack complex (sMAC) was mildly elevated, but not accompanied by abnormalities in the alternative complement pathway. There were no genetic mutations associated with atypical hemolytic-uremic syndrome and TMA. Tacrolimus-related kidney injury was not present on prior protocol biopsy specimens; however, tacrolimus was...
discontinued as it could have been a contributing factor. There was no clinical history of thrombosis or autoimmune disease consistent with antiphospholipid syndrome despite weakly positive antiphospholipid IgM antibody. The prior miscarriage was not due to a coagulation disorder. Severe, early-onset pre-eclampsia was diagnosed; the recent coronavirus disease 2019 infection was regarded as a contributing factor due to its association with TMA and being a risk factor for pre-eclampsia.

After multidisciplinary discussions regarding the benefits and risks of eculizumab, the patient was started on eculizumab for treatment of TMA. She received four doses of eculizumab, 900 mg intravenously weekly for 4 weeks, followed by 1200 mg every 2 weeks, with additional administration intended for 6 months post-delivery. Blood pressure was controlled with nifedipine and labetalol. The sCr and platelet count steadily improved, and haptoglobin and lactate dehydrogenase normalized (Figure 2). The patient was discharged after a 2-week-hospitalization with stable kidney function.

### TABLE. Relevant Laboratory Data

<table>
<thead>
<tr>
<th></th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 month before admission</td>
</tr>
<tr>
<td><strong>Complete blood count</strong></td>
<td></td>
</tr>
<tr>
<td>White blood cell count, /μL</td>
<td>5300</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>9.8</td>
</tr>
<tr>
<td>Platelet count, /μL</td>
<td>308,000</td>
</tr>
<tr>
<td>Reticulocytes, %</td>
<td>2.94</td>
</tr>
<tr>
<td>Peripheral smear</td>
<td>Rare schistocytes</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
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<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.13</td>
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<tr>
<td>eGFR, mL/min per 1.73 m²</td>
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</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
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<tr>
<td>Alanine aminotransferase, U/L</td>
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</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
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<tr>
<td>Albumin, g/dL</td>
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<tr>
<td>Lactate dehydrogenase, mg/dL</td>
<td>740</td>
</tr>
<tr>
<td>Haptoglobin, mg/dL</td>
<td>&lt;14</td>
</tr>
<tr>
<td>Tacrolimus, ng/mL</td>
<td>4.0</td>
</tr>
</tbody>
</table>

**Serology**

- Beta-2 glycoprotein-1 Ab, IgM: <9.4 <15
- Beta-2 glycoprotein-1 Ab, IgG: <9.4 <15
- Phospholipid Ab, IgM: 18.7 <15
- Phospholipid Ab, IgG: <9.4 <15
- Serum protein electrophoresis: No M-spike
- Total complement, U/mL: >75 30-75
- Alternative complement path function, %: >110 ≥46
- Factor B, mg/dL: 45.9 15.2-42.3
- Factor H, mg/dL: 30.9 18.5-40.8
- C3d, μg/mL: 5.4 <9.9
- C4b, μg/mL: 1.1 <1.7
- SC5b-9, ng/mL (sMAC): 290 <251
- C3, mg/dL: 119 75-175
- C4, mg/dL: 27 14-40

**Coagulation**

- ADAMTS13 activity, %: 99 ≥70
- Fibrinogen, mg/dL: 473 200-393

**Urine studies**

- Protein-creatinine ratio, g/g Cr: 0.29 0.35

*Ab, antibody; C, complement factor; eGFR, estimated glomerular filtration; IgG/M, immunoglobulin G/M; sMAC, soluble membrane attack complex.*
function (sCr, 1.50 mg/dL) on immunosuppression with prednisone and azathioprine.

At 27 weeks, she developed intrauterine growth restriction (estimated fetal weight at second percentile) and was readmitted for fetal monitoring due to abnormal umbilical artery Doppler findings (intermittent absent end-diastolic flow). She received betamethasone for fetal lung maturation. She was delivered at 28 weeks and 5 days due to non-reassuring fetal status. The birthweight of the neonate was 1.07 kg, and Apgar scores were 5 at 1 minute, 6 at 5 minutes, and 9 at 10 minutes. Her post-delivery course was notable for uterine atony and hemorrhage, for which she received blood transfusion and was stabilized in the intensive care unit.

After delivery she was maintained on eculizumab for 6 months, following which kidney function remained stable and preserved (sCr, 1.0-1.1 mg/dL). Belatacept was added (rather than restarting tacrolimus) to her immunosuppression regimen. Her infant was discharged from the neonatal intensive care unit after 2 months. At the last evaluation, the child...
exhibited normal growth and development.

Pre-eclampsia is traditionally defined as new-onset hypertension and proteinuria after 20 weeks of gestation in a previously normotensive patient. However, pre-eclampsia may also occur atypically, with the absence of proteinuria and presentation before 20 weeks,\(^1\) the latter manifestation leading us to regard this case as atypical pre-eclampsia. As promising results of C5 complement blockade are recognized in TMA syndromes\(^2\)\(^-\)\(^5\) and because of the pre-viable stage of her pregnancy, we used eculizumab so as to prolong the pregnancy for several weeks; such benefit appeared to outweigh potential risks.

Eculizumab is a monoclonal antibody directed at C5 which prevents the formation of the terminal complement complex (measured by sMAC).\(^3\) Approved in paroxysmal nocturnal hemoglobinuria and atypical hemolytic-uremic syndrome,\(^4\) eculizumab has been successfully used in other TMA syndromes, including lupus-associated TMA,\(^2\) gemcitabine-associated TMA,\(^4\) and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets).\(^5\)\(^-\)\(^7\) The HELLP syndrome may present in early gestation. Our patient had two features of HELLP syndrome (hemolysis and thrombocytopenia), the so-called “partial” HELLP syndrome, which may progress, without treatment, to the complete HELLP syndrome.\(^8\) Inhibition of the complement pathway may be beneficial in pre-eclampsia and HELLP syndrome,\(^3\) consistent with the fact that sMAC levels are higher in women with HELLP syndrome, and in pre-eclamptic women compared with normotensive women at delivery.\(^9\) Clinical trials on the use of eculizumab in pre-eclampsia and HELLP syndrome are ongoing. Eculizumab appears safe in pregnancy, including pregnancy in the setting of paroxysmal nocturnal hemoglobinuria.\(^10\) Detectable eculizumab levels appear in cord blood, but not in breast milk.\(^10\) Through shared decision-making, the patient decided to breastfeed for 6 months after delivery.

This case underscores a novel therapeutic approach in managing severe pre-eclampsia associated with TMA. Specifically, renal function was improved, hematologic indices normalized, and pregnancy was prolonged such that the patient delivered a viable baby in the early third trimester. These successful outcomes all necessitated close monitoring and multidisciplinary expertise and care.

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