Title: Genetic Atypical Hemolytic-Uremic Syndrome *GeneReview* -- Laboratory Findings and Renal Histology
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**Laboratory Findings in Typical and Atypical HUS**

- **Thrombocytopenia** that is usually severe
  - Platelet count should be less than 150,000/$mm^3$ to establish the diagnosis. In most affected individuals, platelet counts are below 60,000/$mm^3$.
  - Platelet survival time is reduced, reflecting enhanced platelet disruption in the circulation.
  - Giant platelets may be seen in the peripheral smear, a finding consistent with secondary activation of thrombocytopoiesis.
- **Microangiopathic hemolytic anemia** that is usually severe
  - Hemoglobin concentrations lower than 10 mg/dL are reported in 99%, and lower than 6.5 mg/dL in 40% of affected individuals.
  - Serum lactate dehydrogenase (LDH) concentrations are increased (>460 U/L), often at very high levels, reflecting not only hemolysis, but also diffuse tissue ischemia.
  - Hyperbilirubinemia (mainly unconjugated), reticulocytosis, circulating free hemoglobin, and low or undetectable haptoglobin concentrations are additional nonspecific indicators of accelerated red cell disruption and production.
  - Detection of fragmented red blood cells (schistocytes) with the typical finding of burr or helmet cells in the peripheral smear together with a negative Coombs test (with the exception of *Streptococcus pneumoniae*-associated HUS) are needed to confirm the microangiopathic nature of the hemolysis.
- **Acute renal insufficiency**
  - Serum concentration of creatinine greater than 97th centile for age
  - Serum concentration of urea (BUN) greater than 97th centile for age
- **Complement studies**
  - Decreased serum C3
  - Normal serum C4
  - Increased plasma Bb (cleaved Factor B)
  - Increased plasma soluble membrane attack complex (sMAC)
  - Increased C5b-9deposits on endothelial cells induced ex-vivo by the serum of individuals with aHUS

- Decreased complement factor H
- Decreased complement factor I
- Decreased complement factor B
- Decreased surface expression of membrane cofactor protein (MCP) in peripheral blood leukocytes by FACS
- Serum anti-CFHIgG autoantibodies present

**Renal Histology in Typical and Atypical HUS**

The common microvascular lesions of HUS consist of vessel (capillary and arteriole) wall thickening with endothelial swelling, accumulation of proteins and cell debris in the subendothelial layer, creating a space between endothelial cells and the underlying basement membrane of affected microvessels. Both the widening of the subendothelial space and intraluminal platelet thrombi lead to a partial or complete obstruction of the vessel lumen.

Kidney biopsy findings in typical and atypical HUS are often indistinguishable. Renal histological features on light microscopy are those of thrombotic microangiopathy (TMA) including arteriolar and/or glomerular intracapillary thrombosis, typically with fibrin rich thrombi, often with accumulation of fragmented erythrocytes within capillary lumens, and focally ischemic or congested glomerular tufts [Benz & Amann 2010, Barbour et al 2012, Sethi & Fervenza 2014].

- In children younger than age two years the lesion is mainly confined to the glomerular tuft and is noted in an early phase of the disease. Glomerular capillary lumina are reduced or occluded. In patent glomerular capillaries packed with red blood cells and fibrin, thrombi occasionally are seen.
- Examination of biopsies taken several months after disease onset shows that most glomeruli are normal; 20% eventually became sclerotic.
- Arterial thrombosis does occur but is uncommon and appears to be a proximal extension of the glomerular lesion.
- In the acute phase, tubular changes include foci of necrosis of proximal tubular cells and presence of red blood cells and eosinophilic casts in the lumina of distal tubules. Occasionally fragmented red blood cells can be detected in the distal tubular lumina.
- In adults and older children, glomerular changes are different and more heterogeneous than in infants, and the classic pattern of thrombotic microangiopathy is less evident.

## References

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