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Case Report

# Distal Angiopathy and Atypical Hemolytic Uremic Syndrome: Clinical and Functional Properties of an Anti–Factor H IgAλ Antibody

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Abnormal regulation of the alternative pathway of the complement system is a well-described trigger of microangiopathy leading to atypical hemolytic uremic syndrome (aHUS). However, the involvement of complement dysregulation in distal angiopathy has not been reported in adults. We describe the clinical course of a patient with severe distal angiopathy (amputation of all fingers and toes) followed 3 years later by aHUS with end-stage renal disease. This course was attributed to a circulating monoclonal immunoglobulin A λ light chain (IgAλ) with unusual properties: it bound complement factor H (CFH) and impaired CFH-glycosaminoglycan interaction and cell-surface protection. Local complement activation with distal angiopathy and microvascular injury was suggested by deposition of IgA, C4d, and C5b-9 in limb and preglomerular arteries. We therefore postulated that the monoclonal IgAλ inhibited activity of endothelial cell–bound CFH, which led to local activation of complement, vasoconstriction (distal angiopathy), and aHUS. While the patient was dependent on dialysis and plasma exchange, treatment with the anti-C5 antibody eculizumab induced remission of distal angiopathy and aHUS. During eculizumab treatment, kidney transplantation was performed. The patient had normal kidney function at the 3-year follow-up. We suggest that the association of distal angiopathy and aHUS in this patient is clearly linked to anti-CFH properties of the monoclonal IgAλ.
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***INDEX WORDS:*** Gammopathy; autoantibody; alternative complement pathway; complement activation; complement factor H (CFH); factor H antibody; macroangiopathy; distal angiopathy; atypical hemolytic uremic syndrome (aHUS); microvascular injury.

Overactivation of the alternative pathway of the complement system may lead to atypical hemolytic uremic syndrome (aHUS).[1-3] Complement activation has also been described in diseases involving middle and large vessels such as myocardial infarction and age-related macular degeneration.[4] To our knowledge, no link has been established to date in adults between distal angiopathic insults and a complement-induced microvascular injury such as aHUS.

In this report, we describe the clinical course of a patient in whom a monoclonal anti–complement factor H (CFH) immunoglobulin A (IgA) λ autoantibody led to severe distal angiopathy. This was followed 3 years later by aHUS, a form of microvascular injury.

## CASE REPORT

A 45-year-old white man developed severe Raynaud-like phenomenon. The disease presented as flares with livedo, mottling, cyanosis, and severe morphine-resistant pain of the extremities. After several months, trophic lesions developed leading to the amputation of one finger 2 years later. No infectious, autoimmune, endocrine, hematologic, or vascular disease was identified. Distal necrosis worsened, and all fingers and toes were amputated.

Several months after these amputations, the patient experienced a severe flare, with reopening of wounds and vascular purpura on his legs (Fig S1, available as online supplementary material).

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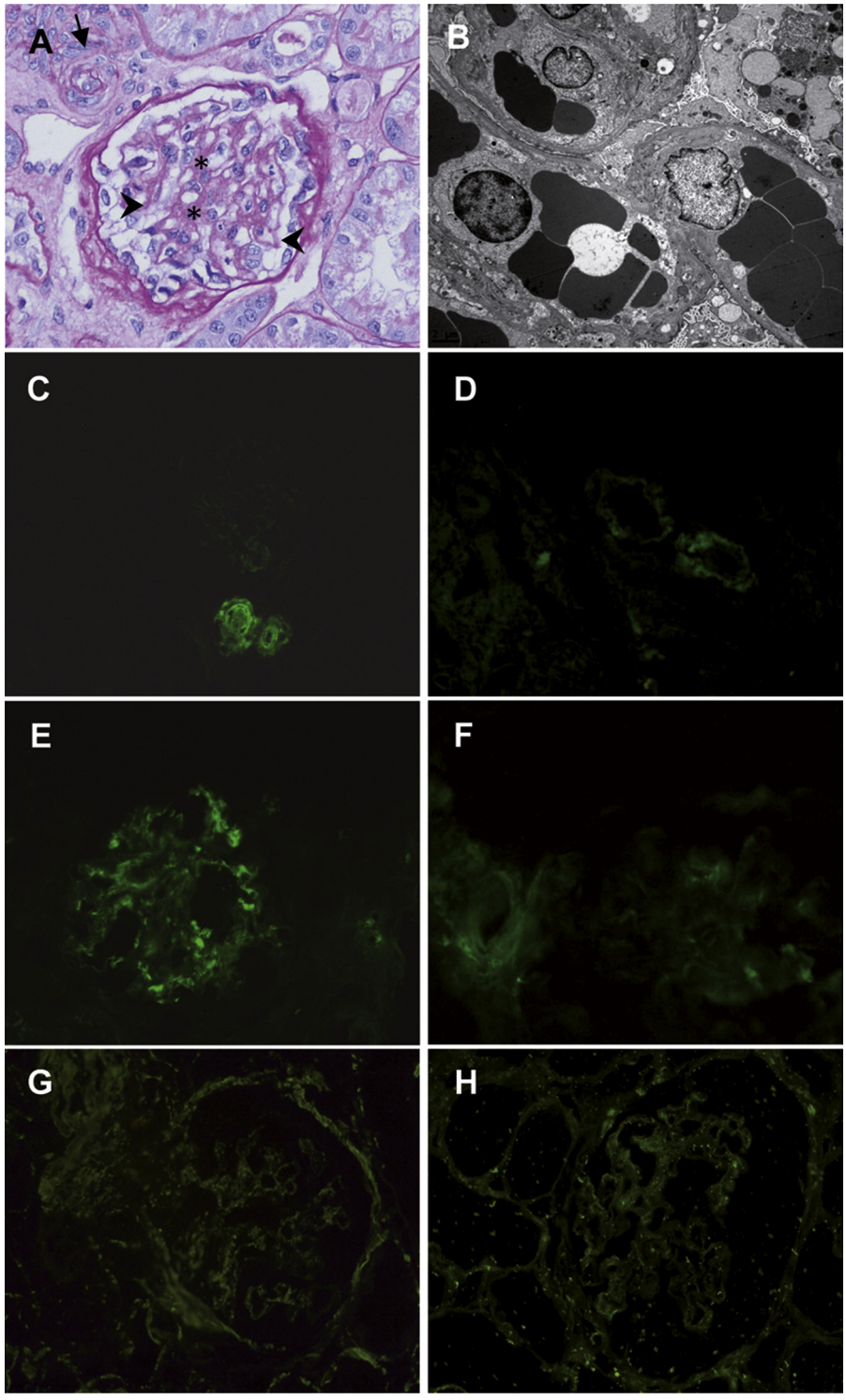


**Figure 1.** Pathology studies. (A) Preglomerular vessels presented intracapillary obstruction (→) associated with fibroproliferative endarteritis. In glomeruli, thickening or splitting of capillary walls (➤) was observed. These abnormalities were associated with swelling of subendothelial space and mesangial widening (*). (B) Electron microscopy was typical of atypical hemolytic uremic syndrome lesions in glomeruli. Immunofluorescence imaging of immunoglobulin A deposits in the (C) preglomerular vessels and (D) limb small arteries, C4d deposits in the (E) preglomerular vessels and (F) limb small arteries, and deposits of (G) C5b9 and (H) factor H in the renal microvasculature.

Hemolytic anemia, thrombopenia, and rapidly progressive kidney failure led to the diagnosis of HUS. Infections, autoimmune diseases, and malignancies are all potential causes of HUS; however, each of these possible causes was ruled out in this case.

A kidney biopsy specimen showed multiple intracapillary glomerular thrombi and vascular lesions characteristic of HUS (Fig 1A and B), as well as IgA, C4d, C5b-9, and CFH deposits on preglomerular vessels (Fig 1C, E, G, and H). No Congo Red staining was detectable