Peripheral Gangrene in Children With Atypical Hemolytic Uremic Syndrome

abstract

Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy with severe clinical manifestation, frequent recurrence, and poor long-term prognosis. It is usually caused by abnormalities in complement regulation. We report 2 cases of children affected by a catastrophic extrarenal complication. A 4-year-old Indian girl developed gangrene of the finger tips 2 days after initial presentation of aHUS. Factor H autoantibodies were identified. Renal function continued to decline despite daily plasma exchanges, and she was started on peritoneal dialysis 5 days after admission. The distal tips of the left hand remained gangrenous with a line of demarcation. Three weeks later, she did not return for follow-up and died at home because of dialysis-related complications. An Arabic girl developed end-stage renal disease due to aHUS in the fourth month after birth. A de novo activating C3 mutation was found. At age 9 months, she suddenly developed ischemic changes in fingers of both hands and several toes. The lesions progressed, and several finger tips became gangrenous despite intense plasma exchange therapy. The decision was made to administer complement blocking therapy with the C5 antibody eculizumab. All nonnecrotic digits rapidly regained perfusion. The 3 already gangrenous fingers healed with loss of the end phalanges. During maintenance, eculizumab aHUS activity subsided completely and some late recovery of renal function was observed. aHUS may present by thrombotic macroangiopathy of small peripheral arteries. Eculizumab appears effective in preserving tissue viability if administered before gangrene occurs and should be considered as first-line rescue therapy in such cases. Pediatrics 2013;131:e331–e335
Hemolytic uremic syndrome (HUS) is a rare disease of microangiopathy, hemolysis, thrombocytopenia, and renal failure.\textsuperscript{1,2} The pathophysiological hallmark feature of HUS is damage to endothelial cells and intravascular formation of microthrombi in renal arterioles and capillaries, which leads to mechanical hemolytic anemia and ischemic kidney injury. The most common form of HUS, associated with gastrointestinal infection by shiga toxin producing \textit{Escherichia coli}, has a good prognosis. The rarer atypical form (aHUS) has a poorer outcome, with 10% to 15% acute mortality and 50% of cases progressing to end-stage renal disease.\textsuperscript{1,2}

The aHUS is usually associated with abnormalities in genes encoding complement regulatory proteins, with mutations in the complement factors H, I, B, MCP, thrombomodulin, and C3 altogether accounting for 50% to 60% of cases.\textsuperscript{3} Furthermore, an autoimmune form of aHUS with inhibitory anti-Factor H autoantibodies is associated with deletions in the CFHR1-R3 gene cluster.\textsuperscript{4} Such abnormalities cause complement hyperactivation on the surface of microvascular endothelium and platelets, leading to endothelial injury and thrombus formation.\textsuperscript{5}

Although the renal microvasculature appears to be the predominantly affected target, extrarenal manifestations do occur. Organ pathology compatible with local thrombotic microangiopathy has been reported for brain, heart, lung, eye, pancreas, liver, and colon.\textsuperscript{6} Much less is known about macrovascular complications in aHUS. We recently encountered 2 children with aHUS due to abnormalities of complement regulation leading to peripheral gangrene. In 1 case, eculuzumab, a specific inhibitor of the terminal complement complex, was administered with remarkable clinical effects.

**PATIENT 1**

A previously healthy 4-year-old Indian girl with unremarkable family history presented to the Division of Pediatric nephrology at All India Institute of Medical Sciences, New Delhi, with pallor, oliguria, and edema of 1-week duration. She had been febrile for 3 days and 2 weeks before admission. Urine output was 1 mL/kg per hour. There was no history of diarrheal or dysenterylike illness at onset, gross hematuria, and jaundice or skin rash. Urinalysis revealed significant proteinuria and microhematuria. Serum creatinine level was 7.5 mg/dL; urea, 180 mg/dL; albumin, 3.2 g/dL; and serum lactate dehydrogenase (LDH), 6000 (normal <400) U/L. The hemoglobin level was 7.2 g/dL after 2 blood transfusions; white blood cell count, 12 600/mm\textsuperscript{3}; and platelet count, 42 000/mm\textsuperscript{3}. Fragmented red blood cells were seen in the peripheral blood smear. Blood cultures were sterile. On ultrasonography, both kidneys revealed increased echogenicity. A kidney biopsy revealed focal interstitial edema and focal dense lymphocytic infiltration. Small arteries and arterioles revealed endothelial swelling and subendothelial edema with fibrin thrombi seen in the arterioles suggestive of a thrombotic microangiopathy. There was no evidence of vasculitis. A diagnosis of aHUS was made. Serum C3 was low (0.32 mg/mL, normal range 0.89–1.78 mg/mL); antinuclear antibodies and antiphospholipid antibodies were negative. Protein C, protein S, antithrombin III, and D-dimers levels were normal, and the patient did not have the factor V Leiden mutation. On the second day of admission, she was noticed to have poor perfusion and cyanosis of tip of fingers of left hand.

A prepheresis plasma sample was tested positive for anti-factor-H antibodies with a titer of 13 300 AU/mL (arbitrary units versus reference positive plasma defined as 1000 AU/mL). The patient also had an underlying deletion in CFHR1-R3. Plasmapheresis was initiated with 150% of plasma volume by using fresh-frozen plasma for replacement. She received daily sessions of plasmapheresis for 8 days followed by 6 alternate day sessions. Oral pentoxifylline was administered to improve peripheral circulation, and blood pressure was controlled by using amlodipine (0.3 mg/kg per day). Despite this intense treatment, the digits became gangrenous over the next 6 days. Renal function continued to decline and peritoneal dialysis (PD) was started 5 days after admission.

A repeat anti factor-H antibody titer after 11 sessions of plasmapheresis was 1355 AU/mL. She was continued on continuous ambulatory PD, and a follow-up 2 weeks later revealed a serum creatinine level of 3.5 mg/dL; hemoglobin level, 9.0 g/dL; platelet count, 150 000/ mm\textsuperscript{3}; and a normal C3 level. The urine output was 100 to 200 mL/day, and a follow-up anti factor-H antibody titer was 345 AU/L.

The distal tips of digits of the left hand remained gangrenous with a line of demarcation. Three weeks later, she did not return for follow-up and died at home from fluid overload due to insufficient home dialysis treatment.

**PATIENT 2**

An Arabic girl first presented in the fourth month after birth to Dubai Hospital, United Arab Emirates, with severe hemolysis (LDH, 4025 U/L; hemoglobin level, 4 g/dL) and acute renal failure (serum creatinine level, 25 mg/dL; phosphorus concentration, 7 mg/dL; bicarbonate, 8.5 mmol/L) with severe fluid retention (stage II arterial hypertension, ventilator-dependent pulmonary edema, massive pericardial effusion). The child was stabilized on PD and plasma infusions but remained oliguric and dialysis-dependent and continued to exhibit multiple biochemical and hemolologic relapses of HUS despite plasma infusions administered every 48 hours. At age 9 months, she was referred to Heidelberg University Hospital for diagnostic workup.

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Upon admission, she showed mild biochemical signs of HUS activity (LDH, 400 IU/L; platelet counts, 135,000/mm³; haptoglobin level, <0.1 g/L) and complement activation (C3 0.5 [nL=0.6]; C3d 75 [nL=40] mg/L). Plasma infusions were discontinued to allow complement diagnostics. Within a few days, she developed a Raynaud-like discoloration of finger tips at the right hand. Within 5 days, the condition progressed to severe, painful ischemia of the fingers and beginning gangrene of the tips of digits II–V, with mild signs of hemolysis (LDH, 550 IU/L) (Figs 1 and 2). Daily plasma exchange by using 200% of plasma volume fresh frozen plasma for replacement as well as continuous prostacyclin infusions were started. Despite these measures, gangrene progressed and perfusion defects with cyanosis and edema appeared also in fingers of the left hand and several toes. At this point it was decided to administer the monoclonal anti-C5 antibody eculizumab (300 mg) as a complement blocking therapy. Within hours after infusion, the ischemia pain ceased; perfusion rapidly recovered in the fingers of the right hand proximally to the gangrenous areas, as well as in the affected left fingers and toes. LDH and platelet count normalized within 5 days (LDH, 207 IU/L; platelets, 387/mm³). The fingers with already established gangrene healed with demarcation and loss of the end phalanges. Eculizumab infusions were continued at 3-week intervals for 18 months with complete remission of aHUS. Although dialysis could not be discontinued, residual urine output gradually increased from 30 to 350 mL per day and glomerular filtration rate (mean of creatinine and urea clearance) from 1.1 to 7.1 mL/minute per 1.73 m². When the eculizumab dosing interval was subsequently increased to 4-week intervals, aHUS relapsed after 5 months triggered by a rotavirus infection. The relapse was rapidly responsive to eculizumab. Dosing frequency was subsequently increased to two-weekly, and the dose from 300 to 600 mg, accounting for the child's increase in weight from 9 to 11 kg. Up to now, 2 years after start of eculizumab, no further recurrences occurred.

A heterozygous de novo mutation in the C3 gene causing loss of C3 convertase regulation by factor H was found as the cause of the disease.

DISCUSSION
HUS is generally considered a thrombotic microangiopathy affecting arterioles and capillaries of parenchymatous organs. In the patients reported here, we noted severe perfusion defects of arteries supplying the fingers and toes, leading to gangrenous lesions of the distal phalanges of several digits. Our observations add to 4 previously reported children who developed peripheral gangrene of fingers and toes as a complication of aHUS.7,8
Considering the fact that the luminal diameter of the digital arteries (1.1 mm in adults) is 100-fold larger than that of the glomerular arterioles typically affected in HUS (11 μm in adult kidneys), these cases suggest that under certain conditions the HUS-specific vascular pathology can also manifest as thrombotic “macroangiopathy.” Thrombotic occlusion of small, middle-sized, and branches of large arteries leading to stroke, ischemic pancreatitis, and peripheral gangrene has also been reported anecdotally in adult patients with thrombotic thrombocytopenic purpura/HUS.

Hypocomplementemia was documented in both patients, as well as in the single previously reported aHUS case with peripheral gangrene in which complement was measured. We identified the genetic and acquired abnormalities underlying complement hyperactivation in both patients (i.e., a homozygous deletion in the CFHR1-3 gene cluster with factor H autoantibody positivity and a mutation in the factor H binding domain of C3. Both anomalies lead to functional factor H deficiency and uncontrolled activation of the alternative pathway C3 convertase. Because complement activation is a systemic process, it is conceivable that endothelial damage due to recurrent or even continuous complement activation in patients with genetic disorders of complement regulation should not be limited to arterioles and capillaries, but also occurs in larger arteries, although thrombus formation may rarely reach a critical size to cause acute obstruction. Of note in this context, multiple stenoses of large arteries recently observed in children with genetic complement dysregulation indicate that chronic, subclinical complement-mediated endothelial damage may lead to a distinct stenosing arteriopathy.

The C5 inhibiting monoclonal antibody eculizumab has recently become available as a specific therapy for aHUS caused by complement hyperactivation. Administration of eculizumab in patient 2 appeared highly effective in stopping the disease process, which had been largely resistant to intense plasma exchange and vasodilatory therapy. All peripheral tissues that had been ischemic but not yet necrotic recovered completely. The remarkable clinical efficacy of rescue therapy with eculizumab argues for its prompt administration as first-line rescue therapy in cases with imminent macrovascular thrombotic angiopathy. Moreover, remarkable late recovery of residual renal function was noted in the child, who had been on dialysis for 5 months and was largely anuric at the time when eculizumab was started. We also learned the need for continuous complement inhibition in this child with a loss of inhibition C3 mutation as a relapse occurred when dosing interval was increased to 4 weeks.

CONCLUSIONS

aHUS can include thrombotic macroangiopathy of small peripheral arteries. Eculizumab appears effective in preserving tissue viability if administered before gangrene occurs and should be considered first-line rescue therapy in such cases.

REFERENCES

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