CASE REPORT

Atypical hemolytic uremic syndrome with peripheral gangrene and homocysteinemia in a child

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Abstract
Atypical hemolytic uremic syndrome (aHUS) is a rare, progressive, life-threatening disease that frequently has a genetic component; it is usually caused by familial, sporadic or idiopathic reasons. We report a case of aHUS in a 21-month-old girl with coexisting of methylenetetrahydrofolate reductase mutations, homocysteinemia and thalassemia trait complicated by peripheral gangrene as extrarenal manifestation.

INTRODUCTION
Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy characterized by intravascular hemolysis, thrombocytopenia and acute kidney injury (AKI). It is classically associated with Shiga toxin-producing Escherichia coli (STEC) which is responsible for 85–95% of cases in children. An atypical classification of HUS is usually defined with origins unrelated to STEC, cobalamin deficiency, streptococci or other infections. Most cases of atypical HUS (aHUS) are associated with genetic dysregulation of the alternative complement pathway or coagulation cascade which suggests a genetic predisposition. Atypical HUS represents 5–10% of HUS cases with 70% of children having their first episode before 2 years of age. About 20% of patients with aHUS have extrarenal manifestations including many organ systems; peripheral gangrene is a very rare manifestation of aHUS [1–3].

In this reported case, we observed digital gangrene in a child with aHUS associated with homocysteinemia and thalassemia trait.

CASE REPORT
A 21-month-old girl was admitted to Children’s University Hospital—Damascus, with pallor, vomiting and fever 5 days before admission. Three days later, she developed dark-colored urine and then anuria.

On examination, her blood pressure was 120/75 mmHg (>99%, hypertension stage 2 [4]), the pulse was 150–160 beats/min, and her weight was 9.5 kg. She had dehydration, mild dyspnea, tachycardia and bilateral cyanosis in the tips of the fingers of both hands (Fig. 1).

There was no history of diarrhea or respiratory infection, and the rest of the examination was normal. Family history for HUS was negative, and the parents were third-degree relatives (cousins). Blood tests were as shown below (Table 1).

The peripheral smear showed many fragmented, burr and helmet red blood cells which are signs of intravascular hemolysis. ADAMS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) level test was not done owing to the unavailability of resources.
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Figure 1: (a) The bilateral cyanosis at the beginning of the illness. (b) The bilateral cyanosis at the beginning of the illness.

Figure 2: Hemoglobin electrophoresis which is consistent with thalassemia trait.

Table 1: Blood tests results

| Tests          | Results | Reference ranges |
|----------------|---------|------------------|
| Hemoglobin     | 6.1 g/dl| 11–14 mg/dl      |
| WBCs           | 7100/ml | 6000–17000/ml    |
| Reticulocyte count | 14.1% | <2%              |
| Platelets      | 84 × 10^5/ml | (150–400) × 10^5/ml |
| Serum urea     | 298 mg/dl| 11–36 mg/dl      |
| Serum creatinine | 7 mg/dl | 0.3–0.7 mg/dl    |
| Serum uric acid | 23 mg/dl| 2.5–5.5 mg/dl    |
| LDH            | 3245 U/l| 160–500 U/l      |
| Total protein  | 5.8 g/dl| 6–8 mg/dl        |
| Albumin        | 3.7 g/dl| 3.4–5.2 g/dl     |
| PT             | 73%     | Within normal    |
| PTT            | 32 s    | 30–40 s          |
| INR            | 1.17    | 0.8–1.2          |
| ESR            | 82 mm/h | 0–20 mm/h        |
| CRP            | 19.8 mg/L| <0.5 mg/L       |
| Direct Coombs test | Negative | —               |

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; WBCs, white blood cells.

Serum level of complement C3 was 0.51 g/L (normal 0.8–1.6 g/L), and complement C4 was 0.17 g/L (normal 0.16–0.48 g/L). Coagulation proteins tests showed protein C activity 132% (normal 65–140%), protein S activity 103% (normal 70–140%) and antithrombin III and antiphospholipid antibodies (IgG-IgM) within normal. Serological markers for hepatitis (B and C), antinuclear antibodies, anti-DNA antibodies and HIV antibodies were negative.

Hemoglobin electrophoresis showed that the patient is a carrier of thalassemia (Fig. 2).

Treatment included blood pressure control (amlodipine 0.6 mg/g) and peritoneal dialysis (PD) to treat AKI, in addition to blood transfusion. She was stabilized but remained anuric and dialysis-dependent. Daily fresh frozen plasma 10 mL/kg was also administered for 3 weeks.

Based on the likely diagnosis of aHUS, genetic testing was carried out for known relevant mutations. The patient was positive for methylenetetrahydrofolate reductase (MTHFR) mutations. Plasma homocysteine was 22.1 μmol/L (normal 5.2–12.5 μmol/L). Vitamin B9 and B12 supplements were given to decrease homocysteine level.

Kidney biopsy was performed and revealed thrombotic microangiopathy. A diagnosis of aHUS was made on the basis of microangiopathy (which had been confirmed by biopsy and peripheral smear), hemolytic anemia, thrombocytopenia and signs of acute kidney injury, in addition to the presence of hypocomplementemia and the absence of diarrhea.

Within 10 days, the cyanosis progressed to severe ischemia, and distal phalanxes of both hands became gangrenous (Fig. 3). She developed purple discoloration over distal phalanxes of the toes (Fig. 4).
Urine output started to become normal during a period of 3 weeks, but creatinine and urea levels did not improve; therefore she was being prepared to switch from PD to hemodialysis. Considering thrombophilia, anticoagulant therapy was started after stopping PD.

A few days later, her renal function deteriorated, and she developed fluid retention with a blood pressure of 140/100 mmHg (>99%, hypertension stage 2). In a couple of hours, she developed generalized edema and respiratory distress. Chest X-ray showed signs of pulmonary edema, and abdominal ultrasound showed large amount of fluid. Hydralazine, metoprolol and furosemide were administered. She suddenly developed severe dyspnea and bradycardia that did not respond to atropine administration and led to "cardiac arrest."
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DISCUSSION
Atypical HUS is a rare disease of uncontrolled complement activation; it is associated with a high mortality rate, and most cases progress to end-stage renal disease. Mutations in genes have been found in 50% of aHUS patients [5].

In this case our patient had AKI, thrombocytopenia and intravascular hemolysis. Hypocomplementemia was noted; kidney biopsy showed thrombotic microangiopathy; the history and clinical observation were negative for bloody diarrhea; all of this was consistent with aHUS.

She had peripheral cyanosis in the fingers and toes which had developed to gangrene in the distal phalanxes of the fingers, and this is considered as a rare complication of aHUS. As known, the luminal diameter of the glomerular arterioles which are typically affected in HUS is smaller than the digital arteries. This suggests that the pathophysiological process has progressed to involve arteries larger than the glomerular arterioles [6]. Small vessel vasculopathy secondary to complement abnormalities is considered the reason of these ischemic changes [3].

Recent evidence suggests that eculizumab (monoclonal antibody against C5) is efficacious in inducing remission and preventing life-threatening complications of aHUS [3]; unfortunately, it was not available.

We remarked homocysteinemia and the MTHFR mutations were positive; MTHFR mutations influence the homocysteine metabolism leading to increase plasma homocysteine. Homocysteinemia is known to be associated with increased thrombotic tendency [7]. A recent study about the polymorphism of hemostasis genes in children with aHUS showed that the MTHFR mutation could be a risk factor for aHUS [8].

Hemoglobin electrophoresis was consistent with thalassemia trait and that was found while investigating the anemia. Persons with thalassemia trait are usually clinically asymptomatic but sometimes have mild anemia [9]. There is no evidence that this could be a contributing factor to aHUS, and it is not clear whether it had worsened the clinical course or not.

This reported case comes after nine reported cases that include aHUS associated with peripheral gangrene. But this is the first one about aHUS complicated with peripheral gangrene in association with MTHFR mutations and thalassemia trait.

In conclusion, this reported case shows that aHUS can affect small peripheral vessels. The presence of MTHFR mutations can support considering hereditary thrombophilia as one of aHUS risk factors.

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GUARANTOR
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