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Case Report

Skin Involvement in Atypical Hemolytic Uremic Syndrome

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Skin involvement in atypical hemolytic uremic syndrome (aHUS) is very uncommon and therefore often unrecognized as a specific symptom of aHUS. We describe 3 cases of patients with aHUS who developed skin lesions that completely recovered when disease-specific treatment was established. These cases suggest that in individuals with aHUS, when skin lesions of unknown origin occur, the possibility that they are due to thrombotic microangiopathy should be considered.

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Atypical hemolytic uremic syndrome (aHUS) is severe thrombotic microangiopathy (TMA) characterized by platelet consumption, mechanical non–immune-mediated hemolysis, and multiorgan damage.[1] As many as 70% of patients with aHUS have mutations in the genes encoding complement regulatory proteins, which lead to uncontrolled activation of the C5b-9 membrane attack complex and consequent endothelial damage.[2]

Until 2009, the only available treatment for aHUS was plasmatherapy,[3] with incomplete or transient benefit.[4] Since then, eculizumab, a humanized recombinant monoclonal antibody targeting C5,[5] has been used successfully in patients with aHUS.[6,7] The most severely affected organ is the kidney, with other organs (liver, heart, and central nervous system) also affected,[6,8] but skin involvement has not been reported. We describe 3 cases of patients with complement factor H (CFH)-associated aHUS who developed persistent and otherwise unexplained skin lesions that were treated successfully by means of CFH-specific treatment.

CASE REPORTS

Case 1

In 2004, a 32-year-old woman presented at an adult nephrology unit with end-stage renal disease and was started on maintenance hemodialysis (HD) therapy. Subsequent investigations led to a diagnosis of aHUS with documented CFH gene mutation (an arginine to glutamine substitution at amino acid 1,215). Five months later, the patient started to experience severe night pain in the perimalleolar area (bilateral) followed by the development of skin lesions that evolved into superficial ulcers that came together in a single large and irregular ulcer (Fig 1A). Ten months after the initial presentation, the patient was referred to our center because of the worsening skin lesions. Laboratory tests did not reveal any clear evidence of disease activity except for undetectable haptoglobin (Table 1). On the basis of a working hypothesis that the skin lesions may have been the only clinical expression of the TMA (given the undetectable haptoglobin), plasma exchange with fresh frozen plasma thrice weekly was added to the HD (tandem plasma exchange–HD). The nocturnal pain ceased after the first plasma exchange sessions, and the skin lesions, which had persisted for as long as 6 months, healed within a few weeks (Fig 1B). Plasma exchange then was discontinued and the patient was discharged. Three weeks later, she reported the nocturnal pain had returned in the perimalleolar area; there was no evidence of skin lesions. Tandem plasma exchange–HD was resumed for a further 4 weeks and the symptoms disappeared. Plasma exchange gradually was discontinued and the patient was provided a regimen of weekly fresh frozen plasma infusions for preventing relapses. The skin lesions have not reappeared.

Case 2

In 2009, a 19-year-old man visited an adult emergency unit for severe headache. End-stage renal disease with nephrotic-range proteinuria was diagnosed. A kidney biopsy was not diagnostic, but a tentative diagnosis of membranoproliferative glomerulonephritis was made. A course of steroid therapy was tried without benefit, and soon after diagnosis, he started regular HD therapy. Six months later, he developed poorly controlled hypertension, and laboratory findings were compatible with a diagnosis of TMA.

All genetic investigations for aHUS were negative. Nevertheless, the patient was treated with weekly tandem plasma exchange–HD (for 3 weeks), which led to remission of the TMA and a significant improvement in hypertension. Two years later, while still on HD therapy, the patient was referred to our center because of persistent (10 months) lower-limb skin lesions characterized by numerous violaceous maculopapules that tended to coalesce centripetally, several petechiae, and ulcerative-necrotic lesions with well-defined borders, covered by eschar (Fig 1C). A skin biopsy showed upper dermal edema with swelling and thickening of vessel walls and perivascular inflammatory infiltrates

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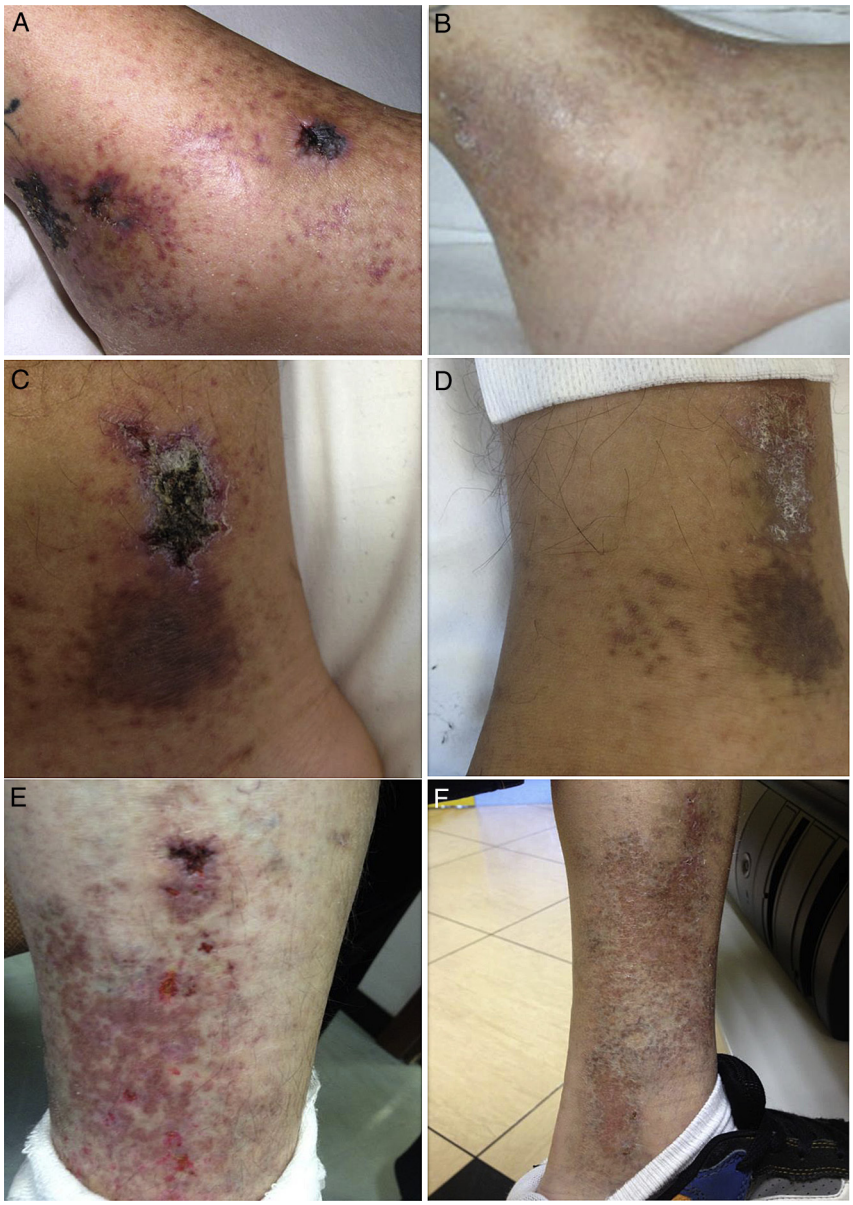

Figure 1. Skin lesions of the 3 patients before and after treatment. (A) Patient 1 before treatment, (B) patient 1 after treatment, (C) patient 2 before treatment, (D): patient 2 after treatment, (E) patient 3 before treatment, and (F) patient 3 after treatment.

mainly composed of lymphocytes (Fig S1, available as online supplementary material). These histopathologic changes were consistent with nonspecific vasculopathy. Direct immunofluorescence microscopy did not detect immunoglobulin or C3 deposits around dermal small vessels. The patient also had thrombocytopenia (Table 1), low C3 level (0.66 mg/mL), and anti-CFH antibodies. Because the lesions looked similar to those observed in case 1, we hypothesized that they may have had the same

Table 1. Laboratory Test Results Before and After Treatment

	Pretreatment				Posttreatment			
	Platelets ($\times 10^3/\mu L$)	LDH (U/L)	Haptoglobin (mg/dL)	SCr (mg/dL)	Platelets ($\times 10^3/\mu L$)	LDH (U/L)	Haptoglobin (mg/dL)	SCr (mg/dL)
Patient 1	265	378	<20	—[a]	189	397	NA	—[a]
Patient 2	105	295	116	—[a]	136	261	144	—[a]
Patient 3	318	313	146	2.49	355	296	136	2.37

Note: Treatment was with either fresh frozen plasma or eculizumab. Conversion factor for SCr in mg/dL to μmol/L, ×88.4.
Abbreviations: LDH, lactic dehydrogenase; NA, not available; SCr, serum creatinine.
[a]Receiving renal replacement therapy.