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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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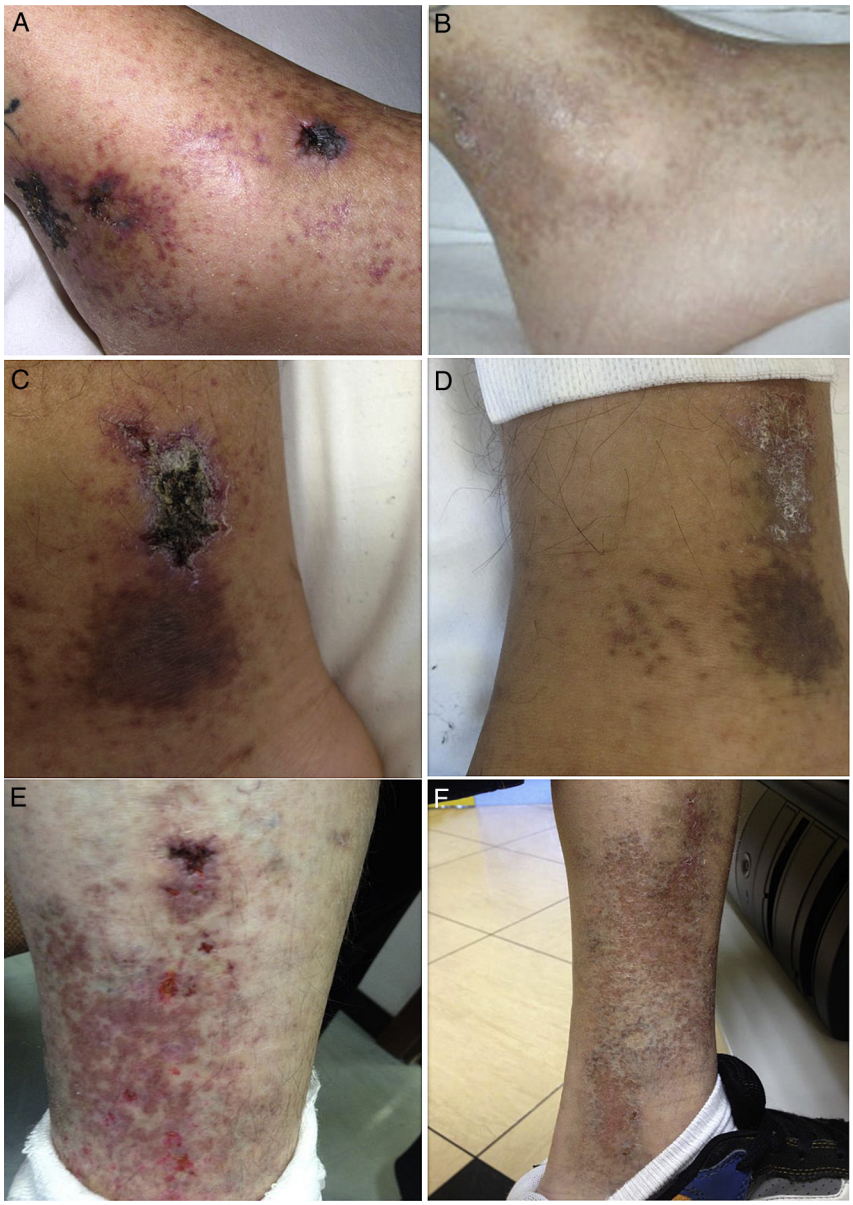

Figure 1. Skin lesions of the 3 patients before and after treatment. (A) Patient 1 before treatment, (B) patient 1 after treatment, (C) patient 2 before treatment, (D): patient 2 after treatment, (E) patient 3 before treatment, and (F) patient 3 after treatment.

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.

pathogenetic mechanism and treated the patient with one session of tandem plasma exchange–HD followed by eculizumab, 900 mg. The thrombocytopenia resolved and skin lesions fully recovered (Fig 1D).

Case 3

A 19-year-old man with aHUS developed purpuric and ulcerative-necrotic skin lesions on the lower limbs similar to those described in the preceding cases (Fig 1E). aHUS onset dated to when he was 6 months old and led to end-stage renal disease. Investigations showed a CFH gene mutation (the same arginine to glutamine substitution at amino acid 1,215 as described in case 1). Two years prior presentation, the patient successfully underwent kidney transplantation with preventive plasma exchange followed by regular plasma infusions. Because the skin lesions on the lower limbs were strikingly similar to those of the previously described cases, we suspected that they were a subtle expression of active TMA (no laboratory sign of disease activity was present, see Table 1) and switched the patient's treatment from weekly plasma infusions to eculizumab, 900 mg, every 2 weeks. The skin lesions immediately improved and disappeared within a few weeks, leaving a persistent dark brown hyperpigmentation (Fig 1F), although no significant change was observed in laboratory values relevant to TMA (Table 1).

DISCUSSION

HUS is a systemic TMA, and thus it is not surprising that various organs can be involved. Blood and kidneys are the most frequently affected organs, but the liver, brain, heart, and pancreas often are targeted.[6,8] Careful review of the available literature (we searched in PubMed and Google Scholar using a combination of key words and text words related to HUS and skin without language restrictions) did not show any reports mentioning the possibility of skin involvement in patients with aHUS, although Ehlayel and Akl[9] have reported mucocutaneous involvement in 4 patients with typical HUS who presented with necrotic mucosal and skin lesions that healed spontaneously within a few days.

We believe that the lesions reported in the present case reports can be attributed to TMA for the following reasons. First, the patients had well-documented and pathogenetically defined aHUS. Second, the patients were young, making it unlikely that the skin lesions were of a different origin (such as stasis dermatitis). Third, the macroscopic clinical picture was very similar in all 3 cases and was compatible with a diagnosis of cutaneous small-vessel vasculopathy. Fourth, histology of the only patient who underwent skin biopsy is highly compatible with microangiopathic lesions. Fifth, the skin lesions had a history of several months without spontaneous remission when the pathogenetic hypothesis was formulated and the aHUS-specific treatment was started. Sixth, the response to the treatment itself was clear and unmistakable. It also is interesting to note that the site of the skin lesions (lower limbs) was the same in all 3 patients and is the site typically affected in cutaneous vasculopathies of different origin.[10,11] The 3 patients were receiving renal replacement therapy, which may explain the absence of clear laboratory signs of active TMA; platelet consumption and hemolysis may be significantly reduced if there is no glomerular circulation.[12]

Our patients' skin manifestations resembled those of cutaneous small-vessel vasculitis, which is the most common form of vasculitis in dermatology affecting mainly cutaneous postcapillary venules.[10] Typically, the histopathologic pattern of cutaneous small-vessel vasculitis is leukocytoclastic vasculitis, which is characterized by upper dermal perivascular infiltrates, primarily comprising neutrophils with karyorrhexis of nuclei and fibrinoid necrosis of vessel walls. Direct immunofluorescence microscopy studies typically show deposits of immunoglobulin M (IgM) and/or C3 (less often, IgG) around the dermal small vessels in biopsy specimens taken from skin lesions of recent onset. The pathogenetic mechanism of cutaneous small-vessel vasculitis is an immune complex reaction; the circulating immune complexes interact with the complement system, generating C3 and C5a anaphylotoxins, which initiate chemotaxis of neutrophils, causing endothelial cell damage.[10] Thus, it could be argued that the recovery of the skin lesions after eculizumab therapy (in cases 2 and 3) may have been merely a nonspecific anti-inflammatory action of complement inhibition. However, this view would not explain the efficacy of plasma exchange in case 1. Moreover, the lack of frankly vasculitic changes on histology and the negative direct immunofluorescence microscopy findings in the only patient with a skin biopsy makes such a hypothesis unlikely.

In conclusion, we describe what to our knowledge are the first cases of skin involvement associated with (and possibly caused by) CFH-associated aHUS and encourage physicians caring for patients with aHUS to consider any skin lesions of unknown origin as possible manifestations of TMA, although the TMA may not be fully evident in laboratory tests.

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SUPPLEMENTARY MATERIAL

Figure S1: Skin pathology images of patient 2.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2013.09.020) is available at www.ajkd.org

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