Atypical hemolytic uremic syndrome with *MCP* mutations preceded by respiratory infection

Keiko Yasuda · Koichi Sasaki · Masaya Yamato ·
Hiromi Rakugi · Yoshitaka Isaka · Terumasa Hayashi ·
Rossella Piras · Elena Bresin

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Abstract A 14-year-old boy was referred to our hospital with general fatigue and sore throat. A chest X-ray and computed tomography revealed diffuse bilateral bronchitis. A laboratory examination showed anemia, thrombocytopenia, and renal insufficiency. He had a past medical history of hemolytic uremic syndrome (HUS) without diarrhea at the age of 3; moreover, his elder brother suffered from HUS at the age of 12. These findings indicated that the patient had a familial relapsing form of HUS (atypical HUS). Therefore, he was immediately treated with plasma exchange (PE), as suggested by guidelines, obtaining complete remission. Fifteen months later, he suffered another relapse of atypical HUS preceded by respiratory infection and was cured again with PE. His ADAMTS-13 activity was normal and its inhibitory antibody was undetectable. Two different mutations were found in the gene encoding membrane cofactor protein (MCP). Respiratory infections preceded all three episodes of HUS, but we

could not detect the pathogenic agent. Although the long-term outcomes of patients with atypical HUS who have mutations in the *MCP* gene appear favorable, recurrences are nevertheless frequent. Few reports have described Japanese patients with atypical HUS and complement regulatory abnormalities. This is the first report of a Japanese patient with atypical HUS and mutations in the *MCP* gene.

Keywords Atypical hemolytic uremic syndrome · Membrane cofactor protein · Mutations

Introduction

Mutations in the gene encoding membrane cofactor protein (MCP) have been identified in 10–15 % of patients with atypical hemolytic uremic syndrome (HUS) [1]. Although the long-term outcome appears favorable in these patients, with 80 % remaining dialysis-free, recurrences are nevertheless frequent [1]. Guidelines suggest that plasma therapy should be started within 24 h after diagnosis, without waiting for the results of definitive investigations such as genetic tests [2]. However, plasma therapy should not be useful in patients with *MCP* mutations, since MCP is a membrane-bound protein [3]. Our patient was effectively treated with plasma exchange (PE) before he was found to be heterozygous for two mutations in the *MCP* gene. There are many reports of atypical HUS patients all over the world, as well as many reports of genetic complement abnormalities associated with atypical HUS, especially in Europe. However, few reports have described Japanese patients with atypical HUS and complement abnormalities [4]. This is the first report of a Japanese patient with atypical HUS and two mutations in the *MCP* gene.

K. Yasuda · K. Sasaki · M. Yamato
Department of Nephrology, Rinku General Medical Center,
Osaka, Japan

K. Yasuda (✉) · H. Rakugi · Y. Isaka
Department of Geriatric Medicine and Nephrology, Osaka
University Graduate School of Medicine, B6, 2-2 Yamada-oka,
Osaka 587-871, Japan
e-mail: k-yasuda@rgmc.izumisano.osaka.jp;
k-yasuda@kid.med.osaka-u.ac.jp

T. Hayashi
Department of Kidney Disease and Hypertension, Osaka General
Medical Center, Osaka, Japan

R. Piras · E. Bresin
Mario Negri Institute for Pharmacological Research, Clinical
Research Center for Rare Diseases Aldo e Cele Daccò, Ranica
(Bergamo), Italy

Case report

A 14-year-old Japanese boy was referred to our hospital with general fatigue and sore throat. Chest X-ray and computed tomography (CT) revealed diffuse bilateral bronchitis. Laboratory evaluation (Table 1) showed elevated serum creatinine concentration (3.32 mg/dL), anemia (hemoglobin 12.8 g/dL), thrombocytopenia (platelets $7.1 \times 10^4/\mu\text{L}$), and schistocytosis. A search for Shiga toxin producing *Escherichia coli* (STEC) using PCR in the stool sample was negative. He had developed HUS without diarrhea at the age of three, and his two-year older brother had developed HUS at the age of 12. On the basis of these findings, a diagnosis of atypical HUS was made. Plasma exchange was immediately performed because of fast progressive hemolytic anemia and renal insufficiency. After four consecutive days of PE, his platelet count increased and his renal function recovered. At that time, his ADAMTS-13 activity was normal and its inhibitory antibody was undetectable. The activity of complement factor H was also normal and its inhibitory antibody was undetectable.

Fifteen months later, the patient was referred to our hospital for a new relapse of atypical HUS, with general fatigue and sore throat, again preceded by respiratory infection. Laboratory findings (Table 2) revealed elevated serum creatinine (3.19 mg/dL), anemia (hemoglobin 12.5 g/dL), and thrombocytopenia (platelets $5.9 \times 10^4/\mu\text{L}$).

Chest X-ray and CT showed diffuse bilateral bronchitis; these images were similar to those obtained during the previous episode of HUS. We knew that he had neither ADAMTS-13 inhibitory antibody nor factor H inhibitory antibody, so fresh frozen plasma (FFP) transfusion was performed on the first day of admission to the hospital. However, renal insufficiency led to oliguria, and his respiratory status worsened. We therefore decided to perform PE, since the FFP transfusion had led to volume expansion. A four-day course of PE was effective at increasing his platelet count and improving renal function.

It is known that infection can trigger atypical HUS episodes. Common infectious events such as upper respiratory tract infections or gastroenteritis appear to trigger HUS episodes in approximately two-thirds of atypical HUS patients [4, 5]. The occurrence of atypical HUS after specific bacterial or viral infections is exceptional. Respiratory infection preceded all three HUS manifestations in our patient. We therefore attempted to investigate the trigger for his respiratory infection. However, sputum cultures, influenza virus A and B antigens, respiratory syncytial virus, parainfluenza virus and adenovirus antibodies, measles virus RNA, human herpes virus 6 DNA, and cytomegalovirus DNA were all negative.

We also investigated the presence of genetic complement abnormalities in the DNA of the patient, identifying two heterozygous mutations in the short consensus repeats (SCRs) 1–4 of *MCP*, the hotspot mutation region of this

Table 1 Laboratory data on admission

CBC:	Blood chemistry:	
WBC 13180/ μL (neu. 87.0 %, eo. 1.1 %)	T-bil 5.2 mg/dL	CRP 6.0 mg/dL
RBC $432 \times 10^4/\mu\text{L}$	D-bil 0.2 mg/dL	PT 75 %
Hb 12.8 g/dl	AST 55 IU/L	PT(INR) 1.25
Plt $7.1 \times 10^4/\mu\text{L}$	ALT 9 IU/L	APTT 27.8 s
	LDH 1756 IU/L	D-dimer 4.00 $\mu\text{g/mL}$
	CK 319 IU/L	
Urinalysis:	Cr 3.32 mg/dL	Serology:
Specific gravity 1.020	BUN 45.7 mg/dL	CH50 32.2 U/mL
pH 5.0	TP 6.3 g/dL	C3 71 mg/dL
Prot (3+)	Alb 3.5 g/dL	C4 7 mg/dL
Glucose (–)	T-cho1 146 mg/dL	ANA 40
Occult blood (3+)	Na 136 mEq/L	ADAMTS-13 activity 64.2 %
		ADAMTS-13 antibody <0.5 Bethesda unit/L
RBC 124.7/HPF	K 5.7 mEq/L	IgG 761 mg/dL
Cr 326 mg/dL	Cl 100 mEq/L	IgM 64.9 mg/dL
UN 279 mg/dL	Ca 8.9 mg/dL	HBsAg (–)
Na 34.0 mEq/L	P 4.5 mg/dL	HCVAb (–)
		TPAb (–)
		RPR (–)

Table 2 Laboratory data when he suffered atypical HUS 15 months later

CBC:	Blood chemistry:	
WBC 14340/ μL (neu. 90.0 %, eo. 1.1 %)	T-bil 3.7 mg/dL	CRP 2.6 mg/dL
RBC $405 \times 10^4/\mu\text{L}$	D-bil 0.2 mg/dL	PT 78 %
Hb 12.5 g/dl	AST 74 IU/L	PT(INR) 1.18
Plt $5.9 \times 10^4/\mu\text{L}$	ALT 7 IU/L	APTT 29.5 s
	LDH 1986 IU/L	D-dimer 19.50 $\mu\text{g/mL}$
	CK 231 IU/L	
Urinalysis:	Cr 3.19 mg/dL	Serology:
Specific gravity 1.025	BUN 42.9 mg/dL	CH50 26.2 U/mL
pH 6.0	TP 6.3 g/dL	C3 82 mg/dL
Protein (3+)	Alb 3.9 g/dL	C4 8 mg/dL
Glucose (–)	T-cho1 180 mg/dL	ANA 40
Occult blood (3+)	Na 139 mEq/L	ADAMTS-13 activity 87 %
		ADAMTS-13 antibody <0.5 Bethesda unit/L
	K 4.6 mEq/L	HBsAg (–)
	Cl 103 mEq/L	HCVAb (–)
	Ca 9.1 mg/dL	TPAb (–)
	P 3.7 mg/dL	RPR (–)

gene. A new heterozygous deletion of 4pb (c.475+1_4delGTAA), predicted by GENSCAN web server (<http://genes.mit.edu/GENSCAN.html>) to delete seven aminoacids and change the eighth aminoacid, was found in the intronic region of SCR2. Moreover, a previously described heterozygous c.565T>G missense mutation, leading to the aminoacid substitution Tyr189Asp [7], was identified in the SCR3 of *MCP*. The sequences of complement factors H (CFH), I, C3, and of the thrombomodulin genes were normal, as were the levels of CFH antigen and activity.

Discussion

HUS is characterized by nonimmune hemolytic anemia, thrombocytopenia, and renal impairment [8]. Approximately 10 % of all HUS cases are classified as atypical, since they are not caused by Stx-producing bacteria or streptococci [8, 9]. Atypical HUS has a poor prognosis, with death rates as high as 25 % [9] and progression to end-stage renal disease in half of the patients [8, 10]. During the past decade, multiple genetic abnormalities associated with atypical HUS have been described [1]. Less than 20 % of all atypical HUS cases are familial [1]. Atypical HUS that develops in patients without a family history of the disease is classified as sporadic. Triggers for the sporadic form include infection by the human immunodeficiency virus, cancer, organ transplantation, pregnancy, and the use of certain anticancer drugs, immunotherapeutic agents (e.g., cyclosporine and tacrolimus), and antiplatelet agents (e.g., ticlopidine and clopidogrel) [11–13].

Complement regulatory abnormalities, either inherited or acquired through autoantibodies, are frequent causes of atypical HUS [6]. In patients with atypical HUS, a variety of mutations in members of the complement alternative pathway have been described, accounting for 50–60 % of cases [1]. Mutations in the *MCP* gene have been identified in 10–15 % of patients with atypical HUS [1]. Obtaining an etiologic diagnosis should help the patient to get better clinical advice and treatment. In the first week after disease presentation, clinicians usually do not have the results of definitive investigations such as genetic tests and plasma concentrations of complement factors and ADAMTS13 activity/antibody. Therefore, clinicians must decide empirically whether to implement initial treatment such as plasma therapy. According to the guidelines, the first plasma therapy (plasma exchange, 1–2 plasma volumes/day; plasma infusion, 20–30 ml/kg/day) should be instituted as soon as it is practicable within 24 h of diagnosis [2]. However, the atypical HUS patients who should benefit most from plasma treatment are those with mutations in plasma proteins, such as CFH and CFI. Overall, the published data [14, 15] on patients with CFH mutations show

either complete or partial (hematological normalization with renal sequelae) remission in around 60 % of plasma-treated episodes. Patients with CFI mutations show a partial response to plasma, and remission is achieved in about 30–40 % of treated episodes [14, 15]. However, patients with isolated MCP (CD46) dysfunction do not appear to benefit from plasma therapy [3, 4, 6]. This may be because MCP is a membrane-bound complement regulator, not a circulating one, and there is a high spontaneous remission rate. In fact, the patient's elder brother also suffered from atypical HUS when he was 12 years old, and he was cured without plasma therapy.

Moreover, plasmapheresis is not without risk [16]. The justification for urgent treatment when the etiological diagnosis is unknown is the high risk of early death, irreversible kidney damage, or the risks associated with prolonged disease activity [5, 6]. Recently, eculizumab (a humanized monoclonal antibody against C5) has been demonstrated to be effective in the management of atypical HUS refractory to plasma therapy [17, 18].

Our patient was diagnosed with atypical relapsing HUS and treated with plasma therapy. The presence of two *MCP* mutations was subsequently demonstrated, and this is the first published report of a Japanese patient with atypical HUS and mutations in the *MCP* gene. Obtaining an etiological diagnosis should avoid the need for excess treatment, such as plasma therapy, in this patient, who could benefit from conservative treatment alone in the future. In addition, we were able to inform the patient and his family that his long-term renal outcome should be good. However, another goal for this patient was to avoid recurrences. Respiratory infections preceded all three manifestations of his HUS. Detecting the trigger for his respiratory infection may help to elucidate the mechanism of his HUS recurrence.

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