

CASE REPORT

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March hemoglobinuria progressed to acute kidney injury after kendo practice: a case report

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Abstract

Background: March hemoglobinuria is caused by a hemolytic mechanism due to transient hematuria after physical exercise which, although rare, may lead to acute kidney injury. We report a case of a patient with march hemoglobinuria induced by kendo, which was diagnosed by the presence of Berlin blue iron staining in the proximal tubules through renal biopsy.

Case presentation: A 15-year-old male complained of fever (37 °C), general malaise, and nausea after hard kendo sessions. Laboratory findings revealed indirect bilirubin dominant hyperbilirubinemia (total bilirubin 3.8 mg/dL), high lactate dehydrogenase (LDH), and acute kidney injury (serum creatinine: 3.11 mg/dL and estimated glomerular filtration rate: 26 mL/min/1.73m²). Urine test was positive for occult blood but without hematuria. Renal biopsy was performed to clarify the cause of renal injury, which showed minor glomerular abnormalities. Meanwhile, hemosiderin deposition was identified in the proximal tubules by Berlin blue iron staining, and lysosomes were observed to contain granular iron. In addition to clinical background of strenuous kendo exercise, renal biopsy led to a definitive diagnosis of march hemoglobinuria.

Conclusions: March hemoglobinuria is a hemolytic disease that can occur after intense exercise, especially kendo. Considering its rarity due to the lack of critical symptoms, it is important to note that occult blood-positive findings may be indicative of march hemoglobinuria if the patient underwent strenuous exercise. Therefore, clinicians should be aware of this possibility to provide timely and appropriate treatment.

Keywords: March hemoglobinuria, Exertional hemoglobinuria, Hemosiderin deposit, Renal biopsy, Acute kidney injury

Background

March hemoglobinuria is a hemolytic disease characterized by transient hematuria after strenuous exercise, especially long-walking and running; it was first recognized by Fleisher in 1881 [1]. In addition to the exercise distance and speed, the hardness of the road surface and properties of the shoes worn were shown

to greatly influence the onset of march hemoglobinuria. In Japan, kendo, a martial art, is one of the triggers of march hemoglobinuria [2]. Gross hematuria triggered by kendo is caused by physical and mechanical intravascular hemolysis in the capillaries on the sole of the foot as a result of stepping exercises on bare feet. Since macroscopic hematuria disappears shortly after the end of exercise, it is often left unattended without visiting a hospital. Major symptoms associated with hemoglobinuria include nausea, abdominal pain, myalgia, and foot pain [3].

Cases of march hemoglobinuria accompanied by acute kidney injury are very rare [4]. Thus, we report a case of march hemoglobinuria induced by kendo in which Berlin

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blue iron staining was observed in proximal tubular cells obtained via renal biopsy.

Case presentation

A healthy 15-year-old Japanese male presented with fever (37°C), general malaise, and nausea after intense kendo exercise for 2 days. Laboratory findings revealed hyperbilirubinemia (total bilirubin 3.8 mg/dL), acute kidney injury (serum creatinine: 3.11 mg/dL, and an estimated glomerular filtration rate (eGFR) of 26 mL/min/1.73m²). The levels of serum creatine kinase was within normal limit. Thus, it is suggested that the cause of hemoglobinuria is hemolysis, but not rhabdomyolysis. It was no metabolic acidosis and electrolyte abnormalities. He had no history of kidney disease and was not taking any medications. He had hyperuricemia (uric acid 12.7 mg/dL), hyperbilirubinemia (indirect bilirubin dominant), high

lactate dehydrogenase (LDH), and his urine test indicated positive results for occult blood; however, hematuria was not detected (Table 1). At the time of the renal biopsy, the patient's height, weight, the percentiles of the length and the body weight, heart rate and blood pressure were 173.5 cm, 64.6 kg, 71.57 percentile and 72 percentile, 53/min and 144/83 mmHg, respectively. Physical examination findings were normal. Abdominal computed tomography (CT) revealed no abnormalities in both kidneys. We performed renal biopsy for a definitive diagnosis.

Histological findings showed minor glomerular abnormalities (Fig. 1a). We observed cast and hemosiderin deposition in the tubules (Fig. 1b). There were no significant findings in immunofluorescence analysis (Fig. 1c). Massive hemosiderin deposition was detected in the proximal tubules by Berlin blue iron staining (Fig. 1d). Electron dense deposits were not detected by electron

Table 1 Clinical data at the time point of renal biopsy

Parameter	Value (reference range)	Parameter	Value (reference range)	Parameter	Value (reference range)
Hematological		Blood biochemistry		Immunological test	
White blood cell count, /μL	8100 (4000-8000)	Total protein, g/dL	7.0 (6.7-8.3)	CH50, IU/mL	77 (32-49)
Hemoglobin, g/dL	15.6 (14-18)	Albumin, g/dL	4.7 (3.9-4.9)	C3, mg/dL	128 (65-135)
Platelets, × 10 ⁴ /μL	14.1 (15-35)	Blood urea nitrogen, mg/dL	30 (8-22)	C4, mg/dL	28 (13-35)
Reticulocyte, %	1.3 (0.2-2.8)	Creatinine, mg/dL	2.98 (0.61-1.04)	IgG, mg/dL	867 (870-1700)
		eGFR, mL/min/1.73m ²	27 (>60)	IgA, mg/dL	197 (110-410)
Coagulation test		Cystatin C, mg/dL	1.35 (0.63-0.95)	IgM, mg/dL	56 (35-220)
within normal range		Uric acid, mg/dL	12.7 (2-7)		
		Creatinine kinase, mg/dL	127 (60-287)	Antinuclear antibody, IU/mL	<40 (<40)
Urinalysis		Sodium, mmol/L	139 (138-146)	MPO-ANCA, IU/mL	<1.0 (0-3.5)
pH	5.0 (4.5-8.0)	Potassium, mmol/L	4.4 (3.6-4.9)	PR3-ANCA, IU/mL	<1.0 (0-3.5)
Specific gravity	1.011 (1.005-1.025)	Chloride, mmol/L	99 (99-109)	anti-GBM, U/mL	<2.0 (0-3)
Protein urea, g/g creatinine	<0.15 (<0.15)	Calcium, mg/dL	9.2 (8.7-10.3)	ASO, IU/mL	<10 (0-239)
Red Blood Cell, /HPF	1~4 (<5)	Glucose, mg/dL	98 (70-109)	ASK	<20 (<20)
White Blood Cell, /HPF	5~9 (<5)	Bilirubin totally, mg/dL	2.9 (0.2-1.3)	cryoglobulin	negative
U-NAG, IU/L	7.4 (0.7-11.2)	Bilirubin direct, mg/dL	0.9 (0-0.3)		
U-β2MG, μg/L	10 (0-230)	AST, IU/L	14 (13-33)	Haptoglobin, mg/dL	183 (19-170)
U-α1MG, mg/L	2.3 (1-15.5)	ALT, IU/L	11 (8-42)	DAT	negative
L-FABP, μg/g creatinine	0.81 (0-8.4)	LDH, IU/L	313 (124-222)		
Blood gas analysis		Total cholesterol, mg/dL	139 (128-219)		
pH	7.313 (6-8)	LDL cholesterol, mg/dL	82 (70-139)		
HCO ₃ , mmol/L	25.9 (0-99.9)	Triglyceride, mg/dL	83 (30-149)		
Base excess, mmol/L	-1.1 (-99~99)	C-reactive protein, mg/dL	1.9 (0-0.3)		
		HbA1c, %	5.3 (4.6-6.2)		
Hemolysis test					
Ham test	negative				
erythrocyte fragility test	negative				

U-NAG Urinary N-acetyl-β-D-Glucosaminidase, U-β2MG Urinary beta2-microglobulin, U-α1MG Urinary alpha1-microglobulin, eGFR Estimated glomerular filtration rate, L-FABP, L-type fatty acid-binding protein, AST Aspartate amino transferase, ALT Alanine aminotransferase, LDH Lactate dehydrogenase, LDL Low density lipoprotein, HbA1c Hemoglobin A1c, Ig Immunoglobulin, MPO Myeloperoxidase, PR3 Proteinase, ANCA Anti-neutrophil cytoplasmic antibody, GBM Glomerular basement membrane, ASO Anti-streptolysin, ASK Anti-streptokinase antibody, DAT Direct antiglobulin test

microscopy; however, lysosome incorporated iron granules were observed in the proximal tubules (Fig. 1e). Renal biopsy certified hemosiderin deposition in the proximal tubules, suggestive of march hemoglobinuria.

The patient was advised to rest and underwent fluid replacement with 1000 ml of hypotonic solution contained 90 mmol/L of sodium from day 1 to day 3 during hospitalization in addition to whole hospital diet and 1000ml of oral rehydration solution with electrolyte. The output of each day was about 1500-2000ml/day, thus leading to a normal kidney function (eGFR was improved from 27 to 90 mL/min/1.73m²) and bilirubin level. Hyperbilirubinemia and occult blood in the urine test were due to hemolysis. We also examined red blood cell fragility; however, the osmotic fragility test of erythrocytes and Ham's test were negative (Fig. 2a,b). This patient did not show any abnormalities in numbers of erythrocyte as well as peripheral smear. Moreover, hyperbilirubinemia and occult blood in the urine were improved after resting and hydration. Thus, we did not measure glucose-6-phosphate dehydrogenase (G6PD) in present case. We have followed up 1 year. This patient has

resumed kendo practice, however it has been stable without any acute renal injury and hemolysis due to avoiding dehydration and hard exercise.

Discussion and conclusions

March hemoglobinuria is a disease that presents with transient hemoglobinuria after strenuous exercise, such as a marathon, karate, and kendo. Kendo is a form of Japanese fencing characterized by repetitive stepping and is thought to result in intravascular hemolysis due to mechanical stress. Aspartate aminotransferase, creatine kinase, and lactate dehydrogenase (LDH) increased, serum haptoglobin decreased, and urinary occult blood was positive immediately after a stress test in kendo [5]. March hemoglobinuria developed not only with foot but also hand hemolysis, which was caused by playing the conga drum [6]. In the present case, hemolytic findings, such as an indirect predominant increase in bilirubin and an increase in LDH, were observed. If the urinary occult blood is positive but urinary red blood cells are not found, hemoglobinuria and myoglobinuria need to be differentiated, and paroxysmal nocturnal hemoglobinuria

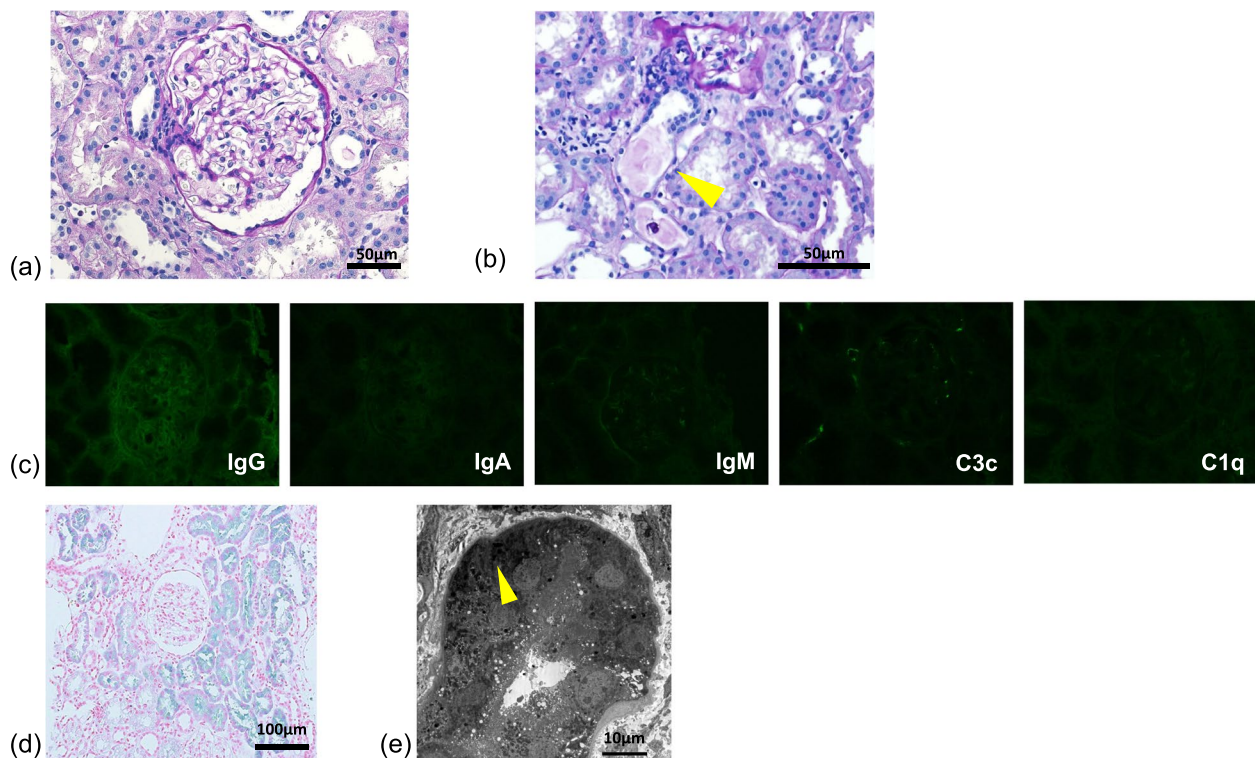


Fig. 1 Light microscopy Olympus BX53, OLYMPUS DP73 camera, and cellSense (Olympus Corporation, Center Valley, PA, USA) was used to capture the images. The images were obtained with eyepiece at 10X magnification and objective at 20X and 40X. No enhancement of the images was performed. The measured resolution was 4800 × 3600. **a** Histological findings show minor glomerular abnormalities (periodic acid–Schiff, 400 ×). **b** There is cast and hemosiderin deposition in the tubules (periodic acid–Schiff, 400 ×). **c** There are no significant findings in the immunofluorescence analysis. **d** Massive hemosiderin deposition detected in the proximal tubules by Berlin blue iron staining (200 ×). **e** Electron dense deposits was not detected by electron microscopy; however, lysosomes incorporated with iron granules are observed in the proximal tubules

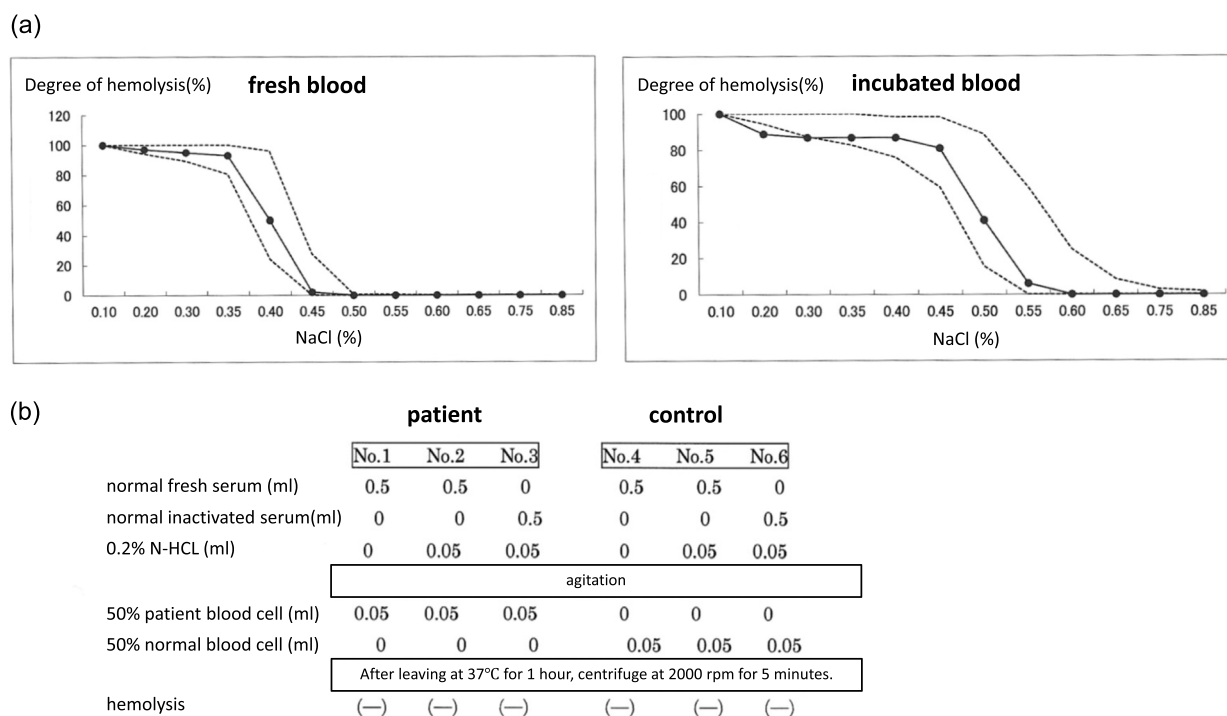


Fig. 2 **a** The osmotic fragility test. The inside of the broken line is hemolysis in the normal range, and the solid line shows the degree of hemolysis of this patient. The patient's red blood cells showed a degree of hemolysis within the normal range in both fresh and incubated red blood cells. **b** The test tubes of No. 1 to 3 were patient's group with patient's red blood cells and No. 4 to 6 test tubes were control group with normal red blood cells. Paroxysmal nocturnal hemoglobinuria (PNH) shows hemolysis with a mixture of acidified serum and patient erythrocytes (the No.2 test tube is positive), but inactivated serum and patient erythrocytes do not hemolyze even with acidification (the No. 3 test tube is negative). Present case showed negative response in all No. 1 to 3 test tubes

(PNH), rhabdomyolysis, and march hemoglobinuria should be considered.

When intravascular hemolysis persists, free hemoglobin released into the plasma by hemolysis strongly adsorbs nitric oxide, which has smooth muscle relaxation and platelet aggregation inhibition actions, resulting in vascular spasm and digestion. The function of vascular endothelial cells is often impaired, causing intravascular thrombosis [7]. In patients with PNH, 65% of the population had chronic kidney disease (CKD) and 21% were in CKD stages 3–5 [8]. It is believed that the mechanism of renal dysfunction caused by intravascular hemolysis is due to the deposition of progressive hemosiderin in the proximal tubules, which was not filtered because of its high molecular weight. Hemosiderin is thought to accumulate in the epithelium, causing tubular atrophy and interstitial fibrosis, leading to renal injury [9]. Case reports of acute kidney injury caused by march hemoglobinuria are rare because the volume of hemolyzed blood is small compared to PNH. Gilligan DR, et al. reported that the volume of hemolysis is only 6–40 mL in patients with march hemoglobinuria [10]. There were no abnormalities in urinary levels of NAG, β 2MG, α 1MG and

L-FABP in present case (Table 1). Previous report also indicated no tubular dysfunction [11]. Thus, there are very few case reports of renal biopsy for march hemoglobinuria [11–13]. In the present case, hemosiderin deposition was observed in the proximal tubule, and iron granules were also taken up in lysosomes, as observed in electron microscopic findings, which led to a definitive diagnosis of march hemoglobinuria.

It is also noteworthy that the cause of march hemoglobinuria may be an abnormality in the erythrocyte membrane. Banga JP, et al. found absent low-molecular-weight protein bands of the erythrocyte membrane structure in three cases of march hemoglobinuria [14]. Although the mechanism that explained the defect causing hemolysis has not yet been elucidated, march hemoglobinuria may be induced when patients with erythrocyte membrane anomalies exercise. However, no abnormalities in the erythrocyte membrane were detected in present case. This patient did not show any abnormalities in numbers of erythrocyte as well as peripheral smear. Moreover, hyperbilirubinemia and occult blood in the urine were improved after resting and hydration. Thus, we did not measure G6PD

in present case. Even in patients with no abnormalities in the erythrocyte membrane, exercise itself has the potential to cause changes in the erythrocyte fragility and impaired membrane structure, eventually promote to hemolysis [15]. Platt OS, et al. proved that dehydrated cells were more sensitive to shear stress and were turned to fragile [16]. It is suggested that severe dehydration during hard exercise enhanced intravascular hemolysis and tubular atrophy due to accumulation of hemosiderin, leading to acute kidney injuries.

It could be possible to prevent the recurrence of hemoglobinuria by wearing shoes [17], which would function to defend the feet from external stimuli. It was previously reported that hemoglobinuria after exercise caused by karate disappeared through the use of a sponge rubber cushion [18]. March hemoglobinuria is a hemolytic disease that occurs after intense exercise, and its prevalence is very rare due to a lack of a definitive diagnosis. However, it is beneficial for patients to receive lifestyle guidance via a definitive diagnosis.

In conclusion, this report serves as a reminder that march hemoglobinuria can occur in occult blood-positive cases after intense exercise.

Abbreviations

eGFR: Estimated glomerular filtration rate; LDH: Lactate dehydrogenase; CT: Computed tomography; CKD: Chronic kidney disease; G6PD: Glucose-6-phosphate dehydrogenase; NAG: N-acetyl- β -D-glucosaminidase; β 2MG: Beta2-microglobulin; α 1MG: Alpha1-microglobulin; L-FABP: L-type fatty acid binding protein.

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Authors' contributions

MY and HS reviewed the patient's clinical data and wrote the initial draft of the manuscript. SH, MI, HF, and HT assisted in the preparation of the manuscript and contributed to data collection and interpretation. ST provided the pathology of renal biopsy. HS and YS conceived the idea for this case report, carried out the analysis of the patient's clinical course, outcomes, and interpretation of findings, and provided critical review comments for the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The patient was informed about the availability and importance of the data, including the clinical data, images, and health information, described in this article.

Consent for publication

Written informed consent was obtained from the patient's parent for the publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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