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【 CASE REPORT 】

Successful Treatment of Acute Chest Syndrome with Manual Exchange Transfusion in a Patient with Sickle Beta^{+}-thalassemia

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Abstract:

Acute chest syndrome (ACS), characterized by fever, respiratory symptoms, and new pulmonary infiltration, is a serious complication of sickle cell disease (SCD). Regardless of the etiology, the conventional treatment options for ACS include empirical antibiotic therapy, the administration of analgesics, and red cell transfusion. The indications and methods of red cell transfusion are critical. We herein report the case of a 26-year-old African-American man with SCD who developed ACS and who was successfully treated with manual exchange transfusion. Despite increasing globalization, SCD remains extremely rare in Japan. Manual exchange transfusion can be performed easily anywhere and should be considered for treating SCD patients presenting with ACS.

Key words: acute chest syndrome, sickle cell disease

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Introduction

Sickle cell disease (SCD) is an expanding global health problem, with approximately 300,000 babies homozygous for sickle mutation estimated to be born with sickle cell anemia (SCA) each year (1). The disease is caused by a missense point mutation in the beta-globin gene that changes the sixth amino acid from glutamic acid to valine, which produces hemoglobin S (HbS) consisting of two alpha-globin and two beta-globin proteins with the sickle mutation ($a_2b^s_2$). HbS in red cells polymerizes reversibly in deoxygenated blood, leading to the sickling of red cells. Sickle cells have altered sticky membranes that adhere to the capillary endothelium and provoke episodes of microvascular occlusion, which can lead to acute pain and organ infarction as well as chronic pain and tissue ischemia (2).

An additional consideration in the increasing significance of SCD is individuals with the sickle cell trait (SCT), who are heterozygous for the beta-globin gene, with one beta-globin with the sickle mutation and one normal allele. These individuals are benign carriers with milder clinical symptoms. The probability that the genetic trait will be transferred to their descendants is 50%. Consequently, approximately 8% of African Americans have the SCT, and 1 in 6,000 is homozygous for SCA. SCT is considered to persist in the human population because it provides substantial resistance to severe malaria. A recent epidemiological study in Gabon, Africa, demonstrated a positive correlation between the prevalence of *Plasmodium falciparum* and the prevalence of individuals with SCT (3), implying that malaria continues to serve as a selection factor for SCT in the current world

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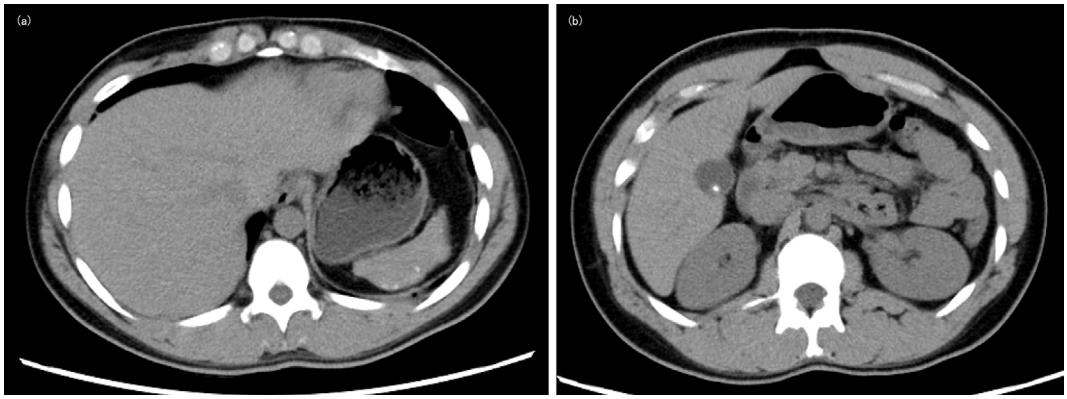

Figure 1. Transverse computed tomography without contrast medium on the day of presentation. The images show a relatively small spleen with multiple small calcifications (a) and a calcified gall stone (b).

population. As we stated previously, SCT itself is a benign carrier condition because the hemoglobin A (HbA) level is higher than that observed in patients with SCD. However, when SCT is co-inherited with another globin gene mutation, such as alpha, beta, or gamma globin, it can lead to the development of variant SCDs according to the elevation of the HbS level. In our patient, beta$^+$-thalassemia was co-inherited with the sickle mutation, which contributed to the development of the variant SCD of sickle beta-thalassemia by reducing the normal HbA level. Sickle beta-thalassemia is categorized into sickle beta$^+$-thalassemia and sickle beta^0-thalassemia on the basis of the presence of reduced amounts of beta-globin or the complete absence of beta-globin, respectively. The clinical manifestations of patients with sickle beta$^+$-thalassemia vary in accordance with the normal HbA (a_2b_2) levels in each genotype, and higher HbA levels are associated with a milder clinical course of SCD (4). Nearly 200 different mutations are reported to give rise to beta-thalassemia (5), and the prevalence of sickle beta-thalassemia has been estimated to be one-tenth that of SCA (6).

Acute chest syndrome (ACS) is an acute condition that uniquely develops in patients with SCD. It is characterized by fever, respiratory symptoms, and new pulmonary infiltration on chest X-ray. According to the Cooperative Study of Sickle Cell Disease reported in 1994 by Castro et al. the incidence of ACS was higher in patients with SCA (12.8/100 patient-years) and patients with sickle beta^0-thalassemia and lower in patients with sickle beta$^+$-thalassemia (3.9/100 patient-years) (7). Among the various complications of SCD, ACS is the second most common cause of hospitalization and is a leading cause of deaths in patients with SCD (8).

We herein report the case of a patient with sickle beta$^+$-thalassemia presenting with a second episode of ACS who was successfully treated with manual exchange transfusion.

Case Report

A 26-year-old African-American man presented to the outpatient department of our hospital with severe chest and abdominal pain. He had no other complaints before the emergence of faint pain in his lower abdomen during the early morning of the same day. The pain gradually progressed and spread to his chest, prompting him to leave work to seek medical help.

The patient had been regularly followed up by hematologists in his country since childhood, after being diagnosed with SCD with a sickle beta$^+$-thalassemia genotype. The patient had been working as an English teacher in Japan for the past 6 months and had a medical record in case of emergency. Eight months earlier, he experienced several acute pain episodes as well as an episode of ACS that required hospitalization for 10 days. His family history included thalassemia in his father and SCD in his mother and younger sister. He consumed alcohol occasionally and had never tried tobacco or illicit drugs. His medications included oral ibuprofen and oxycodone tablets as pain killers and oral folic acid (1 mg/day, tablet).

On presentation, the patient was alert. On the bed, he reported that he felt warm and he was sweating. His body weight was 70.0 kg, and his height was 172 cm. His vital signs were as follows: blood pressure, 142/81 mmHg; pulse rate, 120 beats per min; body temperature, 36.8℃; respiratory rate, 38/min; and oxygen saturation, 100% while breathing ambient air. A physical examination revealed guarding and slight tenderness on the left side of the abdomen and normal bowel sounds. Electrocardiography revealed sinus tachycardia. Abdominal computed tomography (CT) without contrast media revealed partial, small calcifications in the spleen and a calcified gall stone, which suggested chronic red cell destruction in the spleen (Fig. 1). The laboratory data showed marked leukocytosis and thrombocytosis, 18.53×10^3/μL and 347×10^4/μL, respectively, with mild elevation of the transaminase level (Table). However, subsequent CT with contrast media did not reveal any vessel thromboses or organ infarction. Giemsa staining of a peripheral blood smear showed various forms of red blood cells, including target cells, partially sickled and canoe-shaped cells,

Table. **The Laboratory Data on Admission.**

Complete blood count		Biochemistry	
WBC	18.53 $\times 10^3/\mu L$	Total protein	7.8 g/dL
RBC	5.27 $\times 10^4/\mu L$	Albumin	4.5 g/dL
Hemoglobin	12.9 g/dL	Total bililubin	1.4 mg/dL
hematocrit	37.3 %	AST	39 U/L
MCV	70.8 fL	ALT	26 U/L
MCH	24.5 pg	LD	426 U/L
MCHC	34.6 %	ALP	382 U/L
RDW	19.2 %	γ-GTP	30 U/L
N-Seg	61.5 %	CK	135 U/L
Eosino	0.5 %	UN	8.1 mg/dL
Baso	2 %	Creatinine	0.79 mg/dL
Mono	11.5 %	Coagulation	
Lymph	22.5 %	PT	100 %
Erythroblast	4 %	PT-INR	1
Platelet	347 $\times 10^4/\mu L$	APTT	25.8 s
Plasma		Fibrinogen	311.2 mg/dL
HbA1c	undetectable	FDP	6 μg/mL
Blood Sugar	97 mg/dL	D-dimer	3.7 μg/mL
Serological test		AT-III	91 %
CRP	0.93 mg/dL		
Arterial Blood Gases			
pH	7.361		
PCO_2	42.6 mmHg		
PO_2	78.9 mmHg		
HCO_3^-	23.5 mmol/L		
Base excess	-1.4 mmol/L		

WBC: white blood cell, RBC: red blood cell, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, N-Seg: neutrophil, Eosino: eosinophil, Baso: basophil, Mono: monocyte, Lymph: lymphocyte, HbA1c: hemoglobin A1c, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LD: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, CK: creatine kinase, UN: urea nitrogen, PT: prothrombin time, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation product, AT-III: antithrombin-III

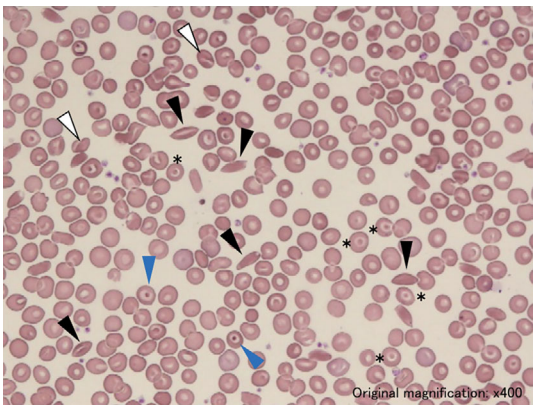

Figure 2. **Giemsa staining of a peripheral blood smear obtained from the patient showing various forms of red blood cells, including target cells (asterisk), partially sickled canoe-shaped cells (black arrowheads), folded (pita bread) cells (white arrowheads), and cells with Howell-Jolly bodies (blue arrowheads).**

folded (pita bread) cells, and cells with Howell-Jolly bodies; however, typical sickle cells were not observed (Fig. 2).

Based on the history and clinical findings, the patient was diagnosed with an acute painful SCD episode and was admitted to the intensive care unit of our hospital. Immediate consultation was arranged with hematologists, and treatment was initiated.

After the administration of one liter of crystalloid solution, intravenous infusion of fentanyl was started at a rate of 0.05 mg/h to alleviate pain, and the infusion rate was adjusted in accordance with the pain level. Simultaneously, the patient was started on intravenous ceftriaxone (2 g/day), a 3-day course of oral azithromycin (500 mg/day), and subcutaneous heparin (10,000 units/day). A microbiological examination did not reveal any infectious organisms. However, high-grade fever persisted for 5 days despite treatment, and new infiltration in his left lower lung appeared on chest X-ray (Fig. 3).

Based on the chest X-ray finding, the patient was diag-

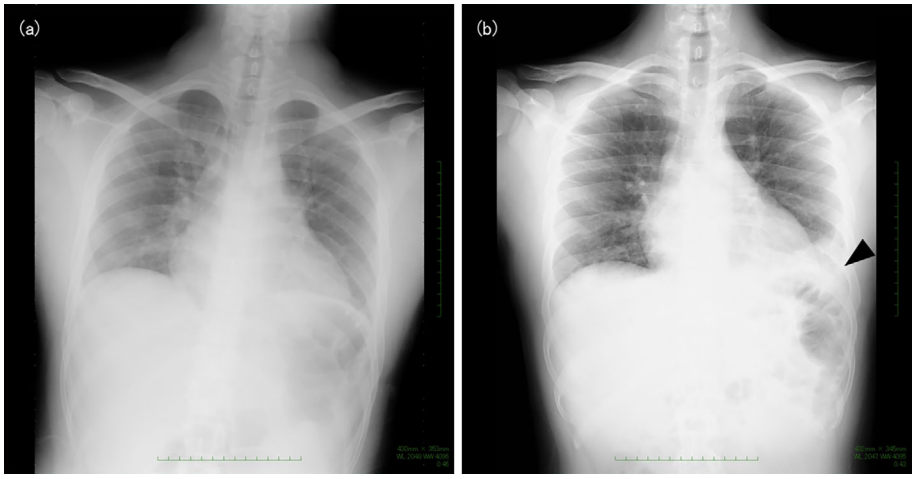

Figure 3. **Chest X-ray on the second (a) and fifth (b) days of hospitalization. Note new consolidation (arrowhead) that appeared on the fifth day of hospitalization.**

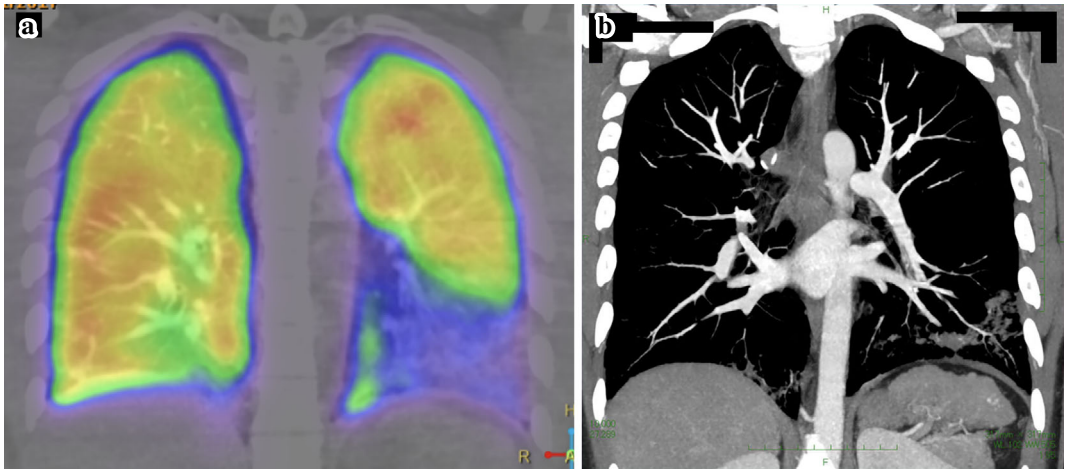

Figure 4. **Lung perfusion scintigraphy on the sixth day of hospitalization (a) and computed tomography angiography of the pulmonary artery on the seventh day of hospitalization (b). A marked decrease in blood flow can be observed on the left lower lobe (a). No apparent embolism can be found in the pulmonary artery (b).**

nosed with ACS on the fifth day of hospitalization. Simultaneously, however, the patient developed hypoxemia, with a blood oxygen saturation of 92%, and an abnormal, transient sensation in his left finger and appeared to deteriorate clinically. Because the patient had a relatively high hemoglobin level of 12.2 g/dL on the fifth day, top-up transfusion might have exacerbated his blood viscosity. Thus, we selected manual exchange transfusion, which was planned as follows:

1. Bleed (400 mL) and infuse (500 mL) saline simultaneously
2. Infuse two units of red cell concentrate, derived from 400 mL of whole blood in Japan
3. Repeat steps 1 and 2 until clinical improvement is obtained.

Specifically, ABO-compatible, extended Rh^- and Kell-matched red cells were used according to the guidelines of the British Society for Hematology (9). Pulmonary perfusion scintigraphy performed on the sixth hospitalization day revealed a marked decline in blood flow to the left lower lung (Fig. 4a). However, repeated CT angiography of the pulmonary artery revealed no evidence of embolism (Fig. 4b).

After the two courses of manual exchange transfusion, the patient's body temperature and C-reactive protein level began to decrease concomitantly with improvement in the chest and abdominal pain, and we decided to stop manual exchange transfusion. The patient was discharged on the 11th day of hospitalization (Fig. 5). After discharge, we planned to administer hydroxyurea to prevent another episode of ACS; however, the patient did not visit our hospital and was lost to follow-up.

Discussion

Although information on the patient's beta-thalassemia gene status was not available in his medical records, the medical history, imaging studies, laboratory tests, and pe-

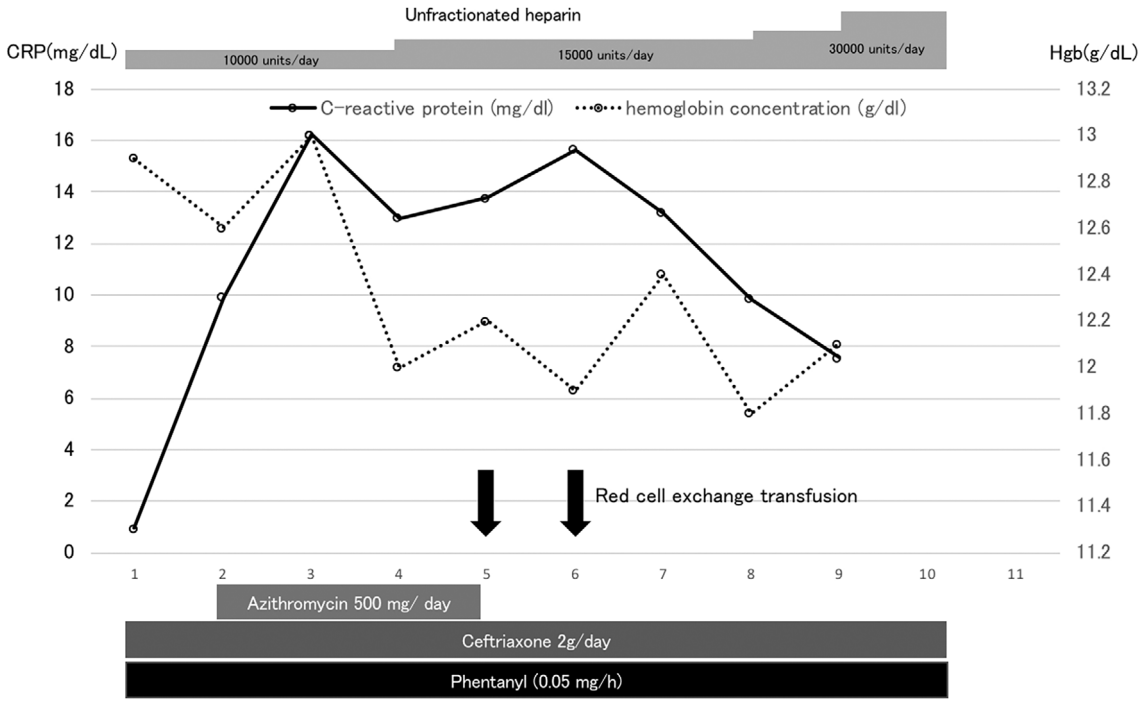

Figure 5. **The clinical course of the patient.**

ripheral blood smear showing the imperfect sickling of red blood cells were consistent with the diagnosis of sickle beta^{+}-thalassemia.

The patient was admitted to the intensive care unit for close monitoring without delay because, in addition to ACS, acute painful SCD episodes can occur due to several other serious conditions, including multiorgan failure (10), splenic or hepatic sequestration (11), acute coronary syndrome (12), and pulmonary embolism (13).

The patient was immediately started on a conventional treatment for ACS even before the confirmation of pulmonary infiltration due to the presence of severe chest pain, marked tachypnea, high-grade fever, and a white blood cell count of up to 18.53×10^{3}/μL, all of which are common manifestations of ACS (14). Howard et al. recommended that ACS should be strongly suspected in patients with pulmonary symptoms and signs, even in those with normal chest X-ray findings (9). In addition, radiological signs of ACS are often absent in the early stage, and nearly half of the patients with ACS were admitted for another reason, mainly pain (15).

The current patient exhibited the typical manifestations of ACS, and the diagnosis was relatively straightforward. However, other reported adult cases presented without fever (15) or with few clinical features of ACS (16), implying that the diagnosis of ACS can be difficult.

Although the cause of ACS in the current patient was not confirmed, several case series documented bone marrow and/or fat emboli as the leading cause of ACS episodes (17). In addition, bacterial infections, particularly atypical pathogens such as *Chlamydia* and *Mycoplasma* species, are important organisms that can cause ACS; thus, empirical antibiotic treatment to target these pathogens is critical (9).

We used unfractionated heparin from the beginning of the treatment because hypercoagulability and an enhanced platelet function are known characteristics of SCD. It has been reported that the prevalence of pulmonary embolism in hospitalized SCD patients below 40 years of age is 3.5 times higher than that in African-American controls; however, clinical trials evaluating anticoagulation the treatment and prevention of venous thromboembolism in SCD patients are lacking (18).

Red cell transfusion is an important approach in the treatment of SCD. Transfusion therapy is indicated for ACS patients who develop hypoxemia (oxygen saturation of <93% on room) air or worsening anemia (hemoglobin ≤10 g/dL) (19). Both simple top-up transfusions and exchange transfusions can be beneficial in cases of severe ACS (20). In our patient, exchange transfusion was chosen as the patient had a relatively high hemoglobin level. Exchange transfusion has several advantages over simple top-up transfusion, including reduced iron accumulation, more effective reduction in the percentage of hemoglobin S, and the avoidance of hyperviscosity, which may occur in cases with hemoglobin levels of >11 g/dL. Given that SCD patients receive red cell transfusions repeatedly, the amount and frequency of the transfusions should be minimized to avoid iron accumulation, alloimmunization, and hyperviscosity. Additionally, there is no evidence for an optimal HbS % target after exchange transfusion. We therefore, decided the amount of red cells to be exchanged based on the clinical response to the treatment (8).

The authors state that they have no Conflict of Interest (COI).

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