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The First Case of Bernard-Soulier Syndrome Presenting with Isolated Hemoptysis and Probable Diffuse Alveolar Hemorrhage: A Case Report and Literature Review

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ABSTRACT

Bernard-Soulier syndrome (BSS) is a rare platelet function disorder due to an impaired GPIb-V-IX complex, with an estimated incidence of one per million. Usual presentations include gingival bleeding, epistaxis, easy bruising, and post-traumatic excessive bleeding, among others, but not hemoptysis. The patient was a 46-year-old male who presented with three cups of hemoptysis two days before the presentation. He also had moderate burning chest pain for the past two weeks, which was getting better. He was diagnosed with BSS 45 years ago and had approximately 100 prior presentations for bleeding from various locations, including three prior episodes of hemoptysis. The mainstay of treatment was platelet transfusions, and the patient was carefully observed.

Only one case of hemoptysis in a patient with BSS was found, but the patient had hemoptysis due to underlying pulmonary tuberculosis. Therefore, hemoptysis or DAH were never reported in the literature due to BSS. This patient was the first case of massive hemoptysis and possible DAH related to BSS, emphasizing the need for proper attention due to its possible detrimental outcomes.

Introduction

Bernard-Soulier syndrome (BSS), or hemorrhagioparous thrombocytic dystrophy, is an exceedingly rare disorder of platelet function with an estimated incidence of one in a million people [1]. However, this estimation is likely underestimated due to the difficulty in its diagnosis, with many patients being diagnosed and treated with impressions of other disorders, especially immune thrombocytopenia (ITP) [2].

This syndrome results from an impaired GPIb-V-IX complex due to abnormalities in the subunits of this complex [3]. The GPIb-V-IX complex mediates platelet adhesion after an insult to the vascular endothelium via binding to von Willebrand factor (vWF) [4]. BSS is

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associated with consanguinity and is usually inherited as an autosomal recessive disease, but autosomal dominant inheritance has also been reported [3].

The diagnosis is usually made with moderate to severe thrombocytopenia, prolonged bleeding time (BT), large-sized (giant) platelets, normal clot retraction, and platelet aggregation studies, especially an abnormal ristocetin-induced aggregation [2]. Epistaxis, gingival bleeding, petechiae and purpura, menorrhagia, or excessive bleeding after trauma or surgery are among the most common presentations of BSS, but not hemoptysis [5].

Case presentation

The patient was a 46-year-old man with a history of Bernard-Soulier syndrome (BSS) who experienced three episodes of hemoptysis, coughing up about one cup of blood each time, two days prior to his presentation. After the last episode, he sought treatment at our hospital's platelet dysfunction unit, where he received six units of platelets. Although the hemoptysis stopped, he was concerned about its severity and was admitted to the emergency department, later transferred to the ward. He reported moderate burning chest pain over the past two weeks, radiating to his back, which differed from his previous coronary pain and resolved spontaneously after several hours. He denied fever, chills, night sweats, weight loss, dyspnea, nasal congestion, nausea, vomiting, or any signs of bleeding from other sites and had no recent trauma or foreign body ingestion.

His medical history includes a diagnosis of Bernard-Soulier syndrome (BSS) 45 years ago at our institution when he was one year old, and chest pain that led to coronary angiography without stenting four years ago. Records from 45 years ago indicated a bleeding time (BT) of over 20 minutes, clotting time of 5 minutes, thrombin time of 13.5 seconds, prothrombin time of 13.5 seconds, and partial thromboplastin time of 42.5 seconds. He had a platelet count of 56,000, normal clot retraction of 50% in one hour, and a peripheral blood smear showing over 10% giant platelets with no aggregation. He was officially diagnosed with BSS and had an ID card from the national blood bank to inform healthcare workers. His medications included atorvastatin, metoprolol, nitroglycerin, clonazepam (self-prescribed for sleep issues), and propranolol. Family history revealed consanguineous parents, a 25-pack-year smoking history, and opium abuse. On examination, he was awake, alert, and oriented. Vital signs were: pulse 80/min, blood pressure 107/76 mmHg, respiratory rate 22/min, temperature 36.3°C, and oxygen saturation 93% in ambient air. Cardiac auscultation revealed normal S1 and S2 without any murmurs. Lung auscultation demonstrated bilateral coarse crackles in the middle and lower lung fields. The abdomen was soft, non-tender, and without organomegaly.

Abnormal physical findings included an oxygen saturation of 86% and bilateral coarse crackles in the middle-to-lower portions of the lung. Laboratory studies revealed low platelet counts (PLT: 36,000), anemia (Hb: 9.8), and signs of defective gas exchange (pCO2: 60.7), without leukocytosis. A chest CT scan demonstrated bilateral ground glass opacities (GGOs), emphasized in the lower lobes, without evidence of other lesions. A possible diagnosis of diffuse alveolar hemorrhage (DAH) was made based on the massive hemoptysis, underlying platelet dysfunction, gas exchange abnormalities, and diffuse GGOs Initial lab tests showed a decreased hemoglobin concentration with normal leukocyte and platelet count. The coagulation panel was also within normal limits. (Table 1). A chest CT scan was ordered which demonstrated bilateral diffuse GGOsmore prominent at the middle and lower portion of the lungs, most compatible with DAH (Figure 1).

A pulmonology consultation suggested platelet transfusion under the supervision of the specialized service for platelet disorders, plus a pulmonary CTA and interventional radiology consultation for possible angioembolization if the hemoptysis happened again. They scheduled him for an elective bronchoscopy procedure in the upcoming days. on Platelet transfusions were administered, and dextromethorphan, intravenous tranexamic acid, and intravenous hydrocortisone were given to the patient. Levofloxacin was also given to protect against possible bacterial pneumonia.

The next day, the hemoglobin and leukocyte counts were unchanged, but the patient's platelet count decreased to 33,000. COVID-19 and influenza PCR tests returned negative. We ordered a PBS that confirmed the low platelet count and the presence of giant platelets. The same day, the patient complained of three episodes of coughing up half a cup of blood clots. We conducted an urgent chest CTA and observed diffuse bilateral GGOs. These findings were more noticeable in the lower lobes, along with new reticular changes, which are likely attributed to the subacute phase of DAH. However, no active extravasations were seen in the CTA (Figure 2). Therefore, the interventional radiology service did not find the patient to be a candidate for the angioembolization procedure.

Table 1. Laboratory values of the patient during the course of his disease

Laboratory study	Normal range in this institution	Day 0 (Emergency department)	1st day	2nd day	3rd-9th day	10th day	11th day	12th day
WBC (per µl)	4,000-11,000	8,900	9,800	7,900	7,900-12,300	7,300	9,400	9,200
Neutrophils (per µl)	1,100-7,700	5,790	7,480					
Lymphocytes (per µl)	1,000-4,800	2,580	1,950					
Monocytes (per µl)	200-1,200	530	370					
Eosinophils (per µl)	0-500	0	0					
Basophils (per µl)	0-100	0	0					
Hb (g/dl)	12.0-16.0	9.8	9	9.2	9.2-12	9	9.2	8.8
Hematocrit (%)	36.0-46.0	30.7	29.2	29.8	29.8-33.8	29.3	29.4	28.9
MCV (fl)	80-100	88.4	88.6	89.6	86.3-89	87.4	89.5	88.3
Platelets (per µl)	150,000-450,000	162,000	33,000	23,000	23,000-31,000	74,000	85,000	116,000
Na (mmol/l)	135-145	144	139	142	137-142	140	140	
K (mmol/l)	3.5-5.0	5.1	5.0	4.9	4.3-3.9	4.6	4.6	
Urea (mg/dl)	15-50	38	34	29	20-31	34	29	
Creatinine (mg/dl)	0.6-1.50	0.6	0.9	0.9	0.7-0.8	1.0	0.9	
FBS (mg/dl)	60-100	97	102	92	88-104	83	127	
ESR	<23 by age and sex	39						
CRP (mg/l)	<9 by age and sex	27						
Uric acid (mg/dl)	3.5-7.2	2.6				2.6		
Magnesium (mg/dl)	1.6-2.6				1.9			
aPTT (s)	25-40	25	27					
PT (s)	11-13.5	13.0	12.7					
INR	0.8-1.2	1.14	1.11					
Troponin-hs (ng/l)	<14				13.6-12.6			
COVID-19 PCR	-	Negative						
Influenza PCR	-	Negative						
Rheumatologic panel:								
ANA	<4				2.5 (-)			
Anti-dsDNA (U/ml)	<10				1.1 (-)			
C3 (mg/dl)	70-250				211 (NL)			
C4 (mg/dl)	10-40				20 (NL)			
CH50 (U/ml)	150-250				180 (NL)			
C-ANCA (U/ml)	<19				Negative			
P-ANCA (U/ml)	<1.4				Negative			
Anti-GBM (U/ml)	<2				Negative			
Anti-β2-glycoprotein IgM (U/ml)	<20				Negative			
Anti-β2-glycoprotein IgG (U/ml)	<20				Negative			
Anti-cardiolipin IgM (U/ml)	<20				Negative			
Anti-cardiolipin IgG (U/ml)	<20				Negative			
Lupus anticoagulant (U/ml)	<40				Negative			
VBG values:								
pH	7.35-7.45	7.266			7.371			
pCO2 (mmHg)	35-45	60.7			46.2			
PaO2 (mmHg)	60-100	33			58.3			
HCO3 (mmol/l)	22-26	27.6			26.7			

Abbreviations: WBC: White blood cells, RBC: Red blood cells, MCV: Mean corpuscular volume, FBS: Fasting blood sugar, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, aPTT: Activated partial thromboplastin time, PT: Prothrombin time, INR: International normalized ratio, ANA: Antinuclear antibody, Anti-dsDNA: Anti-Double-stranded DNA, NL: Normal, C-ANCA: cytoplasmic antineutrophil cytoplasmic antibodies, P-ANCA: perinuclear ANCA, Anti-GBM: Anti-glomerular basement membrane

On the second day, the platelet count again returned low at 23,000, but the hemoptysis began to decrease in amount. Platelet transfusion was continued. We requested a complete rheumatologic panel and asked for cardiology and anesthesiology consultations to confirm the feasibility of bronchoscopy.

As the platelet count was not increasing, we also administered intramuscular romiplostim (Nplate) on day 4 in the ward. His lowest platelet count between days 3 to 9 was 23,000, and the highest was 31,000.

Despite symptoms consistent with hemoptysis, we conducted an upper GI endoscopy due to the patient's history of frequent melena to rule out GI diseases and confirm the pulmonary source. The endoscopy on day 10 showed no abnormalities or signs of bleeding. Echocardiography on day 10 demonstrated normal left and right ventricular size and function; moderate pulmonary hypertension was observed. No pericardial

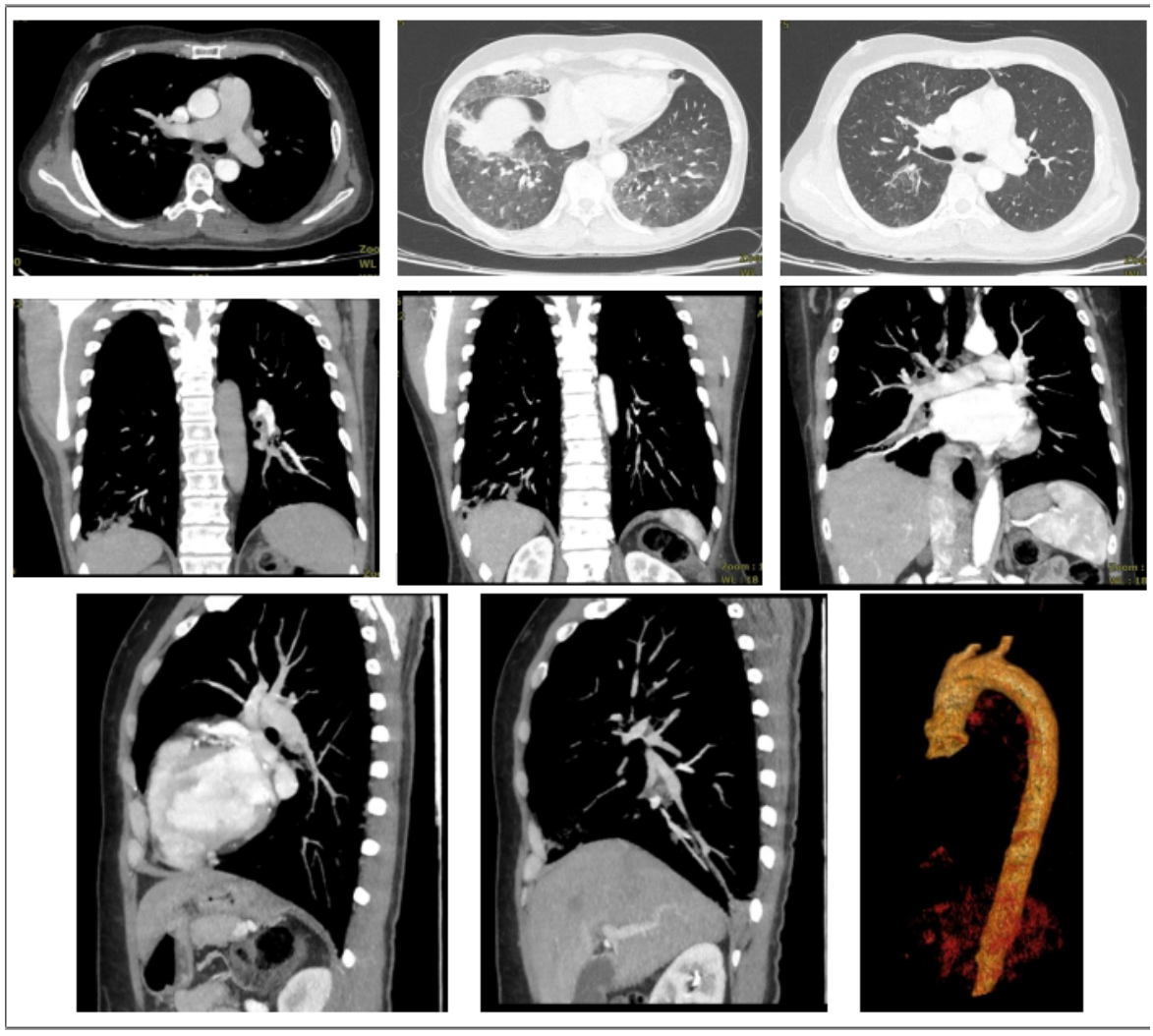

Fig. 1. Images from the patient's chest CT scan without contrast captured on the emergency room

effusion was evident. As a result, the cardiology and anesthesiology teams announced the bronchoscopy was without high risk. A bronchoscopy on the 11th day revealed no significant endobronchial lesions in the right lung, but there was a large clot in the origin of B8 that was extracted after washing. A bronchoalveolar lavage (BAL) was obtained from the right lower lobe and was negative for bacterial and fungal infections. All the rheumatologic tests also returned negative, including antinuclear antibody, anti-double-stranded DNA, complement levels, and antinuclear cytoplasmic antibodies.

On the 12th day, the patient reported no episodes of hemoptysis and his platelet count returned to 116,000. Based on the aforementioned findings, the favorable bronchoscopy reports, and the patient's preference to return home, we decided to discharge the patient. An appointment was scheduled in two weeks to reassess the patient's situation, but he has not shown up until now, two months after his admission.

Literature review

On February 4th, 2023, we searched the following term in PubMed, Cochrane, Scopus, and Web of Science: "(Bernard-Soulier[Title/Abstract]) AND (((Hemoptysis[Title/Abstract]) OR (Alveolar hemorrhage[Title/Abstract])) OR (Diffuse Alveolar Hemorrhage[Title/Abstract]))". The Web of Science and Cochrane databases found no records, PubMed had one [7], and Scopus yielded three [2, 7, 8], totaling four records, with one duplicate. One was a review unrelated to BSS [8], and another was a case report on BSS without hemoptysis [2]. Only one case of hemoptysis in a BSS patient was found; however, it was not directly related to the syndrome [7]. This 2014 case report from Iran described a 14-year-old girl with massive hemoptysis ultimately diagnosed with pulmonary tuberculosis. A key difference between

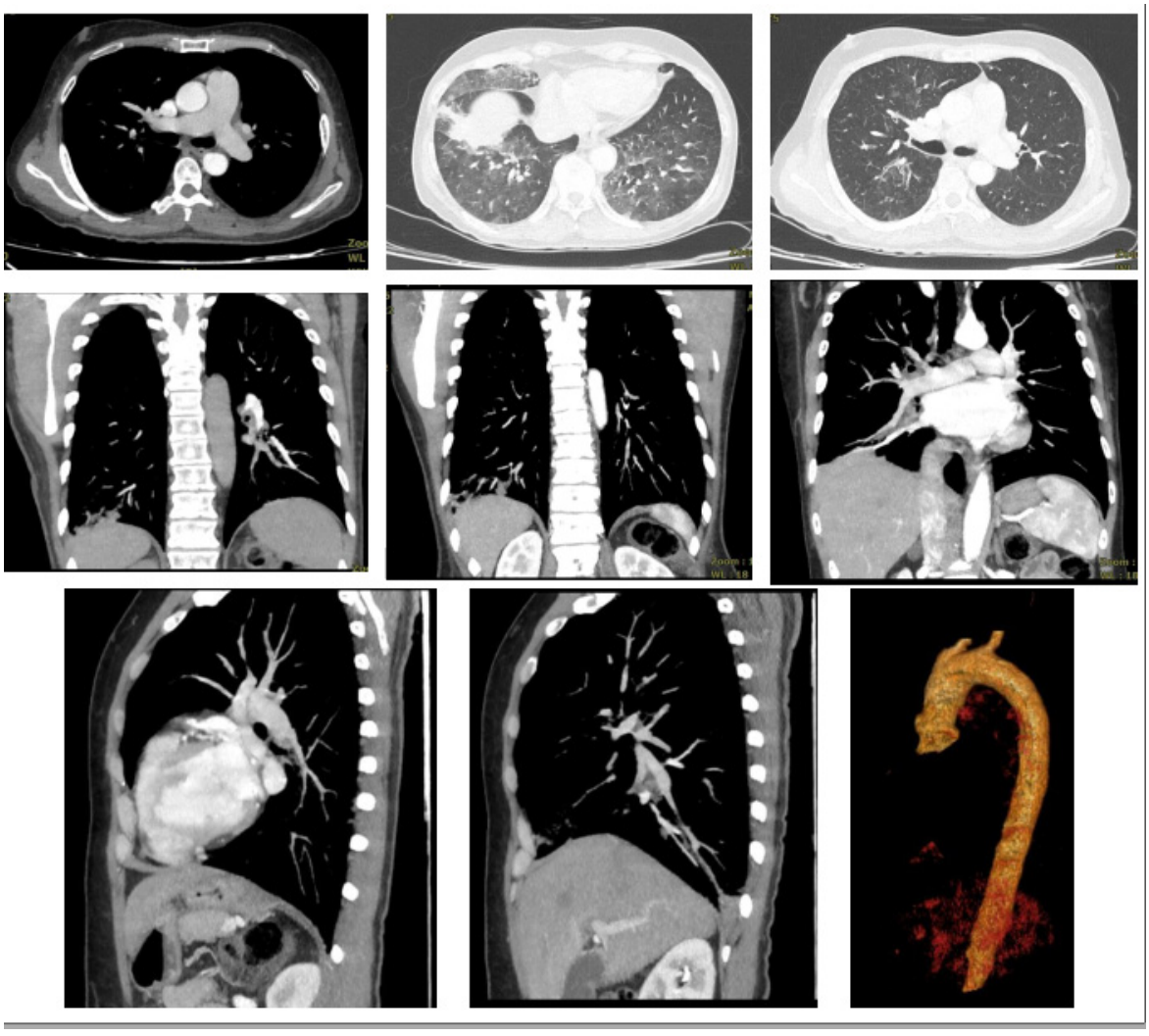

Fig. 2. Images from the patient's pulmonary CTA captured in the first night in the ward (slightly less than 48 hours after the chest CT scan)

this case and ours was the response to platelet transfusion. In our patient, two episodes of massive hemoptysis subsided with transfusions, while the previous case required anti-tuberculosis treatment for a clinical response [7]. The study also noted no hemoptysis cases in BSS patients as of 2014 [7].

Discussion

The patient with a history of Bernard-Soulier syndrome (BSS) presented with isolated, life-threatening hemoptysis due to diffuse alveolar hemorrhage (DAH), without signs of bleeding from other organs or secondary disorders. Despite varying definitions of massive hemoptysis, our patient met most criteria [9, 10]. Other causes of DAH were unlikely given the absence of related findings and a negative rheumatologic panel. His history of platelet disorder, previous hemoptysis episodes that resolved with transfusions, and the lack of infectious or neoplastic diseases suggest DAH related to BSS. This case is unique for several reasons: 1) BSS has an incidence of 1 in 1 million [3]; 2) It typically presents with gingival bleeding or epistaxis, making hemoptysis rare [2, 3]; only one other hemoptysis case in BSS was found, which was unrelated to platelet dysfunction [7]; 3) The patient experienced massive hemoptysis and prior non-massive episodes; 4) DAH is itself an uncommon cause of hemoptysis [12]; 5) Massive hemoptysis with DAH is unexpected without other bleeding signs. Reversal of bleeding diathesis is crucial in treating DAH in patients with bleeding disorders [11]. A limitation of this study was the delay in bronchoscopy due to the pulmonology unit's schedule. Additionally, genetic testing was not performed due to the patient's unwillingness, which could have provided insights into his unusual presentation. Follow-up referrals may yield more information regarding his status.

Ethical Considerations

Ethics approval and consent to participate

This study was conducted according to the Helsinki Declaration and approved by the local institutional review board. The patient consented to participate in the study.

Consent for publication

The patient gave written informed consent for the publication of this case report and any accompanying images. The editor-in-chief of this journal has a copy of the consent for review.

Availability of data and materials

Data are available upon request from the corresponding author.

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors declare no competing interests regarding any content published in this study.

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