Favorable outcomes of patients with sickle cell disease hospitalized due to COVID-19: A report of three cases

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Abstract. Sickle cell disease (SCD) is one of the most frequent and severe monogenic disorders, affecting millions of individuals worldwide. SCD represents a fatal hematological illness, characterized by veno-occlusive events and hemolytic anemia. Hemolytic anemia is caused by abnormal sickle-shaped erythrocytes, which induce parenchymal destruction and persistent organ damage, resulting in considerable morbidity and mortality. During the coronavirus disease 2019 (COVID-19) pandemic, patients with SCD were characterized as a 'high-risk' group due to their compromised immune system, caused by functional hyposplenism, as well as systemic vasculopathy. COVID-19 is characterized by endothelial damage and a procoagulant condition. The present study describes the clinical features, management and outcomes of 3 patients with SCD who were hospitalized due to COVID-19, who all had favorable outcomes despite the complications.

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Introduction

Sickle cell disease (SCD) is one of the most frequent and severe monogenic disorders, affecting 20-25 million individuals worldwide. It is caused by a single point mutation (Glu6Val) in the β-globin gene. Of note, >300,000 children with SCD are anticipated to be born each year globally, with almost 75% of these births occurring in Sub-Saharan Africa (1). SCD is a fatal hematological illness, characterized by veno-occlusive events and hemolytic anemia. Abnormal sickle-shaped erythrocytes, along with other blood cells that form aggregates, impair blood flow in small vessels, resulting in distal tissue ischemia and inflammation. When this process affects the bones, it causes the typical vaso-occlusive crisis (VOC), with the clinical manifestation of severe pain; however, every organ can be affected by vaso-occlusion. Sickling and persistent hemolytic anemia, even when mild or asymptomatic, induce parenchymal injury and chronic organ damage, resulting in significant morbidity and early mortality (2). Endothelial inflammation and predisposition to thrombosis are also hallmarks of SCD, which has recently been identified as a thrombophilic condition, and the incidence of venous thromboembolism (VTE) is increased in patients with SCD (3).

The definition of acute chest syndrome (ACS) includes a new pulmonary density on a chest radiograph and at least one of the following: Temperature ≥38.5˚C, tachypnea or shortness of breath, chest pain, cough and a decrease in oxygen saturation (SpO_2) (4). ACS is the second-most prevalent complication of SCD, accounting for ~25% of all deaths among patients with SCD. In the majority of cases, ACS presents following a VOC or surgery (5). A number of factors have been implicated in the pathophysiology of ACS, including infections, sickling and vaso-occlusion, inflammation, fat emboli caused by bone marrow necrosis, VTE and hypoventilation related to pain or

opioids. The incidence of viral infections causing ACS in adult patients with SCD has been reported to be <10% of cases (6). The severe form of ACS can lead to multi-organ failure. Transfusions or exchange transfusions are mandatory for the treatment of ACS when respiratory failure is developed (6).

Patients with SCD have been classified in the 'high-risk' category of the population during the coronavirus disease 2019 (COVID-19) pandemic due to their weakened immune system, caused by functional hyposplenism, as well as systemic vasculopathy, which poses them at risk of end organ failure and thrombosis (7). COVID-19 has been reported to trigger the development of ACS (8).

Endothelial damage and a procoagulant state appear to be distinct hallmarks of COVID-19 (9). In COVID-19, it has been observed that a shift in the vascular equilibrium with endothelitis with lymphocyte infiltration and subsequent ischemia is linked to a procoagulant condition, particularly in high-risk ethnicities, such as African Americans (10,11). As a result, the SCD population appears to be at an increased risk of developing severe pulmonary vascular damage as a result of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (12). There is a serious concern that the overlap in the pathophysiology of COVID-19-related lung disease and ACS will lead to unfavorable outcomes in these patients. Furthermore, as both COVID-19 and SCD promote the incidence of thromboembolic events, the combination of these two disorders may significantly raise the risk of complications (13).

Reports of patients with SCD infected with COVID-19 have previously been published, with contradictory outcomes. In some of these reports, the patients were shown to present with a surprisingly satisfactory clinical outcome, which was unexpected given the vulnerability of patients with SCD to infections and vaso-occlusive complications (14,15). The present study describes the clinical characteristics, management and outcomes of 3 unvaccinated patients with SCD who were hospitalized due to SARS-CoV-2 infection in a hospital in Greece.

Case report

Case 1. The first case is that of a 54-year-old male patient with S/β-thalassemia. His medications included hydroxyurea at 1,000 mg daily, folic acid at 5 mg daily and acetylsalicylic acid at 100 mg daily.

The patient presented to the Emergency Department (ED) of Laiko General Hospital (Athens, Greece) with complaints of fever over the last 14 days. He was unvaccinated for SARS-CoV-2. He had a positive reverse transcription-polymerase reaction (RT-PCR) test of a nasopharyngeal specimen for SARS-CoV-2 infection 10 days prior to his visit to the ED. In the ED, the patient was noted to have a SpO_2 of 90% in room air, a blood pressure (BP) of 120/50 mmHg, a heart rate (HR) of 88 bpm and a temperature of 39.2˚C. The clinical characteristics of the patient are summarized in Table I.

A clinical examination revealed crackles on auscultation at the right lung base. The remaining results of the clinical examination did not reveal any notable findings. A chest X-ray was performed and revealed patchy infiltrates, mostly in the lower lung fields (Fig. 1A). The analysis of arterial blood gas revealed partial pressure of oxygen (pO_2) levels of 52 mmHg, partial pressure of carbon dioxide (pCO_2) levels at 28 mmHg, pH 7.47 and HCO_3- at 20.2 mmol/l in room air. The results of the laboratory analysis are summarized in Table II.

The patient underwent a chest computed tomography (CT) scan and computed tomography pulmonary angiogram (CTPA), which revealed nodular ground glass opacities in all lung fields (Fig. 1B and C). Pulmonary embolism was not detected.

The patient received oxygen therapy with a nasal cannula delivering oxygen at a flow rate of 3 liters/min. He was also treated with fluid replacement therapy, subcutaneous enoxaparin, intravenous remdesivir, dexamethasone and ceftriaxone. He received a simple transfusion of 1 unit of red blood cells (RBCs). After 3 days of hospitalization, his clinical condition and oxygen levels improved. No other complications occurred, and the patient was discharged following a hospitalization duration of 8 days.

Case 2. The second case is that of a 45-year-old male patient with S/β-thalassemia. He had a past medical history of splenectomy and hospitalization for acute painful VOCs, 3 years prior. His current medications included folic acid at 5 mg daily and acetylsalicylic acid at 100 mg daily.

The patient presented to the ED of Laiko General Hospital with complaints of low-grade fever, pain in the upper extremities and chest pain over the last 24 h. In the ED, the patient was noted to have a SpO_2 of 93% in room air, a BP of 140/70 mmHg, a HR 85 bpm, and a temperature of 36.7˚C. The clinical characteristics of the patient are summarized in Table I.

A clinical examination revealed diminished breath sounds on auscultation at the left lung base. It also revealed yellow eyes and skin, indicating jaundice. A chest X-ray was performed and this revealed mild infiltrates in both lungs and blunting of the left costophrenic angle (Fig. 2A). The analysis of arterial blood gas revealed pO_2 levels of 70 mmHg, pCO_2 levels of 31 mmHg, pH 7.42 and HCO_3- at 20.5 mmol/l in room air. The results of the laboratory analyses are summarized in Table II.

The patient was tested for SARS-CoV-2 infection and had a positive detection of SARS-CoV-2 nucleic acid in an obtained nasopharyngeal sample using RT-PCR. He had been vaccinated against SARS-CoV-2. The patient underwent a chest CT scan and CTPA, which revealed nodular ground glass opacities in all lung fields and a small left pleural effusion (Fig. 2B and C). Pulmonary embolism was not detected.

A diagnosis of VOC complicated by ACS was made. The patient received oxygen therapy with a nasal cannula delivering oxygen at a flow rate of 3 liters/per min. He was also treated with fluid replacement therapy, subcutaneous prophylactic enoxaparin, intravenous morphine, remdesivir, dexamethasone and ceftriaxone. In total, he received four simple top-up transfusions of 4 units of RBCs. Following 3 days of hospitalization, the pain and oxygen levels had improved. The biochemical abnormalities had also gradually improved. The patient was discharged following a hospitalization duration of 16 days.

Case 3. The second case is that of a 50-year-old female patient with S/β-thalassemia. She had a past medical history of splenectomy, cholecystectomy, hypothyroidism and depression.

Table I. Clinical characteristics of the patients in the present study.

Case	Age/sex	Genotype	Blood group	Vaccination status	Imaging findings	Complications	Management	Days of hospitalization	Outcome
1	54/M	S/β-thalassemia	0	Unvaccinated	Chest CT scan and CTPA revealed nodular ground glass opacities in all lung fields. Pulmonary embolism was not detected	None	Oxygen therapy; fluid replacement; remdesivir; enoxaparin; dexamethasone; antibiotics; transfusion of RBCs	8	Recovery
2	45/M	S/β-thalassemia	0	Unvaccinated	Chest CT scan and CTPA revealed nodular ground glass opacities in all lung fields and a small left pleural effusion. Pulmonary embolism was not detected	VOC, ACS, hemolysis	Oxygen therapy; fluid replacement; morphine; remdesivir; enoxaparin; dexamethasone; antibiotics; transfusion of RBCs	16	Recovery
3	51/F	S/β-thalassemia	A	Unvaccinated	Chest CT scan and CTPA revealed ground glass opacities and consolidation in lower lung lobes and pulmonary embolism located in proximal subsegmental branch of the left pulmonary artery	VOC, ACS, pulmonary embolism	Oxygen therapy; fluid replacement; morphine; tramadol; remdesivir; enoxaparin; dexamethasone; antibiotics; transfusion of RBCs	21	Recovery

ACS, acute chest syndrome; CT, compute tomography; CTPA computed tomography pulmonary angiogram; F, female; M, male; RBCs, red blood cells; VOC, veno-occlusive crisis.

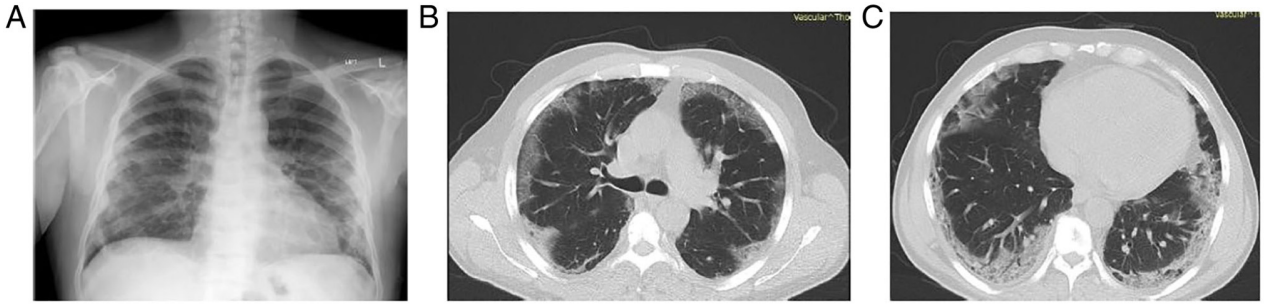

Figure 1. Case 1. (A) Chest X-ray illustrating patchy infiltrates, mostly in the lower lung fields. (B and C) Computed tomography scan of the chest illustrating nodular ground glass opacities in all lung fields.

Table II. Laboratory analyses of the three cases in the present study.

Parameter	Case 1	Case 2	Case 3
Hematocrit, % (normal range, 40-54%)	21.3	22.5	27.6
Hemoglobin (normal 13.5-18 g/dl)	6.8	7.4	9.3
White blood cell count, K/μl (normal range, 4.5-11 K/μl)	7.29	11.52	16.68
Neutrophil count, K/μl (normal range, 1.5-6.6 K/μl)	5.3	7.8	11.48
Lymphocyte count, K/μl (normal range, 1.2-3.4 K/μl)	1.49	2.78	4.1
Red blood cell count, M/μl (normal range, 4.6-6.2 M/μl)	2.71	2.84	4.15
Platelet count, K/μl (normal range, 140-440 K/μl)	304	70	312
Aspartate transaminase, U/l (normal range, 10-40 U/l)	31	493	50
Alanine transaminase, U/l (normal range, <41 U/l)	24	111	60
Creatine kinase, U/l (normal range, 38-190 U/l)	175	15,003	40
Lactate dehydrogenase, U/l (normal range, 135-225 U/l)	238	8,440	380
Gamma-glutamyl transferase, U/l (normal range, 8-61 U/l)	44	87	237
Alkaline phosphatase, U/l (normal range, 40-129 U/l)	74	774	149
Ferritin, ng/ml (normal range, 30-400 ng/ml)	552	>100,000	854
C-reactive protein, mg/l (normal range, 0-5 mg/l)	120.51	339.56	38
D-dimer, μg/ml (normal range, <0.5 μg/ml)	18.90	>20	1.13

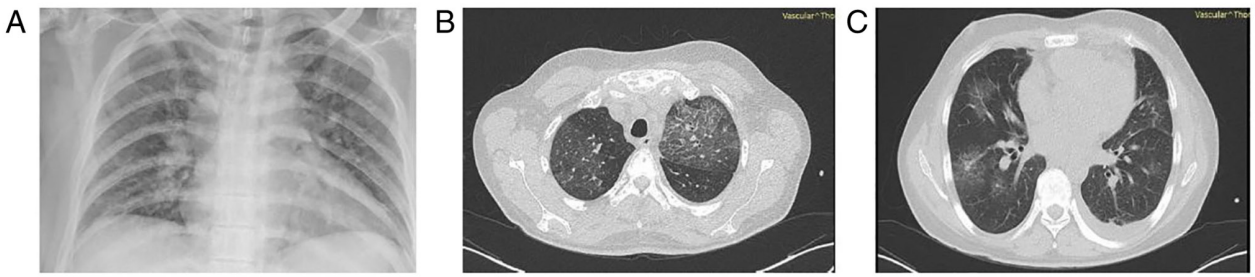

Figure 2. Case 2. (A) Chest X-ray illustrating mild infiltrates in both lungs and blunting of the left costophrenic angle. (B and C) Computed tomography scan of the chest shows nodular ground glass opacities in all lung fields and a small left pleural effusion.

Her medications included acetylsalicylic acid at 100 mg daily, crizanlizumab at 250 mg every 4 weeks, levothyroxine at 50 μg daily and sertraline at 100 mg daily.

The patient presented to the ED of Laiko General Hospital with complaints of fever, headache, vomiting and pain in the upper and lower extremities over the past 2 days. In the ED, the patient was noted to have a SpO_2 of 94% in room air, a BP of 115/70 mmHg, a HR 88 bpm, and a temperature of 37.4˚C. The clinical characteristics of the patient are summarized in Table I.

At the initial presentation, the clinical examination revealed crackles on auscultation in both lung bases. A chest X-ray was performed and this revealed consolidation in both lower lung lobes (Fig. 3A). The analysis of arterial blood gas revealed pO_2 levels of 73 mmHg, pCO_2 levels of 35 mmHg, pH 7.40 and HCO_3- at 20.7 mmol/l on room air. The results of the laboratory analyses are summarized in Table II.

The patient was tested for SARS-CoV-2 infection and had a positive detection of SARS-CoV-2 nucleic acid in an obtained nasopharyngeal sample using RT-PCR. She had not received the vaccine for SARS-CoV-2. The patient received oxygen therapy with a nasal cannula delivering oxygen at a flow rate of 2 litres/min. She was also treated with fluid replacement therapy, subcutaneous prophylactic enoxaparin, intravenous morphine and tramadol due to VOC, remdesivir, dexamethasone and cefipime. On the 6th day of hospitalization, the patient presented with a deterioration in oxygen levels and an increase in inflammatory indices with C-reactive protein levels of 269.48 mg/l and ferritin levels of 1,142 ng/ml.

The patient underwent a chest CT scan and CTPA, which revealed ground glass opacities and consolidation in the lower lung lobes and pulmonary embolism located in the proximal subsegmental branch of the left pulmonary artery (Fig. 2B and C). The diagnosis of ACS was thus made.

Antimicrobial treatment was modified to include meropenem and vancomycin empirically. The patient also received therapeutic enoxaparin and oxygen therapy with a nasal cannula delivering oxygen at a flow rate of 4 liters/min. No specific microorganism was isolated from blood, urine or sputum cultures. She received two simple top-up transfusions of RBCs.

The patient's condition gradually improved, the inflammatory indices decreased within 5 days, and there was complete resolution of the fever after 10 days. The patient was discharged following a hospitalization duration of 21 days.

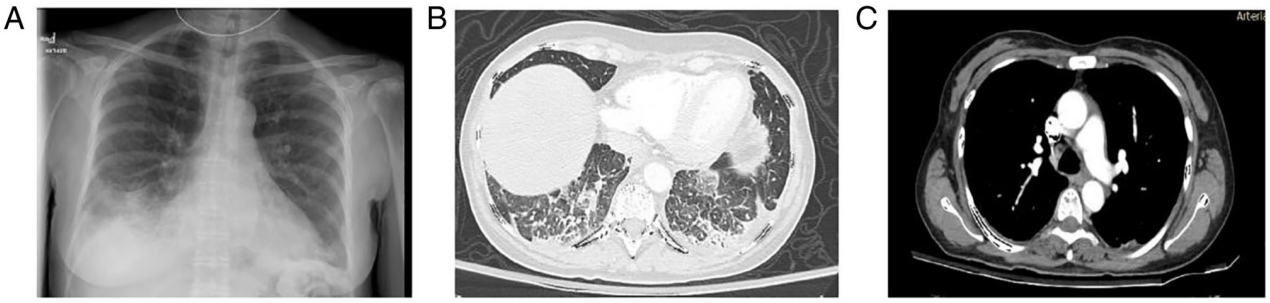

Figure 3. Case 3. (A) Chest X-ray illustrating consolidation in both lower lung lobes. (B) Computed tomography scan of the chest illustrating ground glass opacities and consolidation in the lower lung lobes. (C) Computed tomography pulmonary angiogram illustrating pulmonary embolism located in the proximal subsegmental branch of the left pulmonary artery.

Discussion

In the Hemoglobinopathy Center of Laiko General Hospital, ~320 patients with SCD are being treated. Since the onset of the COVID-19 pandemic, 29 patients of these (29/320) have been infected, with 5 of these patients requiring hospitalization. The cases of 3 patients hospitalized in the COVID-19 Unit of Laiko General Hospital are described in the present study.

The reports regarding hospitalization rates and outcomes of patients with SCD with COVID-19 disease are conflicting. It has been reported that the number of patients with SCD requiring hospitalization due to SARS-CoV-2 infection is unexpectedly low, raising the hypothesis that patients with SCD are potentially not as vulnerable to this infection as had been considered at the beginning of the pandemic, probably due to chronic inflammation (13). Moreover, in a retrospective study on 24 patients with SCD and COVID-19 infection by Balanchivadze *et al* (16), 54% required hospitalization; however, they were shown to have a generally a mild course of the disease, with low rates of intubation, intensive care unit (ICU) admission and mortality. Of note, in the case series by Chen-Goodspeed and Idowu (17), while the hospitalization rate was 60%, the ICU admission rate and the mortality rate were 0%. Moreover, McCloskey *et al* (7), in their case series of patients with SCD with SARS-CoV-2 infection, reported a full recovery in the majority of patients, with no requirement for admission to the ICU, mechanical ventilation or non-invasive ventilation.

On the contrary, based on other published case series reporting the experience with COVID-19 in patients with SCD, the disease was identified as a main risk factor for severe COVID-19 infection. There are published case series which have reported an increased risk of hospitalization, VOC and ICU admission or mortality (18-21). A previous matched cohort analysis of mortality in African American individuals reported a higher risk of hospitalization and development of pneumonia. The case fatality rates for those with SCD compared with African American individuals without SCD or sickle cell trait did not differ significantly; however, the reported mortality was relatively high (3.2%) (22). Another large cohort study found that patients with SCD had a 4-fold increased risk of COVID-19-related hospitalization and a 2.6-fold increased risk of COVID-19-related mortality (23). The largest series of patients has been reported by the international SECURE-SCD, including 750 COVID-19 cases of patients with SCD. A mortality rate of 4.7% was mentioned in adult patients with SCD with COVID-19 (24).

Risk factors for hospitalization and severe COVID-19 illness in patients with SCD have been identified and are worth mentioning. In the study by Arlet *et al* (19), it was found that age and the SC genotype were strong independent risk factors for mechanical ventilation or mortality. Mucalo *et al* (24), in a large series of the SECURE-SCD Registry, reported that frequent previous acute care visits for pain in children and adults and heart/lung and renal comorbidities in children were risk factors for the development of severe disease and hospitalization. Treatment with hydroxyurea decreased the risk of presenting with pain during COVID-19 (24).

Minniti *et al* (21), in a smaller group of 66 patients, reported that an older age with underlying chronic organ damage to the kidneys, heart, lungs and brain were risk factors of morbidity regardless of the hemoglobin genotype, with pulmonary hypertension being a factor for a higher risk of mortality. The researchers also mentioned that elevated levels of lactate dehydrogenase and D-dimer were associated with a higher risk of mortality (21). Menapace and Thein (25) highlighted racial health disparities among patients with SCD, based on the higher rates of symptomatic infection needing hospitalization and mortality in African American and Hispanic patients.

Of note, all the patients described herein had favorable outcomes despite the varying clinical presentations, and different medical history and medications. More specifically, the patient (case 1) who did not have a history of painful crises and was receiving hydroxyurea, which exerts a protective effect against COVID-19, had a successful outcome, similar to the other patients (cases 2 and 3) who had a history of painful crises and were not receiving hydroxyurea. Furthermore, the patients depicted as cases 2 and 3 had severe complications, such severe hemolysis and pulmonary embolism. All the patients received specific treatment for COVID-19 and required RBC transfusion.

In the Hemoglobinopathy Center of Laiko General Hospital, 5 patients with COVID-19 disease required hospitalization among the 29 infected patients (5/29, 17.2%) and there were no deaths (0/29, 0%). In Greece, by March 8, 2022, there were 26,303 deaths due to COVID-19 of non-SCD patients among the 2,538,168 infected patients (mortality 1%; https://www.worldometers.info/coronavirus/country/greece/) According to the country's (Greece) data regarding mortality of COVID-19 (https://www.

worldometers.info/coronavirus/country/greece/), patients with SCD with SARS-CoV-2 infection do not experience a higher mortality than thosw without SCD as a comorbidity.

Of note, all our 3 patients described herein had not been vaccinated against SARS-CoV-2. This was an additional risk factor for the hospitalization of these patients (26). Jan *et al* (27) performed the first study to explore hesitancy of patients with SCD concerning the vaccine for SARS-CoV-2. The researchers reported that, according to the majority of the beliefs of unvaccinated participants, the adverse effects of vaccination represented the most significant barrier for this patient group to receive the vaccine (27). The positive outcome of the hospitalized patients described in the present study may be attributed to their relatively young age and the absence of severe related comorbidities. The patient that was on treatment with hydroxyurea (case 1) had the least severe clinical course. Another protective factor may be the ABO blood group type, since it has been reported that group O is associated with a relative protection against SARS-CoV infection (28).

In conclusion, the patients with SCD described in the present study that were hospitalized for COVID-19, developed significant complications such as VOC, pulmonary embolism and ACS; however, they did not require ICU admission and all had a favorable outcome. Patients suffering from SCD who present with VOC, even in the absence of the typical clinical features of COVID-19, need to be tested for SARS-CoV-2. Recognizing the various clinical scenarios of SARS-CoV-2 infection in patients with SCD is critical for therapeutic interventions to be initiated promptly. The importance of transfusions/exchange transfusions in patients with SCD who develop ACS as a complication of COVID, along with other therapeutic interventions for COVID-19, should be stressed for all clinicians managing patients with COVID-19, and a hematological consultation is critical.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CSi, AT and CSt were involved in the conception and design of the study. VEG and MND wrote and prepared the draft of the manuscript and advised on patient treatment. CD, SB, PS and NT analyzed patient data and wrote and prepared the draft of the manuscript. DAS was involved in the writing of the final draft, provided critical revisions and was also involved in the design of the study. SM and PP obtained the medical images. MND, SM, PP and VEG made substantial contributions to conception, and analysis and interpretation of data. VEG and SM confirm the authenticity of all the data. All authors contributed to manuscript revision and approved the final version of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

No ethical approval was required for this publication. Written informed consent was obtained from the patients for the publication of this case series and accompanying images.

Patient consent for publication

Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have not competing interests.

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