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CASE SERIES
Cardiac imaging

Definity, an affinity for painful crisis: a case series describing vaso-occlusive pain crises in sickle cell patients undergoing echocardiogram with Definity contrast

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Background Individuals with sickle cell disease (SCD) are at risk for painful crises and long-term cardiopulmonary morbidity. Echocardiogram is recommended if signs or symptoms of cardiopulmonary disease develop in previously asymptomatic patients, or worsen in those with known disease. Second-generation echocardiogram contrast agents (ECAs) improve the diagnostic capacity of echocardiogram; however, these agents have risks in SCD populations that have yet to be investigated.

Case summary We report a case series of two patients who experienced vaso-occlusive crises following administration of the ECA, Definity. Both patients were referred for echocardiogram from our institution's sickle cell clinic because of concern for SCD-related cardiopulmonary complications. Both patients were in their usual state of health at the time of their exams. The first patient experienced acute back and hip pain minutes after receiving Definity and was diagnosed with acute vaso-occlusive crisis requiring admission for 6 days for pain management. The second patient developed dyspnoea and chest pain within 90 min of her echocardiogram. She was diagnosed with acute chest syndrome and admitted for further management. Her hospitalization was complicated by hyper-haemolysis and multiple organ failure syndrome. After 13 days, she was discharged home.

Discussion The safety profile of ECAs has not been fully evaluated and warrants further study in individuals with SCD. Proposed mechanisms for our observations include the release of pro-inflammatory metabolites from Definity contrast agent's shell and ultrasound-induced haemolysis secondary to ECA administration. Alternative imaging modalities and proper precautions should be considered when evaluating cardiopulmonary function in this patient population.

Keywords Case series • Contrast • Echocardiography • Haemolysis • Occlusion • Crisis

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Learning points:

- Educate providers about the risk associated with the use of newer ECAs like Definity in sickle cell disease (SCD).
- Consider echocardiograms without ECA or use alternative imaging modalities for SCD patients who require cardiopulmonary evaluation.
- Recognize the presentation of vaso-occlusive crisis and its associated complications to ensure prompt treatment is not delayed.

Introduction

Sickle cell disease (SCD) refers to a group of haemoglobinopathies in which inherited beta-globin gene mutations result in a less soluble haemoglobin (Hgb) product. While disease severity varies, affected individuals are at risk of cardiopulmonary complications such as pulmonary hypertension (pHTN) and heart failure (HF).[1,2] Consequently, cardiac evaluation via echocardiogram is warranted if cardiopulmonary signs or symptoms begin to develop (e.g. chest pain, dyspnoea, or volume overload) or worsen in those with known disease.[2,3] Echocardiogram contrast agents (ECAs) were developed to improve the diagnostic ability of echocardiogram. In 2007, cardiopulmonary adverse events (AEs) and four deaths in those without SCD were described following ECA administration, resulting in a black box warning.[4] The FDA revised this warning following additional safety studies and supported the use of ECAs in pHTN, intracardiac shunts, and unstable cardiopulmonary conditions.[5,6] No study has since evaluated the safety of such agents in individuals with SCD.

In this case series, we present two cases of vaso-occlusive crisis (VOC) in patients with known SCD following administration of the ECA, Definity (perflutren lipid microsphere; Lantheus Medical Imagine, Billerica, MA, USA), and review potential mechanisms responsible for this adverse reaction.

Case presentation

Patient 1

A 42-year-old African American male presented to our institution for echocardiographic evaluation due to complaints of long-standing exertional dyspnoea discovered at his initial sickle cell clinic visit. He was in his routine state of health without pain at the time of his echocardiogram. As part of the echocardiogram, he received 3 mL of diluted Definity contrast (2 mL Definity diluted in 8 mL of preservative-free saline). Seven minutes following contrast administration, he experienced severe, throbbing lower back and left hip pain, which he described as being similar to past VOC. Initially, he was managed at the SCD infusion centre. However, his pain remained poorly controlled, so he was transferred to our emergency department (ED).

Medical history was significant for sickle-beta thalassaemia ($Hgb\beta^{+}S$) disease and left acetabulum fracture. He denied fevers, chest pain, or dyspnoea. He was haemodynamically stable, afebrile, and oxygenating well on room air. Physical exam revealed a middle-age male in moderate distress due to generalized pain. His cardiopulmonary exam, neurologic exam, and abdominal assessments were benign.

Initial laboratory workup revealed an elevated lactate dehydrogenase (LDH) of 369 (120–240) Units/L, microcytic anaemia [Hgb: 10.2

Timeline

Patient 1	
Day 1: 8:30	Presents for echocardiography and receives Definity contrast
Day 1: 8:44	Begins developing acute leg and hip pain
Day 1: 9:30	Received IV diphenhydramine and analgesics
Day 1: 9:48	Pain remained uncontrolled and transferred to emergency department (ED)
Day 1: 10:07	Diagnosis of vaso-occlusive pain crisis confirmed; transferred to sickle cell infusion clinic
Day 1: 11:50	Receives IV fluids and analgesics
Day 1: 16:37	Improvement in pain and discharge home
Day 1: 21:00	Presented to outside hospital due to persistent pain while at home; admitted for pain management
Day 6	Discharge following improvement of pain and haemolytic parameters
One month after	Improvement of back pain, fatigue, and haematologic parameters; no additional hospitalizations or ED visits
Patient 2	
Day 1 7:38	Presents for echocardiography and received Definity contrast
Day 1 9:00	Develops progressive ascending pain in lower extremities while returning home
Day 1 14:05	Calls our institution to report worsening pain despite oral analgesics; instructed to proceed to ED
Day 1 15:43	Presents to ED with acute chest syndrome following Definity administration and was admitted for management
Day 4	Develops acute splenic sequestration and 8-unit exchange transfusion was initiated
Day 7	Develops hyper-haemolysis and multi-organ failure syndrome
Day 12	Receives intravenous immunoglobulin
Day 14	Discharged following improvement of symptoms and metabolic and haematologic parameters
One week after	Improvement in abdominal pain and haematologic parameters

(baseline: 12–12.8) g/dL], thrombocytopenia [90.2 (baseline: 150–197) $\times$ 10^3/mm^3], and reticulocyte count of 3.2% (0.7–2.4). He was diagnosed with Definity-induced VOC and treated with IV fluids and analgesics. Once adequate pain control was achieved, he returned home. However, his pain persisted and he presented to an outside hospital for which he was admitted for 6 days and further treated with IV fluids and analgesics. Laboratory analysis during his admission was notable for worsening anaemia (Hgb: 6.9 g/dL), thrombocytopenia (67 $\times$ 10^3/mm^3), leukocytosis (13.5 $\times$ 10^3/mm^3), and indirect hyperbilirubinaemia (1.1 mg/dL), all of which improved prior to discharge.

One month later, he was seen in clinic for follow-up without acute complaint. He denied any recent ED visits since the admission above. Laboratory studies showed improvement in his anaemia (Hbg: 11.8 g/dL), normalization of his white blood cell (WBC) count (7.7 $\times$ 10^3/mm^3), and resolution of his thrombocytopenia.

Patient 2

A 53-year-old African American female was referred for echocardiogram from our sickle cell clinic due to persistent hypertension and pedal oedema with concern for congestive HF. She was in her usual state of health at the time of her appointment. Upon arrival, 3 mL of diluted Definity solution was administered and echocardiogram completed. While returning home, she experienced progressive pain and swelling in her lower extremities and she developed dyspnoea and non-radiating pleuritic chest pain. The patient returned to our institution and was emergently transferred to the ED for severe shortness of breath.

She denied any prior history of dyspnoea or episodes of acute chest syndrome (ACS). Her medical history was significant for Hgbβ^+S, hypertension, hyperlipidaemia, and type II diabetes mellitus. Physical exam revealed a well-developed female in mild distress. She was afebrile and normotensive, with a normal heart rate and a respiratory rate of 20 breath/min. Her O_2 saturation was 89% on room air, but improved to 99% when placed on 3 L oxygen by nasal cannula. Chest examination was positive for both tenderness and reproducible pain with palpation of the left lateral chest wall and sternum. Lungs were clear to auscultation bilaterally and no murmurs, rubs, or gallops were heard on cardiac examination. Abdominal exam was unremarkable.

Laboratory analysis revealed a normal high-sensitivity troponin-I and mild anaemia [Hgb: 10.2 g/dL (baseline: 10.3–10.8)]. Her reticulocyte count was 1.6% with a reticulocyte index of 0.79, platelet count was 207.6 (baseline: 196–222) $\times$ 10^3/mm^3, and WBC count was 7.43 $\times$ 10^3/mm^3. Electrocardiogram was unremarkable for ischaemia. Imaging studies consisted of a chest radiograph which revealed an ill-defined opacity (*Figure 1*) and chest computed tomography angiography that was negative for pulmonary thromboembolism. Given the patient's low oxygen saturation and chest pain, a presumptive diagnosis of developing ACS was established and she was admitted to the general medicine service.

Upon admission, she was started on intravenous ceftriaxone and azithromycin for pneumonia. Two days later, she developed fever (39.4°C), tachycardia (104 b.p.m.), and left upper quadrant pain. Laboratory analysis was significant for leukocytosis (22.14 $\times$ 10^3/mm^3), worsening anaemia (Hgb: 7.6 g/dL), and thrombocytopenia (117 $\times$ 10^3/mm^3) (*Figures 2* and *3*). Her antibiotic coverage was broadened to vancomycin and piperacillin-tazobactam due to concern for sepsis. Her constellation of findings, including the drop in Hgb >2 g/dL, thrombocytopenia, and left upper abdominal fullness, raised suspicion for acute splenic sequestration, which was confirmed on left upper quadrant ultrasound (heterogeneously enlarged spleen to 15 cm). A double lumen vascular catheter was placed and the patient underwent automated erythrocytopheresis.

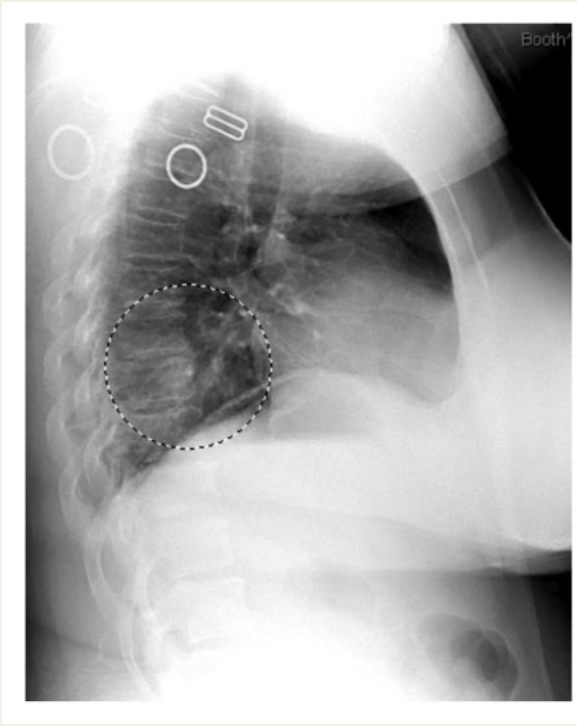

Figure 1 Chest radiograph showing ill-defined opacity suspicious for acute chest syndrome. Chest computed tomography angiography returned negative.

Despite exchange transfusion, the patient continued to have severe haemolysis indicated by rising serum LDH (Peak: 2174 Units/L) and worsening anaemia (Hgb: 7.2 g/dL) (*Figures 2* and *4*). Direct Coombs test was negative but there was concern for transfusion-induced hyper-haemolysis contributing to her anaemia. Additionally, she developed acute kidney injury with a peak creatinine (sCr) of 6.5 (baseline: 0.7–1.0) mg/dL, and she was diagnosed with SCD-induced multi-organ failure syndrome given renal, pulmonary, and haematologic/splenic involvement.

Due to ongoing haemolysis concerning for a transfusion-related haemolytic process, epoetin alfa was initiated on hospital Day 6 (four doses administered over 7 days; 1 dose = 20 000 Units), and intravenous immunoglobulin was administered on hospital Days 11 and 12 (75 g/day). Over the following 2 days, her Hgb began improving (6.8 g/dL) and LDH trended down (870 Units/L) (*Figures 2* and *4*). Antibiotics were discontinued on hospital Day 9 after blood cultures returned negative.

The patient was discharged on hospital Day 14 following improvement of her pain and laboratory parameters. Outpatient evaluation a

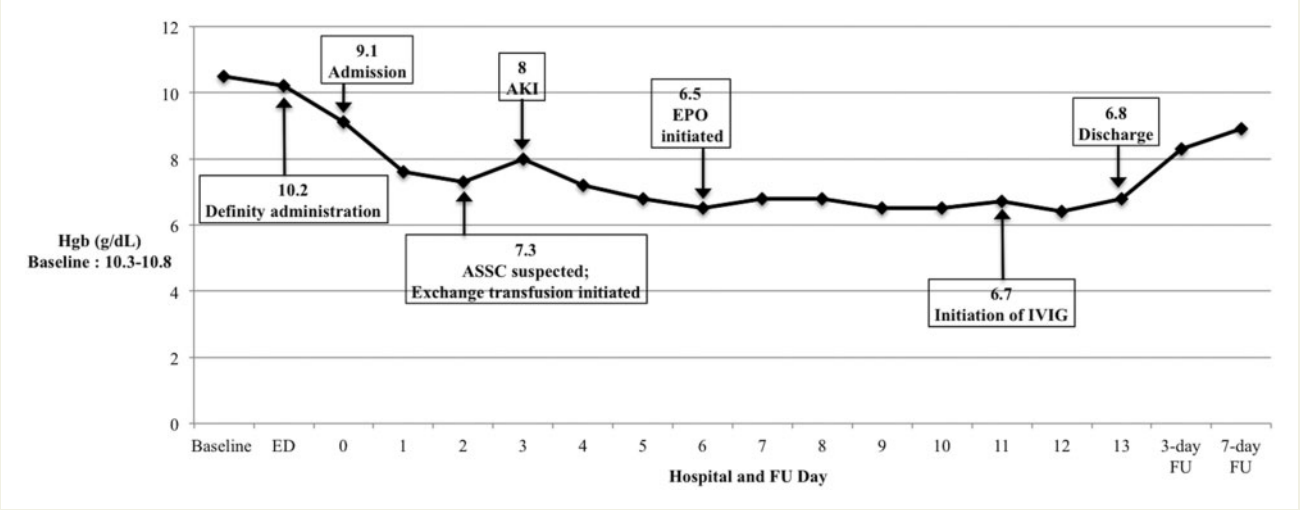

Figure 2 Haemoglobin measurements during Patient 2's hospitalization. AKI, acute kidney injury; ASSC, acute splenic sequestration crisis; ED, emergency department; EPO, erythropoietin; Hgb, haemoglobin; IVIG, intravenous immunoglobulins.

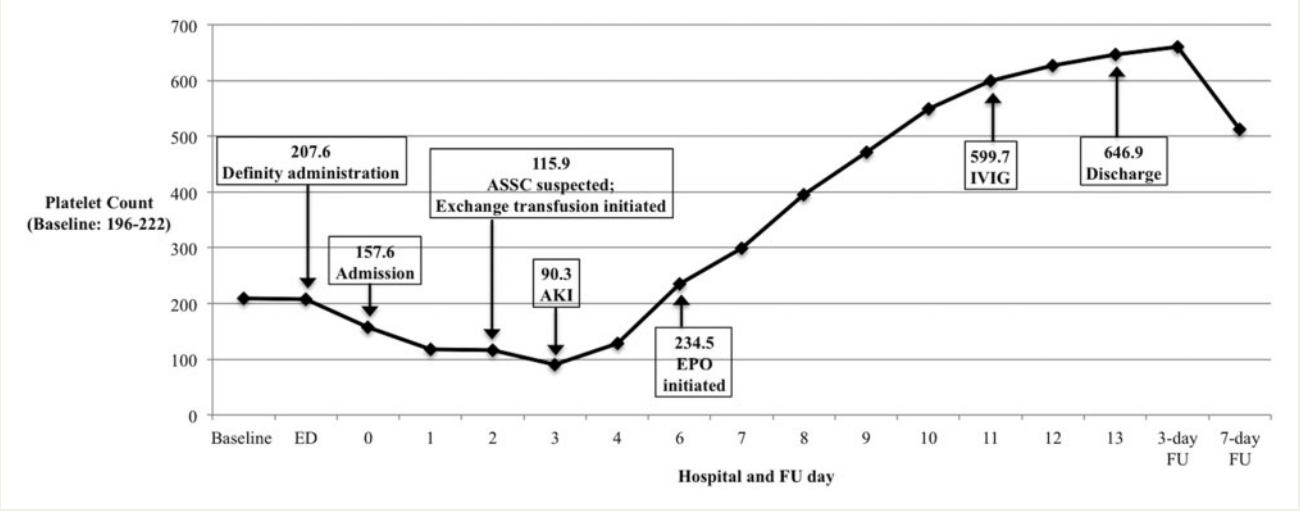

Figure 3 Platelet measurements during Patient 2's hospitalization. AKI, acute kidney injury; ASSC, acute splenic sequestration crisis; ED, emergency department; EPO, erythropoietin; IVIG, intravenous immunoglobulins.

week later showed overall improvement in her pain and fatigue and resolution of dyspnoea. Laboratory analysis revealed improvement of her renal and haemolytic parameters (sCr: 1.3 mg/dL; Hgb: 8.9 g/dL; WBC: 8.90 10^3/mm^3; Platelets: 512 $\times$ 10^3/mm^3; LDH: 604 Units/L) (*Figures 2–4*).

Discussion

The above cases highlight our observed relationship between Definity administration and VOC in SCD patients. Sickle cell disease refers to any condition in which inheritance of haemoglobin S (HgbS) leads to the sickled shape of red blood cells (RBCs), and includes individuals with both homozygous (HbSS) and heterozygous (HgbSC and Hgbβ^+S/Hgbβ^0S) abnormalities.[7] Cardiopulmonary complications, such as pHTN and HF, are becoming increasingly recognized in this population.[1,2]

As a result, the American Society of Hematology recommends screening echocardiogram in those who develop signs or symptoms of cardiopulmonary dysfunction, or those with known disease.[3] Furthermore, diastolic dysfunction is thought to contribute to increased mortality in SCD patients, and early intervention of the underlying aetiology could improve long-term prognosis.[8] ECAs provide enhanced diagnostic power during echocardiogram assessments.[9] Though cardiopulmonary AEs and even death have been reported with Definity use in non-SCD patients, the FDA declared its

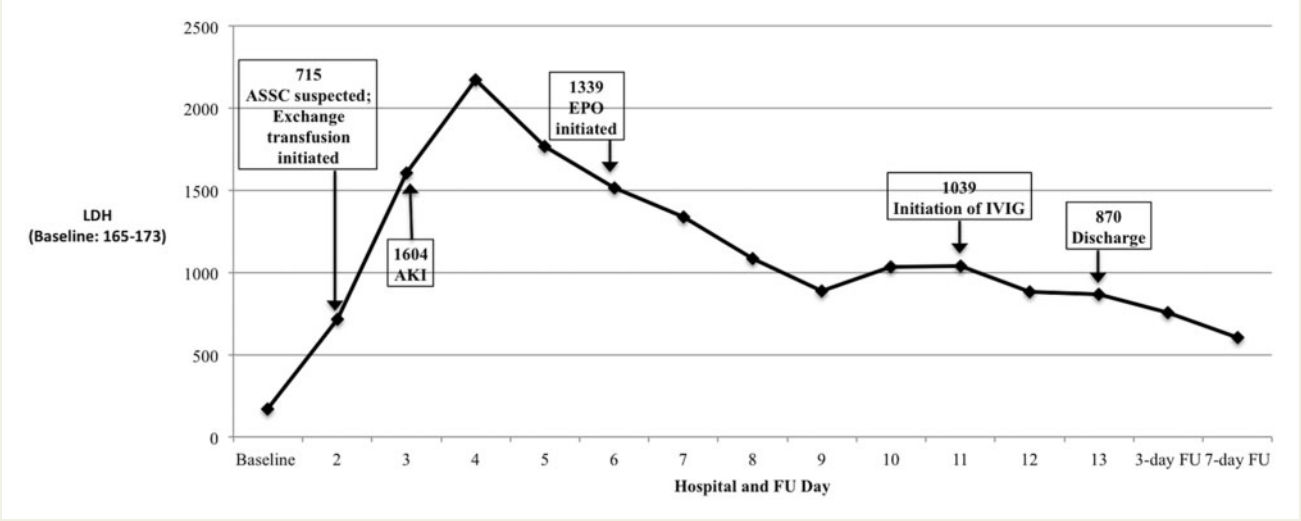

Figure 4 Lactate dehydrogenase measurements throughout Patient 2's hospitalization. AKI, acute kidney injury; ASSC, acute splenic sequestration crisis; ED, emergency department; EPO, erythropoietin; Hgb, haemoglobin; IVIG, intravenous immunoglobulins; LDH, lactate dehydrogenase.

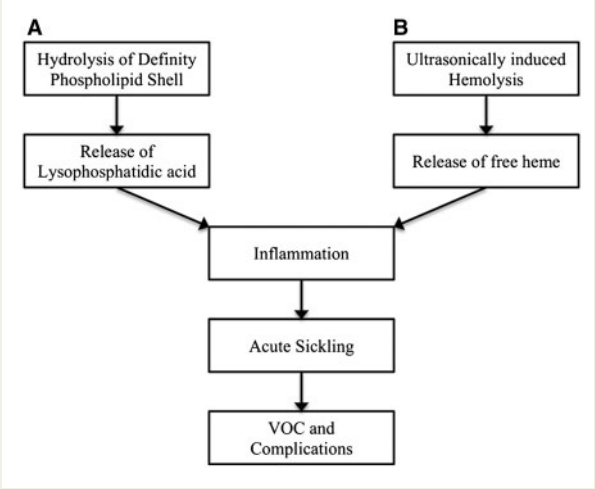

Figure 5 (*A*) Suggested mechanism of Definity lipid shell hydrolysis and inflammation; (*B*) Proposed mechanism of ultrasound-induced cavitation and haemolysis.

use as safe in those with cardiopulmonary disease, pHTN, and intracardiac shunts.[6] Definity's haematologic safety profile, however, has yet to be reported or studied, and its potential to precipitate VOC has not been previously described.

Vaso-occlusive crisis is a complication of SCD and occurs when aggregates of sickled RBCs obstruct microvasculature, resulting in tissue ischaemia and can be precipitated by dehydration, hypoxia, or inflammation.[10] In these two cases, we hypothesize that VOC was precipitated by Definity contrast. Our patients presented for cardiac evaluation with echocardiography and experienced acute pain and VOC. Both individuals were in their usual state of health, and both presentations occurred in close temporal relationship with Definity administration. While there are no well-defined mechanisms to describe this observation, release of pro-inflammatory components from Definity's shell and ultrasonically induced haemolysis (UIH) in the presence of ECAs are two possibilities that should be considered (*Figure 5*).[11,12]

The inflammatory effects of Definity contrast have been previously described.[12] Definity's shell contains three phospholipids, one being dipalmitoylphosphatidic acid (DPPA). One hypothesis is that hydrolysis of DPPA results in formation of lysophosphatidic acid (LPA).[12] Lysophosphatidic acid has been shown to release pro-inflammatory cytokines and increase neointimal hyperplasia in damaged vasculature.[13] Furthermore, antagonists of LPA receptors have shown to lower inflammatory cytokine release in peritoneal sepsis models.[14] The pro-inflammatory effects of LPA may act as a precipitating factor for VOC in SCD (*Figure 5A*). Interestingly, Lim *et al.*[15] has shown increased splenic uptake of ECAs. This tropism for splenic tissue could have increased our patient's (Patient 2) susceptibility to having acute splenic sequestration by creating localized inflammation within the spleen.

Ultrasonically induced haemolysis is another proposed mechanism by which Definity may induce VOC in these patients (*Figure 2B*).[11] When a fluid with dissolved gas, such as blood, is exposed to an ultrasonic field, the gas bubbles undergo volumetric changes and grow larger. This phenomenon is known as cavitation.[16] Growing bubbles are prone to rupture if high acoustic waves are delivered and may damage local structures.[17] Mechanical index (MI) is a measure of the ultrasound's acoustic power. At low MI, cavitation is less likely to occur, however, some studies suggest that addition of ECAs can result in a decreased threshold for cavitation.[18] Recent studies have shown that FS0-69, an ECA that utilizes a fluorocarbon gas like Definity, causes haemolysis via cavitation and is more haemolyzing when compared with other ECAs.[11] Studies have also shown that UIH is increased in the setting of a low haematocrit and may lead to lysis of platelets.[17] Given SCD patients have low baseline haematocrit, this finding could explain the ECA's detrimental effects described in both cases, along with their progressive thrombocytopenia.

In cardiology, ECAs have shown to enhance delineation of the endocardial border. This enhancing property of ECAs aids cardiologists in assessment of regional wall motion abnormalities, detection of left ventricular thrombus, and ejection fraction estimation.[19] As a result, utilization of ECAs should be considered when diagnostic outcomes rely on enhancement of the endocardial border for accurate measurements and cardiac assessments. At our institution, it is the standard-of-care to use ECAs with echocardiographic evaluation for all patients due their diagnostic benefits; both patients presented in this case series received this agent. While echocardiographic evaluation of SCD patients could be improved with the use of ECAs, the potential risks associated must be weighed against the benefits gained from such interventions. Moreover, we advocate for the creation of a national registry of ECA-related AEs in patients with SCD to better understand the nature of this illness. While echocardiogram is considered the gold standard for left ventricular evaluation, other imagine modalities, such as mutidetector computed tomography or cardiac magnetic resonance imaging may be alternately utilized if additional evaluation is needed.[20] Given our findings, we recommend against the use of ECAs in SCD patients.

In conclusion, Definity's safety profile in SCD patients warrants further examination. Though the diagnosis of this syndrome is founded on observed temporal relationships with Definity administration, we firmly believe that clinical judgement should be used when determining the best strategy for cardiac evaluation in this patient cohort. Moreover, further research into the use of alternative contrast agents or imaging modalities is needed.

Lead author biography

Alex D'Amico is a 4th year medical student at the University of Alabama at Birmingham. Prior to medical school, Alex attended Auburn University where he obtained a degree in Biomedical Sciences. As Alex begins his final year of medical school, he has decided to pursue a residency in Internal Medicine, with a particular interest in cardiology. Alex sees research playing a large role in his professional career and thus hopes to continue collaborating with others in order to contribute to the medical literature.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that verbal consent for submission and publication of this case series including image(s) and associated text has been obtained from both patients in line with COPE guidance.

Conflict of interest: none declared.

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