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CASE REPORT
Heart failure

A case report of extramedullary haematopoiesis within left ventricle myocardium and apical thrombus in acute heart failure: diagnosis, treatment, and long-term outcome

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Background Extramedullary haematopoiesis (EMH) within myocardium is a rare phenomenon, and its occurrence in left ventricle myocardium or apical thrombus of a young female has never been reported.

Case summary A 23-year-old active female with progressive worsening of dyspnoea. A transthoracic echocardiogram demonstrated a left ventricular ejection fraction of 10–15% and apical thrombus. Bilateral upper extremity Doppler showed deep venous thrombus in the left arm and superficial vein thrombus in both arms. She had reduced activity of antithrombin III, deficiency of protein C and S. Computed tomography of the head showed right thalamic infarct. Having failed optimal medical therapy, rapidly worsening of symptoms (New York Heart Association Class IV and clinical Class C) and cardiogenic shock, she underwent HeartWare® left ventricular assist device (LVAD) placement as a bridge to heart transplant. Intraoperative apical thrombus was carefully extracted while maintaining adequate anticoagulation with heparin infusion. Pathology report of the excised apical myocardium and thrombus demonstrated haematopoietic cells. Twenty-six months since LVAD implantation, she remains active and Status 7 on transplant list (due to body mass index) without any further episodes of thromboembolic events.

Discussion We report an unprecedented case of an active young female with EMH within left ventricular myocardium and apical thrombus. Although redirected differentiation and embolic haematopoietic cells seem to explain this phenomenon, the exact pathophysiology remains unknown. Despite having pre-existing apical thrombus and acute deep vein thrombus, the key towards success was meticulous extraction of apical thrombus while preserving inherent trabecular architecture and adequate anticoagulation.

Keywords Extramedullary haematopoiesis • Left ventricle myocardium • Left ventricular assist device • Prothrombotic state • Apical thrombus • Case report

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Learning points

- An unprecedented case report of extramedullary haematopoiesis in the left ventricle myocardium and apical thrombus of a young adult female.
- Left ventricular assist device can be successfully implanted and maintained in a patient with acute heart failure with pre-existing apical thrombus, prothrombotic state, acute deep vein thrombus, and right thalamic infarct.
- Warfarin can be safely used for anticoagulation (goal international normalized ratio 2.0–3.0) in such patients with multiple comorbidities, with successful prevention of thromboembolic events and pump thrombus.

Introduction

Extramedullary haematopoiesis (EMH) in the myocardium is a very rare finding, and its incidence in young adults remains unknown. In a small group of surgical cases, its incidence in adult (≥18 years) females were reported to be ∼1.4%. However, these patients had age >45 years and ischaemic heart disease.[1] Extramedullary haematopoiesis within left ventricle myocardium and apical thrombus in a young adult female had never been reported up until now; herein, we present a similar case with acutely decompensated heart failure and prothrombotic state, requiring left ventricular assist device (LVAD) implantation as a bridge to heart transplant (BTT).

Timeline

Date	Events
14 May 2016	Bilateral lower extremity oedema, paroxysmal nocturnal dyspnoea, and orthopnoea. Transthoracic echocardiogram (TTE) notable for left ventricular ejection fraction (LVEF) of 10–15%.
13 June 2016	Admission for worsening of dyspnoea and bilateral lower extremity oedema
14 June 2016	Right heart catheterization demonstrated right brachial vein obstruction, markedly elevated right atrial pressure and pulmonary capillary wedge pressure, low cardiac output. Bilateral Upper extremity Dopplers showed deep venous thrombus in the left arm and superficial thrombus in both upper extremities. Started on Heparin drip.
15 June 2016	TTE showed LVEF of 10–15%, left ventricular apical thrombus, normal right ventricle function, and diastolic dysfunction Grade 2.
16 June 2016	Cardiogenic shock. Started on Milrinone drip which was gradually tapered off.
17 June 2016	Extraction of apical thrombus and placement of HeartWare® left ventricular assist device (LVAD)
20 June 2016	Pathology report demonstrated presence of extramedullary haematopoiesis in both apical thrombus and myocardium.
21 June 2016	Computed tomography (CT) of head showed right thalamic infarct.
6 July 2016	A CT-guided bone marrow biopsy which showed trilineage haematopoiesis, mild erythroid hyperplasia, and polytypic plasmacytosis. Markedly depleted iron stores. Normal cytogenetic analysis.
8 July 2016	Started bridging to warfarin with a goal international normalized ratio of 2.0–3.0
17 October 2016	LVAD driveline infection with methicillin-susceptible *Staphylococcus aureus*.
05 November 2018	Patient remains active and stable on LVAD with Status 7 (due to body mass index) on heart transplant list.

Case presentation

A 23-year-old Caucasian female with past medical history of papillary thyroid cancer status post-complete thyroidectomy in total remission, iron deficiency anaemia, and Class 2 obesity [body mass index (BMI) 38.7 kg/m^2] presented to an out of network hospital with 1 day history of abdominal pain and diarrhoea, worsening dyspnoea on exertion, bilateral lower extremity oedema, paroxysmal nocturnal dyspnoea, and orthopnoea. A transthoracic echocardiogram (TTE) was notable for left ventricular ejection fraction (LVEF) of 10–15%, she was treated with diuretics and later discharged on guideline-directed medical therapy. Her symptoms progressively got worse for which she was transferred to the University of Pittsburgh Medical Center to be managed by the heart failure team.

On examination, she had a jugular venous pressure of ∼10 cm of water, clear lung sounds, Grade II systolic murmur best heard in the left upper sternal border, right upper quadrant tenderness to deep

Table 1 Admission blood work report

Laboratory study	Test results	Reference value
Haematology		
White blood cells ($\times 10^9$/L)	10	(3.8–10.6)
Red blood cells ($\times 10^9$/L)	4.31	(3.73–4.89)
Haemoglobin (g/dL)	10.6	(11.6–14.6)
Haematocrit (%)	33.2	(34.1–43.3)
Mean corpuscular volume (fL)	77	(82.6–97.4)
Mean corpuscular haemoglobin (pg)	24.5	(27.8–33.4)
Mean corpuscular haemoglobin concentration (g/dL)	31.8	(32.7–35.5)
Red blood cells distribution width (%)	18	(11.8–15.2)
Platelets ($\times 10^9$/L)	150	(156–369)
Mean platelet volume (fL)	11.1	(6.8–10.4)
Neutrophils (%)	69	(44–77)
Lymphocytes (%)	23	(13–44)
Monocytes (%)	7	(4–13)
Eosinophils (%)	0	(0–6)
Basophils (%)	1	(0–1)
Hypercoagulability panel		
Antiphospholipid IgM (MPL)	<6.3	<15.1
Antiphospholipid IgG (GPL)	<6.3	<15.1
Antithrombin III activity (%)	43	(85–140)
Factor V Leiden gene mutation	Absent	Absent
Factor II (prothrombin) gene mutation	Absent	Absent
Protein C (%)	30	(70–150)
Protein S (%)	52	(58–128)
Hepatic function		
Total bilirubin (mg/dL)	3.2	(0.3–1.5)
Direct bilirubin (mg/dL)	0.7	(0.1–0.5)
Aspartate aminotransferase (AST) (IU/L)	104	(15–41)
Alanine aminotransferase (ALT) (IU/L)	101	(14–54)
Alkaline phosphatase (ALP) (IU/L)	143	(38–126)
Iron profile		
Iron (µg/dL)	16	(28–170)
Total iron binding capacity (µg/dL)	405	(250–420)
Iron saturation (%)	4	(25–50)
Ferritin (ng/dL)	28	(10–282)
Renal function		
Blood urea nitrogen (mg/dL)	38	(8–26)
Serum creatinine (mg/dL)	1.4	(0.5–1.4)

palpation, and 2+ bilateral lower extremity pitting oedema. Clinical assessment of decompensated heart failure corresponding to Class C. Laboratory studies showed a beta natriuretic peptide of 1687 pg/mL (normal high <100), unremarkable serum electrolytes, electrocardiogram (ECG), and troponin I, remaining blood work is summarized in *Table 1* Right heart catheterization (RHC) was initially attempted in the right brachial vein, but access could not be established due to an obstruction, therefore, left brachial vein was used to complete the procedure. Pressure findings from RHC were right atrium 26 mmHg, right ventricle 46/13 mmHg, pulmonary capillary wedge pressure 35 mmHg, pulmonary artery 47/33 mmHg, cardiac output 3.36 L/min, and cardiac index 1.59 L/min/m^2. Coronary angiography was not performed to absence of ischaemic findings (normal ECG and Troponin I) and high normal creatinine. Bilateral upper extremity venous Dopplers demonstrated bilateral superficial venous thrombosis with acute left brachial vein thrombus, immediately following which, hypercoagulability panel was drawn and started on intravenous anticoagulation with heparin. A repeat TTE showed a left ventricular (LV) diastolic diameter of 6.1 cm, LV systolic diameter of 5.7 cm, sever hypokinesia was noted in entire anterior wall, septum, apex, mid and distal lateral, inferior and posterior wall; in addition to unchanged LVEF, left ventricular apical thrombus and Grade II diastolic dysfunction.

She deteriorated rapidly exhibiting hypotension (89/44 mmHg), increased lactate level of 3.4 mMol/L (0.5–1.6), symptoms corresponding to New York Heart Association function Class IV while on 4 L of oxygen. Milrinone infusion (0.375 µg/kg/min) was started, and the decision was made to proceed with HeartWare® LVAD (HeartWare, Inc., FL, USA) implantation as a BTT. Intraoperative transoesophageal echocardiogram again demonstrated an apical thrombus (*Figure 1A* and *B*). A circular ventriculotomy at the apex was performed, and the thrombus was extracted while taking care to preserve inherent trabecular architecture (*Figure 2A* and *B*). Pathological analysis of the excised apical myocardium demonstrated endomyocardial fibrosis, EMH cells which stained positive for erythroid and myeloid series, and also haematopoietic cells were noted in the apical thrombus (*Figure 3A–D*). In the post-operative period, due to a persistent altered level of consciousness a computed tomography (CT) of the brain was done which showed the presence of right thalamic infarct. In retrospect, the patient reported an episode of left arm weakness which had resolved 1 week before current hospitalization. A CT-guided bone marrow biopsy from the right iliac crest showed normal trilineage haematopoiesis and markedly reduced iron staining. Flowcytometry and cytogenetic studies were normal. She was transitioned to oral warfarin for long-term anticoagulation [goal international normalized ratio (INR) 2.0–3.0] and discharged in stable condition.

Three months post-implant, she developed a driveline exit site infection for which she received vancomycin and underwent incision and drainage, during which an 8 cm pocket of infected haematoma was noted. Wound cultures grew Methicillin-susceptible *Staphylococcus aureus* (MSSA); accordingly, her antibiotic regimen was tailored. Due to multiple readmissions with driveline exit site infection and bacteraemia from MSSA, she was placed on cefadroxil for

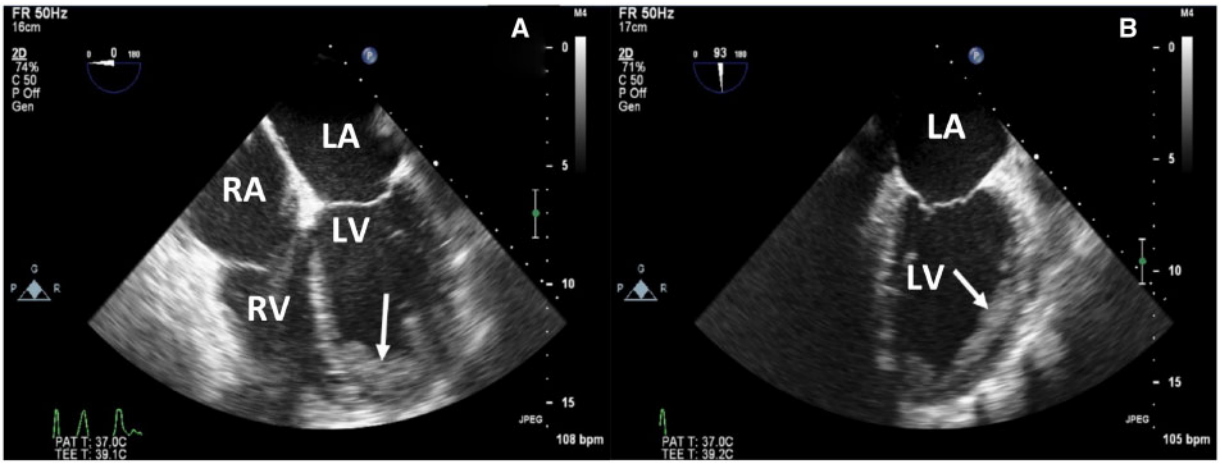

Figure 1 Transoesophageal echocardiographic four-chambered view (*A*) and two-chambered view (*B*). Arrow points towards left ventricular apical thrombus. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Figure 2 Intraoperative post-ventriculotomy intracardiac view of the left ventricle (*A*) and the extracted apical thrombus (*B*). Arrow points towards apical thrombus.

long-term antibiotic prophylaxis. Twenty-six months since LVAD implantation, she remains fairly active and Status 7 (due to BMI) on the transplant list without further thrombotic events.

Discussion

We report an unprecedented case of a young female with EMH within left ventricle myocardium and apical thrombus in acute heart failure. Extramedullary haematopoiesis in the heart is noticed during foetal life, but this gradually disappears soon when bone marrow becomes the primary site of haematopoiesis. There have been reports of EMH in non-hepatosplenic organs such as paravertebral column (mostly in the thorax), lymph nodes, retroperitoneum, lung, and pleura.[2] They often coexist with myelofibrosis, solid tumours, and other non-neoplastic disorders like thalassaemia. Multiple theories have been set forth to explain EMH, most common among them are, neoplastic, compensatory, and myelostimulatory.[3,4] However, since our patient had no hepatosplenomegaly or retroperitoneal lymphadenopathy on CT scan of the abdomen and pelvis, in addition to unremarkable bone marrow biopsy, none of these theories seem to explain EMH. Most plausible explanation could be 'redirected differentiation theory' proposed by Koch *et al.*[2] Secretion of stimulatory factor in response to patient's severe iron deficiency anaemia and acute stress from decompensated heart failure could have stimulated differentiation of adult stem cell in the myocardium into

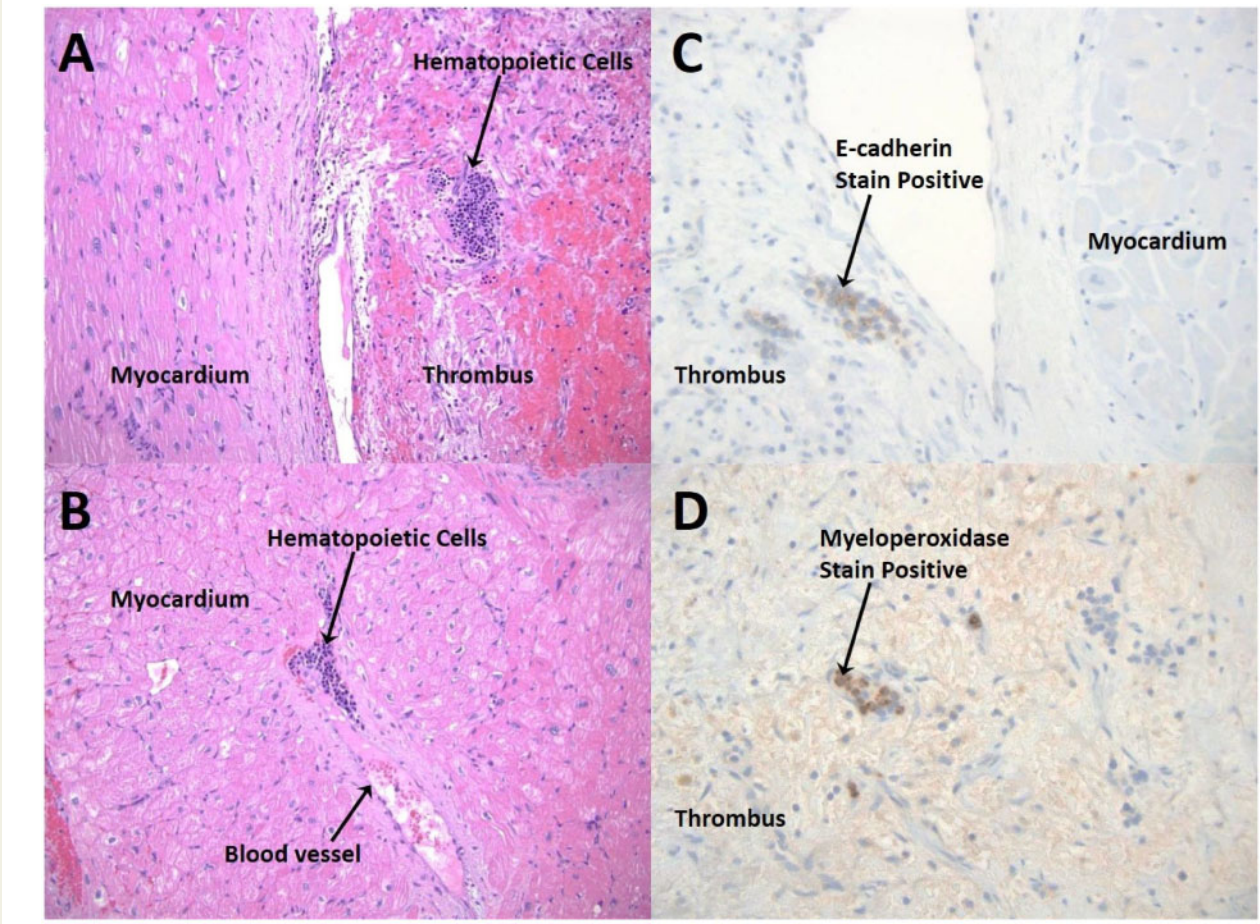

Figure 3 Extramedullary haematopoiesis in the extracted thrombus. (*A*) Haematopoietic cells in the thrombus. (*B*) Haematopoietic cells in the apical myocardium. (*C*) E-Cadherin positive erythroid cells in the thrombus. (*D*) Myeloperoxidase positive myeloid cells in the thrombus.

haematopoietic lineage, while presence of haematopoietic cells in the apical thrombus could be explained by entrapment of haematopoietic precursor cells spilled into the blood stream during an accelerated bone marrow differentiation.

Our case was unique and challenging in multiple ways. First, rapid decompensation without an immediate identifiable cause for non-ischaemic cardiomyopathy. Second, preserving trabecular architecture during surgery to extract the LV thrombus whilst keeping the patient anticoagulated with a co-existing stroke. Finally, our patient had three relative contraindications (prothrombotic state, pre-existing LV thrombus and obesity) for LVAD implantation. However, after discussion with the multidisciplinary team and in light of published literature[5] it was felt unfair to deny advance therapies, given her age and baseline functional status. Low antithrombin III, Protein C and S could be due to congenital deficiency, and/or acute thrombosis. Although there could have been a false positive effect due to active thrombosis, we could not repeat the test as this would require her anticoagulation to held, and given LVAD *in situ* this was deferred in patients best interest. Our experience aids the medical community in shared decision making during a similar challenge if faced during their clinical practice.

Conclusion

Extramedullary haematopoiesis in the LV myocardium and apical thrombus can be seen in active young females, pathophysiology of this phenomena needs further investigation. Left ventricular assist device can be successfully implanted and maintained in an acute heart failure patient with pre-existing LV thrombus, prothrombotic state, and cerebral infraction; while utilizing warfarin (goal INR 2.0–3.0) for therapeutic anticoagulation.

Lead author biography

Deepak Kumar Pasupula, MD, graduated from MediCiti Institute of Medical Science, India. He completed his Internal Medicine Residency programme at the University of Pittsburgh Medical Center, Pittsburgh, PA, USA. Currently, he is a Research Fellow and Internal Medicine faculty at the University of Pittsburgh Medical Center.

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 author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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