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HEART FAILURE AND CARDIOMYOPATHIES

CLINICAL CASE

tMCS Causing Myocardial Extramedullary Hematopoiesis Secondary to Massive Hemolysis

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ABSTRACT

In severe heart failure with hemodynamic failure, when inotropic therapies no longer suffice (INTERMACS [Interagency Registry for Mechanically Assisted Circulatory Support] 1), temporary mechanical support is used as a bridging measure until a more definitive treatment, such as a left ventricular assist device, a total artificial heart or transplantation, is performed. Due to shear stress during the passage of blood through the pump, limited hemolysis is to be expected. We describe the case of a 37-year-old patient with terminal heart failure who suffered severe hemolysis during treatment with temporary mechanical support. Examination of the cardiac apex after left ventricular assist device implantation revealed a poorly differentiated tumor. Histopathologic examination revealed underlying extramedullary hematopoiesis, triggered by severe hemolytic anemia. Following exclusion of neoplasia, the patient subsequently underwent heart transplantation. Post-transplantation, the patient was diagnosed with alpha-thalassemia and heterozygote hemoglobin E. This combination can result in mild thalassemia with chronic low-level hemolysis and mild anemia, probably severely exacerbated in the presence of high-shear stress. (JACC Case Rep. 2025;30:103127) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A previously healthy 37-year-old woman of South East Asian origin with newly diagnosed severe idiopathic dilated cardiomyopathy in cardiogenic shock (ie, INTERMACS [Interagency Registry for Mechanically Assisted Circulatory Support] 1-2) was referred to our tertiary center for consideration of advanced heart failure therapy. The patient initially presented to a regional hospital with a 2-week history of

TAKE-HOME MESSAGES

- This case highlights that severe hemolysis can result from temporary mechanical support and can lead to extramedullary hematopoiesis.
- Extramedullary hematopoiesis should be considered as differential diagnosis of cardiac neoplasms, because it is not a contraindication for cardiac transplantation.

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ABBREVIATIONS AND ACRONYMS

EMH = extramedullary hematopoiesis

LVAD = left ventricular assist device

tMCS = temporary mechanical support

TTP = thrombotic thrombocytopenic purpura

dyspnea and gastroenteritis and a rapid deterioration of her general condition. Initial echocardiography revealed biventricular dysfunction with a reduced ejection fraction of 26%, dilatation of the left ventricle with a left ventricular end-diastolic diameter of 56 mm, and moderate mitral and tricuspid insufficiency. Coronary angiography showed no signs of coronary artery disease, and cardiac magnetic resonance was unable to establish an etiological diagnosis. Despite treatment with levosimendan, followed by a combination of vasopressin and norepinephrine, the patient could not be stabilized adequately.

On arrival in the intensive care unit, faced with an increase in lactate (4.5 mmol/L) and central venous pressure (25 mm Hg) (ie, INTERMACS 1), a temporary mechanical cardiac support (tMCS) device via the femoral route (Impella CP, Abiomed) was implanted. This treatment was complicated by major hemolysis (hemoglobin 63 g/L, visual hemoglobinuria (brown urine), lactate dehydrogenase 1,200 U/L, reticulocytes 209 g/L, haptoglobin <0.1 g/L) and secondary deterioration of renal function.

After initial hemodynamic stabilization, the patient further deteriorated, progressing to right heart failure. This was evidenced by right ventricular dilatation, an empty left ventricle, numerous suction alarm episodes associated with a decrease in tMCS flow despite several attempts at repositioning by transesophageal echocardiography. The therapy was escalated with right ventricular support (venopulmonary extracorporeal membrane oxygenation with ProtekDuo cannula [LivaNova]), and a switch to a larger pump (Impella 5.5 via the subclavian artery) was attempted to reduce the amount of hemolysis.

Severe hemolysis continued (transfusion requirements: 6× red blood cells in 5 days), depleted haptoglobin (<0.1 g/L), and free hemoglobin at 7.5 g/L (upper norm in left ventricular assist device [LVAD] and tMCS 0.4 g/L),[1] (as well as quantitatively high levels of fragmentocytes [+++] [Figure 1]), accompanied by worsening of renal function.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hemolysis in intensive care patients with ventricular mechanical support is wide-ranging and includes autoimmune hemolytic anemia, drug-induced hemolysis, infections, innate causes such as G6PD deficiency or hemoglobinopathy, as well as intravascular causes that include thrombotic microangiopathies (thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, hemolytic uremic syndrome) and mechanical causes linked to tMCS itself (device thrombosis, incorrect positioning).

In our case, the presence of fragmentocytes suggested an intravascular cause of hemolysis. In thrombotic thrombocytopenic purpura, a lower value of ADAMTS13 (here 13%) is expected. Elevated fibrinogen level ruled out disseminated intravascular coagulation as the primary cause. These factors, as well as the strong temporal correlation with tMCS implantation (Figure 1), led us to strongly suspect a mechanical cause.

MANAGEMENT

The placement of a total artificial heart was considered, but this was technically impossible due to the small size of the patient (1.5 m for 53 kg, thoracic diameter of 95 mm). The decision was taken to implant an LVAD (Heartmate 3, Abbott) with right ventricular support (ie, surgical venopulmonary extracorporeal membrane oxygenation).

During LVAD implantation, macroscopic examination of the apex revealed a poorly defined tumorous mass. The tMCS, removed by the surgeon revealed no deposits or thrombus in or on the device, the patient's cardiac transplantation listing was put on hold, awaiting definitive diagnosis.

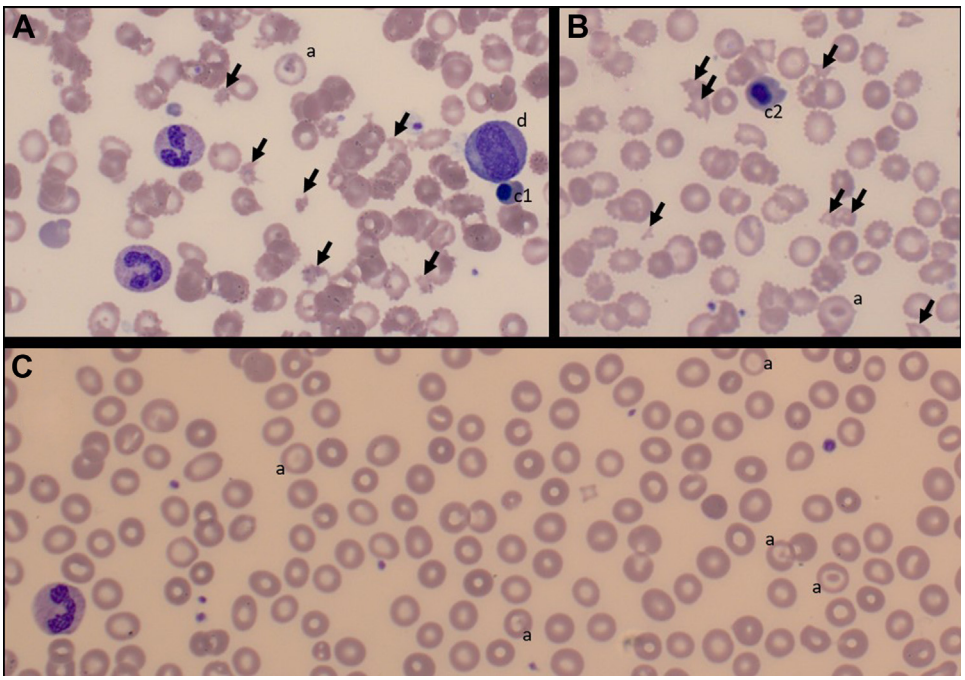
OUTCOME AND FOLLOW-UP

HEMOLYSIS. The severe acute hemolysis presented with reticulocytosis (209 g/L), hyperbilirubinemia (41 mg/dL), depleted haptoglobin levels (<0.1 g/L), and increased free hemoglobin (7.5 g/L), a hematocrit of 27%, a red blood cell count of 2.5 T/L, a white blood cell count of 29.4 g/L, and platelets at 80 g/L. Blood films revealed high numbers of fragmentocytes and normoblasts and detected polychromasia as well as leukocytosis with circulating and, in part, dysplastic myeloid and erythroid precursor cells (Figures 1A and 1B).

After LVAD implantation, hemolysis abated within a few days (Figure 2). Following heart transplantation, the number of fragmentocytes decreased rapidly, and neutrophils showed no more signs of dysplasia; however, erythrocytes still showed abnormal morphology with target cells and polychromasia.

POORLY DEFINED TUMOROUS MASS. The histopathologic examination of the cardiac apex showed a perivascular infiltrate of atypical, loosely cohesive cells along with subendocardial fibrosis and granulation tissue containing erythropoietic precursors exhibiting minimal cytological atypia. The erythroid

FIGURE 1 **Peripheral Blood Smear**



(A, B) Day 1 postimplantation Impella: marked anisopoikilocytosis with target cells (a), fragmentocytes, cells indicating polychromasia, and frequent normoblasts (c1), in part with dysmorphic features (c2). In addition, myeloid precursor cells with abnormal maturation (d). (C) Day 9 post heart transplantation: polychromasia and anisocytosis with target cells. No immature granulocytes and no normoblasts are present and no signs of dysplasia.

population displayed a physiologically high proliferative activity with numerous mitotic figures, in keeping with a nest of extracellular hematopoiesis inside an organized apical cardiac thrombus. No evidence of malignancy (including carcinoma, melanoma, neuroendocrine neoplasm, angiosarcoma, intimal sarcoma, liposarcoma, or lymphoma) was observed (**Figure 3**).

After the apical mass was diagnosed as nonmalignant, the patient's listing for cardiac transplantation was reactivated and the patient received a heart transplant within 1 week.

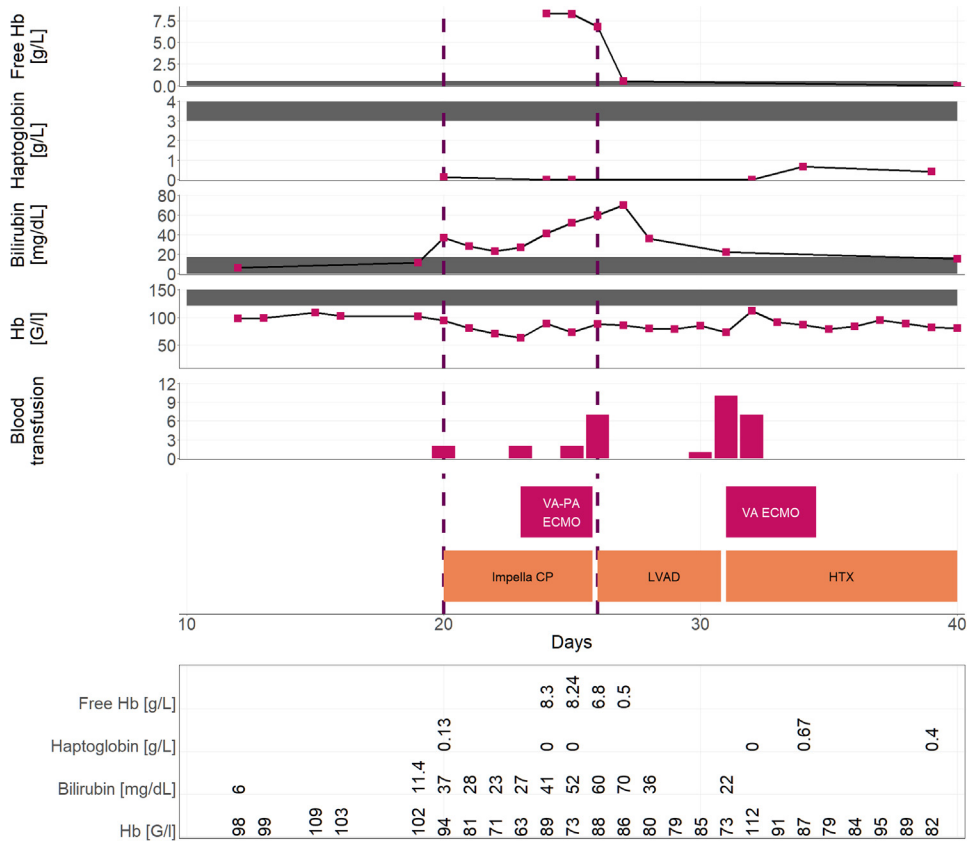
Several months after heart transplantation, hemoglobin electrophoresis followed by genetic testing revealed the patient to harbor a combination of hereditary hemoglobinopathies, with a heterozygous mutation c.427T>C in the alpha-globin cluster, resulting in the hyper unstable hemoglobin constant spring, a heterozygote deletion alpha 3.7, resulting in the loss of an alpha globin gene, and a heterozygote hemoglobin E, affecting the beta-chain. This combination has not been well described previously[2] in the literature. Prior to hospitalization for heart failure, the patient had been in good health and had not been aware of her hemoglobinopathy. She had never required any blood transfusions. Hemoglobin E can, to some degree, balance the defects of the alpha genes and might contribute to a milder picture in this patient. At the onset of shear stress induced by tMCS, however, severe hemolysis combined with a limited compensatory capacity of the bone marrow led to extramedullary hematopoiesis (EMH).

DISCUSSION

EMH in the heart is rare but has been reported, particularly in older patients in the context of myocardial infarction.[3] Stress conditions as well as hemolysis can trigger EMH,[4-6] which, on imaging, can mimic neoplasm.[7] Mechanical hemolysis is a non-immune-mediated destruction of red blood cells.

In this patient, the various differential diagnoses of hemolysis with anemia and fragmentocytes pointed to an acquired intravascular cause. In acute renal failure and shock, it was difficult to distinguish between macro- and microvascular causes. Clinically, a

FIGURE 2 Trends in RBC Transfusions and Hemolysis Lab Values



Trend in red blood cell (RBC) transfusions and hemolysis lab values (ie, bilirubin, haptoglobin, and free hemoglobin [Hb]). No point means no data. No haptoglobin or free hemoglobin values are available until 20 and 22 days, respectively, post admission. ECMO = extracorporeal membrane oxygenation; HTX = heart transplantation; LVAD = left ventricular assist device; PA = pulmonary arterial; VA = venoarterial.

mechanical etiology due to tMCS was most likely. Differential diagnoses (see **Figure 4**), such as microangiopathies, hemolytic uremic syndrome, including thrombotic thrombocytopenic purpura (TTP), or disseminated intravascular coagulation, were considered to be less likely, with an ADAMTS13 activity of 13% and high D-dimers but also elevated fibrinogen level.

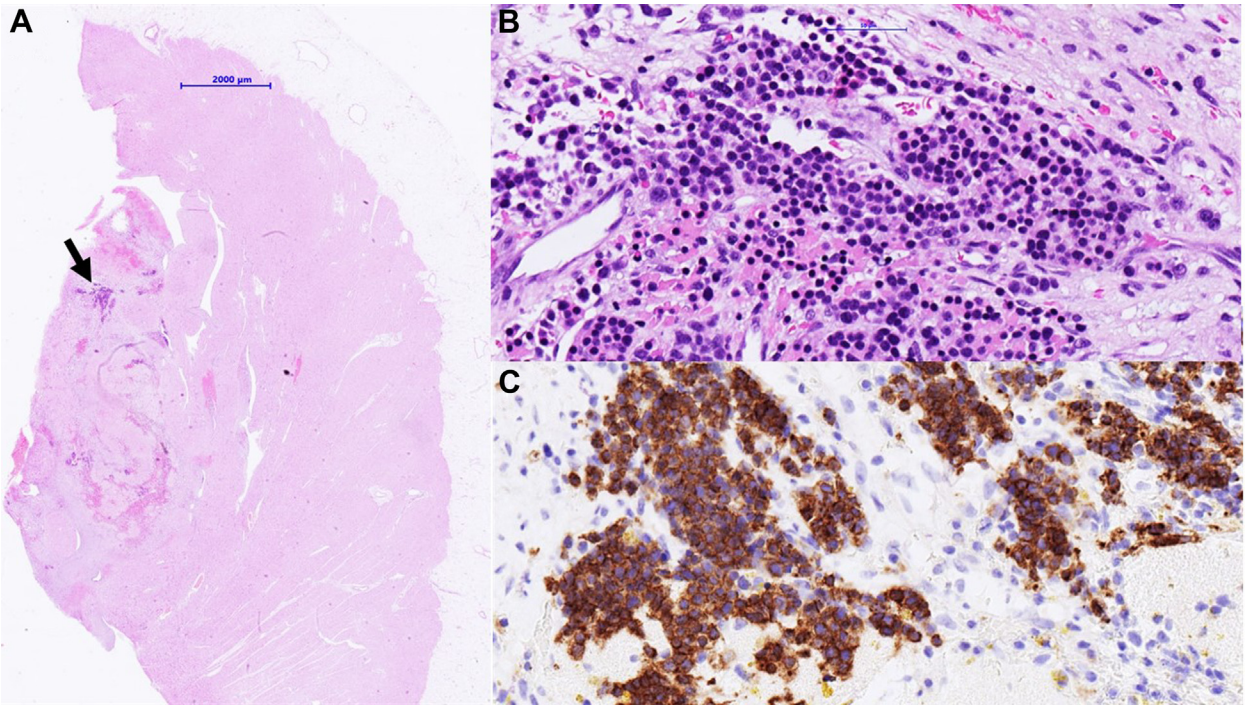
Abnormal hemoglobin leads to decreased erythrocyte deformability,[8] accounting for higher susceptibility to shear stress and probably explaining the exceptionally high level of hemolysis seen in this patient.

In this young patient with no rapid improvement in ventricular function and a complication of tMCS, tMCS was exchanged for a more permanent solution with an LVAD. Cessation of intravascular hemolysis confirmed this treatment strategy's success.[9]

Several classic parameters of hemolysis were challenging to interpret. Lactate dehydrogenase and reticulocyte count in a freshly operated patient were elevated for other reasons. Haptoglobin was undetectable at low levels of hemolysis and only became measurable several days following the LVAD implantation due to its high sensitivity but poor specificity to hemolysis. The remaining common parameters included fragmentocytes, for which only semi-quantitative measurements were possible, and free hemoglobin. The latter proved the most informative, with a virtually instantaneous disappearance of free hemoglobin after LVAD implantation. This confirmed the diagnosis of macroangiopathic acquired intravascular hemolysis.

The incidental finding of a poorly differentiated tumor in the apex of the left ventricle is unusual. Neoplasms in the heart are exceedingly rare, with

FIGURE 3 Staining of Heart



(A) Histology showing an overview (1×, hematoxylin and eosin stain) of the heart from epicardium (right) to endocardium (left) with granulation tissue and herein areas of high cellularity (black arrow). (B) These hypercellular regions are shown at higher magnification (40×, hematoxylin, and eosin stain), revealing a proliferation of relatively monomorphic cells reminiscent of nucleated erythroid precursors, in addition to fewer myeloid precursors. (C) Immunohistochemical staining for CD71 (40×) positively identifies these cells mainly as erythroid precursors (brown staining).

FIGURE 4 Diagram for Hemolysis Investigation

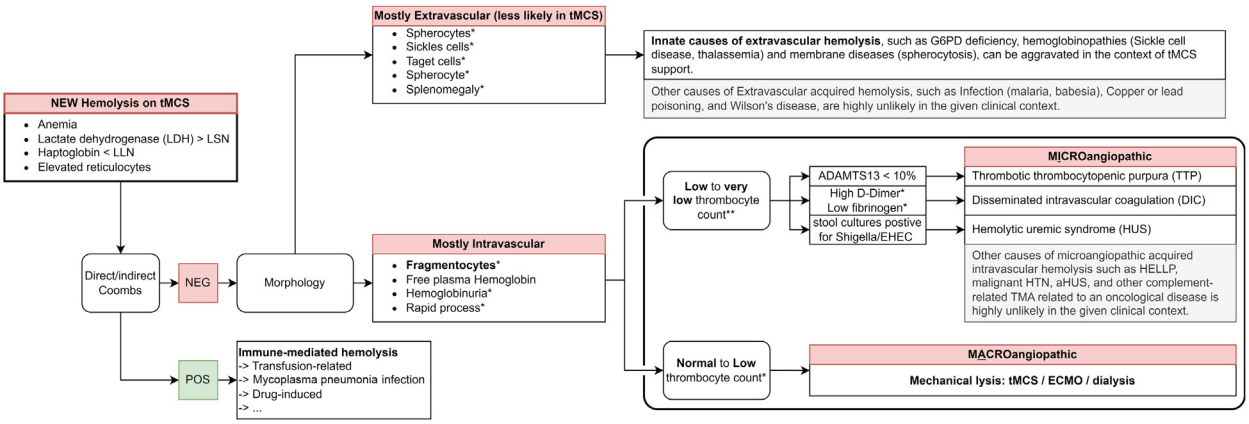


Diagram for investigating the cause of hemolysis in a patient on temporary mechanical cardiac support (tMCS). *Not pathognomonic. **In case of thrombocytopenia in the context of tMCS treatment, heparin-induced thrombocytopenia must be excluded. aHUS = atypical hemolytic uremic syndrome; DIC = disseminated intravascular coagulation; EHEC = enterohemorrhagic *Escherichia coli*; HELLP = hemolysis, elevated liver enzymes, and low platelets; HTN = hypertonia, LDH = lactate dehydrogenase; LLN = lower limit of the norm; NEG = negative; POS = positive; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura; other abbreviation as in Figure 2.

metastasis to the heart being more common than primary cardiac malignancies. The presence of unresolved oncological disease is an absolute contraindication to transplantation. Adding to this, the presence of dysplasia in the peripheral blood smear could have led to suspicion of a myelodysplastic neoplasia. However, it was interpreted as a consequence of inflammation and EMH. In this case, the rapid histopathologic diagnosis of EMH and exclusion of a neoplastic disease allowed for immediate reactivation of the patient's listing for heart transplantation.

EMH results from the expansion and differentiation of hematopoietic stem and progenitor cells outside the bone marrow. It typically affects the liver, spleen, and thorax, where it can present with masses that mimic other pathologies. EMH after fetal development is rare but can be triggered by stress conditions, including infections, metabolic abnormalities, and anemia. We found a similar case in the literature[10] of a young patient with heart failure and EMH in the setting of a left ventricular thrombus.

CONCLUSIONS

We report an unprecedented case of a young patient with EMH in the heart in the setting of tMCS. EMH should be considered in the differential diagnosis of cardiac neoplasms, particularly in the setting of additional factors such as severe hemolysis. Diagnosis typically requires a combination of imaging studies and histopathologic examination. A biopsy of the affected tissue is usually required for a definitive diagnosis. The rapid development of hemolysis in the setting of tMCS and compensatory EMH represents an important complication for clinicians to be aware of when treating patients with tMCS.

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