

# Acute Myeloid Leukemia Presenting as Effusive Constrictive Pericarditis



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## INTRODUCTION

Acute myeloid leukemia (AML) is frequently associated with pericardial effusion but infrequently presents with cardiac tamponade or effusive constrictive pericarditis. This case report highlights a presentation of cardiac tamponade identified with transthoracic echocardiography (TTE). The patient was subsequently diagnosed with effusive constrictive pericarditis (ECP) suspected by physical examination and echocardiography after pericardiocentesis and confirmed by cardiac magnetic resonance imaging (CMR). These findings were associated with a new diagnosis of AML.

## CASE PRESENTATION

A 60-year-old man with no significant medical history presented with increasing shortness of breath for 10 days after a viral-like syndrome with cough, sinus congestion, and decreased urine output. Other family members had similar symptoms but recovered. On physical examination, the patient was mildly tachypneic with a heart rate of 100 beats/min, blood pressure of 130/87 mm Hg with a pulsus paradoxicus of 14 mm Hg, and oxygen saturation 95% on room air. He had elevated jugular venous pressure, a distended abdomen without shifting dullness, and 2+ bilateral lower extremity edema. Laboratory results were notable for creatinine of 1.6 mg/dL, hemoglobin of 7.8 g/dL, a white blood cell count of  $14.1 \times 10^9/L$ , a platelet count of  $150 \times 10^9/L$ , aspartate aminotransferase of 2,671 IU/L, alanine aminotransferase of 2,064 IU/L, and ferritin of 19,318 ng/mL.

Initial electrocardiography showed sinus tachycardia with low-voltage QRS (Figure 1). Posteroanterior and lateral chest radiography showed cardiomegaly (Figure 2). Transthoracic echocardiography showed a large pericardial effusion with fibrinous strands, left ventricular ejection fraction of 55%, diastolic right ventricular free wall collapse, significant respiratory variation of the mitral inflow E-wave velocity, and a dilated inferior vena cava with no respiratory variation, consistent with tamponade physiology (Figure 3, Video 1).<sup>1</sup> Invasive hemodynamics were notable for equalization of diastolic pressures: right atrial (RA) pressure 22 mm Hg, right ventricular pressure 46/23 mm Hg, pulmonary artery pressure 44/22 mm Hg, pulmonary capillary wedge pressure 24 mm Hg,

and mean pericardial pressure 21 mm Hg, consistent with tamponade. Pericardiocentesis yielded 750 mL of frankly bloody fluid. Pericardial fluid analysis was consistent with an exudate with total protein 6.1 g/dL, lactate dehydrogenase 3,460 IU/L (serum total protein 6.7 g/dL, serum lactate dehydrogenase 3,839 IU/L), glucose of 18 mg/dL, a red blood cell count  $2,000,000/mm^3$ , and a white blood cell count of  $8,720/mm^3$ . Pulmonary arterial saturation improved from 21% to 35%, cardiac output from 3.0 to 3.9 L/min, and cardiac index from 1.5 to 2.0 L/min/m<sup>2</sup>. Right atrial pressure fell by <50% to 16 mm Hg, and RA and right ventricular diastolic pressures were unequal (right ventricular pressure 44/4 mm Hg).

The patient's dyspnea and tachycardia resolved. He was started on colchicine for pericarditis. Nonsteroidal anti-inflammatory drugs were not given, because of the anemia of unclear etiology. The pericardial drain output gradually decreased over several days, but the patient was noted to have Kussmaul's sign. Repeat TTE showed a small pericardial effusion, with findings consistent with constriction (Figure 4). Cardiac magnetic resonance imaging was performed to assess for constrictive physiology and pericardial pathology. Cardiac magnetic resonance imaging demonstrated a persistent, circumferential, hemorrhagic pericardial effusion with heterogeneous appearance and fibrinous stranding. The pericardium was thickened and enhanced on late gadolinium imaging (Figures 5 and 6, Video 2). Constrictive physiology was noted with ventricular interdependence and septal bounce during the respiratory cycle, confirming a diagnosis of ECP (Figure 5, Video 2).<sup>2</sup>

The patient continued to have cytopenia throughout his hospital course, and the platelet count gradually dropped to  $41 \times 10^9/L$ . Heparin-induced thrombotic thrombocytopenia and disseminated intravascular coagulation panels were negative. Bone marrow biopsy showed high-grade myelodysplastic syndrome with early conversion to AML. The patient was started on chemotherapy with decitabine, with a favorable response. The patient received a short course of high-dose steroids and then continued on colchicine for 4 months, with no examination findings of constriction. Repeat TTE after 4 months of colchicine showed a trivial pericardial effusion and persistent paradoxical septal motion (Figure 7, Video 3). Follow-up computed tomography showed a small pericardial effusion but no pericardial thickening or calcification (Figure 8). Pericardial biopsy was never obtained given the patient's overall clinical improvement and the noninvasive imaging findings. He underwent successful bone marrow transplantation for AML and is doing well.

## DISCUSSION

A pericardial effusion and tamponade are often associated with malignancy. Nearly 20% of large, symptomatic effusions without obvious etiology will represent the first presentation of a malignancy.<sup>3</sup> The reported sensitivity of pericardial fluid cytology for malignancy ranges from 67% to 92%.<sup>4-6</sup> Additional case series and cohorts have also found only modest yield of pericardial fluid cytology in suspected or known malignancies. In a single-center case series of 81 otherwise

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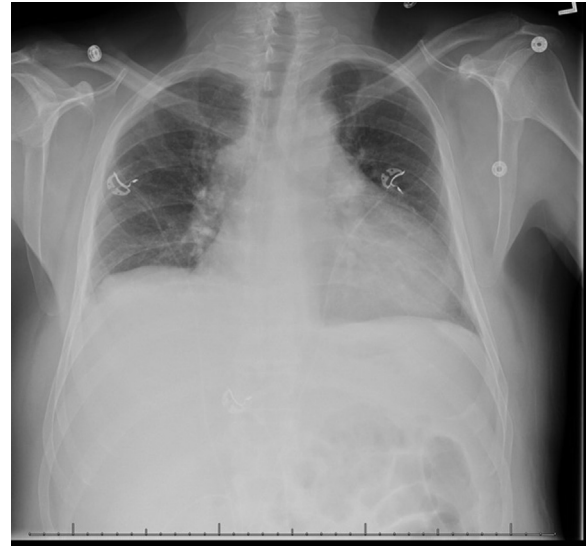
## VIDEO HIGHLIGHTS

**Video 1: (A, B)** TTE, parasternal views, showing a large pericardial effusion with diastolic right ventricular free wall collapse (arrow).

**Video 2: (A)** CMR cine frame demonstrates a persistent, circumferential, hemorrhagic pericardial effusion with heterogeneous appearance and fibrinous stranding adjacent to mostly right ventricular free wall. The pericardial effusion appears gray. **(B)** Free-breathing real-time cines in the short-axis orientation reveal that with inspiration and the descent of the diaphragm, the ventricular septum shifts toward the left ventricle, and with expiration, the ventricular septum shifts toward the right ventricle because of pericardial constraint and ventricular interdependence.

**Video 3: (A, B)** Follow-up TTE, parasternal long- and short-axis views, after 4 months of colchicine and decitabine treatment for AML showing a small residual pericardial effusion with paradoxical septal motion.

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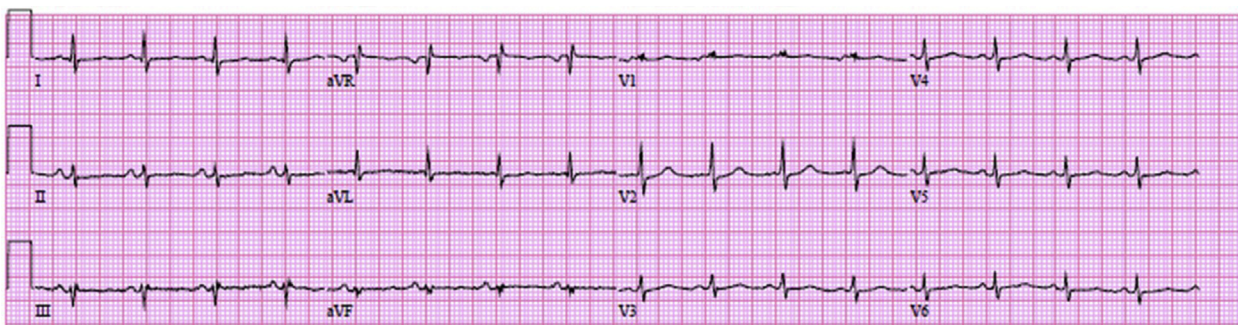
**Figure 2** Posteroanterior chest radiograph showing cardiomegaly.

healthy patients presenting with cardiac tamponade who underwent pericardiocentesis, 47 of 81 (58%) had underlying malignancy, eight of which were leukemia or lymphoma. Only eight of those 47 patients had positive pericardial fluid cytology.<sup>7</sup> Kim *et al.*<sup>8</sup> studied 98 patients with known active malignancy who underwent pericardiocentesis for tamponade or imminent tamponade and reported that 75 of 98 samples (77%) had positive cytology. All 23 negative samples were exudative, and there were no alternative explanations for the effusions, so they were considered malignant.<sup>8</sup> Gornik *et al.*<sup>9</sup> followed 182 patients who underwent pericardiocentesis for cardiac tamponade, of which 96 cases (53%) were deemed “cancer related,” but only 52 of 96 (54%) had positive cytology. However, the presence of malignant or atypical cells in the effusion conferred a worse prognosis.

In a retrospective cohort study of 2,592 patients with leukemia from a single center (acute lymphocytic leukemia, myelodysplastic syndrome, or AML), 21% were found to have pericardial effusions, although only 26% of those cases were found before therapy was started. Most (70%) were trivial in size, and only 5% to 7% were mod-

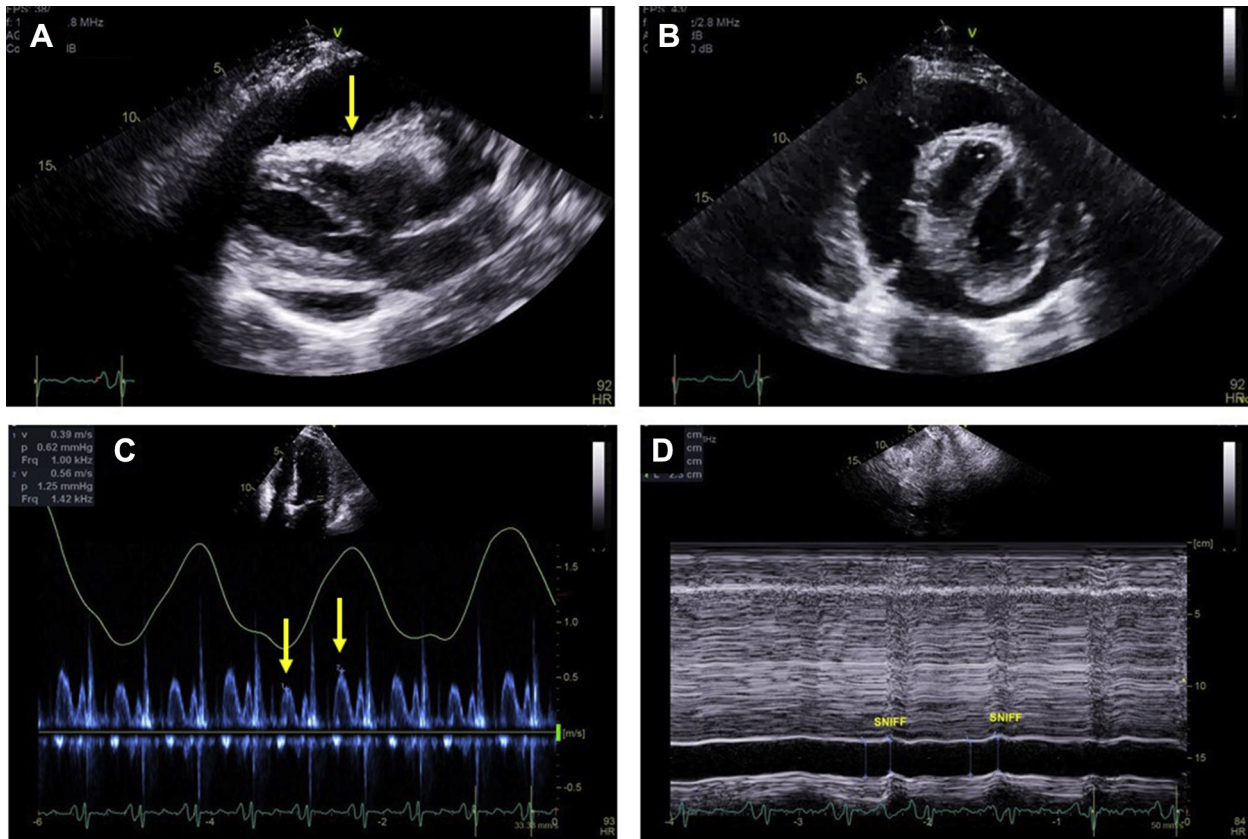
erate or large.<sup>10</sup> Ten of these patients first presented with cardiac tamponade requiring pericardiocentesis. Of these cases, only four of 10 yielded leukemic cells on pericardial fluid cytology; the remaining six samples were hemorrhagic or serosanguinous. The larger effusions generally reduced with chemotherapy. The study did not provide information about the white blood cell count on presentation or the presence of monocytic differentiation. Extramedullary disease is a frequent manifestation of AML, and it is associated with monocytic differentiation and high white blood cell count.<sup>11</sup> Pericardial involvement, however, is not well studied. Four more case reports of AML presenting as pericardial tamponade have been published.<sup>12</sup> In all four cases, pericardial fluid cytology yielded leukemic cells. In our case, pericardial fluid cytology was negative for malignant cells, the white blood cell count was minimally elevated, and there was no evidence of monocytic differentiation.

The pathophysiology of pericardial effusions in AML is not well described, but there are a few proposed mechanisms. There may be direct malignant infiltration of the pericardium by leukemic cells, leading to effusion.<sup>12</sup> Other proposed mechanisms include bleeding diathesis in the setting of thrombocytopenia, infection due to relative immunodeficiency state in leukemia, and effusions resulting as a side effect of chemotherapy.<sup>3,13</sup> Our patient had negative fungal, acid-fast bacilli, mycobacterial, and bacterial pericardial

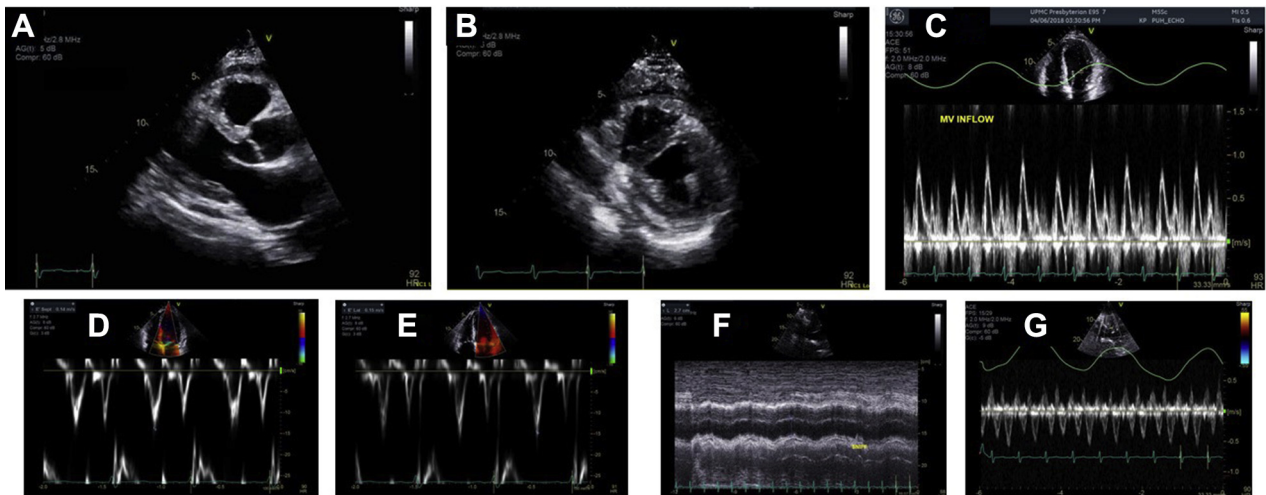


**Figure 1** Twelve-lead electrocardiogram showing sinus tachycardia with low-voltage QRS.

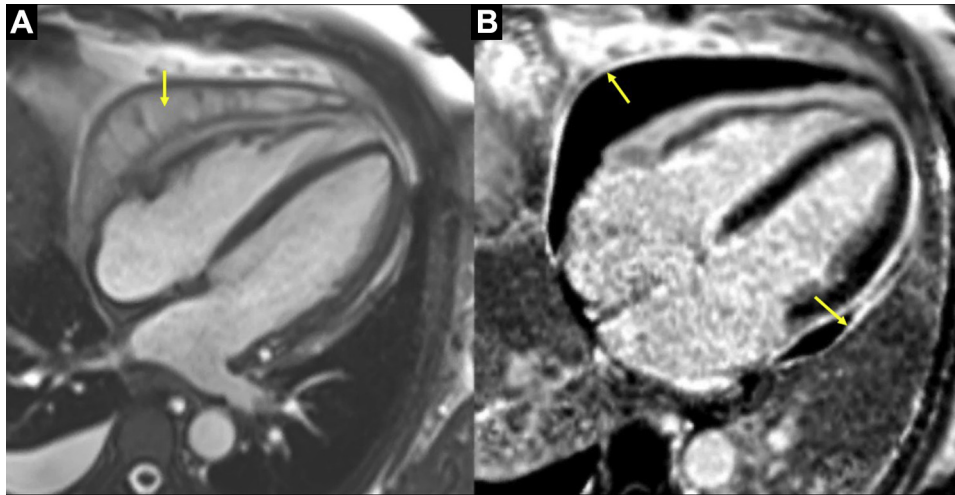




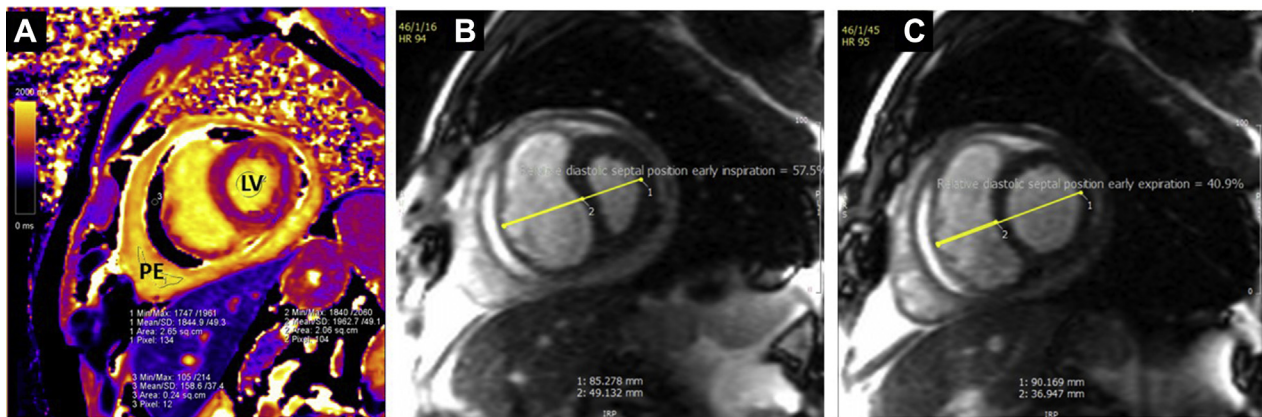
**Figure 3** (A, B) TTE, parasternal views, showing a large pericardial effusion with diastolic right ventricular free wall collapse (arrow). (C) Pulsed-wave Doppler of mitral inflow showing a significant variation of the E-wave velocity (arrows) with inspiration consistent with tamponade. (D) Dilated inferior vena cava with no respiratory variation (plethora) consistent with tamponade.



**Figure 4** Follow-up TTE after pericardial fluid drainage with findings supportive of constriction. (A) Parasternal long-axis view with minimal residual pericardial fluid. (B) Short-axis view showing interventricular septal shift toward the left. (C) Mitral inflow Doppler showing respiratory variation of the mitral inflow E-wave velocity. (D, E) Medial and lateral tissue Doppler of the mitral annulus demonstrating pulsus reversus of the annular E'-wave velocities with medial E' greater than lateral E'. (F) Dilated inferior vena cava with no respiratory variation (plethora) consistent with constriction. (G) Pulsed-wave Doppler of a hepatic vein showing diastolic flow reversal.



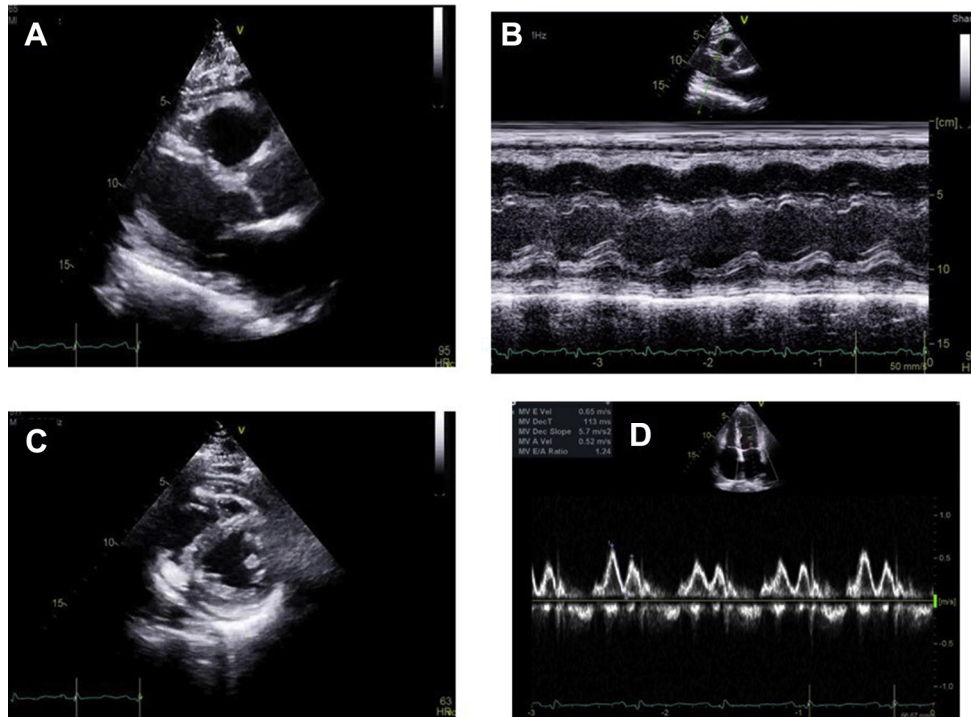
**Figure 5** (A) CMR cine frame demonstrates a persistent, circumferential, hemorrhagic pericardial effusion with heterogeneous appearance and fibrinous stranding (arrow) adjacent to mostly right ventricular free wall. The pericardial effusion appears gray on the cine frame. (B) On the CMR phase-sensitive reconstructed late gadolinium enhancement image, the pericardial effusion appears black. The parietal pericardium is thickened and enhanced with late gadolinium imaging (arrows).



**Figure 6** (A) CMR native T1 map shows a hemorrhagic pericardial effusion (PE) with a native T1 similar to blood in the left ventricle (LV; 1,845 vs 1,960 msec). Most transudative pericardial effusions exhibit native T1 similar to water, about 2,900 msec for this pulse sequence. There is also epicardial fat noted with a very low T1 (~160 msec, dark color). (B, C) Free-breathing real-time cinés in the short-axis orientation reveal interventricular septal flattening during inspiration consistent pericardial constraint and/or ventricular interdependence. Short-axis slices of the ventricles show septal shift with the respiratory cycle because of ventricular interdependence. The ventricular septum shifts toward the left ventricle with inspiration (B) and toward the right ventricle with expiration (C). The early diastolic relative septal excursion during deep breathing measured from real-time short-axis cinés is 16.6% (abnormal >11.8%), consistent with constriction.

fluid cultures. Viral panels were not sent. Given the hemorrhagic, exudative nature of the effusion and the time course of the patient's symptoms and cytopenia, we believe AML to be the most likely cause. The patient's viral-like prodrome could be explained by his newly diagnosed AML, but it does raise the possibility of a viral upper respiratory tract infection leading to viral pericarditis. If the pericardial effusion was caused by a viral etiology, it is possible that this patient's relative immunocompromised status secondary to AML contributed to the severity of his case, unlike his family members, who all recovered from a similar viral upper respiratory tract infection.

After resolution of the tamponade, this patient was found to have ECP as evidenced by Kussmaul's sign, the RA pressure dropping by <50% after pericardiocentesis, and the subsequent findings on TTE and CMR. To our knowledge, no studies have documented the prevalence of ECP among malignant effusions, although case reports do exist.<sup>14,15</sup> Our patient responded favorably to treatment with colchicine, with no evidence of constriction on follow-up imaging. Pericardial biopsy was never needed given the patient's clinical improvement and the noninvasive imaging findings. He underwent successful bone marrow transplantation.



**Figure 7** (A) Follow-up TTE, parasternal long-axis view, after 4 months of colchicine and decitabine treatment for AML showing a small residual pericardial effusion. (B) M-mode imaging of the parasternal long-axis (C) showing paradoxical septal shift but (D) with no significant mitral E-wave variation.



**Figure 8** Chest computed tomography showing a small pericardial effusion but no pericardial thickening or calcification that would suggest constriction.

## CONCLUSION

We report a rare case of AML presenting as cardiac tamponade, which is to our knowledge the first case of AML-associated ECP. This case demonstrates the importance of considering underlying hematologic malignancy in patients presenting with hemorrhagic pericardial

effusions, even with negative pericardial fluid cytology. Although the exact pathophysiologic mechanism causing the effusion is unknown, the patient's underlying AML is most likely related to the development of the effusion and ECP. Transthoracic echocardiography and CMR played key complementary roles in the identification of tamponade and ECP.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2019.09.002>.

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