

Pericardial Involvement with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: A Rare Case of Constrictive Pericarditis



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INTRODUCTION

Cardiac malignancies are rare, ranging in prevalence from 0.05% to 4.8%¹⁻⁵ in large autopsy series, with secondary involvement being more common compared with primary malignancies of the heart. Although the hematopoietic system is the second most common cause (behind the lung) of secondary malignancies involving the heart, this remains a rare clinical entity with variable presentations. Malignancies secondarily involving the pericardium account for 75% of all cardiac malignancies, but constrictive pericarditis is present in only 4% of these cases.⁵ In this report, we present a case of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) involving the pericardium presenting with symptoms of constrictive pericarditis.

CASE PRESENTATION

A 57-year-old man presented to an outside hospital with a 2-month history of intermittent fevers, night sweats, and chest pain with radiation to the back that was worsened by lying supine and deep breathing. History was notable for hypertension and chronic obstructive pulmonary disease with frequent oral steroid use. One month prior, his family physician prescribed levofloxacin 500 mg/d and oral prednisone 20 mg/d for similar symptoms. Other regular medications included inhaled albuterol 90 μ g as needed, fluticasone 50 μ g nasal spray daily, aspirin 81 mg/d, and hydrochlorothiazide 25 mg/d.

On physical examination, there was no evidence of volume overload, and heart sounds were normal with no pericardial friction rub. There was no hepatosplenomegaly or lymphadenopathy. The patient's laboratory investigations were significant for a leukocytosis of 28×10^3 cells/ μ L, with an elevated absolute lymphocyte count of

$14 \times 10^3/\mu$ L. On review of his prior blood work, his leukocyte count was noted to be intermittently elevated over 5 years preceding presentation but had been thought to be secondary to intermittent steroid use for chronic obstructive pulmonary disease exacerbations. The platelet count was $242 \times 10^9/L$, and hemoglobin was 12.1 g/dL, with normocytic normochromic red cell indices. Troponin was undetectable, and the erythrocyte sedimentation rate was within normal limits. Electrocardiography revealed tachycardia with no ST-segment changes. A computed tomographic imaging study of the chest was done to assess for pulmonary embolism. This study was negative for pulmonary embolism but revealed thickening of the pericardium (with a small pericardial effusion) and multiple anterior mediastinal and precarinal lymph nodes, all <8 mm in size (Figures 1A–1C). The patient was started on aspirin 325 mg three times daily and colchicine 0.6 mg twice daily for possible acute pericarditis.

Within 1 week, the patient presented to our institution with ongoing symptoms of pain and shortness of breath despite aspirin and colchicine use. Echocardiography showed evidence of a thickened pericardium and signs of pericardial constrictive physiology. Two-dimensional imaging revealed a diastolic septal bounce and respirophasic variation of the interventricular septum (Videos 1 and 2). Continuous-wave Doppler across the mitral and tricuspid valves revealed an early-to-late diastolic mitral inflow (E/A) ratio of 1.8, a short deceleration time of 96 msec, and significant flow variation across the mitral (41%) and tricuspid (97%) valves with respiration (Figures 2A and 2B). There was also annulus reversus with a septal mitral annular tissue velocity of 13 cm/sec compared with 10 cm/sec of the lateral mitral annulus (Figures 2C and 2D) and prominent expiratory diastolic flow reversal on continuous-wave Doppler of the hepatic veins (Figure 2E).

Cardiac magnetic resonance imaging revealed abnormal septal motion and pericardial tethering, especially along the basal to mid right ventricular free wall (Video 3). Prominent respirophasic septal shift of the interventricular septum was seen (Video 4). Late gadolinium enhancement showed mild delayed pericardial enhancement adjacent to the right ventricular free wall and anteriorly (Figure 3). Overall findings were consistent with constrictive pericarditis with mild active inflammation.

Given the patient's unexplained elevated leukocyte count, peripheral blood flow cytometry was done. This revealed B cells that displayed an abnormal immunophenotype diagnostic of a B-cell lymphoproliferative disorder consistent with CLL/SLL with an unmutated immunoglobulin variable heavy-chain gene status.

The patient continued to have symptoms despite the aspirin and colchicine. Prednisone 20 mg/d and azathioprine 100 mg/ were added with little benefit. Given the lack of response to immunosuppressive therapy, the patient was referred for radical pericardiectomy 3 months following his initial presentation. The patient did well following radical pericardiectomy with improved breathing and

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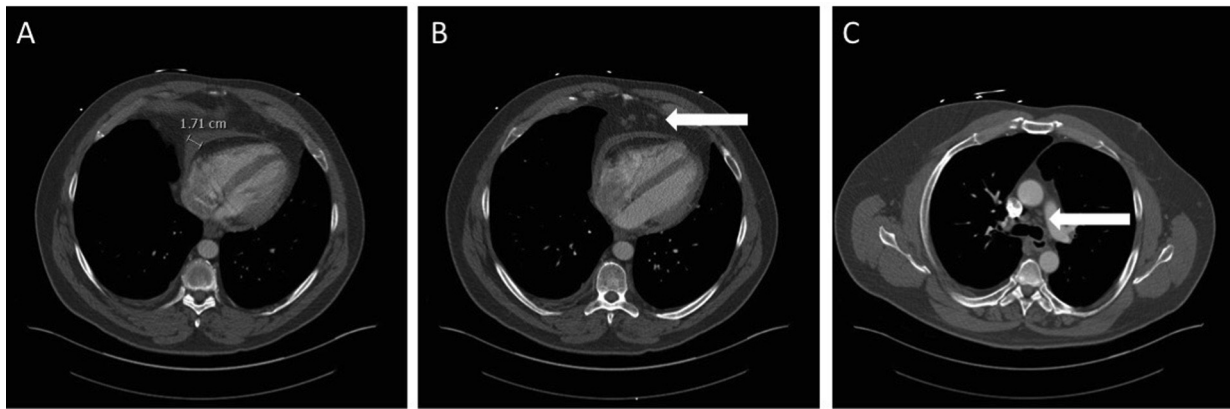


Figure 1 Computed tomography of the chest for assessment of pulmonary embolism demonstrating pericardial thickening and effusion anteriorly (**A**) and scattered anterior mediastinal lymph nodes (*white arrow* in **B**) and precarinal lymph nodes (*white arrow* in **C**).

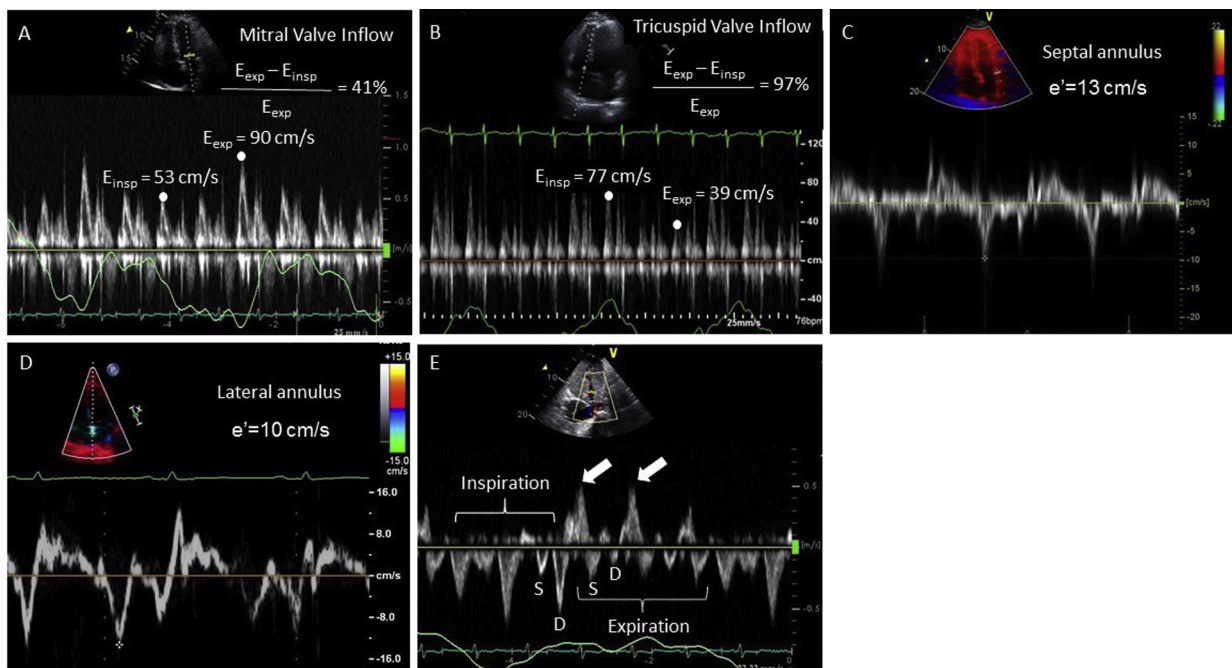


Figure 2 Pulsed-wave Doppler recording across the mitral valve (**A**) and tricuspid valve (**B**) shows significant inspiratory decrease in flow across the mitral valve and expiratory decrease in flow across the tricuspid valve. The ratio of early to late diastolic mitral inflow was 1.8 with a short deceleration time (96 msec). Mitral annular tissue Doppler velocity reveals a septal mitral annular tissue Doppler velocity of 13 cm/sec (**C**) and a lateral mitral annular tissue Doppler velocity of 10 cm/sec (**D**), consistent with annulus reversus. Continuous-wave Doppler of the hepatic vein reveals prominent diastolic flow reversal during expiration (*exp*; *white arrows* in **E**). The respirometer is not accurate, but the expiratory phase can be determined on the basis of a decrease in forward systolic (S) and diastolic (D) flow in the hepatic veins. *insp*, Inspiration.

exercise tolerance. The pathology lab received multiple segments of tissue measuring in aggregate $20.5 \times 14.9 \times 5.0$ cm. The outer surface demonstrated adipose tissue and hemorrhage. The inner surface was smooth with areas of minute hemorrhage. The wall ranged in thickness from 0.1-0.8 cm. Sectioning revealed a fibrotic and calcified cut surface. No areas of nodularity or necrosis were identified. The gross characteristics of the specimen did not differ from the typical pericardial appearance of chronic constrictive pericarditis. Final histopathology revealed chronic pericarditis with fibrosis and involvement by B-cell CLL/SLL (**Figure 4**). Adjacent

lymph nodes and adipose tissue also demonstrated involvement with B-cell CLL/SLL. breathing and exercise tolerance. Final pathology revealed chronic pericarditis with fibrosis and involvement by B-cell SLL/CLL (**Figure 4**). Adjacent lymph nodes and adipose tissue also demonstrated involvement with B-cell CLL/SLL. Chemotherapy was discussed with bendamustine and rituximab, fludarabine, cyclophosphamide, and rituximab, or ibrutinib, which the patient initially declined before subsequently agreeing to start bendamustine and rituximab therapy. He remains free of symptoms now >1 year postoperatively.



Figure 3 Cardiac magnetic resonance imaging phase-sensitive inversion recovery images showing delayed gadolinium enhancement of the pericardium in four-, three-, and two-chamber views (A–C, white arrows), respectively.

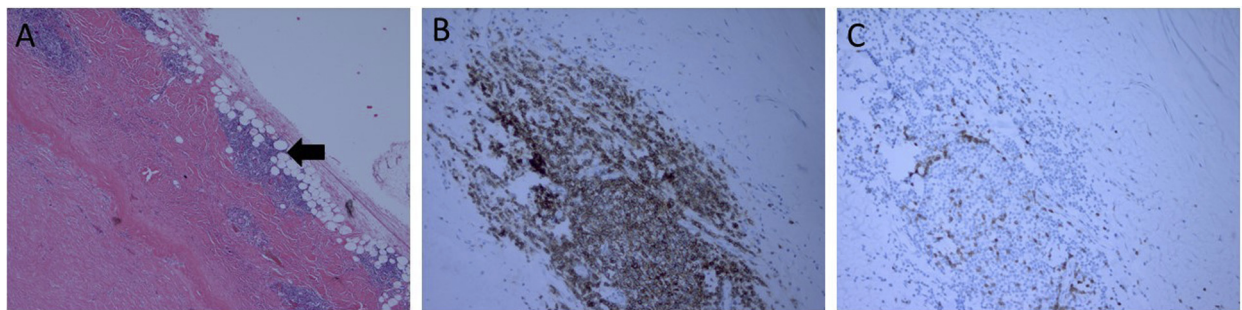


Figure 4 Final pathology from radical pericardiectomy demonstrates a thickened pericardium with prominent lymphocyte infiltration on the epicardial surface (A, 200× magnification, epicardial surface marked by black arrow). Staining for CD20 was positive, revealing B lymphocytes predominantly on the epicardial surface (brown staining in B, 200× magnification); in addition, CD3 staining revealed the presence of few T-lymphocytes (brown staining in C, 200× magnification).

DISCUSSION

CLL, the most common leukemia in the Western world, is a malignancy of B cells characterized by a monoclonal production of small, mature-appearing lymphocytes in the blood, marrow, and lymphoid tissue.⁶ The average incidence varies widely ranging from <0.01% in patients from Asian countries to ~0.06% in patients from Eastern countries or the United States.⁶ The majority of patients are asymptomatic at diagnosis, having been diagnosed incidentally on routine blood work. The minority of patients present with symptoms that range from constitutional symptoms to symptomatic lymphoid tissue enlargement.

Cardiac involvement of CLL is rare, with pericardial involvement being exceedingly rare. In a retrospective analysis of 94 patients with cardiac involvement of non-Hodgkin's lymphoma from 1990 to 2015, Gordon *et al.*⁷ found that CLL/SLL was the underlying malignancy in six cases (7%). The presenting symptoms for these cases were heart failure (four cases), arrhythmia (one case), and cardiac arrest (one case). Only two prior cases of pericardial involvement of B-cell CLL/SLL have been reported, both presenting with symptoms of constrictive pericarditis.^{8,9} The first patient presented with an asymptomatic incidentally discovered isolated lymphocytosis ($\sim 49 \times 10^9/L$), several years before developing subacute symptoms of constrictive pericarditis. The second patient presented with progressive dyspnea and anasarca,

although the time frame of symptom development was not clear on the basis of the report. Neither patient had evidence of aggressive transformation of the CLL at the time of symptom development. The first patient underwent anterior pericardiectomy before dying of cardiac arrest shortly after surgery. The second patient underwent radical pericardiectomy and also died shortly after surgery, this time of postoperative infection.

Constrictive pericarditis can be a difficult diagnosis to make and often requires multimodality cardiac imaging. While echocardiography remains the initial diagnostic test of choice, cardiac MRI can have added value. Not only can cardiac MRI provide anatomic characterization of the pericardium and functional assessment for constrictive physiology, it also allows tissue characterization. Studies correlating the presence of pericardial delayed hyperenhancement (DHE) with surgical histopathology have shown that the presence of DHE correlates with greater fibroblastic proliferation, more prominent granulation tissue and neovascularization, while lack of DHE correlates with more fibrosis and calcification. Furthermore, medical therapy in patients with constrictive pericarditis with DHE can reduce the degree of DHE, suggesting that the DHE may be due in part to active inflammation rather than fibrosis. In our case, the cardiac MRI revealed mild DHE. This correlates well with the final pathology, which showed minimal neovascularization, a predominance of fibrosis with some calcification in addition to lymphocyte infiltration.

CONCLUSION

We present a rare case of CLL/SLL with unmutated immunoglobulin variable heavy-chain gene status and associated constrictive pericarditis and report for the first time a favorable outcome with the use of multimodality imaging.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2018.02.002>.

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