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CASE REPORT

CLINICAL CASE

Ventricular Thrombus Formation Caused by Subendomyocardial Inflammation in Eosinophilic Granulomatosis With Polyangiitis

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ABSTRACT

Cardiac involvement of eosinophilic granulomatosis with polyangiitis is a rare but life-threatening complication. We present a case of eosinophilic granulomatosis with polyangiitis with moderately impaired ventricular function forming a ventricular thrombus. Pathological assessment of endomyocardial biopsy specimen revealed aggregated eosinophils in the subendocardium, suggesting ventricular endothelial damage leading to thrombus formation. (J Am Coll Cardiol Case Rep 2024;29:102321) © 2024 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 78-year-old woman was referred to the department of immunology in our hospital owing to fever lasting 14 days, tingling, weakening of her extremities, and chest discomfort. On admission, her heart rate and blood pressure were 90 beats/min and 96/58 mm Hg, respectively. Her body temperature was 36.9 °C and saturation or peripheral O_2 level was 98% (ambient air). She had lost 7 kg of body weight within the 6 months before the current hospitalization. Moreover, no remarkable abnormalities in lung and heart sounds were detected. Bilateral weakening of grip strength was observed (right: 5.3-kg force, left: 8.9-kg force). A nerve conduction test showed multiple dysfunctions in both motor and sensory nerves, which was consistent with mononeuritis multiplex. Furthermore, laboratory examination revealed elevated inflammatory markers with markedly increased eosinophils (4,998 μ/L). Rheumatoid factor was positive, whereas either proteinase-3 and myeloperoxidase antineutrophil cytoplasmic antibody were negative (Table S1). Chest radiography revealed

LEARNING OBJECTIVES

- To recognize that eosinophilic myocarditis accompanied with EGPA have a great risk of ventricular thrombus formation even in cases without significant systolic dysfunction.
- To see the merit of considering the initiation of prophylactic anticoagulation therapy at the time of initial diagnosis of EGPA with cardiac involvement.

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ABBREVIATIONS AND ACRONYMS

CEL = chronic eosinophilic leukemia

EGPA = eosinophilic granulomatosis with polyangiitis

EMB = endomyocardial biopsy

LV = left ventricle

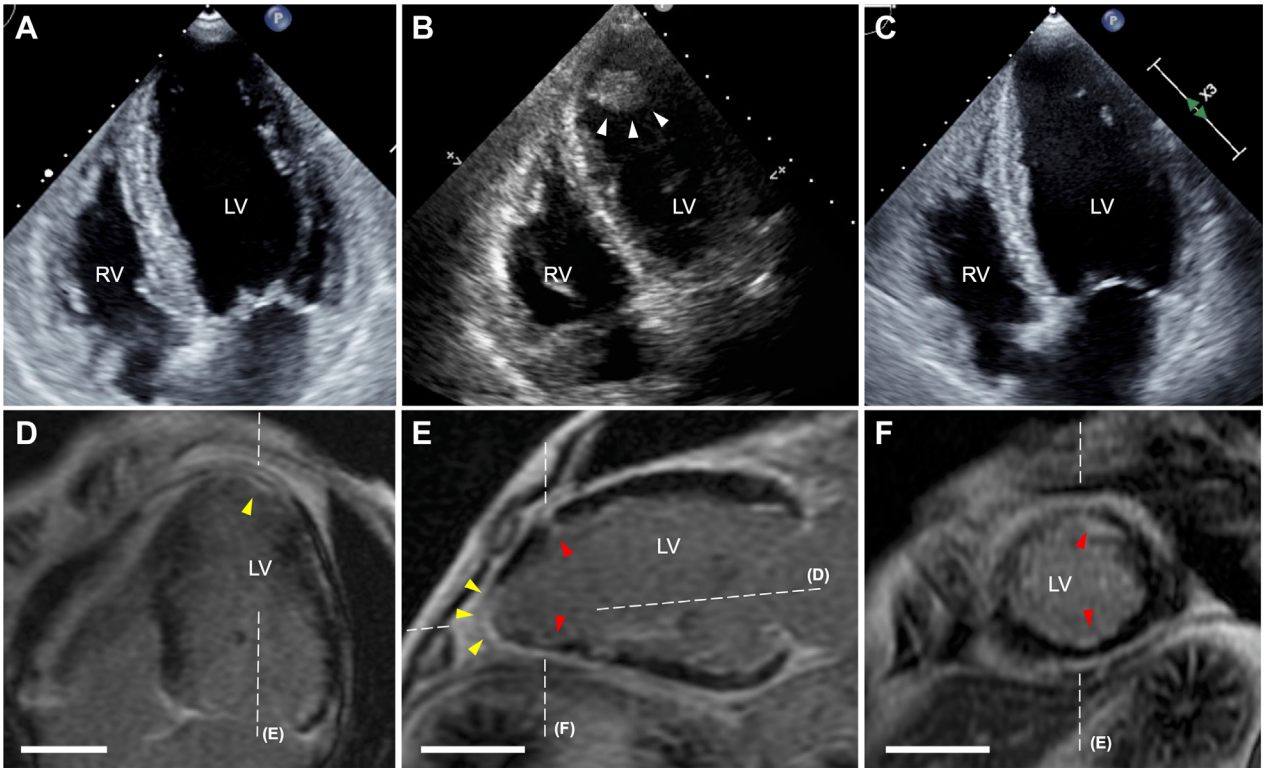
TTE = transthoracic echocardiography

cardiomegaly (cardiothoracic ratio: 59%) with slight congestion in the lung fields (Supplemental Figure 1A). Additionally, 12-lead electrocardiography showed sinus rhythm with complete right bundle branch block (Supplemental Figure 1B). Transthoracic echocardiography (TTE) revealed no left ventricular (LV) dilatation (LV diastolic/systolic dimension of 42.3/34.8 mm and interventricular septal/posterior wall thickness of 8.2/8.8 mm) with reduced LV ejection fraction of 42.5%. Notably, at the time of initial TTE examination on admission (day 1), there was no apparent ventricular thrombus (**Figure 1A**, Video 1). Because the initial laboratory test also revealed the elevation of cardiac enzymes (Supplemental Table 1), the patient was referred to the cardiovascular department.

PAST MEDICAL HISTORY

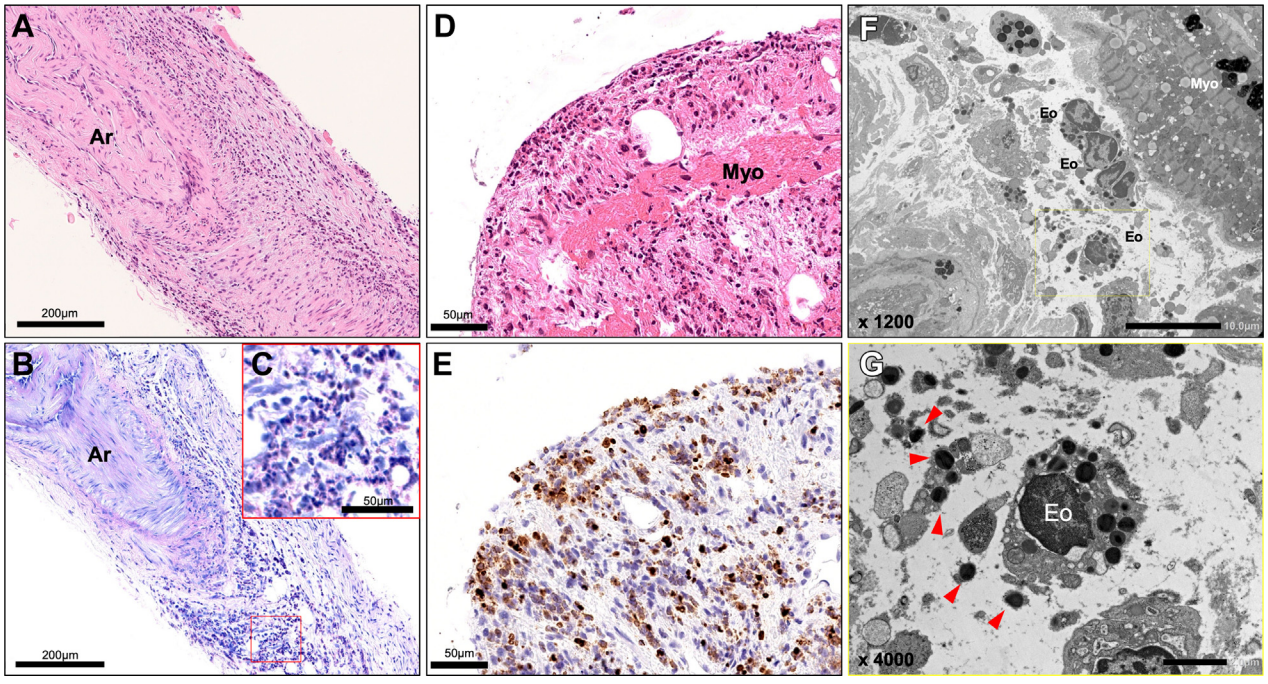
The patient had a 5-year history of bronchial asthma and chronic sinusitis. No regular therapeutic intervention had been offered for these conditions within the past several years. Although her bronchial asthma was well-controlled without regular medication, a pulmonary function test on admission revealed obstructive ventilatory disorder (1% forced expiratory volume: 67.0%, percentage of volume capacity: 102.7%). Elevated exhaled fraction of exhaled NO

FIGURE 1 Serial Changes of TTE and Gadolinium-Enhanced CMR Findings



(A to C) Four-chamber view of transthoracic echocardiography (TTE) findings. On admission, no intraventricular thrombus was observed (day 1) (A). A large and mobile thrombus (19 × 15 mm) (white arrowheads) was observed at LV apex (day 4) (B). The apical thrombus was not detected on day 11 (C). (D to F) Gadolinium-enhanced cardiac magnetic resonance (CMR) findings on day 11. Long-axis 4-chamber (D), 2-chamber (E), and short-axis (F) views. White dotted lines in D-F represent the location of slice in each image. Yellow and red arrowheads indicate late gadolinium enhancement lesions, suggesting eosinophilic granulomatosis with polyangiitis–derived myocardial injury site. Corresponding arrowheads in different slices are shown in the same color. Note, left ventricular (LV) apex wall, which showed intraventricular thrombus formation, has obvious late gadolinium enhancement depth in luminal endocardial side. White scale bars in D-F are 3 cm. RV = right ventricle.

FIGURE 2 Histopathological Findings of Myocardial EMB Specimen



(A, B) Low-power images of subendocardial tissue around intramyocardial arteriole (A: hematoxylin and eosin, B: Giemsa staining). (C) High-power image of red rectangular field in B. (D, E) High-power images of subendocardium (D: hematoxylin and eosin, E: immunohistochemistry for major basic protein of eosinophils). Inflammation with eosinophils (Eo) aggregation accompanied by loss of myocardium (Myo) were observed around arteriole (Ar) (A to C) and endomyocardium (D, E). (F, G) Transmission electron microscopy showed accumulation of eosinophils around myocardial fiber (E: 1,200×). High-power image showed eosinophil degranulation, indicating activated eosinophils (F: 4,000x). Read arrow heads indicate released granules from eosinophils. EMB = endomyocardial biopsy.

level (51 parts per billion) was also determined, suggesting her active allergic airway inflammation was caused by asthma.

DIFFERENTIAL DIAGNOSIS

Possible differentials considered were eosinophilic granulomatous with polyangiitis (EGPA), parasitic infections, allergic bronchopulmonary aspergillosis, drug allergy, chronic eosinophilic leukemia (CEL), and idiopathic hypereosinophilic syndrome. Parasitic infections were ruled out by stool examination and chest/abdominal computed tomography. Regarding allergic bronchopulmonary aspergillosis, low serum *Aspergillus* antigen and *Aspergillus*-specific immunoglobulin E antibody levels were confirmed. Typical pulmonary shadows for allergic bronchopulmonary aspergillosis by chest computed tomography, such as central bronchiectasis and mucoid impaction, were lacking. Any drugs that could induce allergic reaction had not been prescribed before the hospitalization. Regarding CEL, the *FIP1L1-PDGFRA* fusion gene mutation was not detected. Because this case had the evidence of vasculitis, hypereosinophilic syndrome was excluded.

INVESTIGATION

The patient was diagnosed with EGPA.[1] Because the cardiac involvement of EGPA was suspected by the initial examination, cardiac catheterization was performed on day 4. No significant coronary artery stenosis was observed by coronary angiography. Right heart catheterization revealed elevated pulmonary artery wedge pressure (mean pressure of 23 mm Hg) with low cardiac output volume (cardiac index: 1.38 L/min/m^2). Subsequently, an endomyocardial biopsy (EMB) from the right ventricular septal wall was performed to confirm the diagnosis for cardiac involvement of EGPA.

HISTOPATHOLOGY OF EMB SPECIMEN. Pathological examination of EMB specimens revealed aggregation of inflammatory cells around subendocardial myocytes as well as intramyocardial small vessels. Giemsa

staining and immunohistochemistry for major basic protein of eosinophils indicated aggregation of eosinophils at the subendocardium. Transmission electron microscopy revealed accumulation of eosinophils with notable degranulation around cardiomyocytes. These findings strongly suggest the presence of subendocardial inflammation by aggregated eosinophils (**Figure 2**).

MANAGEMENT

A bedside TTE was performed on the day of cardiac catheterization to rule out delayed EMB complication. Unexpectedly, a large iso- to high-echoic apical LV mass (19 × 15 mm) was detected. According to the serial TTE findings, the LV mass had been developed within 4 days after the hospitalization (**Figures 1A and 1B**, Video 1 and 2). Simultaneously, D-dimer level was increased (7.5 μg/mL on day 4). Thus, we considered the LV mass as a thrombus. Notably, moderate hypokinesis was detected at the apical LV but there was no apical aneurysmal formation.

Surgical thrombectomy was considered. However, left ventriculotomy carried substantial risk of bleeding. In addition, the initiation of immunosuppressive therapy for EGPA carries the risk of delayed wound healing and wound infection. Thrombus resection in a retrograde manner via the aortic valve or the mitral valve with left atriotomy was an alternative approach. However, the procedure is associated with a risk of systemic embolization because complete thrombus resection may not be attained. Therefore, conventional anticoagulation therapy by intravenous unfractionated heparin and subsequent oral warfarin was selected. Congestive heart failure was controlled by the administration of diuretics (furosemide and tolvaptan), enalapril (1.25 mg/d), spironolactone (12.5 mg/d), and bisoprolol (initiated from 0.3125 mg/d and increased thereafter). For EGPA, immunosuppressive therapy with high-dose corticosteroids (3 days of 1,000 mg of methylprednisolone followed by 1 mg/kg of prednisolone per day) was initiated.

Laboratory inflammation biomarkers including C-reactive protein, white blood cell count, and eosinophil count, as well as cardiac biomarkers, all rapidly decreased after the initiation of immunosuppressant treatment. The size of apical thrombus gradually became smaller. By TTE observation on day 11, it had completely disappeared without any embolic symptoms (**Figure 1C**, Video 3). Brain magnetic resonance imaging and whole-body contrast-enhanced computed tomography revealed multiple cerebral and splenic embolisms (Figure S2). Fortunately, no apparent symptoms caused by systemic embolization were observed. Cardiac magnetic resonance on day 11 showed no apparent apical LV thrombus, but patchy distribution of high-intensity lesion of late gadolinium enhancement, including LV apex area, was observed, suggesting endomyocardial damage due to EGPA (**Figures 1D to 1F**).

DISCUSSION

EGPA is a systemic vasculitis characterized by various organ dysfunctions.[1] Cardiac involvements are rare but life-threatening complications in cases of EGPA, which are caused by infiltrated eosinophils in myocardium, leading to cardiac systolic dysfunction, heart failure, and ventricular thrombus formation.[2] In general, most LV thrombus is observed in patients with significant myocardial dysfunction with low LV ejection fraction and/or ventricular aneurysm. However, in the present EGPA case, a large LV thrombus was formed despite mildly reduced LV systolic function (LV ejection fraction: 42.5%) and absence of LV aneurysmal formation. Virchow's triad describes the 3 main factors related to intravascular thrombus formation: 1) disturbance of blood flow; 2) endothelial injury; and 3) blood hypercoagulability. Healthy endothelium releases anticoagulant agents that prevent platelet aggregation and fibrin formation.[3] Endothelial injury can lead to local thrombus formation by bringing blood into contact with highly prothrombotic subendothelial extracellular matrix.[4] To the best of our belief, subendocardial histopathologic findings in a patient with EGPA with ventricular thrombus formation has rarely been reported. In the present case, as shown in the EMB histopathology, subendocardial inflammation caused by infiltrated eosinophils may cause endothelial injury, resulting in luminal thrombus formation even when LV systolic function is only moderately impaired. Similarly to the present case, a previous report documented large LV thrombus formation without LV dysfunction accompanied by EGPA.[5] In the report, subendocardial damage was confirmed by cardiac magnetic resonance at the adjacent site of LV thrombus. The subendocardial damage caused by infiltrated eosinophils is a pivotal characteristic of eosinophilic myocarditis. Indeed, previous clinical case series of eosinophilic myocarditis reported the incidence of intracardiac thrombus as 12.3%.[6] Therefore, prophylactic anticoagulation therapy should be considered in case of

eosinophilic myocarditis, especially with the evidence of endomyocardial injury detected by cardiac magnetic resonance.

FOLLOW-UP

After controlling the state of EGPA by immunosuppression (glucocorticoid therapy alone), the patient was transferred to a rehabilitation hospital. Anticoagulation therapy was continued thereafter.

CONCLUSIONS

Intracardiac blood stasis due to ventricular systolic dysfunction as well as endothelial damage caused by subendocardial eosinophilic inflammation might be strong contributors to frequent ventricular thrombus formation in EGPA. Prophylactic anticoagulation therapy might be considered at the time of diagnosis of EGPA with cardiac involvement, even in cases without apparent ventricular thrombus.

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KEY WORDS cardiac magnetic resonance, endomyocardial biopsy, eosinophilic granulomatous with polyangiitis, ventricular thrombus

APPENDIX For supplemental table, figures, and videos, please see the online version of this paper.