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Eosinophilic Granulomatosis with Polyangiitis (EGPA) with an Unusual Manifestation of Mid-Ventricular Obstruction Caused by Endocardial Thrombus

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 46
Final Diagnosis: Eosinophilic granulomatosis with polyangiitis
Symptoms: Chest pain
Medication: —
Clinical Procedure: Skin biopsy
Specialty: Cardiology

Objective: Rare co-existance of disease or pathology

Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic vasculitis of unknown cause accompanied by prominent eosinophilia. Intracardiac thrombosis is one of the major cardiac complications in EGPA that may cause thromboembolism.

Case Report: A 46-year-old male presenting with intermittent chest pain and numbness of the lower extremities was admitted to our center. His case was complicated by multiple brain infarcts and endocardial thrombosis in the left ventricle. A condition of restrictive cardiomyopathy was also found. After a thorough workup, he was diagnosed with antineutrophil cytoplasmic antibody (ANCA) positive EGPA. Interestingly, the thrombus was accompanied by a pressure gradient producing mid-ventricular obstruction. The patient improved reasonably with immunosuppression and anticoagulation treatment, in addition to heart failure treatment, and had a concomitant regression of the thrombus and reduction of the pressure gradient.

Conclusions: For an EGPA patient complicated by intraventricular obstruction caused by endocardial thrombosis, which could accelerate the release of the thrombus into the systemic circulation resulting in a life-threating condition, timely and aggressive measures against cardioembolic complications should be considered.

MeSH Keywords: Cardiomyopathy, Restrictive • Churg-Strauss Syndrome • Echocardiography • Embolism and Thrombosis

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Background

Eosinophilic granulomatosis with polyangiitis (EGPA), which was formerly called Churg-Strauss syndrome, is a rare systemic vasculitis of unknown cause accompanied by prominent eosinophilia. Cardiovascular involvement, such as restrictive cardiomyopathy and pericarditis, is the major cause of mortality in EGPA [1–4]. Intracardiac thrombosis is a rare complication of this syndrome which can lead to a fatal condition due to thromboembolism. Here, we described a case of a 46-year-old male with EGPA complicated by multiple brain infarcts and endocardial thrombosis. This case also illustrated an unusual finding of an intraventricular obstructive condition caused by the thrombus.

Case Report

The patient, a 46-year-old male with a 12-year-history of asthma and sinusitis, presented with intermittent chest pain and numbness of the extremities lasting for about 3 months. An electrocardiography performed at a local hospital showed extensive T-wave inversions. An echocardiography revealed an immobile left ventricle mass over the endocardial surface suggestive of a thrombus. There was also a small lesion attached to the aortic valve indicative of vegetation. Peripheral blood tests found a marked elevation of eosinophil count (67.6%, 12 844/μL). Markers of myocardial cell damage such as troponin I at 3.356 ng/mL (normal range, <0.04 ng/mL) and creatine kinase-muscle/brain (CK-MB) at 9.61 ng/mL (normal range, 1.9–5.9 mg/mL) were elevated. The patient was admitted to the hospital with a possible diagnosis of EGPA, and he was started on unfractioned heparin intravenously. On the day of admission, he had a high fever of 38.5°C. Hemoculture for suspected infective endocarditis was negative. Five days later, he developed behavioral abnormalities; magnetic resonance imaging (MRI) demonstrated multiple brain infarcts (Figure 1). After intravenous methylprednisolone was administered for EGPA-related cardiac involvement, he was transferred to our institution for further diagnosis and treatment.

Upon admission to our center, his temperature was 35.9°C, pulse was 96 beats/min, and blood pressure was 104/62 mmHg. Neurological findings were unremarkable except that he was drowsy, and when asked, described numbness of the extremities. Cardiac examination revealed a grade III/VI systolic murmur along the left sternal border. No peripheral edema was noted. There was purpura, partly papular, lesions on both feet. His peripheral eosinophil count was already within the normal range (4.9%, 287/μL). The patient had elevated levels of B-type natriuretic peptide (BNP) of 707.5 pg/mL, C-reactive protein of 6.02 mg/dL, and D-dimer of 2.4 μg/mL (normal range, <1.0 μg/mL). Autoimmune and rheumatologic analyses

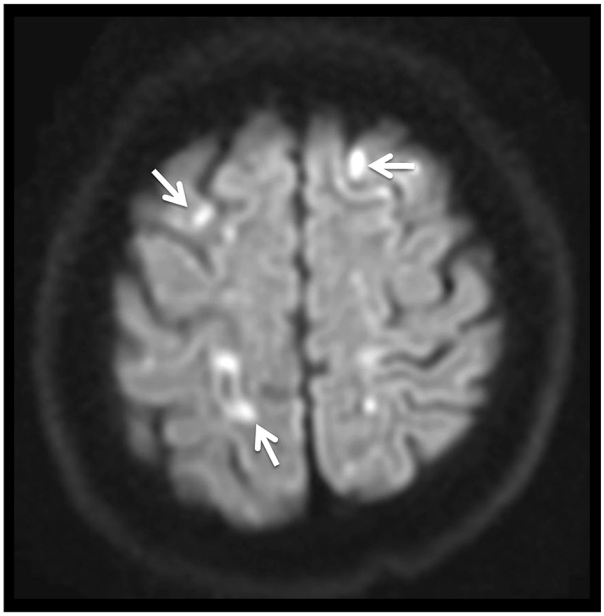

Figure 1. Diffusion-weighted imaging on brain magnetic resonance imaging showing multiple infarctions (arrows).

showed increases in rheumatoid factor (104 U/mL normal range, <15 U/mL) and myeloperoxidase (MPO)-ANCA of 11.5 U/mL (normal range, <1.0 U/mL). A chest x-ray showed a low level of pulmonary infiltrate without pleural effusion.

On echocardiography, left ventricular ejection fraction was reduced (42%) and there was a large left ventricle thrombus over the endocardial surface (Figure 2A). The thrombus had a stenotic lesion with a substantial degree of pressure gradient (56 mmHg) (Figure 2B). The aortic valve was bicuspid, having a small, round-shaped mass (10×8 mm) on the tip of the valve leaflet (Figure 2D). A mild degree of aortic regurgitation was found. The transmitral flow profile showed a restrictive pattern (Table 1). Cine-mode MRI of the heart revealed a jet signal the thrombus (Figure 3A). T_2-star imaging identified a low-intensity area over the endocardial boarder indicative of the presence of blood components (Figure 3B). Endocardial fibrosis was not observed. On consultation with a neurologist, the multiple brain infarcts were due to cardioembolism rather than to EGPA-related vasculitis. Histological findings from a skin biopsy of the foot bottom revealed eosinophilic infiltrates surrounding small vessels with fibrinoid degeneration (Figure 4). The patient had 4 of the 6 conditions listed in the criteria for EGPA, proposed by the 1990 American College of Rheumatology [5]: 1) preceding history of asthma and sinusitis, 2) peripheral eosinophilia, 3) polyneuropathy, and 4) eosinophilic vasculitis.

With the diagnosis of EGPA, the patient was given anticoagulant (unfractioned heparin followed by warfarin), corticosteroid, and immunosuppression (azathioprine and cyclophosphamide)

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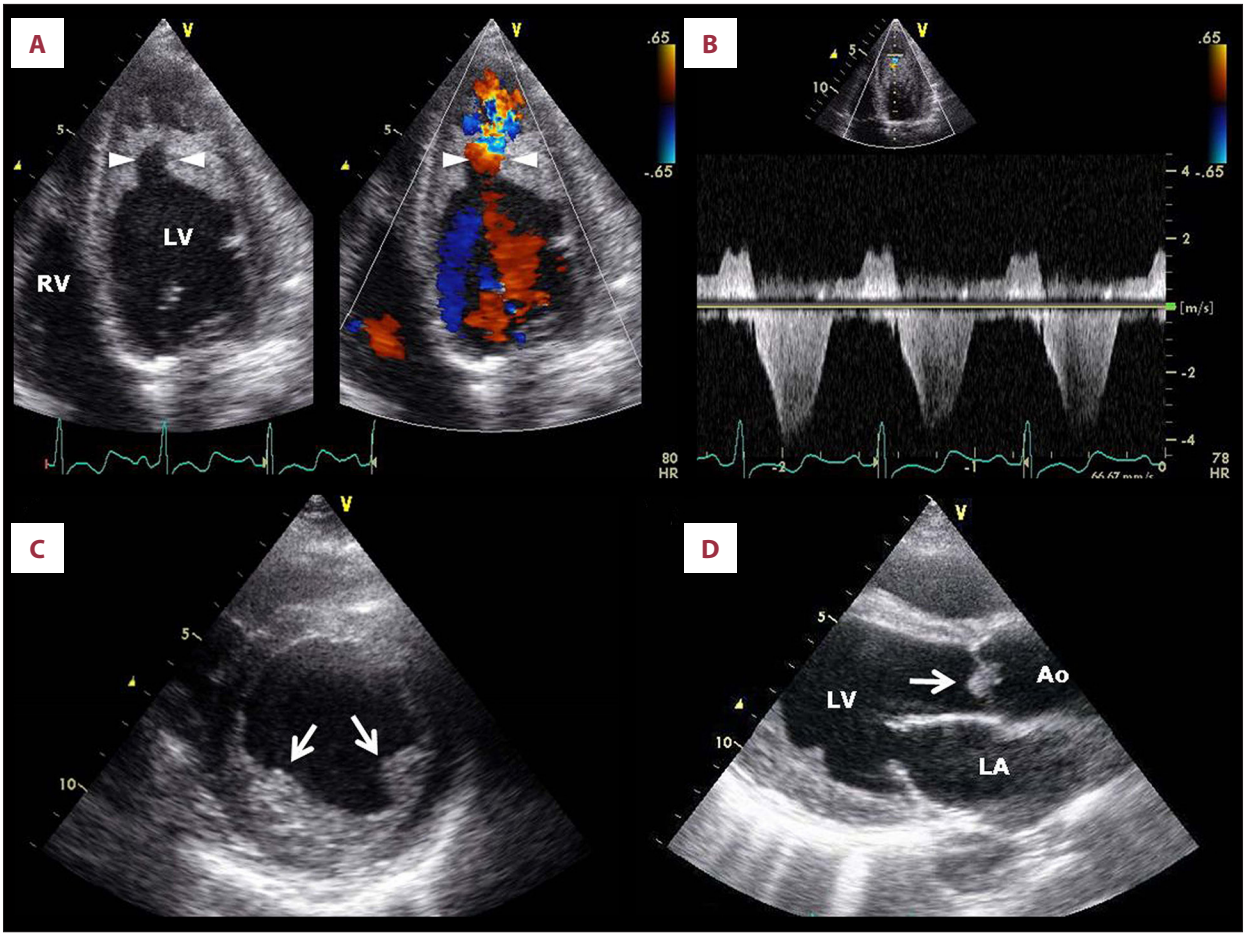

Figure 2. Echocardiography on admission to our institution. (**A**) Apical 4-chamber views illustrating a stenotic lesion within the thrombus (arrow heads) (left) with an acceleration flow detected on color Doppler mapping (right). (**B**) Continuous-wave Doppler profile showing the pressure gradient at the stenotic lesion during systole, the value measured as 56 mmHg. (**C**) Parasternal short-axis view at the papillary muscle level showing the intraventricular thrombus (arrows). (**D**) Parasternal long-axis view depicting a small lesion attached to the aortic valve (arrow). Ao, ascending aorta; LV, left ventricle; RV, right ventricle

treatment, in addition to conventional treatment for heart failure. Within the next 2 months, his condition was reasonably stabilized and almost all laboratory findings, including MPO-ANCA (<1.0 U/mL), became normal (Table 1). On the repeated echocardiogram, left ventircular systolic and diastolic function were recovered with a concomitant regression of both the thrombus and mid-ventricular pressure gradient (Table 1, Figure 5). The round-shaped lesion on the aortic valve also disappeared. Six months after the first finding of eosinophilia, while still on the medications aforementioned, he was free from sequelae without recurrence of eosinophilia. Coronary angiography and endocardial biopsy were not performed.

Discussion

EGPA is a rare systemic vasculitis of unknown cause accompanied by prominent eosinophilia. Multiple organs are involved including the lung, kidney, heart, and gastrointestinal tract. Cardiac involvement in EGPA is a major cause of morbidity and mortality occurring in 15% to 65% of cases [1–4]. The most frequent cardiac involvement is restrictive cardiomyopathy and pericarditis, each occurring in 30% and 15% of cases, respectively. Valvular lesions are also detected in up to 30% of cases [3]. Intracardiac thrombosis is one of the serious cardiac complications in EGPA, with a limited number of cases that fulfill the diagnostic criteria of EGPA [6–10]. The pathogenesis of cardiac thrombosis in EGPA is unclear but the thrombogenic potential of eosinophils has been considered to play a crucial role [11,12]. The location of the thrombus formation varies, either in the left ventricle or the right ventricle, or both [7–14], and in most cases, echocardiography and MRI have been used as diagnostic modalities for detecting a thrombus.

MPO-ANCA is not frequently detected in EGPA patients with cardiac involvement, which is reportedly detected in one-third

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Table 1. Follow-up data on blood tests and echocardiography after the patient was admitted to our hospital.

	2 days	7 days	14 days	21 days	42 days	56 days	*195 days
Variables on blood tests							
WBC, cells/μL	5860	7450	7540	7860	8730	9460	5580
Absolute neutrophil count, cells/μL	4618	4999	5120	5754	6687	6489	3811
Absolute eosinophil count, cells/μL	287	45	75	231	44	76	22
Hemoglobin, g/dL	11.9	9.8	12.4	11.1	13.7	14.0	14.7
C-reactive protein, mg/mL	6.02	6.00	0.26	0.08	0.02	0.02	0.03
MPO-ANCA, U/mL	11.5	–	1.8	–	<1.0	–	<1.0
BNP, pg/mL	707.5	692.3	166.1	183.0	28.2	24.9	44.5
Variables on echocardiography							
Left atrial diameter, mm	41	38	36	39	34	31	32
LV diastolic dimension, mm	58	57	53	55	53	54	47
LV ejection fraction, %	42	55	55	56	55	67	59
E/A	1.37	2.03	1.43	2.02	1.08	1.35	0.87
Deceleration time, ms	125	126	179	188	213	211	185
E' (septal), cm/s	6.8	6.1	7.2	8.6	10.5	9.8	8.9
E/E'	13.7	11.0	11.3	9.4	4.6	5.2	4.0
Intraventricular PG, mmHg	56	51	46	26	25	4	2

* 120 days after the patient was discharged. BNP – B-type natriuretic peptide; E' – early diastolic annular velocity recorded by tissue Doppler imaging; LV – left ventricular; MPO-ANCA – myeloperoxidase-antineutrophil cytoplasmic antibody; PG – pressure gradient; WBC – white blood cell.

of EGPA patients [2]. Our patient had elevation of MPO-ANCA, suggesting his cardiac involvement was attributed not only to eosinophilic infiltrates but also to necrotizing small vessel vasculitis. In fact, the patient seemed to suffer from the most severe form of cardiac damage in EGPA, involving both myocardium and endocardium, the former being confirmed by the elevated blood markers for myocardial injury and the latter by the presence of endocardial thrombosis with a pathology of restrictive cardiomyopathy. In addition, he fulfilled 2 components of the 5 factors score (cardiomyopathy and central nervous system involvement) [15]. A possible explanation for the favorable clinical course in our patient is that aside from the aggressive introduction of corticosteroid and immunosuppression treatment, his EGPA status might have been diagnosed relatively earlier with the absence of endocardial fibrosis (still in necrotic and/or thrombotic stage) [16].

In EGPA, neurological manifestation is common, usually consisting of peripheral neuropathy due to small-vessel vasculitis, whereas cerebral manifestation is less frequent, especially when due to brain embolism [17]. The source of brain embolism includes the left ventricle and even the ascending aorta [18]. However, according to one series of cases, none of the EGPA patients had any known cause in the heart that could account for cerebral/cerebellar infarcts [17,19]. Psychogios et al. reported a case of EGPA in which multiple cerebral infarcts, along with purpuric skin rash, was the first manifestation of EGPA, although in the case of a 63-year-old female, no apparent findings suggestive of cardioembolism were detected on echocardiography [20]. Psychogios et al. speculated that a mechanism of stroke might involve hypercoagulability on the endocardium resulting from subendocarditis [20]. Even though cerebral infarcts occurring in an EGPA patient seem to result from cardioembolism, small vessel vasculitis or hypereosinophilia cannot be ruled out.

In reports of EGPA patients with cardiac manifestations, a thrombus large enough to obliterate a ventricular cavity has been reported [7-14], although no description provided about the presence of a high pressure gradient within the ventricle. In our case of EGPA, complicated by multiple cerebral infarcts,

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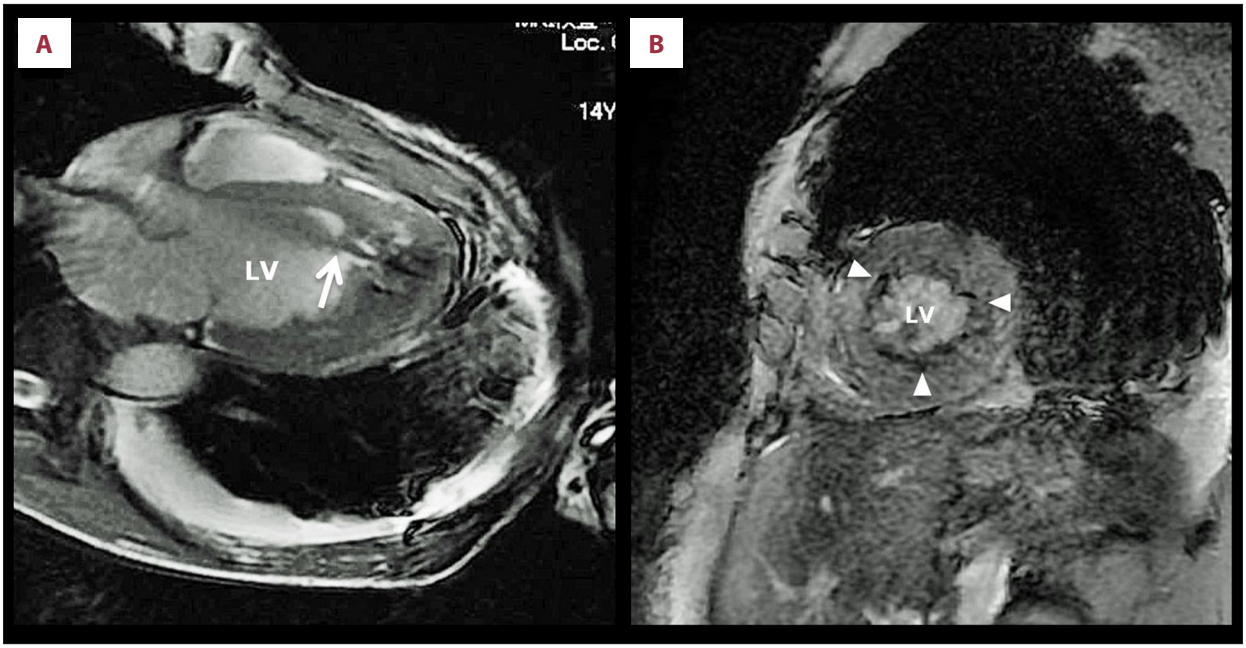

Figure 3. Cardiac magnetic resonance imaging. (**A**) Cine-mode imaging illustrating a jet signal across the intraventricular thrombus (arrow). (**B**) T_2-star imaging showing a low-intensity area along the endocardial boarder of the left ventricle (LV) (arrow heads).

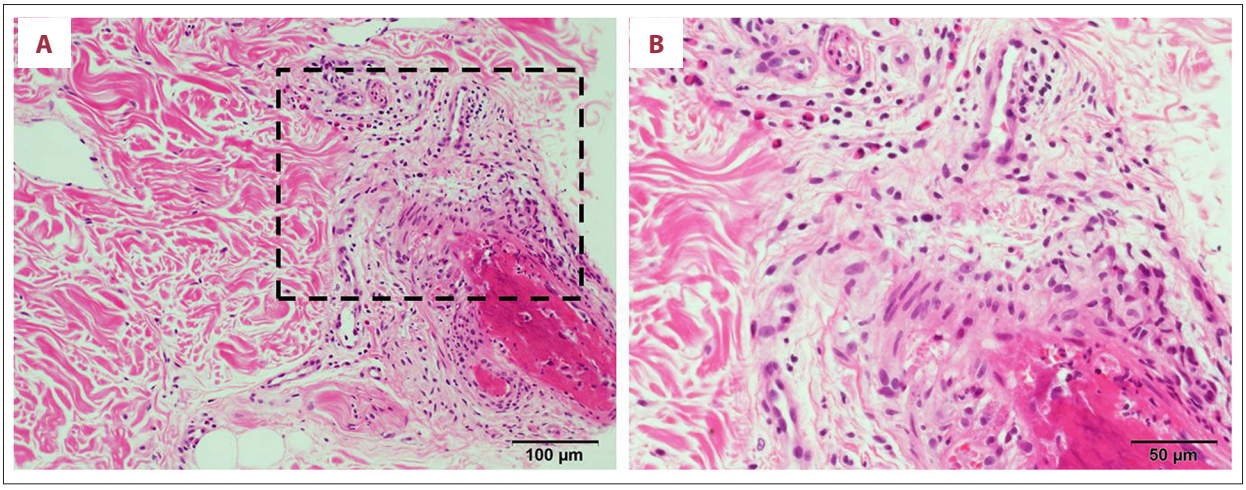

Figure 4. Hematoxylin and eosin staining of the foot skin biopsy, which shows infiltrates of eosinophils, to a lesser extent, neutrophils surrounding capillaries, and also adipose tissue infiltrates as well as fibrinoid degeneration (**A**: 200×, **B**: 400×, magnification of the rectangle indicated by the dotted line in **A**).

both the echocardiography and the MRI revealed an intraventricular thrombus (Figures 2, 3). The echocardiography, in particular, exhibited changes in pressure gradient within the thrombus after the treatment (Table 1, Figure 5). A finding of thrombus-induced ventricular obstruction occurring in an EGPA patient may be clinically important because it could accelerate the release of the thrombus into the systemic circulation resulting in a life-threating condition.

Hypertrophic cardiomyopathy in conjunction with eosinophilia may be an important consideration as a cause of intraventricular obstruction. There have been 2 case reports showing an association of hypertrophic obstructive cardiomyopathy and eosinophilia. Miller et al. described a case of hypereosinophilic syndrome in which clinical and echocardiographic parameters became normalized after corticosteroid and anticoagulant treatment [21]. They speculated that this improvement resulted from reduction of the inflammatory process and thrombus resolution, although it was unclear whether the thrombus was

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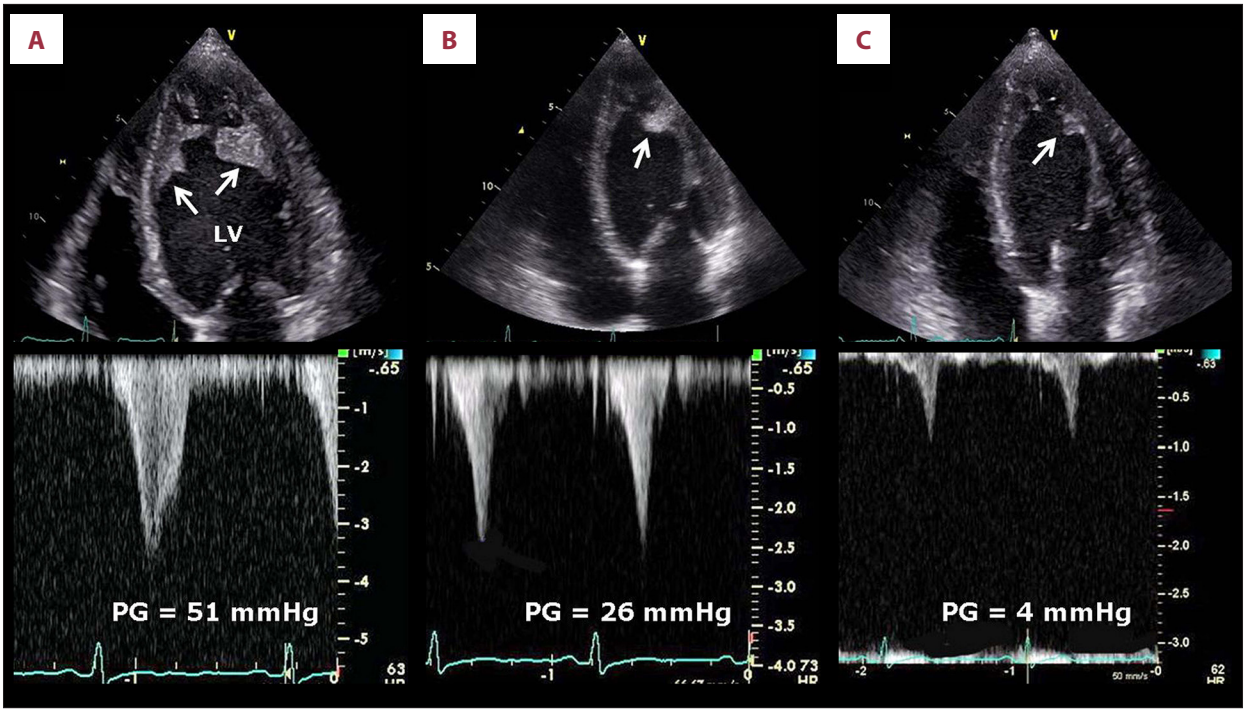

Figure 5. Follow-up of intraventricular thrombus (top) and pressure gradient (PG) (bottom). Note the gradual regression of the thrombus and the PG in the left ventricle (LV) (**A**: 7th hospital day, **B**: 21st hospital day, **C**: 56th hospital day).

responsible for the ventricular obstruction. Nakaoka et al. reported a case of a hypereosinophilic syndrome with marked endocardial thickening and systolic obliteration of the left ventricle [22]. Given that they did not find eosinophilic infiltrates on endocardial biopsy, eosinophilia in their patient might have not been a relevant finding to the hypertrophied ventricle.

Conclusions

We reported a case of EGPA presenting with an unusual finding of mid-ventricular obstruction caused by endocardial thrombosis that might have led to multiple brain infarcts. When seeing a (suspected) EGPA patient, clinicians should check for intracardiac thrombosis, and if present, introduce timely and aggressive measures against cardioembolic complications.

Conflict of interest

None.

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