Letter to the Editor

Acute cerebral infarction caused by cardiac subvalvular thrombus shedding in eosinophilic myocarditis: a case description

Xiao-Hang Liu[1#], Tian-Chen Guo[1#], Yi-Ning Wang[2], Li Huo[3], Wei Chen[1]

[1]Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [2]Department of Radiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [3]Department of Nuclear Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

[#]These authors contributed equally to this work.

Correspondence to: Wei Chen, MD. Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 1 Shuaifu Yuan, Dongcheng District, Beijing 100730, China. Email: chenweipumch@126.com.

Submitted Feb 12, 2023. Accepted for publication Aug 10, 2023. Published online Aug 17, 2023.
doi: 10.21037/qims-23-175
View this article at: https://dx.doi.org/10.21037/qims-23-175

Introduction

Eosinophilic myocarditis (EM) is a rare disease whereby myocardial injury is mediated by eosinophilic infiltration. It can also cause multifocal involvement through thrombotic complications (1). Approximately 10% of patients with EM have cardiac thrombosis in the left ventricle, mostly at the apex; subvalvular thrombus is rare (2). Herein, we describe a case of acute cerebral infarction caused by mitral valve thrombus shedding in a patient with eosinophilic granulomatosis with polyangiitis (EGPA)-related EM, a rare condition that could be easily misdiagnosed.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the research committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 47-year-old woman presented with sudden-onset amyasthenia of the left lower extremity and disordered consciousness. *Table 1* shows her diagnosis and treatment process. Clinical examination revealed left foot drop. She then underwent some imaging examinations of her head (*Figure 1*). Cranial magnetic resonance imaging (MRI) revealed multifocal patchy acute and subacute cerebral infarction in bilateral parietal lobes, temporal lobes, occipital lobes, and cerebella (*Figure 1A-1J*). However, cranial magnetic resonance angiography performed 2 days later was normal (*Figure 1K,1L*). Carotid artery, vertebral artery, and subclavian artery ultrasound examinations were normal. Therefore, the cause of cerebral infarction in this middle-aged woman without traditional risk factors of atherosclerosis was further explored.

Laboratory tests showed significantly elevated eosinophil count (EC; 13.95×10^9/L). Her past medical history included asthma and allergic rhinitis. Considering the eosinophilia, asthma, left peroneal nerve paralysis, and potential wandering pulmonary shadow (Figure S1), EGPA was considered according to the 1990 American College of Rheumatology (ACR) and 2022 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria (3,4). Bone marrow examination was performed to exclude other causes of eosinophilia, showing negative *FIP1L1-PDGFRA* mutation.

Meanwhile, her cardiac troponin I (cTnI; 48.99 μg/L) and N-terminal pro-B-type natriuretic peptide (NT-proBNP; 7,833 pg/mL) also significantly increased. Transthoracic echocardiography (TTE) revealed left

Table 1 Timeline

Timeline	Events
2 years before presentation	Cough, dyspnea repeatedly, diagnosed with "allergic rhinitis" and "asthma"
1 day before presentation	Amyasthenia of the left lower extremity
At presentation	Consciousness disorder
1 day after presentation	Echocardiography and cardiac MRI showed cardiac thrombosis. Cranial MRI showed multifocal patchy acute and subacute cerebral infarction in bilateral parietal lobes, temporal lobes, occipital lobes, and cerebella. Started on anticoagulant therapy
2 days after presentation	Cranial magnetic resonance angiography performed 2 days later was normal. Cerebral vascular wall enhanced MRI was normal. Started on steroid pulse therapy
5 days after presentation	Cyclophosphamide (0.6 g once a week) with tapering prednisolone
1 month after presentation	Repeat echocardiography and cardiac MRI showed improvement of cardiac function and disappearance of cardiac thrombosis

MRI, magnetic resonance imaging.

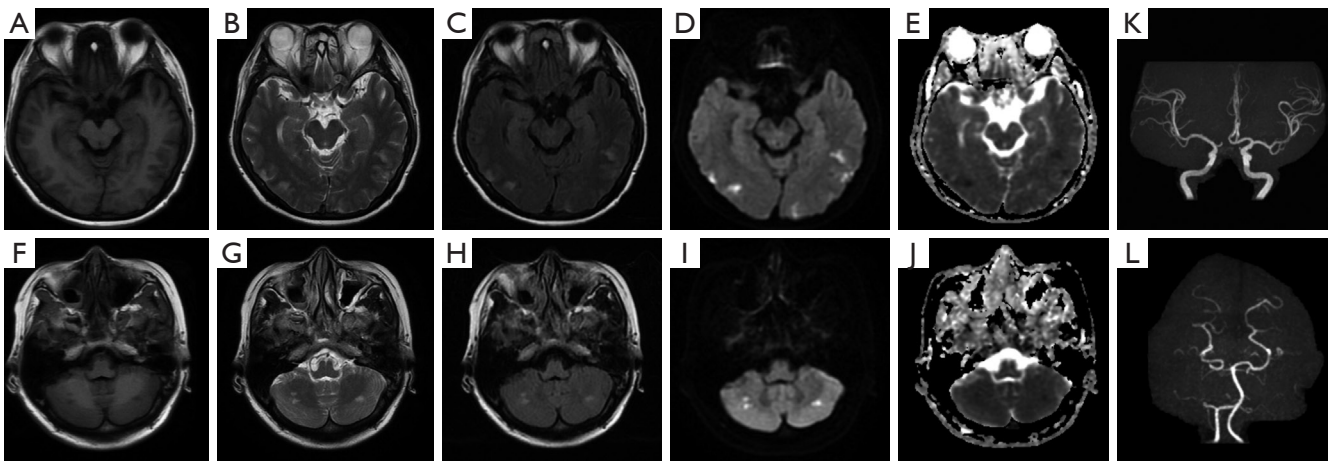


Figure 1 Cranial imaging of the patient's cerebral infarction. (A-J) MRI shows multiple patchy shadows with long T1, long T2, high signal intensity on DWI and decreased ADC value; (K,L) MRA is normal. MRI, magnetic resonance imaging; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; MRA, magnetic resonance angiography.

ventricular hypertrophy, systolic dysfunction, and an isoechoic mass with a size of 1.4 cm × 1.2 cm on the ventricular surface of the posterior lobe of mitral valve (*Figure 2A*,*2B*, *Video 1*). Cardiac MRI showed diffuse endocardium and subendocardial late gadolinium enhancement in the left ventricle, and multiple low signals around the papillary muscle (*Figure 2C*,*2D*, *Video 2*). ^{68}Ga-tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate (DOTATATE) positron emission tomography (PET) (5) demonstrated diffuse macrophage infiltration [maximum standardized uptake value (SUVmax), 1.9], and ^{68}Ga-fibroblast activation protein inhibitor (FAPI) PET (6) showed significant fibroblast activation (SUVmax, 5.2) in the left ventricle (*Figure 2E*,*2F*). Coronary computed tomography angiography helped to exclude coronary heart disease. Endomyocardial biopsy was canceled considering the risk of cardiac thrombosis. Although without pathological evidence, considering her medical history and all cardiac imaging findings, EM and cardiac thrombosis caused by EGPA was clinically diagnosed. The sequential cardiac thrombus shedding led to acute cerebral infarction. In order to further rule out that the cerebral infarction had been caused by EGPA blood vessel involvement, cerebral vascular wall enhanced MRI was performed; it showed

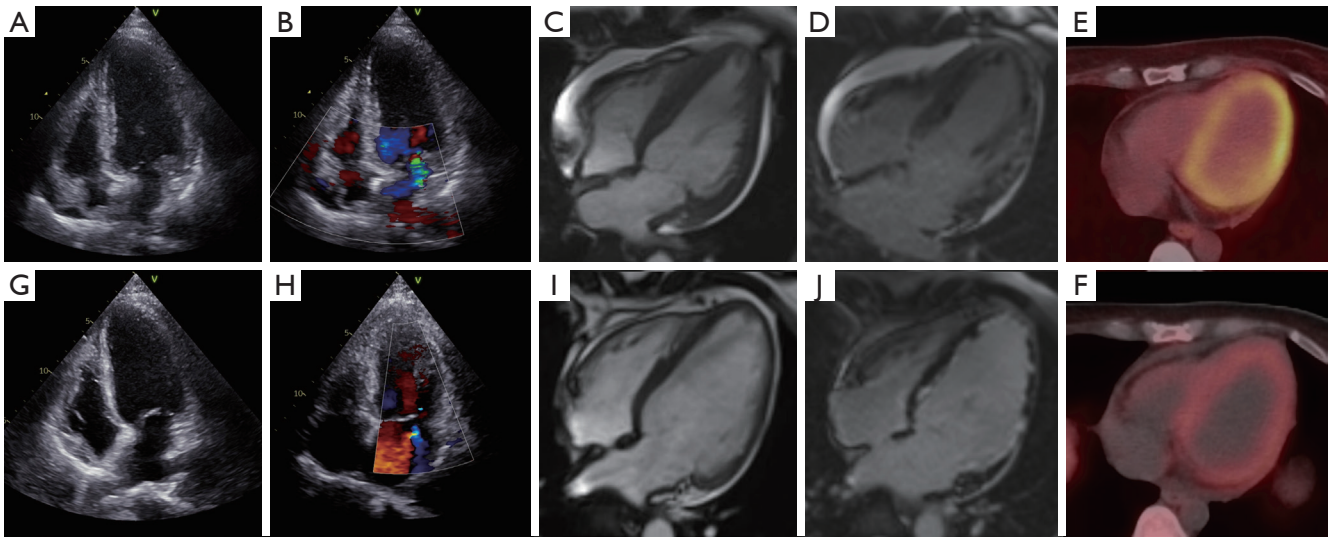
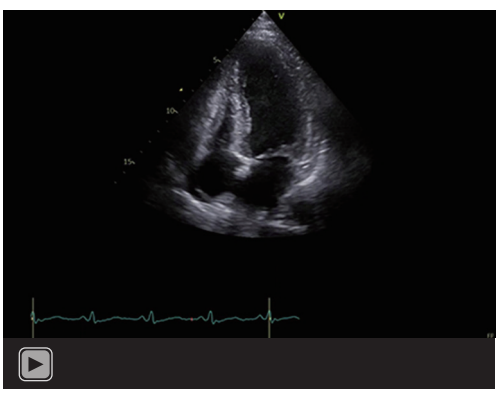
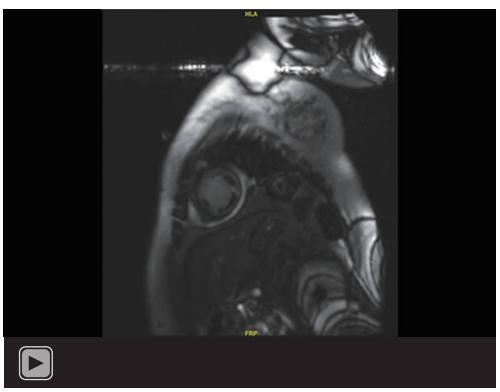


Figure 2 Serial multi-modality imaging of the patient's thrombus, cardiac structure, and function. (A,B) Echocardiography shows the thrombus on the ventricular surface of the posterior lobe of mitral valve, and mitral regurgitation; (C,D) cardiac MRI shows low signal intensity in left ventricle, interventricular septum and the ventricular side of posterior mitral valve leaflet. It also shows diffuse endocardium and subendocardial late gadolinium enhancement in the left ventricle; (E) ^{68}Ga-DOTATATE PET shows diffuse macrophage infiltration, SUVmax 1.9; (F) FAPI PET shows significant fibroblast activation in the left ventricle, SUVmax 5.2; (G,H) reexamination of echocardiography shows the disappearance of cardiac thrombus and the improvement of mitral regurgitation; (I,J) cardiac MRI shows the disappearance of cardiac thrombus and the improvement of late gadolinium enhancement. MRI, magnetic resonance imaging; ^{68}Ga-DOTATATE PET, ^{68}Ga-tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate positron emission tomography; SUVmax, maximum standard uptake value; FAPI PET, ^{68}Ga-fibroblast activation protein inhibitor positron emission tomography.



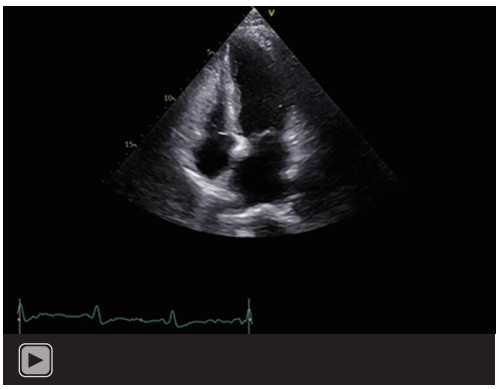
Video 1 Echocardiography revealed left ventricular hypertrophy, systolic dysfunction, and an isoechoic mass on the ventricular surface of the posterior lobe of mitral valve.



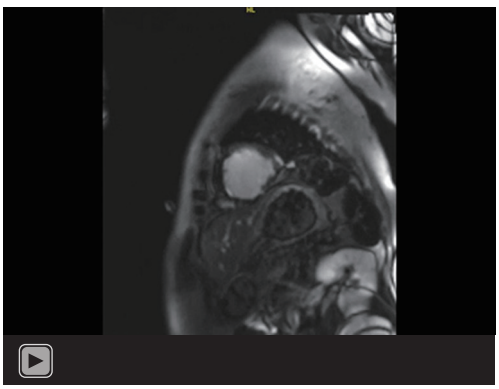
Video 2 Cardiac magnetic resonance imaging showed diffuse endocardium and subendocardial late gadolinium enhancement in the left ventricle.

neither thickening of the vessel wall, nor other evidence of vasculitis.

Methylprednisolone 1,000 mg for 3 days and anti-coagulant treatment of low molecular heparin 6,000 U every 12 hours were initiated. Her symptoms relieved, EC and cTnI gradually decreased. She was discharged after 20 days, with prednisone 60 mg and cyclophosphamide. A month later, TTE and cardiac magnetic resonance were



Video 3 Reexamination of echocardiography showed the disappearance of cardiac thrombus, and left ventricular ejection fraction improvement.



Video 4 Reexamination of cardiac magnetic resonance imaging showed the improvement of late gadolinium enhancement.

reexamined, showing the disappearance of cardiac thrombus, the improvement of late gadolinium enhancement, and left ventricular ejection fraction (LVEF) improvement from 41% to 58% (*Figure 2G-2J*, *Videos 3*,*4*).

Discussion

We have described a rare case of acute cerebral infarction caused by mitral valve thrombus shedding in a patient with EM related to EGPA. EM is a rare form of infiltrative cardiomyopathy. Until 2017, less than 300 patients had been reported worldwide, among whom, 13.6% had cardiac thrombosis in the left or right ventricle (2). It is worth mentioning that except for two reports of valve thrombus instead of mural thrombi, nearly all the thrombi were at the apex of heart (7,8). To our knowledge, it is the first report of cerebral embolism caused by subvalvular thrombus shedding in EM. Also, we provided serial multi-modality cardiac and neurological imaging before and after treatment.

The disease of EM has been detected for over 50 years. However, before 2017, neither large case series nor clinical trials on this specific myocarditis had been reported. Until 2017, 179 histologically proven and 65 non-histologically proven EM had been reported. EGPA accounted for 12.8% of the underlying diseases associated with EM (2), other etiologies include hypersensitivity reactions, other immune-mediated disorders, undefined complex hypereosinophilic syndrome (HES), infections, and cancer. The diagnosis of EGPA is based on the 1990 classification criteria for EGPA by the ACR (3), or 2022 ACR/EULAR classification criteria of EGPA (4). The classical course of EGPA develops in three phases: years of asthma and allergic rhinitis, eosinophilic infiltration of target organs, and manifestations of necrotizing vasculitis. Presently, three steps are recognized in the development of EM, that are likely to coexist: direct damage of eosinophils and related substance release, endogenous coagulation activation, and autoimmune system activation (9). The role and mechanism of eosinophils in arterial thrombosis still remains unclear. Marx *et al.* demonstrated that eosinophils interact with platelets, leading to eosinophil activation. These direct interactions induce the formation of eosinophil extracellular traps decorated with the granule protein major basic protein, which are present in human thrombi and cause platelet activation by eosinophils (10). The typical site of cardiac thrombosis in EM is the apex, and apical obliteration is one of the best-known involvements among heart lesions induced by hypereosinophilia (11). Valve thrombosis has been rarely reported (7,8), with none of the previously documented cases having been related to thrombus shedding and cerebral embolism.

Eosinophils have been shown to play an important role in thrombosis. The administration of mepolizumab, as a monoclonal antibody against interleukin-5 (IL-5), has been shown to result in a significant reduction in peripheral blood and tissue eosinophils. Although our patient unfortunately could not gain access to this drug, its therapeutic effect has been mentioned in some previous case reports (12-14). For example, Sakurai *et al.* (14) reported a 50-year-old woman diagnosed as EGPA with cardiac involvement. She accepted glucocorticoid and cyclophosphamide therapy, but she reported emerging symptoms of systemic involvement or exhibited an increased EC several times in the process of glucocorticoid reduction. After using mepolizumab, her

symptoms gradually improved and the glucocorticoid was gradually reduced to 10 mg once daily.

In recent years, there has been some remarkable progress in the research of eosinophil and eosinophil-related diseases. The concept that eosinophils are terminally differentiated cells has been altered. Different subgroups of eosinophils have been detected under steady-state and pathological conditions, respectively (15). The normal lung contains resident eosinophils; a study reported that inflammatory eosinophils were recruited during dust mite-induced airway allergy, which increased T helper 2 (Th2) cell responses to inhaled allergens (16). Morgan *et al.* reported that in eosinophilic esophagitis, peripheral pathogenic effector Th2 (peTh2) clonotypes can upregulate the esophagus-homing receptor G protein-coupled receptor 15 (GPR15) to enhance the esophagus homing potential (17). However, limited progress has been achieved in EM, possibly due to the low incidence. In our perspective, the characteristics of the certain subgroup of eosinophils targeting the heart and the detailed contribution of eosinophils in thrombosis are worth investigating in the future.

Conclusions

Cerebral infarction is a common condition in clinical practice, but is associated with various underlying diseases. Mitral valve thrombus shedding in EM could be a rare cause of cerebral infarction, showing a rare manifestation of a rare disease.

Acknowledgments

We are grateful to Dr. Yu-Bo Guo and Dr. Na Niu (Department of Radiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College) for providing the high-quality cardiovascular images.

Funding: This work was supported by the Capital's Funds for Health Improvement and Research, CFH (No. 2020-2-40110), the CAMS Innovation Fund for Medical Sciences (No. CIFMS, 2020-I2M-C&T-B-006), and the National High-Level Hospital Clinical Research Funding (Nos. 2022-PUMCH-C-069 and 2022-PUMCH-B-025 to Chen W).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-175/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the research committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Cheung CC, Constantine M, Ahmadi A, Shiau C, Chen LYC. Eosinophilic Myocarditis. Am J Med Sci 2017;354:486-92.
2. Brambatti M, Matassini MV, Adler ED, Klingel K, Camici PG, Ammirati E. Eosinophilic Myocarditis: Characteristics, Treatment, and Outcomes. J Am Coll Cardiol 2017;70:2363-75.
3. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-100.
4. Grayson PC, Ponte C, Suppiah R, Robson JC, Craven A, Judge A, Khalid S, Hutchings A, Luqmani RA, Watts RA, Merkel PA; DCVAS Study Group. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis with Polyangiitis. Ann Rheum Dis

2022;81:309-14.
5. Tarkin JM, Calcagno C, Dweck MR, Evans NR, Chowdhury MM, Gopalan D, Newby DE, Fayad ZA, Bennett MR, Rudd JHF. 68Ga-DOTATATE PET Identifies Residual Myocardial Inflammation and Bone Marrow Activation After Myocardial Infarction. J Am Coll Cardiol 2019;73:2489-91.
6. Varasteh Z, Mohanta S, Robu S, Braeuer M, Li Y, Omidvari N, Topping G, Sun T, Nekolla SG, Richter A, Weber C, Habenicht A, Haberkorn UA, Weber WA. Molecular Imaging of Fibroblast Activity After Myocardial Infarction Using a 68Ga-Labeled Fibroblast Activation Protein Inhibitor, FAPI-04. J Nucl Med 2019;60:1743-9.
7. Tanino M, Kitamura K, Ohta G, Yamamoto Y, Sugioka G. Hypereosinophilic syndrome with extensive myocardial involvement and mitral valve thrombus instead of mural thrombi. Acta Pathol Jpn 1983;33:1233-42.
8. Karthikeyan K, Balla S, Alpert MA. Non-infectious aortic and mitral valve vegetations in a patient with eosinophilic granulomatosis with polyangiitis. BMJ Case Rep 2019;12:e225947.
9. Zhong Z, Yang Z, Peng Y, Wang L, Yuan X. Diagnosis and treatment of eosinophilic myocarditis. J Transl Autoimmun 2021;4:100118.
10. Marx C, Novotny J, Salbeck D, Zellner KR, Nicolai L, Pekayvaz K, et al. Eosinophil-platelet interactions promote atherosclerosis and stabilize thrombosis with eosinophil extracellular traps. Blood 2019;134:1859-72.
11. Eicher JC, Bonnotte B, L'huillier I, Cottin Y, Potard D, Abou Taam J, Muller G, Guy H, Tent JP, Wolf JE. Cardiovascular manifestations of eosinophilia: clinical and echocardiographic presentation. Rev Med Interne 2009;30:1011-9.
12. Asatani S, Kobayashi H, Nagasawa Y, Nishihara M, Tanikawa Y, Hamaguchi M, Yoshizawa S, Tsuzuki H, Sugiyama K, Tsukamoto M, Kitamura N, Nakamura H. Successful treatment for eosinophilic granulomatosis with polyangiitis causing severe myocarditis followed by cardiac magnetic resonance. Mod Rheumatol Case Rep 2022;6:248-53.
13. Buchanan CE, Kakkar E, Dreskin SC, Allen LA, Groves DW, Altman NL. Allergy and the Heart: Eosinophilic Myocarditis With Biventricular Thrombi. JACC Case Rep 2020;2:1942-6.
14. Sakurai Y, Oshikata C, Katayama T, Takagi S, Kaneko Y, Yo K, Kaneko T, Kubota H, Matsubara T, Tsurikisawa N. A case of eosinophilic polyangiitis with granulomatosis that evolved to cardiac arrest due to advanced atrioventricular block. Nagoya J Med Sci 2023;85:171-8.
15. Kanda A, Yun Y, Bui DV, Nguyen LM, Kobayashi Y, Suzuki K, Mitani A, Sawada S, Hamada S, Asako M, Iwai H. The multiple functions and subpopulations of eosinophils in tissues under steady-state and pathological conditions. Allergol Int 2021;70:9-18.
16. Mesnil C, Raulier S, Paulissen G, Xiao X, Birrell MA, Pirottin D, Janss T, Starkl P, Ramery E, Henket M, Schleich FN, Radermecker M, Thielemans K, Gillet L, Thiry M, Belvisi MG, Louis R, Desmet C, Marichal T, Bureau F. Lung-resident eosinophils represent a distinct regulatory eosinophil subset. J Clin Invest 2016;126:3279-95.
17. Morgan DM, Ruiter B, Smith NP, Tu AA, Monian B, Stone BE, Virk-Hundal N, Yuan Q, Shreffler WG, Love JC. Clonally expanded, GPR15-expressing pathogenic effector T(H)2 cells are associated with eosinophilic esophagitis. Sci Immunol 2021;6:eabi5586.

Cite this article as: Liu XH, Guo TC, Wang YN, Huo L, Chen W. Acute cerebral infarction caused by cardiac subvalvular thrombus shedding in eosinophilic myocarditis: a case description. Quant Imaging Med Surg 2023;13(10):7356-7361. doi: 10.21037/qims-23-175

