Embolic Stroke in a Patient with Marantic Endocarditis: A Case Report

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Abstract

Non-bacterial thrombotic endocarditis (NBTE) is an unusual valvular heart disease which may occur in patients with underlying malignancies or systemic autoimmune diseases. "Marantic endocarditis" is named specifically for the cardiac vegetation pertaining to malignancies. It can cause embolus propagation to distal organs, occluding blood vessels that nourish these organs. Symptoms can vary based on the affected ischemic sites; for instance, focal neurological deficits as a consequence of cerebral vessel occlusion.

Herein, we described a 64-year-old woman with an advanced stage of adenocarcinoma of the lung presenting with two episodes of left hemiparesis within a week. Brain MRI showed restricted diffusion in multiple vascular territories of the brain, along with severe stenosis of the M2 segment of the right middle cerebral artery. Transesophageal echocardiography revealed vegetations on the mitral and tricuspid leaflets. A series of blood cultures showed no organism. Thrombophilic test indicated a dramatic increase in D-dimer level. She was diagnosed with embolic stroke related to marantic endocarditis and treated with parenteral anticoagulants. She was discharged from the hospital with modified Rankin Scale of 4. The prognosis of NBTE with distal embolism depends on the malignancy stage and the severity of the embolic strokes.

Keywords: Non-bacterial thrombotic endocarditis, marantic endocarditis, embolic stroke, lung adenocarcinoma (J Thai Stroke Soc. 2024;23(2): 30-38)

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รายงานผู้ป่วยโรคหลอดเลือดสมองอุดตันจากลิ่มเลือดในผู้ป่วยเยื่อบุหัวใจอักเสบมารันติก

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บทคัดย่อ

Non-bacterial thrombotic endocarditis คือความผิดปกติของเยื่อบุลิ้นหัวใจที่พบได้ในผู้ป่วยโรคมะเร็งหรือโรคภูมิคุ้มกันต้านตนเอง โดยคำว่า “marantic endocarditis” ใช้เรียกความผิดปกติที่สัมพันธ์กับโรคมะเร็ง ที่มีการสะสมของ vegetation บริเวณลิ้นหัวใจและเกิดการหลุดลอยไปอุดตันหลอดเลือดที่อวัยวะต่างๆ ของร่างกาย อาการแสดงมีลักษณะหลากหลายขึ้นกับอวัยวะที่ได้รับผลกระทบ เช่น ความผิดปกติของระบบประสาทเฉพาะที่เกิดจากการขาดเลือดของสมอง เป็นต้น

ในรายงานผู้ป่วยนี้ ผู้นิพนธ์นำเสนอผู้ป่วยหญิงอายุ 64 ปี ได้รับการวินิจฉัยเป็นมะเร็งปอดระยะลุกลามมาแสดงด้วยอาการอ่อนแรงร่างกายซีกซ้ายสองครั้งภายใน 1 สัปดาห์ การตรวจคลื่นแม่เหล็กไฟฟ้าพบสมองขาดเลือดหลายตำแหน่งที่เลี้ยงโดยหลอดเลือดที่ต่างกัน และยังพบการตีบของหลอดเลือดแดง middle cerebral artery ด้านขวา การบันทึกภาพหัวใจด้วยคลื่นเสียงความถี่สูงทางหลอดอาหารพบ vegetation บริเวณลิ้นหัวใจไมทรัลและลิ้นหัวใจไตรคัสปิด ผลการเพาะเชื้อในเลือดไม่พบเชื้อ การตรวจ D-dimer ในเลือด มีค่าสูงผิดปกติ ผู้ป่วยได้รับการวินิจฉัยเป็นโรคหลอดเลือดสมองอุดตันจากลิ่มเลือดที่พบในภาวะลิ้นหัวใจอักเสบมารันติก ได้รับการรักษาโดยยากลุ่มเฮพารินที่มีน้ำหนักโมเลกุลต่ำ ผู้ป่วยจำหน่ายจากโรงพยาบาลโดยมี modified Rankin Scale เท่ากับ 4 พยากรณ์ของโรคขึ้นอยู่กับระยะของมะเร็งและความรุนแรงของโรคหลอดเลือดสมองอุดตัน

คำสำคัญ: โรคหลอดเลือดสมองตีบ, เยื่อบุหัวใจอักเสบมารันติก, โรคหลอดเลือดสมองขาดเลือดจากการอุดตัน, มะเร็งปอด (J Thai Stroke Soc. 2024;23(2): 30-38)

Introduction

Non-bacterial thrombotic endocarditis (NBTE) is characterized by the sterile deposition of fibrin and platelet thrombi on the cardiac valves. This condition is associated with a hypercoagulable state from various causes, such as underlying malignancy (marantic endocarditis) and autoimmune disease (Libman-Sacks endocarditis). Patients with NBTE are typically asymptomatic, but some develop symptoms due to embolic thrombi or clots affecting the distal organs. The common sites of embolic occlusion are the brain, spleen, and kidney[1, 2].

Case Description

A 64-year-old female with an advanced stage of adenocarcinoma of the lung with bone metastases presented to the emergency department with an acute onset of left hemiparesis 2 hours ago. She had no feature that suggests systemic autoimmune diseases and denied a prior history of cardiac intervention or a family history of autoimmune diseases. On examination, she had unilateral weakness in her left arm and leg (motor power grade 4), mild dysarthria, and a flattened left nasolabial fold. She had no aphasia or neglect of her left side. Her initial NIHSS score was 4. No cardiac murmur or irregular heart rate was noted. Contrast-enhanced brain computed tomography (CT) scan was performed to exclude brain metastasis. A wedge-shaped hypodense lesion in the right parietal lobe consistent with an acute cerebral infarction without occlusion of major cerebral arteries was found (Figure 1). She was a candidate for receiving intravenous thrombolysis despite the presence of malignancy[3]. However, she and her daughter denied to proceed because they were expecting the best supportive care and would not accept the risk of thrombolysis, specifically intracerebral hemorrhage. Eventually, she was admitted to a medical ward and received dual antiplatelet therapy and intravenous fluid therapy. Two days later, her motor power on the left side was improved and she could speak clearly. Her NIHSS score became 0. There was no atrial fibrillation detected on 48-hour cardiac monitoring. She was referred to a cardiologist for transthoracic echocardiography (TTE), which first showed no structural abnormalities. She was dismissed from hospital with modified Rankin Scale of 0 at 72 hours.

A week later, she developed a sudden onset of left-sided weakness worse than her discharge status. She was brought to the hospital within 90 minutes after experiencing symptoms. Upon examination, her left arm and left leg were totally paralyzed. She also exhibited left facial weakness (upper motor neuron type), moderate dysarthria, gaze preference to the right, and complete loss of sensation on the left side. Her NIHSS score was 16. A non-contrast brain CT revealed a subacute infarction in the right temporoparietal area without hemorrhagic transformation (Figure 2). In addition, contrast-enhanced CT angiography of the brain showed severe stenosis at the proximal part of M2 segment of the right middle cerebral artery (Figure 3). At the moment, she was not a candidate for intravenous thrombolysis due to the recent cerebral infarction, which evolved into a subacute stage. Moreover, mechanical thrombectomy was not indicated because of advanced cancer[4], and could cause reperfusion injury to the brain parenchyma distal to the occluded artery.

TTE was repeated and found suspicious small vegetations on the mitral and tricuspid valves without intracardiac thrombus. She was proceeded to transesophageal echocardiography (TEE), visualizing masses adhering to the mitral and tricuspid valves (Figure 4). A series of

hemocultures was collected to exclude infective endocarditis (IE), which subsequently showing a negative result. She had her blood tested for a hypercoagulable state. D-dimer level was 24793 ng/mL (reference normal range <198 ng/mL), and anti-phospholipid antibodies were negative. A magnetic resonance (MR) imaging of the brain revealed multiple territories of restricted diffusion, predominantly in the right temporoparietal area, with some scattered cortico-subcortical lesions in the left occipital and left frontoparietal areas, reflecting an acute cerebral infarction. There was also a T2 hyperintense lesion in the right cerebellar hemisphere, indicative of an old cerebral infarction (Figure 5, 6). Brain MR angiography confirmed the occlusion of the proximal M2 segment of the right MCA. She was finally diagnosed with acute ischemic stroke secondary to the marantic endocarditis. As reported in many case series[1, 2, 5, 6] the standard dose of low molecular weight heparin was administered to prevent further clot propagation, along with a rehabilitation program for motor recovery.

She was released from the hospital after a 10-day period of hospital stay, with the modified Rankin Scale of 4. She had still left hemiparesis of grade 1. Upon the last follow-up visit, she was doing well although she largely depended on her family members to do most of daily activities.

Discussion

NBTE is a rare cardiac condition, commonly associated with malignancies, especially adenocarcinoma of various primary sites (e.g., lung, pancreas, colon, ovary[2]). NBTE is also associated with systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), or antiphospholipid syndrome[1, 2, 7]. This condition generally affects patients aged from fourth through eighth decades of life[1]. Males and females are equally impacted[1].

The exact pathogenesis remains elusive. Autopsies reveal that the cardiac valve vegetation is composed of agglutinated blood cells, platelets, and fibrin, in the absence of infective pathogen or inflammatory reaction[1]. The initial process is believed to include the accumulation of inflammatory cytokines, complements, circulating immune complexes, and related substances, leading to the damage to the endothelial layer of cardiac valves, which serve as the site for thrombus formation[1, 2, 8]. Some data indicates that pre-existing valvular damage, including rheumatic heart disease, is a predisposing factor for developing NBTE[1]. This process is aggravated by a hypercoagulable state in cancers, autoimmune diseases, and hypoxemia, the latter can explain why NBTE developed in patients with COVID-19 infection[2, 9, 10, 11]. The mitral and aortic valves are primarily affected, although other valves can be involved[1].

Several clinical clues have been found to suggest the possibility of NBTE, including but not limited to types and stages of underlying cancer pathologies, hypercoagulability, and the coexistence of systemic autoimmune diseases[1, 2, 7, 12]. Mucinous adenocarcinomas (e.g. lung, pancreas, breast) were more associated with marantic endocarditis compared to other pathology types (64.6% vs. 35.4%, p<0.001), accounting for around 65% of paraneoplastic forms of NBTE[1, 12]. Unsurprisingly, advanced stages of cancers and presence of distant metastasis showed a higher correlation with NBTE in comparison with early stages of cancer (p<0.001)[1, 12]. Interaction between tumor cells and macrophages leads to the release of circulation cytokines (e.g. interleukin-1, tumor necrosis factor) promotes endothelial damage with subsequent thrombus formation and platelet deposition[13], increasing the susceptibility to NBTE[2].

Coexisting autoimmune diseases, such as SLE and antiphospholipid syndrome, pose a risk for developing NBTE[1, 2, 7]. Besides, antiphospholipid antibodies (specifically anticardiolipin antibody) have been detected in patients with various types of malignancies, both solid organ and hematologic malignancies, rising the thromboembolic events in those with higher titers[14]. Nevertheless, antiphospholipid antibodies were not found in our patient, and elevated D-dimer level only reflected the degree of thrombotic burden.

Marantic endocarditis is the term used for the malignancy-related endocarditis, while Libman-Sacks endocarditis stands for the autoimmune disease-related endocarditis, which is a common cardiac manifestation of SLE. There are no pathognomonic symptoms or signs. Cardiac murmurs are rarely noted[1]. Clinical presentations are results of organ dysfunction attributable to the occlusion of vascular supply. Brain, spleen, and kidneys are commonly affected[1, 2]. Infrequently, some patients with advanced disease may also experience cardiac complications, including acute heart failure or syncope[2]. Patients may remain asymptomatic, particularly in the early stage of the disease.

The diagnosis can be very challenging for clinicians in the early stages of the disease until thrombi are embolized to distant organs[2, 15, 16]. In the brain, emboli typically travel into multiple territories of the major intracranial vessels, as in our case demonstrating the involvement of the right MCA territory, the left occipital cortex and the left frontoparietal region. It is also likely to bring about a hemorrhagic transformation[17]. On the contrary, embolism in the IE is more commonly localized in single vascular territory of the brain[17].

TTE should be the first cardiac investigation to search for the presence of cardiac vegetation. However, in cases with small vegetations (below 5 mm), TEE is more reliable for detection (sensitivity 90% vs. 70% for TTE)[18]. Findings from either TTE or TEE cannot provide the information regarding etiology of the vegetation.

In some instances, various advance cardiac imaging may play the role in the diagnosis, such as cardiac CT, cardiac MR imaging, ^{18}FDG-PET/CT, and ^{99}Tc-labeled leukocyte single-photon emission computed tomography/CT (SPECT/CT) scan[19].

Previous IE studies supported the use of cardiac CT for detecting cardiac vegetation, with a good performance comparable to TEE, although TEE is still superior for identifying small vegetation (<10 mm)[20]. Additionally, cardiac MRI is a valuable tool in diagnosing IE and its complications, providing details of tissue characteristics to differentiate NBTE from other cardiac masses[21]. Cardiac metabolic imaging has been found to be efficacious in differentiating infective from other thrombotic endocarditis in a small cohort study of patients with cardiac vegetation, as the sterile vegetations in NBTE would not be labelled with inflammatory cells in cardiac SPECT/CT and should lack metabolic activity in ^{18}FDG-PET. Hence, these imaging modalities could be very useful in patients with clinical suspicion of NBTE, when TTE and TEE are not diagnostic[21]. Together with aforementioned imaging studies, serial tests of hemocultures to exclude IE and serological tests for autoimmunity and hypercoagulable states should be performed[2]. Definite diagnosis can be made through histological examination of heart valve tissues, which is now less commonly performed due to its invasive nature.

Appropriate treatments for NBTE are based on case series and a few retrospective studies. Most evidence supports the use of anticoagulants, either subcutaneous low molecular

weight heparin or intravenous unfractionated heparin, as the mainstay treatment[1, 2, 5, 6]. Efficacy of oral anticoagulants, including warfarin and direct oral anticoagulants, for prevention of systemic embolism in these cases is unclear[2, 22]. Data on valve replacement procedures for NBTE is also limited. Notably, the underlying disease preceding NBTE should be appropriately treated from the time of NBTE diagnosis. In those with marantic endocarditis, stages and pathological types of malignancies should be determined, as they would influence the proper treatment (e.g. radiation, targeted therapy) and also predict the prognosis. Clinicians should closely monitor cardiac function and echocardiography for changes in vegetation[2, 7, 23]. The prognosis of a marantic endocarditis patient is heterogeneous, depending on the stage of cancer and complications from systemic embolism.

In this case report, the author underlines the role of TEE after a negative TTE test in patients with embolic stroke with suggestive features of NBTE. Treatment with dual antiplatelet was changed to parenteral anticoagulants, as supported by current evidence. Unfortunately, cardiac CT and MRI are not included in our standard protocol for the diagnosis of endocarditis. ^{18}FDG-PET/CT and SPECT/CT are unavailable in our hospital.

Conclusion

Marantic endocarditis should be concerned when patients with malignancies present with acute ischemic stroke. This case report emphasizes the importance of TEE in those suspicious of NBTE. There is currently no guideline for the management of NBTE. Early diagnosis guides the proper treatment, and may reduce the complications of embolic strokes, leading to the best quality of life.

References

1. Lopez JA, Ross RS, Fishbein MC, Siegel RJ. Nonbacterial thrombotic endocarditis: A review. Am Heart J [Internet]. 1987;113(3):773–84. Available from: http://dx.doi.org/10.1016/0002-8703(87)90719-8
2. Al Chalaby S, Makhija RR, Sharma AN, Majid M, Aman E, Venugopal S, et al. Nonbacterial thrombotic endocarditis: Presentation, pathophysiology, diagnosis and management. Rev Cardiovasc Med [Internet]. 2022;23(4):137. Available from: http://dx.doi.org/10.31083/j.rcm2304137
3. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with Acute Ischemic Stroke: 2019 update to the 2018 guidelines for the early management of Acute Ischemic Stroke: A guideline for healthcare professionals from the American Heart Association/ American stroke association. Stroke [Internet]. 2019;50(12). Available from: http://dx.doi.org/10.1161/str.0000000000000211
4. Siegler JE, Nguyen TN. Thrombectomy in patients with active malignancy. Stroke Vasc Interv Neurol [Internet]. 2023;3(3). Available from: http://dx.doi.org/10.1161/svin.123.000835
5. Sack GH Jr, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. Medicine (Baltimore). 1977;56(1):1–37.
6. el-Shami K, Griffiths E, Streiff M. Nonbacterial thrombotic endocarditis in cancer patients: Pathogenesis, diagnosis, and treatment. Oncologist [Internet]. 2007;12(5):518–23. Available from: http://dx.doi.org/10.1634/theoncologist.12-5-518
7. Roldan CA, Sibbitt WL Jr, Qualls CR, Jung RE, Greene ER, Gasparovic CM, et al. Libman-sacks endocarditis and embolic cerebrovascular disease. JACC Cardiovasc Imaging [Internet]. 2013;6(9):973–83. Available from: http://dx.doi.org/10.1016/j.jcmg.2013.04.012
8. Eiken PW, Edwards WD, Tazelaar HD, McBane RD, Zehr KJ. Surgical pathology of nonbacterial thrombotic endocarditis in 30 patients, 1985–2000. Mayo Clin Proc [Internet]. 2001;76(12):1204–12. Available from: http://dx.doi.org/10.4065/76.12.1204
9. Gupta N, Zhao Y-Y, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res [Internet]. 2019;181:77–83. Available from: http://dx.doi.org/10.1016/j.thromres.2019.07.013
10. Balata D, Mellergård J, Ekqvist D, Baranowski J, Garcia IA, Volosyraki M, et al. Non-bacterial thrombotic endocarditis: A presentation of COVID-19. Eur J Case Rep Intern Med [Internet]. 2020;(LATEST ONLINE). Available from: http://dx.doi.org/10.12890/2020_001811
11. Chan KH, Joseph O, Ahmed E, Kommidi A, Suleiman A, Szabela ME, et al. Marantic endocarditis associated with COVID-19: A rare case report of a potentially deadly disease. Eur J Case Rep Intern Med [Internet]. 2021;(LATEST ONLINE). Available from: http://dx.doi.org/10.12890/2021_002409
12. Rahouma M, Khairallah S, Dabsha A, Elkharbotly IAMH, Baudo M, Ismail A, et al. Lung cancer as a leading cause among paraneoplastic non-bacterial thrombotic endocarditis: A meta-analysis of individual patients' data. Cancers (Basel) [Internet]. 2023;15(6):1848. Available from: http://dx.doi.org/10.3390/cancers15061848
13. Hurrel H, Roberts-Thomson R, Prendergast BD. Non-infective endocarditis. Heart. 2020; 106(13): 1023–9. Available from: http://dx.doi.org/10.1136/heartjnl-2019-315204

14. Pessach I, Kyriakou E, Kalampokas E, Kalampokas T, Bitsani A, Kotsianidis I. Antiphospholipid syndrome in cardiovascular disease and cancer. Eur J Haematol. 2023; 111(6): 834–843. Available from: http://dx.doi.org/10.1111/ejh.14096.
15. Rosen P, Armstrong D. Nonbacterial thrombotic endocarditis in patients with malignant neoplastic diseases. Am J Med [Internet]. 1973;54(1):23–9. Available from: http://dx.doi.org/10.1016/0002-9343(73)90079-x
16. González Quintela A, Candela MJ, Vidal C, Román J, Aramburo P. Non-bacterial thrombotic endocarditis in cancer patients. Acta Cardiol. 1991;46(1):1–9.
17. Dutta T, Karas MG, Segal AZ, Kizer JR. Yield of transesophageal echocardiography for nonbacterial thrombotic endocarditis and other cardiac sources of embolism in cancer patients with cerebral ischemia. Am J Cardiol [Internet]. 2006;97(6):894–8. Available from: http://dx.doi.org/10.1016/j.amjcard.2005.09.140
18. Durães Campos I, Marques AR, Sousa L, Fonseca S, Oliveira C, Vieira C, et al. Endocardite trombótica não bacteriana. Rev Port Cardiol [Internet]. 2019;38(7):511–4. Available from: http://dx.doi.org/10.1016/j.repc.2018.05.021
19. Tonutti A, Scarfò I, La Canna G, Selmi C, De Santis M. Diagnostic work-up in patients with nonbacterial thrombotic endocarditis. J Clin Med [Internet]. 2023;12(18):5819. Available from: http://dx.doi.org/10.3390/jcm12185819
20. Saeedan MB, Wang TKM, Cremer P, Wahadat AR, Budde RPJ, Unai S, et al. Role of cardiac CT in infective endocarditis: Current evidence, opportunities, and challenges. Radiol Cardiothorac Imaging [Internet]. 2021;3(1):e200378. Available from: http://dx.doi.org/10.1148/ryct.2021200378
21. Elagha A, Meshaal M, Elaroussy W, Beniamin Y. The use of Cardiac MRI in diagnosis of infective endocarditis: a comparative study with echocardiography. Eur Heart J [Internet]. 2020;41(Supplement_2). Available from: http://dx.doi.org/10.1093/ehjci/ehaa946.0222
22. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease. Chest [Internet]. 2012;141(2):e576S-e600S. Available from: http://dx.doi.org/10.1378/chest.11-2305
23. Rabinstein AA, Giovanelli C, Romano JG, Koch S, Forteza AM, Ricci M. Surgical treatment of nonbacterial thrombotic endocarditis presenting with stroke. J Neurol [Internet]. 2005;252(3):352–5. Available from: http://dx.doi.org/10.1007/s00415-005-0660-z

Figure 1. *Axial brain non-contrast CT in the first visit showed the hypodense lesion in right parietal lobe*

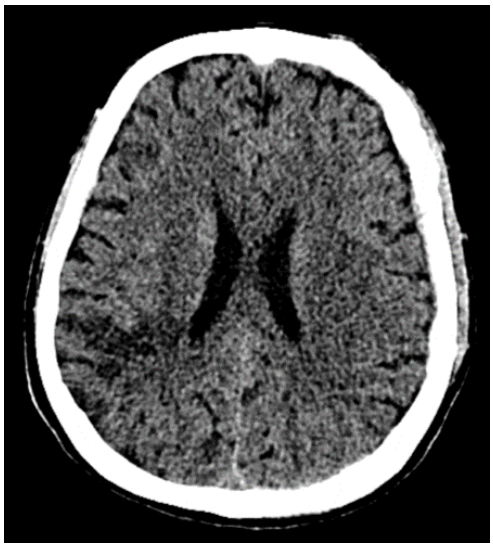

Figure 2. *Axial brain non-contrast CT in the subsequent visit showed the hypodense lesion in right temporoparietal area*

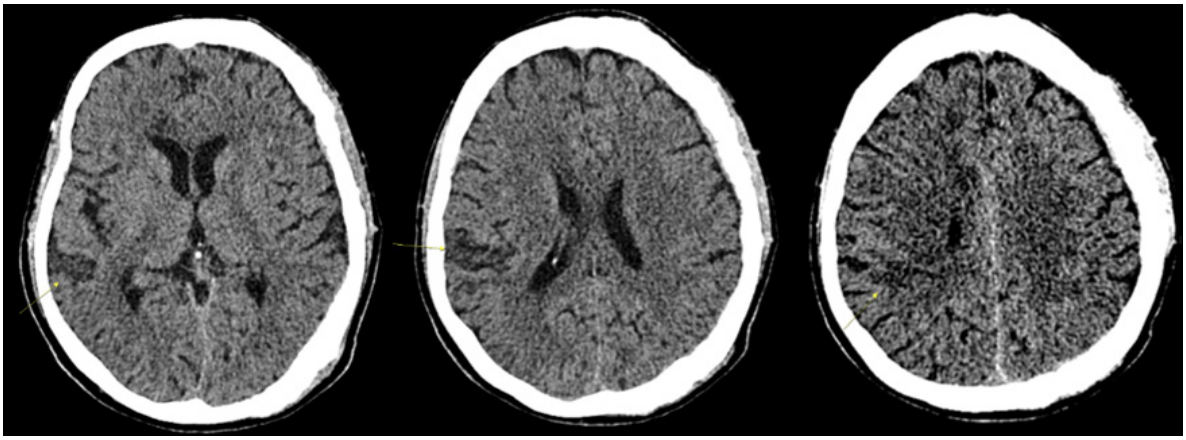

Figure 3. *Brain and neck reconstructed CT angiography in the second stroke attack image showed severe luminal narrowing of the M2 part of right middle cerebral artery*

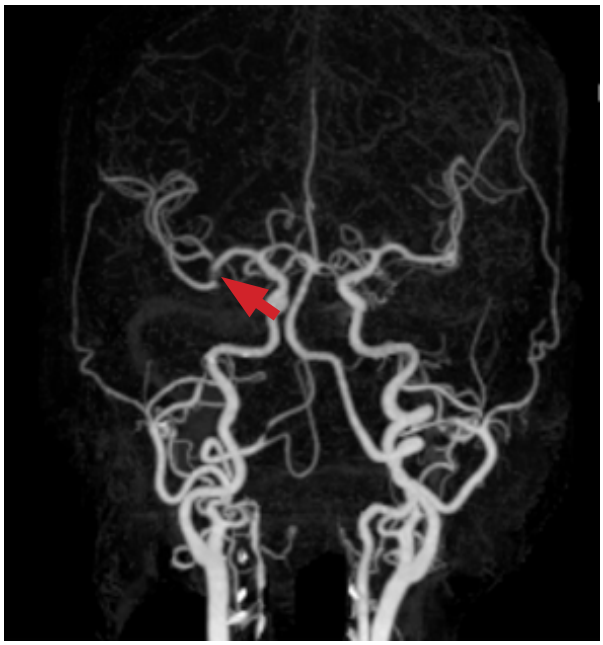

Figure 4. *Transesophageal echocardiogram showed a thickened mitral leaflet with a small vegetation attaching to both mitral leaflets. The maximal size was 6x4 mm (1 = anterior mitral leaflet) and 5x3 mm (2 = posterior mitral leaflet). The vegetation on the tricuspid leaflet measured 8x6 mm in size (3).*

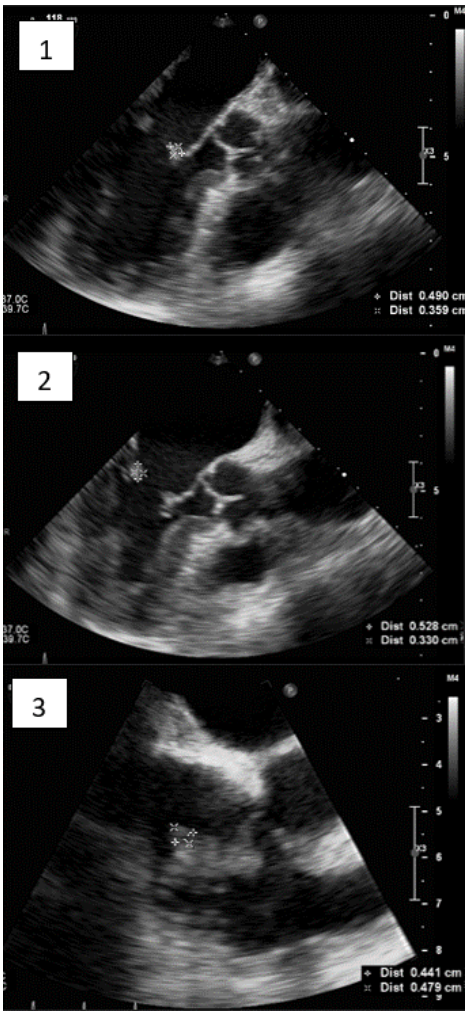

Figure 5. *Axial brain MRI in DWI and ADC sequences showed restricted diffusion in the right MCA territory and small restriction diffusion in cortex of the left occipital and left frontoparietal area*

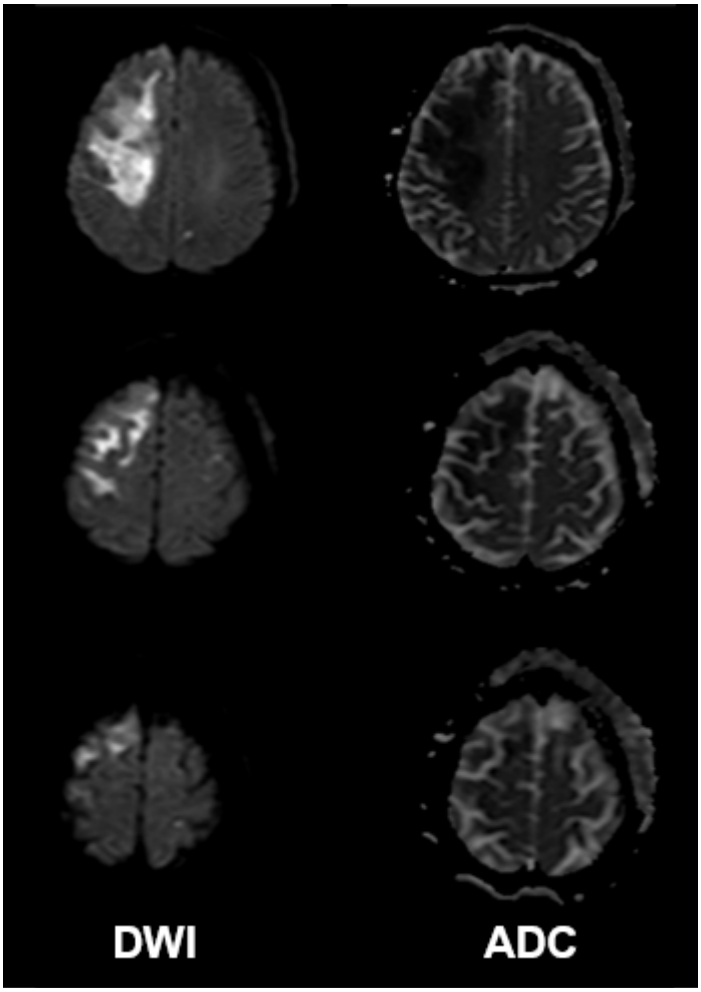

Figure 6. *Axial brain MRI in T2 FLAIR sequence showed multiple areas of T2 hyperintense in the right cerebellar hemisphere, right MCA territory and small cortical area of left occipitoparietal lobe*