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Non-Bacterial Thrombotic Endocarditis in the Setting of Stage IV EGFR-Positive Lung Cancer

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Abstract

A 58-year-old male initially presented to the hospital with deep vein thrombosis, pulmonary embolism and cerebral infarctions ultimately leading to diagnosis of metastatic epidermal growth factor receptor (EGFR) positive lung cancer, likely in the setting of marantic endocarditis. He was then treated under the FLAURA-2 trial and received chemotherapy (cisplatin and pemetrexed) plus Osimertinib. The patient did initially sustain clinical and radiographic response with treatment. However, he later developed recurrent cerebrovascular events, which temporally coincided with progression of the patient's lung cancer. This subsequently led to the diagnosis of non-bacterial thrombotic (NBTE) or marantic endocarditis pertaining to not only initial diagnosis of patient's EGFR mutated pulmonary malignancy, but also correlated with progression of disease.

Keywords: EGFR-positive Lung Cancer; Non-bacterial thrombotic endocarditis; Marantic endocarditis; Malignancy

Introduction

Non-bacterial thrombotic endocarditis (NBTE), though rare, can be an underdiagnosed complication of advanced malignancy due to the prothrombotic state in patients. This disorder involves the deposition of fibrin thrombi and sterile platelets on cardiac valves, often leading to increased embolic events in patients with chronic disease states such as cancer, systemic lupus erythematosus, and antiphospholipid antibody syndrome [1,2]. While this traditionally manifests clinically as recurrent ischemic cerebrovascular strokes, the diagnosis requires astute clinical suspicion, reliance on imaging, such as echocardiography, to identify potential thrombi, and adept disease management including, but not limited to, the use of anticoagulation, treatment of malignancy, and supportive care. We report the case of a patient with metastatic epidermal growth factor receptor (EGFR) mutation-positive lung cancer (L858R mutation in exon 21) who was diagnosed with marantic endocarditis after an embolic event and developed subsequent episodes of NBTE correlating with progression of his disease.

Case Presentation

A 58-year-old man with a medical history of skin cancer and hernia repair initially presented with right groin and lower extremity pain leading to a diagnosis of right lower extremity deep vein thrombosis and bilateral subsegmental pulmonary embolism involving the pulmonary artery branch vessels to the right upper, lower, and left lower lobes. Computed topography (CT) Angiogram revealed a 9 x 6 x 2.5cm left upper lobe lung mass with spiculated margins extending to the hilum with associated mediastinal lymphadenopathy as shown in (Figures 1 and 2). A biopsy of the left upper lobe mass showed poorly differentiated adenocarcinoma with immune-stains positive for TTF1 and negative for P40, indicative of lung origin. The patient was thereafter managed with Eliquis for his DVT.

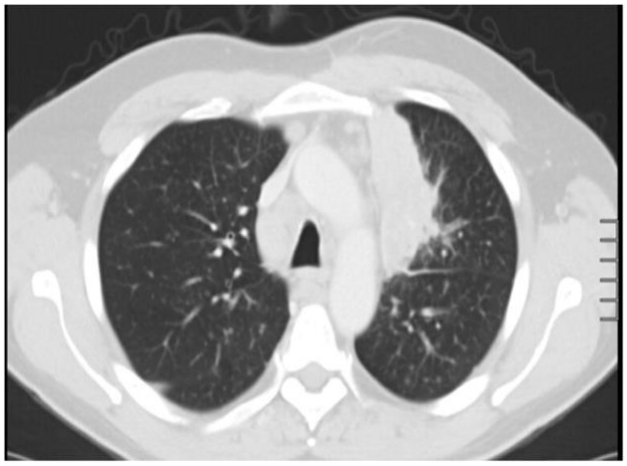

Figure 1: CT-TAP axial cross-section showing L hilar mass measuring 9.6 x 4.4cm at initial Diagnosis.

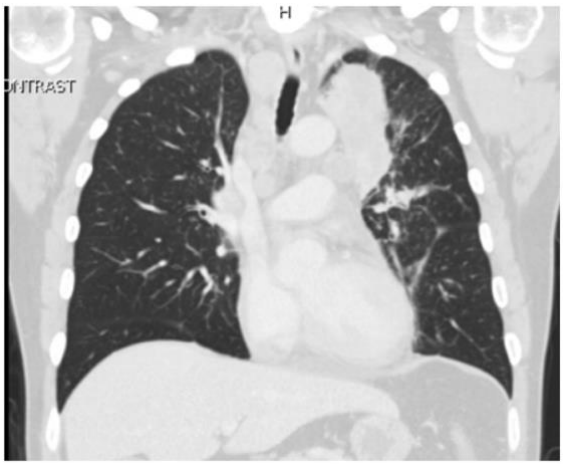

Figure 2: CT-TAP coronal cross-section showing L hilar mass measuring 9.6 x4.4cm at initial diagnosis.

Outpatient MRI demonstrated acute infarcts in bilateral cerebral hemispheres and cerebellum, as shown in (Figure 3), that were hypothesized to originate from a central embolic source. A transthoracic echocardiogram (TTE) with a bubble study revealed a patent foramen ovale. No vegetations were discovered at this time; however, suspicion for marantic endocarditis remained high in the setting of acute infarcts and a patent PFO. Due to the imaging findings, the patient was suggested to come to the emergency department where he attested intermittent dizziness and gait instability due to lack of sleep associated with a cancer diagnosis. However, he denied any focal weakness, alterations in mental status, paresthesia, chest pain, or difficulty breathing. Only left-sided facial droop was appreciated on physical exam (NIHSS score of 1), and the patient was transitioned to Lovenox. The patient's initial diagnosis of malignancy was in the setting of presumed marantic endocarditis.

Initial staging positron emission topography (PET) scans revealed localized areas of activity in the hyoid bone and neck along with mediastinal adenopathy and bony metastases in the left proximal humerus, thoracic, lumbar, sacral, and pelvic regions. Next-generation sequencing of the tumor revealed an L858R mutation in exon 21 of EGFR, high PDL1 expression and TPS 100%. The patient began treatment with chemotherapy (cisplatin and pemetrexed) plus Osimertinib arm under the FLAURA-2 trial. He sustained a notable response with decrease in size of the left upper lobe mass and mediastinal and hilar adenopathy based on restaging scans. He was also transitioned to Xarelto at this time.

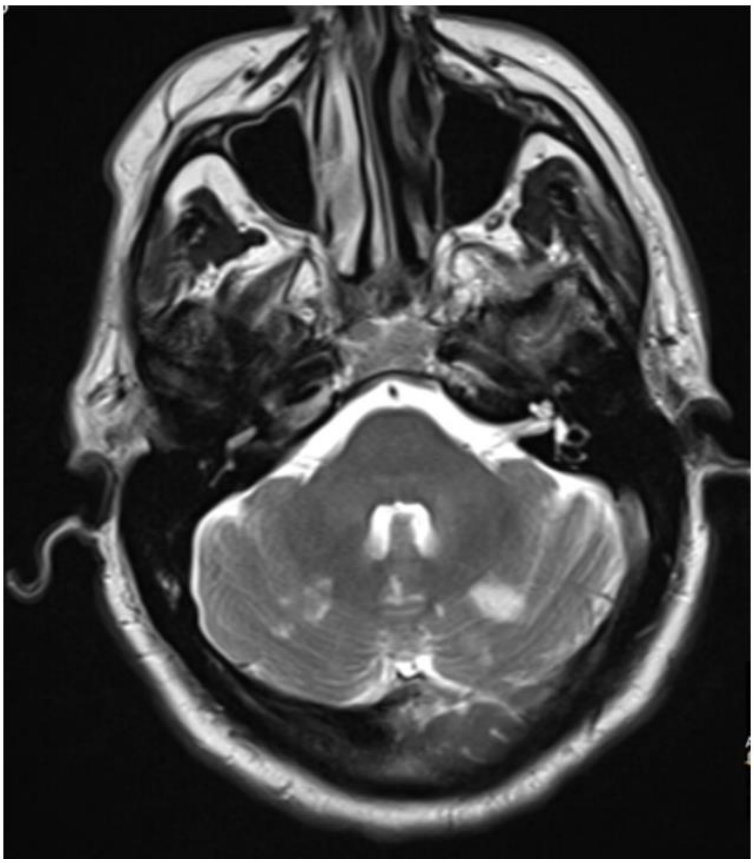

Figure 3: MRI brain showing left cerebellar infarct at initial diagnosis.

Approximately 8 months later of chemotherapy and targeted therapy, scan showed an increase in the primary left upper lobe mass, a new 8mm right lower lobe nodule, and an enlarging 9mm lymph node around the diaphragmatic crura, consistent with progression of disease. He presented to the ER after outpatient TTE showed echo-dense vegetations on the atrial aspect of the posterior mitral valve leaflets, with the larger one measuring 1.3 x 0.7cm. Physical exam was within normal limits, other than bilateral splinter hemorrhages on multiple fingernails, and lab work showed hemoglobin of 12.5, creatinine of 1.77, and slight ALT elevation of 42. Transesophageal echocardiogram (TEE) revealed an EF of 60-64%, a 1.1 x 1cm echo density on the anterior leaflet, and a 1.2 x 1cm echo density of the posterior leaflet with 3+ moderate-severe mitral regurgitation and evidence of intrapulmonary shunting. Blood cultures were negative. This was thought to be a case of non-bacterial marantic endocarditis in the setting of progression of patient's disease burden. Patient was ultimately discharged with Lovenox anticoagulation.

The patient re-presented a month later for left upper and lower extremity weakness. CT head showed potential subacute/chronic insults in the right occipital lobe. MRI brain showed subacute embolic infarction in the right frontal cortical/subcortical region, a small lacunar infarct in the left thalamus, tiny infarcts in the cerebellar vermis and right cerebellar hemisphere, and potential recent left basal ganglia and frontal infarcts. Subsequent TEE now revealed moderate to severe MR with mitral valve endocarditis. Over the hospital course, the patient's platelet count began declining to 46,000.

Due to consideration of heparin-induced thrombocytopenia, the patient was placed on argatroban while awaiting the HIT panel, which eventually returned negative. Patient's 4T score was four. The ISTH score was 2, leading to low suspicion for disseminated intravascular coagulation. Antiphospholipid syndrome antibodies also returned negative. Peripheral smear revealed scattered schistocytes, giant platelets, spherocytes, and teardrop cells, along with good myeloid and lymphoid lineage.

Two days after admission, a stroke alert was called due to altered mental change and episodes of receptive aphasia (NIHSS score of 7). CT of the head revealed evolving multifocal infarcts without evidence of intracranial hemorrhage, and CTA revealed left distal M2 occlusion within the Sylvian fissure. MRI also revealed a new area of infarction in the left temporoparietal and insular region with some associated subarachnoid hemorrhage in the left Sylvian fissure. Afterward, the patient underwent endovascular therapy for MCA stroke, and repeat TEE revealed multiple mobile nodular densities on the mitral valve leaflets and 3-4+ mitral regurgitation. The patient was then taken for an endovascular procedure with angiovac to extract the mitral valve vegetation without difficulties; however, the receptive aphasia remained.

Two weeks into admission, the patient was noted to have more right-sided weakness and an increase in somnolence. CT of the head and CTA demonstrated evolving left MCA stroke and new occlusion of the left distal M1 segment. The left MCA CVA continued progressing with vasogenic edema leading to a midline shift and petechial hemorrhagic transformation. Unfortunately, the patient deteriorated with decreased mental status and passed within a few days.

Discussion

Nonbacterial thrombotic endocarditis (NBTE), referred to as marantic endocarditis, is a non-infectious condition due to the deposition of sterile platelet and fibrin thrombi on cardiac valves, most commonly aortic and mitral [1]. It has been discovered at autopsy with an incidence of less than 2% [1,3]. In a single-center retrospective cohort study, 40.5% of patients with nonbacterial thrombotic endocarditis had malignancy, and 38.1% of patients who died had advanced malignancies [2]. One in seven hospitalized cancer patients who succumb to their disease state also arises from cases of pulmonary embolism [4]. The malignant neoplasms associated with NBTE were frequently lung, pancreatic, gastric, ovarian, biliary, and breast and were associated with the histologic adenocarcinoma type [5-9].

This form of endocarditis is often associated with procoagulant states and related to chronic inflammatory conditions such as cancer, systemic lupus erythematosus (Libman Sacks vegetations), and antiphospholipid antibody syndrome [1,2]. Factors contributing to the hypercoagulable state in cancer include procoagulant expression by tumor cells, tissue factor expression, expression of tissue-type plasminogen activators, tumor-derived cytokines such as tumor necrosis factor-a or interleukin-1, and treatment-related factors [1]. Immobilization, recent surgery, chemotherapy, and indwelling central venous catheters can also place cancer patients at a higher risk for venous thromboembolism [10]. NBTE can manifest with systemic emboli affecting cerebral, coronary, renal, and mesenteric circulations, with common clinical presentations occurring after sudden neurological deficits [1]. Patients with NBTE were seen to have a typical stroke pattern with multiple, widely distributed, small and large strokes likely due to low cellular organization of vegetations [11].

Prior case reports have identified the manifestation of marantic endocarditis in cancer patients [6,8,12-14]. However, scarce amounts discuss marantic endocarditis in the setting of driver mutations. In a retrospective review at MD Anderson described 41 cases of NBTE with the most common primary malignancies including non-small cell lung cancer (n=14) and pancreatic cancer (n=11). The most common driver mutations in the patient population included KRAS (n=8), TP53 (n=7), EGFR (n=4) and BRAF (n=2), posing the question of how these mutations may lead to hypercoagulability [15].

We discovered four cases of marantic endocarditis in EGFR mutated pulmonary adenocarcinoma patients [9,13,16,17]. The diagnosis of Stage IV EGFR mutant adenocarcinoma was identified in a patient who presented with visual defects, leading to initial infraction of the left occipital territory and subsequent identification of vegetations on the aortic valve and marantic endocarditis [9]. Another incidental finding of EGFR positive non-small-cell adenocarcinoma of the lung was noted in a patient presenting with right hand numbness leading to multiple thromboembolic events such as strokes, pulmonary embolism, and renal/splenic infarctions secondary to NBTE [13]. The third case also describes the diagnosis of pulmonary adenocarcinoma post workup for neurological findings such as dysarthria and confusion. MRI revealed a large infarct involving the left middle cerebral artery, and TEE showed subsequent mitral valve vegetation [16]. Finally, the diagnosis of marantic endocarditis was made concomitantly with metastatic pulmonary adenocarcinoma in a patient who presented with dyspnea and chest pain. However, this patient did not present with any symptoms of stroke [17]. As described above, many of the cases presented in the literature reviewed align describe NBTE in the setting of lung adenocarcinoma, and some with the EGFR mutation. Notably, in three of the four cases described above cancer presented with marantic endocarditis and stroke like symptoms.

Our patient case is unique as NBTE led to the patient's initial diagnosis and progression of EGFR-positive cancer. This case and prior case reports/reviews described above raise the question of whether EGFR mutations are associated with a higher incidence of NBTE. Due to the paucity of cases overall, it remains difficult to definitively draw this conclusion; however, this hypothesis remains of great interest for further research. This case also highlights an exceedingly rare phenomenon of recurrent marantic endocarditis in a non-small cell lung cancer patient.

Conclusion

Non-bacterial thrombotic endocarditis (NBTE) represents a non-infectious condition that remains a topic of interest in advanced malignancies. The diagnosis should be considered in patients presenting with recurrent thromboembolic events, in the setting of underlying hypercoagulable states. This requires a high degree of clinical suspicion, monitoring of laboratory values, and diagnostic imaging such as CT, MRI, and echocardiography. Further management of NBTE is multifactorial and requires systemic anticoagulation and treatment of the underlying malignancy.

REFERENCES

1. El-Shami K, Griffiths E, Streiff M. Nonbacterial thrombotic endocarditis in cancer patients: pathogenesis, diagnosis, and treatment. The Oncologist. 2007; 12: 518-523.
2. Zmaili MA, Alzubi JM, Kocyigit D, et al. A Contemporary 20-Year Cleveland Clinic Experience of Nonbacterial Thrombotic Endocarditis: Etiology, Echocardiographic Imaging, Management, and Outcomes. The American Journal of Medicine. 2021; 134: 361-369.

3. Borowski A, Ghodsizad A, Cohnen M, et al. Recurrent embolism in the course of marantic endocarditis. The Annals of Thoracic Surgery. 2005; 79: 2145-2147.
4. Kakkar AK, Levine M, Pinedo HM, et al. Venous thrombosis in cancer patients: insights from the FRONTLINE survey. The Oncologist. 2003; 8: 381-388.
5. Deppisch LM, Fayemi AO. Non-bacterial thrombotic endocarditis: clinicopathologic correlations. American Heart Journal. 1976; 92: 723-729.
6. Borowski A, Ghodsizad A, Cohnen M, et al. Recurrent embolism in the course of marantic endocarditis. The Annals of Thoracic Surgery. 2005; 79: 2145-2147.
7. Itzhaki Ben Zadok O, Spectre G, Leader A. Cancer-associated non-bacterial thrombotic endocarditis. Thrombosis research. 2022; 213: 127-132.
8. Tai ML, Tan EC, Ang CC, et al. Recurrent cerebral infarcts secondary to marantic endocarditis in a patient with adenocarcinoma of the lung. Singapore medical journal. 2016; 57: 524-525.
9. Savarapu P, Abdelazeem B, Isa S, et al. Cancer-Related Non-Bacterial Thrombotic Endocarditis Presenting as Acute Ischemic Stroke. Cureus. 2021; 13: e14953.
10. Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. The Lancet. Oncology. 2005; 6: 401-410.
11. Singhal AB, Topcuoglu MA, Buonanno FS. Acute ischemic stroke patterns in infective and nonbacterial thrombotic endocarditis: a diffusion-weighted magnetic resonance imaging study. Stroke. 2002; 33: 1267-1273.
12. Perrone F, Biagi A, Facchinetti F, et al. Systemic thromboembolism from a misdiagnosed non-bacterial thrombotic endocarditis in a patient with lung cancer: A case report. Oncology letters. 2020; 20: 194.
13. Kaufmann CC, Wessely E, Huber K. Non-bacterial thrombotic endocarditis in the context of pulmonary adenocarcinoma: a case report. European Heart Journal: Case Reports. 2020; 4: 01.
14. Wang HY, Kuo PH. Marantic Endocarditis in a Patient with Lung Cancer: Report of a Case and Review of the Literature. 2013; 28: 290-295.
15. Aaroe A, Alfaro-Munoz K, Bornstein C, et al. NCMP-20. A retrospective single -center experience with nonbacterial thrombotic endocarditis and stroke-outcomes, anticoagulation strategies and incorporation of next-generation sequencing DAT. Neuro-Oncology. 2022; 22: 127.
16. Mitma AA, Varghese JG, Witt D, et al. Stroke and a valvular lesion in a patient with stage IV non-small cell lung cancer. Case Reports. 2016.
17. Xie Z, Zhong R, Lin X, et al. Management of nonbacterial thrombotic endocarditis (NBTE) in advanced non-small cell lung cancer (NSCLC) patients with driver mutation: two case reports. Annals of Palliative Medicine. 2021; 10: 3475-3482.