Case Reports in Oncology

Case Rep Oncol 2024;17:686–694
DOI: 10.1159/000539454
Received: March 12, 2024
Accepted: May 14, 2024
Published online: June 26, 2024

Case Report

Incidentally Discovered Endocarditis Leading to the Diagnosis of an Epidermal Growth Factor Receptor Mutant Metastatic Pulmonary Malignancy of Occult Primary Tumor

Gregory L. Guzik[a] Joy W. Li[a] Joshua B. Wiener[a] Debora S. Bruno[a, b]

[a]Department of Medicine, University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [b]Division of Hematology and Oncology, Seidman Cancer Center, University Hospitals, Cleveland, OH, USA

Keywords
Endocarditis · Epidermal growth factor receptor mutant · Non-bacterial thrombotic endocarditis · Adenocarcinoma · Lung cancer

Abstract
Introduction: Non-bacterial thrombotic endocarditis is well documented in the literature to occur in patients with known malignancies. It is, however, much less common for patients to be diagnosed with marantic endocarditis as the presenting sign of an unknown primary malignancy. ***Case Presentation:*** We discuss a case in which a patient was undergoing routine surveillance for his known heart failure with a transthoracic echocardiogram when an aortic valve vegetation was discovered. After further investigation, he was found to have metastatic adenocarcinoma of the lung. Next-generation sequencing was utilized to identify an EGFR mutation, which led to the patient being treated with osimertinib. ***Conclusion:*** Adequate treatment of his primary malignancy, along with anticoagulation, led to overall clinical improvement of the patient.

Correspondence to:
Gregory L. Guzik, gregorylguzik@gmail.com

Case Rep Oncol 2024;17:686–694
DOI: 10.1159/000539454

Introduction

Cancer is often associated with hypercoagulability and can infrequently present with non-bacterial thrombotic endocarditis (NBTE) [1]. Endocarditis is an inflammation of the endocardium, the internal lining of the heart. It is most often caused by an infectious etiology, but it can also rarely be the result of other causes of inflammation, such as malignancy [1]. While the overall incidence is unknown, much of the known data on NBTE are gleaned from patients who have undergone a post-mortem biopsy [2]. As a result, it is now recognized that NBTE is significantly more common in those who had a known malignancy, and even more-so when the malignancy was adenocarcinoma [2]. The growing use of next-generation sequencing (NGS) to identify targetable mutations has transformed cancer diagnosis and therapy, but few studies have elucidated the connection between specific mutations and the incidence of endocarditis [3]. Here, we describe the case of a patient with a history of heart failure, who during routine outpatient echocardiogram was found to have a valvular lesion suspicious for endocarditis, leading to the identification of NBTE and occult primary pulmonary adenocarcinoma with an epidermal growth factor receptor (EGFR) mutation.

Case Report

A 62-year-old man initially presented to an outpatient heart failure cardiology appointment for work-up of new anemia and routine transthoracic echocardiogram. The echocardiogram showed an aortic lesion suspicious for a new aortic valve vegetation. At the outpatient appointment, he had new interval complaints of progressive dyspnea on exertion and fatigue. He also endorsed anorexia associated with an unintentional weight loss of 16 kg over 2 months. He denied night sweats, fevers, chills, bleeding, chest pain, or palpitations. Past medical history was relevant for heart failure with recovered ejection fraction and persistent atrial fibrillation on anticoagulation with elective cardioversion 3 years prior. The patient also reported two incidences of stroke within the past 2 months where he was evaluated and treated at another hospital. CTA head and neck showed no significant abnormalities aside from the left MCA stroke noted. No echocardiogram was completed at that time. It was assumed the etiology of the stroke was embolic from patient's known atrial fibrillation. Family history was remarkable for breast cancer in the patient's mother and sister, but otherwise no other malignancy history was reported. He had a 20-pack-year smoking history but had recently quit.

His cardiologist requested an urgent admission for work-up and treatment. At the time of admission, the patient was afebrile and hemodynamically stable. Physical exam was unremarkable. Echocardiogram showed a mildly reduced left ventricular ejection fraction of 40–45% and a mobile aortic valve echodensity (12 mm × 4 mm) seen on the non-coronary cusp suspicious for vegetation, with mild valvular regurgitation (Fig. 1). Laboratories were most notable for a hemoglobin of 5.9 g/dL with an MCV of 90, a normal white blood cell count (5.2×10^9 g/L), and platelets (210×10^9 g/L). He also had normal TSH, BNP, and troponin levels. Serum B12, folate, iron, and TIBC were likewise within normal limits. His haptoglobin level was elevated at 269 mg/dL, and INR was normal at 1.1 with near-normal PT and PTT. Antiphospholipid and lupus studies were negative, and ESR was <1. Blood cultures were drawn, and then antibiotics were started. The cultures eventually demonstrated no growth.

A CT chest, abdomen, and pelvis with IV contrast was ordered for evaluation of possible underlying malignancy in the setting of new normocytic anemia without an identifiable source of bleeding. A transesophageal echocardiogram (TEE) was ordered to better characterize the aortic valve vegetation (Fig. 2). The CT findings were significant for diffuse

Case Rep Oncol 2024;17:686–694
DOI: 10.1159/000539454

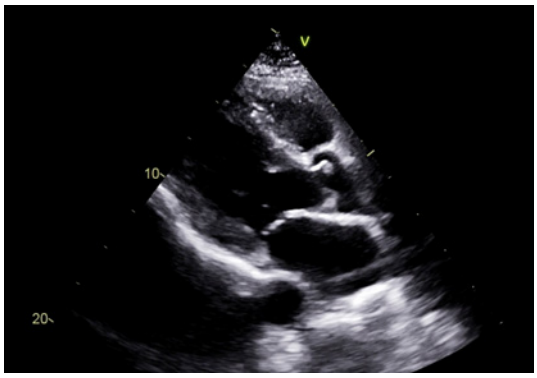

Fig. 1. Transthoracic echocardiogram showing the aortic valve vegetation.

thickening of the right adrenal gland with nonspecific focus of hypo-attenuation, peritoneal carcinomatosis, along with multiple hepatic hypo-dense lesions too small to characterize, and a splenic infarct. No lung masses or nodules, nor intrathoracic adenopathy was identified. A PET scan later performed showed no signs of a primary malignancy (Fig. 3, 4). Cancer markers were ordered with CA19-9, AFP, and PSA within normal limits. Carcinoembryonic antigen was elevated at 11.8. Gastroenterology performed an esophagogastroduodenoscopy and colonoscopy but was unable to identify a luminal malignancy or source of bleeding.

Meanwhile, the TEE showed small-to medium-sized echodensities with small mobile components on all three cusps of the aortic valve. The neurology-stroke team was consulted and agreed that the patient's prior strokes were likely thromboembolic in nature from the aortic valve with primary differential being infectious or neoplastic process. The infectious diseases team concurred that the patient's brain MRI with and without contrast findings (Fig. 5, 6), along with strokes and splenic infarct were most likely caused by a marantic, noninfectious endocarditis. Notably, there were no lesions concerning for metastatic disease.

Biopsy of the adrenal gland was performed with pathology demonstrating metastatic adenocarcinoma, which was CK7 and TTF-1 positive, and CK20 and CDX-2 negative, compatible with metastasis from a pulmonary adenocarcinoma. NGS of the sample demonstrated an EGFR exon 19 deletion. ALK, BRAF, KRAS, NTRK, ROS1, RET, and MET mutations were negative. The anemia was thought to be multifactorial in the setting of anemia of chronic inflammation as well as the patient's splenic infarcts. After being stabilized and the source of anemia identified, the patient was restarted on appropriate oral anticoagulation and was discharged from the hospital with outpatient oncology follow-up. At the time of oncology follow-up, he was noted to have an ECOG performance status of two and was subsequently started on osimertinib treatment. Targeted therapy led to a quick improvement and correction of his anemia with no subsequent strokes. Re-staging CT scans were obtained 2 months after initiation of osimertinib, which showed interval improvement in disease burden without new metastatic lesions. The patient was able to regain his weight, and his systemic symptoms improved. A timeline demonstrates the sequence of clinical events (Fig. 7).

Discussion

The association between malignancy and hypercoagulability has been well documented, dating back to observations as early as the 1800s [4]. It is estimated that nearly 50% of cancer patients have evidence of thromboembolic disease on post-mortem exam; however, only about 15% of cancer patients have manifestation of symptoms during their disease course [5].

Case Rep Oncol 2024;17:686–694
DOI: 10.1159/000539454

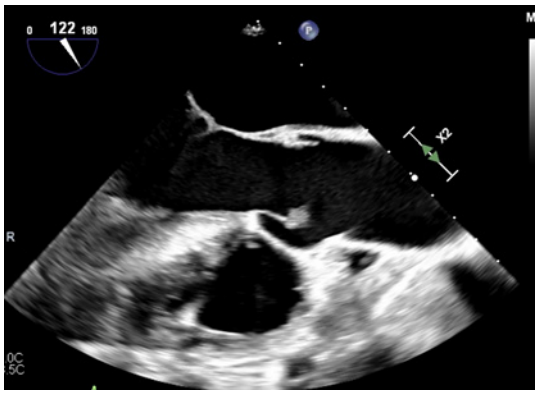

Fig. 2. TEE showing the aortic valve vegetation.

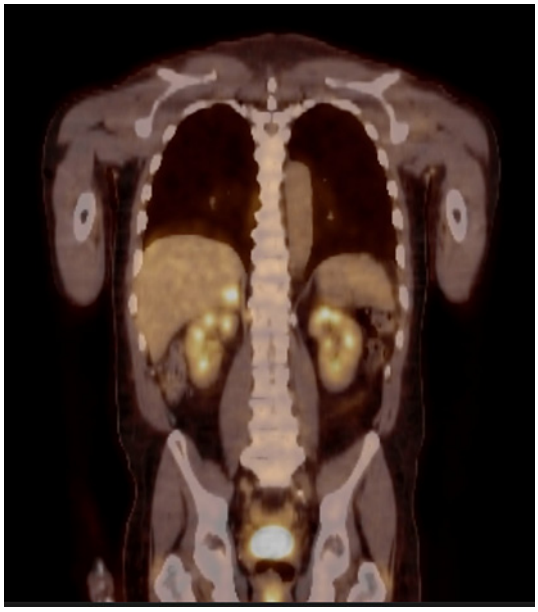

Fig. 3. Coronal view of PET CT scan showing hypermetabolic activity in the right adrenal gland.

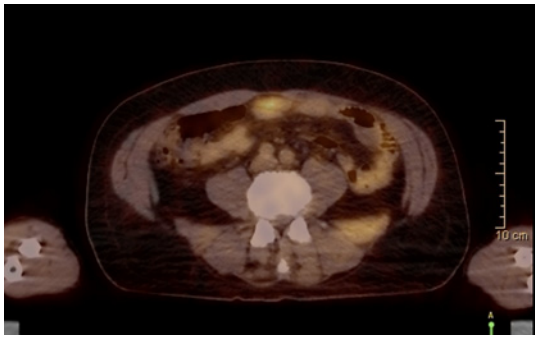

Fig. 4. Transverse view of PET CT showing hypermetabolic activity in the peritoneum.

The pathogenesis of the procoagulant state in malignancy is multifactorial but mostly related to the production of prothrombotic molecules by cancer cells such as tissue factor, vascular endothelial growth factor, and tumor necrosis factor alpha. Cancer cells also interact directly with endothelial cells, platelets, and macrophages/monocytes, leading to the activation of clotting, platelet aggregation, and further production of procoagulant tissue factor [6]. Other

Case Rep Oncol 2024;17:686–694
DOI: 10.1159/000539454

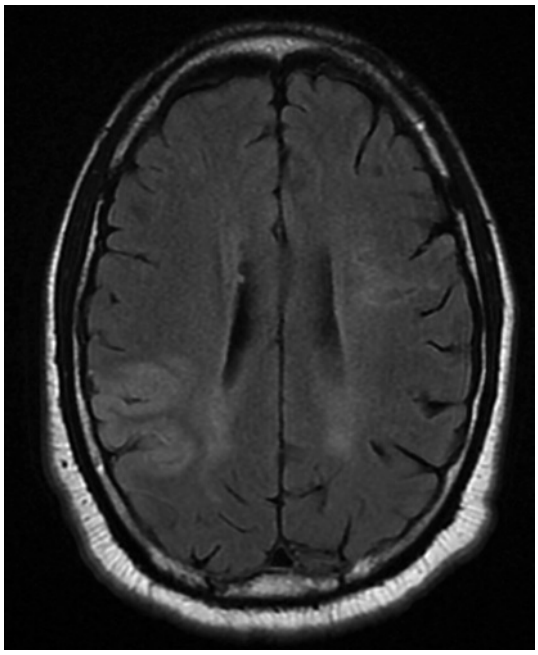

Fig. 5. MRI brain showing multiple strokes, likely of embolic origin.

factors include direct compression of vasculature by the tumor or metastasis, use of indwelling catheters, as well as subsequent effects of cancer treatment from surgery, chemotherapy, and hormonal therapies [7]. While thromboembolism is the most common outcome of hypercoagulability of malignancy, other procoagulant manifestations include superficial thrombophlebitis, arterial thrombosis, and NBTE.

While any of the cardiac valves can be affected, the most common is the aortic valve followed by the mitral valve [7]. Interestingly, the vegetations typically have no effect on function of the valve [8]. While the exact etiology of NBTE is unknown, it is thought to be initiated by endothelial damage in a pro-inflammatory and hypercoagulable state of disease [8]. The vegetations are composed of degenerating platelets mixed with strands of fibrin, immune complexes, and mononuclear cells [8]. In an animal model study reviewing the pathogenesis of NBTE, both increased level of tissue factor and elevated expression of tissue factor mRNA were associated with an increased risk of vegetation formation [9].

The typical presentation for a patient with NBTE is nonspecific and can be quite the clinical challenge. Since the vegetations rarely cause valvular dysfunction, there are often few to no symptoms until an embolic event occurs [8]. Nearly 50% of these vegetations embolize; the high propensity to embolize is thought to stem from the significant friability of the vegetation [10]. Therefore, patients can present with symptoms of emboli to cerebral, coronary, renal, and mesenteric circulations [8]. If NBTE is suspected, a TEE is the gold standard for diagnosis as transthoracic echocardiograms typically have less than 50% sensitivity in detecting valvular vegetations [11]. Once a diagnosis is established, the treatment is focused on treatment of the underlying disease as well as anticoagulation. Aside from malignancy, other disorders such as systemic lupus erythematous and antiphospholipid syndrome are also potentially associated with NBTE and are part of the differential diagnosis [11].

Low-molecular-weight heparin has been the anticoagulant of choice to reduce the risk of recurrent embolic events in patients with underlying malignancy. Vitamin K antagonists are specifically avoided in cases of NBTE as recurrent thromboembolism has been demonstrated in these patients along with increased bleeding risk [12]. The effectiveness of direct oral

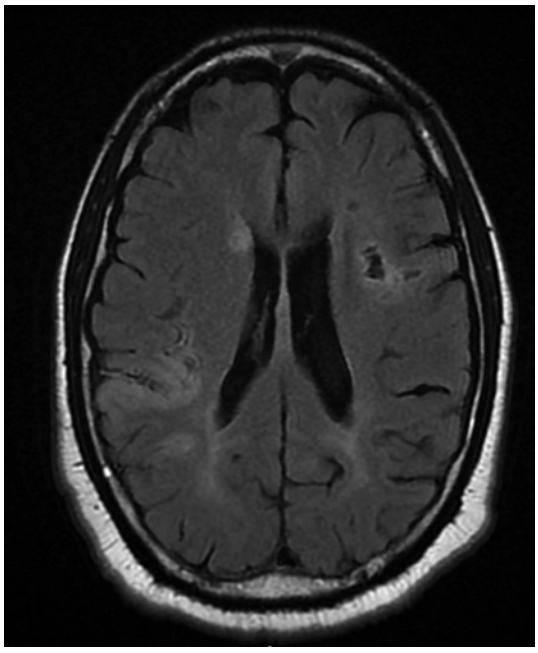

Fig. 6. MRI brain obtained 2 months after initial MRI showing worsening of stroke burden.

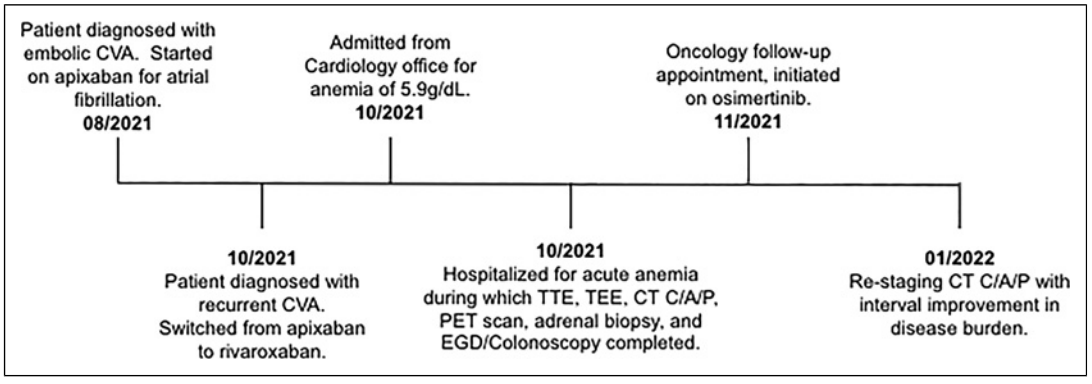

Fig. 7. Timeline of patient's clinical course from first CVA to first follow-up re-staging scans after osimertinib treatment.

anticoagulants such as direct Xa inhibitors and thrombin inhibitors in treating specifically NBTE is unknown at this point but has been used off-label due to their established efficacy in treating and preventing complications from hypercoagulability associated with cancer [12]. In our patient's case, he was placed on rivaroxaban and clopidogrel but went on to develop subsequent thromboembolic events. It was only after starting effective targeted therapy for his cancer that his clinical status stabilized, including correction of his anemia and no further neurological events. This underscores the need to effectively treat and control the primary cause of NBTE for best outcomes.

The association between malignancies and NBTE has been well established in the literature up to this point. Mucin-producing adenocarcinomas, such as from the lung and GI tract, are the most common types of cancers to be associated with NBTE [13, 14]. In our patient's case, his adenocarcinoma demonstrated an EGFR exon 19 deletion. Non-small-cell lung cancers with classic EGFR mutations as oncogenic drivers demonstrate dramatic clinical response to EGFR tyrosine kinase inhibitors [15]. Targeted therapies are extremely effective,

leading to extended survival times [16]. The incidence of EGFR mutations is higher in lung adenocarcinomas of never or light smokers, individuals of Asian ethnicity, and females [17]. In one other case report, a patient with an EGFR-mutated lung adenocarcinoma presented with both NBTE and DIC and was subsequently treated with osimertinib [18]. The patient experienced a decrease in size of the vegetation within 1 month of starting the osimertinib, suggesting, as in our patient, that once an uncontrolled cancer is effectively treated, the propensity to develop NBTE decreases [18].

This is, to our knowledge, the first case reported of EGFR mutant NSCLC presenting with NBTE in the setting of an occult primary tumor. Metastatic carcinomas of occult primary site are rare presentations of solid malignancies and associated with a very aggressive course. Adenocarcinomas account for most of the cases [19]. Up until recently, immunohistochemistry has been the only ancillary test able to point toward a primary site of origin and guide therapy [20]. The use of NGS, however, has demonstrated the potential to help guide therapy in cases where the metastatic primary tumor cannot be identified [21]. Our patient's case underscores not only the need to investigate an underlying malignancy in patients presenting with unprovoked thromboembolic events, but also the ability of new testing methods (NGS) to provide further insight in both determining the origin of the cancer and identifying potential targets for systemic therapy.

To this point, there have been only small observational studies to evaluate the most effective treatment for malignancy-related NBTE. In several case reports, it appears that patients who do have an actionable EGFR mutation experience both decreased tumor burden and decreased size of the cardiac valve vegetation with tyrosine kinase inhibitor therapy [18, 22]. Oftentimes, these patients are also placed on some form of anticoagulation, so it is unclear which of the therapies provides the most benefit of vegetation reduction/resolution. Our patient suffered another thromboembolic event after being started on anticoagulation, and it was only after initiation of effective targeted therapy that his hypercoagulable state was controlled. Larger randomized controlled trials would likely provide greater insight into the effectiveness of NBTE treatment when related to malignancy but are unlikely to occur due to the relative unusual presentation of this complication.

Conclusion

We presented the case of a patient whose initial presentation of NBTE led to the diagnosis of a metastatic EGFR mutant adenocarcinoma of lung origin without an established primary tumor. This case emphasized the importance of evaluating for underlying malignancy when patients present with NBTE, and the importance of genomic testing in uncovering the underlying primary as well as providing treatment options. Early investigation of underlying disease can help accelerate the cancer diagnosis process and initiation of treatment. Future studies should also investigate the relationships between genomic alterations in lung adenocarcinomas and incidence of NBTE. The CARE checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539454).

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

We have no conflicts of interest to disclose.

Funding Sources

No funding was received.

Author Contributions

D.S.B. designed the case. J.W.L., G.L.G. and J.B.W. collected the patient data. G.L.G. and J.W.L. completed the literature review. D.S.B., J.W.L., and G.L.G. reviewed and edited the manuscript. All authors contributed to the article and approved for submission.

Data Availability Statement

All data from this study are included in this article and the supplementary material files. Further inquiries should be directed to the corresponding author.

References

1 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.
2 Itzhaki Ben Zadok O, Spectre G, Leader A. Cancer-associated non-bacterial thrombotic endocarditis. Thromb Res. 2022;213(Suppl 1):S127–32. https://doi.org/10.1016/j.thromres.2021.11.024
3 Mitchell CL, Zhang AL, Bruno DS, Almeida FA. NSCLC in the era of targeted and immunotherapy: what every pulmonologist must know. Diagnostics. 2023;13(6):1117. https://doi.org/10.3390/diagnostics13061117
4 Trousseau A. Clinique médicale de l'Hôtel-Dieu de Paris. Paris: Ballière; 1865.
5 Dvorak HF, Colman RW, Hirsh J, Marder VJ. Abnormalities of hemostasis in malignant disease. In. Lippincott JB, editor. Hemostasis and thrombosis. Philadelphia; 1994. p. 1238–54.
6 Caine GJ, Stonelake PS, Lip GY, Kehoe ST. The hypercoagulable state of malignancy: pathogenesis and current debate. Neoplasia. 2002;4(6):465–73. https://doi.org/10.1038/sj.neo.7900263
7 El-Shami K, Griffiths E, Streiff M. Nonbacterial thrombotic endocarditis in cancer patients: pathogenesis, diagnosis, and treatment. Oncologist. 2007;12(5):518–23. https://doi.org/10.1634/theoncologist.12-5-518
8 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. 2022;23(4):137. https://doi.org/10.31083/j.rcm2304137
9 Nakanishi K, Tajima F, Nakata Y, Osada H, Ogata K, Kawai T, et al. Tissue factor is associated with the nonbacterial thrombotic endocarditis induced by a hypobaric hypoxic environment in rats. Virchows Arch. 1998;433(4):375–9. https://doi.org/10.1007/s004280050262
10 Kooiker JC, MacLean JM, Sumi SM. Cerebral embolism, marantic endocarditis, and cancer. Arch Neurol. 1976;33(4):260–4. https://doi.org/10.1001/archneur.1976.00500040044006
11 Zmaili MA, Alzubi JM, Kocyigit D, Bansal A, Samra GS, Grimm R, et al. A contemporary 20-year Cleveland clinic experience of nonbacterial thrombotic endocarditis: etiology, echocardiographic imaging, management, and outcomes. Am J Med. 2021;134(3):361–9. https://doi.org/10.1016/j.amjmed.2020.06.047
12 Kraaijpoel N, Carrier M. How I treat cancer-associated venous thromboembolism. Blood. 2019;133(4):291–8. https://doi.org/10.1182/blood-2018-08-835595
13 Green KB, Silverstein RL. Hypercoagulability in cancer. Hematol Oncol Clin North Am. 1996;10(2):499–530. https://doi.org/10.1016/s0889-8588(05)70349-x
14 Luzzatto G, Schafer AI. The prethrombotic state in cancer. Semin Oncol. 1990;17(2):147–59.
15 Metro G, Crinò L. Advances on EGFR mutation for lung cancer. Transl Lung Cancer Res. 2012;1(1):5–13. https://doi.org/10.3978/j.issn.2218-6751.2011.12.01

16 Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. N Engl J Med. 2020;382(1):41–50. https://doi.org/10.1056/NEJMoa1913662
17 Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2016;7(48):78985–93. https://doi.org/10.18632/oncotarget.12587
18 Shen HC, Hsu YF, Chiang CL. Successful treatment of nonbacterial thrombotic endocarditis and disseminated intravascular coagulation in a patient with advanced lung adenocarcinoma using osimertinib. JTO Clin Res Rep. 2020;1(3):100066. https://doi.org/10.1016/j.jtocrr.2020.100066
19 Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012;379(9824):1428–35. https://doi.org/10.1016/S0140-6736(11)61178-1
20 Dennis JL, Hvidsten TR, Wit EC, Komorowski J, Bell AK, Downie I, et al. Markers of adenocarcinoma characteristic of the site of origin: development of a diagnostic algorithm. Clin Cancer Res. 2005;11(10):3766–72. https://doi.org/10.1158/1078-0432.CCR-04-2236
21 Ross JS, Wang K, Gay L, Otto GA, White E, Iwanik K, et al. Comprehensive genomic profiling of carcinoma of unknown primary site: new routes to targeted therapies. JAMA Oncol. 2015;1(1):40–9. https://doi.org/10.1001/jamaoncol.2014.216
22 Kaufmann CC, Wessely E, Huber K. Non-bacterial thrombotic endocarditis in the context of pulmonary adenocarcinoma: a case report. Eur Heart J Case Rep. 2020;4(1):1–5. https://doi.org/10.1093/ehjcr/ytaa008