A 72-Year-Old Man With Recently Diagnosed Lung Cancer

Introduction. A 72-year-old man presented to the hospital for an apparent thrombotic stroke.

Patient history. Regarding the present illness, the patient's history began about 3 months prior, when a friend noticed that the patient's left eye was unusually fixed to the lateral and downward direction. Despite this, he denied headache or double vision. Prompt consultation to ophthalmology, neurology, and neurosurgery resulted in the diagnosis of an orbital mass of the left orbit, emerging through the canal of Schlemm, with major differentials being metastatic orbital neoplasm, orbital lymphoma, or sarcoidosis.

The patient's medical history was significant and positive for at least 50 pack years and the known presence of moderate chronic obstructive pulmonary disease. There was no known coronary artery disease, diabetes, or hypertension. Four years prior, he experienced thoracic-level spinal stenosis requiring laminectomy. The patient is also a Vietnam War veteran, with heavy exposure to Agent Orange during his time in the war.

Physical examination. There was consideration for orbital biopsy to obtain tissue diagnosis, and further preoperative studies revealed an alarming and markedly nonstandard chest x-ray, demonstrating a large mass of the left lower lobe with contiguous bilateral hilar and mediastinal adenopathy. Upon seeing the irregular chest radiology, a full evaluation was performed.

Diagnostic examination. There was a 5 cm mass-like consolidation in the left lower lobe with irregular borders, contiguous multifocal left hilar, and mediastinal adenopathy consistent with metastases measuring more than 2 cm. A small unilateral left pleural effusion and reticulonodular right lower lobe opacity suspicious for lymphangitic carcinomatosis was also found.

Transbronchial needle biopsy was performed and confirmed the presence of poorly differentiated adenocarcinoma of the lung with lymphangitic spread. Immuno-histochemical stains and genetics showed the tumor cells positive for PD-L1 greater than 50% and negative for estimated glomerular filtration rate and anaplastic lymphoma kinase genes, suggestive for sensitivity to the immunotherapeutic pembrolizumab.

The patient was scheduled to begin that therapy as an outpatient in 1 week. However, 3 days prior to his therapy date, his daughter found him at home obtunded, incoherent, and disoriented. He was hospitalized and an emergency computed tomography (CT) and magnetic resonance imaging (MRI) of his brain revealed the presence of multiple bilateral

acute to subacute cerebral infarctions with flow findings consistent with multiple thrombi. He had not manifest pain or fever throughout this period of evaluation.

(Answer and Discussion on next page)

Answer: C. Transesophageal echocardiography (TEE) is the preferred imaging study to confirm the suspected diagnosis.

The presented patient has apparently sustained an acute thrombotic stroke on clinical and radiological grounds. The answers offered relating to diagnosis and management are all within the realm of possibility for several of the causes of acute thrombotic stroke. However, there are some salient clinical/radiologic clues that need be considered here, particularly in the patient's subacute history prior to the acute event. I rarely accept as coincidence two seemingly disparate diagnoses (eg, widely disseminated lung cancer and acute thrombotic stroke) Are they connected? Is there a logical pathophysiologic mechanism that can explain this?

In this case, the answer is yes: a condition called marantic endocarditis (also known as nonbacterial thrombotic endocarditis [NBTE]), which is the diagnosis here.

Regarding the possible selections, for Answers B and D, antibiotics and mechanical thrombectomy are therapies for other diagnoses, namely bacterial endocarditis, and classical thrombotic stroke, respectively, which the patient does not have. Answer A would be appropriate in the setting of NBTE related to lupus or rheumatoid arthritis but not in this case. Therefore, Answer C is the most accurate statement and would confirm the presence of NBTE.

Discussion. The demographics, pathophysiology, and clinical and imaging findings of NBTE, are well-defined in the literature. Previously published studies noted that NBTE is uncommon, even to the point of rare. One study found that the incidence levels of NBTE are between 0.3% and 9.3%,[1] while more current studies report an incidence range between 0.9% to 4%.[2,3] One recent study reported only 42 diagnoses out of nearly 700,000 TEEs performed in 20 years.[4]

A more detailed analysis of the patient demographics reveals two distinct subsets of patients comprise most of the NBTE population. The first subset involves cases related to the presence of profound inflammatory states (eg, antiphospholipid antibody syndrome, systemic lupus, and rheumatoid arthritis), who have an average age of 45 to 50 years and a female preponderance.[1,4] The second demographic group is predominantly male with an average age of approximately 65 years and a pathophysiology of advanced widespread malignancy: bronchogenic (47%) breast (24%), and pancreas (18%).[4] The presented patient fits this demographic profile very well.

The proposed pathophysiology in NBTE, either related to malignancy or inflammatory state, remains poorly understood. A far too simplistic explanation of NBTE relates to the

thrombotic part and the acquired clinical thrombophilia seen in these conditions. This acquired thrombophilia is associated with increased production of coagulation factors and cancer cell induced increased tissue factor, which results in the increased adhesion of cells and vegetation growth on heart valves.[4] The vegetations are friable and tend to be located at the valve edges and easily embolize, which results in the NBTE syndrome.[3]

Whatever the true and likely complicated pathophysiology of NBTE, the most common initial finding is thrombotic cerebrovascular accident (CVA), with a presentation in 50% to 60% of cases.[1,3,4] It is this CVA that prompts the subsequent evaluation and correct diagnosis. The routine studies in stroke-CT scans and brain MRI demonstrate and confirm the presence of a thrombotic stroke, with two additional associated findings: (1) the cerebral lesions are multiple rather than, for example, a single middle cerebral artery lesion; (2) that there exist in the arterial circulation multiple other embolic ischemic infarcts such as splenic and renal.

The above findings point to a systemic embolization from the left side of the heart. As the evaluations continue, the absence of fever and positive blood cultures essentially exclude bacterial endocarditis. Also, unlike bacterial endocarditis, classical pathologic cardiac murmurs are usually not impressive. This is explained by the previously mentioned friability of NBTE valve lesions, which embolize quickly and easily before causing any valvular dysfunction.3 Indeed, an overwhelming majority of cases will have one of the two predominant demographic risk group characteristics-presence of an inflammatory disease or advanced malignancy such as adenocarcinoma.

The confirmatory imaging study is echocardiography. Previous studies have demonstrated that transesophageal echocardiography is the most optimal approach with sensitivity of 45.2% for NBTE.4 Specific findings in malignancy cases show vegetations to be mitral more so than aortic by a roughly 2:1 ratio, location along valve tips and size approximately 1 cm on average.[2,4]

Treating NBTE can become quite problematic in the malignancy-associated demographic group. Most cases occur in the setting of advanced malignancy, which has a short survivorship even in the absence of NBTE. In the most current study examining 12 cases of cancer-related NBTE, eight of 12 patients died within 2 months of diagnosis.[4] Since NBTE, as a rule, does not affect cardiac function (e.g., ejection fraction, valvular function) this very high acute mortality is carcinomatosis-related rather than cardiac-related and limits therapeutic maneuvers such as valve surgery.3 Anticoagulants have more of a role in the "benign" demographic, which has a far better prognosis.[1,3,4] The heparin family of medicines seem superior to warfarin, according to the literature.[3,4]

Patient Follow-Up. Generally, as was the case here, a diagnosis of NBTE leads to mortality within days or weeks. In this case, the patient remained in an arousable, but very obtunded state. The multiple thrombotic lesions on the brain CT and MRI suggested an embolic source. Although acknowledging the superiority of TEE as the preferred imaging method, the patient's clinical status made transthoracic echocardiogram (TTE) an easier initial and less invasive approach. The TTE demonstrated echogenic material on both leaflets of the mitral valve. Three sets of blood cultures remained negative at 24 hours. His neurologic status deteriorated, and by 48 hours, the patient was comatose. According to patient's living will and family, no further diagnostic or therapeutic maneuvers were performed, and he died on day 4.

What's the Take Home? Nonbacterial thrombotic endocarditis is an uncommon syndrome heralded by widespread thrombosis/embolization in multiple vascular territories of the body. By far the most common (50% to 60% of cases) and morbid initial clinical event is cerebral embolization, causing thrombotic strokes. The broad differential diagnoses include paradoxical emboli from the right heart crossing into the systemic circulation, left heart lesions of mural thrombosis from left ventricular cardiomyopathy or left atrial myxoma, bacterial endocarditis with vegetation embolization, and NBTE. The latter has its demographics the settings of profound inflammatory states (e.g. lupus, rheumatoid arthritis, antiphospholipid syndromes) or advanced malignancy usually adenocarcinomas. In NBTE, there is formation of friable, sterile vegetations on the edges of the left heart valves which are quick to embolize.

When NBTE is considered, assuming other causes have been excluded, the diagnosis can be confirmed by echocardiography, with TEE being the preferred to TTE, with a specificity of 97% compared to 45%, respectively.[4]

In the malignancy group, prognosis is very poor due to the usually associated advanced stage of cancer. Unfortunately, survivorship is usually measured in weeks.

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CITATION

Rubin RN. A 72-year-old man with recently diagnosed lung cancer. *Consultant*. 2024;64(3):e4. doi:10.25270/con.2024.03.000002

DISCLOSURES The author reports no relevant financial relationships.

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