CLINICAL VIGNETTE

A Case of Non-Bacterial Thrombotic Endocarditis

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A 61-year-old woman presented to the emergency department with a three-day history of dizziness, intermittent confusion, and mild generalized headache. She denied any muscle weakness, sensory changes, speech, or swallowing problems. Her past medical history was significant for Lynch Syndrome with metastatic uterine cancer and stage III colorectal cancer with dermatomyositis as a paraneoplastic manifestation of her cancer diagnosis. She had prior right popliteal deep vein thrombosis and hypertension were also noted. Colorectal cancer was diagnosed at the age of 41 and treated with right hemicolectomy followed by adjuvant chemotherapy without recurrence. Her uterine cancer was diagnosed a few months prior to her current presentation with extensive abdominopelvic lymphadenopathy. She began palliative chemotherapy with carboplatin and paclitaxel shortly prior to admission. Her family history was significant for breast cancer in her sister, uterine cancer in her maternal aunt and colon cancer in her maternal uncle. Her medications consisted of Rivaroxaban 15 mg daily for deep vein thrombosis, prednisone 15 mg daily for dermatomyositis, amlodipine 10 mg daily and Esomeprazole 20 mg daily. She denied tobacco or alcohol use. Review of systems was negative for fever, night sweats, weight loss, new skin lesions, chest pain, shortness of breath, cough, hemoptysis, or any gastrointestinal symptoms. On physical examination, she appeared in no acute distress. Her blood pressure was 144/97 mmHg with heart rate of 89 beats per minute and respiratory rate of 16 breaths per minute. Her temperature on admission was 37.3 degrees Celsius and her pulse oximetry showed an oxygen saturation of 100% breathing room air. Her neck was supple with no cervical lymphadenopathy or jugular venous distention; cardiovascular exam showed regular heart rate with no murmurs or gallops, respiratory examination and abdominal examination did not reveal any significant pathology. No new skin or subungual lesions were detectable. She appeared alert but slightly slow to respond, cranial nerves, motor, sensory and reflexes were grossly intact. Laboratory workup revealed a hemoglobin of 9.1 g/dl, WBC count of 8600/microliter and platelet count of 262,000/microliter. Her coagulation panel, renal function, and liver function tests were all within normal range. She had ESR of 62 and CRP of 2.8.

Her initial presentation was concerning for acute stroke versus central nervous system metastatic disease. Brain MRI with gadolinium enhancement revealed a 4 cm acute non-hemorrhagic stroke involving left parietal and occipital lobes plus multiple bilateral sub-centimeter acute infarcts involving both cerebellar and cerebral hemispheres. CT angiogram of head and neck showed no significant stenosis in the cerebral circulation. Involvement of multiple brain territories supplied by anterior and posterior circulation was concerning for acute embolic source. She was started on Clopidogrel 75 mg daily, Atorvastatin 80 mg daily and Rivaroxaban was switched to therapeutic dose of Enoxaparin 1mg/kg twice a day. Review of her cardiac rhythm did not show any cardiac arrhythmia. Transthoracic Echocardiogram with bubble study revealed early right to left shunting consistent with a likely Patent Foramen Ovale. This finding was concerning for paradoxical emboli with right to left shunting as the etiology of her embolic stroke. Ultrasound of her lower extremities revealed resolution of old thrombosis in her right lower extremity and no new thrombosis was detected in bilateral lower extremities.

Her transesophageal echocardiogram (TEE) revealed a large irregularly shaped mobile lesion on the mitral valve measuring 1.2 x 0.6 cm with mild mitral regurgitation concerning for an infectious vegetation versus nonbacterial thrombotic endocarditis (NBTE) or Marantic Endocarditis in the setting of advanced malignancy. She was evaluated by a cardiothoracic surgeon who offered surgical intervention in view of the size of the lesion, but patient declined cardiac surgery and opted for medical management. She had multiple blood cultures drawn from various peripheral veins as well as her Port-A catheter. One set of blood cultures came back positive for coagulase negative Staphylococcus but all other blood cultures (six in total) including subsequent cultures drawn from Port-A catheter were negative. Based on the Infectious Disease consultant evaluation, growth of coagulase negative Staphylococcus in only one bottle of blood culture was considered a contaminant and she was diagnosed with Blood Culture Negative Infective Endocarditis. Further testing included negative Coxiella, Bartonella, and Brucella antibodies. Aspergillus galactomannan, coccidioidomycosis serology also returned negative. Subcutaneous therapeutic Enoxaparin was continued as well as intravenous Ampicillin 2 grams every 4 hours and Ceftriaxone 2 grams every 12 hours. Her neurological deficit improved during her course of rehabilitation. She was eventually discharged home with plan to complete a total of six weeks of intravenous Ampicillin and Ceftriaxone. Repeat transesophageal echocardiogram after completion of intravenous antibiotics showed normal appearing mitral valve with resolution of previously visualized vegetation/thrombus. This result was felt to be more likely due to continuation of enoxaparin to treat her NBTE.

Discussion

Infective endocarditis occurs on native and prosthetic valves. Native valve endocarditis is more common on the left side of the heart.[1] The most common organism involved in native valve endocarditis is *staphylococcus aureus* followed by *viridans streptococci* and *enterococci*. Diagnosis of infective endocarditis is based on fulfillment of modified Duke Criteria:

Definite endocarditis[1] is diagnosed when the patient has any of the following:

- Pathologic evidence of valve disease
- Two major criteria
- One major criterion plus three minor criteria
- Five minor criteria.

Possible endocarditis is diagnosed in presence of either three minor criteria or one major plus one minor criterion.[1]

The two major criteria in modified Duke include:

1- Abnormal echocardiogram
2- Positive blood cultures. If the organism is the one that typically causes endocarditis (*Staphylococcus. aureus, viridans streptococci, Streptococcus bovis, or enterococci*), two positive blood cultures, drawn 12 hours apart is sufficient to fulfill the blood culture criterion. If the organism is not one that typically causes endocarditis, there must be at least three positive blood cultures drawn at least an hour apart from first to last.

Five minor criteria include:

1- Presence of predisposing factor (valve disease or injection drug use)
2- Fever greater than 38 degrees Celsius
3- Vascular phenomena (e.g., arterial emboli or stroke)
4- Immunological phenomena (e.g., acute glomerulonephritis)
5- Positive blood culture that does not meet the major criterion for major criteria.

Blood culture-negative IE is defined as endocarditis without etiology following inoculation of at least three independent blood samples in a standard blood-culture system with negative cultures after seven days of incubation. Cultures may remain negative in two to seven percent of patients with infective endocarditis, even when the utmost care is taken in obtaining the proper number and volume of blood cultures and patients with prior antibiotic treatment are excluded.[2] The frequency is higher in patients already being treated with antibiotics. Other reasons for failure to diagnose the pathogen in infective endocarditis are suboptimal microbiological technique and infection caused by highly fastidious bacteria or non-bacterial pathogens. Fastidious organisms are the most common cause of blood culture negative infectious endocarditis. Bartonella species, Brucella species and Coxiella Burnetti are examples of fastidious bacteria which can cause infective endocarditis.

When obtaining the history from patients diagnosed with infective endocarditis, it is imperative to ask about their zoonotic exposure. Contact with farm animals including sheep and goats and consuming unpasteurized milk or dairy products raises the risk of Brucella and Coxiella infection. Occupational exposure to soil or farm animals is also associated with Tropheryma Whipplei infection. Prolonged contact with infected cats is associated with risk of contracting Bartonella infection. Obtaining an accurate travel history is also important as Brucella is common in many parts of the world. Immunosuppression and having cardiac devices or central intravenous access increases the risk of fungal endocarditis.

The AACEK organisms, specifically **A**ggregagatibacter aphrophilus, **A**ggregatibacter actinomycetemcomitans, **C**ardiobacterium hominis; **E**ikenella corrodens; and **K**ingella kingae, were traditionally thought to be the most common agents of culture-negative endocarditis. However, studies have found that the AACEK organisms can be isolated with current blood culture systems when incubated for at least five days. AACEK usually can cause large vegetations with a high risk of embolization but fortunately, all are susceptible to penicillin.[1]

The etiologic agents in culture-negative infective endocarditis is best identified by serology and include Coxiella burnetii, Bartonella species, Legionella species, and Brucella species.

Molecular testing of excised valve material using polymerase chain reaction (PCR)[2] is most useful in cases in which definitive microbiologic diagnosis cannot be established based on culture or serology alone. PCR is particularly useful in blood culture-negative patients with previous antibiotic exposure since bacterial DNA frequently persists even when organisms are present in quantities too low to be detected via culture.[3] The sensitivity of PCR for pathogen identification in culture-negative endocarditis ranges from forty to sixty percent. The specificity is laboratory dependent but reaches nearly 100 percent in some settings.[4]

Defining the types of culture negative endocarditis is important. Non-bacterial Thrombotic endocarditis (NBTE) also known as Marantic endocarditis or Verrucous endocarditis is characterized by sterile vegetations of fibrin and platelets on the endocardium and heart valves. It is associated with mucin-secreting adenocarcinomas and other hypercoagulable states often inherent in autoimmune disease and carries a high incidence of embolic events. It was first described by Gross et al in 1936.[5] NBTE may also be associated with sepsis, infections (such as pneumonia or pyelonephritis) or severe burns. Although malignancy is the most common underlying cause, it often also occurs in the setting of connective tissue [most commonly systemic lupus erythematosus (SLE)], autoimmune diseases and rheumatic heart disease. When associated with SLE, this is sometimes referred to as Liebman-

Sachs endocarditis. Nonbacterial thrombotic endocarditis is characterized by the high incidence of embolic events up to 42% (range 14.1%-90.9%), the most frequent ones being brain.[6]

Our patient fulfilled the criteria for probable infective endocarditis as she had one major criterion (abnormal echocardiogram) and one minor criterion (vascular phenomena in form of embolic stroke). She did not fulfill the blood culture criterion and was diagnosed with blood culture negative infective endocarditis. Her history did not suggest any specific causative organism and she denied recent antibiotic use, which may have accounted for her negative blood cultures. Serological testing including Brucella serology, Bartonella serology and Q fever serology all came back negative as did her fungal work up. As she refused valve surgery, pathology and culture from the valve lesion was not be obtained and PCR could not be performed. She received total of six weeks of intravenous ampicillin plus ceftriaxone for blood culture negative infective endocarditis. She remained asymptomatic after the treatment and repeat trans-esophageal echocardiogram after systemic anticoagulation and completion of an intravenous antibiotic regimen revealed resolution of previously visualized vegetation. In her case, underlying malignancy is the most likely precipitating cause. She was advised that she needed to be on lifelong systemic anticoagulation.

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