Infected Marantic Endocarditis With Leukemoid Reaction
– The Uncertain Role of Positron Emission Tomography/Computed Tomography –

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A 66-year-old woman presented to the emergency department with aphasia. She had been diagnosed with metastatic pancreatic cancer 1 month previously. On physical examination, significant findings included normal blood pressure, regular heart rate, normal pulses and a temperature of 37.3°C. Cranial computed tomography (CT) showed a large area of hypoattenuating tissue in the right hemisphere suggesting ischemic brain damage.

On complete blood count, total leukocyte count was 33,900/µl, with 77% neutrophils and 13% eosinophils. Hemoglobin was 12.7 g/dl, and platelet count was 250,000/mm³. Renal and liver function tests, coagulation studies, serum electrolyte, and...
Ten days later, however, she had a pulmonary embolism and a new episode of expressive aphasia and right hemianopsia. Cerebral CT showed new hypoattenuating areas in occipital lobes, and new TEE did not find any changes. At this moment, the suspicion of marantic endocarditis was high, so anticoagulation was started and positron emission tomography/CT (PET/CT) with 18F-fluorodeoxiglucose (FDG) was performed to definitively rule out inflammatory and infectious processes. There was no FDG uptake in the mitral valve nor in the microaortic continuation (Figure 1B), supporting the etiology of thrombophilic cancer-related valvulopathy instead of IE. Multiple FDG uptakes suggestive of malignancy were detected in the liver, pancreas, left adrenal gland, abdominopelvic lymph nodes, and left occipital lobe. Bilateral FDG-avid ground-glass opacities not present in the lung CT performed 5 days before were found. Given that the patient’s prognosis was terminal, she was not considered a candidate for valvular surgery.

Subsequent laboratory data showed C-reactive protein rising, and a leukocyte count of 35,000/µl with 8,000 eosinophils/µl. Additional laboratory findings showed that interleukin (IL)-1 and IL-6 were high, and procalcitonin was within normal limits. During the ensuing days, her clinical status deteriorated significantly and finally she died.

Necropsy was performed revealing large, loose, non-adher-
ent vegetation on the atrial surface of the anterior mitral leaflet, and smaller vegetation tightly adhered to the posterior leaflet (Figure 2A). Mitral leaflets were normal (Figure 2B). There were no microorganisms on the vegetation and Gram stain was negative. Histology showed that the large vegetation consisted of platelets and fibrinous aggregations with a substantial red blood cell component and scanty neutrophils (Figure 2C). In contrast, the smaller vegetation had acute valvulitis with massive infiltration of polymorphonuclear cells as typically occur in IE (Figure 2D). Huge tumoral masses were present in the liver, spleen, pancreas and adrenal gland. The lungs showed intra-arterial thrombi. Multiple ischemic infarcts without evidence of microorganisms were found in the brain.

This case demonstrates a well-known complication, non-bacterial thrombotic endocarditis (NBTE), of an advanced pancreatic adenocarcinoma. Two clinical aspects are especially relevant: the leukemoid eosinophilic reaction and the potential diagnostic value of PET/CT in NBTE.

Numerous reports have documented an association between NBTE and a variety of malignancies. Mucin-secreting adenocarcinomas, among them pancreatic carcinoma, are the most frequent. The pathogenic mechanisms of NBTE are not well-known, but the hypercoagulable state associated with these malignancies would result in the development of valvular verrucous lesions. In the present case, vegetations in NBTE are histologically characterized by an amorphous mixture of platelets, fibrin, and red blood cells. Importantly, there are neither microorganisms nor inflammation or destruction of the underlying valve leaflets. Not surprisingly, these small friable vegetations frequently embolize, involving different territories, especially the brain. Pulmonary embolism has been documented in up to 50% of patients with NBTE, due to either embolization of right-sided vegetations or, as in the present case, facilitated by a thrombophilic environment. Exceptionally, NBTE verrucous lesions may become infected, as might possibly be the case in the present patient’s smaller vegetation. This vegetation could have become infected during the course of the disease. A prolonged stressful situation could have contributed to suppressing the immune system.

Echocardiography is the technique of choice for the detection of these non-infectious vegetations. Due to their small size, TEE is more sensitive than conventional echocardiography. Echocardiographically, these lesions are indistinguishable from those of IE, but there are neither signs of valvular destruction (perforations, leaflet or chordal rupture) nor periannular complications. FDG PET/CT, recently used in patients with IE, could play a role in the differential diagnosis of IE vs. NBTE. Inflammatory cells are strongly involved in the pathogenesis of IE. FDG PET/CT is based on increased uptake of FDG by inflammatory cells located on valvular leaflets. This technique has emerged as a promising tool for diagnosing IE. In fact, some authors have suggested inclusion of abnormal FDG uptake on PET/CT as a major criterion for the diagnosis of IE due to its high sensitivity and specificity.

It is in this setting where FDG PET/CT could play an important role in the differential diagnosis of blood culture-negative infective and non-infective endocarditis, including NBTE. In the present case, the presence of vegetations on TEE and the leukemoid reaction prompted us to consider an infectious process in the differential diagnosis. This was definitely ruled out by the absence of FDG uptake on PET/CT. Surprisingly, at histology, a huge inflammatory pattern (typical of infective endocarditis) was documented in the smaller vegetation in spite of the negative PET/CT. There are several possible explanations for this. First, it could be a false-negative PET/CT in the context of a bacterial endocarditis with lower inflammatory activity. Moreover, the PET/CT could have been performed too long after antibiotic therapy initiation, when its sensitivity is lower. Finally, the infection of the vegetation after PET/CT cannot be excluded. The contribution of this technique to the diagnosis of NBTE remains to be established, however, given that the specificity for excluding IE is still unknown. Thus, more studies are needed on the value of PET/CT in IE before the establishment of definitive recommendations.

Finally, the simultaneous occurrence of an eosinophilic leukemoid reaction must be highlighted in the present case. Leukemoid reactions are usually found in response to severe infection, inflammation or therapeutic agents, but they are also a well-known paraneoplastic syndrome of some cancers such as lung carcinoma. Most reported leukemoid reactions have been myeloid, with the exception of a handful of cases of Hodgkin lymphoma, most of which involved marked eosinophilia. Eosinophilic leukemoid reactions associated with pancreatic carcinoma are extremely rare. It has been suggested that the appearance of a leukemoid reaction in patients with lung cancer is a sign of poor prognosis. The rapid and fatal course in the present patient has inclined us to think that this might also be valid for other malignancies.

Disclosures
Conflicts of Interest: None declared.

References