Pulmonic Regurgitation Due to Valvular Tophi

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SUMMARY Documented cardiac tophi are rare and have not previously been reported to cause clinically manifest valvular disease. A 31-year-old male with complex cyanotic congenital heart disease (Taussig-Bing anomaly) and secondary tophaceous gouty arthritis is described. Terminally, he presented with clinical evidence of a brain abscess and a new semilunar regurgitant murmur. Two-dimensional echocardiography suggested vegetative lesions as the cause of the murmur. The patient was treated for infective endocarditis. At autopsy, the cause of the semilunar regurgitant murmur was shown to be sterile tophi located along the line of pulmonic valvular coaptation. Tophaceous deposits were also present in the mitral valve.

ALTHOUGH clinically evident valvular heart disease may have many causes, gout has not previously been reported as one of them. Tophi are frequently observed in the periarticular tissues, skin, subcutaneous tissues and kidneys, but their presence in other anatomic sites is rare.1 Only five documented cases of macroscopic urate deposits in the heart have been reported.2-6 In each, the mitral valve was involved, but clinically manifest valvular disease attributable to the tophi was not described. The unique aspect of the present case was the occurrence of cardiac semilunar leaflet tophi leading to a regurgitant murmur.

Case Report

The patient was a 31-year-old white male who was cyanotic at birth. He was cyanotic when evaluated by physicians at Johns Hopkins University at 7 years of age. At age 15 years, he presented to Children’s Hospital of Pittsburgh with hemoptysis. Physical examination disclosed gross central cyanosis and digital clubbing. A grade II/VI systolic murmur was present at the upper left sternal border, but no diastolic murmur was audible. There were no tophi or joint abnormalities. The hematocrit was greater than 70% and the arterial PO2 was 32 mm Hg. Cardiac catheterization confirmed the presence of a double-outlet right ventricle (Taussig-Bing type) with Eisenmenger’s physiology.

He was lost to follow-up until 29 years of age, when he presented to another hospital with a draining tophus of the right thumb. His serum uric acid was 12.4 mg/dl. A grade II/VI systolic murmur was described, but no diastolic murmur was found. At age 30 years, he was admitted to the hospital because of rectal bleeding, and again, no diastolic murmur was heard by the examining cardiologist.

Eleven months later, the patient developed gingival abscesses and was placed on erythromycin. During the next 2 weeks, he became intermittently confused and stuporous. On admission to his local hospital, he had a temperature of 39.4°C and a new diastolic murmur was present. The patient was begun on i.v. antibiotics; two blood cultures before the institution of therapy showed no growth. During the next 2 days, he had grand mal seizures beginning on the right side.

The patient was transferred to Presbyterian-University Hospital, where physical examination revealed a temperature of 37.2°C, marked peripheral and central cyanosis, 4 + digital clubbing and tophi over the interphalangeal joints of the left hand, right thumb, olecranon bursae and external ear. A grade II/VI basal systolic ejection murmur radiated to the carotids; a grade III/VI early decrescendo blowing murmur was audible along the left sternal border, lasting two-thirds of diastole and radiating to the apex. The liver and spleen were firm and palpable 8 cm and 6 cm below their respective costal margins. He was oriented to person only; a central left seventh cranial nerve paresis and bilateral Babinski signs were present. Laboratory data disclosed a hemocrit of 67%, leukocyte and platelet counts of 8500 and 20,000/mm3, respectively, an arterial PO2 of 31 mm Hg and a uric acid of 15.2 mg/dl. A spinal tap yielded clear fluid that was unremarkable on laboratory examination. Two-dimensional echocardiography disclosed dense echoes in the region of a semilunar valve.

The patient was begun on chloramphenicol, gentamicin and cefazolin as empiric therapy for presumed endocarditis with a brain abscess. A CAT scan subsequently demonstrated a contrast-enhanced ring lesion in the left temporal region consistent with such an abscess. Renal insufficiency supervened associated with development of anemia and a further fall in platelet count. On the seventh hospital day, the patient developed erythema, swelling and pain in the right knee; arthrocentesis revealed class II fluid and intracellular crystals consistent with monosodium urate. His tenuous hematologic, renal and cardiac status was felt to preclude a surgical approach to the brain abscess. He developed aspiration pneumonia and died after profound pulmonary and gastrointestinal bleeding.

At autopsy, the heart weighed 650 g and showed the typical anatomic features of the Taussig-Bing anomaly. The aortic valve was normal. There were several firm, irregular, opaque white vegetations, 0.5-0.7 cm in diameter, on the free edges of the pulmonic valve cusps and within the subpulmonic endocardium and superficial myocardium (fig. 1). The anterior and posterior mitral valve leaflets each contained single similar nodules measuring 0.6 cm and 0.5 cm, respectively, adjacent to their free edges (fig. 2). In formalin-fixed, paraffin-embedded sections stained with hema-toxylin-eosin, the vegetations consisted of fibrillar
eosinophilic material surrounded by granulation tissue containing foreign body giant cells (fig. 3). Under polarized light, focal deposits of birefringent material were evident in the centers of the vegetations. Compensated polarized light microscopy of crushed material taken from unstained sections of these areas demonstrated negatively birefringent crystals, and treatment with uricase digested portions of the deposits. The limitation of the deposits to the lesion centers was attributed to formalin fixation, which leaches out urate crystals. There were scattered foci of peripheral calcification in sections of vegetations from both valves, but apart from the areas containing tophi, the valves were histologically normal and there were no areas of isolated calcification. Further chemical analysis of the lesions was hampered by fixation of the heart in 10% formalin before cutting; a small (1-mm) sample of the periphery of one of the pulmonic valve vegetations analyzed by infrared spectrophotometry (Reference Laboratory) contained only carbonate-apatite. No areas of acute inflammation were present in the valvular lesions and both cultures and stains for organisms were negative. Additional findings at autopsy included urate granulomata in both kidneys, a left temporal lobe brain abscess, congestive splenomegaly, and severe changes of pulmonary hypertension.

Discussion

In 1940, Bunim and McEwen reported the first histologically documented case of gross cardiac urate deposition. This patient had long-standing tophaceous gouty arthritis of primary origin and no cardiac murmurs were audible during life. A sharply circumscribed concretion in the posterior mitral leaflet was found at autopsy. There were typical histologic features of a tophus, consisting of amorphous eosinophilic material surrounded by granulation tissue containing multinucleated giant cells. Qualitative chemical analysis of this material disclosed no calcium. The authors argued that a previous report by Coupland in 1873, which purported to demonstrate tophi in a calcified aortic valve based on a positive murexide test, merely represented incidental urate deposition in an old calcareous deposit.

Three additional cases of cardiac valvular tophi with histologic documentation have since been reported. In each case, tophaceous gouty arthritis of primary origin and mitral valve tophi were present. In two cases, a mitral regurgitant murmur was audible during life, but the regurgitation was due to causes other than the valvular urate deposition.

In the present case, hyperuricemia was due to the polycythemia associated with long-standing cyanotic congenital heart disease. The unusual aspect of this case was the presence of pulmonary valvular tophi along the line of coaptation producing a clinically evident murmur compatible with semilunar regurgitation. Echocardiographic findings suggested vegetative lesions as opposed to valvular ectasia as the cause of the murmur. Despite the rare association between relatively large, isolated, brain abscesses in cyanotic congenital heart disease and infective endocarditis, the last was assumed to explain the echocardiographic findings.

The tophi in both the mitral and pulmonic valves
contained calcium in addition to urate deposits. The presence of typical histologic features of a tophus precludes "incidental" urate deposition in a calcific accretion, as suggested by Bunim and McEwen. Our patient's course represented an unusually long survival for the Taussig-Bing anomaly with an Eisenmenger reaction. Although calcification of the pulmonic valve is rare in the absence of pulmonic stenosis, the long-standing pulmonary hypertension may have resulted in hemodynamic valvular trauma followed by calcium deposition and, subsequently, tophus formation. However, except for the tophaceous areas, there was no calcium deposition in the pulmonic valve. Indeed, one can speculate that valvular trauma, in the setting of sustained hyperuricemia, was instrumental in tophus formation at this unusual site. In addition, tophi with minimal associated calcification were observed in the mitral leaflets at sites that could not be attributed to hemodynamic trauma. Therefore, it is likely that the tophi were primary lesions with subsequent dystrophic calcification. However, the alteration in compliance of the tophi produced by the calcification may have been fundamental in production of the clinically manifest pulmonic regurgitation.

References
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