Fever and a New Heart Murmur

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A 43-year-old male stockbroker presented with fever and general malaise. Two weeks prior to admission, he began to experience night sweats and fatigue, in addition to fever ranging from 38.6˚C to 39.1˚C. He denied any nausea, vomiting, cough, rigors, or headache.

History revealed that the patient had rheumatic fever as a child, and had an aortic valve replacement six months ago due to calcified valve leaflets. The aortic valve was replaced with a mechanical prosthetic valve and no post-operative complications were noted. He was on a 5 mg daily dose of warfarin to maintain an international normalized ratio of 2.0 to 3.0.

Physical examination revealed a temperature of 38.8˚C, a pulse of 114 beats per minute, blood pressure of 120/80 mmHg, and a respiratory rate of 15 breaths per minute. A grade III/VI high-pitched, systolic murmur radiating towards the neck was heard over the upper right sternal border. Paradoxical splitting of the S_2 heart sound was also present and was best heard over the upper left sternal border. No other abnormalities were present on physical examination.

Laboratory values revealed white blood cell count of 18,000/mm^3, erythrocyte sedimentation rate (ESR) of 30 mm/hr and elevated C-reactive protein. All other values were normal. He subsequently underwent transthoracic echocardiography which uncovered an annular abscess surrounding the aortic valve accompanied by a prominent perivalvular leak.

What's Your Diagnosis?

Prosthetic valve endocarditis (PVE) is characterized by any infection of a mechanical or biological valve prosthesis. PVE comprises 10% to 20% of endocarditis cases and afflicts 2% to 4% of patients with prosthetic valves. PVE develops in 2% to 3% of patients within one year of surgery and has a constant risk of 0.5% per year thereafter. Mortality occurs in about 50% of PVE cases. During the first six months following surgery, mechanical valves carry a greater risk of infection than bioprosthetic valves. Aortic valves are more typically affected than mitral valves.

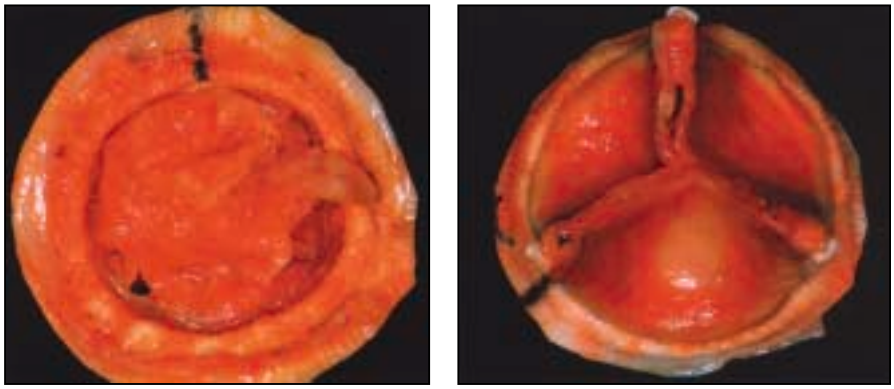

Figure 1. Thrombotic vegetations and thin thrombi covering an Ionescu-Shirley prosthetic mitral valve. Used with kind permission of Willerson JT, Cohn JN, McAllister HA, et al: Atlas of Valvular Heart Disease: Clinical and Pathologic Aspects. Churchill Livingston, New York, 1998, p. 163, Figures 246-247.

How is PVE classified?

PVE is classified into early (< 60 days post-operatively) and late (> 60 days post-operatively) onset. Although a plethora of organisms cause PVE, early PVE is often initiated by staphylococci, while late disease is commonly found with streptococcal species. Streptococcal PVE often resembles native valve endocarditis (NVE).

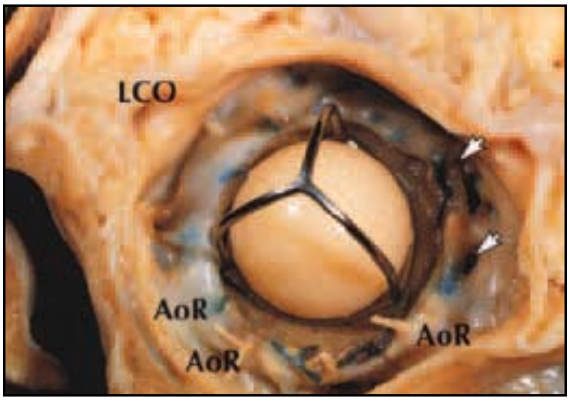

Figure 2. Perivalvular leaks (arrows) around a Starr-Edwards mechanical prosthetic aortic valve. Used with kind permission of Rahimtoola SH: Atlas of Heart Diseases, Volume XI: Valvular Heart Disease. Current Medicine, Philadelphia, 1997, p. 1.30, Figure 1-59A.

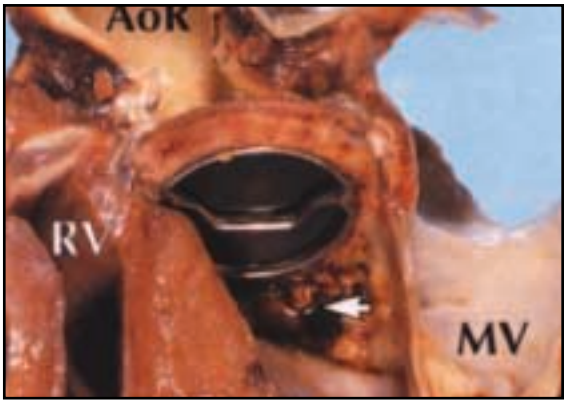

Figure 3. Ring abscess (arrow) posterior to a Bjork-Shiley valve in the aortic position. Used with kind permission of Rahimtoola SH: Atlas of Heart Diseases Volume XI: Valvular Heart Disease. Current Medicine, Philadelphia, p. 1.30, Figure 1-57A.

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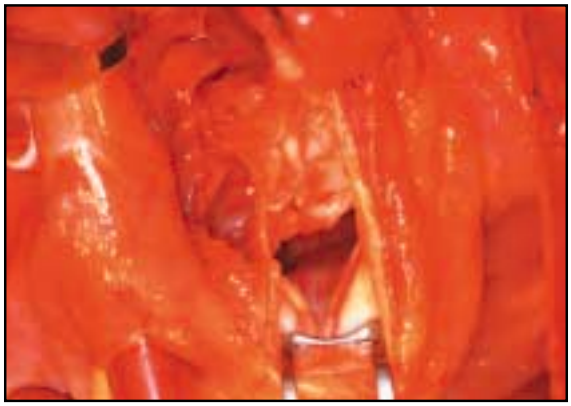

Figure 4: Ring abscess (arrow) posterior to a Bjork-Shiley valve in the aortic position. Used with kind permission of Willerson JT, Cohn JN, McAllister HA, et al: Atlas of Valvular Heart Disease: Clinical and Pathologic Aspects. Churchill Livingstone, New York, 1998, p. 120, Figure 176.

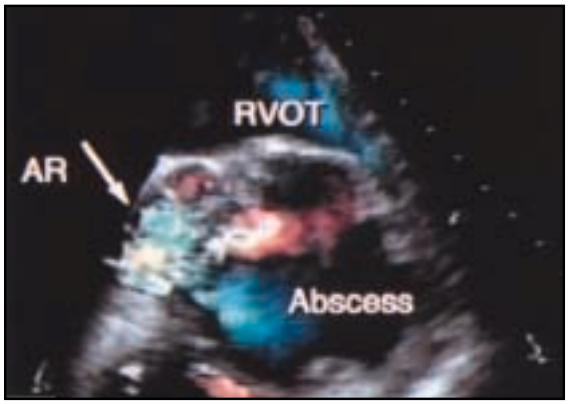

Figure 5. Diastolic frame showing regurgitation and flow into an abscess. [AR = aortic regurgitation; RVOT = right ventricular outflow tract.] Used with kind permission of Rahimtoola SH: Atlas of Heart Diseases Volume XI: Valvular Heart Disease. Current Medicine, Philadelphia, p. 3.25, Figure 3-50C.

How does PVE develop?

Pathophysiology varies considerably between bioprosthetic and mechanical valve prostheses. In both cases, the characteristic endocardial lesion is a non-bacterial thrombotic vegetation (NBTV). This sterile constellation of platelets and fibrin can be colonized during transient bacteraemia and can shield microorganisms from antimicrobial agents and phagocytic cells (Figure 1). However, while bioprosthetic valves often harbour

Table 1
Common Manifestations of Endocarditis

Clinical Findings	Laboratory Findings
Fever	Anemia
Weight loss	Elevated erythrocyte
Arthralgia or myalgia	Sedimentation rate
Murmur	Rheumatoid factor
Petechiae	Elevated C-reactive protein
Roth's spots	Proteinuria
Osler's nodes	Microscopic hematuria
Janeway lesions	Leukocytosis
Clubbing	Circulating immune complexes
Emboli	Decreased serum complement
Splenomegaly	Level
Neurologic symptoms	

vegetations on valve cusps directly, mechanical valve infections typically originate from the sewing cuff or from thrombi located in areas adjacent to the sewing ring where blood pools. Subsequent periprosthetic leaks and ring abscesses often result (Figures 2 to 4). Intravascular sutures and pacemaker wires may also be foci of infection.

How to diagnose

Clinical diagnosis of PVE is based on a cluster of clinical

Table 2
American Heart Association Cardiac Conditions and Endocarditis Prophylaxis (EP) Recommendations

EP Recommended

High-Risk Category

- Prosthetic cardiac valves, including bioprosthetic and homograft valves
- Previous bacterial endocarditis
- Complex cyanotic congenital heart disease (*i.e.,* single ventricle states, transposition of the great arteries, tetralogy of Fallot)
- Surgically constructed systemic-pulmonary shunts or conduits

Moderate-Risk Category

- Congenital cardiac malformations other than those listed in the high-risk category
- Acquired valvular dysfunction (*i.e.,* rheumatic heart disease)
- Hypertrophic cardiomyopathy
- Mitral valve prolapse with valvular regurgitation and/or thickened leaflets

EP Not Recommended

Negligible-Risk category

- Isolated secundum atrial septal defect
- Surgical repair of atrial septal defect, ventricular septal defect or patent ductus arteriosus (without residual beyond six months)
- Previous coronary artery bypass graft surgery
- Mitral valve prolapse without valvular regurgitation
- Physiologic, functional or innocent heart murmur
- Previous Kawasaki disease without valvular dysfunction
- Previous rheumatic fever without valvular dysfunction
- Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators

signs and symptoms, as well as histologic and echocardiographic valvular and perivalvular evaluations.

Duke University Medical Centre has proposed criteria for clinical diagnosis of infective endocarditis, including histological and echocardiographic findings. The most prevalent clinical findings are fever, and a changing or new heart murmur. Other less typical manifestations of PVE are found in Table 1.

Many clinical expressions of endocarditis occur as a result of embolic phenomena that result from thrombotic vegetations that break away from the valvular surface and cause local hemorrhage, including Janeway lesions, Roth spots, Osler's nodes, and splinter hemorrhages.

Other hematologic sequela of late PVE include a normochromic normocytic anemia, leucocytosis, circulating immune complexes, an elevated ESR, and an elevated level of C-reactive protein. Although no diagnostic features appear on chest X-ray or electrocardiogram (ECG), patients with aortic valve endocarditis should be assessed daily for any prominent new rhythm disturbances seen on ECG. With the weakest part of the annulus situated near the membranous septum and the atrioventricular node, expansion of an aortic infection to flanking tissues may be discerned as a new heart block, as in this case.

A rapid and accurate microbiological assessment, including minimal inhibitory (MIC) and minimal bactericidal concentrations (MBC), is critical to determining an appropriate combination of antibiotic treatment. Although six sets of blood cultures are traditionally taken, PVE can be reliably diag-

nosed with two or more positive cultures for the same organism.

Echocardiography is the diagnostic tool of greatest benefit. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) detect vegetations as small as 2-3 mm and 1-1.5 mm respectively. TEE, with a superior sensitivity and specificity for detecting vegetations and abscesses to TTE, is ideal for imaging perivalvular injury, the atrial side of the valve and the aortic root (Figure 5). Unfortunately, mechanical valves are strongly echogenic and acoustic reverberations may prevent detection of abnormalities.

What is the treatment?

Treatment of PVE is based on appropriate antibiotic therapy balanced with surgical management of mechanical complications. PVE is generally treated with either penicillin G (18-30 million units per day intravenously [IV]) or vancomycin (15 mg/kg IV every 12 hours) for six weeks accompanied by gentamycin (1 mg/kg IV every 8 hours) for at least the first two weeks. Antibiotic therapy should be withheld until microbiology results are confirmed unless the patient is seriously ill. All antibiotic therapy should be administered parenterally to permit adequate absorption. Specific to patients with mechanical valve prostheses, oral anticoagulation therapy should immediately be suspended and intravenous heparin instituted. Successful treatment is detected by negative blood cultures for five to seven days and a reduction in fever.

Surgical valve replacement should be considered if bactericidal therapy is unavailable, positive blood cultures persist following antibiotic treatment, or when infection relapse occurs after therapy. Immediate valve replacement is indicated in patients with heart failure secondary to severe valvular regurgitation, uncontrolled sepsis, new heart block or to drain myocardial or valve-ring abscesses.

How is it prevented?

All patients with prosthetic valves and patients at risk for endocarditis should receive appropriate antibiotic prophylaxis for invasive procedures with a risk of transient bacteraemia. These include dental and periodontal procedures, respiratory, genitourinary and gastrointestinal procedures and obstetrical or gynecologic procedures. All prophylactic antibiotic administration is directed against organisms endogenous to the investigated area. The American Heart Association has developed clinical guidelines for the prevention of PVE (Table 2).

In conclusion...

Late PVE is a major source of mortality and morbidity and attention must be granted to its early diagnosis and prophylaxis. Following diagnosis, prompt and appropriate bactericidal treatments, as well as judiciously chosen surgical interventions, underlie successful therapy.