Infective endocarditis with left to right intracardiac fistula due to Streptococcus anginosus - a rare complication caused by an even rarer bacterium
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ABSTRACT

Although infective endocarditis (IE) has been described in reports dating from the Renaissance, the diagnosis still challenges and the outcome often surprises. In the course of time, diagnostic criteria have been updated and validated to reduce misdiagnosis. Some risk factors and epidemiology have shown dynamic changes since degenerative valvular disease became more predominant in developed countries, and the mean age of the affected population increased. Despite streptococci have been being well known as etiologic agents, some groups, although rare, have been increasingly reported (e.g., \textit{Streptococcus milleri}.) Intracardiac complications of IE are common and have a worse prognosis, frequently requiring surgical treatment. We report a case of a middle-aged diabetic man who presented with prolonged fever, weight loss, and ultimately severe dyspnea. IE was diagnosed based on a new valvular regurgitation murmur, a positive blood culture for \textit{Streptococcus anginosus}, an echocardiographic finding of an aortic valve vegetation, fever, and pulmonary thromboembolism. Despite an appropriate antibiotic regimen, the patient died. Autopsy findings showed vegetation attached to a bicuspid aortic valve with an associated septal abscess and left ventricle and aortic root fistula connecting with the pulmonary artery. A large thrombus was adherent to the pulmonary artery trunk and a pulmonary septic thromboemboli were also identified.

Keywords: Endocarditis; Bicuspid Aortic Valve; \textit{Streptococcus anginosus}; Aorta-pulmonary artery fistula; Pulmonary Embolism; Autopsy.

CASE REPORT

A 56-year-old male had a 2-month history of recurrent low-grade fever, occasional chills, cough, and progressive shortness of breath. He also described malaise and loss of appetite with an 8 kg weight loss over the 2 last months. A few days before presentation to the emergency unit, his temperature rose to 39 °C and he had shaking, chills, and diaphoresis. Dyspnea supervened. He had been
treated with a 7-day regimen of levofloxacin and antipyretics for a presumed diagnosis of pneumonia, and studies for tuberculosis were initiated. There was a mild and temporary relief of symptoms. Past medical history included hypertension, uncontrolled type II diabetes mellitus, asthma, and smoking. The patient was unaware of previous heart disease. Approximately 2 months before the onset of symptoms, the patient underwent dental root canal treatment. On admission showed an ill-appearing, obese (111.5 kg body weight) patient, was conscious and febrile (39.5 °C axillary temperature). Blood pressure was 140/60 mmHg, pulse 112 per minute, respiratory rate 44 per minute. With room air oxygen saturation was 69%. Diffuse expiratory wheezing and bilateral rales were present. The remainder of the examination was unremarkable except for mild lower limb edema. Capillary glucose determination was 330 mg/dL; other laboratory test results were unremarkable. Thoracic plain radiography demonstrated expressive pulmonary congestion and an apparently normal heart silhouette. The ECG showed sinus tachycardia without signs of ischemia, conduction block, or QRS axis deviation.

The diagnosis of sepsis due to pulmonary infection was made and treatment with ceftriaxone plus clarithromycin and non-invasive respiratory support was started. Episodes of sudden respiratory worsening ensued, and the appearance of a diastolic parasternal murmur was detected. On hospital day three, blood cultures grew Gram-positive cocci, subsequently identified as *Streptococcus anginosus* (microbial identification system VITEK® 2 Compact, bioMerieux). Doppler echocardiography showed enlarged left cardiac chambers, left ventricle hypertrophy, left ventricle ejection fraction of 71%, and a thickened aortic valve with a vegetation as well as mild to moderate aortic insufficiency. Thoracic computed tomography (CT) showed diffuse and bilateral ground-glass opacities, pulmonary parenchyma consolidation, and interlobular septa thickening.

Figure 1 – Multidetector computed tomography (CT) of the thorax with coronal reconstruction showing diffuse bilateral ground-glass opacities, pulmonary parenchyma consolidation, and interlobular septa thickening.

![Figure 1](image)

Figure 2 – Multidetector CT of the thorax. **A** – Coronal reformation. The presence of filling defects in the upper lobar and interlobar branches of the right pulmonary artery is evident (arrows); **B** – The axial plane showing filling defects in the trunk (yellow arrow) and right pulmonary artery branches (white arrow).
opacity suggestive of pulmonary parenchyma consolidation with interlobular septa thickening (Figure 1). Laminar atelectasis in both lung bases and mediastinal lymphadenomegaly were present.

Intraluminal filling defects of the pulmonary artery trunk, and of the segmental and subsegmental branches of the right pulmonary artery were detected (Figure 2). In the sagittal reconstruction, a filling defect communicating the aortic root and the pulmonary artery trunk was observed (Figure 3).

Abdominal imaging showed an enlarged spleen with peripheral wedge-shaped hypo-enhancing images in the spleen indicative of multiple infarctions (Figure 4).

The antibiotic regimen was changed to penicillin and gentamycin, but the patient died soon after due to complete atrioventricular (AV) block followed by AV dissociation and asystole, unresponsive to advanced cardiovascular life support maneuvers.

**AUTOPSY FINDINGS**

The external examination was unremarkable except for obesity.

The brain weighed 1398 g (reference value (RV): 1400 g) and showed an 8.0 long cm right temporo-parietal superficial hemorrhagic area, which, on section surface, was limited to the subdural space and meningeal surface.
Mild bilateral pleural serosanguineous effusion was present. The lungs were congested with increased volume and weight. The right lung weighed 1240 g (RV: 350-450 g) and the left weighed 927 g (RV: 250-350 g). A subpleural peripheral yellowish wedge-shaped infarct was present in the right lung, confirmed microscopically to be an ischemic infarction with pulmonary parenchyma necrosis (Figures 5A and 5B). Multiple thromboemboli of segmental branches were present in the pulmonary artery system (Figure 5C). Both the infarction and the thrombi showed Gram-positive cocci (Brown-Hopps modified Gram method) (Figure 5D). Many alveolar spaces were filled with polymorphonuclear leukocytes and fibrin and surrounded by areas of organization as well as pulmonary edema.

The heart weighed 477 g (RV: 350g). A firm white 1.5 cm yellow and friable vegetation was attached to a bicuspid aortic valve (Figures 6B and 7A) with an adjacent septal abscess, a subvalvar opening orifice in the left ventricle and a cleft-shaped fistula connecting the aortic root with the right posterior sinus of the pulmonary valve and the pulmonary artery trunk were found (Figures 6A and 6D; 8A and 8B, 9A and 9B). The left-to-right heart fistulous path was partially obliterated by a large 3.0 cm thrombus adherent to the pulmonary valve cusp (Figures 6A and C). The histologic examination of the aortic valve vegetation (Figures 7B and 7C) and the thrombus into the pulmonary valve cusp showed many Gram-positive coci (Figure 7D).

The spleen was greatly enlarged (721 g; RV: 150 g), and was soft with scattered small, yellowish nodules throughout the parenchyma and a larger area of necrosis. The liver was congested and weighed 2880 g (RV: 1500 g). On microscopy, congestion and moderate macrovesicular steatosis were observed. Both kidneys were enlarged, and showed acute tubular necrosis. The remaining organs and tissues did not have significant alterations.

Figure 5 – Photomicrography of the lung. A – Ischemic infarction with necrosis of the pulmonary parenchyma (HE, 10X); B – The ischemic area of the lung with evidence of Gram-positive cocci by Brown-Hopps staining (BH, 4X); C – Thromboembolism of the pulmonary artery subsegmental branches (HE, 10X); D – The presence of Gram-positive cocci into the thrombosed pulmonary blood vessels (BH, 10X).
Figure 6 – Gross view of the opened right (A) and left (B) ventricular outflow tracts. A shows a large 3.0 cm thrombus filling the right posterior sinus of the pulmonary valve, partially obliterating the left-to-right heart fistulous path (white arrow); In B note the vegetation on the distorted but originally bicuspid aortic valve (white arrow), the cleft-shaped organizing fistula connecting the aortic root with the pulmonary valve (black arrow), and the orifice of the fistula opening in the left ventricle, below the valve (arrow head); C – Photomicrography of the organizing pulmonary valve cusp thrombus with granulation tissue (HE, 20X); D – Photomicrography of the cleft-shaped organizing fistula (black arrow) (HE, 4X).

Figure 7 – A – Photomicrography of the aortic valve vegetation (HE, 1.25X); B and C – The presence of Gram-positive cocci by Brown-Hopps staining (BH, 1.25X, in B) (BH, 40X in C); D – Photomicrography of the pulmonary valve cusp thrombus with Gram-positive cocci (BH, 20X).
Sir William Osler gave the Gulstonian Lecture, calling the entity “malignant endocarditis.”

Due to its variable clinical presentation, the diagnosis of IE often requires a high index of suspicion. Over time, diagnostic criteria have been validated and updated. In 1994, investigators at Duke University (Durham, NC, USA) modified the previously used von Reyn criteria to include
echocardiography data and intravenous drug abusers. The “Duke criteria,” are now widely used for diagnosis. More recently, it received the amendment of positive serology for Q-fever among the major criterion.

The incidence of IE is steadily increasing, affecting as many as 12.7 persons per 100,000 per year. The mean age is 60.8 years. The most important risk factors include prosthetic heart valves, intracardiac devices, congenital heart disease, valvular heart disease, and a previous history of IE. While degenerative valve disease, prosthetic valves, and invasive procedures became the most frequent predisposing factors for IE in developed countries, rheumatic valvular disease still remains the predominant factor in developing countries. Other risk factors include hemodialysis, and coexisting conditions, such as diabetes mellitus, HIV infection, and intravenous drug use. Diabetes mellitus is not only associated with the increased prevalence of non-rheumatic aortic valve disease, and therefore constitutes a risk factor for IE development, but also is associated with a worse clinical course and outcome. In one institutional series of native valve endocarditis, bicuspid aortic valve (BAV) was the most important cardiac predisposing factor for IE. BAV was detected at autopsy in our patient and represents a frequent congenital heart anomaly, affecting 1–2% of the population. It may be inherited in an autosomal dominant pattern occurring sporadically and is not only associated with aortic stenosis or regurgitation, but also represents an important risk factor for IE.

Streptococci are the second most frequently involved etiological agents in IE, which are only surpassed by Staphylococcus aureus. In our case, the isolated pathogen was S. anginosus, which belongs to the Streptococcus milleri (S. milleri) group. Despite their close phylogenetic relationships with the other viridans streptococci, the clinical disease spectrum caused by members of the S. milleri group is different from that caused by other viridans streptococci, since they are more prone to abscess formation. In 1984, revising the nomenclature, Facklam divided the group of S. milleri into three species: S. intermedius, S. constellatus, and S. anginosus. The latter pertains to Lancefield groups F, A, C, and G, and the existence of some ungroupable strains. S. milleri is considered a part of the resident flora of the oral cavity and upper respiratory tract. The gastrointestinal tract and urogenital system may also harbor these bacteria but are less commonly colonized. In the mouth, S. milleri seems to have predilection for the gingival crevice and the fitting surface of dentures; therefore, it is associated with periodontal diseases such as gingivitis, periodontitis, and odontogenic abscesses. The latter was probably the source of the bacteraemia in our case.

Transient bacteremia is common and unsuspected in many cases and may follow vigorous tooth brushing. S. milleri bacteremia has been frequently documented after dental extraction or manipulation. Our patient underwent a root canal treatment, which was most probably the triggering event. IE by S. milleri is infrequent, compared with other streptococci, and accounts for 4-15% of the cases of α-hemolytic streptococcal endocarditis. S. milleri has been previously implicated in cases of myocardial abscess associated with endocarditis. In a series of six cases of S. milleri endocarditis, all were caused by S. anginosus. Of the S. milleri group, S. anginosus seems to be the most frequently implicated as being the causative agent of IE. Bacteraemia also follows invasion of portal circulation by intestinal flora, often, in older individuals, by transient, subclinical intestinal ischemia.

Normal endothelium of the heart and its valves are resistant to colonization and infection by circulating bacteria. This is supported by the high frequency of bacteremia as opposed to the relatively low frequency of IE. As a reminder, bacteremia can occur not only as a result of invasive procedures, but also after daily events, such as chewing or tooth brushing. Endothelial disruption due to factors such as turbulent blood flow, inflammation, degenerative changes, or catheters and electrodes, can expose the tissue matrix, leading to platelet adherence and fibrin deposition. The resultant micro ulcers and micro thrombi predispose to bacterial adherence and infection. In our patient, the bicuspid valve and consequent abnormal leafllet function and motion likely led to turbulent blood flow and fibrin deposition which then served as a nidus for secondary infection.

Fever and malaise are the most frequent sign and symptom of native-valve endocarditis. In a series of 50 patients with bicuspid valve endocarditis, the next most frequent sign was the presence of a heart murmur (60% of cases), which was regurgitant in 50% of cases. Other frequent symptoms/signs were night-sweats and weight loss, which occurred in more than one-quarter of patients. Dyspnea occurred in 36% of cases, a change in mentation in 22%, and anorexia in 18%.
More than 10% of patients had myalgia, dry cough, diarrhea or vomiting, splenomegaly, chest pain, a non-specific vascular phenomena—such as rashes, splinters, or petechiae—arthralgia, and/or chills.11 Our patient presented with weight loss, dyspnea, anorexia, myalgia, dry cough, and chills. The lack of specificity of these symptoms may explain the delayed diagnosis. A high degree of suspicion for IE is warranted in febrile illnesses with non-specific symptoms.

IE is associated with many non-cardiac as well as cardiac complications. Non-cardiac complications include neurologic complications occurring in 20-40% of IE patients, septic emboli, mycotic aneurysms, immune complex related vascular damage, such as in glomerulonephritis and splenic abscess.22 Cardiac complications are represented by hemodynamic disturbance due to valve dysfunction and/or myocardial abscess, which may result in fistula development with or without conduction abnormalities. In a series of 238 patients, more than 50% suffered from one complication, 25% suffered from two complications, and approximately 8% suffered from three or more complications.23 Although patients with a bicuspid aortic valve may be completely asymptomatic, the association of this condition with aortic stenosis, aortic regurgitation, and IE has been known for almost 150 years.12,24 Clinical diagnosis of this condition was unsatisfactory before the widespread use of cross-sectional echocardiography, approximately 25 years ago,12 but it may still pose a diagnostic challenge. In a series of cases over a 30-year span, echocardiograms that were performed preoperatively showed a sensitivity as low as 35% for BAV. This rate is improving with modern echo-imaging techniques.11 Aortic valve endocarditis can be complicated by periannular extension and abscess formation,25 which as many as 50% of cases.11,26 Increasing patient age and fistulization of the abscess have been previously found to be independent risk factors in both 1-month mortality and overall operative mortality.27

Aortic perivalvular abscesses are associated with first-, second-, and third-degree heart block. High-grade AV block occurred in 10% of cases of IE in a series of aortic perivalvular abscess.27 Additionally, in a large cohort of patients with native aortic valve IE (bicuspid or tricuspid) with perivalvular complications, aorto-cavitary fistula formation was associated with a higher incidence of third-degree heart block (11% vs. 4%, p = 0.07) and moderate to severe heart failure (67% vs. 52%, p = 0.07) compared with unruptured periannular abscess cases.28 In the present case, complete AV block developed as a final event, suggesting that the abscess, until that stage, had not involved the conduction system.

Myocardial abscess is a potential complication of IE and may develop as a consequence a perivalvular infection or as a result of septic coronary emboli. Similar to fistula formation, it represents a class I, level B indication for urgent surgical intervention.22

An aorto-pulmonary fistula in left-sided IE due to S. aureus in a HIV-positive patient and IV drug user was previously reported.29 Septal myocardial abscess leading to later rupture and formation of a fistula to the pulmonary artery, was described in a 12-month-old child after surgical drainage of a leg abscess. S. aureus was isolated in blood cultures.30

To the best of our knowledge this is the first case report of a fistula involving the left ventricle, aorta, and the pulmonary artery due to S. anginosus IE in an adult patient. In our patient, the perivalvar and interventricular abscess and the fistula connected to the pulmonary trunk was somewhat capped by the pulmonary thrombus. The rapid clinical deterioration, manifested as respiratory insufficiency, was most likely due to the opening of the fistula into the pulmonary artery tree, with consequent overflow and pulmonary edema. Moreover, the giant thrombus attached to the endothelial surface of the pulmonary trunk was the source of subsequent septic embolization to the lungs, which worsened the clinical picture.

CONCLUSION

Unfortunately, the diagnosis of IE was missed at the very beginning of this case when specific antibiotics might have prevented this disastrous outcome. The diagnosis of IE often requires a high index of suspicion. A prolonged history of fever and weight loss in a diabetic patient should strongly suggest IE and all efforts should be made to establish the diagnosis. The history of a recent dental procedure certainly should have raised the possibility of IE. Autopsy findings clarified the pathophysiology of this case, and provided further emphasis for the importance of autopsy in the modern era. We should recall the words of William Osler, the father of modern medicine: “Listen to your patient, he is telling you the diagnosis.”
REFERENCES


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