A Rare Case of Group A Streptococcal Endocarditis with Absence of Valvular Vegetation

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Abstract

Group A streptococcal endocarditis has been described in intravenous drug misusers and as a post-varicella infection in children.

We report a 64-year-old man with no prior risk factors who presented with a persistent fever, malaise, polyuria and cola-colored urine. On examination peripheral stigmata of endocarditis without a cardiac murmur and asymptomatic pharyngeal exudates were found. Blood and urine analysis revealed renal failure from suspected glomerulonephritis. Blood cultures revealed fully sensitive Group A streptococci. Transthoracic and transesophageal echocardiographies revealed no vegetation. The Modified Duke’s Criteria aided in the diagnosis of definite infective endocarditis, despite the absence of valvular vegetation.

Key words: Streptococcal, endocarditis, anticoagulation, glomerulonephritis, embolic


Introduction

The diagnosis of infective endocarditis (IE) hinges on the use of the Modified Duke’s Criteria. Transesophageal echocardiography can sometimes fail to identify a valvular vegetation, which can potentially cause diagnostic confusion if there is absence of other features, such as peripheral signs of this disease. We present a man with Group A streptococcal endocarditis with an absent valvular vegetation in which the diagnosis was based on a combination of detailed physical examination, several minor criteria, and positive blood cultures for the organism, a major criterion. This case report reaffirms that the use of the Modified Duke’s Criteria remains central to the diagnosis of infective endocarditis and that physical examination can still be diagnostically revealing despite advances in modern technology with our attendant reliance on it.

Case Report

A 64-year-old Japanese man was admitted to this hospital with persistent fever, malaise, polyuria and cola-colored urine.

He had presented to our emergency department three days earlier where a presumptive diagnosis of a urinary tract infection was based on the symptoms of malaise and polyuria with supportive urinalysis. No gram stain or culture was submitted. He received a 2-gram single dose of intravenous ceftriaxone followed by a 300 mg total daily dose of oral levofloxacin to continue as an outpatient. On the day of admission, he was reviewed in the emergency outpatient clinic, at which time, he had persistent symptoms and his urine had turned a dark cola-color. He was admitted for further investigation and treatment.

The patient denied all common risk factors associated with IE including recent dental treatment, previous rheumatic fever, intravenous drug misuse or existing valvular disease.

He had a history of atrial fibrillation, hypertension, diabetes mellitus, variant angina and an upper gastrointestinal hemorrhage, the latter that had occurred several years previously.

Medications included: aspirin 100 mg/day, warfarin 1.5 mg/day, carvedilol 20 mg/day, amlodipine 5 mg/day and valsartan 80 mg/day.

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Figure 1. Several splinter hemorrhages are evident in the peripheral nail bed.

Figure 2. Multiple small Janeway lesions can be seen on the plantar surface of the right foot.

Figure 3. A larger Janeway lesion is evident on the heel area of the right foot.

Figure 4. Multiple white exudates present on the posterior pharynx. The background mucosa appears erythematous from inflammation caused by infection.

On examination, the patient appeared well but had a pyrexia of 39.3°C. Blood pressure was 124/70 mmHg and heart rate was irregularly irregular at 84 beats per minute. Respiratory rate was 18 per minute with pulse oximetry of 98% breathing ambient room air.

Nail examination revealed several splinter hemorrhages (Fig. 1). His palms, right shoulder and bilateral lower limbs all showed evidence of non-tender and non-blanching petechial hemorrhages, suspected as Janeway lesions (Fig. 2). His right lower eyelid revealed a single conjunctival hemorrhage. The plantar surface of his right foot revealed a discrete lesion consisting of a central accumulation of pus with an outer perimeter of non-blanching erythema of approximately 0.5 mm × 0.5 mm consistent with a further Janeway lesion (Fig. 3).

His pharynx, despite being non-painful, was erythematous and covered with white exudates (Fig. 4). Cardiovascular examination revealed a normal jugular venous pressure, normal 1st and 2nd heart sounds, no added sounds and no murmurs or rubs. The patient had mild bilateral pitting edema of the lower limbs. Respiratory, abdominal and neurological examinations were unremarkable.

Serum blood tests revealed: hemoglobin 12.6 g/dL, neutrophils 10.38×10⁹/L, C-reactive protein 11.23 mg/dL, erythrocyte sedimentation rate 85 mm/hr, blood urea nitrogen (BUN) 30.0 mg/dL (normal range 7.4-19.5 mg/dL), creatinine 2.4 mg/dL (previously 1.07 mg/dL one year before admission) (normal range 0.5-1.2 mg/dL) and a prothrombin time international normalized ratio of 1.82. Creatinine kinase was 123 IU/L (normal range 52-192 IU/L). Urinalysis revealed 50-99 red cells per high power field, 30-49 white cells per high power field, 3+ occult blood, 2+ protein, 2+ casts, consisting of hyaline, waxy and white cell types; no bacteria were seen.

Autoimmune studies were tested including anti-nuclear antibodies, rheumatoid factor, C and P anti-neutrophil cytoplasmic antibodies, and anti-basement membrane antibody, all of which were negative. C3 and C4 were within normal limits but the CH50 was decreased at 25 U/mL (normal range 30-45 U/mL). Urinary beta-2-microglobulin was 3,400 μg/L (normal <250 μg/L) and N-acetyl beta glucosaminidase was 13.2 U/L (normal range 0-10 U/L). Anti-streptolysin-O (ASO) and anti-streptokinase (ASK) antibody titers were within normal limits.

Four blood culture bottles were inoculated on admission to the hospital that yielded fully-sensitive Group A streptococci. Urine and pharynx cultures were negative respectively. Electrocardiogram showed atrial fibrillation, anterior T wave inversion and low voltage. Chest radiography revealed features of cardiomegaly, upper lobe diversion and a left pleural effusion, consistent with cardiac failure.

Abdominal ultrasound (AUS) revealed some mild ascites. In addition, the AUS showed bilateral hydronephrosis, which later was resolved after the placement of a urinary catheter.

Infective endocarditis was strongly suspected with secondary glomerulonephritis. Subsequent transthoracic echocardiography was performed which revealed no vegetation, an ejection fraction of 50%, a small pericardial effusion of
maximum depth 13 mm and no right ventricular collapse. The atrial diameter was 70 mm. In addition, there was first-degree mitral and aortic regurgitation, and second-degree tricuspid regurgitation (TR). Pulmonary artery pressure was elevated at 33 mmHg. Subsequent, transesophageal echocardiography performed one day after the transthoracic study also revealed no vegetation (see Fig. 5-7). Transthoracic echocardiograms were repeated at 8, 20 and 35 days after admission, and in all cases, no vegetation could be visualized.

The patient met the Modified Duke’s Criteria for definite endocarditis. He was treated with $6 \times 10^6$ units of benzylpenicillin and 180 mg of gentamicin per day. Benzylpenicillin monotherapy was subsequently continued for six weeks. Good clinical outcome was shown by resolution of the fever, stable chronic renal impairment as evidenced by persistent elevations of both the BUN at 40.1 mg/dL and creatinine of 1.56 mg/dL, normal inflammatory markers and no further signs of peripheral stigmata of IE.

His inpatient stay was complicated by iatrogenic worsening of heart failure from fluid overload following resuscitation with intravenous fluids for a new upper gastrointestinal hemorrhage caused by the continuation of anticoagulant therapy. The patient underwent urgent esophagogastroduodenoscopy which revealed an acutely bleeding gastric ulcer, which was treated by blood transfusions, vitamin K infusion (INR was 3.3 at the time of the bleed) and intravenous omeprazole. Anticoagulants were temporarily discontinued and he made a good recovery from this episode.

**Discussion**

Group A Streptococcal endocarditis is a rare form of endocarditis representing less than five percent of all documented cases. In a case report by Burkert and Watanakunakorn (1) in 1991, only five cases were reported in a ten-year period. Group A streptococcal endocarditis has been reported in intravenous drug misusers (2), in children following varicella infection (3, 4), and it predominantly affects the right side of the heart with 50% of cases showing embolic phenomena. Risk factors cannot always be identified in such patients (5).

In this case, the patient had normal valvular examinations. However, the clinical course met the defined criteria for endocarditis using the Modified Duke’s Criteria shown by one major criterion (positive blood cultures consisting of a typical organism for endocarditis from two separate blood cultures) and three or more minor criteria (fever $>38^\circ$C, Janeway lesions, conjunctival hemorrhage and suspected glomerulonephritis), respectively. The modified criteria are reported to have 99% specificity and 92% negative predictive value for the diagnosis of endocarditis (6).

Several studies have outlined the excellent negative predictive value of transesophageal echocardiography in ruling out endocarditis. However, as has been highlighted in the literature, endocarditis is a clinical diagnosis and a positive
Echocardiogram result does not necessarily rule in the diagnosis and certainly, a negative study cannot rule it out (7, 8). In view of the potential to miss vegetations on initial inspection by transesophageal echocardiography, some authors have suggested repeating the study in high-risk patients to avoid a missed diagnosis (9). A newer tool to diagnose infective endocarditis in the absence of definable vegetation on echocardiography includes the use of positron emission tomography-computed tomography (PET-CT), which is reported to have a higher sensitivity than current functional methods (10). The use of this technique is expensive and depends on the local facilities that are available. Such a technique is likely not available at many smaller hospitals that still rely on echocardiography for aiding the diagnosis of endocarditis. The use of PET-CT was not performed during this patient’s admission.

Despite the negative transesophageal echocardiogram in this patient, it is nonetheless conceivable that the vegetation had already embolized into the peripheral circulation as indicated by the florid peripheral stigmata. Moreover, despite the absence of prior endocarditis associated risk factors, physical examination revealed asymptomatic pharyngeal infection evidenced by white exudates on inflamed mucosa, which was a possible site of entry of the Group A streptococci despite the negative throat culture result. However, such exudates may have simply represented oral candidiasis secondary to the use of outpatient antibiotics prior to admission to the hospital.

Although endocarditis is associated with valvular destruction and acute heart failure, in this case, no vegetation could be identified. However, in comparison to an echocardiogram performed one year prior to admission, the ejection fraction had decreased by 14% and the TR had worsened by one degree. The pulmonary artery pressure was not dissimilar to that noted during the admission. As this patient had a background of existing chronic heart failure with known left ventricular asynergy and with only modest changes in cardiac function between examinations, it cannot be clearly defined whether the endocarditis led to the worsening of his cardiac function.

The patient was also considered to have developed acute glomerulonephritis (GN) leading to acute kidney injury based on the following: microscopic hematuria, elevations of both NAG and beta-2-microglobulin, a low CH50, normal autoantibody studies and the absence of other definable causes. The patient also had white cell casts, which are consistent with an infectious or inflammatory process. A post-streptococcal glomerulonephritis is a possibility in this case although the ASO and ASK titers were within normal limits. However, the titers were not repeated. Pyelonephritis, another cause of such casts, was not elucidated either by physical examination or by renal ultrasound scan. Waxy casts being a feature of chronic renal failure may also form due to urine stasis in dilated ducts, which is consistent with this patient’s hydronephrotic state on the admission. Although red cell casts were not identified to further support the diagnosis of an acute GN, the fragility of such casts requires that the urine sample is analyzed promptly and false negative results can occur. Hence, the absence of such casts does not rule out the possibility of GN in this case. Although this patient experienced gastrointestinal bleeding with hypovolemia, the renal failure pre-dated this event. A renal biopsy would have been diagnostically useful to identify the underlying cause(s) but was contraindicated in this patient because of anticoagulant usage for atrial fibrillation.

Glomerulonephritis is an uncommon immune complex-mediated manifestation of endocarditis, especially in the post-antibiotic era (11). It has been described in endocarditis resulting from several different inciting organisms (12, 13). To date, Group A streptococcal endocarditis in association with glomerulonephritis has been reported rarely in the literature, mainly in the pediatric population (14) and in intravenous drug misusers (15). Other causes of renal failure associated with endocarditis have either not been elucidated (3) or occur due to embolic phenomena (16). However, although glomerulonephritis from endocarditis can be resolved with antibiotic treatment (17), with or without corticosteroids, the present patient had features consistent with persistent renal damage most likely sustained from the acute kidney injury despite adequate antimicrobial treatment.

It should be borne in mind that the use of anticoagulants such as warfarin and aspirin are contraindicated in infective endocarditis because of the significant risk of stroke (18, 19). Such treatments should be promptly stopped during the septic phase of the endocarditis infection. Despite the notable high risk of Group A streptococcal endocarditis-associated embolization, this patient’s stigmata of endocarditis were nonetheless increased by the addition of the two anticoagulant therapies.

This case also highlights the common indiscriminate prescribing of antibiotics without first taking culture samples. Moreover, such use can sometimes result in negative blood culture results (20, 21) thereby complicating the diagnostic and therapeutic modalities.

**Conclusion**

This case reveals that Group A streptococcal endocarditis can occur in individuals without pre-existing risk factors. In this single case, significant embolic phenomena occurred and were exacerbated by the use of anticoagulants. This case also demonstrates that infective endocarditis cannot be ruled out by a single negative transesophageal echocardiographic study. However, the Modified Duke’s Criteria should be referred to when considering the diagnosis of endocarditis. These criteria can support the diagnosis of endocarditis based on the major and minor criteria even in the absence of positive echocardiographic studies.

Future use of newer diagnostic modalities such as PET-CT show promise and may improve the diagnostic accuracy of this infection although as a word of warning, this should not replace traditional physical examination procedures.
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