CASE REPORT

An Ineffective Differential Diagnosis of Infective Endocarditis and Rheumatic Heart Disease after Streptococcal Skin and Soft Tissue Infection

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Abstract:
We herein report the case of a 68-year-old woman with a skin and soft tissue infection at her extremities. The blood culture results were positive for *Streptococcus pyogenes*, and we started treatment using ampicillin and clindamycin, although subsequent auscultation revealed a new-onset heart murmur. We therefore suspected rheumatic heart disease and infective endocarditis. The case met both the Jones criteria and the modified Duke criteria. Transesophageal echocardiography revealed vegetation on the aortic valve, although the pathological findings were also compatible with both rheumatic heart disease and infective endocarditis. The present findings suggest that these two diseases can coexist in some cases.

Key words: *Streptococcus pyogenes*, skin and soft tissue infection, infective endocarditis, modified Duke’s criteria, acute rheumatic fever, Jones criteria

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Introduction

*Streptococcus* species are well-known bacteria that cause skin and soft tissue infections, as well as bacterial tonsillitis. Clinicians should be concerned if the patient develops an acute rheumatic fever after a streptococcal infection, as the disease has an unpredictable course. In these cases, the diagnosis is made based on the Jones criteria, which include five major manifestations (migratory polyarthritis, carditis and valvulitis, chorea, subcutaneous nodules, and erythema marginatum) and four minor manifestations (arthritis, a fever, elevated acute-phase reactants, and a prolonged PR interval during electrocardiography) (1, 2). In cases of a confirmed previous streptococcal infection, two major manifestations or one major manifestation plus two minor manifestations are sufficient to diagnose an acute rheumatic fever (1, 2). Pharyngitis is typically the cause of an acute rheumatic fever, which is most frequently observed children, although adults can develop acute rheumatic disease, and these cases are infrequently caused by a streptococcal skin infection (3, 4).

Infective endocarditis is a serious complication after Gram-positive coccal bacteremia, and the key clinical signs include a sustained fever, a new-onset heart murmur, and/or peripheral embolic signs. This condition is diagnosed based on the modified Duke criteria, which include two major criteria (positive blood culture results for typical microorganisms and/or evidence of endocardial involvement, such as vegetation, abscess, or new valvular regurgitation) and five minor criteria (predisposing factors, a fever, vascular phenomena, immunological phenomena, and microbiological findings that do not meet the major criteria or serological evidence of active infection with an organism that is consistent with infective endocarditis) (5). A definitive diagnosis...
of infective endocarditis can be made based on two major
criteria, one major criterion plus three minor criteria, or five
minor criteria; a possible diagnosis can be made based on
one major criterion and one minor criterion, or three minor
criteria (5). *Streptococcus* species are an uncommon cause
of infective endocarditis (6), although a new-onset heart
murmur after streptococcal bacteraemia may indicate that the
patient has infective endocarditis. Furthermore, it is possible
to develop both an acute rheumatic fever and infective endo-
carditis after streptococcal bacteraemia.

We herein report a case in which it was difficult to differ-
entiate between infective endocarditis and an acute rheu-
matic fever after a streptococcal skin and soft tissue infec-
tion.

**Case Report**

A 68-year-old Japanese woman was admitted with severe
pain in her upper and lower extremities. At 14 days before
the admission, she had fallen and sustained injuries to her
left palm and right elbow. At 10 days before the admission,
she experienced abdominal pain, nausea, and diarrhea. On
the day of admission, a neighbor called an emergency medici-

cal service after finding the patient lying on the floor of her
house. The patient had a history of endometrial cancer and
hepatitis C, and her vital signs at admission were a body
temperature of 38.8°C, a heart rate of 118 bpm, a blood
pressure of 128/69 mmHg, a respiratory rate of 20/min, and
an arterial blood oxygen saturation (SpO2) of 95% in room
air. A physical examination also revealed a systolic heart
murmur on the third intercostal left sternal border, and her
right upper arm and left knee were red, swollen, and tender.
However, we did not detect any splinter hemorrhaging, Os-
er’s nodes, or Janeway lesions. Laboratory testing revealed
leukocytosis (26,830/μL) and elevated levels of C-reactive
protein (36.46 mg/dL), aspartate transaminase (40 IU/L),
alanine transaminase (29 IU/L), blood urea nitrogen (74.2
mg/dL), and creatinine (1.94 mg/dL). Two sets of blood cul-
tures were taken at the emergency department. Electrocardi-
ography revealed a normal sinus rhythm without ST-T seg-
ment change. There was no apparent vegetation on the
transesophageal echocardiogram obtained at admission, and
chest and abdominal computed tomography revealed normal
findings, with the exception of bilateral renal stones.

On day 3, arthrocentesis was performed on the patient’s
left knee. Gram staining revealed streptococcus-like Gram-
positive cocci, although a culture of the synovial fluid re-
vealed negative findings. The two sets of blood cultures
from the admission revealed growth of *Streptococcus pyo-
genés*. The patient’s tender and erythematous extremities,
combined with the arthrocentesis results, strongly suggested
that she had developed infective arthritis secondary to bac-
teremia from a streptococcal skin and soft tissue infection.
Therefore, we started treatment using ampicillin (2 g every 6
hours) and clindamycin (600 mg every 8 hours). On days 5
and 13, after starting the antibiotic treatment, we collected
two pairs and one pair of blood cultures respectively, and
observed negative results for bacterial growth. Lavage and
debridement of the left knee was performed on day 8. The
streptococcus-like Gram-positive cocci had vanished com-
pletely (based on Gram staining), and culture of the left
to synovial fluid also provided negative results. However,
the patient reported persistent focal pain and warmth at her
left knee, and we detected a mild fever (37-38°C).

On day 4, computed tomography had revealed new-onset
pleural effusion and ascites, which were not present at the
initial evaluation. Based on these findings, we also consid-
ered serositis as a clinical manifestation of an autoimmune
reaction, such as a rheumatic fever. Aspirin was added as a
treatment for the arthritis and fever, which partially relieved
the patient’s symptoms, and the ascites disappeared. How-
ever, the pleural effusion gradually expanded, and ausculta-
don day 18 revealed a newly-onset diastolic murmur on
the second intercostal right sternal border. A transthoracic
echocardiogram also revealed aortal regurgitation without
vegetation. The ejection fraction was 68.7%. We therefore
suggested performing transesophageal echocardiography, al-
though the patient would not consent to this invasive exami-
nation. Her heart failure gradually worsened, despite the use
of diuretics. Her urine output suddenly decreased to 130
mL/day on day 50.

Under suspicion of drug-induced acute kidney injury, anti-
biotics (amoxicillin 500 mg 4 times daily) and aspirin (500
mg 3 times daily) were immediately discontinued on day
51. Her urine output spontaneously recovered, and she did
not exhibit elevated creatinine levels. She ultimately con-
sented to transesophageal echocardiography on day 55. This
examination revealed vegetation and prolapse of the aortic
valve, and we performed aortic valve replacement on day
56. The pathological findings revealed massive neutrophil
infiltration with fibrin deposition, which indicated strong in-
flammation, such as infective endocarditis (Fig. 1). We were
unable to detect Aschoff bodies, which are specific to a
rheumatic fever. Gram staining and culture of the valve
specimen did not reveal any bacteria. The patient has exper-
enced a good recovery since the surgery and subsequent an-
tibiotic treatment. The clinical course is shown in Fig. 2.

**Discussion**

*Streptococcus pyogenes* is an uncommon cause of infec-
tive endocarditis, accounting for only approximately 5% of
cases (6). In this context, clinicians diagnose streptococcal
infective endocarditis using the modified Duke criteria and
results from previous blood cultures positive for *Streptococ-
cus pyogenes* (7, 8). Acute rheumatic fever and rheumatic
heart disease are also major complications of streptococcal
infections. The incidence of an acute rheumatic fever is
highest among 5- to 14-year-old children, although it can also
occur among patients over 45 years of age (9). Reports
from before 1961 estimated that 1.7% of patients who did
not receive antibiotics for streptococcal pharyngitis subse-
sequently developed an acute rheumatic fever, although its incidence has declined in recent decades (10). While previous reports have only described streptococcal pharyngitis as being responsible for the onset of these diseases, recent reports have also described streptococcal skin infections that resulted in an acute rheumatic fever and rheumatic heart disease (3, 4).

In the present case, two sets of blood cultures obtained at admission were positive for *Streptococcus pyogenes*, and a skin and soft tissue infection was considered the most likely entry site. Given the new-onset diastolic heart murmur that we detected after treating the streptococcal skin and soft tissue infection, the most likely diagnoses appeared to be a rheumatic fever or infective endocarditis. The patient met one major criterion and two minor criteria from the Jones criteria for a rheumatic fever (1, 2), suggesting the possibility of an acute rheumatic fever, despite the patient not being from an endemic population. However, the patient also met one major criterion and one minor criterion from the modified Duke criteria (5), suggesting the possibility of infective endocarditis. The patient therefore met the criteria for both a rheumatic fever and infective endocarditis. Our pathological findings from the heart valve specimen were compatible with infective endocarditis. The finding of acute phase inflammatory changes despite prolonged antibiotic therapy might be explained by the ineffectiveness of the conservative treatment for invasive infective endocarditis. The clinical course of the arthritis and fever relief after aspirin treatment
was compatible with that of an acute rheumatic fever. Therefore, there was a possibility that these two diseases were coexisting in this patient.

Table shows a summary of the cases of group A streptococcal endocarditis and whether they fulfilled the Jones criteria. These reports were identified using a PubMed search with the terms “infective endocarditis” or “Streptococcus pyogenes,” and we only considered reports published in English or Japanese. This search identified 21 cases among 14 reports, ranging in age from 5 months to 71 years. Streptococcal infection was confirmed using blood culture in all cases, and most cases met the major Jones criteria for endocarditis from the 1992 update. A fever and elevated acute-phase reactant levels were the main signs and symptoms in the minor criteria. Twelve of the 21 cases (as well as the present case) were also diagnosed with an acute rheumatic fever based on the 1992 update of the Jones criteria.

In conclusion, the present case highlights the difficulty in differentiating between infective endocarditis and an acute rheumatic fever as the cause of a new-onset heart murmur after a streptococcal skin and soft tissue infection. It may be impossible to differentiate between these two diseases based on the current diagnostic criteria, and to our knowledge, no reports have described the possibility of these two diseases coexisting in the same patient. Therefore, further research is needed to develop new diagnostic criteria that can differentiate between infective endocarditis and an acute rheumatic fever in order to facilitate determining the appropriate treatment regimen.

The authors state that they have no Conflict of Interest (COI).

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