CASE REPORT

*Pasteurella multocida* Infective Endocarditis: A Possible Link with Primary Upper Respiratory Tract Infection

Joel Branch, Takuya Kakutani, Shun Kuroda, Yasuhiro Shiba and Izumi Kitagawa

**Abstract**

A 50-year-old Japanese man presented with fever and upper respiratory tract symptoms that required urgent inpatient admission. A physical examination revealed conjunctival hemorrhages and peripheral embolic phenomena. Blood cultures grew *Pasteurella multocida*, and an echocardiography revealed a mitral valve vegetation suggestive of infective endocarditis (IE), which was confirmed using the Modified Duke Criteria. After several antibiotic regimens proved ineffective, valve replacement was performed, with a good eventual outcome. *P. multocida* IE is rare and may sometimes have no preceding risk factors. *P. multocida* infections of the upper respiratory tract are unusual but may be an inciting event for IE. It is essential to check blood cultures and to repeat the performance of physical examinations to appreciate the developing features of IE.

**Key words:** upper respiratory tract infection, infective endocarditis, *Pasteurella multocida*, Janeway lesion, Osler nodes, septic emboli


**Introduction**

Infective endocarditis (IE) is an uncommon infection, which can occur in individuals with underlying cardiac disease, including congenital bicuspid aortic valves (1), valvular regurgitation (2), valvular stenosis (3), prior valve damage from IE or rheumatic fever (2) and the presence of a prosthetic valve (4). The known predisposing factors include invasive dental treatment (5), fiberscopic upper and lower gastrointestinal investigations (6, 7), the presence of polyps (8), the presence of malignancy of the colon (9), liver cirrhosis (10) and the presence of extensive dermatitis (11). The diagnosis is confirmed by the use of the Modified Duke Criteria (12), which requires the fulfillment of one of the following conditions: both of the two major criteria, one major and three minor criteria, or five minor criteria. The diagnosis is often established by identifying a valvular vegetation by echocardiography, and through the growth of bacteria by blood cultures. However, the minor criteria require some knowledge of physical examination to identify endocarditis-specific lesions such as Janeway lesions, Osler nodes and Roth spots. These can sometimes be missed by inexperienced physicians, which may therefore delay the diagnosis of this potentially lethal infection.

The usual causes of IE encompass Gram-positive organisms such as the viridans streptococci and staphylococcal species. *P. multocida* is a very rare cause of IE with very few cases having ever been described in the literature (13). *P. multocida* infection is usually associated with animal bites from cats and dogs, with these animals carrying this organism in their mouths, whereas it is rare for it to be carried by humans (14). *P. multocida* infection can cause several severe illnesses including meningitis (15), pneumonia (16), bacteremia (17), and septic arthritis (17).

We herein report the case of a 50-year-old Japanese man who developed *P. multocida* IE following an upper respiratory tract syndrome, without predisposing factors or contact with animals. To the best of the authors’ knowledge, this is the first case of *P. multocida* IE that has been documented with a preceding upper respiratory tract syndrome, suggesting a possible link for the spread of this organism through the upper airways or associated pharyngeal structures to cause bacteremia and subsequent seeding on the mitral valve.
### Case Report

A 50-year-old Japanese male department store employee experienced a fever of five days in duration, after which he presented to his primary care physician. He was diagnosed with bacterial pharyngitis, and treated with azithromycin (500 mg for three-days). After this, he developed watery diarrhea, which occurred between 2-3 times in 24 hours, and which resolved spontaneously after two days. One day prior to the hospital admission, the patient developed a non-productive cough. He denied the expectoration of sputum, hemoptysis or chest pain. The fever was persistent, which prompted him to seek a second opinion at this hospital.

On further questioning, he also complained of twice-nightly drenching sweats, which necessitated the changing of his bed clothes and which were associated with occasional chills, headache, bilateral knee arthralgia, anorexia, fatigue, thirst, polydipsia and polyuria. He had previously had a dental implant, which had spontaneously loosened and fallen out one year previously. He did not complain of any current dental problems and he had not undertaken recent dental treatment. He admitted to contact with a female commercial sex worker but without penetrative intercourse, one-month prior to the onset of his symptoms. He denied high-risk sexual behavior including unprotected oral, vaginal or anal intercourse. He also denied intravenous drug use, blood transfusions and tattoos. On admission, there were no symptoms of photophobia, nuchal pain or rigidity, pharyngalgia, penile pain or discharge. He had no prior underlying heart conditions. He denied any contact with animals including scratches, bites or licking.

His previous medical history included multiple spontaneous pneumothoracies of the right lung in his late teens and idiopathic sudden deafness one year previously. He took no regular medications, over the counter drugs or herbal supplements. There was no history of any drug or food allergy.

His family history was non-contributory. He was married and he had no unusual hobbies or recent travel outside of Japan. He was a non-smoker and he consumed one small can of regular beer per day. He enjoyed water sports but he had not engaged in these in the recent months prior to admission. Apart from the above information, the review of systems did not elucidate any other symptoms or risk factors for disease.

On physical examination, the patient appeared mildly unwell. His body temperature was 38.6°C (axilla), his heart rate was 116 beats per minute and irregular, his blood pressure was 98/72 mmHg (his usual systolic blood pressure was 130 mmHg), his respiratory rate was 16 breaths per minute, and his pulse oximetry oxygen saturation (SpO₂) level was 98% when breathing ambient room air.

The patient was normoccephalic and atraumatic. There was no conjunctival pallor or icterus, but bilateral palpebral conjunctival hemorrhages were evident. His ears and nose were normal, but his throat demonstrated an erythematous soft palate with a single clear vesicle. There was no evidence of pus, tonsillar swelling or abscess. Two premolar teeth showed evidence of extensive dental caries. There was no cervical, axillary or inguinal lymphadenopathy.

A cardiovascular examination revealed a normal jugular venous pressure, apex position and heart sounds; no murmurs were detectable. Examinations of the respiratory, gastrointestinal, genitourinary, neurological, dermatological and musculoskeletal systems was all entirely normal.

The laboratory data at admission are shown in Table. Tests for *Legionella pneumophila*, *Mycoplasma pneumoniae* and human immunodeficiency virus were negative. The admission chest radiograph revealed no acute infectious process. The electrocardiogram revealed an irregular heart rate of 105 beats per minute, with frequent atrial ectopic beats and compensatory pauses.

In view of the clinical presentation and serum transaminase elevation, the patient was initially admitted to the hospital with a suspected diagnosis of an acute viral upper respiratory tract infection, and he was observed while undergoing diagnostic tests. On the 3rd hospital day of admission the blood cultures grew Gram-negative bacilli in two out of four bottles (aerobic only). The initial microscopic analysis revealed a possible Pasteurella infection. However, the result was not immediately available as the specific bacterial typing was referred to an outside reference laboratory. On the same day, a repeat physical examination revealed two new right-sided small palpebral conjunctival hemorrhages. Blood cultures were repeated because of the suspicion of IE. However, antibiotic treatment was not immediately initiated because it was also considered that the initial growth might have occurred due to contamination especially as his history was not consistent with such an infection, and that the patient otherwise appeared to be well. Repeat blood cultures became positive on the 6th day of hospitalization in all six bottles (aerobic and anaerobic), again with the same organism. As a result, empiric treatment with piperacillin-tazobactam (4.5 grams four-times daily) was commenced for suspected IE.

Despite the antibiotic treatment, the patient had persistent spiking fevers, night sweats and he developed new physical signs on a daily basis, which included hemorrhages of the conjunctivae, uvula, and skin. Osler nodes and Janeway lesions were variably noted in the digits of the upper and lower extremities, with the latter manifestation also affecting the palmar and plantar surfaces (Fig. 1, 2).

A transthoracic echocardiogram revealed a thickening of the anterior leaflet of the mitral valve, consistent with IE (Fig. 3). A formal fundoscopic slit lamp examination of the eyes was normal. An urgent head magnetic resonance imaging (MRI) scan, revealed multiple septic emboli affecting the right cerebral hemisphere (Fig. 4) and a lesion in the right lobe of the cerebellum (Fig. 5). A three-dimensional cerebrovascular MRI reconstruction revealed no evidence of mycotic aneurysms. A computed tomography scan of the
Table. The Initial Laboratory Data on Admission to the Hospital.

<table>
<thead>
<tr>
<th>Complete blood count</th>
<th>Serology</th>
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<tr>
<td>WBC 81×10^9/μL (30-97×10^9/μL)</td>
<td>HA IgM &lt;0.4</td>
</tr>
<tr>
<td>Neut 83.90% (36.6-79.9%)</td>
<td>HBs antigen (-)</td>
</tr>
<tr>
<td>Hb 15.2 g/dL (13.1-17.6 g/dL)</td>
<td>HBs antibody (-)</td>
</tr>
<tr>
<td>Ht 44.40% (38.1-50.8%)</td>
<td>HCV antibody (-)</td>
</tr>
<tr>
<td>MCV 91.7 fl (84.6-100.6 fl)</td>
<td>EBV-IgM &lt;10</td>
</tr>
<tr>
<td>Pt 7.7×10^4/μL (12.4-30.5×10^4/μL)</td>
<td>EBV-IgG 40</td>
</tr>
<tr>
<td>PT % 89.00% (88.3-132.7%)</td>
<td>EBNA antibody &lt;10</td>
</tr>
<tr>
<td>APTT 28.5 secs (23.6-31.3 secs)</td>
<td>CMV-IgM (-)</td>
</tr>
<tr>
<td></td>
<td>CMV-IgG (-)</td>
</tr>
<tr>
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<td>HIV antibody 0.195 COI</td>
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Biochemistry

| CK 32 IU/L (52-192 IU/L) | Protein (-) |
| T.bil 1.6 mg/dL (0.1-1.2 mg/dL) | Occult blood (-) |
| AST 281 IU/L (12-35 IU/L) | Bacteria (-) |
| ALT 223 IU/L (6-40 IU/L) | WBC (-) |
| LDH 461 IU/L (119-229 IU/L) | RBC (-) |
| γGTP 170 IU/L (0-48 IU/L) | |
| ALP 442 IU/L (115-359 IU/L) | |
| TP 7.7 g/dL (6.4-8.3 g/dL) | |
| Alb 3.5 g/dL (3.8-5.2 g/dL) | |


As a result of the above tests, the patient met one major (valvular vegetation), and four minor criteria (septic emboli, Janeway lesions, Osler nodes, fever >38°C) of the Modified Duke Criteria, thereby confirming the diagnosis of definite IE.

On the 15th day of hospital admission, microbiological studies confirmed a definite *P. multocida* infection. The initial antimicrobial sensitivities showed that the organism was susceptible to cephalosporins, but resistant to piperacillin-tazobactam. The sensitivities were determined using the disc diffusion method rather than by formal minimum inhibitory concentrations (MIC), because of the difficulty in performing the latter test on this organism. As a result, the antibiotic was changed to ceftriaxone. However, the patient had persistent daily fevers and his general condition did not improve. Eventually, he underwent mitral valve replacement with a 27 mm mechanical valve (St. Jude’s Medical®, St. Paul, USA) on the 23rd hospital day of admission. In the immediate postoperative period, the patient became afebrile and there were no new embolic phenomena noted. Ampicillin-sulbactam was added to the antimicrobial regimen. His convalescent period was complicated by paroxysmal atrial flutter, which subsided spontaneously. He went on to make a full recovery and he was discharged from the hospital on the 32nd day of hospitalization for follow-up as an outpatient.
**Discussion**

*P. multocida* is a Gram-negative cocccobacillus microorganism that is the main cause of animal bite-associated infection (14). Cats and dogs are the main carriers of this organism in their mouths, whereas it is rare for it to be found naturally in humans (14). IE caused by *P. multocida* is a very rare manifestation (13, 18). In the forty years since the first reports of this type of IE, there have been very few cases reported in the literature.

Soft tissue infections by Pasteurella are frequently associated with animal bites. However, in an analysis of previous cases of *P. multocida* IE, although animal ownership was found in almost 75% of patients, only about 10% had a definite history of an animal bite (16). Khan et al., experienced a patient with an initial presentation of pneumonia but who was later diagnosed with *P. multocida* IE. They suggested that in cases without an animal bite history, the spread may occur via the respiratory route (16).

Pasteurella infection usually begins with a rapid onset of illness, and in an analysis of patients by Camou et al., high rates of mortality were reported in immunocompetent patients (40%) and immunosuppressed patients (up to 57%) (13). Immunosuppression is considered to be a risk factor for the infection. The causes of immunosupression include alcoholic cirrhosis (19), diabetes mellitus (16) and kidney disease (20). Other identified risk factors include chronic obstructive pulmonary disease (16) and the licking of leg ulcers by pets (20). However, native bicuspid aortic valve disease (20), mitral stenosis (3) and mechanical valve replacement (20, 21) are also risk factors for infection. Like other forms of endocarditis, *P. multocida* IE is also associated with clinical manifestations including arterial emboli (18, 22) and mycotic aneurysms (22). The infection appears to show no preference for the valves involved on the left side of the heart, with the aortic and mitral valves being affected nearly equally (13), and with the tricuspid and pulmonary valves having been affected in a patient after a cat bite (23) and in an intravenous drug user (24), respectively.

In our patient, the onset of symptoms was initially subacute and simulated what was considered to be a viral upper respiratory tract syndrome. However, the twice nightly drenching sweats also suggested the possible presence of a biquotidian fever, the differential diagnosis of which includes IE. The presence of chills, although not specific, also suggested the presence of bacteremia (25). A physical examination revealed the presence of a systemic inflammatory response syndrome, (26, 27) hypotension and mucous membrane hemorrhages. These symptoms and signs taken together should have alerted the admitting physician to the possible presence of IE. In such circumstances, antimicrobial therapy should have been commenced after the acquisition of blood cultures. Notwithstanding this, the presence of Pasteurella-like organisms grown on the initial blood cultures should have been an additional stimulus to commence antimicrobial therapy. Therefore, there was a delay before a definitive diagnosis could be made and appropriate treatment was commenced.

Treatment of *P. multocida* IE has previously included penicillin G (18), or ampicillin with gentamicin (21, 22). Recent recommendations from the Infectious Disease Soci-
treatment of this form of endocarditis. Such treatment has been ineffective because of the continued occurrence of embolic phenomena, and the persistence of the daily spikes of fever. Unfortunately, this antimicrobial agent also proved ineffective. Considering that the patient presented with upper respiratory symptoms including pharyngitis, and later, a non-productive cough, and the findings on the physical examination of an erythematous soft palate with a vesicle, we consider that an upper respiratory mode of entry was possible, perhaps via the pharynx and/or the laryngotracheobronchial route. Entry via the upper respiratory tract has been previously found to cause epiglottitis and laryngopharyngitis (35) but not endocarditis. Although the upper respiratory manifestations may be unrelated to the IE in this case, the history of symptoms beginning from the upper respiratory tract and then proceeding to the development of signs of IE, would suggest otherwise. In this case, an upper respiratory tract primary infection leading to bacteremia and the subsequent seeding on the mitral valve of this patient could not be excluded.

It should be borne in mind that there are several other important pathogens that may cause infections of the upper respiratory tract, which can lead to disseminated infection and which may mimic some of the features seen in this patient early in their natural history, and/or result in the development of IE. Such pathogens include Group A streptococci (GAS), Streptococcus pneumoniae, and Neisseria meningitidis.

GAS infection is a common cause of pharyngitis in children (36), but it can also be a rare cause of IE (5% of all cases) (37). Moreover, pharyngeal infection can sometimes be asymptomatic (38). Both S. pneumoniae and N. meningitidis are carried in the human nasopharynx to relatively high degrees in Western individuals (39, 40). However, the carriage of N. meningitidis is not endemic in Japanese individuals (41). Although it is rare, these encapsulated organisms can become invasive, particularly in asplenic individuals, and produce the catastrophic syndrome of purpura fulminans as characterized by disseminated intravascular coagulation (41, 42). Such patients typically demonstrate a rapid and fulminant course, and if they survive, they may suffer limb amputations amongst other severe complications; early disease may produce seemingly innocuous minor hemorrhage (43), similar to this case. Moreover, both organisms may also rarely produce IE (44, 45).

In summary, we experienced a patient who presented with a suspected upper respiratory tract illness, but through close observation and inspection, the signs of IE were eventually ascertained in the absence of a cardiac murmur. The entry of P. multocida via the upper respiratory tract was considered most likely in this case. This case teaches the reader that the empiric antibiotic treatment for IE should include a penicillin derivative with an anti-penicillinase agent along with an aminoglycoside. Moreover, the knowledge of the minimum inhibitory concentrations of available antimicrobial agents can better guide the treatment of this catastrophic infection. Nevertheless, in certain circumstances, basic tests including the disc diffusion method to determine sensitivities may be the only immediately available means of guiding antimicrobial choices. In addition, early surgical valve replacement is essential in selected patients, especially in those with P. multocida IE who may otherwise suffer a fulminant course. The
presence of persistent fever and ongoing embolic phenomenon in IE should alert the physician that antimicrobial treatment alone is insufficient, when sensitivities are known and drug dosing is adequate. Emergent surgical intervention should be undertaken to improve the chances of a cure.

Lastly, this case also highlights other diseases that may potentially mimic the symptoms and signs as experienced by our patient, which may include early purpura fulminans or disseminated GAS infection. Hence, urgent antibiotic administration is imperative in such circumstances, after the acquisition of relevant microbiological cultures.

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

**References**


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