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Infective Endocarditis Caused by Unusual Gram-positive Pathogens

Report of 4 Patients

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ABSTRACT. Of a total of 81 patients hospitalized in the infectious diseases department in 1990–2000 with infectious endocarditis caused by Gram-positive pathogen, unusual etiological agents were found in several cases: *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Corynebacterium diphtheriae*, and *Gemella morbillorum*. Cardiac defects were present in the latter two patients: bicuspid aortic valve and tetralogy of Fallot. Two patients were successfully treated with antibiotics only and one patient with antibiotics and surgery. The patient with *C. diphtheriae* endocarditis died due to progressive sepsis and multiple organ failure.

Infective endocarditis (IE) is a disease with an annual incidence of 2–5 per 10^5 and medium mortality of 20–30 %. The main etiological agents are viridans streptococci and *Streptococcus bovis* (45–60 %), both coagulase-positive and -negative staphylococci (25–40 %), and enterococci (5–10 %) (Durack 1992; Karchmer 1997; Bayer and Scheld 2000). Nevertheless, individual case reports claim that the disease can be caused by virtually any microbe including various anaerobes, legionellae, mycobacteria, or obligatory intracellular pathogens like *Coxiella burnetii* and chlamydiae (Kaye 1994; Menasalvas and Bouza 1998).

Unusual Gram-positive bacteria used to be found in less than 3 % of large groups of IE patients (Durack 1992; Bayer and Scheld 2000). We submit four case reports of such uncommon causes of the disease.

MATERIALS AND METHODS

One hundred and thirty-five patients with a diagnosis of IE were hospitalized in the *Department of Infectious Diseases* (*University Hospital Bulovka*, Prague, Czechia) in 1990–2000. The etiologic agents were Gram-positive microbes in 81 cases (60 %) and Gram-negative microbes in 21 patients (16 %). There were two cases of mycotic endocarditis. Etiology was not established in 31 cases (23 %), mainly due to previous antibiotic treatment.

Viridans streptococci and *S. bovis*, staphylococci, and enterococci caused 76 of the 81 Gram-positive endocarditis cases. Five cases were of unusual etiology. All of them fulfilled the Duke criteria of "definite IE" (Durack *et al.* 1994). One case of IE due to *Listeria monocytogenes* has already been described in detail (Beneš *et al.* 2002); the characteristics of the others are given here.

CASE REPORTS

Patient no. 1. A 59-year-old woman with a history of tonsillectomy in childhood, unilateral mastectomy 15 years previous to admission, and allergy to penicillin became ill several days after taking care of her granddaughter who had been suffering from scarlet fever. The disease started suddenly with a fever of 40 °C and rigor. After the patient had been febrile for 3 d, she was prescribed roxithromycin 2 × 150 mg, but the treatment was ineffective and the high fever and rigor continued. Five d after the first symptoms of the disease, the patient became blind in her left eye. She was examined by an ophthalmologist and treated for

iridocyclitis with local corticosteroids and atropin. Because of prolonged fever and exhaustion, she was referred to our department 10 d after the onset of the disease.

The patient was fully conscious with normal neurological signs. Dehydration, fever 37.8 °C, labial herpes and artificial anisocoria were observed during the initial examination as the only pathological finding. Laboratory tests revealed the following values: white blood cells 13 300/μL, with 84 % polymorphonuclear cells and 10 % band forms, hemoglobin 121 g/L, erythrocyte sedimentation rate 120/h, serum albumin 18 g/L. Serum antistreptolysin-O and rheumatoid factor were below reference levels. Transthoracic echocardiogram showed only mild degenerative changes of aortic valve. Ophthalmologic examination revealed left-sided uveitis and a vitreous abscess. Treatment with clindamycin 1800 mg, gentamicin 240 mg, and hydrocortisone 300 mg daily was started 2 d after admission. The fever fell promptly but reappeared after 7 d. Moreover, the patient began to complain of polyarthralgia.

Streptococcus pyogenes was isolated from five blood cultures taken prior to the beginning of antibiotic treatment. MIC values of relevant antibiotics were: vancomycin 750 μg/L, cephalothin 94 μg/L, clindamycin 380 μg/L. Transesophageal echocardiogram revealed a vegetation 10 mm in diameter on the posterior cusp of the mitral valve. No typical predisposing heart condition was found.

Therapy was changed to vancomycin 2 g daily with prompt effect. Five d later, renal insufficiency compelled replacing vancomycin with cephalotin 6 g daily; this treatment continued for 2 weeks. The patient was discharged in good condition. Later on, vitrectomy was performed in the ophthalmologic department. The patient has not relapsed or suffered from any other late complication in the five years after discharge.

Patient no. 2. A 47-year-old man with a history of alcoholism and smoking was complaining of weakness and malaise for 10 d. At the initial examination the patient was well conditioned, eupnoic, afebrile. Blood pressure was 90/60 mmHg (12/8 kPa), tachycardia 100/min. Physical chest examination was consistent with right-side pneumonia. Other pathological findings included spider nevi and hepatomegaly. Erythrocyte sedimentation rate was 120/h, hemoglobin level 98 g/L, white blood cells 19 500/μL, and platelet count 123 000/μL. Serum aminotransferase values (ALT, AST) were 2.4 and 1.8 μkat/L, respectively, glutamyltransferase 4.0 μkat/L, bilirubin 7.0 μmol/L. Chest X-ray showed an extensive exudation in right pleural cavity and a mild heart enlargement testifying for pericarditis.

After admission to a local hospital, pleural puncture was performed and 550 mL liquid of gray-yellow dense pus was removed. The pus yielded *Streptococcus pneumoniae* with good sensitivity to penicillin, erythromycin, chloramphenicol, and cotrimoxazole. The patient was treated with antibiotics (cotrimoxazole, chloramphenicol, penicillin, ciprofloxacin); corticosteroids were added to antibiotic therapy with respect to pericardial exudation. Pleural drainage and repeated irrigations were also performed. Blood cultures were not taken: the patient remained afebrile during the entire course of his illness with the exception one febrile episode the day chest drain was put in. After the patient had been hospitalized for 6 weeks, a transthoracic echocardiogram revealed a rupture of the noncoronary cusp of the aortic valve and the patient was referred to our department with suspicion of IE.

Treatment with penicillin, 20×10^6 U/d, and gentamicin was started on admission. A transesophageal echocardiogram showed a formation $17 \times 5 \times 5$ mm in size, prolapsing into the left ventricle outlet tract, several small aortic perforations and significant aortic insufficiency. The patient developed congestive heart failure within a week and was transferred to the cardiac surgery unit. A mechanical prosthesis (Sorin Bicarbon) was fitted into the damaged aortic valve. No bacteria were isolated from the excised tissues.

Immediately after the surgery, the patient developed acute ischemia of the left lower extremity. Embolectomia sec. Fogarty was performed without delay and the blood supply of the extremity was restored. The patient was given antibiotics (imipenem–cilastatin) for 16 d after surgery. Twelve months after discharge, the patient had not experienced any late complications.

Patient no. 3. A 24-year-old man from Belarus who had been living in Czechia for several months was admitted to our department with fever of 39–40 °C, exhaustion, headache, muscular weakness and mild sore throat; the illness had lasted 10 d. Two d before admission, he was examined by a general practitioner who noticed large pseudomembranes on both tonsils spreading to the velum, hypopharynx and tongue. The doctor suspected oral candidiasis and prescribed oral ampicillin and fluconazole. Nevertheless, the treatment was not effective and was discontinued at the time of admission.

On admission, the patient was febrile (38 °C), pale, and anxious, with tachypnea and pulse rate of 100–110/min. He had bilateral conjunctivitis, pseudomembranous pharyngitis, scarlet-like tongue and enlarged cervical lymphatic nodes. No heart murmur was present. The only other pathologic finding was mild hepatomegaly (+15 mm) and a few small maculae on the lower extremities that were recognized as probable peripheral skin emboli later on.

Laboratory studies disclosed the following pathological values: hemoglobin level 109 g/L, white blood cells 20 400/μL, platelet count 84 000/μL, erythrocyte sedimentation rate 42/h, blood sodium

129 mmol/L, C-reactive protein 384 mg/L, albumin 21 g/L, and aminotransferases (ALT, AST) 1.5 and 1.0 μkat/L, respectively. Infectious mononucleosis test (Ericson) and HIV-serology were negative, both serum antistreptolysin-O and rheumatoid factor were below reference levels. A tonsillar swab revealed sporadic colonies of *Haemophilus parainfluenzae* and *Candida albicans*. Gram-positive coryneform rods with sensitivity to penicillin, ampicillin, cephalotin, lincomycin, cotrimoxazole, tetracycline, erythromycin and vancomycin grew in all of the three collected blood cultures.

Repeatedly positive blood cultures, a newly discovered heart murmur and skin emboli led to a strong suspicion of infective endocarditis within 2 d. Both the transthoracic and transesophageal echocardiogram confirmed the diagnosis showing vegetation 6× 7 mm on the noncoronary cusp of the bicuspid aortal valve.

Intensive antibiotic therapy (penicillin 20×10^6 U/d and gentamicin 240 mg/d) was started immediately. Rapidly progressing cardiorespiratory failure complicated the disease, and the patient was transferred to the intensive care unit 2 d later. Several hours after the transfer, he developed septic shock. Antibiotic treatment was changed to piperacillin–tazobactam 18 g/d and netilmicin 400 mg/d because of the suspicion of a Gram-negative etiology of the shock. This combination was replaced with vancomycin 2 g/d and netilmicin 400 mg/d after 5 d later when the microbe isolated from blood was recognized as *Corynebacterium diphtheriae*. This result was confirmed at the *National Diphtheria Survaillance Laboratory* (Prague, Czechia); the microbe was characterized as *C. diphtheriae* ssp. *gravis*, non-toxigenic strain.

Despite the complex therapy in the intensive care unit, the patient remained febrile and proceeded to multiple organ system failure. He died 6 weeks after the onset of the disease.

The autopsy revealed aortic endocarditis spreading into myocardium and affecting all the other valves, multiple myocardial abscesses, bilateral heart dilatation, fibrinous pericarditis, adult respiratory distress syndrome (proliferative phase), fibrinous pleuritis, multiple embolic infarcts in the spleen, congestion and centrolobular necrosis in the liver, and septic nephritis with acute tubular necrosis.

Patient no. 4. A 31-year-old man with a history of tetralogy of Fallot. The patient had undergone subclavian-pulmonary anastomosis at the age of two and aorto-pulmonary anastomosis when he was four. He still suffered from ventricular septal defect with bidirectional flow, moderate pulmonary hypertension, hypertrophy and dilatation of the right heart and chronic right-heart failure. He had a history of penicillin allergy.

The patient had been complaining of mild fever and wasting during the preceding 6 weeks. He was unsuccessfully treated with cotrimoxazole and later admitted to a regional hospital. Right-side bronchopneumonia and sepsis was diagnosed. All of the three collected blood cultures (6 vials) yielded *Streptococcus mitis*. Transesophageal echocardiography did not reveal vegetation. The patient was treated with chloramphenicol for 1 week. After discharge he did not feel well: he had several febrile episodes and was given oral antibiotics.

Four months after the previous hospitalization, he was admitted to a regional hospital again because of fever, back pain, vertigo, dysarthria, and memory disorder. Right-sided pneumonia was found in similar extent as in previous X-ray, now complicated with mild pleural effusion. Poorly visible vegetation was observed on the tricuspid valve at transesophageal echocardiography. The laboratory findings were as follows: white blood cells 10 300/μL, hemoglobin 165 g/L, platelet count 184 000/μL, erythrocyte sedimentation rate 20/h, serum urea 19 mmol/L, creatinine 185 μmol/L, C-reactive protein 56 mg/L. Circulating immunocomplexes were 70 U (normal limit 45 U).

Gemella morbillorum with good sensitivity to penicillin, cephalotin, erythromycin, clindamycin, vancomycin, rifampicin, chloramphenicol, tetracycline, ciprofloxacin, cotrimoxazole and high-dosed gentamicin was isolated from five blood cultures taken in the 1st week of hospitalization. The patient was treated with oral ciprofloxacin and clindamycin at first. After 2 weeks with no effect, the therapy was switched to vancomycin 2 g/d (serum creatinine decreased to 110 μmol/L at that time). The patient was referred to our department 4 d after the onset of vancomycin therapy.

On admission he was asthenic, subfebrile (37.3 °C), pale, and cyanotic, with normal neurological signs. Systolic and diastolic murmurs were heard in the whole heart area. Blood pressure was 113/55 mmHg (15/7.3 kPa). His cardiac symptoms were accompanied by mild hepato- and splenomegaly, edemas of lower extremities and clubbing.

The patient was treated with vancomycin and rifampicin 900 mg/d; the dosage of vancomycin was adjusted to the serum levels. He became afebrile after 2 d of treatment with the combination of antibiotics, and the inflammatory markers gradually decreased to normal values. Transesophageal echocardiography that was performed 9 d after the beginning of vancomycin treatment did not reveal vegetations.

Antibiotic therapy was stopped after 14 d because of allergic exanthema. The patient was discharged after 2 weeks of observations: there are neither clinical nor laboratory findings of relapse at this

time. He had not relapsed or displayed any other late complication twelve months after hospitalization in our department.

DISCUSSION

The affinity of *S. pyogenes* for the valve surface has been reported to be 45 times or more lower than the affinity of most strains of viridans streptococci that are known as common etiological agents of IE (Bayer and Scheld 2000). Thus, despite the high incidence of infections due to *S. pyogenes*, this form of endocarditis remains a rare disease (Durack 1992; de Quiros *et al.* 1997; Bayer and Scheld 2000). Our first case report is interesting for its probable epidemiological relation to a case of scarlet fever and for the early embolism to the retinal artery.

S. pneumoniae endocarditis was responsible for more than 10 % of IE cases before 1945 (Straus and Hamburger 1966; Cunningham and Sinha 1995); now it is considered as an infrequent disease. The association with pneumonia, pericarditis, meningitis or abscess formation is relatively common. Our patient developed a pleural empyema and pneumococci were isolated from the pus. Thus, pneumococcal etiology of endocarditis is probable although blood cultivation was not performed. The case is interesting for the absence of fever for a long period. The destruction of the infected valve has been frequently described in pneumococcal endocarditis (Cunningham and Sinha 1995; Scheld and Sande 1995) but we feel corticosteroid treatment could enhance it as well.

Infections caused by *C. diphtheriae* have been extremely rare in Czechia since general vaccination against diphtheria was introduced in the 1940s. Because of excellent vaccination results, neither the general practitioners nor ear–nose–throat specialists were used to thinking of this etiology in their routine practice; international travel was very limited before 1990. The isolation of *C. diphtheriae* from blood in patient no. 3 was rather surprising. The strain was characterized as nontoxigenic which corresponds to the literature data claiming that IE is usually caused by nontoxigenic strains (Bayer and Scheld 2000). Nevertheless, several reports on IE due to toxigenic *C. diphtheriae* have occurred as well (Pike 1951; de Mattos-Guaraldi and Formiga 1998). The course of the disease in our patient remains rather ambiguous: He developed severe tonsillitis with pseudomembranes extending to neighboring tissues at first. This could be interpreted as clinical manifestation of toxin production. On the other hand, no symptoms of malignant diphtheria, such as edema of the throat or myocarditis, were present in the period of apparent *C. diphtheriae* bacteremia and/or sepsis. The explanation could possibly be based on heterogeneity of microbial population. Unfortunately, the microbe was not isolated from the tonsillar swab, perhaps due to the previous antibiotic administration.

G. morbillorum possesses very low virulence compared to the three above pathogens; nevertheless, it was described to cause endocarditis (Nandakumar and Raju 1997; La Scola and Raoult 1998; Farmaki *et al.* 2000; Ubeda-Ruiz *et al.* 2000; Espinosa-Villarreal *et al.* 2001) and other severe diseases. The frequency of severe *Gemella* infections can probably be under-estimated because of problems with correct taxonomical classification (La Scola and Raoult 1998). In the case described above, even the first period of fever might really endocarditis. There are some supporting arguments for this opinion: (*1*) all the three blood cultures drawn in the first episode were positive; (*2*) *S. mitis* used to be associated with endocarditis but it has not been known as an etiologic agent of pneumonia; (*3*) right-side pneumonia that was found in the first episode could be a consequence of embolism – identically as in the second one; (*4*) the negative result of the first echocardiography need not exclude IE even if the approach was transesophageal – the examination was difficult because of the unusual anatomic arrangement and postoperative sequels in the heart. Thus, *Gemella* endocarditis probably followed an episode of endocarditis due to *S. mitis*. We searched for the data of both microbes later on and verified their differences in both biochemical features and resistance pattern.

Our results support the suggestion that virtually any microbe can cause or contribute to the development of infectious endocarditis. Precise identification is necessary for optimal treatment strategy and consequently for good healing results.

REFERENCES

BAYER A.S., SCHELD W.M.: Endocarditis and intravascular infection, pp. 857–902 in *Principles and Practice of Infectious Diseases* (G.L. Mandell, J.E. Bennett, R. Dolin, Eds). Churchill-Livingstone, Philadelphia (USA) 2000.

BENEŠ J., VIECHOVÁ J., KABELKOVÁ M., HOROVÁ B.: Listerial endocarditis in a penicillin-allergic woman successfully treated with a combination of four drugs. *Scand.J.Infect.Dis.* **34**, 383–384 (2002).

CUNNINGHAM R., SINHA L.: Recurrent *Streptococcus pneumoniae* endocarditis. *Eur.J.Clin.Microbiol.Infect.Dis.* **14**, 526–528 (1995).

DURACK D.T.: Infective endocarditis, pp. 1638–1647 in *Cecil Textbook of Medicine* (J.B. Wyngaarden, L.H. Smith, J.C. Bennett, Eds). W.B. Saunders Publishers, Philadelphia (USA) 1992.

DURACK D.T., LUKES A.S., BRIGHT D.K.: New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings – duke endocarditis service. *Am.J.Med.* **96**, 200–209 (1994).

ESPINOSA-VILLARREAL J.G., GONZALEZ-REIMERS E., LECUONA M., RODRIGUEZ-GASPAR M., LOPEZ-LIROLA A.M., RODRIGUEZ-MORENO F., SANTOLARIA F., REVERT C.: Endocarditis por *Gemella morbillorum*. *Enferm.Infect.Microbiol.Clin.* **18**, 293 (2000).

FARMAKI E., ROILIDES E., DARILIS E., TSIVITANIDOU M., PANTELIADIS C., SOFIANOU D.: *Gemella morbillorum* endocarditis in a child. *Pediatr.Infect.Dis.J.* **19**, 751–753 (2000).

KARCHMER A.W.: Infective endocarditis, pp. 1077–1104 in *Heart diseases* (E. Braunwald, Ed.). W.B. Saunders Publishers, Philadelphia (USA) 1997.

KAYE D.: Infective endocarditis, pp. 520–526 in *Harrison's Principles of Internal Medicine* (A.B. Isselbacher, E. Braunwald, J.D. Wilson, Eds). McGraw-Hill, New York 1994.

LA SCOLA B., RAOULT D.: Molecular identification of *Gemella* species from three patients with endocarditis. *J.Clin.Microbiol.* **36**, 866–871 (1998).

DE MATTOS-GUARALDI A.L., FORMIGA L.C.D.: Bacteriological properties of a sucrose-fermenting *Corynebacterium diphtheriae* strain isolated from a case of endocarditis. *Curr.Microbiol.* **37**, 156–158 (1998).

MENASALVAS A., BOUZA E.: Endocarditis infecciosa por microorganismos poco frecuentes. *Rev.Esp.Cardiol.* **52** (Suppl. 2), 79–85 (1998).

NANDAKUMAR R., RAJU G.: Isolated tricuspid valve endocarditis in nonaddicted patients: a diagnostic challenge. *Am.J.Med.Sci.* **314**, 207–212 (1997).

PIKE C.: *Corynebacterium* endocarditis with report of a case due to toxigenic *Corynebacterium diphtheriae*. *J.Pathol.Bacteriol.* **63**, 575–585 (1951).

DE QUIROS B.J.C., MORENO S., CERCENADO E., DIAZ D., BERENGUER J., MIRALLES P., CATALAN P., BOUZA E.: Group A streptococcal bacteremia. A 10-year perspective study. *Med.Baltimore* **76**, 238–248 (1997).

SCHELD W.M., SANDE M.A.: Endocarditis and intravascular infection, pp. 740–783 in *Principles and Practice of Infectious Diseases* (G.L. Mandell, J.E. Bennett, R. Dolin, Eds). Churchill Livingstone, Philadelphia (USA) 1995.

STRAUS A.L., HAMBURGER M.: Pneumococcal endocarditis in the penicillin era. *Arch.Intern.Med.* **118**, 190–198 (1966).

UBEDA-RUIZ P., GUTIERREZ-MARTIN I., RAMIREZ-GALLEYMORE P., PEREZ-BELLES C., GOBERNADO-SERRANO M.: Endocarditis por *Gemella morbillorum* en un adico a drogas por via parenteral. *Rev.Clin.Esp.* **200**, 176–177 (2000).