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CASE REPORT

Successful Treatment of *Pasteurella multocida*-Related Invasive Infections with a Beta-Lactamase Inhibitor-Sparing Combination Antibiotic Regimen: A Case Series

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ABSTRACT

Pasteurella multocida, a Gram-negative, penicillin-sensitive coccobacillus that is frequently a member of the normal respiratory microbiota of different animals, remains a clinically important pathogen with the ability to cause severe disease. Few case reports have involved *P. multocida* infections without animal bites. Moreover, few reports have identified *P. multocida* as the causative agent of septic shock, which usually occurs in patients with cirrhosis and /or immunocompromised patients. To our knowledge, a human submandibular salivary gland abscess caused by *P. multocida* has not been reported. *Pasteurella* spp. are resistant to benzylpenicillin, and human isolates of beta-lactamase-producing resistant strains of *P. multocida* resistant have also been documented. The noteworthy findings of the current study were as follows: (i) the combination of ceftriaxone and ciprofloxacin successfully treated two patients infected with *P. multocida*; (ii) the first reported case of a septicemic patient with no history of animal bites and a submandibular *P. multocida* infection; and (iii) an immunocompetent patient in septic shock due to a *P. multocida* systemic infection.

Key words: *Pasteurella multocida*, sepsis, cat scratch, submandibular gland abscess

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INTRODUCTION

Pasteurella multocida is a Gram-negative microaerophilic coccobacillus that is well-known in veterinary medicine as an opportunistic pathogen and a member of the normal oral and upper respiratory tract microbiota in several animal species. Many species of *Pasteurella* are recognized as agents of endemic diseases and epizootic outbreaks. Zoonotic transmission of *P. multocida* to humans can occur via animal bites (cats and dogs are generally responsible for transmission), or less frequently via nasal secretions. *P. multocida* has been reported as the species of *Pasteurella* most frequently causing infectious disease in humans, and the incidence is on the rise [1-3].

The infectious complications from *P. multocida* that occur more frequently after a cat or dog bite affect the skin and soft tissues; however, there

are descriptions of lower respiratory tract infections (pneumonias, lung abscesses, and pleural empyemata) that are non-specific and generally more commonly involve patients already affected by chronic pulmonary diseases. Septic complications from *P. multocida* are life-threatening for humans, especially immunosuppressed humans [1].

There is also the possibility that localized infections involving the skin and/or soft tissues can become systemic infections, evolving into even more severe clinical entities, that are potentially fatal (e.g., central nervous system infections, bloodstream infections, and cardiac infections), with a higher incidence in patients with severe co-morbidities and immune deficiencies [1].

In rare cases, an invasive *P. multocida* infection can trigger septic shock, a condition described in the literature in < 100 cases [2], usually detected in frail hosts. In immunocompetent patients, *P. multocida* septicemia is uncommon, but the mortality rate is 30% [3].

Typically, patients who develop *P. multocida* bacteremia or septicemia have one or more predisposing conditions, including age > 65 years, a history of debilitating pulmonary disease, diabetes mellitus, advanced liver disease, or an immune response deficit, as well as exposure to bites or scratches from domestic dogs or cats.

We report on a rare case of *P. multocida* sepsis in an immunocompetent male starting that arose after cat scratches, and what we believe to be the first case of non-zoonotic submandibular gland abscess and sepsis due to *P. multocida* in a female patient with no history of animal bites.

We describe the clinical history of these episodes and the safety and efficacy of a beta-lactamase inhibitor-sparing antimicrobial treatment regimen. The relevant literature will also be discussed.

CASE REPORTS

An 82-year-old male with chronic ischemic dilated cardiomyopathy (New York Heart Association Functional Classification class II-III, with a decreased left ventricular ejection fraction <40%) and multiple co-morbidities (chronic kidney disease, G3b stage; hypothyroidism, and chronic hypertension), was admitted to the Infectious Disease Ward via the Emergency Department, where he presented with hyperpyrexia, chills, and multi-organ failure. On examination he was acutely ill and the vital signs were unstable, as follows: blood pressure, 85/55 mmHg; respiratory rate, 32/min; O_2 saturation, 86% (radial artery) on room air; heart rate, 120/min; and temperature, 38.8°C. Blood cultures were obtained to determine the cause of the sepsis with multi-organic dysfunction syndrome.

An A-P chest radiograph obtained in the emergency department showed mild-to-moderate cardiomegaly with redistribution of blood flow to non-dependent portions of the lungs and upper lobes, interstitial edema with peri-bronchial cuffing, and interlobular septal thickening.

The physical examination revealed two ulcerations involving the left lower extremity. The clinical history revealed cat scratches to the left leg 5 days before hospital admission.

Blood analysis revealed an elevated white blood cell (WBC) count (18,200 cells/mm^3) with 85% neutrophils, and a decreased hemoglobin concentration (10.1 g/dL) and platelet count (85,000/mm^3). Laboratory testing was notable for the following: C-reactive protein (CRP), 260 mg/L; procalcitonin (PCT), 45 ng/mL; creatinine, 2.3 mg/dl; sodium,127 mEq/L; potassium level, 5.5 mEq/L; aspartate aminotransferase (AST), 152 IU/L; alanine aminotransferase (ALT); 65 IU/L; lactate dehydrogenase, (LDH) 430 U/L; total bilirubin, 4.5 mg/dl; and direct bilirubin, 3.1 mg/dl.

The patient was treated empirically with piperacillin-tazobactam by the Emergency Department physician and was then admitted to the Infectious Diseases Ward for further care. Blood cultures were positive for Gram-negative bacilli (*P. multocida*) that were phenotypically susceptible to all tested antimicrobial agents.

P. multocida isolates were identified by direct application of matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry (MS) to blood culture broth. *P. multocida* isolates were susceptible to most of the widely used commercial antimicrobial agents, and the minimum inhibitory concentrations (MICs) were as follows: amikacin (8 μg/ml), amoxycillin/clavulanate (≤2 μg/ml), ampicillin (≤2 μg/ml), cephazolin (≤4 μg/ml), cefepime (≤ 1 μg/ml), cefotaxime (≤ 1 μg/ml), ceftazidime (≤ 1 μg/ml), gentamicin (≤ 1 μg/ml), imipenem (≤ 1 μg/ml), levofloxacin (0,12 μg/ml), meropenem (≤ 0,12 μg/ml), norfloxacin (0,12 μg/ml), piperacillin (≤ 4 μg/ml), piperacillin/tazobactam (≤ 4 μg/ml), and trimethoprim/sulfamethoxazole (≤ 20 μg/ml).

Intravenous (i.v.) therapy with ciprofloxacin (200 mg i.v. every 12 h; dose adjustment for renal impairment with creatinine clearance ≈30 mL/min) and ceftriaxone (standard dose = 2 g/day) was started with the blood culture results were available with drug dosages adjusted on the basis of renal function.

He remained afebrile and the leucocytosis resolved following treatment with i.v. ceftriaxone and ciprofloxacin. The patient had a remarkable clinical recovery and was discharged to home 11 days later, at which time he was switched to oral ciprofloxacin (250 mg twice daily for an additional 4 days).

He was evaluated 4 weeks later as an outpatient in the Cardiology Department and was doing better.

To the best of our knowledge, this is a rare case of *P. multocida* septic shock in an immunocompetent patient who was successfully treated with a beta-lactamase inhibitor-sparing antibiotic regimen.

An 85-year-old female who had previously undergone surgical procedures for breast and uterus cancers and had ischemic cardiomyopathy was admitted to the Infectious

Diseases Ward via the Emergency Department of our hospital for further evaluation of hyperpyrexia, vomiting, and altered consciousness, which included confusion, irritability, and disorientation. The patient lived with a small dog, but denied bites or scratches.

The patient had no recent history of odontalgia. The physical examination did not show focal neurologic deficits, but an enlarged, painful, tender right submandibular gland was noted with significant regional lymph node swelling. The vital signs were as follows: blood pressure, 135/85 mmHg; respiratory rate, 22/min; O_2 saturation, 93% (radial artery) on room air; heart rate, 96/min; and temperature, 39.5°C.

Laboratory test results at the time of admission were as follows: moderate leukocytosis with neutrophilia (15,580 and 10,390 cells/μL, respectively), creatinine,1.1 mg/dl; sodium, 129 mEq/L; potassium, 4.2 mEq/L; aspartate aminotransferase (AST), 44 IU/L; alanine aminotransferase (ALT), 51 IU/L; lactate dehydrogenase (LDH), 140 U/L; total bilirubin, 1.5 mg/dl; direct bilirubin, 0.7 mg/dl; PCT, 18 ng/mL; and CRP, 150 mg/L. Pus was aspirated from the submandibular abscess for the purpose of culture and sensitivity; the blood cultures were positive for *P. multocida*, which was phenotypically susceptible to all tested antimicrobial agents.

P. multocida isolates were identified by application of MALDI-TOF MS, and the MICs were as follows: amikacin (8 μg/ml), amoxycillin/clavulanate (≤ 2 μg/ml), ampicillin (≤ 2 μg/ml), cephazolin (≤ 4 μg/ml), cefepime (≤ 1 μg/ml), cefotaxime (≤ 1 μg/ml), ceftazidime (≤ 1 μg/ml), gentamicin (≤ 1 μg/ml), imipenem (≤ 1 μg/ml), levofloxacin (0,12 μg/ml), meropenem (≤ 0,12 μg/ml), norfloxacin (0,12 μg/ml), piperacillin (≤ 4 μg/ml), piperacillin/tazobactam (≤ 4 μg/ml), and trimethoprim/sulfamethoxazole (≤ 20 μg/ml).

Chest X-ray and abdominal ultrasonography failed to reveal a focus of infection, while salivary gland echography disclosed a diffuse enlargement of the right submandibular gland with an associated fluid abscess and swelling of satellite nodes. Intravenous therapy with full-dose ceftriaxone (2 g/day) and ciprofloxacin (400 mg every 8 h) was initiated. After ear, nose, and throat (ENT) and dentistry consultations excluded complications requiring surgical drainage, sequential oral therapy was continued 10 days after hospital admission with oral ciprofloxacin (750 mg every 12 h) until discharge to home after 4 days. Follow-up evaluations continued on an outpatient basis every 2 other weeks for 2 months. In this report, we present the first reported case of a septicemic patient with a submandibular abscess due to *P. multocida* infection without known trauma.

DISCUSSION

In recent years there has been an increase in documented cases of invasive *P. multocida* infections, likely reflecting the increased number of patients with acquired immunodeficiency syndrome and increased cohabitation with domestic pets. Systemic infections tend to predominantly affect individuals with severe chronic co-morbidities.

In a recent Australian study, the crude incidence of *Pasteurella* spp. infections increased from 1.5/100,000 population in 2000 to 11.4/100,000 population in 2021 [4].

In 2011 Vondra *et al.* conducted a systematic literature review, documenting and analyzing 187 cases of bacteremia caused by *P. multicida* [5]. One of the most salient findings of this extensive research derived from a search of Medline and EMBASE databases, was the recognition of septic shock in approximately one-third of the patients described and characterized by significant predisposing chronic co-morbidities [5]. In general, the development of *P. multocida* bacteremia or sepsis is associated with advanced chronic liver disease (18.6%), malignant neoplasms (16.7%), and hypertensive heart disease (13.5%) [3].

Of the 155 patients, 22.6% died mainly of septic shock and had chronic liver disease and/or severe acquired immunodeficiency syndrome [5].

An interesting study involving patients with *P. multocida* sepsis based on articles published in English and Japanese between 1984 and 2003 identified 46 cases of bacteremia / sepsis, 33% of which involved patients who were not immunosuppressed [6].

Another series of bacteremia cases reported between 1975 and 1984 was analyzed by Raffi *et al.* [1], who studied a series of 95 cases with a mortality rate of 37%.

We have performed an extensive literature search on the possible publications of other *P. multocida* submandibular gland infection cases or of the otorhinolaryngologic anatomic region, but we found only one case of bacteremic epiglottitis in a patient with a history of animal exposure [7].

Our analysis did not result in reports of submandibular gland abscess and salivary gland cases caused by *P. multocida*. Some authors have suggested the possibility of oropharyngeal colonization resulting from contact with animals, followed by potential dissemination to other ENT sites [7].

The tendency of *P. multocida* to develop resistance to different antibiotics and the increasing diffusion of toxinogenic strains (mostly serogroup D and some serogroup A) endowed with different virulence factors can complicate the treatment of invasive *P. multocida* infections [8]. For these reasons, the choice of the antibiotic regimen should be based on the antibiogram results [8].

Lin *et al.* [8] documented an increase in cases of clinically relevant infections caused by *P. multocida* strains resistant to erythromycin (100%) and quinolones (37.38%). The percentage of *P. multocida* strains exhibiting sensitivity towards ceftriaxone and quinolones was 80.00% and 62.22%, respectively [8].

Although a rare clinical entity, the prevalence of *P. multocida* disease in humans appears to be increasing, so

clinicians should be aware of the behavior of these infections, especially in frail and immunocompromised patients with severe and chronic co-morbidities. A history of contacts and/or scratches or bites from animals must further raise the clinical suspicion, and is thus worthy of a timely diagnostic and therapeutic approach.

Most of the studies have documented susceptibility of *P. multocida* to beta-lactams, carbapenems, second- and third-generation cephalosporins, and tetracyclines.

Pasteurella spp. are usually resistant to benzylpenicillin; however, beta-lactamase-producing *P. multocida* strains have been documented in human infections [9].

Treatment with beta-lactam antibiotics with beta-lactamase inhibitors, including amoxicillin-clavulanate, piperacillin-clavulanate and ticarcillin-clavulanate, have been reported as the most frequently prescribed antibiotics in invasive *P. multocida* infections. In our two cases, a beta-lactamase inhibitor-sparing antibiotic regimen with a combination of ceftriaxone and ciprofloxacin resulted in an appropriate antimicrobial response.

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CONFLICTS OF INTEREST

The authors declare that they had no funding and they declare that they had no competing interests.

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