IDCases 29 (2022) e01542

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Disseminated *Pasteurella multocida* in a patient with liver cirrhosis and spontaneous bacterial peritonitis – The role of cirrhosis-associated immune dysfunction

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ARTICLE INFO

Keywords:
Pasteurella multocida
Liver cirrhosis
Intra-abdominal infections
Peritonitis
Arthritis infectious

ABSTRACT

Disseminated *Pasteurella multocida* infection is rare and usually occurs in patients who are immunocompromised. Patients with liver cirrhosis seem to be particularly vulnerable; potentially related to cirrhosis associated immune dysfunction syndrome, frequently present in this population. While many patients report pet cat or dog bites or scratches, some patients develop infection even without obvious exposure, just from being in contact with animals. We present a patient with cellulitis and spontaneous bacterial peritonitis by *Pasteurella multocida* in whom infection disseminated and the patient developed bacteremia that seeded in the right acromioclavicular joint. We hypothesize that the port of entry for infection in our patient was contact with a pet cat through a chronic open leg wound. The patient was treated with intravenous ceftriaxone 2 g daily for 6 weeks and attained complete recovery.

Introduction

Spontaneous bacterial peritonitis (SBP) is a primary infection of ascitic fluid, in the absence of a secondary source of intra-abdominal infection [1]. It is the most common bacterial infectious complication in patients with liver cirrhosis (LC), developing in up to 35 % of patients, and this clinical event might herald the onset of liver decompensation [2,3]. The most common isolated pathogens are *Escherichia coli*, *Klebsiella spp*, *Proteus spp*, *Enterococcus faecalis*, and *Pseudomonas spp*. SBP due to *Pasteurella multocida* (PM) is rare and can occur as isolated peritonitis or as part of a disseminated infection.

LC is associated with an increased risk for infections directly proportional to the degree of liver damage. The incidence of bacterial infections in patients with LC is 5 times higher than in the general population [2]. Pathogenesis of bacterial infections in cirrhosis is multifactorial, including changes in gut microbiota, increased intestinal permeability that leads to an increase in bacterial translocation, and immune dysfunction. Cirrhosis-associated immune dysfunction (CAID) is a state of continuous immune system cell activation, leading to the production of proinflammatory cytokines. These cytokines affect both adaptive and innate immunity [2]. Particularly affected are neutrophils and mononuclear phagocytic cells, negatively impacting both their numbers and ability for phagocytosis. Combined with a reduction in reticuloendothelial mononuclear cells and porto-systemic shunting it is not surprising that patients with LC frequently suffer from these infections [2,3].

Bacteremia in patients with LC increases mortality and is frequently caused by multi drug resistant (MDR) bacteria. Mortality from PM bacteremia has been reported to be around 30 % [4].

While both SBP and bacteremia are common in LC, these infections due to PM are rare. We report about a patient with alcoholic LC who developed a disseminated PM infection, manifested as cellulitis followed by bacteremia, SBP, and septic arthritis.

Case presentation

A 44-year-old man with decompensated alcoholic LC presented with a one day history of worsening jaundice, diffuse abdominal pain,

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https://doi.org/10.1016/j.idcr.2022.e01542
Received 21 March 2022; Accepted 15 June 2022
Available online 21 June 2022

subjective fevers, progressive erythema in his left leg, and dull right shoulder pain. He denied recent trauma or prolonged immobilization. He reported regular 2–4 soft consistency bowel movements per day and denied any insomnia or confusion. He resided in Wisconsin and lived with one dog and three cats. He presented with no animal bites or scratches. In addition to LC, he also had a chronic left leg wound secondary to chronic venous stasis (see Graphic 1A), chronic thrombocytopenia secondary to LC, anemia of chronic disease, portal hypertensive gastropathy, esophageal varices grade 1, and recurrent ascites needing weekly paracentesis (last paracentesis was 6 days before admission). He had no history of prior SBP, but he had low total protein ascites. He was not on SBP prophylaxis due to non-compliance.

His temperature was 38.4 °C, blood pressure 160/65 mmHg, heart rate 114 beats per minute, respiratory rate of 22 breaths per minute with oxygen saturation normal at room air. Physical exam was significant for alert, pale and icteric, distressed due to abdominal pain. Mucous membranes were dry. The neck was supple without rigidity. Heart and lung exam was normal. Abdomen was distended with positive ascitic wave, and diffuse tenderness to palpation without guarding or rebound. Lower extremities had bilateral pitting edema, predominant on the left. There was an open wound with irregular borders located in distal third of anterior left shin with yellowish secretion and some black discoloration (see Graphic 1B) associated with surrounding erythema which extended medially up to posterior aspect of left thigh. Distal pulses were palpable. Right shoulder was non-tender to palpation and had no limitation for flexion and extension. There was no other joint tender to palpation.

Initial laboratory workup showed hemoglobin 9.3 g/dL, platelet count 86 $\times$ 10^9/L (both at his baseline), leukocytosis 17.0 $\times$ 10^9/L with neutrophilia, lactic acid 6.5 mmol/L, ammonia 43 mcmol/L, INR 2.2, C-reactive protein 45.5 mg/L, magnesium 2.2 mg/dL, potassium 5.2 mmol/L, sodium 136 mmol/L, bicarbonate 14 mmol/L, anion gap 20, creatinine 1.19 mg/dL (patient's baseline), glucose 93 mg/dL, AST 66 U/L, ALT 26 U/L, alkaline phosphatase 48 U/L, total serum protein 6.5, serum albumin 3.0 g/dL, LDH 273 U/L, total bilirubin 5.1 mg/dL, lipase 18 U/L, SARS-Coronavirus-2 PCR negative. Urinalysis was negative for infection. Ascitic fluid obtained from paracentesis showed yellow cloudy fluid appearance, total nucleated cells of 20,375/mcL with 86 % neutrophils and 14 % lymphocytes, LDH was 86 U/L, total protein 1.0 g/dL, albumin 0.5 g/dL, glucose 61 mg/dL, amylase 20 U/L. The Gram stain did not show any organisms. Computed tomography of abdomen and pelvis with oral and IV contrast was negative for intra-abdominal source of infection. Chest x-ray did not show any infiltrates. X-ray of left tibia and fibula with diffuse soft tissue edema and no definite acute bone abnormality. Ultrasound of the left lower extremity was negative for deep venous thrombosis.

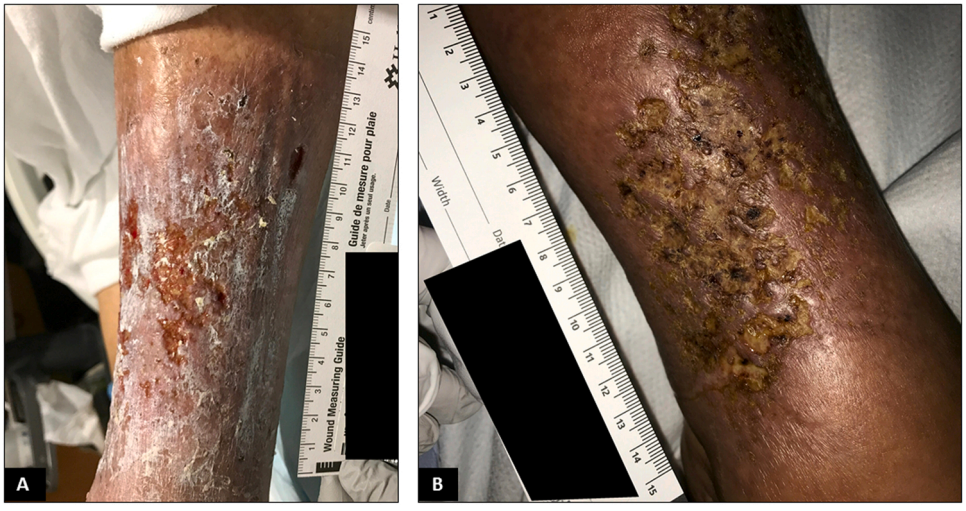
The patient was treated with 2 liters IV fluids and started on intravenous (i.v.) Ceftriaxone and Vancomycin. He was admitted to the intensive care unit under the diagnosis of sepsis secondary to SBP. He received IV albumin 1.5 g/kg on day 1, and 1 g/kg on day 3. Blood cultures collected on admission and ascitic fluid culture grew PM (see Graphic 2). Patient's abdominal pain started to improve, and he remained afebrile. However, on the third hospital day he developed persistent right shoulder pain with new mild limitation for flexion and extension of right arm. Magnetic resonance imaging (MRI) of the right shoulder without and with IV contrast showed osteolytic change at the distal clavicle with some edema seen at the adjacent acromioclavicular (AC) joint worrisome for septic arthritis. Debridement and irrigation of the right shoulder revealed significant acute osteomyelitis of the distal clavicle and tip of the acromion, purulence and necrotic tissue surrounding the AC joint. Patient's abdominal pain and right shoulder pain gradually improved. Blood cultures were obtained on day 2, and right shoulder surgical cultures remained negative. IV Ceftriaxone was continued for 6 weeks. Patient was discharged to a short term rehabilitation facility to complete antibiotic therapy with plans to continue antibiotic SBP prophylaxis indefinitely with oral Norfloxacin or Bactrim.

Discussion

Pasteurella spp are small, nonmotile, non-spore-forming Gram-negative coccobacilli. PM, the organism cultured from the blood and ascitic fluid in this case, is the most common pathogen that resides in the normal upper respiratory flora of animals and fowls. Ten minutes of direct exposure to sunlight kills the organism, but it can live in soil for up to 21 days and in water for up to 25 days. Potential bacterial virulence factors include capsule, lipopolysaccharide, sialidases, hyaluronidase, surface adhesions, iron acquisition proteins, and toxin [5].

PM has the ability to infect a multitude of hosts, including humans, companion animals, livestock, and wildlife and is found worldwide. In a prospective case series conducted to define the bacteria responsible for infections of dog and cat bites, it was found that *Pasteurella spp* were the most frequent isolates from both dog (50 %) and cat bites (75 %) [6]. Although pet cat and dog bites are commonly reported to cause infection, it may also result from bites of other animals.

Upper extremities bite lesions have been more common than lower extremity lesions which may be explained by pet handling. Non-bite infections have been reported as well. In a study of 79 cases with 34 non-bite infections, open wounds in the lower extremities (especially in



Graphic 1. A. Chronic left lower extremity wound. Photo taken approximately 6 weeks before hospital admission, B. Area of cellulitis seen around chronic left lower extremity wound at the time of hospital admission.

Graphic 2. Left picture: chocolate agar plate. Right picture: blood agar plate.

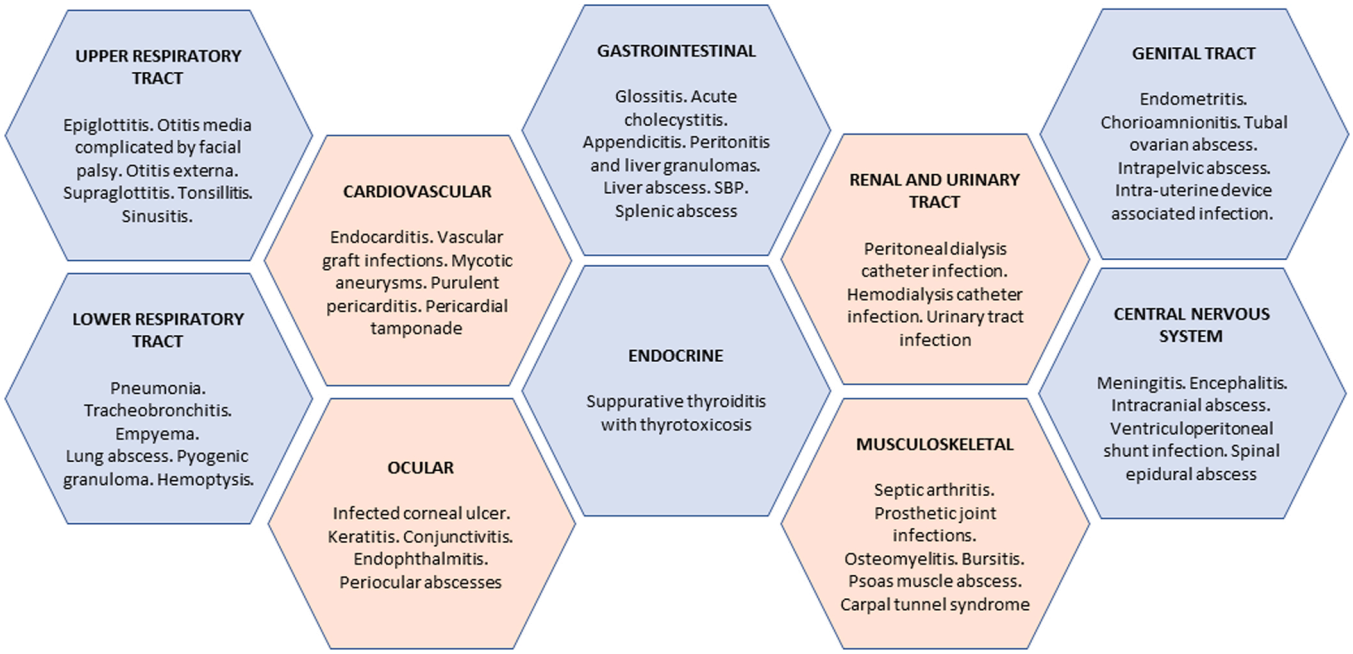
the feet) were the most common entry point for non-bite infection, followed by inhalation [7]. Abrasions or wounds contaminated with animal saliva, and fomites like a contaminated pacifier have been identified as transmission sites of PM [7]. Kissing and sharing food with pets should also be avoided as this has been found to be related to cases of meningitis and sinusitis [8,9]. Human to human, vertical infection, and infection by contaminated blood products have also been documented [10,11].

PM infections most commonly present as localized infections such as cellulitis or abscesses. Respiratory and oropharyngeal infections are more commonly seen in patients with underlying chronic pulmonary diseases. Other sporadic types of PM infections [7] are described in Graphic 3. Systemic infections are rare and usually present without a recent bite [4]. Endocarditis, meningitis, and peritonitis are considered rare manifestations [4,8,12–15]. PM bacteremia can occur from a localized bite wound infection or from another localized source of infection. Patients with bacteremia are usually immunocompromised with most of them having a history of LC, solid tumors, and hematologic malignancies [4].

Severe PM infections have been reported mostly in neonates, elderly, and immunocompromised people. Patients presenting without a bite are more frequently bacteremic, have more comorbidities, or are immunosuppressed. They also tend to develop more severe disease requiring hospitalization, an intensive care level of care, with longer hospital stay, and higher mortality compared to individuals who develop bite related infections [4,7], which is similar to our case presentation.

The dynamic immune dysfunction seen in the progression of LC and acute LC decompensation may significantly affect the susceptibility of the host and explain the increased risk of developing uncommon infection presentations like the one described in our case. CAID involves a low-grade and a high-grade phenotype of systemic inflammation, the latter being more common in decompensated LC and causing higher levels of inflammation with significant immune deficiency; increasing the susceptibility of the host to infection and organ failure, short-term mortality, and poor prognosis. In addition, alcohol consumption can promote inflammation in other organs which has additional consequences on host immunity [16].

Clinical manifestations of infection by PM are non-specific and depend on the localization of the infection. Soft tissue infections have a characteristic rapid and intense inflammatory response with extreme



Graphic 3. Other sporadic types of PM infection by systems.

pain and swelling usually present within 24 h of the initial injury, earlier if the injury was related to a cat bite. Most infections involving a joint have no history of direct injury and are acquired by hematogenous spread as illustrated in the case we described. While PM has predilection for prosthetic joints or joints affected by degenerative joint diseases, native joints can be affected as well [17]. Osteomyelitis is usually a consequence of local extension of the primary soft tissue infection, or direct inoculation into the periosteum. Cats have long sharp teeth with high probability to penetrate periosteum, hence, cat bites are more prone to cause bone infection than dog bites.

SBP in patients with LC caused by PM is rare. Search of PubMed database of case reports in the last 20 years (2002–2022) using the keywords "spontaneous bacterial peritonitis", "liver cirrhosis" and "*Pasteurella multocida*" yielded 4 cases after excluding a case secondary to *Pasteurella dagmatis*. Wallace et al., reported a case with bacteremia and peritonitis after right lower extremity cellulitis following a puncture injury from a cactus in a property with feral cats [12]. Lutz et al., reported a non-bite case of a patient with a cat at home. This case claimed to be the first case that occurred while a patient was taking Rifaximin for SBP prophylaxis [13], like in our case. However, routine full susceptibility testing of Pasteurella isolates is not always needed for management, and there is no evidence that Rifaximin is effective for treatment of PM infections in humans. Rifaximin is not the first drug of choice for PM treatment, and susceptibility testing does not routinely include Rifaximin as per Clinical Laboratory Standards Institute (CLSI) guidelines [18]. Tamaskar et al., reported a non-bite case. Their review of the literature before 2002 found a total of 12 case reports of SBP by PM with 9 cases related to animal exposure [14]. Hey et al. reported a case where the exposure was related to a cat licking a serous exudate from cellulitis with no open wound [15].

Our patient met criteria for SBP based on ascitic fluid culture and neutrophil count in ascitic fluid. The serum-ascites albumin gradient was 2.5 (>1.1), suggestive of portal hypertension which increases the probability of SBP. The total protein in ascitic fluid is important to differentiate SBP from secondary bacterial peritonitis. If ascitic fluid total protein is <1 g/dL (1.0 g/dL in our case) it means dilute ascites with higher risk of SBP. Perforation peritonitis usually shows a polymicrobial infection in Gram stain, ascitic total fluid protein >1 g/dL, glucose <50 mg/dL, and LDH > the upper limit of normal of serum (none of these criteria were met in our case). Ascitic fluid amylase is increased in patients with pancreatitis or gut perforation. It is critical to differentiate SBP from secondary bacterial peritonitis as surgical intervention is essential to decrease mortality in these patients. In our case, the patient had a chronic open wound which was most likely the point of entry of the infection.

Penicillin is typically the treatment of choice for PM. Rare penicillin-resistant *Pasteurella spp* infections have been reported [19]. PM has also shown susceptibility to other antibiotics such as fluoroquinolones, third or later generation cephalosporins, tetracyclines, carbapenems and trimethoprim-sulfamethoxazole which offer other options for penicillin resistant strains [20]. Non-complicated infections can be treated with oral antibiotic therapy such as amoxicillin-clavulanate for 10 days or longer depending on clinical response. Intravenous therapy is recommended in high risk patients and patients with rapid progression of symptoms despite oral therapy. Once clinical response is achieved, IV antibiotics could be switched to oral therapy to complete 5–14 days of treatment [20]. For patients with moderate to severe disease, intravenous therapy is also recommended. Monotherapy treatment can be initiated with ampicillin-sulbactam, piperacillin-tazobactam, carbapenem, or combination of ceftriaxone with metronidazole or clindamycin [20]. PM bacteremia is usually treated for 14 days from first negative culture [12]. The most frequent duration of treatment for cases of meningitis is 14–21 days but it could be extended based on presence of complications and clinical response [8]. Third generation cephalosporins are the most recommended empiric treatment for SBP suspected by PM [15]. In our case, ceftriaxone was used alone as cultures and sensitivities showed no other microorganism and PM had predictive sensitivity to penicillins. Therefore, monotherapy for septic arthritis and osteomyelitis with IV ceftriaxone for 6 weeks was recommended. In addition to antibiotic treatment, PM infections may require surgical intervention for wound debridement, drainage of abscesses or cleaning of septic joints. In our case, the patient required incision and debridement of the right shoulder for treatment of septic arthritis.

Conclusions

PM could be considered an opportunistic pathogen, and can cause severe, life-threatening infection. Patients with liver cirrhosis seem to be particularly vulnerable due to CAID. While most infections develop after direct contact with animals through bites or scratches, non-bite infections are associated with more severe clinical presentation. In cirrhotic patients, such as the patient we report, localized infection (cellulitis) can progress to bacteremia and disseminate to distant sites (AC joint and peritoneal fluid). Prompt recognition and aggressive and appropriate management is crucial for a positive outcome.

CRedit authorship contribution statement

Libardo Rueda Prada: Study Design, Data Collection, Statistical Analysis, Data Interpretation, Manuscript preparation, Literature search; **Milena Cardozo**: Manuscript preparation, Literature search; **Ann Hudson**: Manuscript preparation, Literature search; **Matthias McDermott**: Literature search; **Diana C. Urbina Verjel**: Literature search Igor Dumic: Manuscript preparation, Literature search

Ethical approval

Not applicable.

Consent

Written, informed consent for publication was obtained from the patient for the case report and imaging.

Sources

None to be reported.

Conflict of interest

None to be reported.

Acknowledgements

Alyssa R. Fedie, Microbiology Technical Coordinator, Department of Laboratory Medicine and Pathology at Mayo Clinic Health System, Eau Claire, WI, for providing culture graphics.

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