Medical Laboratory Journal
Online ISSN: 2538-4449
Golestan University of Medical Sciences

Isolation of *Pasteurella multocida* and pan-drug-resistant bacteria causing nosocomial infection in a patient with multiple sclerosis: A Case Report and Literature Review

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Abstract

Pasteurella species are one of the most common pathogenic bacteria in domestic animals, and they are seen more in people with weak immune systems. This research aims to investigate a case of a patient with multiple sclerosis from whose sputum *Pasteurella multocida* (*P. multocida*) was isolated. The patient was a 28-year-old man with multiple sclerosis who had persistent coughs due to food being stuck in his throat. The patient was a 28-year-old man with multiple sclerosis who had persistent coughs due to food being stuck in his throat. The primary diagnosis was pneumonia hydropneumothorax and complete collapse of the left lung. The patient's sputum culture after the first visit to the hospital was positive for *P. multocida*, which was not found in a second culture. In the subsequent cultures of the patient, *Acinetobacter*, *Klebsiella*, *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Citrobacter* were found, which had extensive drug resistance to all antibiotics. In the secondary computerized tomography (CT) scan, mild pleural effusion on the left side, pneumothorax, and complete collapse with bronchiectasis was seen. Despite the treatments, the patient finally died of cardiac arrest and bradycardia. Infection with *P. multocida* was found in a patient with multiple sclerosis. Also, hospital-acquired infections with drug resistance caused by the weakness of the patient's system appeared in the patient who was hospitalized in the intensive care unit (ICU), and finally, the patient died. According to antibiotic patterns, the best antibiotic to which the bacteria is sensitive can be considered the primary treatment to avoid irrational antibiotic prescriptions.

Article History

Received: 31 May 2023
Received in revised form: 27 August 2023
Accepted: 12 September 2023
Published online: 20 August 2024
DOI: 10.29252/mlj.18.4.27

Keywords

Pasteurella Multocida
Drug Resistance, Bacterial
Cross Infection
Multiple sclerosis

Article Type: Case Report

Introduction

Hospitalization of patients with multiple sclerosis (MS) is associated with the risk of various infections. The frequency of hospital infections in these patients is 4.26%, and MS patients have a higher rate (1.76%) of different infections (1.25%). The one-month mortality rate in patients with multiple sclerosis after hospitalization due to infection was associated with a relative risk of 4.69% (1,2). Pathogens associated with the development or exacerbation of MS include bacteria such as *Chlamydia pneumoniae*, *Staphylococcus aureus*, *Candida*, herpesviruses such as Epstein-Barr virus and human herpesvirus and human endogenous retroviruses (HERVs) (3). *Pasteurella* species are one of the most common pathogenic bacteria common to domestic animals and humans. *Pasteurella* species are commonly cultured from the oral cavity of cats and dogs (4). *Pasteurella multocida* (*P. multocida*) is the most frequently isolated species of the *Pasteurella* genus, linked to both chronic and acute infections. Overall, mortality rates associated with this pathogen are generally low. Most human infections are wound infections associated with cat (75% of injuries from cat bites) and dog (50% of injuries from dog bites) bites or scratches (5). Also, infections may include septic arthritis, osteomyelitis, artificial joint infection, meningitis, respiratory tract infections in patients with underlying airway or lung disorders, endocarditis, sepsis, bacteremia, and colonization in the lower part (6,7). There is evidence that this infection is more common in people with underlying diseases and weak immune systems. In multiple sclerosis, an autoimmune disorder, the body's immune system attacks normal tissues. Individuals affected are susceptible to infections, respiratory issues, muscle spasms, and swallowing difficulties. (7,8). This article presents a patient with multiple sclerosis from whose sputum *P. multocida* was isolated.

Case presentation

The patient was a 28-year-old man living in the village with a history of multiple sclerosis who complained of difficulty in swallowing food and persistent coughs due to food getting stuck in the throat. About a month ago, until the time of referral, food got stuck in the patient's throat when eating. For a month until the time of referral, he had numerous coughs during the day; after a month, the patient's coughs were more frequent. The patient has been unable to swallow and chew food since October 4, 2022, due to excessive phlegm and secretions. He was also observed to have increased breathing sounds, fever, chills, and sweating. The patient was referred to Ayatollah Rouhani Educational Hospital in Babol after approximately 30 days on May 11, 2022. The patient exhibited several symptoms, including a cough with phlegm, difficulty breathing, sharp chest pain, anxiety, wheezing, headaches, and dizziness. He also experienced a punctured lung and breathlessness, and sometimes noted by a whistling sound during breathing. The patient's initial diagnosis was performed using a computerized tomography (CT) scan. Real-time PCR did not show any sign of Coronavirus disease (COVID-19). Other observations included pneumonia, extensive hydropneumothorax in the left hemithorax and complete collapse of the left lung, pneumothorax, cystic bronchiectasis in the right middle lobe, ground glass appearance or opaque glass opacity, and lymphadenopathy in the paravascular space. Following the patient's initial diagnosis in the intensive care unit (ICU), tracheostomy, nasogastric intubation, and tracheal and intrathoracic intubation were performed (Figure 1).

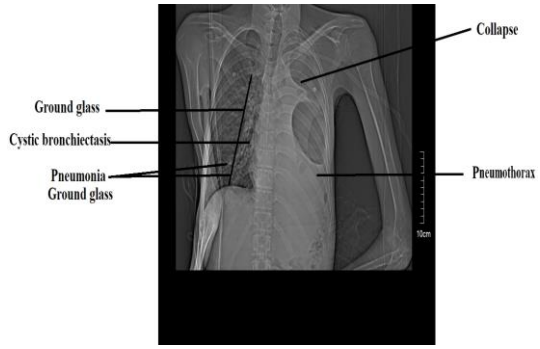

Figure 1. Initial CT scan findings in the patient suffering from multiple sclerosis with a lung infection.

Following the initial hospital visit, the patient's sputum culture was positive for *P. multocida* (4) and the *Candida* genus. We ensured the patient did not come into contact with the related animal. Moreover, there were no signs of bites or wounds caused by the animal's grip on the patient's body. Also, the patient and the patient's family stated that they did not have any pets and that the patient was not in contact with any animals outside of their residence. It should be noted, however, that the patient might have been in contact with the animal unintentionally or accidentally. However, the patient and his companions did not clarify this and denied any association with pets. In the second culture of the patient's sputum, *P. multocida* and *Candida* genus were not found, but *Acinetobacter* and *Klebsiella* were positive. The patient seemed to suffer from associated bacterial infections or nosocomial infections. It is worth mentioning that the bacteria were resistant to all antibiotics tested in the laboratory. The culture of the patient's sputum and pleural fluid for the third time was again positive due to the presence of *Acinetobacter* and *Klebsiella*. Moreover, testing

their antibiotic sensitivity pattern for all the antibiotics mentioned in the third and second times, except for colistin (10 µg) in the pleural fluid, was conducted. Pan-drug-resistant *Acinetobacter* and *Klebsiella* were observed for the third and second time. The fourth culture to check the infection revealed the presence of *Acinetobacter*, which was sensitive to amikacin. The Fifth and sixth microbiological cultures showed the presence of *Candida* in the patient's urine sample. The seventh culture round included *Citrobacter* infection urine and sputum infected with *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Citrobacter* with a pan-drug-resistant to all antibiotics (9,10). Because the patient was in a critical condition, information about the antibiogram of the specimens taken from the patient was done urgently. Therefore, a phone call was made to the ICU department, and necessary explanations were given to the relevant nurse and specialist. Also, the antibiogram results were sent to the ICU department in writing and recorded in the hospital's health information system (HIS).

Antimicrobial susceptibility testing was performed using the disc diffusion method, following the recommendations of the Clinical and Laboratory Standards Institute (CLSI) (Table 1) (9). Selective and repeated antibiotic treatments included: amikacin (100 mg), ampicillin/sulbactam (1.5 g) (1 g ampicillin/0.5 g sulbactam), and clomycin (1000000 units), clindamycin (150 mg and 300 mg), imipenem (1 g) and meropenem (1 g and 500 mg). Caspofungin (50 mg) and fluconazole (150 mg) were also prescribed to the patient. Chlorhexidine mouthwash 0.2% was recommended to wash the patient's mouth and reduce oral microbes, and diphenhydramine 12.5 mg/ml was used to reduce cough. Following the treatments, bronchoscopy and tracheostomy were performed for the patient. Respiratory distress syndrome was diagnosed in the patient, and fentanyl was prescribed for the patient. The patient's sputum was still abundant and in the form of green and foul-smelling secretions. Acetylcysteine was prescribed to the patient to help expel phlegm from the respiratory tract. Clinical tests revealed a decrease in blood potassium (Hypokalemia) in the patient, and furosemide (40 mg) was prescribed. Since the patient was hospitalized for a long time and many tests were performed, only the first and last tests were presented to check how the treatment progressed. Only the significant tests were mentioned in the text (Table 2).

Table 1. Bacteriology findings and antibiogram of the patient suffering from multiple sclerosis.

The name of the bacteria	Appointment and date of sampling	Type of the sample taken	Sensitivity to antibiotics	Intermediate pattern to antibiotics	Resistance to antibiotics
Pasteurella multocida	First 2022 - 5 - 13	Sputum	Amikacin (30 µg), gentamicin (10 µg), ciprofloxacin (5 µg), colistin sulfate (10 µg), ceftazidime (30 µg), meropenem (10 µg)	-	Nalidixic acid (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), cefazolin (30 µg) and ceftriaxone (30 µg)
Acinetobacter	Second 2022 - 5 - 25	Sputum	-	-	Amikacin (30 µg), gentamicin (10 µg), nalidixic acid (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), ciprofloxacin (5 µg), ceftazidime (30 µg), ceftriaxone (30 µg) and meropenem (10 µg)
Klebsiella	Second 2022 - 5 - 25	Sputum	-	-	Amikacin (30 µg), gentamicin (10 µg), nalidixic acid (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), ciprofloxacin (5 µg), ceftazidime (30 µg), ceftriaxone (30 µg) and meropenem (10 µg)
Acinetobacter	Second 2022 - 5 - 25	Pleural fluid	Colistin (10 µg)	-	Amikacin (30 µg), gentamicin (10 µg), nalidixic acid (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), ciprofloxacin (5 µg), ceftazidime (30 µg), ceftriaxone (30 µg) and meropenem (10 µg)
Klebsiella	Second 2022 - 5 - 25	Pleural fluid	Colistin (10 µg)	-	Amikacin (30 µg), gentamicin (10 µg), nalidixic acid (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), ciprofloxacin (5 µg), ceftazidime (30 µg), ceftriaxone (30 µg) and meropenem (10 µg)
Acinetobacter	Third 2022 - 5 - 30	Sputum	-	-	Amikacin (30 µg), gentamicin (10 µg), nalidixic acid (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), ciprofloxacin (5 µg), ceftazidime (30 µg), ceftriaxone (30 µg) and meropenem (10 µg)
Klebsiella	Third 2022 - 5 - 30	Sputum	-	-	Amikacin (30 µg), gentamicin (10 µg), nalidixic acid (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), ciprofloxacin (5 µg), ceftazidime (30 µg), ceftriaxone (30 µg) and meropenem (10 µg)
Acinetobacter	Fourth 2022 - 6 - 10	Sputum	Gentamicin (10 µg)	Amikacin (30 µg)	Ciprofloxacin (5 µg), ceftazidime (30 µg), Ceftriaxone (30 µg) and Meropenem (10 µg)
-	Fifth 2022 - 6 - 10	Urine	-	-	-
-	Sixth 2022 - 6 -21	Urine	-	-	-
Citrobacter	Seventh 2022 - 7 - 5	Urine	-	-	Amikacin (30 µg), gentamicin (10 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), ciprofloxacin (5 µg), ceftazidime (30 µg) and ceftriaxone (30 µg)(
P. aeruginosa	Seventh 2022 - 7 - 5	Sputum	-	-	Amikacin (30 µg), gentamicin (10 µg), nalidixic acid (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), ciprofloxacin (5 µg), ceftazidime (30 µg), ceftriaxone (30 µg) and meropenem (10 µg)

µg= Micrograms

Table 2. General tests were performed (first and last tests) on the patient

First General tests 11 - 5 - 2022	Test	Results	Unit	Reference value	Last General tests 21 - 7 - 2022	Test	Results	Unit	Reference value
Complete blood count	White blood cells	17700	cells/mcL	4000-10500	Complete blood count	White blood cells	6500	cells/mcL	4000-10500
	Red blood count	3.55	cells/mcL	4.2-5.4		Red blood count	3.21	cells/mcL	4.2-5.4
	Hemoglobin	9.8	g/dL	11.6-15		Hemoglobin	8.7	g/dL	11.6-15
	Hematocrit	29.7	cells/mcL	0.36-0.46		Hematocrit	27.43	cells/mcL	0.36-0.46
	MCV	83.7	fL	79-98		MCV	85.4	fL	79-98
	MCH	27.6	pg/cell	27-30		MCV	27.1	pg/cell	27-30
	MCHC	33	g/dL	31-37		MCHC	31.8	g/dL	31-37
	Platelets	698000	cells/mcL	450000-15000		Platelets	101000	cells/mcL	450000-15000
Biochemistry	BUN	17	mg/dL	9-20	Biochemistry	BUN	32	mg/dL	9-20
	Creatinine	0.6	mg/dL	0.7-1.4		Creatinine	9.2	mg/dL	0.7-1.4
	Sodium	135	mmol/L	131-146		Sodium	133	mmol/L	131-146
	Potassium	4	mmol/L	3.6-5.1		Potassium	3/4	mmol/L	3.6-5.1
	RBS	81	mg/dL	140 >		RBS	105	mg/dL	140 >
	Lactate dehydrogenase	428	U/L	480 >		Lactate dehydrogenase	-	-	-
	C-reactive protein	*174	mg/L	10 > negative, 10 < positive		C-reactive protein	-	-	-
Hemostatic	PT	*13.4	S	11-13.5	Hemostatic	PT	13.5	S	11-13.5
	PTT	12	S	11-13.5		PTT	12	S	11-13.5
	INR	1.2	S	2.0-3.0		INR	1.2	S	2.0-3.0
	PTT	44	S	25-45		PTT	26	S	25-45

MCV= Mean Corpuscular Volume, MCH=Mean Corpuscular Hemoglobin, MCHC= Mean Corpuscular Hemoglobin Concentration, BUN= Blood Urea Nitrogen, RBS= Random Blood Sugar levels, PT= Prothrombin Time, PTT= Partial Thromboplastin Time, INR= International Normalized Ratio, PTT=Partial Thromboplastin Time, mcL= Million red blood cells per microliter, g/dL= Grams per deciliter, fL= Demtoliter, pg/cell= Picograms per cell, mg/dL= Milligrams per deciliter, mmol/L= Millimoles per liter, U/L= Units per liter, mg/L=Milligrams per liter, S= Second

A CT scan was conducted on the patient. A Centrilobular lung nodule with a branched appearance in the left lobe of the lung indicated aspiration pneumonia. Para-aortic lymph node and abdominal ascites were prominent. The results of the secondary CT scan in the patient showed mild pleural effusion on the left (With a significant reduction compared to the previous CT scan), pneumothorax, complete collapse, and mild peri-bronchovascular ground glass in the right lobe (Figure 2).

Oxygen saturation measurement (SpO2) indicated a level of less than 95% (Normal SpO2 for both adults and children is between 95% - 100%). Therefore, the patient was connected to a ventilator due to tachycardia and symptoms of stricture and defecation problems. No other abnormal presentations were observed in the patient. On July 14, 2022, the patient was moved to the ward without any signs of respiratory distress. On July 16, 2022, the patient exhibited severe symptoms of the disease and was admitted to the ICU, where a ventilator was connected. Despite the treatments administered, on July 20, 2022, the patient's vital signs deteriorated, leading to a coma and eventual death from cardiac arrest and bradycardia. (Ethic code: IR.MUBABOL.HRI.REC.1401.140).

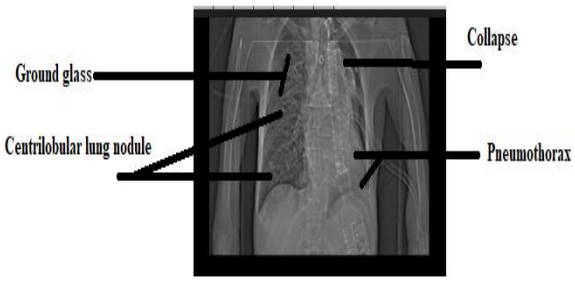

Figure 2. Final CT scan findings in multiple sclerosis patients with a lung infection

Discussion

P. multocida is part of the natural flora in the nasopharynx or in many digestive tracts in domestic and wild animals. Meningitis related to this bacterium is caused by cat bite (11%), animal contact without a bite (72%), and the absence of recognized animal contact (17%) (11). In the present study, a patient with multiple sclerosis who was referred to the hospital due to difficulty in swallowing food was diagnosed with *P. multocida* pneumonia and was admitted to the ICU. Bacteremia and septicemia caused by this bacterium are typically observed in immunocompromised patients; however, the infection has also been reported in individuals with healthy immune systems and can be equally dangerous if not treated properly. Non-bite infections from this bacterium require more intensive care than bite infections from animal bites, are more likely to occur in patients with severe comorbidities, and are also more likely to result in death. In a case report, fever, chills, and greenish sputum are reported as clinical manifestations of infection with *P. multocida* is reported in a 70-year-old man; these presentations were also seen in our patient (12). Moreover, in the literature, there are clinical reports of patients infected with *P. multocida* who were treated using cefepime (Fourth-generation cephalosporins), amoxicillin (Penicillin)/clavulanic acid (Beta-lactamase inhibitor), piperacillin-tazobactam (Penicillin and beta-lactamase inhibitors), amoxicillin (Penicillin family and beta-lactams) (Table 3) (13-22).

In our patient, the antibiotic resistance pattern showed that the bacteria were sensitive to ceftazidime (Third-generation cephalosporins), meropenem (Beta-lactam antibiotic), and ampicillin (Beta-lactam family)/sulbactam (Beta-lactamase enzyme inhibitor) was used. Antimicrobial resistance in *Pasteurella* isolates has rarely been reported in human infections. Ampicillin-sulbactam and amoxicillin-clavulanic acid are excellent empirical options and first-line parenteral antibiotic treatments for animal bite injuries. Some studies have shown amoxicillin resistance but sensitivity to amoxicillin-clavulanic acid. This can be attributed to the β-lactamase Temorina (TEM)-1 gene that is detected by the polymerase chain reaction (PCR) (23). The repetition of sample cultures in the following days, according to the treatment with the mentioned antibiotics in various types of research, and negative and partial recovery in patients have also been reported. Similarly in our study, sputum sample cultures were negative in the next visit. Therefore, these results indicate that the mentioned antibiotics can be effective against *P. multocida*. Thus, treatment with antibiotics that are in the group or family of these antibiotics (Such as ampicillin/sulbactam and piperacillin/tazobactam, tobramycin, trimethoprim/sulfamethoxazole) was the first choice of treatment, and cured a 59-year-old female patient (24). *P. multocida* can be dangerous and even fatal in 35% of immunocompromised people. There were 49 patients suffering from *Pasteurella* species peritoneal dialysis (25,26). Infection in people with multiple sclerosis can cause relapse. Chronic prophylactic treatments work differently, but they all modulate and interfere with the patient's immune response. Therefore, these immune system active therapies are likely to help with the emergence of viral, bacterial, or fungal infections. On the other hand, hospital infections in intensive care units are severe problems due to high mortality and complications. Lower respiratory tract infections, pneumonia, ventilator and central venous catheter-related pneumonia, bloodstream infections, and catheter-related urinary tract infections are the most common infections, respectively. *Acinetobacter*, *Klebsiella* pneumonia (K. pneumonia), *P. aeruginosa*, and *Candida* have been isolated from patients with multi-microbial or mono-microbial infections. In our study, the patient appeared after the treatment of *P. multocida* infection with *Acinetobacter*, K. pneumoniae, *P. aeruginosa*, *Citrobacter*, and *Candida* infections which were widely resistant to antibiotics and were isolated from a different patient sample. This indicates a weakness of the immune system and the possibility of hospital infections (27). Hospital infections are widespread in hospitals, especially in intensive care units, and one of the vital goals of hospitals should be to control and manage such a situation. Timely and appropriate therapeutic interventions should be designed to reduce the rate of hospital infections. Hospitals must develop and control comprehensive antibiotic treatment programs based on their surveillance data.

Table 3. A comparison of results of similar studies as a literature review

Diseases	Experimental treatment antibiotics	Exposed to animals/Yes, No	Type of sample	Age (Years old)/Sex	Year of publication	References
Influenza-like illness-respiratory tract involvement	Cefazolin, Cephalosporin	-	Bronchoscopy sample	75/Female	1990	13
Pneumonia	Penicillin G	-	Lung tissue, Sputum	12/ Male	2009	14
Shortness of breath and short coughs	Ampicillin / Sulbactam	Dog	Sputum	58/ Male	2010	15
COPD	Tazobactam/Piperacillin	Dog	Blood	89/Female	2016	16
Phlegm, rhinorrhea, chest discomfort	Ampicillin, Penicillin, Amoxicillin-Clavulanate	-	Sputum	70/Male	2018	17
Respiratory failure	Amoxicillin-Clavulanate	Cat	Sputum	71/Female	2018	18
Shortness of breath and short coughs	Amoxicillin-Clavulanate	Cat	Blood	75/ Male	2019	19
Pneumonia	Amoxicillin-Clavulanate	Cat	Blood	70/ Male	2021	20
Pneumonia	Amoxicillin-Clavulanate	Dog	Sputum	41/Male	2022	21
Pneumonia	Ampicillin / Sulbactam	Cat	Blood	77/ Male	2022	22

COPD= Chronic Obstructive Pulmonary Disease

Conclusion

The case reported was a patient with multiple sclerosis who complained of difficulty swallowing without contact with animals. The diagnosis was pneumonia, extensive hydropneumothorax, pneumothorax, cystic bronchiectasis, and lymphadenopathy. The patient's specimens were positive for *P. multocida*, *Acinetobacter*, *Klebsiella*, *Citrobacter*, *P. aeruginosa*, and *Candida*. The patient was resistant to almost all prescribed antibiotics and ultimately died of nosocomial infection and bradycardia, leading to cardiac arrest.

Acknowledgement

The authors wish to thank all the personnel in the Department of Pathology of Babol University of Medical Sciences.

Funding sources

The authors received no financial support for this article's research, authorship, or publication.

Ethical statement

Informed consent was obtained from the patient, and ethical approval was granted by Babol University of Medical Sciences under the code IR.MUBABOL.HRI.REC.1401.140.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions

ZA, SR, HM: Case Presentation and Management, AF, HG, MP: Pathology diagnosis, MR, SS, MB: Preparation of the manuscript.

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How to Cite:

Ahmadnia Z, Rouhi S, Mehdinezhad H, Sabaghi S, Firouzjahi A, Ranaei M, et al. Isolation of *Pasteurella multocida* and pan-drug-resistant bacteria causing nosocomial infection in a patient with multiple sclerosis: A Case Report and Literature Review. *Med Lab J.* 2024;18(4):27-31.