Brief report

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Pleural effusion due to *Parvimonas micra*. A case report and a literature review of 30 cases

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ABSTRACT

The clinical and microbiological characteristics of infections caused by *Parvimonas micra* is described, including 30 cases in the literature and a new case handled at the present centre. Out of the 31 patients, 18 were male; mean age at diagnosis was 65.1 ± 13.0 years. Infection site was the vertebral spine in 14 patients and joints and heart valves in 5 each one; pain was present in all patients with articular localization and in almost all patients with vertebral involvement. The diagnosis was obtained from fluid aspirate or drainage in 13 cases and blood cultures in 11. In 8 cases, molecular techniques were also applied. The most frequently used antimicrobials were clindamycin, penicillin, amoxicillin and ceftriaxone. The outcome was positive with the medical treatment in 28 patients. *P. micra* infections are uncommon and requires a high index of suspicion.

KEY WORDS: Pleural effusion, *Parvimonas micra*, treatment, anaerobes.

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Derrame pleural debido a *Parvimonas micra*. Descripción de un caso y revisión de la literatura de 30 casos

RESUMEN

Se describen las características clínicas y microbiológicas de las infecciones causadas por *Parvimonas micra*, incluyendo 30 casos revisados de la literatura y un nuevo caso tratado en nuestro centro. De los 31 pacientes, 18 eran hombres; la media de edad al diagnóstico fue de 65,1 ± 13,0 años. En 14 pacientes, la localización de la infección fue la columna vertebral, mientras que las articulaciones y las válvulas cardiacas lo fueron en 5 cada una; en todos los pacientes con localización articular hubo dolor, y en caso todos los pacientes con afectación vertebral. El diagnóstico se obtuvo mediante aspiración de líquido o drenaje en 13 casos y mediante hemocultivos en 11. En 8 casos se aplicaron técnicas moleculares. Los antimicrobianos más frecuentemente utilizados fueron clindamicina, penicilina, amoxicilina y ceftriaxona. El pronóstico fue favorable con el tratamiento médico en 28 pacientes. Las infecciones por *P. micra* son raras y requieren un alto índice de sospecha.

PALABRAS CLAVE: derrame pleural, *Parvimonas micra*, tratamiento, anaerobios.

INTRODUCTION

Parvimonas micra is a fastidious anaerobic Gram-positive coccus which was originally classified as *Peptostreptococcus micros*, being transferred to the *Micromonas* genus in 1999 and known as *Micromonas micros*[1]. Later, Tindall and Euzeby in 2006 replaced *Micromonas* by *Parvimonas*, with only one species[2].

P. micra is a member of gastrointestinal and oral cavity microbiota[3,4], and is mainly recognised as an oral pathogen being usually isolated from polymicrobial infections such as periodontitis[5]. However, it has also been implicated in pol-

ymicrobial infections such as skin infections and abscesses[6-8]. As isolated infections, few cases have been reported until this moment in the medical literature.

We were recently confronted with a rare case of pleural infection caused by *P. micra* in a patient without risk factors for *Parvimonas* infection such as periodontitis, dental abscess, dental work or systemic diseases. A review of case reports with infections caused by this microorganism was performed, recording epidemiological data as well as diagnostic and therapeutic approaches for this pathogen.

METHODS

We describe a case of a patient admitted at the University Hospital Virgen de las Nieves (Granada, Spain) with a pleural effusion due to *P. micra*.

Using the key words "*Parvimonas micra* infections", "*Micromonas micros* infections" and "*Peptostreptococcus micros* infections" we searched MEDLINE (National Library of Medicine, Bethesda, MD), Web of Science, CINAHL, and Cochrane systematic review databases for case reports. We also checked the references cited in the papers for additional case reports published before 1966.

We traced 30 cases caused by *P. micra* and described in sufficient detail. These cases, along with our patient, are the basis of the present report. Data on age and sex, infection site, risk factors, time until diagnosis, clinical manifestations, laboratory findings, microbiologic diagnostic method, treatment, outcome and follow-up were recorded.

CASE REPORT

A 75-year-old women underwent an aortic and mitral valve replacement due to a degenerative valvulopathy in September 2016. She had a diabetes mellitus and hipercholesterolemia for over 30 years, but no dental alterations (including dental prosthesis) nor periodontitis were observed. On the first postoperative day at the intensive care unit (ICU), a small pleural effusion was seen by performing a pulmonary ultrasound, which was treated with pleural drainage. This fluid was considered to be as a consequence of a congestive heart failure after surgery. At this time the patient was no febrile but a pulmonary X-ray showed a basal right infiltrate, and in the blood cell count a leukocytosis was observed (19,000 cells/mm^3). At the end of this day, the mechanical ventilation was withdrawn. On the postoperative day 8, fever of 38ºC and an increase of the white cell count (23,000 cells/mm^3) was seen, and empirical treatment with piperacillin/tazobactam (4 g/iv/8 h) and daptomycin (400 mg/iv/24 h) was started. Also, the C-reactive protein (CRP) level was 480 mg/dl.

On postoperative day 11, a pulmonary CT-scan was performed showing a loculated right pleural effusion that was drained and sent to the microbiology laboratory for culture. After centrifugation, the sample was inoculated in aerobic and anaerobic blood agar (BD Columbia Agar 5% Sheepblood®, Becton Dickinson), chocolate agar (BD Choco Agar, Becton Dickinson) and thioglycolate broth (BD™ Fluid Thioglycollate Medium, Becton Dickinson), all incubated at 37ºC. Gram staining of the pleural fluid exhibited no microorganisms, but on the third day of incubation the growth of Gram positive cocci in small chains was reported only in the anaerobic blood agar. White and smooth colonies were observed and a mass spectrometry method (Bruker Biotyper, Billerica, MA, USA) was employed to identify the strain as *P. micra* (score 2.35). The MIC of the bacteria to different antibiotics was carried out by the E-test method, being susceptible to all antimicrobials tested, including penicillin (0.16 mg/L), amoxicillin/clavulanic acid (0.16 mg/L), piperacillin/tazobactam (0.16 mg/L), clindamycin (0.25 mg/L), metronidazole (0.38 mg/L), and imipenem (0.08 mg/L).

No blood cultures were taken at this stage. Treatment with piperacillin/tazobactam and daptomycin was administered for 10 days, and the patient was then discharged from the ICU. At 2 months of follow-up, the patient remained clinically stable, and laboratory findings were normal.

RESULTS

A review of the medical literature identified 30 cases of *P. micra* infections with sufficient details for comparison, so this manuscript therefore comprised 31 patients, including the present case.

General characteristics. Table 1 summarizes the main findings for the 31 patients. There were 18 (58%) men. The mean age of patients was 65.1 ± 13.0 years (range, 30-86 years). Regarding infection sites, 14 (45.1%) cases were located in the vertebral spine[9-18]; 5 (16.1%) each in heart valves[19-23], and in joints[24-28], 3 (9.6%) in pleura[29,30,present report], and 1 each in brain[31], lung and head and neck[32], chest wall[33] and meninges[34]. The mean interval from onset of symptoms to infection diagnosis was 48 days (range, 1 to 180), although this interval was not reported for 9 (29%) patients.

Risk factors for *P. micra* infection such as various dental procedures were found in 16 (72.7%) patients. Other possible risk factors such as systemic diseases (e.g. myeloma multiple, diabetes mellitus, corticosteroids treatment) were seen in 6 (27.2%) patients. In 9 (29%) patients, risk factors were not reported.

Clinical manifestations. The symptoms differ depending on the localization of infection, but pain was reported in all cases with joint infection (n=5) and in 12 from 14 patients with vertebral involvement. Fever was recorded in 10 (45.4%) patients, always accompanied by other symptoms. Patients with valvular infection had constitutional syndrome (asthenia, anorexia and weight loss) in almost all cases.

Microbiology and laboratory findings. At the diagnosis

of infection, data on the C- reactive protein (CRP) level was not reported in 14 (45.1%patients). CRP was reported in 17 (54.8% patients). The mean CRP level was 156.8 mg/L (range 8-480).

The majority of cases of this infection has been published from 2008 (n=21) with the denomination of *P. micra*. However, 4 cases published in 2000, 2004, 2008, and 2013 were named as *P. micros,* when this microorganism was already replaced in the *Parvimonas* genus[10,11,21,32]. Before 1999, the 5 cases published were named as *P. micros*, and one case in 2005 as *M. micros*.

P. micra infections were diagnosed by drainage or aspiration of infected fluid in 12 (38.7%) cases, blood cultures in 9 (29%) cases, and tissue culture sample in 6 (19.3%). The remaining samples were diagnosed by a combination of different methods. Molecular techniques such as polymerase chain reaction and gene sequencing were used in 7 (22.5%) patients in which other techniques were also positives, but a patient was diagnosed by gene sequencing on aortic valve tissue[23]. Blood cultures were taken in 19 (61.2%) patients and were positive for *P. micra* in 11 of them (57.8%).

Susceptibility tests for *P. micra* were performed in 18 (58%) isolates. From them, resistance to metronidazole were reported in 2 strains[14, 20] and to penicillin, amoxicillin/clavulanic acid, meropenem, moxifloxacin and cefoxitin in one strain [14].

Antimicrobial treatment. All patients underwent antibiotic treatment, with a single drug in 5 (16.1%) cases, with two drugs in 11 (35.4%) cases, and more than two in 15 (48.3%). Overall, clindamycin was used in 8 (25.8%) patients, and amoxicillin and ceftriaxone in 7 (22.5%) each one; treatment with penicillin was applied in 5 (16.1%) patients. As it can see in table 1, a great heterogeneity regarding treatment regimens could be observed.

Outcome and follow-up. A favourable outcome was recorded in 29 (93.5%) patients after antimicrobial treatment, although in 2 patients the outcome was not reported. The follow-up was reported in 17 (54.8%) patients, with a mean time of 8.1 months (range 1-55 months).

DISCUSSION

The presence of *P. micra* in human samples are mainly framed within a context of polymicrobial infections, especially in the oral cavity. These anaerobes have been particularly implicated in oral pathology, associated with periodontal infections [4]. Moreover, several studies have demonstrated the presence of *P. micra* into abscesses from numerous localizations, such as both soft-tissue and ano-rectal infections and pleural empyemas, along with microaerophilic streptococci, *Bacteroides* and *Fusobacterium* species[8].

However, the prevalence of infection by *P. micra* as the sole pathogen is low. We were able to trace 30 case reports of *P. micra* infection published in sufficient detail. In our knowledge, the first documented case of *P. micra* (formerly *P. micros*) infection was reported in 1986 by Papasian et al[9], although the majority of cases have been published from 2008 (n=21). In the reviewed literature, spine seems to be the preferred location of the infection, followed by joints, heart valves and pleura. Until this moment, it is not known why the vertebral area is the main target for these infections.

As *P. micra* is part of the oral cavity microbiota, main risk factors for infection may include dental procedures such as periodontitis, tooth extraction, apical abscesses or dental caries. Sixteen patients (72.7%) showed any of these factors, and 6 patients showed systemic diseases than may influence in the development of infections for anaerobes. Conversely none of them was reported in 9 (29%) patients, indicating the involvement of other factors in triggering the infection.

In oral infections, pathogenicity of *P. micra* has been attributed to their adhesion to gingival epithelial cells[35], cell morphotype[36] and/or the proteolytic activity [37], as well as other factors such as the response of human macrophages[38]. However, in isolated infections these factors are not clear. The majority of patients here reviewed had suffered dental procedures sometime before the infection, but risk factors were not reported in 9 patients while the remaining 6 patients had systemic diseases. Our patient, in addition to diabetes mellitus, was also subjected to mechanical ventilation during 48 h., suggesting that the endotracheal tube may serve as vehicle of transmission of oral pathogens such as *P. micra*.

According to our analysis, the symptoms are no specific and depend on localization of infection. Osteoarticular infections have been the most frequent focal expression of these infections, so the associated pain has been the main symptom in this case series. Pain is present in all patients with articular involvement, and in almost all patients with vertebral disease. Moreover, fever was documented in 45% of patients, and constitutional syndrome in almost all patients with heart involvement. However, the onset of symptoms can be insidious and development of the disease can be slow. Based on data from 22 patients, the mean time between onset of symptoms and *P. micra* infections diagnosis was 48 days; therefore, this disease should be suspected in cases with chronic symptoms.

The diagnosis of *P. micra* infection is mainly based on culture of an adequate sample obtained from the site of infection. Culture of drainage or aspiration fluid, tissue samples or blood cultures are adequate for the diagnosis of *P. micra*. In the cases here included, the majority of patients were diagnosed by culture of drainage or fluid or by tissue culture obtained from the site of infection. On the other hand, blood cultures were taken in 19 (61.2%) patients, being positives in 11 (57.8%) of them. Blood cultures were positive in all patients with valvular infection; however, in one of them the diagnosis of species was not obtained, being finally performed by molecular techniques from the aortic valve tissue[23]. Moreover, 5 patients with vertebral involvement had positive blood cultures being the method of diagnosis. In general, the results of the microbiolo-

Table 1 Main findings in 31 patients with infection caused by *Parvimonas micra*.

Patient (year of publication) Author	Age (years)/ sex	Localization of infection	Risk factors and/or underlying diseases	Time until diagnosis (days)	Clinical manifestations	Laboratory findings	Microbiologic diagnosis	Treatment	Outcome/ follow-up (months)
1 (1986) Papasian CJ[9]	70/M	Vertebral	NR	90	Back pain, weight loss, fever, chills, night sweats	NR	Tissue culture from needle biopsy Tissue culture from an open biopsy	Nafcillin Clindamycin	Cure/5
2 (1995) Wenisch C[19]	30/F	Aortic valve	NR	180	Abdominal pain, fever, chills, malaise, weight loss	CRP 104 mg/l	Blood cultures (+)	Teicoplanin Fusidic acid	Cure/12
3 (1996) Stoll T[24]	68/F	Knee prosthesis	Periodontal abscess	6	Knee pain, fever	CRP 358 mg/l	Synovial fluid culture	Imipenem Clindamycin + rifampin	Cure/55
4 (1998) Úbeda P[20]	51/M	Prosthetic aortic and mitral valve	NR	14	Asthenia, anorexia, weight loss, fever	NR	Blood cultures (+)	Penicillin	Cure/2
5 (1999) Riesbeck K[25]	86/M	Knee	Multiple myelomas	70	Left knee pain	CRP 312 mg/l	Synovial fluid culture into anaerobic blood bottle	Penicillin	NR
6 (2000) Leder KS[10]	70/M	Vertebral	Spine osteoarthritis Ulcerative colitis 8 years ago	NR	Back pain	NR	CSF culture	Penicillin Amoxicillin Metronidazole	Cure/12
7(/2004) Frat JP[11]	61/M	Vertebral	Diabetes mellitus Retropharyngeal surgery	NR	Meningo-encephalitis signs	NR	Abscess drainage culture into anaerobic blood bottle	Ceftriaxone + amoxicillin + cotrimoxazole Fosfomycin + ceftriaxone + metronidazole	Cure/2
8(2005) Bartz H[26]	63/F	Hip prosthesis	Dental treatment	NR	Hip pain	CRP 89 mg/l	IoS culture	Cefuroxime + gentamycin Clindamycin	NR
9(2008) Bassa Malondra A[21]	74/M	Prosthetic mitral valve	Tooth extraction	90	Constitutional syndrome	NR	Blood cultures (+)	Ceftriaxone + vancomycin Penicillin + gentamycin	Cure/NR
10 (2009) Kwon O[31]	49/F	Brain	Periodontitis	22	Fever, headache, vomiting	CRP 126.2 mg/l	Abscess aspirate culture Gene sequencing	Ceftriaxone + isepamicin + metronidazole Ceftriaxone + metronidazole	Cure/2

Table 1 Main findings in 31 patients with infection caused by *Parvimonas micra* (cont.).

11(2010) Minces LR[22]	63/F	Prosthetic mitral valve	NR	NR	Syncope	NR	Blood cultures (+)	Ampicillin/ sulbactam Penicillin + gentamycin	Cure/1
12(2013) Ubukata S[32]	46/M	Pulmonary and head and neck	NR	60	Otorrhea, ocular motility disorder, dizziness and loss of appetite	CRP 23.5 mg/l	Blood cultures (+) Otorrhea specimens PCR from sputum, BAL, neck abscess	Meropenem + ampicillin	Cure/1
13(2014) García González M[12]	62/M	Vertebral	Diabetes mellitus	NR	Back pain, left lower limb weakness	CRP 86.1 mg/l	Percutaneous intervertebral biopsy culture	Clindamycin	Cure/4
14(2014) Gorospe L[33]	67/M	Chest wall	Periodontitis	NR	Cough, constitutional syndrome, pain	NR	Culture from chest wall mass aspiration	Clindamycin	Cure/2
15(2014) Uemura H[13]	83/M	Vertebral	Periodontitis	NR	Back pain	NR	Vertebral bone biopsy Gene sequencing	Ampicillin/ sulbactam Amoxicillin-clavulanate	Cure/10
16(13/2014) Uemura H	85/F	Vertebral	Periodontitis	NR	Malaise, anorexia	NR	Blood culture (+)	Doripenem Ampicillin Amoxicillin	Cure/NR
17(2014) Poetter C[29]	72/M	Pleura	Periodontitis	14	Somnolence, confusion, loss of appetite, fluctuating memory deficits, fever	CRP 230.5 mg/l	Pleural drainage culture	Amoxicillin-clavulanate + ofloxacin	Cure/NR
18(2015) Jones SL[14]	72/M	Vertebral	Tooth extraction	28	Back pain	CRP 40 mg/l	Tissue culture from a core biopsy Gene sequencing	Piperacillin/ tazobactam Amoxicillin-clavulanate	Cure/12
19(2015) Jones SL[14]	72/F	Vertebral	Corticosteroid treatment	90	Back pain	CRP 69 mg/l	Abscess aspirate culture	Piperacillin-tazobactam	Cure/5
20(2015) Pilmis B[15]	83/M	Vertebral	NR	NR	Back pain	CRP 30 mg/l	Blood cultures (+) IoS culture	Amoxicillin + gentamycin Clindamycin + rifampicin	Cure/6
21(2015) Ko JH[34]	61/M	Meninges	Tooth extraction Chronic periodontitis	8	Fever, headache	CRP 12.15 mg/l	Blood cultures (+) Gene sequencing	Ceftriaxone + vancomycin + ampicillin Metronidazole	Cure/NR

Table 1 Main findings in 31 patients with infection caused by *Parvimonas micra* (cont.).

22(2015) George IA[16]	49/M	Vertebral	Tooth extraction	21	Back pain	CRP 234 mg/l	IoS culture	Ceftriaxone + metronidazole	Cure/3
23(2015) Gómez CA[23]	71/M	Aortic valve	NR	7	Respiratory distress, pulmonary edema, chest pain, fever	NR	Gene sequencing on aortic valve tissue	Vancomycin + nafcillin + gentamicin Ampicillin/ sulbactam	Cure/12
24(2015) Gahier M[17]	59/F	Vertebral	Dental caries	42	Cervical pain, fever	NR	Blood cultures (+)	Gentamycin + metronidazole + amoxicillin	Cure/NR
25(2015) Gahier M[17]	82/F	Vertebral	Dental caries	90	Back pain	NR	Blood cultures (+)	Ceftriaxone + gentamycin Amoxicillin	Cure/NR
26(2015) Gahier M[17]	60/F	Vertebral	NR	60	Back pain	NR	Blood cultures (+)	Ceftriaxone + gentamycin Amoxicillin	Cure/NR
27(2015) Rodríguez-Segade S[30]	49/M	Pleural	Dental caries and periodontitis	90	Dyspnea, productive cough, fever	NR	Pleural effusion culture	Linezolid + imipenem Amoxicillin-clavulanate	Cure/NR
28(2015) Endo S[18]	55/F	Vertebral	Dental treatment	60	Back pain	CRP 8 mg/l	IoS cultures Epidural abscess culture Gene sequencing	Ampicillin/ sulbactam Metronidazole	Cure/NR
29(2016) Baghban A[27]	65/M	Knee	Dental treatment, periodontitis	1	Knee pain	CRP 295 mg/l	Synovial fluid culture	Clindamycin Ampicillin/ sulbactam	Cure/NR
30(2016) Dietvorst M[28]	68/F	Knee	NR	3	Knee pain, fever	CRP 169 mg/l	Synovial fluid culture + Gene sequencing	Flucloxacillin Clindamycin	Cure/NR
31(2016) Cobo F[PR]	75/F	Pleura	Diabetes mellitus Mechanical ventilation	10	Pleural effusion	CRP 480 mg/l	Pleural drainage culture	Piperacillin/ tazobactam + daptomycin	Cure/2

M: male; F: female; PR: present report; NR: not reported; CRP: C-reactive protein (acceptable values 0.02-5 mg/dl); IoS: intraoperative sample; CSF: cerebrospinal fluid; PCR: polymerase chain reaction; BAL: bronchoalveolar lavage.

gy diagnosis were poorly reported, so a detailed account of the microbiological methods would be useful for future studies.

CRP level can also be used as infection marker, and may be included in the diagnostic algorithm. CRP is mainly limited by their poor specificity, but out of 17 patients in the present series for whom CRP studies were requested, all of them had elevated CRP levels, which might suggest the presence of infection. According to our results, this parameter may be useful detecting an initial infection.

The treatment of choice for *P. micra* infections has not yet been established, although overall this pathogen is highly susceptible to antibiotics. A recent study shows only one strain of *P. micra* resistant to metronidazole, but no other significant resistances were found[39]. At the same year, other study found 2.7% resistance to amoxicillin and none to metronidazole[40]. In the case reports here included, there was resistance only to metronidazole in one strain[20]. Furthermore, patient number 19 had resistance to penicillin, amoxicillin/clavulanic acid, metronidazole, meropenem, moxifloxacin and cefoxitin[14]. Treatment with antimicrobial agents has been reported to be successful in all patients here included. In the majority of patients with *P. micra* infection more than one drug was used for treatment (26/83.8%), but this fact may be due to the use of various antibiotics as empirical treatment until obtaining the culture results.

However, the heterogeneity of studies prevents any conclusion being drawn on antimicrobial treatments. Initially, antibiotic resistance in *P. micra* is not considered a problem, but monitoring through susceptibility testing is advisable.

Infections caused by *P. micra* are rare and require a high index of suspicion because of their non-specific symptoms and insidious evolution. The diagnosis may be suspected by elevation of CRP and/or ESR especially in patients with dental procedures and must be confirmed microbiologically, taking samples of blood, organic fluids and/or intraoperative tissues from affected areas. Although nowadays resistance to antibiotics is not an emerging problem to the species *P. micra*, antimicrobial susceptibility testing of *Parvimonas* strains is highly recommended in order to make a correct therapy. There is no a treatment of choice for this infection, but it seems that some strains of *Parvimonas* may be resistant to metronidazole, so this drug could be avoided as empiric therapy until the susceptibility testing results.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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