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Case report

Pyogenic arthritis caused by *Streptococcus agalactiae*: report of four cases and a review of the literature

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ABSTRACT

Most infections by group B streptococcus of the Lancefield classification (*Streptococcus agalactiae*), were reported in pregnant women or during the puerperal period, as well as in neonates. During the past three decades there have been reports of increasingly invasive infections in adults unrelated to pregnancy, although arthritis and osteomyelitis are still very rare. In this article, we describe four new adult patients with arthritis by *S. agalactiae* (two postmenopausal women and two men), two of them with affection of the sternoclavicular joint. We also review the medical literature.

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Artritis piógena por *Streptococcus agalactiae*. Aportación de cuatro casos y revisión de la literatura

RESUMEN

En su mayoría, las infecciones por estreptococos del grupo B de la clasificación de Lancefield (*Streptococcus agalactiae*) afectan a mujeres gestantes o durante el puerperio, así como a neonatos. Durante las tres últimas décadas, se han comunicado cada vez más infecciones invasivas en adultos sin relación con la gestación, aunque las artritis y osteomielitis siguen siendo muy poco frecuentes. En este artículo, describimos 4 nuevos pacientes adultos con artritis séptica por *S. agalactiae* (2 mujeres posmenopáusicas y 2 varones), dos de ellos con afectación esternoclavicular, y realizamos una revisión de la literatura.

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Introduction

Palabras clave:

Artritis piógena

Prótesis articular

Streptococcus agalactiae

Articulación esternoclavicular

Streptococcus agalactiae is a gram-positive coccus belonging to group B of the Lancefield classification that organizes in chains and in pairs (diplococci). It is one of the bacteria in the vaginal flora of pregnant women, the male and female urethra, rectum and pharynx. It has been a traditional cause of serious illness in pregnant women during the postpartum period as well as in neonates.^{1,2} In adults, the first case of septic arthritis by *S. agalactiae* was described in 1940 by Ranz,³ but this complication was considered unique until the 80s,

when the number of cases in adults began to increase gradually. A review of the literature until December 2008 using Medline, EMBASE and Ovid has allowed us to locate only 147 cases.⁴⁻²⁰ For this reason, we considered it of interest to provide four new cases of septic arthritis by this organism, 3 on native joints, two of them of sternoclavicular localization, and one on a knee prosthesis.

Case reports

Case 1

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Fifty-eight year old male with a history of COPD and diverticulosis of the colon, which had abandoned smoking 10 years earlier after being diagnosed with tongue squamous cell carcinoma (stage pT1, N0, M0) for which, apart from surgical removal, he received radiotherapy. He came to the emergency department of our hospital with pain and functional disability of the right shoulder. The symptoms had started six days earlier, after performing several dental fillings.

Examination revealed an axillary temperature of 37.5 °C, blood pressure of 160/80 mmHg, painful swelling of the right sternoclavicular joint associated with limitation of active movement of the right shoulder, rhonchi upon inspiration and wheezing in both lung bases as well as a 2 cm soft liver enlargement and a diffuse increase in the size of the prostate.

Laboratory measurements found an ESR of 66 mm/1st h, 19.4x109 white blood cells/l (89% polymorphonuclear neutrophils), glucose: 303 mg/dl (normal: 70-110 mg/dl) urea: 58 mg/dl (normal: 10-50), GOT-AST (61U/l; normal: 9-37), GPT-ALT (95 U/l; normal:10-65), fibrinogen (455 mg/dl; normal: 200-400). The following parameters were normal or negative: creatinine, total cholesterol, triglycerides, uric acid, GGT, AP, Bi, CPK, Ca, P, RF (latex) and ANA. Three blood cultures were negative. The arterial blood gas pH (7.41), pCO₂ (35 mmHg), pO₂ (76.4 mmHg), O₂ saturation (94.3%), HCO₃ (22, 6 mEq/l). The chest x-ray showed findings consistent with COPD. Abdomen ultrasound showed there was an increase in liver echogenicity and volume compatible with steatosis, and a diffuse enlarged prostate without nodular images. MRI was performed right shoulder and sternoclavicular joints showing hyperintensity on T2-weighted sequences and a hyposignal on T1, involving the bony ends of the right sternoclavicular joint with erosions and an image compatible with an abscess (Figure 1).

A fine needle aspiration of the right sternoclavicular joint yielded 2 ml of pus which showed a Gram positive cocci, subsequently these were cultured and classified as *S. agalactiae* (group B). The patient was treated with surgical debridement and intravenous infusion of clavulanate (200 mg) and amoxicillin (1000 mg) every 6 hours for three weeks and then continued with 875 mg oral amoxicillin associated with clavulanic acid 125 mg every 8 hours. Treatment was discontinued at the sixth week with good clinical and functional results.

Case 2

An 80 year old female with a history of psoriasis, hypertension and chronic kidney failure, admitted to a nursing home five years prior, came to the emergency department of our hospital with pain and loss of function of the left shoulder, with symptoms appearing acutely 3 weeks before and with no response to diclofenac (100 mg/ day).

Examination revealed an axillary temperature of 37.6 °C, blood pressure of 140/70 mmHg, mucocutaneous pallor, systolic ejection murmur loudest over the aortic valve, and tenderness and swelling of the left sternoclavicular joint. The abduction of the ipsilateral shoulder pain exacerbated and, therefore, obliged an antalgic position with the arm in internal rotation and adduction.

Laboratory determinations highlighted normochromic normocytic anemia (Hb: 73 g/l), 8.7x10⁹ cells/l, platelets 303x10⁹/l, ESR 140 mm/1st h, CRP: 127 mg/l, creatinine: 1.9 mg/dl, urea: 83 mg/dl, uric acid: 6.9 mg/dl, serum iron: 24 µg/ml (Normal: # 35-150 mg/ml), TSH: 6.8 mIU/ml (Normal: 0.5 to 4.5). Urine sediment contained 45-55 leukocytes and 12-15 red cells per field. The following parameters were normal or negative: glucose, urea, creatinine, uric acid, GOT-AST, GPT-ALT, GGT, AP, Bi, total cholesterol, triglycerides, CPK, Ca, P, protein, immunoglobulins (IgM, IgG, IgA) and complement (C3, C4), RF (latex), ANA and ANCA. Urine cultures isolated more than 10⁵ CFU of bacilli that were identified as *Escherichia coli*, sensitive to amoxicillin. No bacterial growth was obtained in three serial blood cultures.

A CT of the sternoclavicular joint was performed and erosions were observed as well as an increase in volume and density of soft





Figure 1. A) Computerized tomography coronal cut of the sternoclavicular joints of case 1. The right one shows an increase in volume and density of soft tissue, apart from erosions of the bony surfaces of the joint (arrows). B) Axial weighed magnetic resonance image in T2, from the same patient. Destruction of the joint surfaces and a marked increase in soft tissue (arrows), which later gave way to a retrosternal abscess that required surgical drainage can be seen.

tissues (Figure 2). Aspiration of the joint yielded 1.5 cc of purulent exudate and culture showed abundant colonies of *S. agalactiae* (GBS). The patient was treated for 4 weeks with intravenous amoxicillin and clavulanate (1,000 mg/200 mg) every 6 hours and then continued orally (875 mg/125 mg) every 8 h completing six weeks. The outcome was favorable, although there was a mild deformity and mechanical pain in the left sternoclavicular with some movements.

Case 3

34 year old male admitted to the emergency department because of fever and acute arthritis in his right knee which started 10 days earlier. Among his history he been in a traffic accident in which he suffered a fracture of the right femoral shaft and splenic rupture, for which he had been splenectomized.

Examination revealed an axillary temperature of 38.4 °C and tense effusion of the right knee which active flexion unable to reach 25°. There were no surrounding skin lesions. Except for pyorrhea and a laparotomy scar, no other abnormalities were identified.

The hemogram showed leucocytosis (15.8x10⁹/l, 87% neutrophils) and thrombocytosis (479x10⁹/l). There was a marked elevation of ESR (79 mm/1st h) and CRP (84.7 milligrams per liter). The following biochemical parameters were normal or negative: glucose, urea, creatinine, uric acid, GOT-AST, GPT-ALT, GGT, AP, Bi, total cholesterol,



Figure 2. Computerized tomography of the sternoclavicular joints in case 2. The left joint presents erosions of its joint surface (arrow).

triglycerides, CPK, Ca, P, protein, immunoglobulins (IgM, IgG, IgA) and complement (C3, C4). Plain x-rays of the knees showed only an increase in volume and soft-tissue density on the right side, with arthrocenthesis yielding 158 cc of pus. No microorganisms were visualized using Gram stains, Zielhl-Neelsen and auramine-rhodamine stains, but cultures revealed abundant colonies of Gram positive cocci subsequently identified as *S. agalactiae.* This bacteria was also recovered in two of the three blood cultures drawn upon admission. The patient was treated with cefuroxime intravenously (2 weeks) and then orally (four weeks). Bacterial growth ceased to be observed in the arthrocentesis samples (daily aspiration) by the fourth day.

The outcome was favorable, although the aftermath was a deficit of right knee flexion of about 20°.

Case 4

A 72 year old woman who presented resting and motion associated pain of her right knee, where seven years before she had undergone a total arthroplasty for arthritis. Three months before the consultation, after a dental cleaning, she presented local joint pain, symptoms which worsened gradually, prevented walking and were accompanied by anorexia and weight loss of 5 kg.

Examination showed an axillary temperature of 37.8 °C, stroke and erythema of the right knee, with painful restriction of flexion (75°) and extension (-5°). In the left knee, subpatellar crepitus was appreciated, varus deformity and limitation of flexion (97°). The hands showed Heberden's and Bouchard nodes, and signs of bilateral trapeziometacarpal osteoarthritis.

Tests showed elevated C-reactive protein (95 mg/l) and ESR (43 mm/1st h), microcytic hypochromic anemia (Hb: 95 g/l) and hypercholesterolemia (292 mg/dl, LDL cholesterol 198 mg/dl). X-ray showed signs of loosening, with osteopenia of the prosthesis-bone interface, as well as increased volume and density of soft tissue. We obtained 25 cc of purulent-looking joint fluid through arthrocentesis with glucose of 31 mg/dl (blood glucose: 117 mg/dl) and a cellularity of 62,700/mm³ (95% polymorphonuclear neutrophils). Gram stain showed positive diplococci and culture yielded *S. agalactiae*, isolated in one of the three blood cultures taken UPON admission.

Antibiotic treatment with cefuroxime axetil-(1 g/iv/8 h) for 8 weeks was indicated and the patient underwent a prosthetic replacement in two days with a good functional outcome. After 24 months after the placement of the second prosthesis, there have not been symptoms or signs suggestive of recurrence.

Table 1 summarizes the main clinical features of the 4 patients presented.

Discussion

In 1938, Fry²¹ write the first report of human pathogenicity of group B streptococcus, and two years later, Ranz³ described the first joint infection in a diabetic elderly patient. However, until the 1980's, most reported infections occurred in neonates and pregnant women, being very rare in other groups of adult patients.^{1,22} Over the past 25 years, there has been a notable increase in invasive infections caused by *S. agalactiae* in adults,²² among which one finds pneumonia, pleural empyema, cellulitis, endocarditis, meningitis, endophthalmitis, necrotizing fasciitis, bursitis,²³ osteomyelitis,²⁴ and septic arthritis.³⁻¹⁹

S. agalactiae causes between 4% and 10.5% of septic arthritis.^{4,5,7} Its frequency increases in parallel to the age of the patients, which is reflected in the wide range of the series by Drawer et al,¹² where *S. agalactiae* was responsible for 13% of cases in patients under 60,

Table 3

Summary of clinical data from 4 patients with septic arthritis due to Streptococcus agalactiae

| Gender Age, years | Male (58) | Female (80) | Male (34) | Female (72) |
|---------------------------|-------------------------|--------------------------------|--------------------------------------|-------------------------|
| Predisposing factors | COPD | Chronic renal failure | Splenectomy | Unknown |
| Axillary temperature (°C) | Low grade fever (37.5) | Low grade fever (37.6) | Fever (38.4) | Fever (37.8) |
| ESR, mm/1 st h | 66 | 140 | 79 | 43 |
| CRP, mg/l | Undetermined | 127 | 84.7 | 95 |
| Leukocytosis | Yes | No | Yes | No |
| Point of entry | Dental | Unknown | Dental | Dental |
| Affected joint | Right sternoclavicular | Left sternoclavicular | Right knee (native) | Right knee (prosthesis) |
| Blood cultures | (-) | (-) | (+)2/3 | (+)1/3 |
| Antibiotic therapy | Amoxicillin+clavulanate | Amoxicillin+clavulanate | Cefuroxime | Cefuroxime |
| Progression | Favorable | Deformmity and mechanical pain | Restriction in joint range of motion | Prosthetic replacement |

COPD indicates chronic obstructive pulmonary disease; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

31% of cases of patients 60-80 years and 41% in those over 80. In our hospital, during the 1995-2008 period, we collected 95 cases of pyogenic arthritis in adults, 6 of them (6.3%) caused by *S. agalactiae* (Table 2), two of which occured on joint replacements. Along with older age,^{4,7,22} other factors that predispose to septic arthritis by *S. agalactiae* are diabetes mellitus, malignancy, chemotherapy, alcoholism, neurogenic bladder, decubitus ulcers, rheumatoid arthritis and liver cirrhosis,^{4,18,22} although risk factors are not always identified.^{4,19} While men are the most affected by pyogenic arthritis, the relationship tends to be inverted in those cases due to *S. agalactiae*^{4,7} (1:1,1), a fact explained by the gradual increase in the percentage of women with septic arthritis after 60 years of age¹² and by a higher prevalence of streptococcal arthritis in women.⁷

A in the rest of septic arthritis, the main joint affected is the knee,⁴ while small joints of hands and feet together with the facet joints of the spine are less affected.¹⁰ However, S. agalactiae shows a remarkable tropism for axial joints, compared with 2% of sternoclavicular or sacroiliac involvement in the general series of pyogenic arthritis in adults, S. agalactiae affectes these joints in 16% and 12% respectively.⁴ Yet only 3% of sternoclavicular arthritis¹³ and 12%-14% of pyogenic sacroiliitis^{25,26} in adults are caused by group B streptococci, the latter with female predominance. Two of our patients had sternoclavicular arthritis, in which pain may be referred to the shoulder and constitute the first clinical manifestation (25%), with the clinical course complicated by osteomyelitis of the clavicle or sternum (56%) or chest wall abscess (25%) and, more rarely, with mediastinitis or pleural effusion.¹³ Sternoclavicular arthritis has been reported by S. agalactiae a few days after birth and an increased susceptibility for the development of infectious complications in that joint in women undergoing radiation therapy for breast cancer has been noted.²⁷ Over 80% of cases of pyogenic arthritis are monoarticular, but S. agalactiae causes oligo or polyarthritis in a third of the patients,^{4,5} which is related to the high frequency of bacteremia and high positivity of positive blood cultures in up to 66% of cases according to Nolla et al.⁴ Oligo or polyarticular infections, especially in elderly patients where comorbidity is common, oblige a differential diagnosis with other inflammatory arthritis and help delay the diagnosis.^{4,5} Its coexistence with other foci of infection (30%) is also frequent,^{4,17,19,23,28} especially with vertebral osteomyelitis and urinary tract infections.

The point of entry can be identified in almost half of the cases. Two of our patients had a history of dental manipulation in the days before the onset of symptoms (cases 1 and 4) while another presented pyorrhea (case 3). In the second patient described, the skin lesions of psoriasis may have been the front door. In fact, skin and oral colonization by *S. agalactiae* increases with age, and is particularly

Table 4

Etiology of septic arthritis at the POVISA hospital during the 1995-2008 period

| Microorganisms | Native joints | Prosthesis | Total |
|------------------------------|---------------|------------|------------|
| Staphylococcus aureus | 50 | 7 | 57 (60%) |
| Staphylococcus coagulase (-) | 6 | 4 | 10 (10.5%) |
| Streptococcus | | | |
| Group A | 2 | | 2 (2.1%) |
| Group B (agalactiae) | 4 | 2 | 6 (6.3%) |
| Group C | 2 | 1 | 3 (3.2%) |
| Group D | 1 | | 1 (1.1%) |
| Group G | 1 | | 1 (1.1%) |
| Gram negatives | | | |
| Pseudomonas aeruginosa | 4 | 1 | 5 (5.3%) |
| Salmonella sp. | 2 | | 2 (2.1%) |
| Serratia sp. | 1 | 1 | 2 (2.1%) |
| Enterobacter | 1 | | 1 (1.1%) |
| Escherichia coli | 2 | 2 | 4 (4.2%) |
| Proteus | 1 | | 1 (1.1%) |
| Totals | 77 | 18 | 95 |

high in elderly patients in residences,²² with this being considered the main point of entry for this organism.⁷

Late infections of prosthetic joints are mostly a consequence of bacteremia but early infections occur with less systemic symptoms.⁸ There have been fewer than 16 cases produced by *S. agalactiae* and the mean delay in diagnosis is of more than 4 months.^{8,22} In case 4, the arthritis of the right knee prosthesis was subacute and preceded by a dental cleaning, which could be the point of entry of bacteria. In this sense, the Spanish Society of Infectious Diseases and Clinical Microbiology recommends antibiotic prophylaxis in denture wearers when they undergo procedures involving a high risk of bacteremia,²⁹ which includes some types of dental cleaning.

The diagnosis is made with the identification of *S. agalactiae* in joint fluid culture, synovial membrane samples of the affected joints or two or more blood cultures when the clinical context is compatible, in addition, the specificity of blood cultures is high.⁴ Other common but nonspecific findings include leukocytosis (50%-60%), increased erythrocyte sedimentation rate (95%) and C-reactive protein.^{45,7,8} The differential diagnosis poses difficulties in cases with little clinical manifestations, unusual locations,¹⁶ polyarticular joint affection^{4,5} or after comorbidity,^{15,30} which is common among elderly patients.

As with any septic arthritis, treatment should not be delayed. Empiric treatment starts after obtaining synovial fluid samples and serial blood cultures. *S. agalactiae* remains highly susceptible to penicillin G, ampicillin and cephalosporins, but there is a gradual increase in resistance to macrolides, clindamycin and tetracycline, which makes the treatment of patients allergic to beta-lactams difficult.³¹ In addition, less and less susceptible strains to penicillin have been reported recently³² and some resistance to fluoroquinolones has been reported to occur.³³ The duration of antibiotic therapy has not been agreed upon, but should not be less than four weeks and it is usually recommended for six weeks⁴ when axial joints are affected. The coexistence of infective endocarditis, vertebral osteomyelitis or involvement of a prosthetic joint requires prolonged treatment.

As for other pyogenic arthritis, the outcome depends on host factors and the delay in treatment initiation. Its tendency to affect older people with comorbidity favors a late diagnosis and worsens prognosis.^{4,5} The morbidity and mortality increases proportionaly to the age of the patients, the degree of immune compromise, the delayed in the onset of treatment and oligoarticular or polyarticular involvement. Although in the case serioes of pyogenic arthritis by Dubost et al,⁷ mortality was lower among those with streptococcal etiology than among those caused by staphylococci (3.6% vs 7.8%); joint infections by *S. agalactiae* have a mortality rate of approximately 9%.⁴ Relapses or recurrences are very rare.

The virulence of *S. agalactiae* depends on the capsular surface molecules such as sialic acid or polysaccharides. Moreover, the expression of a potent cytotoxin, the betahemolysin also leads to a greater arthritogenic capacity.³⁴ Vaccination of patients with risk factors by capsular polysaccharide antigens of streptococcal bacyerial could reduce the incidence of invasive infections caused by *S. agalactiae*, including joint infections.²²

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