

Septic Arthritis Due to *Bacteroides fragilis* in a Patient With Non-Hodgkins Lymphoma and Mixed Connective Tissue Disease

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We present a 53 year old woman with pre-existing mixed collagen tissue disease who developed highly-malignant non-Hodgkin lymphoma and 2 years later had left groin abscess, then septic tenosynovitis of the left ankle, septic arthritis of the right shoulder, and purulent tenosynovitis of the right hand. *Bacteroides fragilis* was identified in synovial fluid drawn from the right shoulder, in blood cultures and in culture of a central venous catheter tip. The primary infection site is presumed to have been the abdominal cavity, and the presence of an indwelling central venous catheter the reason for recurrence of infection. We treated her empirically with intravenous ampicillin/sulbactam and clindamycin then oral metronidazole until definite resolution of the infection. Septic arthritis due to *Bacteroides fragilis* is a rare entity mainly occurring in immunocompromised patients, as shown in this case.

Key words: Septic arthritis. *Bacteroides fragilis*. Non-Hodgkin lymphoma.

Artritis séptica por *Bacteroides fragilis* en paciente con linfoma no hodgkiniano y enfermedad mixta del tejido conectivo

Presentamos una paciente de 53 años de edad con enfermedad mixta del tejido conectivo que desarrolló un linfoma no hodgkiniano de alto grado de malignidad y 2 años más tarde, un cuadro de absceso inguinal izquierdo, luego tenosinovitis supurada de tobillo

izquierdo y, finalmente, artritis séptica del hombro derecho y tenosinovitis supurada del tercer dedo de la mano derecha. Se logró aislar *Bacteroides fragilis* en líquido sinovial del hombro, en hemocultivos y en punta de catéter central intravenoso. El foco infeccioso primario se presume que haya sido intraabdominal, y el catéter central en permanencia, el factor de mantenimiento de la infección crónica. Utilizamos un tratamiento empírico secuencial de ampicilina/sulbactam y clindamicina intravenosos y más tarde metronidazol por vía oral hasta la cura definitiva de la infección. La artritis séptica por *Bacteroides fragilis* es una entidad rara que ocurre principalmente en pacientes inmunodeficientes, tal como refleja este caso.

Palabras clave: Artritis séptica. *Bacteroides fragilis*. Linfoma no hodgkiniano.

Introduction

Septic arthritis caused by anaerobic germs is a rare occurrence in the daily clinical practice, and experience in managing it is limited for the average rheumatologist or internal medicine specialist. As an example, only 15 cases of arthritis due to anaerobes had been reported in English literature until 1997, and data from the rest of the world is fragmentary.

The management of joint infections, on the other hand, is shared with other colleagues, mainly orthopedic surgeons and infectious disease specialists.

We present an interesting case that exemplifies the above-mentioned matter and, through its discussion we aim to improve the study and treatment of future similar cases.

Clinical Observations

The case is a 53 year old female patient with mixed connective tissue disease, which was diagnosed in 1985

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Figure 1. Ankle x-ray: erosive deterioration of the tibio-astragalus joint.

characterized by Raynauds' phenomenon, 2 late trimester fetal losses, sicca syndrome, intermittent bilateral parotid inflammation, malar erythema, photosensitivity, alopecia, angle cheilytis, positive anti-RNP antibodies, and who never presented joint deterioration or significant systemic affection. ANA titers at 400 dilutions, with a speckled pattern were found, in addition to positive LE cells, positive anti-U1RNP, anti-Ro and anti-La, Rose Ragan 128 dilutions and negative native anti-ADN, negative IgG and IgM anticardiolipins, non-reactive VDRL, and normal KPTT were all documented in 2002.

In august 2003 she presented polyadenopathy, mild bilateral parotid hypertrophy, and signs of polyneuropathy in her lower limbs, leading to the diagnosis of non-Hodgkins lymphoma with a high degree of malignancy, and axomyelinic polyneuropathy. She received eight monthly chemotherapy sessions with prednisone/cyclophosphamide/doxorubicyn/vincristin and later 4 weekly infusions of rituximab 375 mg per square meter of body surface area (m²BMA), with partial remission of the lymphoma and stabilization of the neuropathic symptoms. Prolonged, low dose maintenance corticosteroid therapy was applied and pain was treated with methadone up to 30 mg per day, gabapentin 900 mg daily and diclofenac 50/acetaminophen 500 mg up to 3 tablets a day. The patient presented gammaglobulin concentration values inferior to normal from 2003 onward: 0.48 g/% to 0.41 g/%, in the context of a generalized hypoproteinuria.

Starting at the end of 2004 here general state, as well as the polyneuropathy worsened which, in addition to a single positron emission computed tomography (SPECT) positive for gallium, led her physicians to a relapse of the lymphoma, making it necessary to place a permanent central catheter for rescue chemotherapy, which was delayed afterward in relation to the polyneuropathy and

due to a fear of severe worsening, apart from the patients own doubts on an aggressive therapy.

At the end of March 2005 a sterile abscess was drained in the left inguinal zone and she was treated with cephalexin 2 g a day for 1 week, with a complete resolution of the problem.

At the beginning of April 2005 she presented left ankle inflammation, which initially was attributed to a sprain or a neuropathic joint

At the beginning of may, a small purulent external perimaleollar collection of pus was drained on the same ankle and underwent magnetic resonance, showing no intraarticular or periarticular collections; the bacteriologic study was negative for common germs and the patient was treated empirically with intravenous cephotaxime and clindamycin for a week and afterward with ciprofloxacin, rifampin, and oral clindamycin for 1 more month with slow improvement; she persisted with residual mild inflammation of the ankle, which made her physicians reconsider the diagnosis of post-infectious arthritis.

In mid-July 2005 she presented rapidly evolving pain in her right shoulder, fever, and mildly painful flexor tenosynovitis of the third finger of the right hand. Shoulder arthrocentesis allowed us to obtain 2 µL of purulent fluid that after culture isolated a Gram-negative anaerobe. For this, tioglycolate and anaerobe culture media (agar brucella, hemine, vitamine K, lacquered blood, and gentamycin) were employed. The following tests were performed, aerobiosis testing was negative, esculine testing was positive and indole testing was negative. Kanamycin (1000 µg), vancomycin (5 µg), and colistyne (10 µg) disks were used and she proved to be resistant. An ulterior typification of the germ was done at a microbiology reference center and demonstrated the presence of *Bacteroides fragilis*, but no antibiogram was done because such a procedure is not systematically carried out for anaerobes.

In a parallel way, 2 blood cultures were done, 1 of the central catheter and afterwards, the culture of the catheter tip which was definitively extracted, all of which allowed us to isolate the same germ. We also extracted purulent-white fluid with no odor from the tendon sheath.

Initial empirical treatment consisted in drainage through puncturing the affected sites, IV ampicillim/sulbactam, and clindamycin; the former was suspended due to intestinal dysbacteriosis and the second one had to be switched to metronidazole at 2 weeks, adding intravenous cephotaxim, due to hyperthermia secondary to the antibiotic treatment; the patient was discharged after 3 weeks of intravenous treatment and completed 5 weeks with PO ciprofloxacin-metronidazole, with a complete resolution of fever and joint disease. An x-ray of the tibial-astragalus joint presented erosive deterioration (Figure 1).

Parallel to the development of the infection, the lymphoma worsened, with progressive abdominal pain and intermittent illeus, leading to the identification of hepatic

nodules and a relapse in the peritoneal adenopathy on the computed tomography (CT) (Figure 2). A CT guided needle biopsy of the hepatic nodule showed evidence of lymphoma. Some months after her discharge posterior to the osteoarticular infection, the patient presented a new episode of intestinal obstruction, complicated by sepsis and died.

Discussion

Septic arthritis due to anaerobe germs represent 1.5%–3% of the bacteriologic findings, according to some series¹⁻⁵; frequency is low, possibly due to inadequate culture techniques. As an example, only 15 cases of arthritis due to anaerobes had been reported in English language literature until 1997.⁶ Anaerobes require culture media with a reduced oxygen pressure and must be maintained for at least 2 weeks due to slow growth¹; 50% of cases of arthritis due to anaerobes are polymicrobial and occur, preferentially, in critical patients, in cases of surgical wound infection or due to direct dissemination from an intra-abdominal or intra-pelvic locus to the hip; the commonest germs are *Bacteroides* species, *Propionibacterium acnes*, several anaerobe Gram positive cocci, species of *Fusobacterium*, and *Clostridium*.

Isolated cases of septic arthritis due to anaerobes such as *Prevotella bivia* or *Gemella morbillorum*.^{1,7-11} *Bacteroides fragilis* represents 58%–90% of cases of Gram-negative anaerobe bacteria.⁶ The suspicion of arthritis due to anaerobes increases if the synovial fluid smells bad or if intra-articular air is found on plain radiographs¹ and its clinical presentation includes an insidious start without any signs of inflammation or systemic problems.⁸

Bacteroides fragilis is the most common anaerobe associated to bacteremia and is frequently isolated in intraabdominal infections, female genital tract infections, wounds, and abscesses, but is a rare cause of septic arthritis.¹² Septic arthritis due to *Bacteroides fragilis* is generally a disease of older patients, with an average age of 50–60, and with an underlying chronic and debilitating disease such as ischemic cardiopathy, diabetes mellitus, neoplasia, blood dyscrasia, corticosteroid therapy, or immunosuppressants.^{6,13} The largest part of arthritis cases due to *Bacteroides fragilis* has been attributed to hematic dissemination due from an infected site⁶; sites of seeding have been colon tumors, intestinal anastomosis, apendicular abscess, gangrenous appendicitis, and pylonalid cyst resection.⁶ Ninety-two percent of patients with septic arthritis due to *Bacteroides fragilis* have a preexisting joint disease, especially rheumatoid arthritis¹²; rheumatoid arthritis, on the other hand, is well recognized as a precipitating factor for the development of bacterial arthritis.⁶⁻⁸ Joints frequently affected by *Bacteroides fragilis* are the knee, elbow, ankle, and hip.^{6,11} It may have a destructive course.¹⁴

Figure 2. Computed tomography of the abdomen: peritoneal adenopathy.

There are multiple mechanisms by which anaerobe bacteria turn resistant to antibiotics such as betalactamase synthesis, alterations in penicillin binding proteins, changes in permeability, and inactivation through acetylation, or efflux. Finding out the antimicrobial sensitivity of these germs is not systematically performed, and such a procedure has been reserved for severe infections, non-microbial or intravascular infections, and those that do not respond to the usual treatments. Because the pattern of sensibility cannot always be predicted and resistance to antimicrobial agents is increasing, it is valid to perform susceptibility tests to any clinically important isolation.¹⁵

Because of the increase in cost that this implies, at least those germs whose frequency and aggressiveness justify it should be typified, as are those germs in the *Bacteroides* group.¹⁶

As a complementary reference, the clinician must also be alerts to the isolation of other anaerobe germs in samples sent to the laboratory.

While waiting for culture results, empirical treatment of a possible joint infection due to an anaerobe germ should include joint drainage as well as of all of the purulent collections, apart from starting the patient of antimicrobial treatment which provides adequate coverage, such as metronidazole, clindamycin, imipenem, or a combination of a betalactamase inhibitor and penicillin.^{8,11,17}

Our case reflects, in part, all of the above mentioned points: an infection by a rare germ in a patient with a predisposing debilitating disease, such as the association of a collagen vascular disease, a malignant hematological disease, prolonged hypogammaglobulinemia, and immune suppression. The patient did not have any previous joint damage, in contrast to the majority of cases that occur in patients with rheumatoid arthritis. The ankle affection showed a destructive course. We assumed that the retroperitoneal adenopathy, when coming into contact to

the intestine, carried out a pathogenic role favoring hematological dissemination from an intestinal source, and the tunneled, Port-A-Cath type, central venous catheter acted as a motive for recurrence of infection to different sites.

There were initial difficulties for the isolation of the germ and the antibiogram was not performed in a systematic manner, leading to empirical treatment according to the presumed susceptibility of *Bacteroides* to ampicillin/sulbactam, clindamycin, and metronidazole.

Our experience reinforces the need for a change in microbiologic conduct in health centers, where culture for anaerobe germs and systematic antibiograms are the norm, not the exception, in the typification of samples, especially those coming from severely ill patients.

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