Case study

Title : Febrile polyarthritis : should we think about disseminated gonococcal infection

Abstract:

Gonococcal disease is a sexually transmitted infection. The responsible agent is Neisseria gonorrhoeae. Disseminated gonococcal infection results from blood dissemination of N. gonorrhoeae from its mucosal first site of infection. In our cases, two patients had systematic lupus erythematous, in which one patient developed a dermetitis-arthritis syndrome and the other patient developed a febrile polyarthritis. The third patient was a healthy female who developed a dermetitis-arthritis syndrome. The treatment consisted of intravenous antibiotic and immobilization. The evolution was favorable in all of our cases.

Keywords: polyarthritis, fever, dermatitis, systemic lupus erythematous, gonococcal dissemination

Introduction:

Gonococcal disease is a sexually transmitted infection. The responsible agent is Neisseria gonorrhoeae. Clinical manifestations are more common in men such as urethritis, prostatitis (1) . In some predisposed subjects, gonococcal infection spreads which leads to dissemination of gonoccal infection, typically manifests as a combination of dermatitis, tenosynovitis and migratory polyarthralgia, or as

purulent arthritis without skin lesions (2). Many risk factors have been identified such as autoimmune diseases especially systemic lupus erythematous (SLE)(3). We report three cases of disseminated gonococcal infection with cutaneous and articular involvements affecting large and small joints in internal medicine department. Among these patients, two had SLE.

Case presentation

Observation 1:

23 years old woman was hospitalized for acute fever, asthenia and weight loss. The patient mentioned photosensitivity. On examination, she was feverish at 39.6 ° C, blood pressure was at 160 / 90mmHg. The skin examination showed papular, pustular and necrotic skin lesions affecting both legs and soles of the feet (figure n°1). There was also arthritis of the left knee and right metatarso-phalangeal (MTP). (figure n°1).

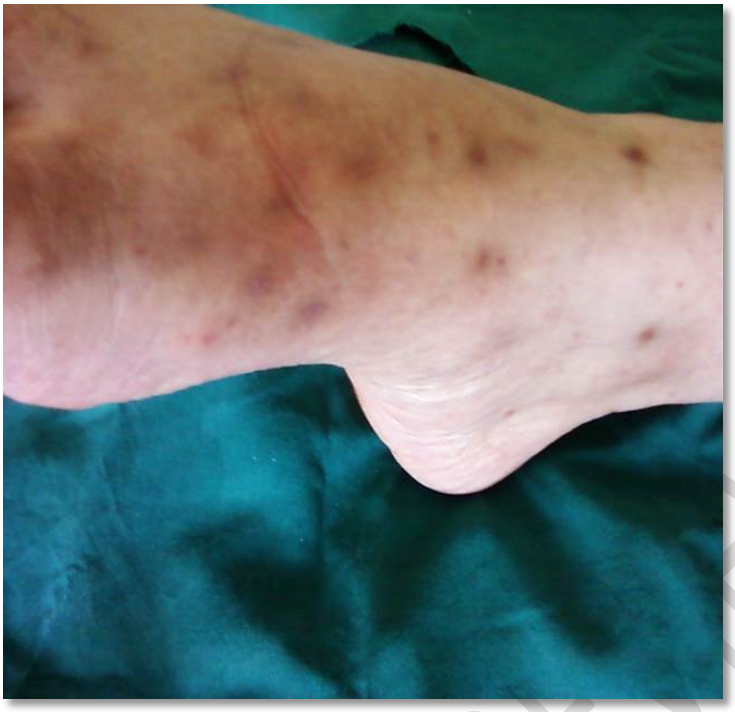

Figure 1: papular, pustular and necrotic skin lesions affecting both legs and soles of the feet

Laboratory tests showed an inflammatory syndrome (VS at 130mm H1; CRP at 110mg / l), an auto-immune hemolytic anemia at 8.5g / dl, leukolymphopenia (GB at 2490E / mm3 and lymphocytes at 600E / mm3), and proteinuria at 2.4g / 24H without hematuria and without renal insufficiency. ECBU, hepatitis B and C, atypical, syphilis and HIV serologies were negative. The anti-nuclear antibodies (ANA) were positive 1/1280 with anti-DNA, the serum complement was low. The chest, two knees, two feet x ray and cardiac ultrasound were normal. The abdomino-pelvic ultrasound showed a discrete homogeneous hepatosplenomegaly. The diagnosis of systemic lupus erythematous (SLE) was made based on photosensitivity, general signs impairment, arthritis, hematological involvement, low complement and positive ANA. The renal biopsy was refused by the patient.

She was treated with a high dose of corticosteroids (1 mg / kg / day) combined with an ACE inhibitor. The immediate course was favorable with apyrexia and disappearance of arthritis of the MTP. One day later, fever resumed with

persistent knee arthritis. The knee puncture showed a purulent liquid with innumerable isolated leukocytes with elevated neutrophil count (95%), the culture identified Neisseria gonorrhoeae germ. Blood cultures were positive for the same bacteria.

Resuming the interrogation, we found the notion of unprotected intercourse, of a genital infection two months ago treated without bacteriological evidence. The patient benefited from a synovectomy with articular washing, antibiotic therapy based on ampicillin 200 mg / kg / day in IV for 15 days then relay with Amoxicillin (6 g / day) for a total duration of three weeks and an immobilization.

The subsequent course was favorable with lasting apyrexia, disappearance of the skin lesions and biologically improvement of the hemoglobin level to 10.3 g / dl, normalization of CRP and negativation of proteinuria. In the evolution, the patient remained stable with no sign of flare up of her SLE.

Observation 2:

28 years old man, is followed for SLE with cutaneous, hematological and renal involvement stabilized by corticoids and Azathioprine. He kept a moderate kidney failure. He presented with febrile polyarthritis affecting the ankles, knees and wrists, evolving for five days, not improved with high-dose of corticosteroid therapy. Clinically, there were no skin lesions, no hepatospenomegaly, cardiac and pulmonaire auscultation was normal.

In biology, there was an inflammatory syndrome (VS level was 130mm H1, CRP at 213mg, GB at 13800E / mm³and Hemoglobin at 12g/dl). Anti-nuclear antibody test was positive at >1:160 dilution. The complement fractions (C3 and C4 were within normal). Rheumatoid arthritis factor was negative. The cardiac ultrasound and the chest X ray were normal. The joint puncture of both knees isolated the Neisseria gonorrhoeae. The blood cultures were sterile. There was

no urethritis. The diagnosis of gonococcal arthritis was established. The patient was treated with third generation Cephalosporin, Quinolone and a cast immobilization. The evolution was favorable with apyrexie, regression of the polyarthritis and of the inflammatory syndrome.

Observation n°3:

53 years old woman with no medical history, was hospitalized for acute arthritis of the large and small joints. On examination, the patient was feverish at 38.2 ° C, she had skin lesions: annular with clear center and circular outline with erythematous halot in the palm of the left hand (figure n°2) and erythematous macules in the left ankle (figure n°3). We found arthritis of the left ankle, MCP of the 2nd 3rd 4th fingers of both hands, proximal inter phalangeal (PPI) of the 4th and 5th finger of the right hand and a tenosynovitis of the 4th and of the 5th finger of the right hand. The cardiac and pulmonary auscultation was normal. There were no lymphadenopathy or hepatosplenomegaly. (figure 2 and 3).

Figure 2: annulare with clear center and circular outline with erythematous halot in the palm of the left hand

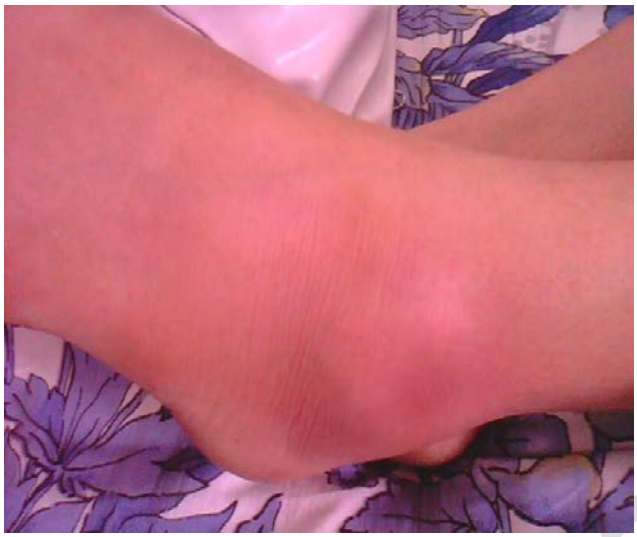

Figure 3:erythematous macules in the left ankle

Speculum examination found a minimal fetid yellowish haematic leukorrhea. Biologic tests showed, inflammatory syndrome (VS = 100 mm H1, CRP = 174mg / l), hepatic cytolysis (ASAT = 95 (2N), ALAT = 163 (3-4N)) and cholestasis (GGT = 239 (4N), PAL = 1080 (3N)). The cardiac ultrasound and the chest X ray were normal. An ankle joint puncture had shown a purulent leukocyte formula composed of more than 95% neurtophil and the presence of Gram-negative diplococci. The research of gonococcal DNA with PCR from the vaginal swab was positive.

The patient was treated with cefotaxime (3g / day) iv for 14 days then relayed by cefixime 800mg / day for 7 days and Immobilization with good clinical and biological progress.

Discussion:

Gonorrhea is an infection caused by the Neisseria gonorrhoeae, bacteria which usually infects the reproductive tracts and urethra in women and men. However, infections of the mouth, throat and rectum (collectively referred to as extra genital infections) are also possible (4).

Though not as common as chlamydia, gonorrhea is the second most frequently reported infectious disease nationwide, with 583,4 cases reported in 2018.

The risk of disseminated gonoccal infection (DGI) with gonorrhea infection was 0.5% to 3% in the 1970s, depending largely on the regional prevalence of specific strains of N gonorrhoeae (5). Current rates of DGI are low because of declines in the prevalence of these strains, and an overall drop in gonorrhea prevalence since the early 1980s. In the preantibiotic era, DGI was reported primarily in men (6), but studies in the 1960s and 1970s reported a female predominance of 78% to 97% (4,7). Gonorrhea diagnoses among women have increased for several consecutive years up to 241,074 cases in 2018. This is explained by the fact that menstruation is a major risk factor for dissemination, hormonal factors, the more alkaline pH of genital secretions during menses may facilitate growth of N gonorrhoeae and the phenotypes of gonococci expressed during menses may be more likely to disseminate (4). In 45% of affected women, symptoms of DGI begin within 7 days after the onset of menses.

Gonorrhea rates are highest among individuals between the ages of 20 and 24 (8). In our cases, 2 women and 1 men were affected with a mean age of 34 years old. This fact is explained by the predominance of connectivites mainly SLE in woman.

The incubation period is 3–5 days. At least 50% of women with gonorrhea are asymptomatic, allowing bacteria to spread prior to symptoms. Men often experience symptoms (typically urethritis) contrary to case n°2 where the patient didn’t have urethritis.

Gonococcal arthritis (GCA) results from blood dissemination of N. gonorrhoeae from its mucosal portal of entry (9).

Keiser et al (7). proposed two major clinical presentations of GCA :

The first was described as a septic or bacteremia form, characterized by either positive blood cultures for N. gonorrhoeae or the appearance of typical skin lesions, and may be more deserving of the term ‘‘disseminated gonococcal infection’’ (DGI).
The second was described as a non-septic joint localization form, characterized by progressive, localized joint inflammation, usually monarticular, with positive synovial culture, and a low frequency of fever, chills, and skin lesions.
It has been proposed that these Gonococcal arthritis forms are different stages in the evolution of the infection but this view is largely debated.

DGI is associated with a strain causing bacteremia without urogenital symptoms, and usually manifests with fever, chills, and the triad of the Arthritis-Dermatitis syndrome (10):

1. Arthritis: An asymmetric, migratory, often-septic polyarthritis of the knees, wrists, ankles, and finger joints develops in 3/4 of patients.

2. Tenosynovitis develops in 2/3 of patients, predominantly of the hand and wrist extensor tendons.

3. Dermatitis, manifesting as petechial or pustular acral lesions.

Two of our patients (patient 1 and 3) developed Arthritis- Dermatitis syndrome. Subsequent to a gonococcic infection of the urethra or uterine cervix, less frequently of the conjunctiva or rectum, an acute polyarthritis appears. It is often abrupt in onset and is accompanied by all the signs of an intense inflammation involving periarticular tissues and synovial membrane. There are pain, redness and tenderness with limitation of motion. The process is more often polyarticular than monarticular(6). The joints most frequently involved are the knees, ankles and wrists, although any joint of the body may be affected. There is often intense tenosynovitis about the wrists and ankles and in some instances the tendon sheaths are involved without any conclusive signs of associated

arthritis(11). Tenosynovitis is much more common in patients with gonococcic arthritis than in patients with other types of arthritis and is a valuable diagnostic sign. In most cases the arthritis begins within ten to twenty days after the onset of gonorrhea (4,6).

Skin lesions are seen in about 75% of patients with bacteremia, although they usually are painless and patients may be unaware of their presence. They typically number between 5 and 40, appearing on the extremities and sometimes on the trunk, but rarely on the face. Papules or small macules are the most common lesions, followed by pustules, often with a hemorrhagic component (3). A wide variety of skin lesions are associated with DGI, including vesicles and bullae, and immunologic lesions, such as erythema nodosum, erythema multiforme, and urticaria. N gonorrhoeae usually cannot be cultured from skin lesions by culture, and lesions may sometimes appear after appropriate antibiotic therapy has been started (2).

Unusual manifestations of disseminated gonococcal infection can be life-threatening and include gonococcal endocarditis (a major cause of bacterial endocarditis in the preantibiotic era), myocarditis and conduction defects, pericarditis, osteomyelitis (via extension from an infected joint), pyomyositis, hepatitis (Fitz-Hugh–Curtis syndrome), meningitis, Waterhouse–Friderichsen syndrome, and adult respiratory syndrome. These complications have become extremely rare since the introduction of antibiotics (3,12–14). In our cases, there were no severe complication the DGI despite the fact that two SLE patient were immunosuppressed.

The typical patient with acute DGI is a healthy female between 15 and 50 years of age. The clinical diagnosis should be evident when typical skin lesions are found or history reveals sexual exposure to an individual with known or suspected gonorrhea.

Many factors can play a role in gonococcil dissemination such : a female sex, pregnancy, menses, asymptomatic mucosal infection, multiple sexual partners,

low socio-economic status, intravenous drug use, complement deficiency, HIV infection, SLE, gonococcus strain characteristics (Protein 1A serotype, Lack of protein II, Arginine, hypoxanthine and uracil (AHU) strains) (3,9,15).

As risk factors, 2 of our patients had SLE and for patient n°1 the diagnosis of SLE and DGI was made at the same time. This is expalined by the fact that SLE involves a dysregulation of the immune system. The T and B lymphocytes are activated, leading to the production of autoantibodies and the formation of immune complexes, with a decrease in serum complement. In these patients, the decrease in serum levels of complement increases the risk of infections by certain bacteria that depend on the complement system for their opsonization and subsequent lysis (3).

In an earlier work, Ellison concluded that the prevalence of inherited or acquired complement deficiency among patients with disseminated gonococcal infection is higher than in the general population and is an important factor predisposing to systemic infection by NG. In the series by Mitchell et al. of Neisseria infection in SLE, it was reported that young women with renal disease and acquired or congenital hypocomplementemia are most affected (16).

N. gonorrhoeae is a Gram-negative, intracellular, aerobic diplococcus. Diagnosis is made through culture and nonculture tests (nucleic acid amplification tests, polymerase chain reaction, DNA probes, and Gram stain). Nonculture tests do not provide antibiotic sensitivities. Positive samples should be reported to the public health department. Regardless of symptoms, in men the urethra, pharynx, and rectum should be swabbed. In women, the cervix, pharynx, and rectum should be swabbed (17).

Fluid aspiration of swollen tendon sheaths or joints is not necessary in every patient, but should be performed when septic tenosynovitis or arthritis is suspected on the basis of clinical examination (e.g., marked pain, erythema, warmth, or limited range of motion) or significantly elevated inflammatory markers (e.g, serum white blood count, erythrocyte sedimentation rate, or C-

reactive protein). The mean synovial fluid leukocyte count in gonococcal arthritis is typically around 50,000 cells/mm3; in some cases, cell counts below 10,000 cells/mm3 may be observed. A definitive diagnosis of DGI is made by identification of N. gonorrhoeae on a specimen of blood, synovial fluid or tissue, skin lesion, or other nonmucosal site. All persons with a diagnosis of gonorrhea should be tested for other sexually transmitted infections, including chlamydia trachomatis, syphilis, and HIV (10,14). Blood cultures must be obtained before the therapeutic trial, not only to detect gonococcemia but also to help exclude other septic arthritides and infective endocarditis(2).

The epidemiology of antimicrobial resistance guides decisions about gonococcal treatment recommendations and has evolved because of shifts in antimicrobial resistance patterns. In 2007, emergence of fluoroquinolone-resistant N. gonorrhoeae in the United States prompted CDC to cease recommending fluoroquinolones for treatment of gonorrhea, leaving cephalosporins as the only remaining class of antimicrobials available for treatment of gonorrhea in the United States. Reflecting concern about emerging gonococcal resistance, CDC's 2010 STD treatment guidelines recommended dual therapy for DGI.

Hospitalization of patients with gonococcal arthritis is recommended to confirm diagnosis, search for systemic complications (i.e. endocarditis and meningitis) and initiate therapy.

The treatment consist of Ceftriaxone 1 g intramuscular or intravenous every 24 hours plus Azithromycin 1 g orally in a single dose. Parenteral antibiotics should be continued until signs and symtoms have improved or resolved for 24–48 h. Oral therapy may then be substituted to complete at least 7 days of antimicrobial therapy (18).

Infected joints should be aspirated to remove purulent material and to monitor the decrease in cellularity of synovial fluid. Saline lavage can also be used. Surgical or arthroscopic drainage is rarely indicated but should be considered if

improvement is not obtained within a few days. Outcome is usually favourable when appropriate antimicrobials are used promptly.

Conclusion :

Infectious arthritis is the main manifestation of blood spread following a mucosal infection with Neisseria gonorrhoeae. It can occure in predisposed patients such as SLE. The diagnosis of DGI might be diffficult in these patients due to the presence of the same clinical symptoms. But gonococcal infection should be suspected in case of arthritis-dermatitis syndrome. Effective management includes joint puncture with analysis of the synovial fluid and the initiation of empirical treatment, which limits the risk of complications.

Reference

1. Burns JE, Graf EH. The Brief Case: Disseminated Neisseria gonorrhoeae in an 18-Year-Old Female. Burnham C-AD, éditeur. J Clin Microbiol. 26 mars 2018;56(4):e00932-17, /jcm/56/4/e00932-17.atom.

2. Rice PA. Gonococcal Arthritis (Disseminated Gonococcal Infection). Infectious Disease Clinics of North America. déc 2005;19(4):853 -61.

3. Rueda DA, Aballay L, Orbea L, Carrozza DA, Finocchietto P, Hernandez SB, et al. Fitz-Hugh-Curtis Syndrome Caused by Gonococcal Infection in a Patient with Systemic Lupus Erythematous: A Case Report and Literature Review. Am J Case Rep. 29 déc 2017;18:1396 400.

4. Masi AT, Eisenstein BI. Disseminated gonococcal infection (DGI) and gonococcal arthritis (GCA): II. Clinical manifestations, diagnosis, complications, treatment, and prevention. Seminars in Arthritis and Rheumatism. févr 1981;10(3):173 -97.

5. O'Brien JP, Goldenberg DL, Rice PA. Disseminated gonococcal infection: a prospective analysis of 49 patients and a review of pathophysiology and immune mechanisms. Medicine (Baltimore). nov 1983;62(6):395-406.

6. Keefer CS. GONOCOCCIC ARTHRITIS: PATHOGENESIS, MECHANISM OF RECOVERY AND TREATMENT: CLINICAL LECTURE AT ATLANTIC CITY SESSION. JAMA. 30 oct 1937;109(18):1448.

7. Keiser H, Ruben FL, Wolinsky E, Kushner I. Clinical Forms of Gonococcal Arthritis. N Engl J Med. août 1968;279(5):234-40.

8. Centers for Disease Control and Prevention (CDC). CDC fact sheet: reported STDs in the United States: 2018 national data for chlamydia, gonorrhea, and syphilis.

9. Bardin T. Gonococcal arthritis. Best Practice & Research Clinical Rheumatology. avr 2003;17(2):201-8.

10. Carlin E, Urban C, Sidle J, Cirilli A, Larson J, Richman M, et al. Gonococcal Tenosynovitis Diagnosed with the Aid of Emergency Department Bedside Ultrasound. The Journal of Emergency Medicine. juin 2018;54(6):844-8.

11. Vidaurrazaga MM, Perlman DC. A case of purulent gonococcal arthritis. IDCases. 2020;19:e00662.

12. Gharamti AA, Pinto NC, Henao-SanMartin V, Franco-Paredes C, Henao-Martínez AF. Successful treatment of gonococcal osteomyelitis with one week of intravenous antibiotic therapy. Int J STD AIDS. mai 2019;30(6):610-2.

13. Rehnström M, Unemo M, Tunbäck P. Gonococcal Osteomyelitis Resulting in Permanent Sequelae. Acta Derm Venerol. 2016;96(4):562 -3.

14. Belkacem A, Caumes E, Ouanich J, Jarlier V, Dellion S, Cazenave B, et al. Changing patterns of disseminated gonococcal infection in France: cross-sectional data 2009–2011: Table 1. Sex Transm Infect. déc 2013;89(8):613 -5.

15. Ellison RT, Curd JG, Kohler PF, Reller LB, Judson FN. Underlying Complement Deficiency in Patients with Disseminated Gonococcal Infection: Sexually Transmitted Diseases. oct 1987;14(4):201 -4.

16. Mitchell SR, Nguyen PQ, Katz P. Increased risk of neisserial infections in systemic lupus erythematosus. Seminars in Arthritis and Rheumatism. déc 1990;20(3):174 -84

17. Centers for Disease Control and Prevention. Recommendations for the laboratory-based detection of Chlamydia trachomatis and Neisseria gonorrhoeae--2014. MMWR Recomm Rep. 14 mars 2014;63(RR-02):1 -19.

18. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 5 juin 2015;64(RR-03):1 -137.

figure n°1: papular, pustular and necrotic skin lesions affecting both legs and soles of the feet

figure n°2 : annulare with clear center and circular outline with erythematous halot in the palm of the left hand

figure n°3 : erythematous macules in the left ankle