

DERMATOSE FEBRIL – UM DIAGNÓSTICO A NÃO ESQUECER

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RESUMO – Apresenta-se o caso de um doente de 46 anos, com coinfeção VIH-1/VHC e cirrose hepática, internado por febre, prostração e astenia. Ao exame objetivo, observavam-se escassas pústulas necróticas em base eritematosa acantonadas aos dedos das mãos e pés com edema, dor e limitação funcional dos mesmos e da articulação tíbio-társica esquerda. Analiticamente, apenas elevação ligeira da enzimologia hepática e da PCR. Admitiram-se as hipóteses diagnósticas de endocardite, meningococémia ou gonococémia. Após isolamento de *Neisseria gonorrhoeae* em hemocultura, iniciou-se ceftriaxone 1g/dia EV com melhoria clínica. A positividade da PCR para *N. gonorrhoeae* no exsudado orofaríngeo confirmou o diagnóstico de gonococémia disseminada de ponto de partida orofaríngeo. A gonorreia é uma infeção sexualmente transmitida causada pelo diplococo Gram negativo *Neisseria gonorrhoeae*. A gonococémia disseminada na forma da síndrome clássica "dermatite-artrite" acompanha apenas 1-2% das infeções mucosas. A gonorreia orofaríngea é geralmente assintomática em homens e mulheres, constituindo provavelmente um reservatório importante do agente. O aumento da incidência de gonorreia torna este caso pertinente na prática clínica actual do dermatologista.

PALAVRAS-CHAVE – Gonorreia; Doenças da pele; Doença bacteriana de transmissão sexual; Febre.

FEBRILE DERMATOSIS – A DIAGNOSIS NOT TO FORGET

ABSTRACT – A 46 year-old male patient with HIV-1/HCV coinfection and liver cirrhosis admitted with fever, prostration, and asthenia. On physical examination, scarce necrotic pustules on an erythematous base on the fingers and toes with swelling, pain and functional limitation of the left tibiotarsal joint were noted. Laboratory revealed only slight elevation of liver enzymology and CRP. We admitted the diagnostic hypotheses of endocarditis, meningococemia or gonococemia. After isolation of *Neisseria gonorrhoeae* from a blood culture, intravenous ceftriaxone was started with clinical improvement. Pharyngeal swab PCR positivity for *N. gonorrhoeae* confirmed the diagnosis of pharyngeal origin disseminated gonococemia. Gonorrhea is a sexually transmitted infection caused by Gram-negative diplococcus *Neisseria gonorrhoeae*. Disseminated gonococemia in the form of the classical "arthritis-dermatitis" syndrome accompanies only 1-2% of mucosal infections. Pharyngeal gonorrhea is often asymptomatic in men and women, probably constituting an important reservoir of the agent. The rise in gonorrhea incidence makes this case very pertinent in any dermatologist's clinical practice today.

KEY-WORDS – Gonorrhea, skin diseases; Sexually transmitted diseases, Bacterial.

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INTRODUCTION

Febrile dermatoses comprise many different entities, including strictly dermatological and systemic diseases. The clinical picture of arthritis and dermatitis also has a broad differential diagnosis that comprises several entities, mainly of infectious and autoimmune aetiology. The appropriate evaluation of a patient with a febrile dermatosis or arthritis/dermatitis syndrome by the dermatologist should include not only cutaneous but also extracutaneous manifestations, always keeping in mind the importance of the epidemiological context and that both the frequent and the rare entities can be part of everyday practice.

CLINICAL CASE

A 46 year-old male patient with HIV-1/HCV coinfection with liver cirrhosis was admitted with fever, prostration, and asthenia lasting for 3 days. He was under anti-retroviral therapy (tenofovir/emtricitabine and raltegravir) and had a good immune status (CD4+ cell count of 450 cells/mm³ and undetectable viral load). On physical examination, scarce necrotic pustules on an erythematous base on the fingers and toes with swelling, pain and functional limitation of the affected fingers and toes were noted (Fig. 1). One day later, a painful, red and swollen left tibiotarsal joint was also observed (Fig. 2). He was febrile (38,5°C) and hemodynamically stable. Heart auscultation was normal; meningeal signs and urethral discharge were absent. Laboratory evaluation on admission (Table 1) revealed only thrombocytopenia, slight elevation of liver enzymology and C-reactive protein, with no leucocytosis or neutrophilia. Given this clinical picture, we admitted the diagnostic



Fig 1 - On physical examination (admission), scarce acral necrotic pustules on an erythematous base on the hands, lateral borders of fingers and toes with swelling, pain and functional limitation of the affected fingers and toes. The skin lesions were painful and had appeared three days before with accompanying fever.

hypotheses of infective endocarditis, meningococemia or gonococemia. After isolation of *Neisseria gonorrhoeae* from a blood culture, intravenous ceftriaxone 1g IV daily was started with quick clinical improvement and apyrexia after 24h. Antibiotic sensitivity testing revealed susceptibility to cefixime, ceftriaxone and ciprofloxacin. Transthoracic echocardiogram showed no signs of endocarditis. Urine and rectal swab polymerase chain reaction (PCR) for *N. gonorrhoeae* were negative but pharyngeal swab PCR positivity confirmed the diagnosis

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Fig 2 - One day after admission, a painful, red and swollen left tibiotarsal joint was also observed; the swelling and erythema over the toes were also clinically worse.

of pharyngeal disseminated gonococemia. The patient complained of no pharyngeal symptoms whatsoever.

As far as epidemiological context is concerned, the patient was a heterosexual male with just one regular partner on the last year. Apart from HIV and HCV, he denied previous sexually transmitted infections.

DISCUSSION

Gonorrhea is a sexually transmitted infection (STI) caused by Gram-negative bacteria *Neisseria gonorrhoeae*. Despite its natural affinity for the columnar epithelium of lower urogenital tract (usually causing urethritis and cervicitis), there is also a relatively small but definite risk of an ascending infection of the upper genital tract (with rare complications as pelvic inflammatory disease, ectopic pregnancy, infertility in women and epididymitis in men). Other possible sites of infection include rectum, oropharynx and conjunctiva. Another

Table 1 - Laboratory evaluation on admission (normal values in parentheses).

Leukocytes	11.00 x 10 ⁹ /L	4.5 - 11.0
Neutrophils	64.66%	40 - 75
Platelets	80 x 10 ⁹ /L	150 - 450
Total bilirubin	4.07 mg/dL	0.3 - 1.2
Conjugated bilirubin	2.05 mg/dL	0.00 - 0.20
Aspartate aminotransferase	132 U/L	< 50
Alcaline phosphatase	152 U/L	30 - 120
C-reactive protein	32.00 mg/L	< 5.0

peculiar phenomenon concerning *N. gonorrhoeae* is its potential to invade the bloodstream, resulting in gonococemia and disseminated gonococcal affliction of the joints, cardiovascular system and skin. The pathogenetic hallmark of gonococcal infection is a host innate immune-driven inflammatory response, characterized by a potent neutrophil influx¹.

Disseminated disease develops in 1-3% of patients with mucosal gonorrhea. Prompt diagnosis and therapy are mandatory to avoid joint destruction and progression to septic shock². The "arthritis-dermatitis" syndrome is the classic clinical presentation, including arthralgia/arthritis, dermatitis, tenosynovitis, fever and chills. Asymmetric, severe polyarthralgia, in a migratory or additive pattern, most commonly involving the knees, wrists, ankles and fingers is the usual presenting symptom. True arthritis is observed in less than 50% of cases. It has a good prognosis when appropriate therapy is promptly initiated. Destructive arthritis has become rare, with the exception of HIV patients or inappropriately treated long duration gonococemia. Skin lesions occur in over 2/3 of cases and are frequently discrete and few in number; non-pruritic, tiny papules, pustules or vesicles with an erythematous base involving the limbs and trunk and sparing the face and scalp³. As they are caused by bacterial embolization followed by microabscess formation, the papules and pustules frequently are necrotic⁴. Tenosynovitis occurs in more than half of patients, most commonly over the dorsum of hands, fingers, feet, knees and wrists; it is a generally a clinical diagnosis. Fever and chills are also common³.

Risk factors for disseminated gonococcal infection are: female sex, pregnancy, menses, multiple sexual partners, intravenous drug use, complement deficiency, HIV infection, systemic lupus erythematosus and gonococcus strain characteristics such as protein IA serotype and lack of protein II. Asymptomatic local infection, which is more frequent in women and a source

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of delayed antibiotic treatment, favours disseminated infection and is one explanation for this female predominance. The association with HIV infection may be explained by sexual behaviour that leads to higher exposure to gonorrhoea more than by facilitated dissemination of the infection in an immunodeficient patient³.

Oropharyngeal gonorrhoea is vastly asymptomatic in both men and women. All asymptomatic or oligosymptomatic infections represent a long-standing reservoir for transmission and this is particularly true with oropharyngeal gonorrhoea¹.

In this particular clinical case, the more relevant differential diagnoses were infective endocarditis and meningococemia. Patients with infective endocarditis may present with myalgias, arthralgias, fever, chills and hemorrhagic blisters or pustules, also caused by septic emboli. However, most patients with infective endocarditis have cardiac abnormalities detected by echocardiography and have positive blood cultures⁵. Although meningococemia may be clinically difficult to differentiate from disseminated gonorrhoea, meningococcal arthritis is usually more severe and patients frequently have clinical signs of concurrent meningitis⁶. Other entity that can present as an arthritis/dermatitis syndrome is reactive arthritis (i.e., Reiter's syndrome or keratoderma blennorrhagicum). The clinical picture frequently includes subacute arthritis involving the axial skeleton and lower limb joints and ophthalmologic disease (conjunctivitis or uveitis). Patients usually are afebrile and can present with psoriasiform plaques typically involving the hands and feet, palmo-plantar pustulosis, nail dystrophy and circinate balanitis or vulvitis⁷.

Laboratory tests play a crucial role in the diagnosis and effective management of disseminated gonococemia. Leukocytosis, neutrophilia, elevated C-reactive protein and sedimentation rate are usual findings, though unspecific and frequently of mild intensity. A positive culture for *N. gonorrhoeae* is important not only for definite diagnosis but also for determination of drug susceptibility, and its isolation must ideally occur before starting antibiotics. When a synovial effusion is present, it should be aspirated and sent for Gram stain and culture. Blood or synovial fluid cultures are positive in approximately 50% of cases. If a urethral or cervical discharge is present, it should also be sent for direct examination and culture. The same is true for skin lesions but its sensitivity is very low³. Rectal and oropharyngeal smears are not very sensitive because these sites are abundant with other Gram-negative cocci; therefore Gram stain and culture are not routinely recommended for these specific sites. In recent years, nucleic acid

amplification (NAAT)/polymerase chain reaction (PCR) tests have revolutionized detection of *N. gonorrhoeae*. The main reason for this breakthrough is high sensitivity and specificity as well as the possibility of taking specimens in a non-invasive way¹. PCR tests for both *N. gonorrhoeae* and *C. trachomatis* are daily performed on urine, urethral, cervical, rectal and oropharyngeal specimens on our STI Clinic.

The initial recommended regimen for disseminated gonococemia is ceftriaxone 1g IM or IV every 24h. Therapy should be continued for 7 days, but may be switched to an oral regimen according to antimicrobial sensitivity test 24-48 hours after symptoms improve (cefixime 400mg oral twice daily or ciprofloxacin 500mg oral dose twice daily or ofloxacin 400 mg oral dose twice daily)⁸.

Regarding the treatment of oropharyngeal gonorrhoea, studies have demonstrated a lower cure rate when compared with anogenital gonococcal infections, presumably because of inconsistent levels of cephalosporins in pharyngeal mucosa^{9,10}. The recommended treatment is ceftriaxone 500mg IM as a single dose together with azithromycin 2g oral single dose⁸. The role of a test of cure after treatment of gonorrhoea is still under discussion. It appears to be particularly important to ensure effective eradication of pharyngeal infection. Tests of cure in asymptomatic patients should be performed with a NAAT two weeks after completion of treatment; if a test of cure is still positive, then culture of the oropharynx should be performed and antibiotic susceptibility testing performed before further treatment is given⁸.

Gonorrhoea notifications have been rising in several European countries (including Portugal) since the early 2000s, particularly in men who have sex with men (MSM) and young heterosexual individuals of both sexes. Not only is this rise related to high levels of unsafe sexual behaviour but also to increased screening, more sensitive diagnostic methods and improved reporting¹¹.

Notified gonorrhoea cases in Portugal in the period between 2009 and 2012 reached a total of 442, approximately 110 annual new cases. The majority of reported cases (90%) were diagnosed in the region of Lisbon, were males (87%) and the most frequent age group was 25-34 years old¹². At the STI Clinic in our Department, in the period between 2006 and 2013, we diagnosed a total of 114 cases; the most frequent age group was 20-29 years old, with a clear male predominance (91%). Most patients diagnosed with gonorrhoea at our STI clinic were men who had sex with men (55%) and 23% of the 114 cases were HIV positive.

The main concern with the increasing incidence of gonorrhea is related to decreasing susceptibility of this agent to the currently used antimicrobial drugs^{13,14}.

CONCLUSION

The authors report a case of disseminated gonococcal infection presenting with the classic "dermatitis-arthritis" syndrome with pharyngeal gonorrhea as the primary site of infection. In cases of unexplained fever, scarce necrotic pustules and migratory polyarthritis, particularly if anogenital symptoms are absent, a high level of suspicion for all routes of primary gonorrheal infection must be maintained. Although the first documented case of gonococemia complicating gonorrheal pharyngitis was first published in 1970, the rise in gonorrhea incidence makes this topic a very pertinent one in any dermatologist's clinical practice today.

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