Genital ulcers

CPD

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CASE

A man aged 37 years presented with a three-day history of a penile ulcer and fatigue. He had a history of unprotected insertive anal intercourse with multiple male partners in the preceding four weeks. He had not travelled overseas or had contact with returned travellers. He had no significant medical history, no allergies and was not taking human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP).

Examination revealed a 2 cm non-tender indurated ulcer at the penile coronal sulcus that had a clean base (Figure 1). There was a firm, non-fluctuant, non-tender inguinal lymph node on the right side.

QUESTION 1

What are the differential diagnoses for this presentation?

QUESTION 2

What investigations should be requested?

ANSWER 1

A painless genital ulcer in men who have sex with men (MSM) is strongly suggestive of a primary syphilis lesion (chancre), although it is important to note that primary syphilis may present with painful and/or multiple ulcers. Chancres usually occur in the anogenital area or oral cavity as a result of direct contact during unprotected anal and/or oral sex and can occur from nine to 90 days after exposure.

Genital ulcers may be due to infectious or non-infectious aetiologies (Table 1).[1,2] Infectious causes are usually sexually transmitted, the most common being herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) and syphilis. More recently, there has been outbreaks of monkeypox in non-endemic countries, predominantly in MSM.[1] Monkeypox, a pox virus transmitted primarily via skin-to-skin contact in this outbreak, typically presents with a painful, umbilicated rash that progresses through a variety of stages and may or may not be preceded by a prodrome of fever, chills and lymphadenopathy.[1] Other infectious causes of genital ulceration are listed in Table 1, although these are rare in Australia. Non-infectious aetiologies are important to consider once infectious causes are excluded.[1,2]

ANSWER 2

The ulcer should be swabbed for type-specific HSV (1 and 2) polymerase chain reaction (PCR) and *Treponema pallidum* PCR. A swab for chlamydia PCR for lymphogranuloma venereum or monkeypox PCR for monkeypox may be requested if these diagnoses are suspected.

Given the sexual history of the patient, it is recommended to perform a complete sexual health screen, which includes serology for HIV, hepatitis A, hepatitis B, hepatitis C and syphilis, and three-site testing (oropharyngeal swab, first-pass urine and anorectal swab) for chlamydia and gonorrhoea PCR (results in Table 2).[3] In a case of syphilis, serology in combination with a direct swab for *T. pallidum* PCR is required for diagnosis, to confirm the stage of the infection and to monitor treatment success.

Type specific HSV IgG serology adds limited diagnostic value given the high prevalence of HSV-1 and HSV-2 and inability to differentiate from past or active infection.[4]

CASE CONTINUED

The patient underwent testing for HIV, hepatitis A, hepatitis B, hepatitis C

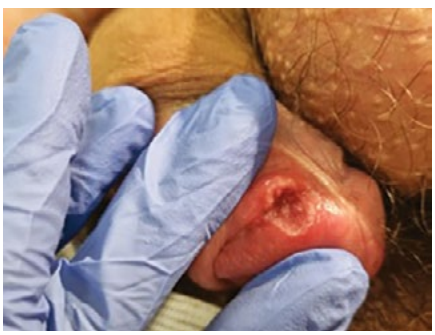

Figure 1. Penile ulcer on coronal sulcus

and syphilis, and three-site testing for chlamydia and gonorrhoea PCR. The results are shown in Table 2.

QUESTION 3

What is the diagnosis and what are the treatment options?

QUESTION 4

What other issues need to be considered in the management of this patient?

ANSWER 3

The patient presents with a primary chancre and has primary syphilis.

If treatment is delayed by more than a few days from the date of serology, the rapid plasma reagin (RPR) should be repeated on the day of treatment to establish an accurate baseline for monitoring as it can markedly increase within a few days without treatment.

First-line treatment for syphilis is with intramuscular benzathine benzylpenicillin 2.4 million units (MU; 1.8 g) as a single dose for early syphilis (primary, secondary and early latent, or infection of <2 years duration) and weekly for three weeks for late latent syphilis, syphilis of unknown duration or infection of >2 years duration.[5] Benzathine benzylpenicillin is available for the general practitioner in the doctor's bag in prefilled syringes of 1.2 MU each. Two vials are required for a single treatment. If there is diagnostic uncertainty, it is important to consider including empirical treatment for HSV with an oral antiviral such as valaciclovir, especially if there are multiple and/or painful anogenital lesions.

Clinicians and patients should be aware of possible reactions to treatment of early syphilis (primary and secondary), which include the Jarisch–Herxheimer reaction, characterised by an acute febrile illness with headache, myalgia, chills and rigors that resolves within 24 hours. Treatment with simple analgesics and bed rest is adequate.[6]

Patients with early syphilis should be advised to abstain from all types of sex for one week after treatment is completed. Complicated cases, such as those with neurological symptoms (where neurosyphilis may be suspected), pregnancy, allergy to first-line regimens, people living with HIV and patients where the stage of infection is unclear, should be discussed with a sexual health specialist or infectious disease specialist.[5]

Table 1. Causes of genital ulceration

Infectious; sexually transmitted (causative agents in parentheses)	• Herpes simplex virus types 1 and 2 • Syphilis (*Treponema pallidum*) • Chlamydia (*Chlamydia trachomatis*) • Lymphogranuloma venereum (*Chlamydia trachomatis* serovars L1–3) • Human immunodeficiency virus types 1 and 2 • Monkeypox (*Monkeypox virus*) • Chancroid (*Haemophilus ducreyi*) • Donovanosis (*Klebsiella granulomatis*)
Infectious; non-sexually transmitted	• Varicella zoster virus • Bacterial (eg group A Streptococcus) • Candidiasis • Tuberculosis • Leishmaniasis • Amoebiasis
Non-infectious (immunological, inflammatory, dermatological)	• Acute genital aphthous ulceration (Lipschütz ulcer)* • Dermatological (eg dermatitis, erosive lichen planus, lichen sclerosus) • Behçet syndrome • Crohn's disease • Coeliac disease • Systemic lupus erythematous • Autoimmune blistering skin disease (eg erythema multiforme, pemphigus, pemphigoid) • Stevens–Johnson syndrome/toxic epidermal necrolysis • Trauma • Fixed drug reaction (eg nonsteroidal anti-inflammatory drugs, tetracyclines, sulfonamides) • Neoplasms

**Associated with recent infection such as Epstein–Barr virus, cytomegalovirus,* Mycoplasma pneumoniae, *SARS-CoV-2 virus*

ANSWER 4

Syphilis is a doctor notifiable condition in Australia.[7] There is an ongoing syphilis epidemic in Australia, with increased cases of infectious syphilis in Aboriginal and Torres Strait Islander people from northern and central Australia, MSM from urban areas and women predominantly from urban areas. Increased notifications in women is a significant public health concern given the increased risk of congenital syphilis.[8] Contact tracing of sexual partners is critical to prevent ongoing transmission and re-infection, and individuals should be advised to avoid sexual contact with current partners until tested.[5,7] For cases of primary syphilis, all partners in the previous three months need to be contacted and tested; however, this time frame may vary depending on the stage of infection of the index case.[7] Lymphogranuloma venereum, chancroid and donovanosis are also notifiable conditions, whereas HSV-1 and HSV-2 are not.

All patients with syphilis should be informed of sexual health harm

minimisation approaches including safe sex counselling and education regarding the increased risk of HIV acquisition and transmission when there is co-infection with another STI.[9] Patients should be assessed for their suitability of HIV PrEP and HIV post-exposure prophylaxis if appropriate. All MSM are advised to be vaccinated for hepatitis A and hepatitis B if not immune.

Follow-up syphilis serology (RPR) is recommended at three, six and 12 months after completing treatment. A four-fold drop in RPR titre (eg 1:8 to 1:2) is indicative of adequate treatment response.[5] Expert advice should be sought if the RPR fails to drop as expected or is rising, which may be suggestive of treatment failure or re-infection. Treponemal tests (syphilis total chemiluminescent microparticle immunoassay antibodies and *T. pallidum* particle agglutination) in isolation should not be used to guide treatment decisions as they are expected to remain reactive for life.

CASE CONTINUED

The patient returned for treatment five days later and had a repeat RPR level on the day of treatment that was 1:16. The patient was treated with a single dose of benzathine benzylpenicillin 2.4 MU (1.8 g), with resolution of the penile ulcer by two weeks. Contact tracing was conducted for his sexual partners from the preceding three months. The patient was commenced on both hepatitis A and B vaccination courses as he had no history of prior vaccination. He was also commenced on HIV PrEP and had follow-up syphilis serology (RPR) at three months. The result was 1:2, indicating successful response to treatment.

Key points

- Genital ulcers may be due to infectious or non-infectious aetiologies, the most common cause being HSV-1 and HSV-2.
- A painless genital ulcer in MSM is strongly suggestive of a primary syphilitic chancre, although syphilitic lesions may be painful and/or multiple.
- Genital ulcers that occur in people who are sexually active should be swabbed for HSV-1, HSV-2 and *T. pallidum* PCR to aid prompt diagnosis and treatment, as syphilis serology may be negative in very early infection.
- RPR should be repeated on the day of treatment to establish an accurate baseline for monitoring.

Table 2. Initial investigation results

Test	Site	Result
Human immunodeficiency virus	Serology/Blood	Negative
Hepatitis A (Hep A IgG)	Serology/Blood	Not detected
Hepatitis B (HBsAg, anti-HBc, anti-HBs)	Serology/Blood	HBsAg not detected anti-HBc not detected anti-HBs <10
Hepatitis C Ab	Serology/Blood	Not detected
Syphilis (syphilis total Ab CMIA, TPPA, RPR)	Serology/Blood	Syphilis total Ab CMIA reactive TPPA reactive RPR 8
Syphilis *(Treponema pallidum* PCR)	Penile ulcer swab	Detected
HSV-1 and HSV-2 PCR	Penile ulcer	Not detected
Chlamydia/gonorrhoea PCR	Oropharyngeal swab Anorectal swab First-pass urine	Not detected Not detected Not detected

Ab, antibody; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; CMIA, chemiluminescent microparticle immunoassay; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; PCR, polymerase chase reaction; RPR, rapid plasma reagin; TPPA, Treponema pallidum *particle agglutination*

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