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Syphilis: A great imitator

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Abstract Despite advances in the control, diagnosis, and treatment of syphilis, its recognition is ill- understood or often not considered by dermatologists and other physicians who either have little specialized training in the minutiae of sexually transmitted infections (STIs) or whose dermatologic practice is only occasionally consulted by individuals from communities where STIs are prevalent. Our aim is to highlight contemporary ideas and findings on syphilis so that not only is an accurate diagnosis of syphilis made and recognized treatment given, but also necessary measures, such as counseling to exclude other STIs and to prevent reinfection, partner notification, and public health epidemiology as for any other infectious disease, are not forgotten. For syphilis, like human immunodeficiency virus (HIV) infection, not only is the biomedical aspect important, but also are the social and psychologic components.

Introduction

Treponema pallidum subspecies *pallidum (T pallidum)* causes syphilis via sexual exposure or via vertical transmission in pregnancy (congenital syphilis). Clinical manifestations result from local inflammatory responses to replicating spirochetes and often imitate those of other diseases (Table 1).[1] This is where dermatologic expertise is required to recall the morphology of syphilis in primary and secondary stages in adults and for pediatric dermatologists to team work with pediatricians in care of neonates and infants.

Epidemiology of syphilis varies throughout the world. Differing patterns are noted. Syphilis is a global public health problem. In high-income and middle-income countries, the majority of cases are in men who have sex with men (MSM),[1] but outbreaks of heterosexual spread must not be forgotten. In many regions where toleration is still not shown to MSM for obvious reasons, inaccurate sexual pathways may be assumed by reporting physicians, which allows for false epidemiology. In contrast, especially in developing nations, several hundred thousand still births and deaths occur every year.

Estimates of the prevalence and incidence of syphilis show differing figures in the World Health Organization (WHO) regions of the world. WHO incident cases from 2012 are: Americas (North and South) 937,000; Europe 440,000; East Mediterranean 496,000; Africa 1,843,000; Southeast Asia (including India) 886,000; and West Pacific (including China) 993,000.[2] As a result, syphilis remains an urgent public health problem in ante-natal care and the newborn in sub-Saharan Africa and developing nations. In high- and middle-income countries, the increase of syphilis in HIV-infected men serves as a reminder of the tenacity of *T pallidum* as a pathogen.[1]

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Table 1 Differential diagnosis of cutaneous manifestations of syphilis

Primary syphilis
Genital ulceration: Genital herpes, chancroid, granuloma inguinale, lymphogranuloma venereum, primary genital tuberculosis, amebiasis, scabies, leishmaniasis, Crohn disease, Behçet disease, fixed drug eruption, trauma, malignancy
Extragenital ulceration: Tularemia, cat-scratch fever, sporotrichosis, mycobacteriosis, leishmaniasis, Behçet disease, pyoderma gangrenosum

Secondary syphilis
Macular: Pityriasis rosea, drug eruption, viral eruption, erythema multiforme
Papular eruption: Psoriasis, drug eruption, cutaneous T-cell lymphoma, lichen planus, pityriasis lichenoides chronica, seborrheic dermatitis, pityriasis rosea, pityriasis rubra pilaris
Annular syphilis: Subacute cutaneous lupus erythematosus, sarcoidosis, granuloma annulare, erythema annulare centrifugum, tinea corporis, actinic porokeratosis
Palmar or plantar eruption: Contact dermatitis, atopic dermatitis, erythema multiforme, psoriasis, clavus, lichen planus
Nodular syphilis: Lymphoproliferative diseases, deep fungal infections, lepromatous leprosy, cutaneous tuberculosis, sarcoidosis, leishmaniasis, Sweet syndrome, adnexal tumors, lymphoproliferative diseases, histiocytosis, panniculitis
Pustular syphilis: Acne vulgaris, varicella, folliculitis, halogenoderma, papulopustular rosacea, bacterial skin infections, steroid acne, Behçet disease, Sweet syndrome
Frambesiform syphilis: Verruca vulgaris, deep fungal infections, pyoderma vegetans, adnexal tumors
Malignant syphilis: Ecthyma, ecthyma gangrenosum, pyoderma gangrenosum, atypical mycobacterial infection, varicella, pityriasis lichenoides et varioliformis acuta, systemic fungal infections, cutaneous vasculitis, drug eruptions
Leucoderma syphiliticum: Kala azar, vitiligo, postinflammatory hypo/hyperpigmentation
Mucous patches: Aphthous stomatitis; candidosis; lichen planus; hand, foot, and mouth disease; herpangina
Syphilitic angina: Streptococcal angina, diphtheria, Epstein-Barr virus–associated tonsillitis, agranulocytic angina
Condyloma lata: Condyloma accuminata, squamous cell carcinoma

Tertiary syphilis
Gummatous lesions: Cutaneous tuberculosis, sarcoidosis, leprosy, leishmaniasis, vasculitis, deep fungal infections

Primary syphilis

The incubation period of primary syphilis is usually 9 to 90 days after sexual contact has been made with an infected individual.[3] The classic description[4] is a painless well-circumscribed indurated ulcer with an ulcer base and a raised borders (Figure 1). Bilateral, painless inguinal lymphadenopathy usually accompanies the chancre.[3] The chancre occurs at the point of inoculation depending on the type of sexual exposure.[5] It is most commonly observed on the glans, coronal sulcus, or prepuce in men, and labia majora, labia minora, or perineum in women.[4,6] Multiple lesions may be seen in some cases[4] (Figure 2). It is rare in recent times to find extragenital chancres at sites such as the oral mucosa, chest, fingers, nipple, arm, toes, trunk, and eyelid[3,4] (Figure 3).

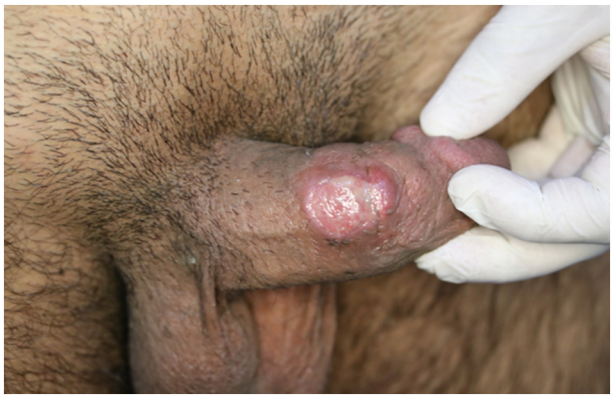

Fig. 1 Indurated ulcer with raised borders—primary chancre.

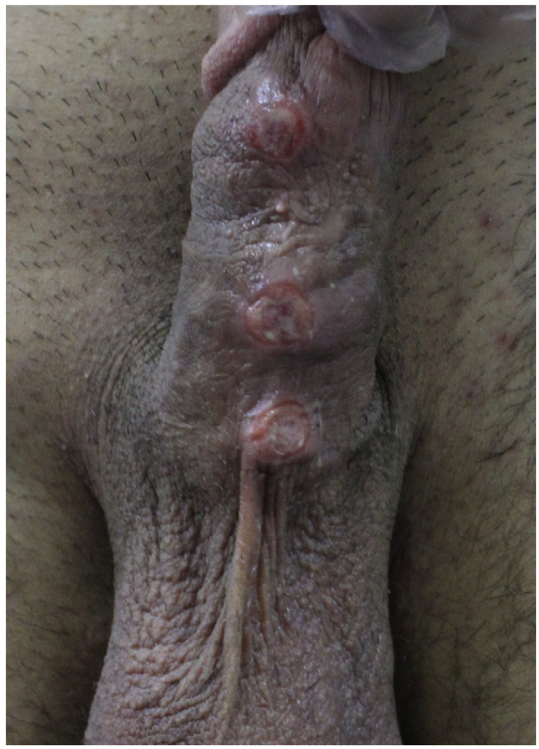

Fig. 2 Multiple chancres.

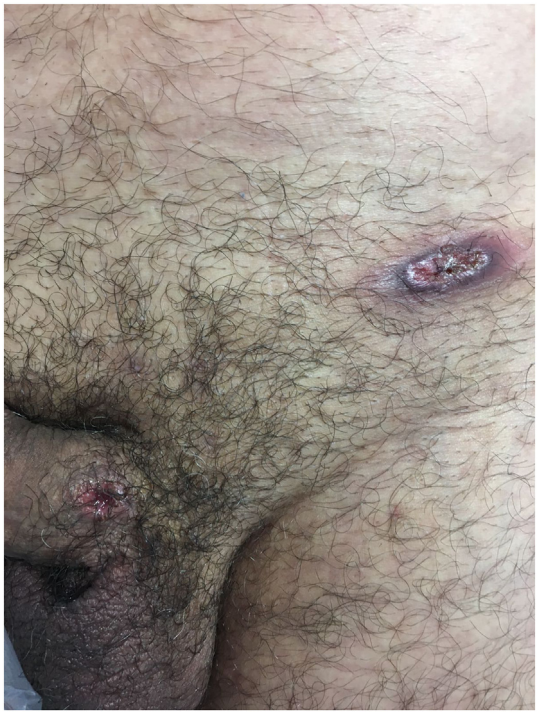

Fig. 3 Extragenital ulcer on the trunk.

Atypical manifestations of primary syphilis include linear chancre, little or no ulceration, multiple lesions with lymphangitis or thrombophlebitis of dorsi of penis, satellite ulcers, erosive balanitis, multiple lesions with accompanying inflammatory edema of the penis or phimosis, giant necrotic chancre, hypertrophic chancre, superficial ulcers, painful ulcers, pruritic ulcers, and nonhealing ulcers[4,7] (Figures 4 and 5).

To a nonspecialist, a chancre may easily go undetected if it is located in the anus or rectum; however, appropriate diagnosis is required from the specialist.[3] Extragenital lesions from the anorectal region are likely to drive ongoing transmission in the changing epidemic in MSM.[8] Chancres usually resolve after a period of 3 to 6 weeks without treatment, and they begin to resolve within a few days if treated.[9]

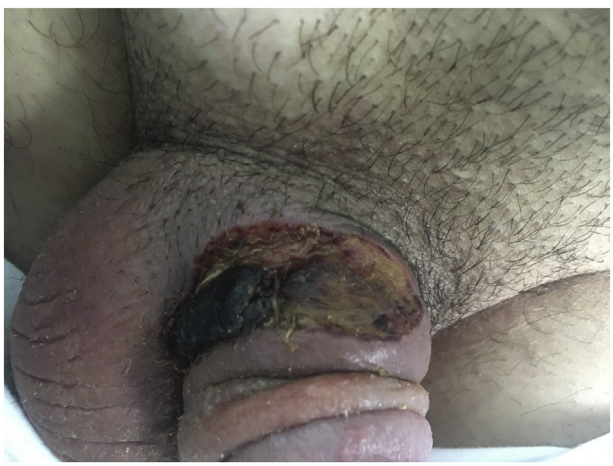

Fig. 4 Giant necrotic chancre.

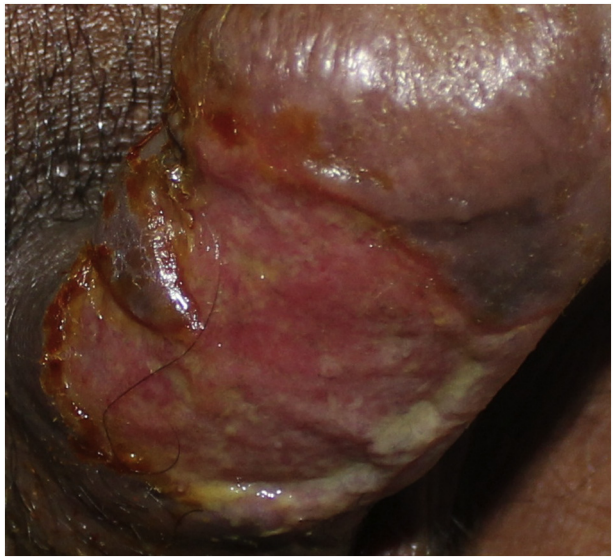

Fig. 5 Giant chancre.

Secondary syphilis

Primary syphilis progresses to secondary syphilis 6 to 8 weeks after the primary infection in untreated patients.[3] As the clinical presentation of secondary syphilis is diverse and may not be preceded by a detectable primary lesion, the diagnosis may be delayed to this stage.[10]

Secondary syphilis is a systemic disease in which *T pallidum* has disseminated to various organs.[10] It can be accompanied by constitutional clinical manifestations, such as fever, malaise, myalgias, arthralgias, sore throat, and headache. Painless, generalized lymphadenopathy will be present in 70% to 85% of patients.[11,12] Secondary syphilis may affect organs other than the skin, including the liver, gastrointestinal tract, kidneys, eye, and neurovascular system.[4] Resolution of the manifestations of secondary syphilis can take weeks to several months if untreated.[13]

Cutaneous manifestations

Skin lesions are the most common findings and are diverse, as might be expected of a great imitator. Macular, papular, maculopapular, papulosquamous, lichenoid, nodular, and pustular lesions may be observed at this stage.[10]

Initially, there is a generalized, symmetric, nonpruritic eruption varying from pink to violaceous to brown, mostly involving the trunk extremities, face, and the palm and soles.[3,14] The eruption is often symmetric and nonitchy.[15] Although early lesions are roseola-like discrete macules, an eruption may later be more infiltrated, with papulosquamous qualities, often deeper in color and polymorphic.[16]

The macular lesions (syphilitic roseolas) are most commonly located on the flanks, and their sizes may range from

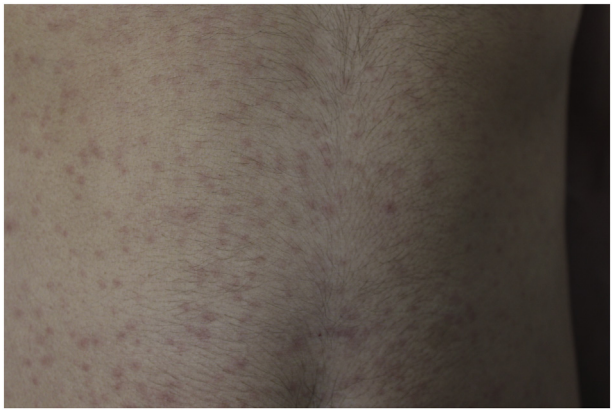

Fig. 6 Syphilitic roseolas on the trunk.

1 to 20 mm[7,17] (Figure 6). The macules disappear under pressure, and their color may change from pink to red and later to brown. They may enlarge, become annular or thickened, and coexist with papules as the eruption progresses.[17]

Papular lesions may be small (miliar) or large (lenticular or nummular), with the most commonly affected areas being the palmoplantar region, trunk, extremities, and the face[14] (Figures 7 and 8). Lesions around the hairline form a crown-like pattern (corona veneris).[6] The thin white ring of scaling on the surface of the secondary syphilis papule is known as "Biett's collarette," which is considered a strong indicator of secondary syphilis[18] (Figure 9). The palmoplantar area is involved in about 70% cases with plantar lesions sometimes becoming hyperkeratotic and often being mistaken for calluses (clavi syphilitica)[6] (Figure 10).

The classic maculopapular eruption can mimic lichen planus with violaceous flat-topped papules. The main difference between these two diseases is that syphilitic lesions are usually non-pruritic and tend to affect the palms and soles. There may also be papulosquamous lesions resembling psoriasis (Figures 11 and 12).[7] The corymbiform eruption is a rare manifestation of secondary syphilis, characterized by larger papules surrounded by

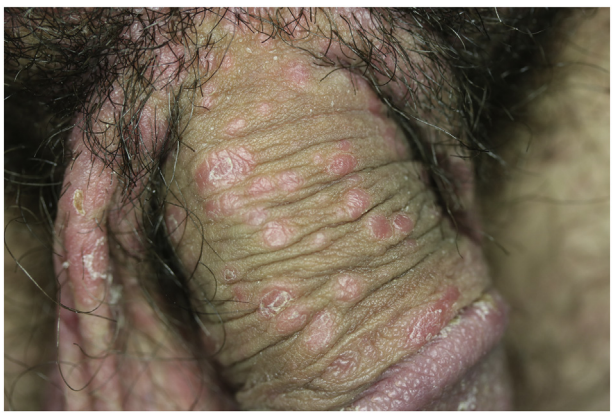

Fig. 7 Papular lesions on the genital region.

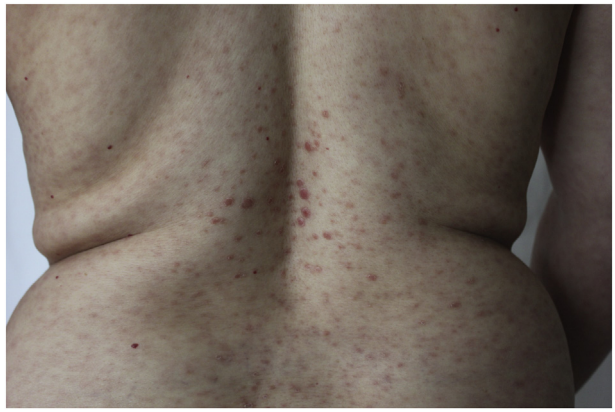

Fig. 8 Maculopapular lesions on the back.

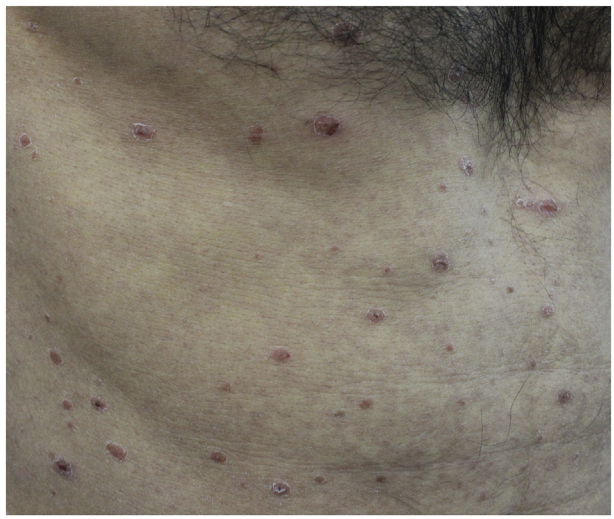

Fig. 9 Thin white ring of scaling on the surface of syphilis papules —"Biett's collarette."

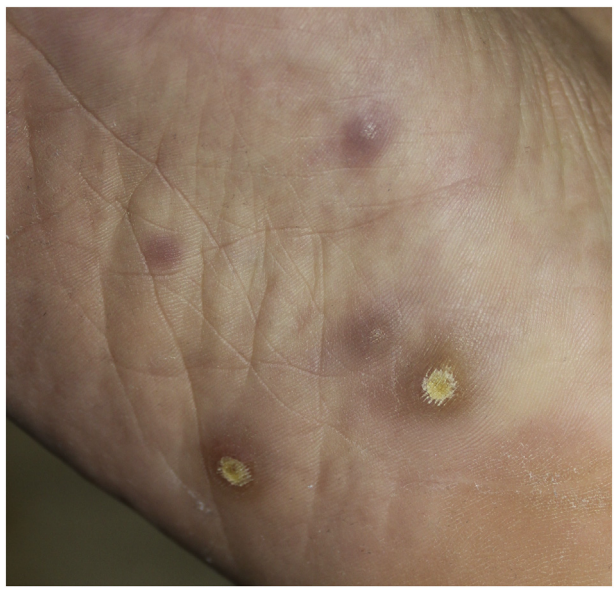

Fig. 10 Clavi syphilitica.

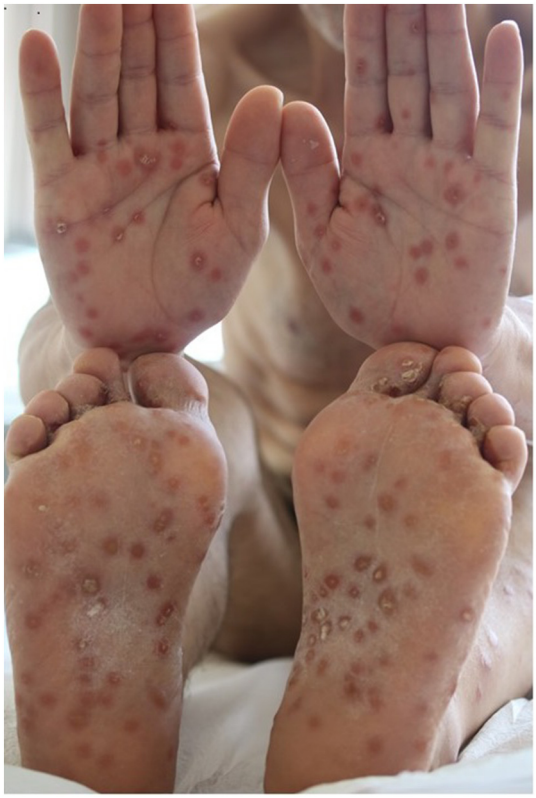

Fig. 11 Papulosquamous typical lesions on the palmoplantar surface.

small satellite lesions.[19] Additional mimics include PLEVA-like papulo- and vesiculo-necrotic lesions, follicular and vesicular lesions, photodistributed papulosquamous syphilis mimicking cutaneous lupus, targetlike erythematous papules and plaques mimicking erythema multiforme, lesions mimicking pityriasis lichenoides chronica, and anetoderma due to secondary syphilis (Figures 13 and 14).[12,20–23]

The morphology of secondary syphilis lesions with annular configuration ranges from delicate, slightly raised lesions with a scaly border to thicker verrucous plaques. They can also be violaceous in color.[12] The most commonly affected sites include the scalp, face, palm, soles, intertriginous areas, and the genitalia. There may be annular or concentric scaling lesions that resemble tinea imbricata.[11]

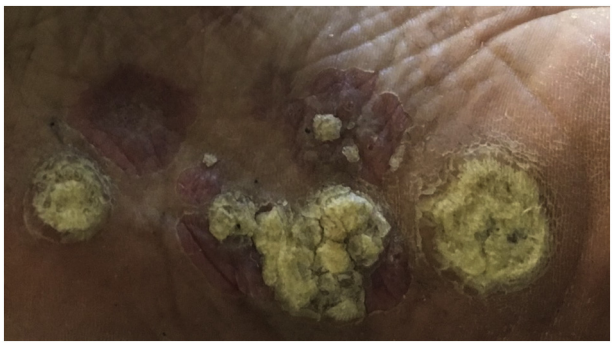

Fig. 12 Psoriasiform lesions on the plantar surface.

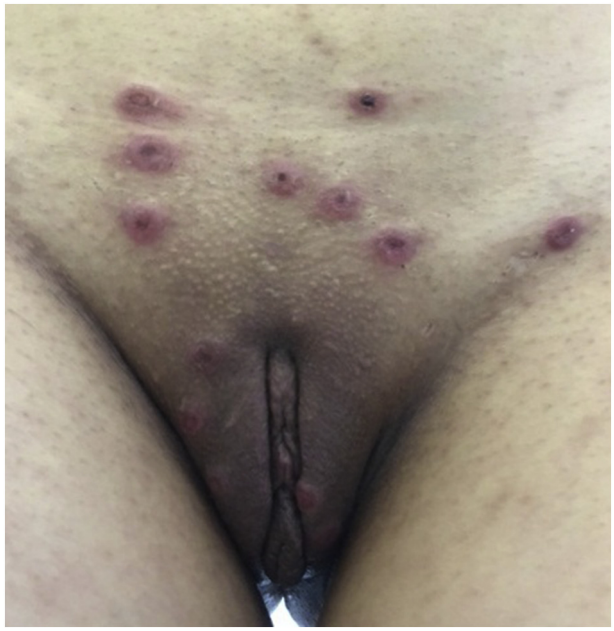

Fig. 13 PLEVA-like lesions on pubis.

The nodular variant can present as localized or generalized erythematous or violaceous plaques and nodules that may adopt an archiform pattern (Figure 15). The palms, soles, and mucosal surfaces are often spared in nodular syphilis. A thick adherent scale mimicking psoriasis may appear over nodular lesions, along with a leonine facies, characterized by diffuse nodular facial involvement.[11] Larger nodules and plaques appearing on the head and neck, characterized histopathologically by granulomas, were often confused with lymphoma or granulomatous diseases.[24] "Syphilis panniculitis," being direct fat inoculation by *T pallidum,* was characterized by painful nodules on the legs.[25] The rarely found frambesiform lesions could appear as red-brown, vegetative, ulcerative, keratotic nodular lesions of syphilis and be multiple or single appearing as tumors.[12,26]

Pustular lesions are uncommon, and they pose a diagnostic challenge. They are more common in patients with poor health and HIV coinfection.[27] Four subgroups of pustular syphilis have been described:

1. Miliary pustular syphilis is characterized by small perifollicular pustules.
2. Acuminate syphilis has two forms:
   - Acneiform syphilis with lesions usually on the face resembling acne
   - Varioliform syphilis with pustules and central crust and ulceration resembling varicella or smallpox
3. Flat variants include:
   - Impetiginoid syphilis with flat pustules and yellow crusts
   - Ecthymiform syphilis with lesions up to 5 cm forming ulcers with an overlying crust
4. Rupioid syphilis is characterized by papules, pustules, and ulcers covered by thick oysterlike crusts and is often accompanied by systemic involvement.[27,28]

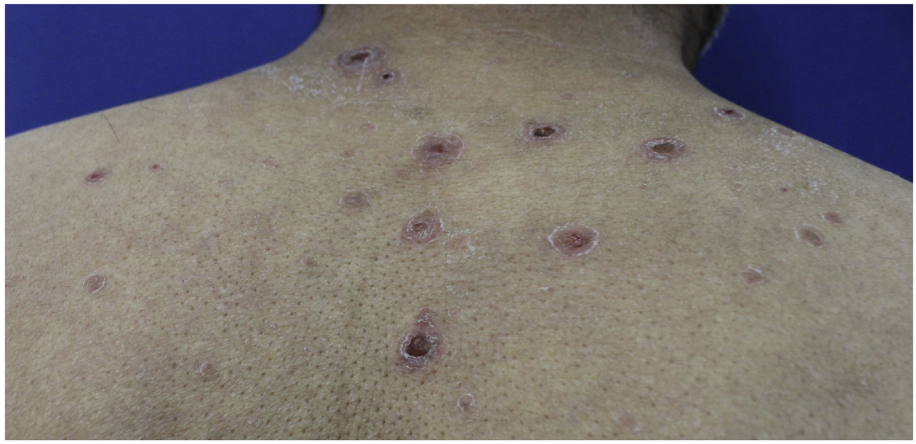

Fig. 14 PLEVA-like lesions on the back.

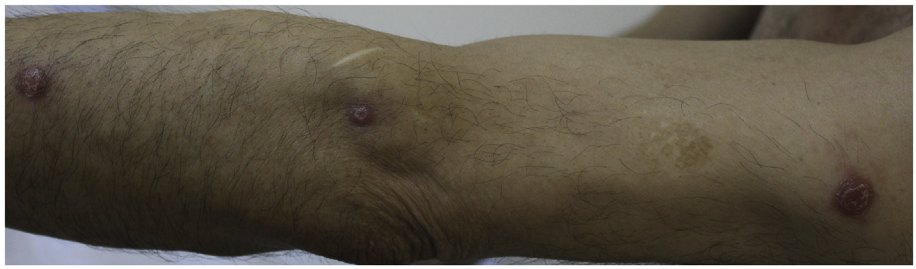

Fig. 15 Nodular lesions on the arm.

Leukoderma syphiliticum (LS), generally localized to the neck, presents with small light or achromic macules, surrounded by pigmented areas (necklace of Venus). Such depigmented macules may appear as primary findings or secondary to the resolving eruption of syphilis.[29] LS is more common in women and may appear upward to 6 months after the onset of syphilis.[30]

Hair involvement

Alopecia may be a manifestation of secondary syphilis. This "moth-eaten" alopecia is characterized by patchy, nonscarring alopecia of the scalp, is pathognomonic, and is the most common type of alopecia. A diffuse, nonscarring hair loss, mimicking telogen effluvium and alopecia areata, may also affect hair-bearing areas other than the scalp.[10]

Mucous membrane involvement

Mucous membrane lesions occur in approximately 30% of the patients.[16,29] Such mucous membrane patches are characterized as being oval-shaped, well-demarcated erythematous or thin white plaques on an erythematous base, with raised borders that occasionally ulcerate. They may be seen on the buccal mucosa, tongue, and lips[4,11] (Figure 16). Irregular serpiginous erosions (snail-track ulcers), small superficial ulcers resembling aphthae, and depapillary erythematous plaques (plaques faucheés) may be seen.[7,31] White, adherent plaques on the tongue, mimicking oral hairy leukoplakia and split papules, known as fissured papular lesions, may develop at the commissures.[11,32]

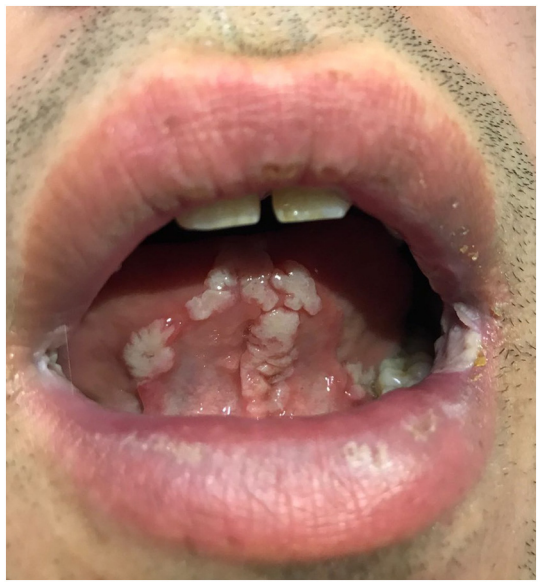

Fig. 16 Mucous patches on the tongue.

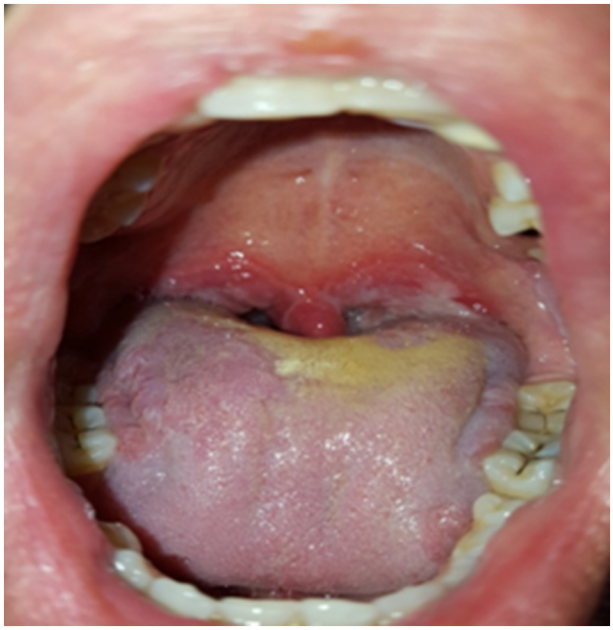

Fig. 17 Syphilitic angina.

Syphilis of the tonsils, also known as angina syphilitica sive specifica, appeared as bilateral tonsillitis, being accompanied by a diffuse pharyngitis. The tonsils were red, swollen, and coated with thin, pale gray exudates[33] (Figure 17).

Condyloma lata are intertriginous gray-white mucosal papules that macerate to form flat, moist, infectious lesions. They occur on the genitalia, perineum, axillae, or perioral areas and might be confused with condyloma acuminata[3] (Figure 18).

Nail involvement is a rare manifestation of syphilis, and it may occur in all stages of the disease. Primary fingernail involvement is most unusual (Figure 19). The nonprimary nail

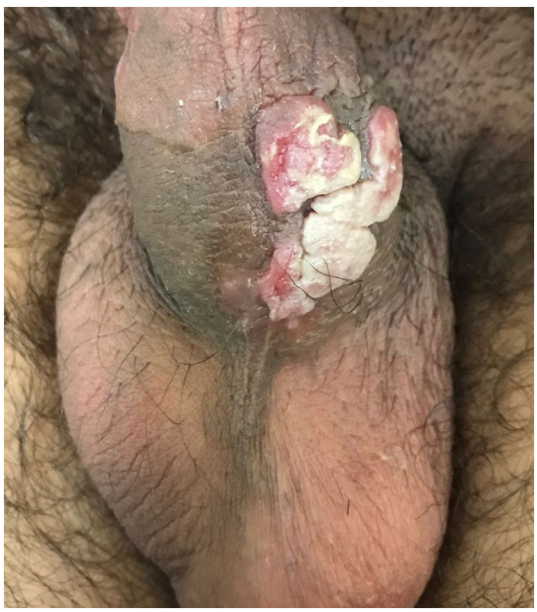

Fig. 18 Condyloma lata.

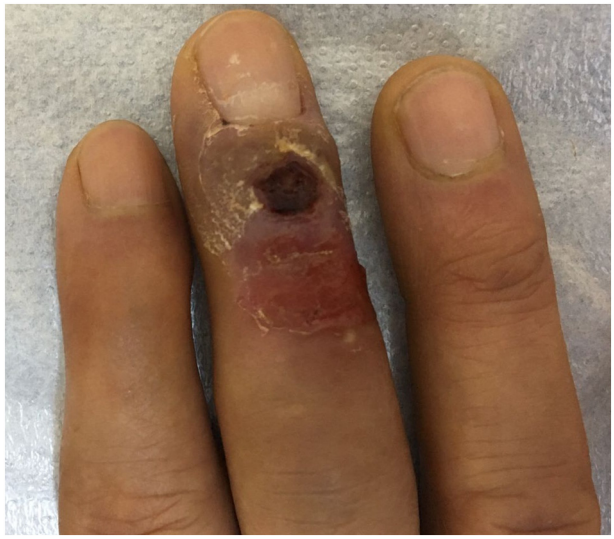

Fig. 19 Extragenital ulcer on the finger.

findings include those involving the nail plate (syphilitic onychia) and manifest as nail pitting, grooves, onycholysis, and onychogryphosis. Paronychia may develop, being painful violaceous nodules and abscesses surrounding the nail folds.[34]

Malignant syphilis (lues maligna) is an uncommon ulcerative variety of secondary syphilis that is occasionally seen in immunosuppressed patients with HIV. Papules that rapidly evolve into pustules and finally form ulcers with an elevated border and necrotic center are observed mainly on the trunk and extremities. Other constitutional clinical manifestations may develop at the same time.[35]

Latent stage

It is the asymptomatic stage between the secondary and tertiary stages where the serology remains reactive but clinical findings may diminish or disappear. Early latent syphilis is defined as the stage that may persist up to the second year of infection. *T pallidum* may be still present in the tissues, which results in recurrent disease. Late latent syphilis is defined after the second year of disease and is usually noninfectious.[3,15] About two-thirds of untreated syphilis patients remain in the latent stage lifelong, and one-third of the patients progress to tertiary stage.[28]

Early and late latent syphilis still exist, but many of the traditional findings are no longer apparent, probably due to the extensive use of antimicrobials for more than 70 years, at least in developed countries.

Late syphilis with dermatologic manifestations

Gummata are uncommon in modern times, no doubt due in the general population to the widespread use of antimicrobials, but they have been reported with HIV immunosuppression

forming within any organ, most commonly in the bones and skin.[36] They are nontender, granulomatous, ulcerated, asymmetric, and grouped lesions that favor sites of previous trauma. Gummata are more common on the scalp, forehead, buttocks, presternal, supraclavicular, or pretibial areas, occur singly or multiple, and vary in size from microscopic to tumorlike masses.[4,6]

Neurosyphilis

Neurosyphilis can occur at any stage of infection, but it is much more frequently seen in the prepenicillin era. Acute changes in mental status, meningitis, stroke, cranial nerve dysfunction, auditory, or ocular abnormalities may occur in secondary syphilis, even when HIV infection is not present. Unfortunately, such findings are being seen again in patients with HIV immunosuppression. A good diagnostician, even when not a neurologist, should be able to diagnose visual and auditory changes if attention is paid to the patient's clinical manifestations. Tabes dorsalis and general paresis, admittedly rare today in high-income countries, are among the manifestations of late neurosyphilis.[15]

HIV and syphilis

Reports from centers seeing many MSM suggest that the incidence of syphilis in HIV-infected patients is greater locally than in the general population. The chancre, with a deficiency of mucosal defense mechanisms, may facilitate the acquisition and transmission of HIV.[36]

It has been thought that, in patients with HIV, the clinical manifestations of syphilis or the response to treatment might be different as a result of the effect of HIV on host immunity, but the differences are not often statistically significant.[13] Patients who are coinfected with HIV may present with atypical clinical manifestations and more rapid progression of syphilis, with an overlapping between stages.[6] Multiple chancres have been observed, as have the primary chancre with secondary lesions.[19] Coinfection of HIV with syphilis may be associated with rapid progression to tertiary syphilis.[6] In immunosuppressed HIV-infected patients, if not under highly active antiretroviral treatment (HAART), progression may occur rapidly from early syphilis to neurosyphilis; likewise, clinical and CSF abnormalities, consistent with neurosyphilis, are not infrequent.[37]

Although there have been reports of serologic abnormalities in HIV-positive patients, including unusually high titers, false-negative results, and abnormally delayed seroreactivity, the consensus is that the interpretation of serology in syphilis is the same as in HIV-positive patients. A skin biopsy sometimes may assist in evaluating HIV-infected patients who have developed cutaneous lesions that might be syphilis but have a nonreactive serology.[11]

Histopathology

Perivascular infiltrates of lymphocytes, histiocytes, and plasma cells are observed irrespective of the disease stage.

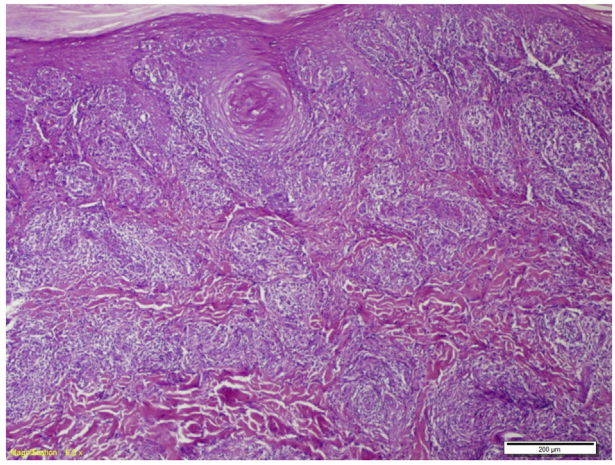

Fig. 20 Dermal and specifically perivascular lymphocyte, plasmocytes infiltration, and endothelial cell hyperplasia in a papular lesion of secondary syphilis (Hemotoxylin eosin (HE), original magnification × 10).

The key findings include vascular involvement with endarteritis and periarteritis, plus an increase in adventitial cells. Treponemes are commonly seen in both primary and secondary lesions. Treponemes may be identified with immunohistochemic staining and adding the Warthin-Starry stain.[4]

In primary syphilis, there may be endothelial swelling and ulceration, plus a diffuse dermal infiltrate of plasma cells, lymphocytes, and histiocytes.[6]

There is great variability in the histopathologic pattern in secondary syphilis. Lymphocytes and plasma cells are present in the dermis in 75% to 100% cases. Psoriasiform hyperplasia, exocytosis of lymphocytes, spongiform pustulation, and parakeratosis in the epidermis and marked papillary dermal edema and perivascular, lichenoid, nodular, or diffuse plasma cells, lymphocytes, and histiocytes in the dermis may be observed (Figures 20 and 21).

In tertiary syphilis, there may be gummas that represent granuloma formation and plasmacytic infiltration.[6,7]

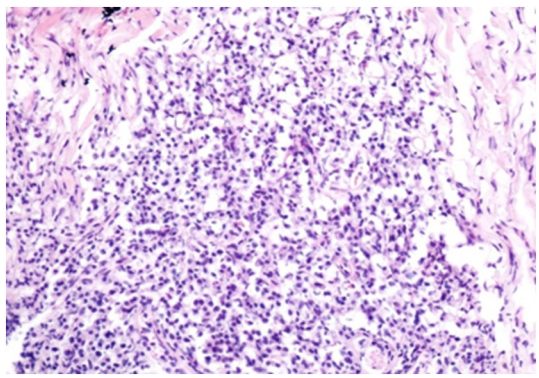

Fig. 21 Dermal infiltration of plasmocytes in a nodular lesion of secondary syphilis (Hemotoxylin eosin (HE), original magnification × 400).

Diagnosis

"How do I diagnose syphilis?"

The diagnosis of syphilis is based on the patient's history, physical examination, and laboratory testing. The laboratory tests used to diagnose syphilis are direct detection methods, including dark field microscopy, direct fluorescent antibody test, and nucleic acid amplification test and serology.[15]

A proper sexual history taking is of the greatest importance. It requires much skill to take an accurate sexual history. It is essential to assure the patient of his or her right to confidentiality and that no legal or moral strictures will result from subsequent diagnosis. Always think of syphilis and HIV-related skin disease when observing a dermatologic presentation that does not fit the pattern usually seen, but do not fall into the trap of procustes of making a false diagnosis by excluding all else.

Direct methods to diagnose syphilis[38] are darkfield microcopy, molecular assays to detect *T pallidum* DNA, and histopathologic examination of biopsies of the skin or mucous membranes. In some cases, they have the advantage of detecting infection before a patient has mounted a reasonable antibody response that results in a reactive serologic test result.

Dark field microscopy

Until 40 years ago, most dermatovenereologists would have been conversant the use of dark field microscopy in diagnosis. Any center seeing many patients with early syphilis will still require it; thus, it is essential that training in its use becomes part of the postgraduate syllabus; however, safety aspects, with awareness of bloodborne other STIs (HIV, hepatitis B and C), are paramount and care must be taken to exclude any risk to the physician and the assistants.

The sensitivity of darkfield microscopy[38] for diagnosis of primary syphilis is approximately 80%. It does not work if topical antibiotics have been applied to the lesions, nor is it of any use in the mouth where nonpathogenic treponemes are indistinguishable microscopically from *T pallidum*. It can be employed in secondary syphilis for moist lesions, such as condylomata lata, but not in the mouth.

Serologic tests for syphilis

Confirmation of the diagnosis relies on serologic tests: treponemal and nontreponemal. Treponemal tests include:

- *T pallidum* particle agglutination assay (TPPA)
- Fluorescent treponemal antibody absorption (FTA-ABS) test
- *T pallidum* hemagglutination assay (TPHA) to detect IgG and IgM antibodies to components of the whole *T pallidum* organisms or to recombinant *T pallidum* proteins

Nontreponemal tests include:

- Venereal Disease Research Laboratory (VDRL) test, which is usually quantified
- Rapid plasma reagin (RPR) test to detect IgG and IgM antibodies to a synthetic cardiolipin, cholesterol, and lecithin antigen complex.

In a newly infected patient, the treponemal tests generally become reactive shortly before the nontreponemal tests, and unlike the nontreponemal tests, whose reactivity declines after treatment, the treponemal tests generally remain reactive for life.[39]

The combined use of a treponemal and nontreponemal test is advised to be used for serologic diagnosis. In the traditional algorithm, the use of a nontreponemal test for screening followed by a treponemal test for confirmation has been used. In recent years, several clinical laboratories have switched to screening with a treponemal test followed by a nontreponemal test for confirmation[28]; however, interpreting false-negative and false-positive test results and identifying serofast reaction can be challenging.[3]

What else at time of diagnosis

- Screening for other STIs must be made when any diagnosis of early syphilis is made. This is sometimes forgotten about by those not adequately trained in STIs.
- Partner notification (contact tracing): This is part of the routine process required in the essential management of syphilis. When skillfully done, it is effective in tracing sexual partners and in reducing local epidemics.
- Counseling: It is not appropriate to give a patient an injection of penicillin or tablets such as doxycycline without advice beforehand. The patient should be forewarned about a possible Jarisch-Herxheimer reaction[40] and the means to alleviate it. A printed notice or text message about how to contact for advice or difficulties and when to return should be given to ensure that there has been an adequate serologic response.
- Sociopsychologic difficulties[41]: It is important to realize that many who have a diagnosis of early syphilis have difficulties caused through street drugs, difficulties caused in interpersonal relationships, and pre-existing psychologic morbidity. As a result, psychologic referral may sometimes be necessary, if the patient is agreeable.

Treatment

Benzathine penicillin G (BPG) is the first-line drug for all stages of syphilis. A single intramuscular (IM) injection of 2.4 million units (MU) of BPG is curative for early, uncomplicated syphilis in adults (ie, primary, secondary, early latent stage); 2.4 MU of BPG given once weekly for 3 weeks is recommended for late latent syphilis, syphilis of unknown duration, and tertiary syphilis. As there are no proven alternatives for pregnant women who are allergic to penicillin, they should be desensitized and then treated with penicillin.[27] In neurosyphilis, 3 to 4 million units of intravenous aqueous crystalline penicillin G every 4 hours for 10 to 14 days is used, and some experts

recommend two or three doses of benzathine benzylpenicillin after completing intravenous therapy.[3]

HIV-infected patients undergo the same treatment as HIV-uninfected patients according to the Centers for Disease Control and Prevention (CDC) recommendations. Macrolides, tetracyclines, and ceftriaxone are alternatives to penicillin in nonpregnant penicillin-allergic patients[37]; however, there have been an increasing number of reports of *T pallidum* chromosomal mutations with azithromycin, as well as with other macrolide resistance.[15]

Alternatives to penicillin in patients allergic to penicillin[42]

CDC recommendations include doxycycline 100 mg twice daily for 14 days or tetracycline 500 mg four times a day (taking into account the gastrointestinal side effects). Both depend on patient self-medication and thus are not reliable. Ceftriaxone 1- to 2-g IM or intravenously daily has been used but studies are limited.

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