CLINICAL REVIEW

Dermatologic Manifestations of Secondary Syphilis

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Introduction/Overview

Syphilis is a sexually transmitted disease (STD) caused by the bacterium *Treponema pallidum*. It persists as a global public health challenge, with an estimated 7.1 million new cases reported worldwide in 2020 in adults between 15 and 49 years of age.[1] Between 2018 and 2022, reported syphilis cases increased by 80% in the United States.[2] Syphilis is a highly contagious yet treatable STD. The vast rise in recent years has been attributed to unsafe sexual activities as well as a shortage of STD screening and poor access to healthcare services.[3] Syphilis testing and identification are critical for timely diagnosis and management, especially in populations at risk for congenital syphilis, where early detection and prompt treatment are crucial in preventing adverse outcomes.[4] Secondary syphilis follows the initial primary stage and occurs several weeks to months after the initial infection. It is marked by systemic dissemination of *Treponema pallidum* and frequently presents with diverse dermatologic symptoms.[5] Of these, palmar rash is particularly significant and serves as a critical diagnostic indicator for healthcare providers.[6] It is also important to consider a range of atypical cutaneous manifestations of secondary syphilis that deviate from the characteristic clinical presentation.[7] The timely and accurate diagnosis at the secondary syphilis stage is imperative in order to effectively treat the disease and prevent its progression to the late (tertiary) stage, which causes internal organ complications, and further spread via congenital syphilis.[6] The skin, being the largest, most visible organ of the body, is an ideal location to diagnose syphilis. This review covers the typical and atypical dermatologic manifestations of secondary syphilis, focusing on the clinical presentation, diagnostic approaches, management strategies, and implications for public health.

Historical Perspective

The recognition and comprehension of the dermatological manifestations of secondary syphilis have progressed over millennia. Early historical records attest to the presence of distinctive skin lesions providing diagnostic clues for syphilis.[8] These initial observations provided the foundation for future advancements in understanding and identifying secondary syphilis.

During the Middle Ages, physicians faced challenges in distinguishing syphilitic lesions from other skin conditions. They frequently relied on rudimentary diagnostic methods, such as visual inspection and trial-and-error treatments.[9]

Diagnostic methods and therapeutic strategies have advanced remarkably, mirroring sustained efforts to address syphilis and its dermatologic manifestations. Since penicillin became widely accessible in the 1940s and provided global regions to effectively treat the infection, syphilis prevalence steadily decreased. Despite the decline, syphilis outbreaks persist around the world.[8] A historical re-emergence of syphilis has occurred among men who have sex with men. However, the recent increase of secondary syphilis infection is driven by increasing rates among females, also resulting in an increased number of congenital syphilis. Dermatological manifestation of syphilis in women can be mistaken for other infections, such as herpes, thus underscoring the relevance of understanding and addressing the dermatological manifestations of secondary syphilis in contemporary healthcare.[10]

Pathophysiology of Secondary Syphilis Dermatologic Manifestations

Secondary syphilis arises from the dissemination of the bacterium *Treponema pallidum* throughout the body. This follows the initial infection via sexual contact or vertical transmission, where it elicits a robust immunological response.[11] The interaction between the bacterium and the host immune system triggers inflammatory responses and tissue damage, resulting in dermatologic manifestations. The diverse clinical symptoms of secondary syphilis stem from hematogenous dissemination of the infection and are protean including: *condyloma lata* (papulosquamous eruption), lesions on the hands and feet, a macular rash, and alopecia.[12]

The pathophysiology driving these symptoms involves multiple mechanisms with complex immunological processes, including recruitment of inflammatory cells, release of pro-inflammatory cytokines, and activation of complement pathways. These processes contribute to tissue damage and the consequent formation of characteristic skin lesions. The bacterium employs various strategies to evade immune surveillance. These include antigenic variation, modulation of host immune signaling pathways, and inhibition of phagocytosis.[13] The spirochete has trace amounts of lipoproteins on the surface that have the ability to increase infectivity. In syphilis lesions, activated T cells contribute to the systemic nature of the disease and clear pathogens via activated macrophages. However, this process also enhances the production of tissue-damaging cytokines, such as tumor necrosis factor (TNF) and IL-6. Immunohisto-

chemical analysis has revealed the presence of CD4+ and CD8+ T cells, activated macrophages, and natural killer cells within syphilitic lesions, which cause local inflammation.[9]

Clinical Presentation and Pathology of Secondary Syphilis Dermatologic Manifestations

Secondary syphilis manifestations follow the resolution of primary lesions. Typical cutaneous presentation is a nonpruritic, symmetric, maculopapular rash with copper-like color occurring on the chest, back, shoulders, arms, and flank.[8] Lesions typically erupt and involve the palmar and plantar surfaces, known as the palmar rash. This rash is characteristic of syphilis and is found in 75-90% of patients. People may mistake this rash with other diseases, such as pityriasis rosea, herpes, eczema, roseola or psoriasis. Secondary syphilis is further known for its physical variability. It can present with a wide spectrum of dermatologic symptoms that are not always characteristic, such as papules, pustules, *condyloma lata*, mucous patches, and alopecia, thus earning syphilis the name of the "Great Imitator" since manifestations often appear similar to other diseases.[9]

Condyloma lata is reported in 6% to 23% of patients with secondary syphilis infection and presents as moist papules or nodules. These lesions are infectious and can be found in the anogenital region as well as the inner thighs or areas of skin-to-skin contact, such as the inframammary creases. These typically appear as raised, gray pustules. Since these lesions resemble diseases other than syphilis, such as condyloma acuminata, a differential diagnosis is necessary.[14]

Syphilitic mucous patches are reported in up to 30% of patients and typically present in the mouth and genitals. The oral mucous patches appear white, elevated, and may develop into serpiginous lesions that have a 'snail-track' appearance surrounded by inflammation. Direct microscopic examination and immunofluorescence for the bacterium confirm the presence of *Treponema pallidum*.[15]

Alopecia is reported in approximately 10% of patients with secondary syphilis. It rarely presents as the only symptom, known as "essential syphilitic alopecia," and can be easily misdiagnosed.[16] Aside from essential alopecia, moth-eaten alopecia (MEA) is another manifestation of secondary syphilis. This form of alopecia could be confused with alopecia areata, traction alopecia, or trichotillomania.[17]

"Leus maligna" is a rare manifestation that occurs in immunocompromised patients, such as those with Human Immunodeficiency Virus (HIV). These lesions appear with an oval shape and well demarcated borders that can contain a lamellar crust and typically affect the trunk and extremities in addition to the scalp, face, palms, and soles. Additional dermatologic manifestations occur through changes in pigmentation, such as leucoderma syphiliticum, and alterations of the nails (paronychia, splitting, onycholysis).[18]

Diagnosis depends on a combination of clinical assessment, serological assays, and dermatologic examination, confirmed by histopathological analysis, which provides further elucidation of lesion attributes.[19] Clinical manifestations commonly present 3-12 weeks after the resolution of the primary chancre. Physicians are advised to examine for mucocutaneous eruption with psoriasiform, follicular, pustular, lichenoid, nodular, or annular morphologies.[20] It is important that physicians conduct a thorough examination and consider the aforementioned symptoms during dermatologic examination at the secondary syphilis stage since the later disease stage can only be detected with serological testing.

TABLE 1. Clinical Manifestations of Secondary Syphilis

Dermatologic Symptom	**Description**
Palmar rash	Redness and warmth of the palms of hands
Mucous patches	Elevated oval plaques adorned with a white or gray pseudomembrane in the soft palate and labial mucosa, 'snail-track appearance'
Condyloma lata	Flat-topped, smooth-surfaced papules and small plaques; painless, warty erosions, typically 1-2 cm in length
Alopecia	Non-scarring hair loss displaying a "moth-eaten" pattern on scalp
Leus maligna	Ulcerated and scabbed pustules, nodules, and ulcers

Management and Treatment of Dermatologic Symptoms

The effective management of secondary syphilis involves a multifaceted approach to alleviate symptoms, resolve the infection, and prevent complications. Secondary syphilis management and treatment requires antibiotic therapy, primarily with penicillin, administered according to disease stage and severity. The recommended treatment regimen consists of intramuscular benzathine penicillin G, administered as a single dose of 2.4 million units. In the event of penicillin allergy, doxycycline or ceftriaxone may be prescribed alternatively.[21]

Addressing dermatologic symptoms may be necessary to relieve discomfort and enhance patient outcomes. In addition to antibiotic treatment, symptomatic management may be needed to relieve discomfort and improve patient well-being. Topical corticosteroids can assist in reducing inflammation and itchiness linked with skin lesions.[22] Patients should also receive guidance on maintaining good hygiene and refraining from sexual activity until the lesions have healed and treatment has completed to prevent transmission to sexual partners. Vigilant

monitoring and regular follow-up are necessary to evaluate treatment efficacy and reduce recurrence.[21]

If treatment failure or syphilis reinfection occurs, thorough reassessment is needed to pinpoint underlying factors and adjust management. This could involve alternative antibiotic regimens for retreatment or referring patients to specialists for additional evaluation and care.[23]

Future Directions and Research Perspectives

Despite advancements in diagnosis and treatment of secondary syphilis, challenges remain in its management and identification of dermatologic manifestations. Emerging diagnostic technologies, such as molecular assays and point-of-care tests, offer promising capabilities for improving the detection and monitoring of syphilis infections. Additional research into the pathogenesis of dermatologic manifestations is necessary to elucidate the underlying mechanisms and to identify novel therapeutic targets.[24]

Emerging Diagnostic Technologies

Novel diagnostic technologies shows promise in enhancing the detection and characterization of dermatologic manifestations in secondary syphilis. Progress in molecular diagnostics, including polymerase chain reaction (PCR) and nucleic acid amplification tests (NAATs), offers the potential for more sensitive and specific detection of *T. pallidum* DNA in skin lesions.[25] Furthermore, point-of-care tests with rapid turnaround times and high accuracy could expedite diagnosis and initiation of treatment, especially in resource-limited settings.[26] Integration of imaging modalities such as ultrasound and dermatoscopy may also improve the diagnostic accuracy of secondary syphilis skin lesions by providing detailed anatomical and morphological information.[27]

Novel Treatment Approaches and Therapeutic Targets

Innovative treatment approaches and therapeutic targets presents promising avenues for enhancing outcomes in secondary syphilis. The emergence of antibiotic-resistant strains of Treponema pallidum underscores the urgency for alternative treatment strategies.[28] Targeted therapies disrupting specific pathways involved in Treponema pallidum pathogenesis, such as adhesion molecules and virulence factors, have potential for improving treatment efficacy and curbing resistance development.[29] Immunomodulatory agents modulate host immune responses to facilitate bacterial clearance and tissue repair represent another avenue for investigation.[30] Repurposing existing drugs with known antimicrobial or anti-inflammatory properties may offer a cost-effective means to address secondary syphilis dermatologic manifestations.[31]

Areas for Further Investigation and Research

Further research and investigation are needed to advance our understanding of secondary syphilis dermatologic manifestations. Longitudinal studies are needed to elucidate the natural history of skin lesions and correlate with disease progression and outcomes.[21] Comparative studies evaluating the efficacy and safety of various antibiotic regimens, including alternative agents for penicillin-allergic patients, are crucial for refining treatment protocols.[32] Investigations into the immunopathogenesis of secondary syphilis may unveil novel biomarkers for disease monitoring and guide the development of targeted therapies.[33] Collaborative efforts between researchers, clinicians, and public health agencies are needed to address research priorities and translate findings into clinical practice.

Future research perspectives in secondary syphilis dermatologic manifestations offer exciting prospects for advancing diagnostic capabilities, refining treatment strategies, and expanding our knowledge of disease pathogenesis. Leveraging innovative technologies, exploring novel therapeutic approaches, and prioritizing research can bolster our capacity to diagnose, treat, and ultimately prevent the dermatologic complications of secondary syphilis.

Conclusion

In conclusion, the dermatological manifestations of secondary syphilis pose a significant challenge in contemporary healthcare, requiring careful attention and comprehensive management strategies. Understanding the mechanisms driving these manifestations is needed for effective management and prevention. There is a pressing need for heightened awareness, education, and expanded screening to decrease the burden of secondary syphilis and its dermatologic implications. The dermatologic manifestations of secondary syphilis represent a significant clinical entity with wide-ranging implications for affected patients and public health. This review examined the multifaceted nature of secondary syphilis, encompassing its historical perspective, etiology, clinical presentation, management strategies, and avenues for future research.

The recognition and understanding of secondary syphilis dermatologic symptoms have evolved, affecting diagnostic and treatment approaches. Early detection and timely administration of appropriate treatment are essential to prevent disease progression, minimize complications, and reduce the likelihood of transmission to sexual partners and offspring. The importance of secondary syphilis symptoms, notably the palmar rash, cannot be emphasized enough, highlighting the importance of heightened clinical suspicion and thorough evaluation in suspected cases. The clinical presentation of secondary syphilis encompasses a diverse array of dermatologic symptoms, spanning from the classic maculopapular rash to atypical manifestations such as *condyloma lata*, mucous patches, alopecia, and leus maligna. Achieving an accurate diagnosis relies on a comprehensive evaluation involving clinical assessment, serological testing, and histopathological examination, and underscores the importance of adopting a thorough diagnostic approach in suspected cases of secondary syphilis.

The management and treatment of secondary syphilis encompass antibiotic therapy, relief of dermatologic symptoms, and vigilant monitoring to gauge treatment efficacy and prevent recurrence. Advancements in diagnostic technologies offer promising opportunities for improving disease detection and characterization of secondary syphilis dermatologic manifestations. Novel treatment approaches and therapeutic targets hold potential for improving treatment outcomes and decreasing risks of antibiotic resistance. Sustained research efforts and collaborative endeavors are needed to bridge existing knowledge gaps, refine diagnostic and treatment modalities, and mitigate the impact of secondary syphilis on individuals and communities.

Concerted actions are needed to bolster screening initiatives, heighten awareness, and facilitate educational campaigns targeting healthcare providers and the general public. By fostering multidisciplinary approaches and prioritizing research endeavors, we can advance diagnostic and therapeutic modalities, leading to improvements in clinical outcomes and eradicating the public health burden caused by this preventable and treatable disease. By collectively confronting the challenges posed by secondary syphilis, we can aspire towards a future where its impact is minimized, and affected individuals receive timely diagnosis, comprehensive care, and support.

REFERENCES

1. World Health Organization. Syphilis. Fact Sheet. Geneva, Switzerland: World Health Organization. (2023). Retrieved from https://www.who.int/news-room/fact-sheets/detail/syphilis.
2. Centers for Disease Control and Prevention. (2021). Sexually transmitted diseases treatment guidelines. Retrieved from https://www.cdc.gov/std/treatment-guidelines/syphilis.htm.
3. Centers for Disease Control and Prevention. STI Surveillance Report 2022. Centers for Disease Control and Prevention. Retrieved from: https://www.cdc.gov/nchhstp/newsroom/2024/STI-Surveillance-Report-2022.html#:~:text=Reported%20syphilis%20cases%20increased%2080,blindness%2C%20deafness%2C%20and%20paralysis. Accessed on 26 Feb 2024.
4. **Nazir A, Masood W, Ahmad S, Nair AM, Aborode AT, Khan HD, Farid S, Raza MA, Audah KA**. Rise of syphilis surge amidst COVID-19 pandemic in the USA: A neglected concern. *Ann Med Surg (Lond)*. 2022 Aug;80:104239. doi: 10.1016/j.amsu.2022.104239. Epub 2022 Jul 31. PMID: 35937637; PMCID: PMC9339075.
5. World Health Organization. (2018). Report on global sexually transmitted infection surveillance 2018. Retrieved from https://www.who.int/publications/i/item/9789241565691.
6. **Balagula Y, Mattei PL, Wisco OJ, Erdag G, Chien AL**. The great imitator revisited: the spectrum of atypical cutaneous manifestations of secondary syphilis. *Int J Dermatol*. 2014 Dec;53(12):1434-41. doi: 10.1111/ijd.12518. Epub 2014 Oct 14. PMID: 25312512.
7. **Dourmishev LA, Dourmishev AL**. Syphilis: uncommon presentations in adults. *Clin Dermatol*. 2005 Nov-Dec;23(6):555-64. doi: 10.1016/j.clindermatol.2005.01.015. PMID: 16325063.
8. **Peeling RW, Hook EW 3rd**. The pathogenesis of syphilis: the Great Mimicker, revisited. *J Pathol*. 2006 Jan;208(2): 224-32. doi: 10.1002/path.1903. PMID: 16362988.
9. **Peeling RW, Mabey D, Kamb ML, Chen XS, Radolf JD, Benzaken AS**. Syphilis. *Nat Rev Dis Primers*. 2017 Oct 12;3:17073. doi: 10.1038/nrdp.2017.73. PMID: 29022569; PMCID: PMC5809176.
10. **Harper KN, Ocampo PS, Steiner BM, George RW, Silverman MS, Bolotin S, Pillay A, Saunders NJ, Armelagos GJ**. On the origin of the treponematoses: a phylogenetic approach. *PLoS Negl Trop Dis*. 2008 Jan 15;2(1):e148. doi: 10.1371/journal.pntd.0000148. PMID: 18235852; PMCID: PMC2217670.
11. **Torrone EA, Miller WC**. Congenital and Heterosexual Syphilis: Still Part of the Problem. *Sex Transm Dis*. 2018 Sep;45(9S Suppl 1):S20-S22. doi: 10.1097/OLQ.0000000000000837. PMID: 29538279; PMCID: PMC6915834.
12. **Tudor ME, Al Aboud AM, Leslie SW, Gossman W**. Syphilis. 2023 May 30. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 30521201.
13. **Radolf JD, Deka RK, Anand A, Šmajs D, Norgard MV, Yang XF**. Treponema pallidum, the syphilis spirochete: making a living as a stealth pathogen. *Nat Rev Microbiol*. 2016 Dec;14(12):744-759. doi: 10.1038/nrmicro.2016.141. Epub 2016 Oct 10. PMID: 27721440; PMCID: PMC5106329.
14. **Walkty A, Shute L, Hamza S, Embil JM**. Condyloma lata. *IDCases*. 2021 Oct 27;26:e01321. doi: 10.1016/j.idcr.2021.e01321. PMID: 34820280; PMCID: PMC8599096.
15. **Liu XK, Li J**. Secondary syphilis-related oral mucous patches. *IDCases*. 2017 May 22;9:34-35. doi: 10.1016/j.idcr.2017.04.015. PMID: 28593145; PMCID: PMC5458642.
16. **Chiu HH, Wu CS**. Alopecia syphilitica. *Indian J Sex Transm Dis AIDS*. 2017 Jul-Dec;38(2):192-193. doi: 10.4103/ijstd.IJSTD_92_16. PMID: 30148279; PMCID: PMC6085945.
17. **Jordaan HF, Louw M**. The moth-eaten alopecia of secondary syphilis. A histopathological study of 12 patients. *Am J Dermatopathol*. 1995 Apr;17(2):158-62. doi: 10.1097/00000372-199504000-00008. PMID: 8600781.
18. **Tucker JD, Shah S, Jarell AD, Tsai KY, Zembowicz A, Kroshinsky D**. Lues maligna in early HIV infection case report and review of the literature. *Sex Transm Dis*. 2009 Aug;36(8):512-4. doi: 10.1097/OLQ.0b013e3181a2a946. PMID: 19455078.

19. **Wood VD, Rana S**. Congenital syphilis presenting as desquamative dermatitis. *J Fam Pract*. 1992 Sep;35(3): 327-9. PMID: 1387676.
20. **Whiting C, Schwartzman G, Khachemoune A**. Syphilis in Dermatology: Recognition and Management. *Am J Clin Dermatol*. 2023 Mar;24(2):287-297. doi: 10.1007/s40257-022-00755-3. Epub 2023 Jan 23. PMID: 36689103; PMCID: PMC9869822.
21. **Workowski KA, Bolan GA; Centers for Disease Control and Prevention**. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015 Jun 5;64(RR-03):1-137. Erratum in: *MMWR Recomm Rep*. 2015 Aug 28;64(33):924. PMID: 26042815; PMCID: PMC5885289.
22. **Tuddenham S, Hamill MM, Ghanem KG**. Diagnosis and Treatment of Sexually Transmitted Infections: A Review. *JAMA*. 2022 Jan 11;327(2):161-172. doi: 10.1001/jama.2021.23487. PMID: 35015033.
23. **Lukehart SA**. Syphilis. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. *Harrison's Principles of Internal Medicine, 20e*. McGraw-Hill Education; 2018. Accessed April 09, 2024. https://accessmedicine.mhmedical.com/content.aspx?bookid=2129&sectionid=192023811.
24. **Gayet-Ageron A, Lautenschlager S, Ninet B, Perneger TV, Combescure C**. Sensitivity, specificity and likelihood ratios of PCR in the diagnosis of syphilis: a systematic review and meta-analysis. *Sex Transm Infect*. 2013 May;89(3):251-6. doi: 10.1136/sextrans-2012-050622. Epub 2012 Sep 28. PMID: 23024223.
25. **Zarakolu P**. Sifilisin Laboratuvar Tanısında Güncel Gelişmeler [Recent Advances in Laboratory Diagnosis of Syphilis]. *Mikrobiyol Bul*. 2023 Jan;57(1):141-155. Turkish. doi: 10.5578/mb.20239912. PMID: 36636853.
26. **Peeling RW, Holmes KK, Mabey D, Ronald A**. Rapid tests for sexually transmitted infections (STIs): the way forward. *Sex Transm Infect*. 2006 Dec;82 Suppl 5(Suppl 5):v1-6. doi: 10.1136/sti.2006.024265. Epub 2006 Dec 6. PMID: 17151023; PMCID: PMC2563912.
27. **Xiong S, Liu Z, Zhang X, Huang S, Ding X, Zhou J, Yao J, Li W, Liu S, Zhao F**. Resurgence of syphilis: focusing on emerging clinical strategies and preclinical models. *J Transl Med*. 2023 Dec 18;21(1):917. doi: 10.1186/s12967-023-04685-4. PMID: 38105236; PMCID: PMC10726518.
28. **Orbe-Orihuela YC, Sánchez-Alemán MÁ, Hernández-Pliego A, Medina-García CV, Vergara-Ortega DN**. Syphilis as Re-Emerging Disease, Antibiotic Resistance, and Vulnerable Population: Global Systematic Review and Meta-Analysis. *Pathogens*. 2022 Dec 15;11(12):1546. doi: 10.3390/pathogens11121546. PMID: 36558880; PMCID: PMC9785152.
29. **Djokic V, Giacani L, Parveen N**. Analysis of host cell binding specificity mediated by the Tp0136 adhesin of the syphilis agent Treponema pallidum subsp. pallidum. *PLoS Negl Trop Dis*. 2019 May 9;13(5):e0007401. doi: 10.1371/journal.pntd.0007401. PMID: 31071095; PMCID: PMC6529012.
30. **Zetola NM, Klausner JD**. Syphilis and HIV infection: an update. *Clin Infect Dis*. 2007 May 1;44(9):1222-8. doi: 10.1086/513427. Epub 2007 Mar 14. PMID: 17407043.
31. **Tuddenham S, Ghanem KG**. Emerging trends and persistent challenges in the management of adult syphilis. *BMC Infect Dis*. 2015 Aug 19;15:351. doi: 10.1186/s12879-015-1028-3. PMID: 26286439; PMCID: PMC4545322.
32. **Janier M, Hegyi V, Dupin N, Unemo M, Tiplica GS, Potočnik M, French P, Patel R**. 2014 European guideline on the management of syphilis. *J Eur Acad Dermatol Venereol*. 2014 Dec;28(12):1581-93. doi: 10.1111/jdv.12734. Epub 2014 Oct 27. Erratum in: *J Eur Acad Dermatol Venereol*. 2015 Jun;29(6):1248. Erratum in: *J Eur Acad Dermatol Venereol*. 2015 Jun;29(6):1248. PMID: 25348878.
33. **Tong ML, Liu D, Liu LL, Lin LR, Zhang HL, Tian HM, Yang TC**. Identification of *Treponema pallidum*-specific protein biomarkers in syphilis patient serum using mass spectrometry. *Future Microbiol*. 2021 Sep;16:1041-1051. doi: 10.2217/fmb-2021-0172. Epub 2021 Sep 8. PMID: 34493087.