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Syphilis, the great mimicker: an inverted diagnostic pathway that still hits the mark

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Dear Editor,

Syphilis, the "great mimicker", remains a diagnostic challenge despite reliable serologic assays and updated management guidelines.[1] Its wide variety of clinical and dermatological manifestations often leads to misdiagnosis, especially when lesions are atypical.[2] We present a case in which secondary syphilis was diagnosed through an inverted pathway, with histopathology preceding clinical suspicion and serologic confirmation.

A 50-year-old heterosexual man presented with a two-month history of perianal lesions associated to burning sensation and unresponsive to topical antifungals and corticosteroids. His medical history was unremarkable, except for an unintended 3-kg weight loss in the previous three months. Clinical examination revealed multiple erythematous papules coalescing into plaques with superficial erosions and whitish patches confined to the perianal area (Figure 1a). No lymphadenopathy or other mucocutaneous lesions were observed.

Routine laboratory tests showed mild normocytic anaemia (Hgb 12.0 g/dL), elevated erythrocyte sedimentation rate (71 mm/hr), and hypergammaglobulinemia (3.48 g/dL). Lesional swabs for bacterial and fungal cultures and for HSV-1/2 were negative. Differential diagnoses included condyloma acuminata, extramammary Paget's disease, and squamous cell carcinoma. A skin biopsy was performed, and histopathologic examination showed epidermal acanthosis, focal parakeratosis, and a dense plasma cell-rich dermal infiltrate. Although nonspecific, these findings raised suspicion for treponemal infection. Immunohistochemical staining with anti-*Treponema pallidum* antibodies revealed abundant spirochetes in the epidermis and adnexal structures, confirming the diagnosis of syphilitic infection presenting clinically as condyloma lata (Figure 1b). Serologic testing for syphilis demonstrated a rapid plasma reagin (RPR) titer of 1:32, a *T. pallidum* hemagglutination assay (TPHA) titer of 1:80, anti-*T. pallidum* IgM 3.96, and anti-*T. pallidum* IgG 11.74. Serologies for HIV, hepatitis B, and C were also tested, but resulted in negative results. The patient reported unprotected extramarital intercourse and denied previous genital ulcers or body rashes. A treatment with intramuscular injection of benzathine penicillin G in a one-time dose of 2.4 million units was administered, resulting in complete resolution of symptoms within three weeks. At four-month follow-up, RPR titres showed a fourfold decline, confirming therapeutic success. Partner notification and testing were conducted according to the European guidelines.[3]

This case shows an atypical and isolated presentation of secondary syphilis manifesting solely as perianal condyloma lata. The diagnostic sequence was reversed compared with standard recommendations from

the last European guideline, which emphasizes the prescription of serological tests in case of clinical suspicion of syphilis, with histopathology examination reserved only for atypical presentation or when direct detection methods and serological tests are inconclusive.[3] However, in our case, histology and immunostaining provided the first clue, highlighting their diagnostic value when clinical indicators are subtle or absent or not sufficiently investigated. The presence of dense plasma cell infiltrate, endothelial swelling, and numerous spirochetes is a histopathologic hallmark that can orient the diagnosis.[4] Awareness of these features is crucial for dermatologists and pathologists, particularly when evaluating anogenital lesions refractory to empirical treatment. Condyloma lata, although a highly specific and characteristic manifestation of secondary syphilis, may resemble other anogenital lesions such as condyloma acuminata, familial benign chronic pemphigus (Hailey-Hailey disease), squamous cell carcinoma, or genital herpes, leading to inappropriate therapies or delayed diagnosis.[5,6] Secondary syphilis continues to surprise clinicians with its protean manifestations.[7] Recent reports have described granulomatous and localized variants, sometimes in immunocompetent heterosexuals, stressing the need for a high index of suspicion.[8] Even in the era of molecular and serologic diagnostics, clinicopathologic correlation must remain essential; histopathology should not replace serology but may precede it in ambiguous diagnostic scenarios.

Syphilis poses a significant global health challenge with social, economic, and public health implications.[9] Its incidence has increased steadily in Europe and Italy, not only among homosexual but also among heterosexual populations.[10] A delayed diagnosis and treatment of syphilis can result in serious complications and sequelae, and, from a public health perspective, allows the infection to continue spreading within the population, perpetuating the transmission chain.[9,10]

The interdisciplinary collaboration among dermatologists, infectious disease specialists, and pathologists is important to ensure prompt detection and early treatment of syphilis and to prevent complications.

In conclusion, this case demonstrates that histopathology can serve as a diagnostic sentinel tool in secondary syphilis, even when clinical suspicion is lacking. Integrating clinical, histologic, and serologic data remains essential for accurate diagnosis and effective control of this enduring and deceptive infection.

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Figure 1. Multiple erythematous papules coalescing into plaques with superficial erosions and whitish patches in the perianal area (**a**). Immunohistochemical staining revealed abundant spirochetes within the epidermis and adnexal structures (**b**).