Did syphilis truly strike the kidneys this time?

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The causative agents of sexually transmitted diseases are seldom involved in kidney disease. Only a handful of cases have been described of pyelonephritis or immune complex-mediated glomerulonephritis in patients with gonococcal infections [1,2]. The most important association is present in human immunodeficiency virus (HIV)-infected patients: HIV-associated nephropathy was diagnosed at autopsy in 12% of HIV-infected black people and in 1% of HIV-infected non-black people [3]. A clear relationship between hepatitis C virus infection and glomerulonephritis has been demonstrated. Cryoglobulinaemic membranoproliferative glomerulonephritis and membranous nephropathy occur in 2.6 and 1.8% of cases, respectively [4]. Hepatitis B virus infection is also associated with glomerulonephritis, but the prevalence is not known. However, it is estimated to be low because of the low endemicity in most Western countries.

Nephropathy associated with syphilis seems to have been more common in the past, presenting as nephrotic syndrome caused by immune complex-mediated membranous or mesangial glomerulonephritis. Nowadays, the possibility of renal involvement in syphilis is no longer even mentioned in textbooks of infectious diseases [5].

Interstitial syphilitic nephritis has been described in the literature only once, by Docolomansky et al., in the Slovakian language, without an abstract in Medline [6].

Clinical features

The manifestations of syphilis can be split up into three different stages. Primary syphilis is characterized by a painless, indurated, clear-based ulcer, accompanied by locoregional lymph node swelling. About 25% of cases progress to secondary syphilis, in several weeks to months, as a consequence of extensive dissemination of the spirochete [8]. The typical presentation of secondary syphilis is a symmetric papular rash on the entire trunk and extremities, including the palms and soles. The latter localization is highly suggestive of secondary syphilis. In moist areas, syphilitic papules can coalesce and lead to painless erosions, condylomata lata. Other possible symptoms of secondary syphilis are described in Table 1. Without treatment, 20–40% of patients will develop tertiary syphilis, independent of former manifestations of primary or secondary syphilis [8,9]. Tertiary syphilis is usually localised in the brain (meningovascular syphilis or parenchymatous syphilis), but the cardiovascular system can also be affected (cardiovascular syphilis). Gummata (late benign syphilis) are another manifestation of tertiary syphilis. These granulomatous-like lesions can most commonly be found in the skeletal system, skin and mucocutaneous tissues, but are not confined to these locations.

Diagnostic pitfalls and solutions

The patient in the presented case developed erosions in the genital region that were not specified further. These

<table>
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<th>Table 1. Symptoms of secondary syphilis [5,17]</th>
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<tr>
<td>Malaise</td>
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<tr>
<td>Weight loss</td>
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<td>Generalized lymphadenopathy</td>
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<tr>
<td>Hair loss ('moth-eaten alopecia')</td>
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<td>Condylomata lata</td>
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<td>CNS syphilis</td>
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<td>Meningitis</td>
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<td>Meningovascular syphilis</td>
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could have been condylomata lata, a manifestation of secondary syphilis. Dark-field microscopy can reveal spirochetes in scrapings of such lesions, which are loaded with spirochetes [10]. Unfortunately, this technique is not broadly used and *T. pallidum* cannot be cultivated in vitro. Therefore, the diagnosis is based mainly on serology, although polymerase chain reaction (PCR) is very promising when performed on swabs of ulcerative lesions [11]. A combination of treponema-specific (*T. pallidum* haemagglutination assay, TPHA) and non-specific tests (Venereal Disease Research Laboratory, VDRL or rapid-plasma-reagin) are necessary to reach the diagnosis. However, there remain many pitfalls. False-positive tests can be found in many patients, either because of cross-reactivity with other members of the family of Spirochaetaceae, because of situations that lead to mono- or polyclonal B-cell stimulation (e.g. multiple myeloma, Epstein–Barr virus or auto-immune disease), or because of other acute infections and immunizations (Table 2). Serological tests of the described patient were positive for both treponema-specific and non-specific tests, but with the lowest possible titre that can be classified positive for both VDRL and TPHA. In particular, during the secondary stage of syphilis, when dissemination occurs, VDRL titres are high, and almost always exceed 1:8. A VDRL titre below 1:8 in the presence of lesions suggestive of secondary syphilis for >1 month virtually excludes this diagnosis [12]. Very low titres, as were found in the patient under discussion, could fit serological testing that is performed too early in the course of the disease. Other possible explanations could be the presence of late latent syphilis or infection with cross-reacting antibodies [10]. For TPHA, a titre of 1:80 is the cut-off value, and any lower titre should be considered negative. Since hyponatraemia was present for at least 6 months, the low titres cannot be explained by short duration of illness, and should be interpreted cautiously. Based on the histopathological findings, mononuclear cell infiltration instead of the characteristic granulomatous reaction, renal gummata are also unlikely in this case. Causes of false-positive tests or (treated) syphilis in the past should be sought, knowing that serology (in particular treponema-specific tests) can remain positive for the rest of life. Altogether, the serological results do not unconditionally support the diagnosis of secondary syphilis.

Another diagnostic opportunity in this patient, besides serology, would have been to search for spirochetes in a swab taken from the genital erosions and in the renal biopsy specimen. In secondary syphilis, a high burden of spirochetes is present, whereas in tertiary syphilis it is mainly the immunological reaction that causes disease. Also, PCR could have been performed, and would have been interesting, in particular on the kidney tissue. PCR is not yet widely used in the clinical setting. However, when the test is applied to genital ulcers, both sensitivity and specificity exceed 95% [13].

**Alternative diagnoses**

A striking phenomenon remains the salt-losing response to treatment with penicillin. Despite the former remarks concerning the validity of the proposed diagnosis, this response supports an infectious disease as the underlying cause. What penicillin-reactive (four consecutive low doses of benzyl benzathine penicillin)
diseases can both cause the clinical manifestations that were described, and might provoke a serological cross-reaction? Leptospirosis can indeed cause interstitial nephritis and can be contracted in Taiwan [14], but is not known to present in a chronic fashion. Borrelia burgdorferi can induce interstitial nephritis in animals, but there is only one case report on this manifestation in humans [15]. No cases of nephritis have been described in relation to ‘Relapsing fever’ (Borrelia recurrentis), and ‘Ratbite fever’ (Spirillium minus). The characteristic clinical picture of these diseases, with recurrent periods of high fever (in combination with local skin lesions at the site of the bite in the latter disease), is also absent in the patient under discussion. Other treponema species, the non-venereal treponemata (Yaws, Pinta and Bejel), are not endemic in Taiwan, nor are they associated with renal disease [5].

Conclusion

One can doubt whether the diagnosis of interstitial nephritis caused by secondary syphilis is correct. On the other hand, after treatment with benzathine penicillin in a schedule that is used for late latent syphilis, complete resolution of hyponatraemia and salt losing occurred. Syphilis is called ‘the great imitator’ and keeps surprising us time after time. Because of the better treatment options for HIV, making this a chronic instead of fatal infection, safe sex is practised less. As a consequence, the incidence of syphilis is rising rapidly now [16]. Therefore, we can expect rare and unlikely manifestations of syphilis to occur more often in the near future.

Conflict of interest statement. None declared.

[See related Case Report by Chen et al., doi:10.1093/ndt/gfh778]

References


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