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Teaching Point
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Secondary syphilis after renal transplantation

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Introduction

Potent immunosuppressive agents make renal transplant recipients at increased risk of infections. Syphilis is a sexually transmitted disease caused by the bacterium *Treponema pallidum* with varied and often subtle clinical manifestations. If unrecognized, it can have devastating consequences [1]. The incidence of syphilis decreased significantly in the 1940s with the advent of penicillin, with later outbreaks being related to HIV infections, sexual practices and the use of drugs [2]. With the declining prevalence of syphilis, many physicians have become unfamiliar with its clinical presentation. We report a case of secondary syphilis in a renal transplant recipient who presented with systemic signs of illness and a mild hepatitis, in whom diagnosis was delayed until he developed a characteristic cutaneous rash.

Case

In June 2007, a 35-year-old man who had received a kidney transplant in 2001 because of end-stage renal disease secondary to anti-glomerular basement membrane (GBM) nephropathy was admitted to the hospital for assessment of a 2-day history of fever, muscle pain and headache. His treatment consisted of tacrolimus (2.5 mg b.i.d.), methylprednisolone (4 mg o.d.) and atorvastatine. On admission, clinical examination was normal, except for a temperature of 38.5°C. Laboratory measurements revealed an acute phase reaction (CRP: 59 mg/L) and abnormal liver tests [AST: 172 U/L (N: 6–33); ALT: 191 U/L (N: 14–63); GGT: 182 U/L (N: 7–50); ALP: 145 U/L (N: 28–94)]. LDH was elevated [350 U/L (N: 98–192)] and bilirubin (total and direct) was normal. Urine analysis was negative. Renal function was stable (Creatinine: 150.3 μmol/L). Serology showed an immune status for hepatitis B and a negative status for hepatitis C and HIV. Hepatitis E was not obtained. CMV antigenemia was negative as well as EBV IgM antibodies. Autoimmune serology including anti-GBM antibodies was negative. Chest X ray as well as hepatic and renal ultrasounds were normal. Within the next 24 h, spontaneous clinical improvement was noted and hepatic enzymes regressed to 2× upper limit of normal (ULN). He was discharged from hospital with a diagnosis of probable viral infection with mild hepatic perturbations.

Two months later, the patient was seen at the outpatient clinic. He complained of persistent low-grade fever (37.7°C), headaches and had recently developed a dry cough. Laboratory tests showed the persistence of elevated CRP (50 mg/L) as well as elevated liver tests 2× ULN. Mycoplasma pneumoniae IgM antibody was positive, and he was treated with moxifloxacine 400 mg/day for 3 weeks. Despite normalization of hepatic enzymes, he kept a mild acute phase response (CRP 30 mg/L) and low-grade temperature. Finally, he presented 3 weeks later with a non-pruritic papillomacular rash on the trunk, back, palms and soles (Figure 1). A clinical diagnosis of secondary syphilis was made.

Retrospective anamnesis revealed that he was homosexual and had developed, a few months earlier, a painless ulcer on the glans penis 3 weeks after having sex with another man. Laboratory tests showed syphilis VDRL (venereal disease research laboratory) positivity at 1/64 and TPHA (*Treponema pallidum* hemagglutination assay) positivity at 1/20 480 titres. HIV serology was controlled negative. Because of a remote notion of allergy to penicillin, he was treated with ceftriaxone 2 g IV/day for 15 days. A few hours after the first administration of the antibiotic, he experienced worsening of fever and rash, chills, malaise and headache. Neurological evaluation excluded neurosyphilis, and a Jarisch–Herxheimer reaction was diagnosed. Serologic control 3 weeks later showed a VDRL titre at 1/64 and a TPHA reactive at 1/40 960 dilution. HIV was again controlled negative. Nine months later, VDRL test was negative.

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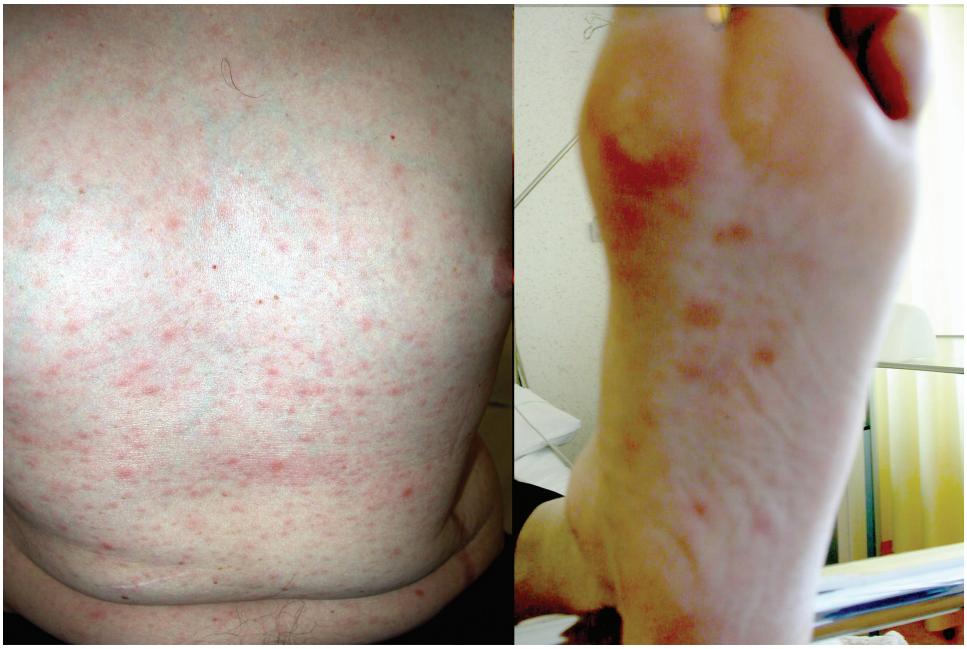

Fig. 1. A maculopapular rash on the abdomen and soles—characteristic of secondary syphilis.

Discussion

The clinical manifestations of syphilis are diverse, occurring in any one individual in different stages over time. The first manifestation of primary syphilis is the classic chancre, an often painless ulcerative lesion that appears at the site of inoculation after a median incubation period of 3 weeks following exposure to *T. pallidum*. Since ulcers are painless and heal spontaneously, many patients, as with ours, do not seek medical attention delaying diagnosis and enhancing the likelihood of transmission. If untreated, patients develop secondary syphilis within weeks to months, a systemic illness, with common features of fever, anorexia, headache, lymphadenopathy, malaise and myalgias. Rash is the most typical finding of secondary syphilis, with macular or papular eruption involving the entire trunk and extremities including the palms and soles [2]. The involvement of the palms and soles is characteristic of secondary syphilis and allows clinical diagnosis, as in our patient. Other manifestations include the so-called moth-eaten alopecia, hepatitis, gastrointestinal, musculoskeletal, renal, neurologic and ocular abnormalities. If untreated, patients can develop tertiary syphilis with late gummatous, cardiovascular and neurologic complications [2].

Syphilitic hepatitis is a rare but well-described syndrome, usually characterized by a mild increase in aminotransferases and a disproportionate elevation in alkaline phosphatase, with a normal or slightly elevated bilirubin level [3]. It usually occurs concomitant to the rash [4], but has also been reported to be the first manifestation of secondary syphilis [5]. Histological findings vary from mild portal inflammation to focal granulomatous hepatic inflammation. The majority of cases recover clinically and biologically with antibiotic therapy. Syphilitic hepatitis occurring after transplantation has been reported so far in two renal and three liver transplant recipients, who were treated efficiently with penicillin [6,7]. The optimal management of immunosuppressed patients is not well defined. A careful follow-up for at least 24 months is advised to ensure complete treatment effectiveness [6]. In our patient, the mild hepatitis first attributed to a viral infection, then to a mycoplasma pneumoniae infection, might have been related to secondary syphilis and should have prompted serologic screening as elevation of hepatic enzymes persisted along with the systemic symptoms 2 months after discharge from hospital.

The diagnosis of syphilis requires two types of serologic tests. Non-treponemal tests such as VDRL or RPR (rapid plasma reagin) are used for screening and monitoring the response to therapy. Treponemal tests such as TPHA and the fluorescent treponemal antibody absorption test (FTA-ABS) must be obtained for confirmation, since false positive non-treponemal tests may occur secondary to various medical conditions. A fourfold decline in titre of the non-treponemal antibody test is necessary to demonstrate an appropriate therapeutic response. Serologic testing for follow-up of primary and secondary syphilis should be obtained at 3, 6 and 12 months after treatment (and at 24 months for latent syphilis) [2].

A single dose of long-acting (benzathine) penicillin G (2.4 million units IM) is the standard therapy for primary, secondary or early latent syphilis. Late or latent syphilis of unknown duration require three doses of 2.4 million units IM at weekly intervals. During therapy for syphilis, patients may develop the Jarisch–Herxheimer reaction, which is an acute febrile reaction frequently accompanied by headache and myalgias within the first 24 h of treatment. Options for the treatment of early syphilis in penicillin allergic patients include ceftriaxone (1 g/day intramuscularly for 8–10 days) or doxycycline (100 mg orally 2×/day for 14 days) [8]. Macrolides can also be used but resistance has been reported [9], and their use in transplant patients may lead

to untoward interactions with calcineurin inhibitors [10]. When alternative agents to penicillin are used, close follow-up is essential to ensure an appropriate decline in titre.

In conclusion, this case illustrates the subtle manifestations of syphilis occurring in a renal transplant recipient, and reminds of the importance of early diagnosis and adequate management.

Teaching points

(1) Despite decreasing prevalence, syphilis should be evoked in immunocompromised patients, especially homosexuals, with systemic and non-specific signs of illness. Early diagnosis and adequate treatment are essential to prevent irreversible neurologic and cardiovascular damage.
(2) Rash involving the palms and soles is characteristic of secondary syphilis.
(3) Syphilis should be considered in the differential diagnosis of unexplained abnormal liver enzymes.
(4) Partners of infected patients should seek medical attention and treatment.

Conflict of interest statement. None declared.

References

1. Hook EW 3rd, Marra CM. Acquired syphilis in adults. *N Engl J Med* 1992; 326: 1060–1069
2. Singh AE, Romanowski B. Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. *Clin Microbiol Rev* 1999; 187–209
3. Young M. Syphilitic hepatitis. *J Clin Gastroenterol* 1992; 15: 174–176
4. Lo JO, Harrison RA, Hunter AJ. Syphilitic hepatitis resulting in fulminant hepatic failure requiring liver transplantation. *J Infect* 2007; 54: e115–e117
5. Ridruejo E, Mordoh A, Herrera F *et al*. Severe cholestatic hepatitis as the first symptom of secondary syphilis. *Dig Dis Sci* 2004; 9: 1401–1404
6. Wolf SC, Kempf VAJ, Tannapfel A *et al*. Secondary syphilis after liver transplantation: case report and review of the literature. *Clin Transplant* 2006; 20: 644–649
7. Camara B, Kamar N, Bonafe JL *et al*. Syphilis-related hepatitis in a liver transplant patient. *Exp Clin Transplant* 2007; 5: 524–526
8. Zetola NM, Engelman J, Jensen TP *et al*. Syphilis in the United States: an update for clinicians with an emphasis on HIV infection. *Mayo Clin Proc* 2007; 82: 1091–1102
9. Lukehart SA, Godornes C, Molini B *et al*. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *N Engl J Med* 2004; 351: 154–158
10. Ferrari SL, Goffin E, Mourad M *et al*. The interaction between clarithromycin and cyclosporine in kidney transplant recipients. *Transplantation* 1994; 58: 725–727

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