CASE REPORT

Nodular mucinosis misdiagnosed as non-responsive secondary syphilis

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SUMMARY

A previously healthy 24-year-old man presented with an erythematous, non-pruritic and painless papulonodular skin rash affecting the trunk, upper arms (excluding palms), neck, face, forehead and scalp. He had a penile ulcer for the past 2 weeks, almost healed at the time of observation. The patient tested positive for syphilis and HIV-1; he claimed being negative for HIV 6 months earlier. As the palms were not affected, we performed a skin biopsy for the differential diagnosis between secondary lues and acute HIV seroconversion reaction. Benzathine penicillin (2 400 000 units) was administered and antiretroviral therapy started. Although the skin biopsy was compatible with secondary syphilis, there was no change in the skin rash 3 weeks after the first penicillin administration. Another 2 doses of penicillin were given but 4 weeks later the rash persisted. A second biopsy revealed a mucinous skin infiltration, compatible with nodular mucinosis.

BACKGROUND

This was a case of syphilitic infection that, apparently, was irresponsive to the recommended treatment. Immunodeficiency caused by HIV infection can modify the known natural course of syphilis described before the HIV epidemic; this has raised the concern of possible treatment failure in these patients. In fact, some authors have reported poor luetic serological response (fourfold drop in RPR—rapid plasma reagin—titre) and a longer time to successful titre in the setting of immunosuppression. Some have raised concerns of clinical syphilis treatment failure, particularly in central nervous system disease, but this seems less consistent. These concerns and the persistent skin rash after penicillin injection led us to consider a possible syphilis treatment failure. The second biopsy excluded our assumption by revealing that the pathological findings of syphilis subsided, diagnosing another condition: nodular mucinosis. As far as we know, this is the first case report in the literature, of an association between healing secondary syphilis and this skin disorder.

CASE PRESENTATION

A previously healthy 24-year-old man with multiple sexual partners presented an erythematous, non-pruritic and painless papulonodular skin rash of 1-week duration (figures 1 and 2). The rash affected mainly the trunk, upper arms (excluding palms), abdomen, neck, face, forehead and scalp. He had a single, indurated, well-circumscribed painless ulcer for the past 2 weeks, almost healed at

the time of observation; he reported unprotected sexual intercourse around that time. He had no other symptoms or physical findings, namely fever or lymphadenopathies. The patient claimed to be negative for HIV in a blood test he did 6 months prior, but could not present those results to us.

INVESTIGATIONS

This skin rash and the painless, healing genital ulcer pointed to a lues diagnosis. HIV testing was also mandatory, given the patient's sexual habits and the hypothesis of this sexually transmitted disease. We performed the following complementary examinations: RPR—1/64 dilutions, TPHA (*Treponema pallidum* haemagglutination assay): positive; fourth generation ELISA test for HIV: positive; hepatitis C virus (HCV) and hepatitis B virus (HBV) serology: negative. Haemoglobin 14×10^9 g/L, leucocytes 5.70×10^9 /L (with normal distribution), platelets 67×10^9 /L, creatinine 0.86 mg/dL, alkaline phosphatase 115 U/L, alanine aminotransferase 19 U/L. HIV subpopulations, viral load and antiretroviral resistance tests were available only 1 week after initial tests: viral load 14 705 copies/mL (4.17 log), CD4 count 121 cells/ μ L with a T4/T8 ratio 0.2. No resistance to antiretroviral drugs was detected.

Usually, secondary luetic skin lesions extend to the palms, which was not the case in this patient. He claimed to be HIV negative in a recent test. Given these facts and the timeline uncertainty about the syphilitic infection duration, we thought the positive syphilis tests could be due to a primary syphilitic ulcer, and the skin rash could represent an acute retroviral syndrome, instead of luetic secondarisation. To clear these doubts, a skin biopsy

Figure 1 Papulonodular erythematous skin rash affecting the upper arms and back.

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Figure 2 Papulonodular erythematous skin rash affecting the trunk, upper arms and abdomen.

was performed, revealing perivascular and perianexial lymphoplasmocytic infiltrate in the dermis, and small epidermic adherent foci with basal hydropic degeneration and melanophages, compatible with secondary lues (figure 3). The absence of clinical response to syphilis treatment motivated a second biopsy 5 weeks later. This showed intense mucin deposition in the superficial dermis between the collagen fibres, compatible with nodular mucinosis (figures 4 and 5).

TREATMENT

The standard treatment for early syphilis, benzathine penicillin 2 400 000 units, was prescribed in the first consultation. Although the first biopsy results were consistent with secondary syphilis, 3 weeks later, the rash persisted. In Portugal, ambulatory benzathine penicillin stock is currently unavailable (we hope temporarily), and, as the prescribed vial was one of the last, it was our concern that the substance could have been

Figure 3 Biopsy 1: perivascular and perianexial lymphoplasmocytic infiltrate in the dermis, and small epidermic adherent foci with basal hydropic degeneration and melanophages, compatible with secondary lues.

Figure 4 Biopsy 2: dermis without infiltrate but with spacing of collagen fibres.

altered due to improper storage. Following this line of thought, we decided to administer two more penicillin injections, 1 week apart, at the hospital. Since the rash was still apparent (although morphologically different) 1 month after this treatment (figures 6 and 7), we opted for another skin biopsy; while waiting for the results and assuming treatment failure, we escalated to second-line syphilis treatment: doxycycline 100 mg two times a day. Simultaneously, highly antiretroviral therapy for HIV infection was started with Tenofovir-Emtricitabine-Efavirenz. With the pathological diagnosis of nodular mucinosis, doxycycline was suspended. The potential for spontaneous long-term regression renders treatment of nodular mucinosis difficult to assess.¹ Some advocate the benefit of topical treatment with tacrolimus, betamethasone or dimethylsulfoxide, or systemic oral aromatic retinoids, steroids or thalidomide.² As there is no preconised treatment for this disorder, we opted for expectant waiting and, 3 months later, with no directed therapy, the skin lesions were evanescent.

DISCUSSION

The patient presented a painless, non-pruritic skin rash of pink papulonodular indurated lesions, symmetrical in distribution, widespread in the trunk, neck, scalp, forehead and arms, but not in the palms and soles. A painless penile ulcer had been

Figure 5 Biopsy 2: immunohistochemistry colouring with Alcian Blue showing intense mucin deposition between the collagen fibres in the dermis.

Figure 6 Scalp and neck lesions 1 month after initial presentation and presumptive treatment for syphilis.

present during the past 2 weeks, and was almost healed at the time of presentation. The differential diagnosis of genital ulcers should include syphilis, chancroid, lymphogranuloma venereum,

Figure 7 Morphologically different skin lesions at the back 1 month after initial presentation and presumptive treatment for syphilis.

Granuloma inguinale and *herpes simplex*.³ A single, indurated, well-circumscribed painless lesion is more typical of syphilis,⁴ as was the case in our patient. Although the demonstration of *T. pallidum* is the definitive method of diagnosis, we considered dark-field microscopy would not give the diagnosis, as the genital ulcer was already at an advanced healing stage, and this test has limited sensitivity (failure to detect *T. pallidum* by this test does not rule out syphilis).⁵ The highly suggestive clinical presentation and the positive serology (Venereal Disease Research Laboratory, VDRL) to *T. pallidum* were in consonance with the diagnosis of secondary lues. Studies regarding the use of IgM anti-*T. pallidum* antibodies may help in the diagnosis of active syphilis, but reported data is conflicting.⁶

Fourth-generation serological tests for HIV were also positive, even though the patient claimed to be negative in a test performed 6 months before. Acute retroviral syndrome may clinically resemble secondary syphilis,⁷ and both diseases can be simultaneously transmitted by sexual intercourse. Moreover, the presence of a genital ulcer can facilitate the transmission of HIV.⁸

Viral load and subpopulation tests were only available several days later; therefore, a possible acute retroviral syndrome was considered, in an exclusively clinical base, in the differential diagnosis of this skin rash. Furthermore, the absence of palm and sole lesions led us to believe that the rash could simply be a manifestation of HIV seroconversion rather than secondary syphilis. Thrombocytopenia has been reported in association with early HIV infection, although its incidence increases with progressive immunosuppression. Although early HIV infection can result in low CD4 levels, markedly elevated HIV RNA levels (>100 000 copies/mL) are an ubiquitous finding,⁹ not present in our patient, in the analysis we received later. The pathological findings in the first skin biopsy confirming secondary lues, together with the aforementioned considerations, made us exclude acute HIV seroconversion reaction as responsible for the clinical picture. Given the unequivocal histological findings in the skin biopsy, the clinical discussion considering the relationship between the genital ulcer's aetiology and the skin rash became less relevant.

Standard first-line treatment for secondary syphilis was administered, but the rash did not subside in a few days as we had thought it would, and was still present after 3 weeks. The efficacy of penicillin for the treatment of all stages of syphilis has been established over approximately 50 years of clinical use;¹⁰ *T. pallidum* remains highly sensitive to this antibiotic, and no resistance has been reported to date.^{10 11} Unfortunately, in our country, benzathine penicillin is temporarily unavailable, which made us consider the first injection bought by the patient could have been from the last of the stock, and possibly ineffective. This fact made us administer two more penicillin injections at the hospital, 1 week apart. The skin rash persistence after these two injections made us perform a second skin biopsy and prescribe doxycycline¹² while awaiting the histological results.

Whether HIV status has an impact on treatment outcomes and serological responses was another concern. An HIV-infected patient with syphilis should be treated with the same regimen as that recommended for HIV seronegative patients.¹³ Serologically defined treatment failures may be more common among HIV-infected patients, but this seems to be the result of slower declines in non-treponemal serologies rather than a lack of clinical response and outcomes to treatment.¹⁴

The nodular mucinosis shown on the last biopsy cleared our doubts by contradicting the hypothesis of syphilis treatment failure.

Mucinoses are a group of disorders characterised by an abnormal amount of dermal mucin deposition. Mucin is an essential component of the dermal extracellular matrix produced by fibroblasts, with the appearance of a jelly-like amorphous material made of glycosaminoglycans (usually hyaluronic acid), capable of absorbing 1000 times their own weight in water.^{15 16} The mechanism responsible for mucin skin accumulation is thought to involve an imbalance between upregulated mucin production by immunoglobulins/cytokines, and a reduction in normal catabolic degradation.¹⁷

Classification of cutaneous mucinoses is rather complex and confusing, and is based on morphological and descriptive criteria, reflecting scarce pathophysiological knowledge. Two major groups of cutaneous mucinoses are accepted: primary mucin deposition is the major histological feature and results in clinically distinct lesions, and secondary mucin is a possible associated finding with other diseases—autoimmune, neoplastic, endocrine, toxic and infectious.

This case seems to fall into this last group of mucinoses secondary to an infectious disease, according to Rongioletti and Reborna's classification,¹⁶ as a papular nodular mucinosis. It has been described as being related to HIV¹⁸ and HCV^{19 20} infections.

We suggest our patient had a secondary papulonodular mucinosis in the evolution of healing disseminated cutaneous syphilis. As far as we know, there are no reports of an association between these two entities.

We wonder if the HIV itself or the immunosuppression had any role in the development of cutaneous mucinosis in this

patient, as there are reports in the literature of healing mucinosis after successful initiation of antiretroviral therapy.²¹

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Contributors CP was the physician who, from the beginning, regularly followed the patient, and was the major contributor to the article. SC revised the article, VS contributed to the dermatological diagnosis and AJ observed and described the skin biopsy.

Competing interests None declared.

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Learning points

- ▶ Medicine is not an exact science, the knowledge extent is overwhelming and biology can trick us. Clinicians must keep their minds open. In the absence of clinical response to preconised treatment, physicians must consider treatment failure and the accuracy of their original diagnosis.
- ▶ Although there is some concern about syphilis treatment failure in HIV/immunosuppressed patients, there is no evidence to support it, or at least clinical irresponsiveness.
- ▶ Cutaneous mucinoses are characterised by abnormal dermal mucin deposition, of which the pathophysiology is still unknown. It can be an isolated skin finding, or associated with various diseases, namely infectious: HIV and HCV.
- ▶ As far as we know, this is the first report in the literature of an association between papular nodular mucinosis and syphilis. Not being scientific evidence, isolated reported cases can be the first clue for further data collection and investigations.
- ▶ The contribution of HIV infection, immunosuppression and genetic factors for the development of this disorder is still an area requiring further investigation.

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