10. A single dose of benzathine

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A single dose of benzathine penicillin G as an effective treatment for malignant syphilis in an HIV-positive patient: a case report

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Abstract

Malignant syphilis (MS) is a rare, atypical manifestation of secondary syphilis. Ulcerative lesions should be suspected as MS when found with supporting microscopic morphology, a high syphilis serology titer test, a Jarisch–Herxheimer reaction (JHR), and rapid disease resolution. To date, there is no specific recommendation for treatment for MS. A 24-year-old HIV-positive MSM patient with a CD4 count of 470 cells/µl presented with a chief complaint of necrotic, ulcerative lesions and oyster shell–like surface plaques on his face, trunk, groin, and extremities. The patient also developed various typical presentations of secondary syphilis. Darkfield microscopy revealed spirochetes. Histopathological examination showed spongiotic dermatitis with many neutrophil cells in the dermis, together with endarteritis and fibrin micro-thrombus in the blood vessels. The patient had a high venereal disease research laboratory (VDRL) titer of 1:512. There was rapid disease resolution following a single injection of 2,400,000-unit benzathine penicillin G (BPG); together with anti-retroviral therapy, this was supportive treatment for MS. JHR was not observed in this study and many other reports. This case showed that ulcerative lesions with an oyster shell–like surface presenting in HIV-positive patients along with supporting microscopic morphology, high VDRL titer, and a dramatic improvement after antibiotic treatment is highly suggestive of MS. JHR may no longer be a characteristic of MS. A single dose of 2,400,000-unit BPG is sufficient for MS treatment.

Keywords: sexually transmitted diseases, syphilis, secondary syphilis, HIV, MSM

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Introduction

Malignant syphilis (MS) is a rare, atypical manifestation of secondary syphilis more commonly found in immunocompromised individuals (1). In 1989, Fishers et al. proposed that clinical findings of syphilis with ulcerative lesions and an oyster shell–like surface resembling skin malignancy are suggestive of MS when found together with supporting microscopic morphology, a high syphilis serology titer, a Jarisch–Herxheimer reaction (JHR), and rapid disease resolution (2). To date, there is no specific recommended treatment for MS (3). Although the most commonly used treatment regimen is three consecutive weekly intramuscular injections of 2,400,000-unit benzathine penicillin G (BPG), a single dose of BPG, which follows the recommendation of secondary syphilis treatment, may be adequate to treat MS (3, 4). JHR is a transient reaction following antibiotic treatment, which may result from a high serology titer in MS (3). We report a case of secondary syphilis in an HIV-positive MSM (men who have sex with men) patient that was eventually diagnosed as MS. The case showed rapid resolution following a single dose of BPG injection with no JHR.

Case report

A 24-year-old HIV-positive MSM patient presented with a chief complaint of generalized rash on his body for the previous 2 months that had not been itchy or painful. His primary concern was visible generalized lesions, which hindered his occupation as a salesperson and part-time model. The lesions were initially believed to be herpes zoster infection; however, no improvement was seen after oral acyclovir treatment. The initial hospital then tested the patient for HIV before referring him to our hospital. The patient had engaged in sexual behavior with no protection with the same male partner for the previous 2 years before breaking up 2 months before referral. The HIV status of the male partner was unknown. He denied having multiple partners.

Dermatological examination revealed multiple ulcerated lesions with an oyster shell–like surface on the patient's face, trunk, inguinal area, and upper extremities (Fig. 1a, 1b), erythematous macules and papules with a crown-like pattern on the frontalis region (corona veneris; Fig. 2a), multiple, well-demarcated, annular erythematous macules on the palms and soles (syphilitic roseola; Fig. 2b, 2d), painless penile and scrotal ulcers varying in size from 1 × 1 cm to 2 × 2 cm, with a depth of 0.2–0.5 cm, some of which had coalesced to form islands with a granulated base without pus (Fig. 2c), and multiple flat-topped lenticular papules measuring 0.8–1 cm in diameter surrounding his anus (condylomata lata; Fig. 2e) without lymph node enlargement.

We performed further analysis on the ulcerated lesions and anal papules and found flat spirochete bacteria that moved in a corkscrew pattern on darkfield microscopy. The skin biopsy and histopathological examination on the ulcerated lesions indicated spongiotic dermatitis with abundant neutrophils in the dermis, endarteritis, and fibrin micro-thrombus in the blood vessels (Fig. 1c, 1d). The anal papules showed characteristics of condylomata lata with acanthosis, spongiosis, rete ridge lengthening, no koilocytosis or papillomatosis, dilated capillary vessels in the dermis, and inflammatory cell infiltrates of neutrophils, eosinophils, and

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lymphocytes (Fig. 2f). Blood examination showed a Venereal Disease Research Laboratory (VDRL) titer of 1:512 with reactive *Treponema pallidum* hemagglutination assay (TPHA). The patient had positive HIV serology testing with a CD4 count of 470 cells/µl.

Based on these findings, the patient was diagnosed with malignant syphilis and HIV. He was treated with a single intramuscular injection of 2,400,000-unit BPG in addition to antiretroviral drugs consisting of efavirenz 600 mg, lamivudine 300 mg, and tenofovir 300 mg. One month after BPG treatment, a remarkable clearance with only residual hyperpigmented patches was observed. The serology test showed a dramatic decrease in VDRL titer to 1:32. We continued the observation for a month before referring the patient back to the initial hospital to continue his HIV medication. The patient was relieved of his primary concern but decided to continue the medication, especially to improve the hyperpigmentation of his skin.

Discussion

The clinical manifestations of secondary syphilis in HIV-positive populations may follow typical presentations such as syphilitic roseola, Biett's collarette, corona veneris, clavi syphilitici, moth-eaten alopecia, plantar lesions, and condylomata lata (5). However, atypical or a more severe form of syphilis may develop due to the decrease in CD4+ T-cell count and increased HIV viral load (3, 6). Although MS cases were more common in HIV-positive individuals, the CD4+ T-cell count was relatively high (200–499 cells/µl) (3). Immunocompetent individuals are also at risk of MS (7). These findings are in line with our case, in which MS was found in an HIV-positive individual with a CD4+ count of 470 cells/µl, supporting the possibility of a more virulent strain of *Treponema* as the etiology (3, 7).

The underlying pathogenesis of MS may differ from classic syphilis due to CD4 T-cell depletion, which leads to an exaggerated action of cytotoxic T cells and neutrophils (3, 8). The most common histopathological finding of MS is lymphohistiocytic infiltrate rich in plasma cells in the dermis (3). Other findings may include endothelial cell swelling, proliferation, necrosis, and lumen occlusion by thrombus in blood vessels (8).

Treatment of syphilis with HIV coinfection follows that of non-HIV patients (9). The Centers for Disease Control and Prevention recommends that HIV-coinfected secondary syphilis be treated with a single-dose of intramuscular 2,400,000-unit BPG injection (5). However, a survey indicated that physicians in the United States and Europe opted for a more intensive regimen of antibiotics for HIV co-infected individuals. Major concerns lie in the difference in clinical features in HIV, impaired host immunity, a higher rate of asymptomatic neurological involvement, and slower serological response (4). There was no notable serological difference in treatment of single-dose versus three-dose BPG in HIV co-infected individuals, suggesting that the international recommendation of a single dose of BPG is sufficient in acute infection

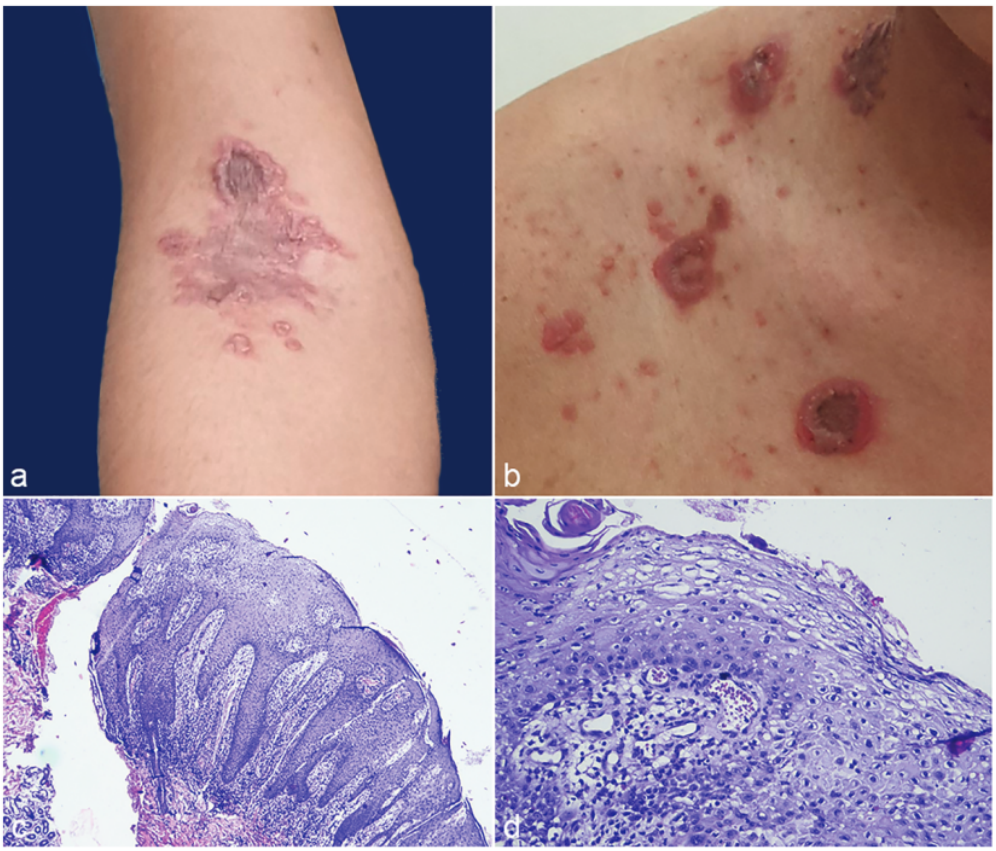

Figure 1 | Multiple erythematous to copper-colored annular maculopapular lesions, some with a necrotic, ulcerative center and an oyster shell–like surface on the (a) arm and (b) trunk. Histopathological examination of the lesions on the arm are shown at (c) 40× and (d) 100×.

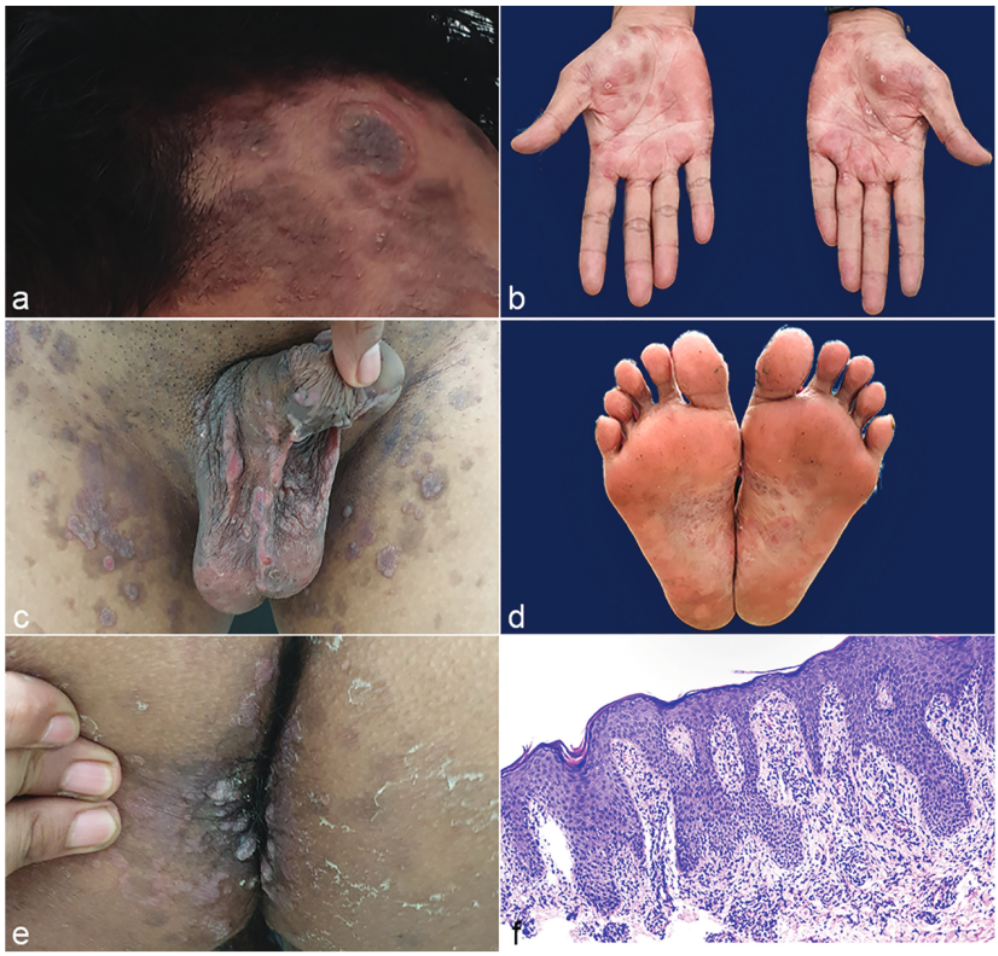

Figure 2 | Lesions of primary and secondary syphilis, showing (a) corona veneris, (b, d) syphilitic roseola, (c) penile and scrotal ulcers, and (e) condylomata lata, as well as (f) histopathological examination of the condylomata lata.

(10). Out of 28 reported MS cases that were treated with BPG in 2014–2018, 71.4% received three doses of BPG whereas only 28.6% had a single dose of BPG. Nevertheless, all cases displayed clinical improvement, regardless of the dose (3). A remarkable clinical improvement with a dramatic decrease in VDRL titer after a single dose of BPG treatment, as in this case, supports the notion that MS can be treated with the same dose as typical secondary syphilis without the need for additional doses.

JHR is a transient immunologic phenomenon hypothesized to result from cytokine release following death of *T. pallidum* microorganisms (5). Clinical manifestations of JHR include high fever accompanied by headache, chills, myalgia, and rigors within 24 hours after initiating therapy (5, 9). Although the high serologic titer found in MS is suggestive of abundant bacteria, the death of which may elicit the JHR formation, a more recent finding has suggested that JHR only occurred in 20% of MS cases (3). The reaction was also not observed in our case.

Rapid disease resolution can be observed in MS patients, in contrast to the slower rate of serologic decline that is more common in syphilis with HIV coinfection (3, 9). Clinical improvement of MS can be observed in as soon as 2 days to 3 months following antibiotic treatment (3). In our case, we observed rapid clinical resolution that completely resolved 4 weeks after treatment.

Conclusions

MS should be suspected in HIV patients presenting with ulcerative lesions with an oyster shell–like surface. A greater action of cytotoxic T cells and neutrophils on the skin with MS may explain the histopathological findings of neutrophil infiltrate in the dermis and lumen occlusion by thrombus in blood vessels found in our case. A single dose of BPG intramuscular injection is a sufficient MS treatment in immunocompromised individuals. High VDRL with dramatic improvement following antibiotic treatment could be observed in this case. JHR may no longer be characteristic of MS, as supported by other studies.

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