Unusual cutaneous features of syphilis in patients positive for human immunodeficiency virus

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Summary
Dermatologists commonly find it difficult to diagnose syphilis, because of its protean clinical features. In cases of co-infection with human immunodeficiency virus (HIV) syphilis may present particularly unusual clinical features, further confounding the diagnosis. We report two cases of syphilis/HIV co-infection in Japanese patients showing uncommon skin features that made the diagnosis of syphilis difficult. These cases underline the need for dermatologists to be more aware of atypical cutaneous features of syphilis in patients positive for HIV.

The diagnosis of syphilis can be challenging because of its diverse clinical and histopathological presentations. Syphilis in patients positive for human immunodeficiency virus (HIV) may present even greater diagnostic problems because it tends to be more aggressive and have atypical clinical features. We report two cases of syphilis presenting uncommon cutaneous features that made the diagnosis of syphilis difficult.

Report
Patient 1 was a 30-year-old Japanese man with a 6-month history outbreak of pigmented eruptions on his legs. Prurigo was the diagnosis of a local dermatologist, who prescribed a topical steroid ointment, but the eruptions did not resolve. Headache and slight fever continued for another 2 weeks, and after which the patient suddenly lost consciousness at his workplace. He was admitted to the neurology ward of Sapporo City General Hospital with multiple brain infarctions. He was referred to the dermatology department for evaluation of pigmented papules and plaques on the legs. Physical examination revealed a mixture of copper-red hyperkeratotic papules, irregularly shaped nodules and plaques up to 30 mm in diameter (Fig. 1a,b). Some of the papules were surrounded by smaller satellite papules. The differential diagnosis included lichenoid eruptions, bromoderma and prurigo. Histopathological examination of the papules in the plaques on the legs showed hyperkeratosis with irregular elongation of rete ridges and dense infiltration by lymphocytes and plasma cells in the superficial and deep dermis (Fig. 1c,d). The titre of the baseline rapid plasma regain (RPR) test was 1:256 and that of the Treponema pallidum haemagglutination assay (TPHA) was 1:327680. The patient tested positive for HIV-1 and had a CD4+ lymphocyte count of 0.22 × 10⁹/L (normal range 0.5–1.5 × 10⁹/L). Examination of the cerebrospinal fluid by lumbar puncture revealed reaction to a treponemal test for syphilis (fluorescent treponemal antibody absorbed; FTA-Abs), raised white blood cell (WBC) count (0.68 × 10⁹/L; normal range 0–0.01 × 10⁹/L) and total protein (135 g/L; 15–40), and decreased glucose (38 mg/dL; 50–75), suggesting syphilitic meningitis. Magnetic resonance imaging of the brain showed multiple cerebral infarctions, which were attributed to meningovascular neurosyphilis. The patient was treated with benzylpenicillin potassium (24 MU daily, given intravenously, daily for 16 days). The skin lesion disappeared after 3 weeks, leaving pigmentation. The headache from the syphilitic meningitis and the abnormal findings of the cerebrospinal fluid also improved after penicillin treatment; however, hemiplegia and
higher brain dysfunction due to multiple cerebral infarctions remained.

Patient 2 was a 37-year-old homosexual Japanese man who presented with a 2-week history of generalized, ulcerated nodules on the face, arms and back. Three months previously, he had visited a local dermatologist, presenting with a temporary maculopapular rash over his whole body. He was diagnosed at that time as having ‘viral exanthema’, which disappeared in 2 weeks. On his presentation to us, a physical examination revealed generalized, ulcerated nodules ranging from 20 to 70 mm in diameter, which were surrounded by erythema (Fig. 2a,b). Scaly, red plaques were also found on the trunk (Fig. 2c). The body temperature was 37.5 °C. The patient had malaise, but no other systemic symptoms. The differential diagnosis included ecthyma, lymphoma and secondary syphilis. Histological examination of a specimen taken from the edge of an ulcer on the arm showed dense dermal and subcutaneous infiltration of lymphocytes and plasma cells (Fig. 2d). Immunohistochemistry revealed thread-like organisms staining positively with antibodies against *T. pallidum* in the dermis. The RPR test gave a false-negative result due to the prozone phenomenon; re-examination with diluted serum resulted in a positive titre (1 : 64). The baseline TPHA titre was 1 : 20480. The patient was positive for HIV-1 with a CD4+ lymphocyte count of 196 cells/mm³. He was treated with benzylpenicillin benzathine (400 kU orally, four times daily for

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**Figure 1** Patient 1. (a) A mixture of copper-red hyperkeratotic papules, nodules and plaques on the legs; (b) papules of various sizes grouped together on the leg (corymbose syphilitic eruption); (c) hyperkeratosis and dense cell infiltration in the upper dermis; (d) dense infiltration of lymphocytes intermingled with plasma cells in the dermis. Haematoxylin and eosin; original magnification (c) × 25; (d) × 250.
8 weeks). Jarisch–Hexheimer reaction, a temporary reaction to penicillin treatment that includes fever, chills, headache, and exacerbation of skin lesions, developed. The skin lesions disappeared in 1 month; the ulcerated lesions healed with depressed scars.

The incidence of syphilis fell in the early 1980s after the outbreak of HIV in Western Europe and the USA, but syphilis rates in those countries have been on the rise since the late 1990s. The more recent outbreaks have been characterized by high rates of HIV co-infection. Most patients with syphilis/HIV co-infection present with the typical cutaneous features of syphilis, but some reports suggest that HIV may alter the clinical presentations of syphilis and accelerate the disease progression. Patients with HIV are at increased risk for malignant syphilis, which is characterized by ulcerating, pustular or rupioid cutaneous lesions. A multicentre retrospective study showed malignant syphilis to be 60 times more common in patients with HIV than in historical syphilis series studied before the advent of HIV. Moreover, multiple primary syphilitic lesions are found in up to 25% of patients with HIV. An atypical rash may result in misdiagnosis as other infection or as malignancy. There are anecdotal case reports of syphilis resembling leprosy, eczema and mycosis fungoides in patients with HIV.

Patient 1 had unusual papular eruptions that were difficult to diagnose without serological tests. Papules of various sizes grouped together on the legs may be consistent with rare corymbose syphilitic eruptions. The word ‘corymbose’ means ‘flower cluster’, which the eruptions resemble, and corymbose syphilitic eruptions occur late in the secondary stage of syphilis, usually 6–8 months after infection. Patient 2 showed rare features of nodulo-ulcerative lesions, for which the differential diagnosis includes ecthyma and lymphoma. The patient was diagnosed with malignant syphilis according to Fisher’s criteria.

Increased prevalence and early presentation of neurosyphilis have been found in patients infected...
with HIV. Meningovascular syphilis as seen in patient 1 is an early feature of neurosyphilis; it is caused by arteritis of varying severity, which results in thrombotic infarction. The peak occurrence is 4–7 years after primary syphilis infection, but it can occur as early as 2 years after the primary infection in patients with HIV co-infection.

Owing to the diverse clinical presentations, serological evaluation of syphilis is essential. However, it should be noted that serological tests for syphilis may show false negatives due to the prozone phenomenon, particularly in patients with HIV, as was seen in patient 2. This phenomenon occurs when there are very high titres of antibodies that interfere with the assay system. The antibodies are detected only after serum dilution. False negative results in treponemal and nontreponemal tests also occur in patients with HIV because of the altered immunological response.

These two cases highlight the difficulty of diagnosing syphilis in patients with HIV, owing to the unusual and diverse clinical features. Dermatologists must be more aware of the atypical cutaneous features of syphilis in such patients.

References
