Malignant Syphilis with Ocular Involvement and Organism-Depleted Lesions

M. Pleimes,1 W. Hartschuh,1 H. Kutzner,2 A. H. Enk,1 and M. Hartmann1

1Department of Dermatology, University of Heidelberg, Heidelberg, and 2Dermatopathology Laboratory, Friedrichshafen, Germany

Diagnosis and treatment of syphilis are challenging because of the condition’s diverse clinical symptoms, histopathological variance, and the lack of definite tests for treatment follow-up. We report a case of secondary pustular-ulcerative malignant syphilis with ocular involvement in a human immunodeficiency virus–infected patient. It was striking to find that ulcerative lesions can be highly organism depleted.

Case report. A 45-year-old, HIV-infected man who has sex with men presented with progressive skin eruptions of the right side of his face, scalp, and arm. Symptoms were first noticed 3 months before presentation and were followed 2 weeks later by eye involvement, with a progressive scleral nodule and red eye. The patient reported experiencing malaise and arthralgias of varying intensity of the feet, wrists, elbows, and knees. At the time of symptom onset, the patient was receiving treatment for HIV infection that included emtricitabine, tenofovir disoproxil fumarate, and ritonavir-boosted atazanavir. His HIV load was less than the lower level of detection, and he had a stable immune status (CD4 T cell count, 465 cells/μL). The patient had a history of secondary syphilis infection, which was diagnosed 2 years earlier on the basis of a rash and a positive serologic test result (Venereal Disease Research Laboratory [VDRL] test titer, 1:128; fluorescent treponemal antibody titer, 1:1280). At that time, the patient received treatment with 3 consecutive weekly intramuscular injections of benzathine penicillin (2.4 million IU). Follow-up serologic tests performed 10 months later revealed an 8-fold reduction in the VDRL titer (1:16) and a fluorescent treponemal antibody titer of 1:10. The patient’s condition remained stable up to the last follow-up serologic test 5 months before the onset of the aforementioned symptoms.

Because of the pustular character of the lesions, prior to the patient’s presentation at our clinic, the patient received ciprofloxacin for suspected impetigo, brivudine for herpes zoster, topical ciclopirox for possible tinea, and topical nadifloxacin. Because no therapeutic response occurred, a skin biopsy specimen was obtained. The histopathologic diagnosis suggested an infectious pathogenesis. Because additional diagnostic tests for spirochetes, Bartonella species, mycobacteria, and fungal species yielded negative results, no specific treatment was initiated. When he experienced progressive skin involvement and ocular changes, the patient was referred to our clinic for further evaluation.

Physical examination findings were notable for large, confluent papules and pustules and plaques on the right temple, nose, scalp, and left arm. Many lesions demonstrated central, crusted ulcerations (figure 1A, 1B, and 1D). The patient’s oral and genital mucosa, palms, and soles were free of lesions.

Ocular examination revealed conjunctival vascular infections with subconjunctival hemorrhage, keratitis, and a scleral nodule of the left eye (figure 1C). Moderate lymphadenopathy was present. Findings of additional examination were unremarkable.

Laboratory diagnostic evaluation was notable for an elevated C-reactive protein level (30.2 mg/L; normal level, <5 mg/L), a 3-fold elevated γ-glutamyl transpeptidase level (171 U/L; normal level, <60 U/L), and an elevated alkaline phosphatase level (155 U/L; normal range, 40–130 U/L). Serologic tests revealed a VDRL titer of 1:512, a positive fluorescent treponemal antibody titer test result, and Treponema Pallidium Particle Agglutination Assay (TPPA) titer of 1:2,621,440. Neither additional serologic tests for other infectious causes nor mycobacterial and fungal stainings and cultures of native skin samples revealed any hints of other infectious agents.

Histologic examination of a newly obtained skin biopsy specimen demonstrated a deep, confluent, nodular cellular infiltrate with lymphocytes, histiocytes, and an abundance of plasma cells. There was notable vacuolization of the basal layer with necrotic keratinocytes, lymphocytes, and plasma cells (figure 2D). The presence of treponemes, however, could be demonstrated by neither immunohistochemical staining nor DNA PCR (followed by PCR-ELISA).

Because of the rapid increase in the VDRL titer and the elevated TPPA titers in this patient, who had stable immunological status (and a history of sexual contacts during the prior...
6 months with different men who have sex with men who had a higher risk of carrying or transmitting syphilis), we diagnosed syphilis reinfection. Secondary syphilis infection plus systemic symptoms, arthralgias, elevated liver enzyme levels, and pustular-ulcerative lesions was classified as malignant syphilis.

The patient received 3 consecutive weekly intramuscular injections of benzathine penicillin (2.4 million IU). The patient also received a 50-mg dose of prednisolone concurrently with the first dose of benzathine penicillin, to prevent a Herxheimer reaction. While receiving therapy, the skin and eye conditions rapidly resolved (figure 2). A VDRL test performed 3 months after completion of therapy revealed a 4-fold reduction of the titer (1:128), indicating a sufficient treatment outcome. The γ-glutamyl transpeptidase, alkaline phosphatase, and C-reactive protein levels returned to normal.

**Discussion.** The clinical manifestations of secondary syphilis vary greatly. Eruptions are often generalized, but localized lesions can occur. In HIV-infected patients, the course of syphilis can be atypical. Primary chancres often stay unrecognized because of their asymptomatic character and frequently hidden (anal, rectal, or enoral) location. Progression from stage to stage can be more rapid, leading to earlier symptoms of secondary or even tertiary syphilis [1]. Secondary syphilis can be classified on the basis of lesions as macular, papular, follicular, papulo-
shown in different experiments to have no impact on the only antibiotics given were quinolones, which have been patient had received should have affected these results, because secondary syphilitic lesions [12]. None of the therapies that the organism-depleted lesions, and Fischer et al. [10] could not find spirochetes at all in patients with malignant syphilis.

It is still unclear why malignant syphilis is more prevalent among HIV-infected patients, because individuals with very low CD4 counts and patients with good immunologic reconstitution are both affected. Malignant syphilis also occurs in HIV-uninfected individuals. Both cellular-mediated immunity and humoral immunity seem to be involved in the pathogenesis of malignant syphilis, and a functional defect (rather than a quantitative one) may be responsible [11].

It has to be recognized that lesions due to malignant syphilis can be highly organism depleted, and treponemes cannot be detected in all secondary syphilitic lesions. Diagnosis, therefore, has to rely on a combination of clinical symptoms, serologic data, histologic data, and the findings of molecular and immunohistologic evaluations. HIV coinfection adds more diversity to the clinical pathology, and syphilis continues to be a diagnostic challenge in HIV-infected patients. Because of the resurgence of syphilis in recent years, it is important to recognize that uncommon lesions that one suspects to have been caused by infectious agents could be syphilitic, and early diagnosis (by serum testing) should be sought.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

References