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CASE REPORT

Varicella Infection in a Pediatric AIDS Patient Presenting as Umbilicated Papules

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SUMMARY **An 8-year-old girl with acquired immunodeficiency syndrome presented with fever and alteration of consciousness. She had a history of persistent cryptococcal meningitis. She developed multiple discrete umbilicated papules that resembled cutaneous cryptococcosis on the second day of admission. Skin biopsy revealed an ulcer with a wedge-shaped necrosis of the dermis. The edge of the ulcer showed intracellular edema, margination of nucleoplasm and multinucleated cells, consistent with herpes infection. The diagnosis of varicella-zoster virus infection was confirmed by the identification of herpesvirus DNA from the lesion and differentiation from other herpesviruses by restriction fragment length polymorphism (RFLP) method. Intravenous acyclovir was given at a dose of 500 mg/m^2, three times daily for 14 days which resulted in resolution of the skin lesions within 2 weeks.**

Varicella (chickenpox) is caused by the varicella-zoster virus (VZV). It occurs most often in children younger than 10 years of age. In normal children, its systemic symptoms are usually mild; serious complications are extremely rare. Immunocompromised patients, with either primary or recurrent (zoster) infection, are at increased risk of severe disease.[1,2] In human immunodeficiency virus infection, during profound immunosuppression, the primary infection with varicella-zoster virus may manifest as an atypical form. We report varicella in a girl, with acquired immunodeficiency syndrome, presenting as umbilicated papules. Only 4 cases of varicella-zoster virus infection presenting as umbilicated papules have been reported.[3,4] The diagnosis of varicella-zoster virus infection was confirmed by detection of herpesvirus DNA from the lesion and differentiation from other herpesviruses by restriction fragment length polymorphism (RFLP) method.[5,6]

CASE REPORT

An 8-year-old girl had vertical transmission of HIV infection. She received d4T and ddI for 2 years, but had to discontinue the medication 4 months prior to admission due to severe bone marrow suppression, confirmed by bone marrow aspiration. Three months before this admission, she was admitted to the hospital due to cryptococcal meningitis, and was treated with intravenous amphotericin B for 78 days, which resulted in some clinical improvement. However, she still had persistent cryptococcal antigen in her cerebrospinal fluid. During

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that admission, she developed generalized vitiligo and had partial spontaneous re-pigmentation without treatment. She was discharged from hospital with oral fluconazole 200 mg once a day.

One week after her discharge, she developed high fever and alteration of consciousness. Two days later, she developed multiple discrete umbilicated papules, which began on her face then extended to her trunk and extremities in the same day (Fig. 1). She also had oral thrush, but there was no other mucosal lesion. She had no history of previous varicella infection. Results of laboratory investigations were: hematocrit 27%, white blood cell count 890 cells/mm^3, platelet count 84,000 cells/mm^3, CD4+ cell count (2 months before admission) 15 cells/mm^3 (4%). Liver function tests revealed total bilirubin 6.3 mg/dl, direct bilirubin 5.25 mg/dl, alkaline phosphatase 304 U/l, aspatate aminotransferase 49 U/l, alanine aminotransferase 10 U/l, albumin 2.2 mg/dl and globulin 4.3 mg/dl. Her skin biopsy revealed an ulcer with a wedge-shaped necrosis of the dermis. The edge of the ulcer showed intracellular edema, margination of nucleoplasm and multinucleated cells (Fig. 2), consistent with herpes infection. Direct immunofluorescent stain for herpes simplex virus antigen and culture for herpes simplex virus from papule were negative. Polymerase chain reaction tests for herpes simplex virus from serum and cerebrospinal fluid were negative.

Human herpesvirus was detected and typed from skin scraping by using consensus primer PCR.[5] The details of the extraction and amplification steps have been reported.[6] Amplified DNA product (234 bp) was visualized under UV light with electrophoresis on a 2% agarose gel stained with ethidium bromide (Fig. 3). Herpesviral DNA PCR product was subjected to human herpesvirus typing by RFLP, using endonucleases *Hinf* I and *Alu* I. After digestion and electrophoresis, polymorphisms yielded a characteristic fragment pattern of varicella-zoster virus (Fig. 4).

The patient was given intravenous acyclovir 500 mg/m^2, three times daily for 14 days. There were no new lesions after 48 hours and most of the existing lesions crusted within 1 week of the onset

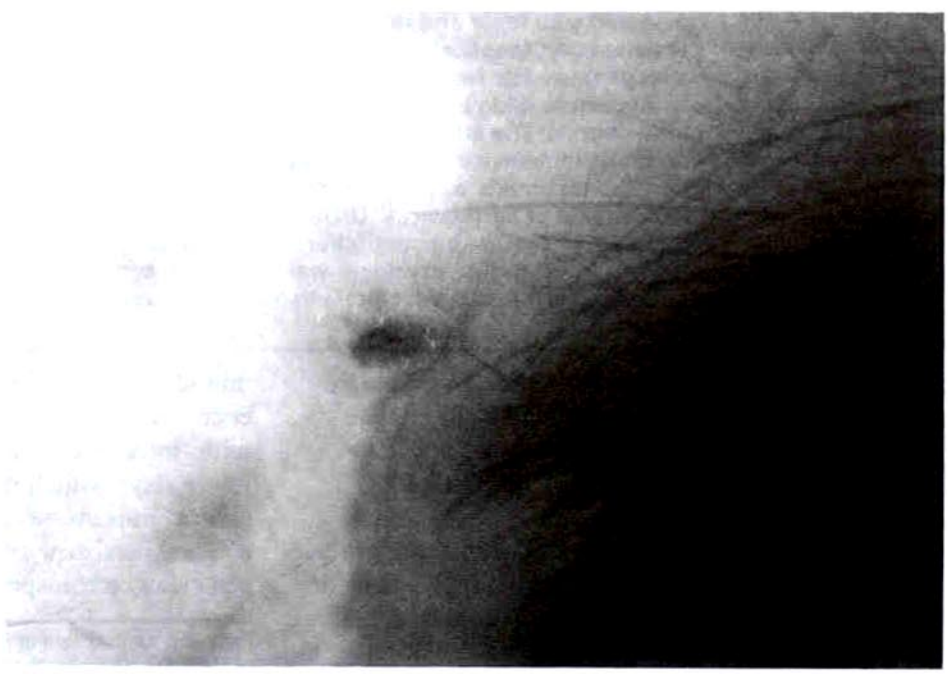

Fig. 1 Umbilicated papules on the patch of vitiligo at the patient's neck.

Fig. 4 Restriction Fragment Length Polymorphisms of human herpersvirus digested with endonuclease *Hinf* I (left panel) and *Alu* I (right panel). M: 100 bp marker, U1-3: undigested PCR products (HSV1, HSV2 and varicella zoster virus, respectively) and C1-3: digested polymorphism products (HSV1, HSV2 and Varicella Zoster virus, respectively).

have defects in cellular immunity are more likely to develop disseminated chickenpox and zoster than those who have B-cell abnormalities.[7] Primary varicella-zoster virus infection in HIV infected patients are often severe with a high frequency of systemic dissemination.[1,7] The incidence of varicella infection in HIV varies from 0.8-3.5%.[3,8] In general, these patients present with typical features of varicella such as a rapid progression from erythematous macules to papules, vesicles, pustules and crusts. Typically, they show superficial and thin-walled vesicles, which look like drops of water lying on top of rather than in the skin. There are a few reports of atypical forms of varicella, which presented as a small number of disseminated cutaneous pox-like lesions;[3,4] few lesions, little vesiculation and central necrosis;[9] disseminated pinpoint-sized papules,[10] and central evolution toward necrosis and ulceration.[11] Usually, the diagnosis of varicella is based on clinical features, laboratory confirmation of diagnosis is not necessary for most cases of varicella. Routine blood tests are neither helpful nor needed for the diagnosis. Asymptomatic elevations in serum level of alanine aminotranferase (ALT) and aspatate aminotransterase (AST) occur in the majority of children and adults with uncomplicated varicella.[12]

Presentation of varicella as umbilicated papules is very rare. To our knowledge, there were only 4 adult cases of varicella presenting as umbilicated papules.[3,4] The differential diagnosis of the skin lesions include cutaneous cryptococcosis, histoplasmosis, molluscum contagiosum and penicilliosis. The presence of multinucleated giant cells and epithelial cells containing acidophilic intranuclear inclusion bodies observed in skin biopsy distinguishes the cutaneous lesions produced by varicella-zoster virus from all other eruptions such as cutaneous cryptococcosis or papillomavirus infection, but are unable to distinguish between HSV and VZV. In cutaneous cryptococcosis, classical infiltrates have been described as consisting of two histopathologic patterns: granulomatous, with sheets of histiocytes phagocytizing abundant budding yeast forms surrounded by clear halos and gelatinous, in which the fungi appear floating free in pools of mucins.[13] For human papillomavirus infection, the histologic features of verruca vulgaris are acanthosis, papillomatosis, and hyperkeratosis. The rete ridges are elongated and, at the periphery of the verruca, are often bent inward so that they appear to point radially toward the center.[13] We confirmed the diagnosis by positive polymerase chain reaction and showed polymorphism for varicella-zoster virus from skin lesions.

Varicella-zoster virus can be recovered from vesicular fluid for a few days after the onset of the

rash, but viral culture results are variable. The reported sensitivity ranges from 26-64% in VZV infection.[3] Accurate interpretation of Tzanck smear depends on experience.[14] It is positive in 75% of VZV cases.[15] Detection of varicella-zoster virus antigens in skin scrapings by fluorescence microscopy is more rapid and more sensitive than culture technique.[7] Detection of varicella-zoster virus DNA from clinical specimen such as vesicle fluid, cells scraped or swabbed from skin lesions, crusts, respiratory secretions, cerebrospinal fluid or tissue by polymerase chain reaction are more sensitive and more specific for the diagnosis[16] and enable differentiation of wild-type strains from vaccine strains.[7] A rapid method for detection and typing of human herpesvirus is to combine a consensus primer PCR with RFLP method, which amplifies a region of herpesvirus DNA-directed DNA polymerase and which uses degenerate primers in a nested format.[5,6] This method is useful in typing herpesvirus infection and clinically complicated vesiculobullous disease, especially in immunocompromised hosts.

Controlled trials[17,18] demonstrate that acyclovir shortens virus shedding and new lesion formation and speeds lesion healing in both healthy and immunocompromised patients with varicella. In immunocompromised children, intravenous acyclovir is the most conservative choice. Famciclovir and valacyclovir have been licensed for the treatment of varicella-zoster virus in adults.[19,20] There is still no pediatric formulation and insufficient data exist about the use or dose recommendation of these two drugs in children. Infections caused by acyclovir-resistant varicella-zoster virus strains should be treated with parenteral foscarnet therapy.[20]

Varicella infection in immunocompromised children may manifest as atypical lesions. The clinical signs and symptoms are difficult and delay diagnosis and treatment. The complications are severe and may be fatal. The varicella vaccine is safe and effective in preventing primary infection. The vaccine can be used in asymptomatic HIV infection (class N1). The varicella vaccine is recommended in patients with CD4+ T-lymphocyte percentages of 25% or greater and mildly symptomatic disease (class A1).[20] Highly active antiretroviral therapy (HAART) allows patients infected with human immunodeficiency virus to live productive and relatively disease-free lives for long periods, but our patient could not afford the cost of HAART therapy.

The varicella-zoster virus is a highly contagious virus that needs isolation and requires high doses of antiviral therapy. Patients with acquired immunodeficiency virus infection may present with atypical forms of varicella as umbilicated papules. These eruptions must be differentiated from other skin infections and require proper antiviral therapy.

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