Clinical Case Report

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Hydroa vacciniforme-like cutaneous T-cell lymphoma in a child

A case report

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Abstract

Rationale: Hydroa vacciniforme (HV)-like T-cell lymphoma is a rare malignancy in childhood associated with Epstein-Barr virus infection.

Patient concerns: A 6-year old girl presented with complaint of 3-year history of recurrent skin lesions, 3 months of fever accompanied by cough for 8 days.

Diagnoses: Skin biopsy revealed a HV-like lymphoma presentation and positive signals of EBER were detected by in situ hybridization. TCR-γ gene monoclonal rearrangement was present. A HV-like cutaneous T-cell lymphoma was diagnosed.

Interventions: The girl was treated with cyclosporine and CHOP.

Outcomes: The girl's condition had been stable for 6 months.

Lessons: Our case highlights the necessity for taking the HV-like lymphoma as a differential diagnosis especially when a patient manifests as recurrent skin lesions accompanied by systemic involvement.

Abbreviations: CAEBV = chronic active EBV infection, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone, CT = computerized tomography, EBER = EBV-encoded RNA, EBV = Epstein-Barr virus, HSCT = hematopoietic stem cell transplantation, HV = Hydroa vacciniforme, TIA = T-cell intracytoplasmic antigen.

Keywords: Epstein-Barr virus, hydroa vacciniforme-like T-cell lymphoma, skin

1. Introduction

Hydroa vacciniforme (HV)-like lymphoma is one of the 2 uncommon T-cell lymphoproliferative disorders associated with Epstein-Barr virus (EBV) in children recognized by the 2008 WHO classification.[1] The disease is reported to more frequently affect Asians and Latin Americans.[2–5] Often refractory to chemotherapy, the outcome of this disease is usually poor. We report a child with a long history of skin lesions and indolent clinical course who had been treated mistakenly as skin infections and allergy leading to delay in diagnosis.

2. Case report

A 6-year-old girl presented to our pediatric department with a 3-year history of recurrent skin lesions, 3 months of fever accompanied by cough for 8 days. Three years ago the girl developed skin lesions involving her scalp, trunk, both lower limbs, and especially her face without obvious causes. The skin lesions showed a slowly progressive relapsing course, changing from papules, vesicles, necrosis, and finally healing with atrophic scars. She had no sensitivity to sun-exposure or mosquito bites. The girl received multiple antibiotics and different kinds of antihistamine drugs in local hospitals but the lesions waxed and waned. 3 months ago she developed intermittent fever (38–39 °C). Eight days ago the patient caught a cold presenting with non-productive cough and persistent fever (38–40.5 °C). She was brought to a local hospital and was found to have hepatosplenomegaly and anemia, and then she was referred to our hospital for further investigation.

Upon admission her temperature was 38 °C. Facial swelling was present. The skin lesions were polymorphic presenting with papules, vesicles, bullae, necrosis, and atrophic scars, which involved her face, scalp, abdominal wall, and both lower limbs (Fig. 1). The liver and spleen were palpable 6 and 4 cm, respectively below the costal margin. Lymphadenopathy was absent. The concentration of hemoglobin was 84 g/L. C reactive protein was 62 mg/L (normal <8 mg/L). Blood biochemical analysis was unremarkable except increased lactate dehydrogenase level (538 U/L). The blood culture, autoimmune antibody tests, and the bone marrow aspiration examination were negative. Serologic assays of EBV-VCA IgG and EBV- NA IgG

Editor: N/A.

JL and YZ are co-first authors and they contributed equally to this work.

This work was partially supported by grant 2015SZ0152 from the Science & Technology department of Sichuan Province and National Natural Science Foundation (no. 81200461) of China.

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:15(e0319)

Received: 13 December 2017 / Received in final form: 10 March 2018 / Accepted: 12 March 2018

http://dx.doi.org/10.1097/MD.0000000000010319

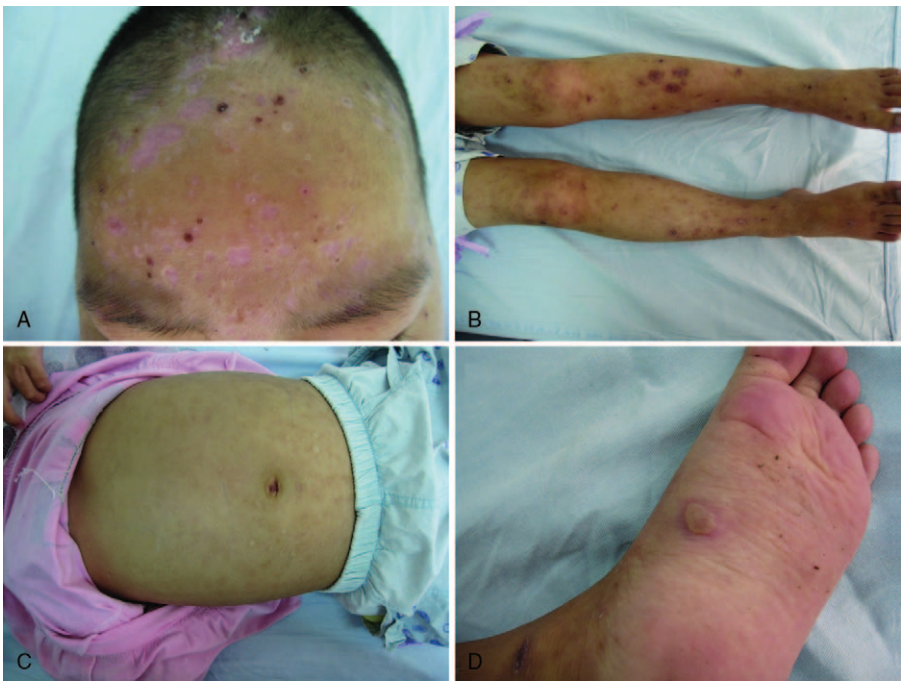

Figure 1. Clinical features. A, Discrete papules, necrosis, crusts, and atrophic scars on the patient's forehead and scalp. B, Small vesicles, red papules, and atrophic scars on both lower limbs. C, A few atrophic scars are present on the trunk. D, A new bulla surrounding with erythema observed on the left sole of foot.

were positive in the absence of EBV IgM, EBV-VCA IgM, and EBV-EA IgM. The amount of EBV DNA in peripheral blood was increased to 7.4×10^7 IU/mL. Chest computerized tomography (CT) was normal, whereas abdominal CT revealed hepatosplenomegaly and a few enlarged lymph nodes around mesentery. Vancomycin and loratadine were given to the patient for 14 days, her cough abated but the fever and rash had no improvement. Meanwhile a skin biopsy was performed. Histopathologic findings revealed epidermal blister formation, dense lymphoid cell infiltration throughout the dermis and surrounding perivascular area, focal necrosis, and presence of lymphocyte with atypia. Immunohistochemically, the infiltrate was composed of lymphocytic cells expressing CD3ε, CD4, TIA-1, but not CD3, CD8, CD20, CD79a, CD30, CD56, and GrB (Fig. 2). Approximately, 50% cells expressed Ki-67. Positive signals of EBV-encoded RNA (EBER) were detected in skin biopsy specimens by in situ hybridization. TCR-γ gene monoclonal rearrangement was present. These findings were consistent with the diagnosis of HV-like primary cutaneous T-cell lymphoma. The girl was first treated with cyclosporine A (5 mg/kg·d) for 4 weeks without response. Then she started chemotherapy with cyclophosphamide (800 mg/m^2), doxorubicin (20 mg/m^2), vincristine (1.5 mg/m^2), prednisone (60 mg/m^2) (CHOP). After 6 cycles of CHOP her fever disappeared and no new skin lesions occurred. The patient's conditions had been stable for 6 months since the initiation of chemotherapy but she was lost to follow-up later. Medical history and reports in this study had been approved by the patient's parents.

3. Discussion

HV-like lymphoma has some common features including facial edema, recurrent papulovesicles that generally proceed to necrosis and vacciniforme scars, before progression to systemic involvement such as intermittent fever, hepatosplenomegaly, and lymphadenopathy.[2,3] Unlike true HV the skin lesions are not induced and/or exacerbated by sun exposure and are present in both sun-exposed and non-exposed areas. In histopathology, there are atypical lymphoid infiltrate in the dermis and subcutaneous tissue, with angiocentric and angioinvasive features. HV-like lymphoma shows a divergent immunophenotype, exhibiting either a T-cell phenotype with expression of CD4, CD8, or an NK-cell marker CD56.[2–6] Another characteristic of HV-like lymphoma is presence of EBER positive cells. In our case based on the long history of recurrent skin lesions, systemic presentations including fever, hepatosplenomegaly and anemia, and skin biopsy investigations indicating the monoclonal expansion of T-cells and detection of EBER the diagnosis of HV-like cutaneous T-cell lymphoma was confirmed.

HV-like lymphoma is thought to be a proliferation of clonal T cells or less frequently NK cells related to EBV infection.[1,3,4,7] It has been reported that a higher frequency of EBER-positive cells is associated with a higher proliferation index, a denser lymphocytic infiltrate with greater cytological atypia and epidermal necrosis.[2] In this case EBER-positive lymphoid cells are present in the skin lesions indicating EBV infection. The serological analysis of EBV-related antibodies and elevated DNA amounts are consistent with chronic active EBV infection (CAEBV). In CAEBV, it was reported a dominant NK-cell clone is usually found in the blood,[8] but in our case a CD4-positive T-cell clone was detected, which was in accordance with Wu's results.[6] The pathogenesis of HV-like lymphoma is not well defined, combination of genetic and environmental factors is implicated in the mechanism.[2] Defects of genes which are essential for regulating lymphocyte activation and proliferation might influence the function of virus-specific or nonspecific lymphocytes and allow expansion of EBV-infected T cells or NK cells.[2] Moreover, the distribution of EBV subtypes with higher tumorigenic potential or lesser immunogenic, mutated EBV-related antigen expression such as LMP-1 may contribute to the prevalence of EBV lymphoma.[9]

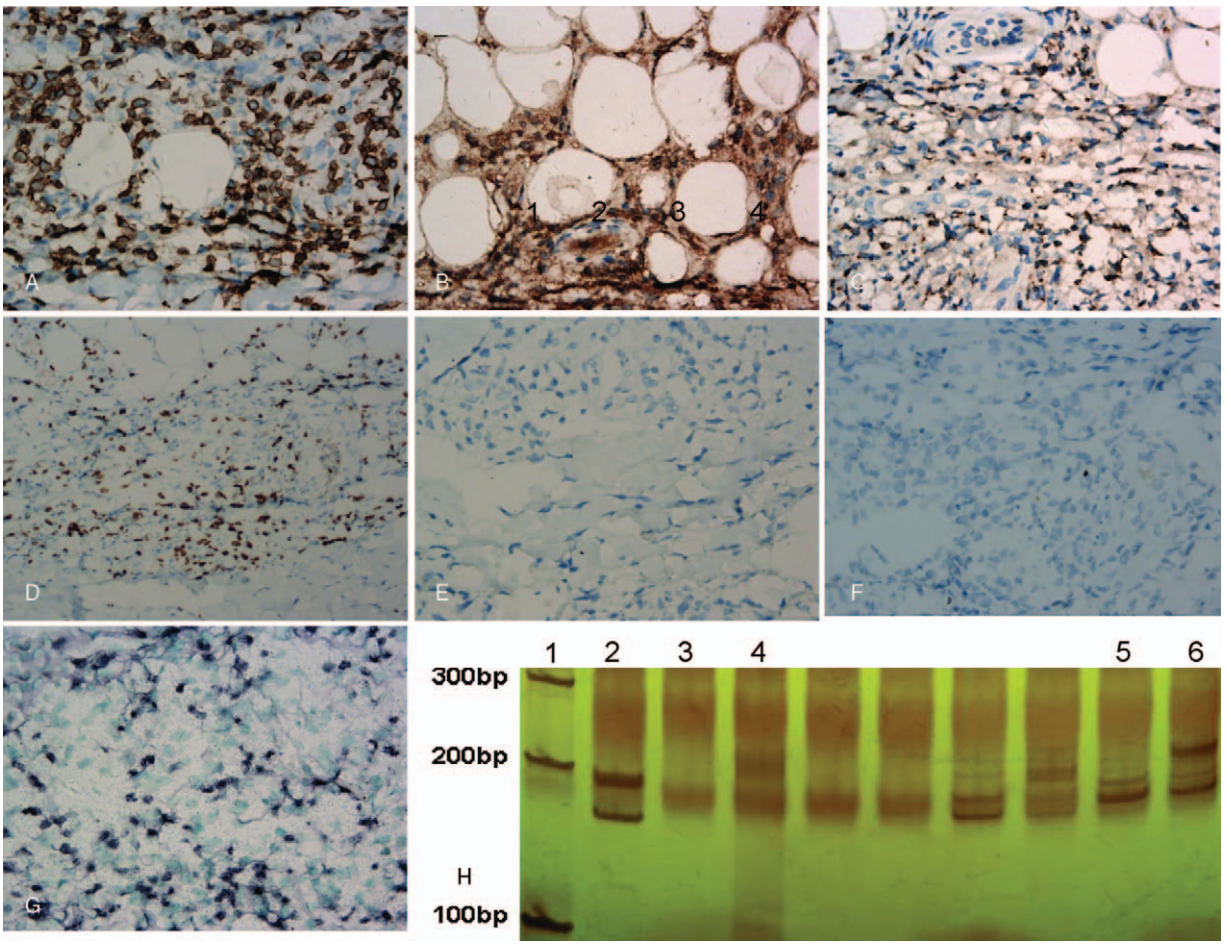

Figure 2. Skin biopsy results. A, CD3ε+ lymphoid cells (×400). B, CD4+ cells (×400). C, TIA-1+ cells (×400). D, Ki-67+ cells (×200). E, CD20- cells (×400). F, CD56- cells (×400). G, Detection of Epstein-Bar virus-encoded RNA-positive lymphoid cells by in situ hybridization (×400). H, Detection of TCR-γ gene rearrangement by PCR amplification and 10% polyacrylamide gel electrophoresis. Lane 1: molecular weight marker. Lane 2: positive control. Lane 3: blank. Lane 4: negative control. Lane 5: skin biopsy specimen. Lane 6: heteroduplex analysis of the same skin biopsy specimen.

HV-like T-cell lymphoma has a variable prognosis because it has an indolent clinical course.[1] The factors associated with poor prognosis include extracutaneous involvement, expression of CD56, and EBV association.[5,10] The most important factor predicting poor outcomes is extracutaneous involvement at presentation, those with skin-only lesions showed better outcomes.[5] Moreover, high expression of Ki67 was reported to be associated with a more aggressive clinical outcome.[2] Although HVLL is characterized by a monoclonal proliferation of T cells or NK cells, the best approach for treatment remains uncertain.[7] Chemotherapy and/or radiotherapy have been used in some reports with variable benefits. Park et al[5] reported two cases receiving CHOP regimen gained much longer survival for 5 and 11 years, respectively, but the patients were both adults without systemic involvement. In a report from Peru, 12 patients received different chemotherapy regimens including CHOP with further adjuvant radiotherapy in 4 cases, only 4 patients remained alive, 10 patients died after a mean follow-up of 11.6 months after initial diagnosis because of either concurrent infections, disease progression or both.[2] In contrast, immunomodulating therapies such as interferon-α, prednisolone, cyclosporine A, and thalidomide have been shown to result in improvement of symptoms,[3,11,12] Xu et al[3] reported a series of 7 Chinese children with HVLL, 4 cases had their skin lesions improved after interferon-α treatment. In the report by Beltrán et al,[11] 2 out of 4 patients had clinical response to thalidomide, which is a drug with immunomodulatory and antiangiogenic properties. Similar results were reported by Kimura et al,[12] where patients who received prednisolone and cyclosporine A had temporary remission of symptoms. Nevertheless, allogeneic hematopoietic stem cell transplantation (HSCT) may be the only curative therapy for this disease, it was reported a child achieved long-term remission through HSCT followed by donor-derived EBV-specific cytotoxic T-lymphocyte immunotherapy.[13] However, a conservative approach was recommended as first-line therapy in HVLL patients to avoid unnecessarily aggressive treatment, because chemotherapy did not induce sustained remission and patients receiving chemotherapy had been reported to have a worse prognosis and short survival.[7,11] In this report the patient presented with recurrent progressive skin lesions and systemic symptoms including fever, anemia, and hepatosplenomegaly that did not respond to cyclosporine A and other conservative treatment, so chemotherapy was started with CHOP, her conditions got improved temporarily but long-term outcome still remained to be seen.

Differential diagnosis should include other inflammatory, autoimmune, and neoplastic conditions such as chronic active infections, lupus erythematosus, and other hematological malignancies. Clinical features including age, presentations , and evidence of CAEBV infection are helpful in the diagnosis of

HV-like lymphoma. Skin biopsy is essential to make a final diagnosis.

In summary, this is a rare case of HV-like cutaneous T-cell lymphoma with long and indolent clinical course. Our case highlights the necessity for taking the HV-like lymphoma as differential diagnosis, especially when a patient presents with recurrent skin lesions accompanied by systemic involvement.

Author contributions

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