Erythema Nodosum Associated with Active Cytomegalovirus Infection

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Erythema nodosum is associated with a wide variety of diseases, and searching for the underlying etiology is important for management of the disease. Most adults have already been infected by cytomegalovirus (CMV), often subclinically and asymptomatically. Immunocompetent individuals very rarely present with cutaneous manifestations of CMV infection. We report a rare case of erythema nodosum associated with active CMV infection. A 40-year-old female presented with several tender nodules over the extensor surface of bilateral lower legs. A few days later, the patient also presented with the symptoms of fever and sore throat. Virological survey revealed anti-CMV antibodies IgM and IgG were both positive. Two weeks of therapy with oral ganciclovir successfully relieved the symptoms of fever and painful sensation of the nodules of the legs. (Dermatol Sinica 22 : 129-133, 2004)

Key words: Erythema nodosum, Cytomegalovirus

INTRODUCTION

Erythema nodosum is a cutaneous reaction consisting of inflammatory, tender nodular lesions located mainly on the extensor surface of the lower extremities. It has been described in association with a number of infectious and noninfectious diseases. Searching for the underlying disease is important for management of erythema nodosum. Although a variety of cutaneous manifesta-
tions have been reported with cytomegalovirus (CMV) infection, the association with erythema nodosum and active CMV infection was rarely reported. Thus we report an immunocompetent female patient with erythema nodosum as the cutaneous manifestation of active CMV infection.

CASE REPORT

A 40-year-old female presented with several painful skin lesions over the lower legs for 10 days. Besides, extracutaneous symptoms including fever and sore throat were also developed for 3 days. Dermatologic examination showed several tender, erythematous subcutaneous nodules over the extensor surface of bilateral lower legs. Other physical examination did not reveal any abnormal findings such as hepatomegaly or lymphadenopathy except for the mild injected throat. The patient denied any systemic disease and did not have any travel history or drug history in the recent one year.

Skin biopsy was taken from one of the nodules on the right shin (Fig. 1). Pathologic examination revealed edema of the septa and massive extravasation of erythrocytes, but destruction of the vessel walls was limited. The inflammatory infiltrate was in the septa with extension into the periphery of the fat lobules. The inflammatory cells were composed of lymphocytes, histiocytes and a few neutrophils (Fig. 2). The results of direct immunofluorescence examination of the same skin biopsy specimen, including fluorescence-labeled anti-human IgG, IgA, IgM, complement and fibrinogen, were negative.

Laboratory data showed WBC 5380/mm³ (segmental cells: 47%, lymphocytes: 45%, monocytes: 6%, and eosinophils: 2%), hemoglobin 13.7 g/dl, and platelet 241000/mm³. Other abnormal data included CRP 3.18 mg/dl (<0.3), ESR 65 mm/hr (1-20), ALT 140 IU/L (3-37), and AST 96 IU/L (13-38). Anti-EBVCA (Epstein-Barr viral capsid antigen) antibody IgG was positive, but IgA and IgM were negative. Anti-CMV antibodies IgM and IgG were both positive. The IgG titer was 102X (<15X). Blood PCR (polymerase chain reaction) for CMV DNA was positive. The results of urine and throat viral cultures proved CMV infection. Other tests including anti-HIV (human immunodeficiency virus) antibody, anti-HAV (hepatitis A virus) IgM, anti-HCV (hepatitis C virus) IgG, HbsAg (hepatitis B virus surface antigen), anti-HSV (herpes simplex virus) IgM, anti-mycoplasma antibody, anti-chlamydia IgM, antistreptolysin O titer, tuberculin skin test, blood cryptococcus neoformans antigen test, C3, C4, and immunoglobulin quantitation of IgG, IgA and IgM were either negative or within normal limits.

Urine routine examination and chest x-ray did not reveal any abnormal findings. Bacterial cultures and fungal cultures from the blood were negative. Bacterial cultures from the throat were negative. In situ CMV DNA hybridization and PCR for CMV DNA of the same skin biopsy specimen failed to identify the possible CMV direct skin tissue invasion.

Our diagnosis was erythema nodosum associated with active CMV infection. Two weeks of therapy with oral ganciclovir successfully relieved the symptoms of fever and painful sensation of the nodules of the legs. Six months later, anti-CMV antibody IgM became negative, but IgG was still positive. The IgG titer was 24X (<15X). Recurrence of the skin lesions was not observed within the six months.
DISCUSSION

It is well known that most adults have already been infected by cytomegalovirus (CMV), often subclinically and asymptptomatically. When symptoms do appear they resemble infectious mononucleosis, but lymphadenopathy and splenomegaly are not so striking. After primary CMV infection, the virus persists in a lifelong latent stage with the potential for reactivation. Cutaneous manifestations of CMV infection, which are rare and nonspecific, have been reported mostly in patients with AIDS, malignant neoplasms, burns and immunosuppression after organ transplantation.\(^2,3\)

Immunocompetent individuals very rarely present with cutaneous manifestations of CMV infection. Urticaria and morbilliform eruptions are reported most frequently in healthy patients who have CMV infection associated with recent ampicillin treatment.\(^2,4\) Rubella-like or morbilliform eruptions have been recently reported in 9 non-immunosuppressed patients with active CMV infection without atypical lymphocytosis. Oral administration of antibiotics was only given to 3 of the patients in the initial phase of the fever and skin eruption.\(^5\) Erythema multiforme, vasculitis, sclerodema, Gianotti-Crosti syndrome, and papular purpuric gloves and socks syndrome were another cutaneous manifestations associated with CMV infection in non-immunosuppressed adults or in childhood.\(^6\) There has been only one report regarding erythema nodosum associated with CMV mononucleosis in an adult.\(^7\)

The presence of IgM antibody or a fourfold rise in IgG antibody titers in the sera of acutely ill patient compared with convalescent sera indicates active CMV infection.\(^2\) CMV reactivation in immunocompetent seropositive individuals may occur frequently and increase with age.\(^1\) Although our case did not have the evidence of atypical lymphocytosis, the presence of IgM antibody or a fourfold rise in IgG antibody titers indicates active CMV infection.

Erythema nodosum is the most frequent clinico-pathological variant of the panniculitis. The disorder is a cutaneous reaction consisting of inflammatory, tender, nodular lesions, usually located on the anterior aspects of the lower extremities.

Erythema nodosum may be associated with a wide variety of diseases and searching for the underlying etiology is important for management of the disease. The etiologies associated with erythema nodosum include infections, drugs, malignant diseases, and a wide group of miscellaneous conditions. However, the cause is unknown in 35%-60% of patients among dif-

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Fig. 2
(A) This field revealed edema of the septa and massive extravasation of erythrocytes. The inflammatory infiltrate was in the septa with extension into the periphery of the fat lobules. (H & E, x 40)
(B) The inflammatory cells were composed of lymphocytes, histiocytes and a few neutrophils. (H & E, x 200)
ferent studies.13-15

Initial approach should include a complete clinical history such as previous diseases, medications, foreign travel, pets and hobbies, as well as familial illness. The relationship between a previous episode of upper respiratory infection by group A beta-hemolytic streptococcus and erythema nodosum is well known, especially in children and young adults. The anti-streptolysin O titers, throat cultures or streptococcal antigen skin tests may help in the diagnosis. A chest x-ray should be performed in all patients to exclude sarcoidosis, tuberculosis, and fungal infections of the lungs.16 In our case, virological survey helped us to make the final diagnosis.

Erythema nodosum is considered to be an immunologic reaction to a wide variety of etiologies.17,18 Erythema nodosum probably results from the formation of immune complexes and their deposition in and around venules of the connective tissue septa of the subcutaneous fat.19 Circulating immune complexes and complement activation have been recorded in patients with erythema nodosum.20 However, other authors failed to demonstrate circulating immune complexes in patients with erythema nodosum, and delayed hypersensitivity reaction may also play an important role in the pathogenesis of the disorder.21 Because the results of direct immunofluorescence examination in our case were negative, and circulating C3, C4, IgG, IgA and IgM were within normal limits, these findings did not support the formation of immune complexes. Thus we suggested that delayed hypersensitivity reaction might be the possible mechanism of erythema nodosum in our case.

Although most cases of erythema nodosum are self-limited and regress spontaneously in 3-6 weeks, searching for underlying disorders help us to learn more about the possible etiologies and pathogenesis of the disease.

REFERENCES