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Systemic lupus erythematosus secondary to infection with Epstein-Barr virus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic, systemic, idiopathic and autoimmune disease. Infection with the Epstein-Barr virus (EBV) is a risk factor associated with the development of SLE. Almost all pediatric patients with SLE have serological evidence of EBV infection. Patients with SLE have increased EBV viral load in serum and saliva. These patients have 15-30 times the amount of viral DNA in peripheral blood. In this case the association between SLE and EBV infection is shown as well as the possibility of viral involvement as a trigger for the development of an aggressive form of LES.

RESUMEN

El lupus eritematoso sistémico (LES) es una enfermedad crónica, sistémica, idiopática y autoinmune. La infección con el virus Epstein-Barr (VEB) es un factor de riesgo asociado al desarrollo de LES. Casi todos los pacientes pediátricos con LES presentan evidencia serológica de infección por VEB. Los pacientes con LES observan un incremento de la carga viral de VEB en suero y saliva. Estos pacientes tienen de15 a 30 veces más cantidad de DNA viral en sangre periférica. En este caso se muestra la asociación entre LES y la infección por VEB y se sugiere la participación viral como desencadenante del desarrollo de una forma agresiva de LES.

BACKGROUND

Systemic lupus erythematosus (SLE) is a chronic, systemic and idiopathic autoimmune disease.[1] Infection with Epstein-Barr virus (EBV) is one of the factors associated with SLE. Current evidence suggests that EBV infection is associated with multiple autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, SLE, among others.[2]

Virtually all pediatric patients with SLE have serologic evidence of EBV infection; while only 70% of healthy patients are seropositive for this virus, nearly 100% of SLE patients have IgG antibodies for EBV viral antigen;[2] it has also been observed that SLE patients have an increased viral load of EBV in serum[1] and saliva.[3] EBV infects B cells and promotes a polyclonal activation of these cells uncontrollably. EBV produces viral proteins that prevent apoptosis and have similar activity to interleukin-10.[1]

SLE patients show an increase in frequency of EBV-infected B cells. Kang *et al* found, by use of quantitative PCR, 40 times EBV viral load in patients with SLE as much as in healthy patients.[4,5]

CASE PRESENTATION

15 year old female patient, previously healthy; showed clinical symptoms with two weeks of evolution that began with fatigue and malaise, a week later nausea appeared and fatigue and discomfort increased. The patient noticed the presence of painless cervical lymphadenopathy and night sweats; no weight loss was reported. Physical examination showed a light jaundiced conjunctive, multiple small cervical lymphadenopathies were found; the largest of these was found in the left retroauricular area, 2 × 2 cm in area, mobile, with well-defined edges and painless. Abdominal auscultation showed a slightly painful enlarged liver. The rest of the physical examination was normal. Previous clinical laboratory studies showed leucopenia (2,450 cells/uL). Infectious mononucleosis was suspected, so more medical tests were requested. A week later she reported increased fatigue and significant abdominal pain localized in the epigastrium, and postprandial vomiting. Physical examination revealed tenderness in the epigastrium; the rest of the examination remained unchanged. The clinical analyses re-

ported: Epstein Barr positive IgM (49 U/mL), negative early Epstein Barr antigen, positive Epstein Barr antinuclear antigen (EBNA) (1:5,120 with homogeneous pattern), positive anti-DNA antibodies (289.8 IU/mL), anti-SM antibodies (17.7 IU/mL), anti-Ro antibodies (SSA) (3.8 IU/mL). With the clinical data and laboratory analyses a diagnosis of systemic lupus erythematosus related to EBV infection was established. Rheumatology valuation was requested, and further laboratory studies found albuminuria (1,960 mg/day albumin); she was admitted to hospital for systemic lupus erythematosus with hepatic, renal and hematological complications. During her hospital stay she presented a poor clinical evolution; she developed pancreatitis and severe anemia that reached hemoglobin levels of 3 g/dL (1 g/dL at the end), she was admitted to intensive care, but her evolution was progressive, she did not respond adequately to treatment and died.

DISCUSSION

Autoimmune diseases affect about 5% of the population in the United States and represent the third most common pathologies after cancer and heart disease. At least 15 known diseases are the direct result of an autoimmune response, while there is circumstantial evidence that points to autoimmune processes in over 80 pathologies.[6]

Systemic lupus erythematosus (SLE) is an idiopathic disease characterized by inflammatory processes in different systems. A variety of autoantibodies is found in the sera of SLE patients, indicating that SLE is an autoimmune disease. However, the mechanism leading to the erroneous autoimmune response is unknown and it is thought that several factors; genetic, as well as environmental; are involved.[7]

The Epstein-Barr virus (EBV) has been the leading candidate for the triggering of certain autoimmune diseases, since the initial description of EBV-specific antibody titers obtained in patients with SLE in 1971.[6] An increased prevalence of viral infections has been found in SLE patients, and the high viral loads seem to be related with reports of similar symptoms to SLE in patients who previously had infectious mononucleosis. Children and young adults with SLE have an increased seroprevalence of antibodies to EBV antigens, compared with healthy controls. In contrast, there is no correlation between SLE and other herpesviruses, including cytomegalovirus.[8] The association between EBV infection and SLE is more compelling in children, where infection is less prevalent in the controls and gives greater statistical significance compared with adults. At this point, not only serological association has been replicated many times, even in adults, but the association has also been documented by isolating sequences of viral DNA.[9]

The EBV is a biologically plausible candidate, as it is ubiquitous in nature, establishes a lifelong latent infection with continuous virus production due to reactivation and immune system modulation. In its role of immune modifier, EBV infects B cells via the expression of latent antigens and promotes its proliferation and differentiation into memory B cells, in which it persists. The EBV-infected B cells can become a continuous source of autoantibodies.[8] Furthermore, the virus continually stimulate strong T cell responses by the chronic presence of antigens.[6-8]

EBV is known to act through different Toll-like receptors (TLRs), which can lead to production of interferon, abnormal antigen presentation, T-cell activation, cytokine production and loss of tolerance. EBV has a viral interleukin homologous to interleukin-10 (IL10), which can induce an inappropriate activation of antigen presenting cells; it also has a homolog of BCL-2, which can inhibit apoptosis of infected cells.[10]

Molecular mimicry may participate as a mechanism to explain how EBV infection leads to SLE development. Two EBV proteins have regions with similar immune activity to some key SLE autoantigens. Some antibodies against EBV nuclear antigen 1 (EBNA 1) cross-react with Sm B', SmD1, SmD3 and Ro. EBNA 2 antibodies also cross-react with SmD. These cross-reacting antibodies are particularly interesting, since Ro and Sm B' antigens are key to the development of SLE. Ro autoantibodies are the first to appear in SLE. Sm autoantibodies are found almost exclusively in sera of SLE patients, and this is regarded as a classification criterion.[2,7,8] EBNA 1 expression in mice induces expression of antibodies against double-stranded DNA and against Sm, showing that EBNA can generate autoimmunity in mammal immune systems.[9]

Patients with SLE show 15^7 to 30^5 times the presence of viral DNA in peripheral blood as much as in control patients; however, no difference is found in levels of DNA from mouthwash samples.[7] The controls in these studies were described as healthy and were assigned by geography, but recruitment is not described in detail. More recent studies using B cell isolates from patients with SLE and healthy controls showed a 10-fold increase in infected cells as well as differences in the expression of EBV genes.[3] These high levels of infection and EBV gene expression in patients with SLE can lead to: A) an intense or altered immune response against EBV proteins resulting in autoimmune response by cross-reaction; B) an increased state of activation of the host's immune response; C) an environment with proinflammatory cytokines, resulting in decreased immune tolerance; or D) potentially auto

reactive EBV infected cells, resulting in formation of autoantibodies and/or a pathological response.[7-9]

As it can be observed, there are multiple ways in which EBV can trigger a response that results in SLE. In our patient's case, it is clear that prior to the SLE diagnosis she had an EBV infection as she was EBNA positive, which indicates that it was a very intense reactivation or secondary infection, as it presented a very high titer. It is not possible at this time to ensure that this situation triggered the autoimmune process; however, it should be kept in mind in order to keep mononucleosis patients under medical surveillance with the purpose to act quickly at the onset of the first SLE symptoms.

We consider that the case of this teenager shows in one hand the association between SLE and EBV infection, and in the other indicates the possibility of viral infection participating as a trigger for SLE, in a very aggressive manner.

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