Viruses and lupus: the viral hypothesis
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In recent decades, many research groups have focused on the role of viral infection in the etiopathogenesis of systemic lupus erythematosus (SLE), the so-called viral hypothesis. The main candidates are herpesviruses such as Epstein–Barr virus (EBV) and cytomegalovirus (CMV), which have a high seroprevalence in the general population with more than 90% of adults presenting immunoglobulin G against these viruses. Some studies have found a higher seroprevalence of previous EBV infection and an abnormally elevated EBV virus load in patients with SLE with respect to controls, suggesting a possible involvement of EBV in the pathogenesis of SLE. However, the mechanisms that lead to the aberrant autoimmune responses related to EBV infection are not clearly understood. Because primary infection by these viruses is not always recognized as such, producing only a mild catarrh or non-specific symptoms, etiopathogenic studies performed after acute infection may be difficult to interpret. This is because the possible molecular changes induced by the first contact with the virus are not susceptible to analysis when the etiopathogenic situation before the primary infection is unknown. Thus, studies centered on the role of the so-called endogenous retroviruses showed inconclusive results, and it is not yet clear if these viruses should be considered as genetic or environmental factors.

The discovery of new viruses has often led to their study in patients with SLE. This has been the case with the human parvovirus B19, herpes viruses 6 and 7, retroviruses, and hepatitis viruses. The search has been always for the external agent that could trigger the autoimmune response and the development of lupus. However, a viral causal agent of lupus has not yet been discovered, but many interesting findings on the complex interactions between viruses and lupus in clinical practice have been made.

The parvovirus B19, an erythrovirus that mainly affects children between 5 and 10 years of age, is a good example. Acute infection in adults is infrequent but may produce systemic symptoms and the synthesis of various autoantibodies, such as antinuclear and antiphospholipid (aPL) antibodies, a situation resembling the onset of lupus. In fact, there are no significant differences in specificity of aPL antibodies between B-19-infected patients and patients with SLE. Acute infection in adults has also been reported to trigger SLE and to mimic lupus flares in already diagnosed SLE. However, as yet there are no studies aimed at identifying the parts of the virus that might be implicated in the etiopathogenesis of SLE.

With respect to chronic viral infections, such as the infections caused by hepatitis C virus (HCV) and the human immunodeficiency virus (HIV), a significant degree of overlap has been found between viral-related manifestations and those of SLE. These manifestations include clinical features such as arthritis, nephritis, and serositis; analytical data such as data on leukopenia, lymphopenia, and thrombocytopenia; and autoantibodies such as antinuclear, anti-DNA, and aPL antibodies; all of the above are included in the current classification criteria of SLE. In some patients, chronic viral infections mimic SLE, in others the two processes coexist. In these cases, the line separating chance from causality is often difficult to draw because of the impossibility of dating the onset of infection and because of the effect of the therapies administered for the two processes. Recent reports illustrate the broad spectrum of clinical situations caused by chronic viral infections in lupus patients. For HIV infection, there are reported cases of SLE reactivated after highly active antiretroviral therapy, HIV-glomerulonephritis mimicking SLE, or the emergence of HIV manifestations after SLE therapy with cyclophosphamide. For HCV infection, there are reports of SLE induced by antiviral therapy (mainly by the administration of interferon-α), and membranous lupus nephritis mimicking HCV nephropathy.
However, the clinical significance of chronic viral infections in patients with SLE should be evaluated according to the geographical area. HCV, for example, has a much higher prevalence in Mediterranean and Central European countries. In contrast, the etiopathogenic role of HCV in patients with SLE from other geographical areas, such as Northern Europe and America, seems to be less important. Likewise, most cases of HTLV-I infection described in patients with SLE have been reported from Japan, where the virus is endemic.

Thus, the complex relationship between viruses and SLE is reflected in our daily practice by a broad spectrum of clinical situations. Acute viral infections (B19, EBV) may mimic SLE, trigger SLE, or trigger lupus flares in patients already diagnosed with SLE. Reports on life-threatening viral infections in patients with SLE are emerging. There are reports on herpetic hepatitis, retinitis, and pneumonitis; EBV pneumonitis; and CMV colitis, retinitis, ileitis, pancreatitis, and pneumonitis. Chronic viral infections (HCV, HIV) may mimic or coexist with SLE, and even antiviral agents may trigger SLE-related manifestations.

There are no clinical guidelines on the management of patients with SLE and suspected viral infections. On one hand, it would be interesting to determine the viral infections that should be tested for, in patients presenting with a clinical syndrome suggestive of SLE. On the other hand, determining which viral serologies should be tested for in SLE patients presenting with fever suspected to be of infectious origin would also be useful. The differential diagnosis of these patients should consider not only common bacterial infections (usually from the respiratory and urinary tracts) and opportunistic infections (in patients with severe immunosuppression) but also acute and chronic viral infections. It is foreseen that the rise in viral infections at the end of the last century will continue to be a global health problem, which will have a significant impact on the clinical management of patients with SLE.


References


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