Epstein-Barr virus-induced systemic lupus erythematosus

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Evidence of virus-induced systemic lupus erythematosus (SLE) is illustrated by documentation of a 10-year old girl who developed SLE (satisfying ARA criteria) soon after infection with Epstein-Barr virus (EBV) infection. She showed complete remission 24 months later following an aggressive course of immunosuppressive therapy. The appearance and disappearance of serological evidence of EBV infection, followed by the onset and complete clinical and serological remission of SLE, which in this case had unusually mild complications, suggest a causal relationship.

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The causation of systemic lupus erythematosus (SLE) remains enigmatic although the pathogenesis is multifactorial. A number of agents appear to trigger a series of events which culminates in the immune dysregulation typical of this disease.[1,2] Some indirect support for viruses as triggering agents has been provided by serological studies which have shown high frequencies and elevated titres of Epstein-Barr virus (EBV) antibodies in sera from patients with connective tissue disease.[3,4] However, the link between SLE and EBV infection remains tenuous. We now report what we believe to be the first case (based on a fruitless Medline search) of EBV infection associated with SLE in a 10-year-old Indian girl. The appearance and disappearance of serological evidence of EBV infection coincided with the onset and remission of SLE.

Case report

The patient presented with a history of fever, sore throat, lethargy and cervical lymphadenopathy. A full blood count showed the following: haemoglobin 11,3 g/l; platelets 251 x 10^9 /l; and leucocytes 3,14 x 10^9 /l with a differential count of 52% neutrophils, 38% lymphocytes, 8,5% monocytes and 1,5% eosinophils. At this stage, clinical diagnosis of infectious mononucleosis was entertained despite the presence of leucopenia. Eleven days later she developed a generalised faint maculopapular rash; the fever and lymphadenopathy remained unchanged.

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Serological tests for EBV showed a positive IgM anti-viral capsid antigen antibody to EBV, and an absence of antibody to EB nuclear antigen that suggested an acute EBV infection (Table I). Three weeks later she developed severe headaches and anorexia; the adenopathy persisted. The week after this she developed vasculitic lesions on the palms and soles, arthritis of the right knee and moderate hypertension. Urinary dipstick testing showed proteinuria + + and haematuria + +. A screen for auto-immune diseases revealed that antinuclear antibodies were positive in a dilution of 1:50; the titre subsequently rose to 1:3 200. SLE was confirmed by the presence of dsDNA auto-antibodies of the homogeneous type. In addition, the extractable nuclear antigen was positive. Other laboratory investigations showed the following: erythrocyte sedimentation rate 60 mm/h; complement (C3 fraction) 0,31 g/l (normal 0,83 - 1,77 g/l); (C4 fraction) < 0,08 g/l (normal 0,72 - 0,36 g/l); white cell count 2,9 x 10^9 /l and severe neutropenia. Her renal biopsy revealed a diffuse membranoproliferative grade VI nephritis.[5] Repeat testing for EBV showed IgG antibodies strongly positive for viral capsid antigen (1:640); IgM antibody was now negative and early antigen positive (1:40) (Table I). This confirmed recent exposure to EBV.

Table I. Serological and clinical events in a 10-year-old girl with EBV infection and SLE

	Time after initial presentation (mo.)					
Features	1	3	6	8	10	24
Clinical						
Fever	+	+	+	+	+	–
Rash	+	+	–	–	–	
Lymphadenopathy	+	+	+	+	–	–
Arthritis	–	–	+	+	+	–
Nephritis:						
Urinary sediment	–	–	+	+	+	–
Laboratory						
Leucopenia	+	+	+	–	–	–
Hypo-complementaemia*	ND	ND	+	+	+	–
EBV antibodies						
VCA IgM	+		–	–	–	ND
VCA IgG	–	+	+	–	–	ND
EA IgG	+		-	–	–	ND
NA IgG	–	+	+	–	–	ND
Auto-antibodies						
ANF	–	1:50	1:800	1:3 200	1:40	1:50
DNA (ds)		–	–	+ve	+ve	–

ND = not done; + = present; – = absent.
* Complement (C3 fraction).

Except for an exacerbation of her disease 3 months after commencement of therapy, she showed steady improvement with complete resolution of constitutional symptoms as well as disappearance of urinary sediment. Her drug dosages were gradually reduced and eventually stopped 24 months after the onset of her disease. Repeat laboratory investigations showed absence of all auto-antibodies and acute phase reactants with normocomplementaemia. Repeat serological tests for EBV were negative. At present, 37 months after the appearance

of SLE, she is in complete clinical remission with no laboratory evidence of disease activity. The development of EBV antibodies and auto-antibodies together with clinical events are shown in Table I.

Discussion

Within 12 weeks of an episode of EBV infection, the child described here developed clinical and laboratory features consistent with ARA criteria for the diagnosis of SLE. The continuity between her EBV infection and the development of SLE makes it highly likely that the virus served as a trigger factor. One drawback of the viral hypothesis is that we have only serological evidence for acute infection with EBV, as viral culture was not performed. Both SLE and EBV infection share similar immune dysregulation. Altered T-cell-mediated control allows the production of auto-antibodies by the EBV-induced B cells which remain latently infected.

Patients with SLE have been shown to have high levels of antibodies to the EBV capsid antigens,[6] nuclear antigens[7] and early antigens.[8] This may be an epiphenomenon. However, there is a molecule link between the EBV-induced nuclear antigen, EBNA-1, and the Sm-D auto-antigens in the sera of patients with SLE.[8]

In developing countries like South Africa, the typical syndrome is rare as virus transmission occurs early in infancy and childhood. Our patient presented typically but had a low white cell count, which is less common.[9] The disease did not settle within a month but progressed to SLE. Although there is overlap in clinical manifestations of both diseases, SLE was confirmed serologically and by ARA criteria. Over a few months the clinical and laboratory indices of both SLE and EBV resolved and all drug therapy was discontinued. At presentation her growth parameters were normal and she maintained her growth pattern throughout her illness unlike most children with SLE, who are underweight and stunted. This also suggests a transient immune disturbance. Quiescent ongoing renal disease in the face of inactive SLE is a possibility that has to be excluded.[10] Delayed relapses after a protracted remission are also possible since the disease is known to run a course of exacerbations and remissions. It could be argued that the child had only SLE, and that the EBV antibodies were due to nonspecific polyclonal B-cell stimulation. Although SLE is rare in the Third World, our experience is that the disease is severe, often fatal and rarely remits either spontaneously or with intensive therapy. At present the child is in prolonged clinical remission, an unusual finding in childhood SLE where the disease is known to run a more aggressive course.

Conclusion

This is the best-documented case of EBV-induced SLE. The diagnosis of both diseases is reliable, but that for EBV could have been strengthened by viral culture. That the diseases were causally related with more than a simple association is evident in the close temporal relationship between the sequential acquisition and disappearance of both diseases, and the unusually mild clinical complications of SLE.

The authors subsequently treated a 7-year-old black boy with SLE, who was also diagnosed as having acute EBV infection on the basis of IGM-positive EBV antibodies. This serves as further corroborative evidence of EBV's being a possible trigger agent for the development of SLE.

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100 years ago . . .

The Corporation of Bloemfontein has imposed a tax of 7s. 6d. on bachelors above 18, to assist in covering the expenses of the small-pox epidemic. It may bring in cash, but we doubt the ulterior effect. It is cheap at that.

A death from chloroform is reported from the New Somerset Hospital. It is regrettable, but no more an indication of the danger attending the administration than a death in a railway or carriage accident is of the danger of travelling by rail or by road.

(*S A Medical Journal*, September 1895, p. 152).