Treatment of EBV driven lymphoproliferation with erythrophagocytosis: 12 year follow up

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Abstract

This is a report of a case of Epstein-Barr virus (EBV) associated haemophagocytic syndrome in a 17 year old woman with antibody deficiency. For two years before this presentation, serology showed abnormally high titres to EBV early antigen, suggestive of persistent infection with EBV. She became acutely unwell with clinical features consistent with virus associated haemophagocytic syndrome (VAHS). Histology showed lymphoproliferation with erythrophagocytosis and evidence of EBV encoded RNAs in liver, spleen, and lymph node. VAHS is often fatal, particularly when it occurs in patients with underlying immunodeficiencies. In this case, treatment with intravenous immunoglobulin, aciclovir, and α interferon was followed by a dramatic recovery. Twelve years later the patient remains relatively well on regular intravenous immunoglobulin.

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Virus associated haemophagocytic syndrome (VAHS) is often fatal, particularly when it occurs in patients with underlying immunodeficiencies.[1 2] We report the case of a woman who survived a severe illness with Epstein-Barr virus (EBV) associated haemophagocytic syndrome on the background of antibody deficiency and after 12 years remains relatively well.

Case history

Immunodeficiency was first suspected when the patient was 12 years old when she suffered from a protracted illness, which was diagnosed on the basis of serology as an acute coxsackie B3 infection with convalescent neutralising titres of 1/512. Immediately after the coxsackie infection, immunoglobulin levels were normal (IgG subclasses and specific antibody values were not checked at this stage). However, one year later a reduced IgG2 was documented and a low IgA was recorded after another 18 months (table 1).

EBV was first implicated at the age of 15 years when the patient suffered an acute illness with jaundice, hepatosplenomegaly, and deranged liver function tests. Before this she had been EBV anti-viral capsid antigen (VCA) IgG seronegative. Acute EBV infection was documented by a high (1/640) EBV anti-VCA IgG titre (table 2). Intramuscular immunoglobulin was started three months after the first positive EBV serology. After this initial infection with EBV the patient made a good clinical recovery; however, the hepatosplenomegaly persisted and repeated liver biopsies showed histological changes of chronic active hepatitis. Serology at the age of 16 years showed abnormally raised titres of IgG antibodies to EBV early antigen (1/2048; table 2), which could not be explained by the immunoglobulin treatment and were suggestive of chronic active EBV infection. Treatment with intravenous aciclovir did not result in any improvement of either the biopsy findings or the serological changes.

At the age of 17 years she suddenly became severely unwell with a fever (40°C), rapid enlargement of her hepatosplenomegaly, haemolytic anaemia, and thrombocytopenia. Her condition deteriorated despite treatment with steroids, high dose intravenous immunoglobulin, and intravenous aciclovir. She remained dependent on blood and platelet transfusions until a splenectomy was performed. Initial histology of spleen, liver, and lymph node suggested a lymphoproliferation indistinguishable from lymphoma, and was previously reported as such.[3] Anti-EBV early antigen (EA) serology remained strongly positive and it was thought that the lymphoproliferation might be EBV driven. After the splenectomy she remained critically ill; however, she responded dramatically to treatment with 3 million units of α interferon (initially daily then reduced to alternate day dosage after one week) for six months, intravenous acyclovir (500 mg/m^2 daily) for 14 days, and intravenous immunoglobulin (350 mg/kg) on alternate days for the first week, then continued weekly. The hepatomegaly resolved and liver biopsy

Table 1 Immunological investigations

Age (years)	*Clinical note*	*Immunoglobulin values (g/litre)*						
		IgG	*IgA*	*IgM*	*IgG1*	*IgG2*	*IgG3*	*IgG4*
12	Coxsackie infection	7.75	0.8	1.25	Not tested			
13		7.8	**0.65**	1.3				
15	EBV infection				3.0	**0.02**	0.26	0.1
16	Regular IMIG	9.25	**0.46**	1.3				
18	Regular IVIG	8.1	**0.28**	0.89				
27	Regular IVIG	13.20	**0.14**	**0.30**				

Values in bold are abnormally low.
EBV, Epstein-Barr virus; IMIG, intramuscular immunoglobulin; IVIG, intravenous immunoglobulin.

Table 2 Virology investigations

Age (years)	*EBV anti-VCA IgM*	*EBV anti-VCA IgG*	*EBV anti-EA IgG*
12	<1/10	<1/10	Not tested
15	Positive	1/640	Not tested
16	<1/8	1/512	1:2048
17	Negative	1/320	1/640
18	Negative	1/320	1/2500
19	Positive	1/320	1/1280
27	Negative	Positive	1/640

EA, early antigen; EBV, Epstein-Barr virus; VCA, viral capsid antigen.

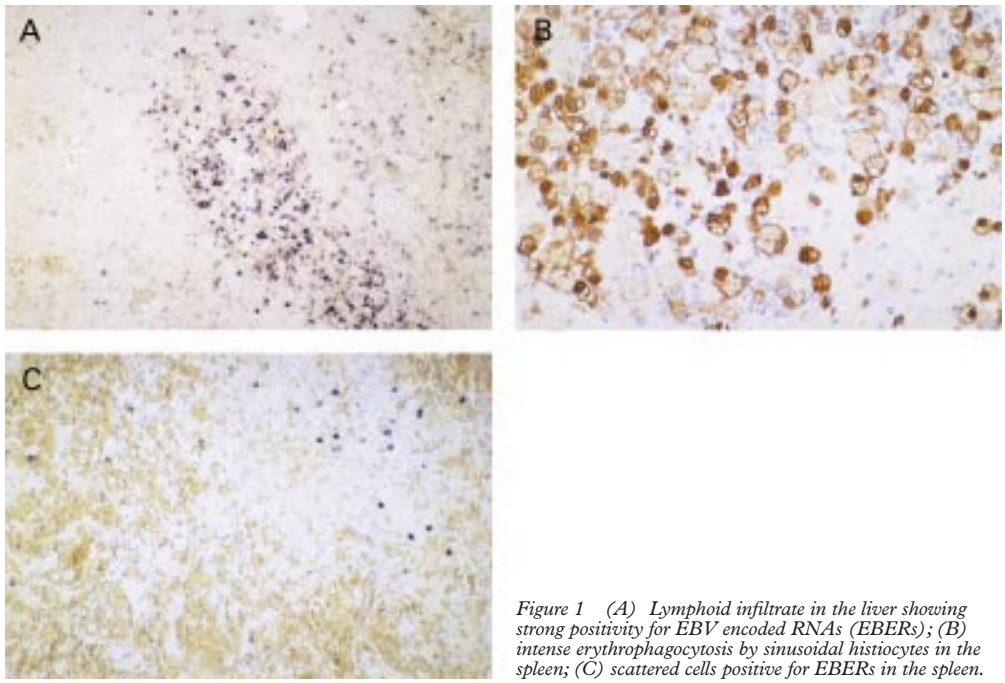

Figure 1 (A) Lymphoid infiltrate in the liver showing strong positivity for EBV encoded RNAs (EBERs); (B) intense erythrophagocytosis by sinusoidal histiocytes in the spleen; (C) scattered cells positive for EBERs in the spleen.

three months into this treatment regimen showed no evidence of lymphoproliferation. Recent review of the histological sections taken at the time of this acute illness has demonstrated evidence of EBV infection and erythrophagocytosis. The cells of the lymphoid infiltrate in the liver show strong positivity for EBV encoded RNAs (EBERs) supporting the diagnosis of EBV driven lymphoproliferation (fig 1A). The splenic sections demonstrated intense erythrophagocytosis by sinusoidal histiocytes with scattered cells positive for EBERs (fig 1B and C). Lymph node histology showed prominent erythrophagocytosis by sinus histiocytes.

Liver biopsy three months after the start of treatment with intravenous immunoglobulin, α interferon, and intravenous aciclovir showed chronic active hepatitis with an almost complete resolution of the atypical lymphoid element of the inflammatory infiltrate.

Twelve years after the splenectomy, she has had no further episodes of deranged liver function or hepatomegaly. However, her EBV serology has remained abnormal, with high titres of anti-EA (1/320 to 1/1280; table 2), which could not be explained by treatment with intravenous immunoglobulin, and which are suggestive of persistent EBV infection. EBV DNA has been detected using a polymerase chain reaction (PCR) method based on the assay of DNA extracted from leucocytes. With this assay, less than 2 copies EBV DNA/10^6 leucocytes are found in healthy, persistently infected people. In our patient, 1.3×10^6 copies/10^6 leucocytes were found. This is consistent with chronic active EBV infection.

The patient has had intermittent episodes of a steroid responsive demyelinating neuropathy, with complete resolution of symptoms between attacks, and has now developed neurological signs consistent with chronic inflammatory demyelinating polyneuropathy (CIDP), confirmed on neurophysiology testing. Recently, she has been receiving oral steroids to treat a haemolytic anaemia. It is possible that these complications might be related to the chronic active EBV; however, they may also be manifestations of other infections or might be autoimmune in aetiology. In an attempt to control the haemolysis a trial of long term oral valaciclovir was initiated. Initially, this was associated with a reduction in haemolysis, allowing her steroid dose to be reduced; however, despite a maintenance dose of valaciclovir (500 mg) the haemolysis has recurred.

Discussion

Our patient appears to have an underlying immunodeficiency, although her symptoms and clinical presentation are atypical, not fitting neatly into a recognised diagnosis. Most of her clinical problems can be attributed to an abnormal response to EBV and the laboratory results demonstrate a progressive deterioration in humoral immunity. This suggests a progressive antibody deficiency, which could be secondary to the preceding coxsackie infection, but which also follows the same pattern as that seen in some patients with common variable immunodeficiency (CVID). It is unlikely to be secondary to EBV infection because the abnormalities in the immunoglobulin values preceded the first detection of positive EBV serology. The findings of low B cell and natural killer (NK) cell numbers are non-specific and do not further the diagnosis (table 3). It is interesting to note that in vitro lymphocyte proliferations to a variety of activators are within normal limits and the NK cell function is also normal (table 3).

This patient's clinical profile is not typical for CVID, in which the clinical features tend to

Table 3 Further investigations at age 27 years

Lymphocyte subsets		*Cells/μl*		
Total CD19+ B cells (normal, 200–400)		**32**		
Total CD3+ Tcells (normal, 1100–1700)		1562		
CD8+ T cells (normal, 500–900)		1008		
CD4+ T cells (normal, 700–1100)		1103		
CD16+CD56+ NK cells (normal, 200–400)		**48**		
Lymphocyte proliferation assays				
Activator	*Patient (cpm)*	*Control (cpm)*	*Patient SI*	*Control SI*
None	93	395		
PHA	15 835	133 751	170	339
Concanavalin A	18 852	111 078	203	281
PMA	13 813	23 845	149	60
PMA + Ionophore	29 060	63 942	312	162
Anti CD3 + IL-2	82 142	52 922	883	134
NK cell function assay				
Expressed as percentage of K562 cells killed by mononuclear cell population				
Patient	10.1%			
Normal range	7.5–40%			

Values in bold are lower than normal.
cpm, counts/minute; IL-2, interleukin 2; NK, natural killer; PHA, phytohaemagglutinin; PMA, phorbol myristyl acetate; SI, stimulation index.

reflect the hypogammaglobulinaemia, manifesting as bacterial infections particularly involving the upper and lower respiratory tracts. Variable T cell abnormalities are seen in CVID; however, problematic viral infections are rare with the exception of echovirus as a cause of a severe progressive meningoencephalitis.

An increased susceptibility to EBV infection is seen in several primary immune deficiencies.[4] Patients with the X-linked lymphoproliferative syndrome have defective EBV specific T cell responses as a result of mutations in the gene encoding SAP (SLAM associated protein).[5 6] These patients are well until they encounter EBV, when they develop either fatal mononucleosis, hypogammaglobulinaemia, or lymphoma. Patients with B cell positive severe combined immunodeficiency are susceptible to overwhelming EBV hepatitis. Patients with Wiscott-Aldrich syndrome frequently develop EBV driven lymphoid malignancies. Susceptibility to EBV is not generally characteristic of CVID, although there are a few case reports suggesting that some patients with CVID suffer from unusual complications of EBV infection.[7–9] These patients might represent a distinct subpopulation. Increased incidences of lymphoproliferative lesions, both monoclonal and polyclonal, have been reported in patients with CVID, some of which have been reported as being associated with EBV.[10 11] Other members of the herpesvirus family, such as varicella zoster and herpes simplex, have been reported as occasionally causing problems in patients with CVID.[12 13]

The use of serological tests to diagnose viral infection in our patient is complicated by the fact that she is now receiving replacement intravenous immunoglobulin. However, the persistently high titres of EBV anti-EA IgG, with titres of 1/1280 (table 2), cannot be accounted for by the intravenous immunoglobulin. Raised titres of anti-EA IgG antibodies are usually only seen during the acute phase of infection, persistent high titres suggest continuing active infection. This is supported by the recent demonstration of significantly higher amounts of EBV DNA in peripheral blood leucocytes than is normally seen after EBV infection.

A diagnosis of VAHS is made based on the histological finding of erythrophagocytosis, together with the clinical features of fever above 40°C, hepatosplenomegaly, and haemolytic anaemia with evidence of EBV infection.[14] This condition can occur in immunocompetent or immunocompromised individuals and has been described in association with several viruses including EBV, cytomegalovirus, varicella zoster, and herpes simplex virus.[15] The prognosis for this condition depends on the underlying immune status. In cases where the degree of immunosupression can be reduced, such as some patients receiving immunosuppressive drugs, a better prognosis can be expected. In patients with X-linked lymphoproliferative syndrome and those with other primary immunodeficiencies the development of VAHS is often fatal.[16–19]

The use of α interferon is well established in the treatment of several viral infections, including hepatitis B and C.[20 21] It has also been used to shorten EBV excretion in renal transplant recipients,[22] and some success has been reported in EBV driven post-transplant lymphoproliferative disease.[23] The use of α interferon in a patient with CVID and chronic EBV infection has been described previously[9]; however, the patient described in that study was not reported as having evidence of VAHS.

In our case, we have described a rapid recovery in an immunodeficient patient with severe EBV associated haemophagocytic syndrome and a favourable outcome 12 years later with no evidence of lymphoproliferation, despite the persistence of active EBV infection.

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