Angioimmunoblastic lymphadenopathy after infectious mononucleosis

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Abstract

Angioimmunoblastic lymphadenopathy occurred in a 46-year-old man 16 months after an episode of infectious mononucleosis induced by Epstein-Barr (EB) virus. The features of infectious mononucleosis included fever, pharyngitis, lymph gland enlargement, hepatosplenomegaly, hyperbasophilic mononuclear cells, and IgM antibodies to EB virus, although heterophile antibodies were not detected. The illness was severe and prolonged and included an asymptomatic measles virus infection. Over a year later massive enlargement of the lymph nodes led to a biopsy, which showed a diffuse infiltration with lymphoid cells and a proliferation of arborising small vessels typical of angioimmunoblastic lymphadenopathy. In spite of corticosteroids, levamisole, chlorambucil, and radiotherapy, no remission occurred, and serious infections led to death 18 months after the onset.

Viral infections with EB virus and measles virus associated with pre-existing or subsequent immunological changes probably resulted in the appearance of angioimmunoblastic lymphadenopathy.

Introduction

Epstein-Barr (EB) virus, a B-cell lymphotropic virus, causes a primary infection, infectious mononucleosis, in which T cells proliferate as a response to B cells transformed by EB virus. In vitro, continuous cell proliferation can be induced by infection of B lymphocytes, and in vivo absence of control of proliferation in immunodeficient patients is likely to lead to a lymphoma-like syndrome, either in immunosuppressed patients with renal allografts¹ or in preconditioned individuals.² EB virus is also associated with Burkitt's lymphoma, which is the malignant proliferation of a B-lymphocyte clone. Angioimmunoblastic lymphadenopathy is a lymphoma-like syndrome in which one or more B-cell clones proliferate through prolonged immunological stimulation, leading to non-malignant growth.³ We describe a case of angioimmunoblastic lymphadenopathy which occurred after a severe episode of infectious mononucleosis associated with EB virus.

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Case report

A 46-year-old man developed a febrile illness in 1976, followed by a maculopapular rash after treatment with amoxicillin. Severe pharyngitis, enlarged lymph glands, and hepatosplenomegaly were noted.

His white cell count was $10.9 \times 10^9/l$, with 21% mononuclear cells and 20% hyperbasophilic lymphocytes. The presence of anti-viral capsid antigen of the IgG class (titre 1280) and of the IgM class (titre 80) was characteristic of infectious mononucleosis induced by EB virus; heterophile antibody test gave repeatedly negative results. The course of the disease, during which a seroconversion to measles virus was noted (see figure), was typical of severe infectious mononucleosis. In spite of treatment with prednisone the patient remained unwell throughout 1977, with persistence of fatigue and hepatosplenomegaly.

Summary of symptoms and diagnostic data.

In February 1978 further enlargement of the lymph nodes was noted together with an erythematous rash, fever, night sweats, fatigue, and increasing hepatosplenomegaly. A moderate anaemia was noted (Hb 9.7 g/dl, 91×10^9 reticulocytes/l) with a positive Coombs test result. Lymph node biopsy showed a diffuse infiltration with lymphocytes, plasma cells, and immunoblasts and an exuberant proliferation of arborising small vessels. Liver biopsy showed considerable lymphocytic and plasma-cell infiltration in the portal triads. Diffuse hypergammaglobulinaemia was present, and smooth-muscle antibodies were detected; the lymphocyte response to phytohaemagglutinin was subnormal.

Treatment with prednisolone and later levamisole failed to influence the glandular enlargement, and in November the patient developed gross lymphoedema of the lower part of the body. A further gland biopsy showed histological features characteristic of "Lukes' type III" angioimmunoblastic lymphadenopathy, with an epithelioid component and lymphocytic hyperplasia. No viral particles were detected. In January 1979 a severe chest infection supervened, and in April he developed ophthalmic herpes zoster with retrobulbar neuritis, followed by lymphocytic meningitis, streptococcal tonsillitis, and finally peripheral neuropathy. The patient died in August but necropsy could not be performed.

Discussion

EB virus stimulates cell division in infected B lymphocytes, not only during infectious mononucleosis but also in vitro in

allowing the establishment of lymphoid cell lines. Infectious mononucleosis and angioimmunoblastic lymphadenopathy are polyclonal lymphoproliferative disorders; some clinical features and biological and immunological changes are similar in both diseases, and both simulate the graft-versus-host response.²

The cause of angioimmunoblastic lymphadenopathy is not clear. It has been suggested that it is caused by proliferation of B lymphocytes associated with a T-cell deficiency.⁴ The disease may be preceded by the administration of drugs⁵ or occur after exposure to an allergen.⁶ Viruses have been implicated in its pathogenesis: rubella antigen has been detected in the lymphocytes of two patients,⁷ and viral-like particles resembling herpes virus have been noted in a few transformed lymphocytes in one case.⁸ In only two cases has EB virus been associated with the disease: in the first⁹ EB virus-DNA was detected in lymph node material, and in the second¹⁰ EB nuclear antigen was detected in lymph nodes and blood lymphocytes from a 5-year-old girl with both severe EB virus infection and a syndrome similar to angioimmunoblastic lymphadenopathy. In another patient infectious mononucleosis was followed by reticulum cell sarcoma but no data on EB virus were available,¹¹ while several cases of Hodgkin's disease have occurred within three years of the diagnosis of infectious mononucleosis.¹²

In our patient angioimmunoblastic lymphadenopathy was certainly not the direct consequence of EB virus infection, since anti-viral capsid antigen IgG titres progressively decreased to normal concentrations. EB nuclear antigen antibody titres, however, did not increase after the episode of infectious mononucleosis, probably because of a deficit in some T-cell functions and consequently a poor cytotoxic response to EB virus-infected lymphocytes, as reported in Hodgkin's disease, X-linked lymphoproliferative syndrome, and ataxia telangiectasia. Our patient is unlikely to have had an inherited immune deficiency, since he was 46 and had no history of repeated or severe infections. Moreover, skin test results and lymphocyte stimulation with phytohaemagglutinin were subnormal.

Measles virus can infect both B and T lymphocytes,¹³ whereas EB virus infection is limited to the B subset. Both viruses^{14 15} create transient immune changes during primary infection. EB virus could have created long-lived lymphoid cells and, shortly after this, measles virus could have indirectly increased B-cell proliferation by decreasing T-lymphocyte responses, thus leading to angioimmunoblastic lymphadenopathy; no monoclonal malignancy was noted. The results of this study suggest two hypotheses. Firstly, viruses such as EB virus (with or without measles virus) could induce immunological perturbations leading to angioimmunoblastic lymphadenopathy.

Secondly, a long time before the lymphadenopathy developed subtle immunological changes not detectable with routine methods might already have been present and have increased the predisposition to viral infections (infectious mononucleosis or measles), which may then have induced the angioimmunoblastic lymphadenopathy.

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ONE HUNDRED YEARS AGO A man, aged 69, was admitted on March 14th, 1881, suffering from retention of urine. He said he had been unable to pass urine in any quantity at a time for several weeks, and that it was constantly dribbling away from him. On admission, his bladder contained two pints of bloody urine, of an acid reaction, having a specific gravity of 1010, and containing albumen; but only revealing blood-cells under the microscope. On passing the finger into the rectum, the prostate could be felt to be enlarged, and was somewhat tender on pressure. There was considerable anasarca. He was ordered a milk-diet, 30 grains of compound jalap powder every morning, and a mixture of perchloride of iron three times a day; a catheter was to be passed twice a day. A few days later, the catheter was ordered to be used three times daily. In four days after admission, the dropsy had all disappeared—revealing, what was not evident before, great emaciation. The dribbling of the urine was as bad as ever—owing, however, not to the bladder being over full, but to its inability to retain any urine. There was a peculiar grating experienced each time on using a catheter coudé, as it passed through the prostate, as if it were rubbing against a calculus. On March 23rd, he was ordered a mixture of acetate of potash, hyoscyamus, and camphor water. About this date, it was suggested that it was not a case of simple enlargement

of the prostate, but probably malignant disease. Death took place on March 27th.

On March 29th, a *post mortem* examination was made. The kidneys, bladder, and portions of the penis were removed together. The bladder was generally thickened, and the mucous lining much congested; the prostate was very hard, and a section showed that it consisted of one mass of scirrhous deposit, which extended outwards and backwards into the wall of the bladder; the growth reached up to the orifices of the ureters, quite obliterating the opening on the right side, and partially constricting that on the left side. Both ureters were dilated and stretched, but the coats were in no way thickened; both were so distended with urine as to look like small intestine. The calyces and pelvis of the right kidney were distended with urine, and so compressed the body of the kidney as to virtually convert it into one large cyst, which was not so large as the left kidney. The latter was much enlarged, somewhat distended with urine, and had a small abscess in the lower half of the body of the kidney. There was also an abscess in the suprarenal capsule. The other organs of the body were healthy, except the right lung, which was bound down by adhesions, the result of an old pleurisy. No other cancerous deposits were found in any other part of the body. (*British Medical Journal*, 1881.)