Acquired Hypogammaglobulinemia Following Infectious Mononucleosis

JOHN F. GREALLY,1,2 EMER LAWLOR,1 JACK LYONS,1 ALAN RICKINSON,3 KIYOSHI SAKAMOTO,4 and DAVID PURTILO5

The case of a 17-year-old male who developed hypogammaglobulinemia following infectious mononucleosis is presented. The family history revealed that a male sibling had died some years earlier with encephalitis also following infectious mononucleosis. Laboratory investigations revealed adequate numbers of T and B cells and normal proportions of helper and suppressor T lymphocytes but poor in vitro responses to mitogens and an absence of hypersensitivity to skin test antigens. Serial serological examinations for Epstein-Barr virus antibodies indicated a primary immune response to this virus in a hypogammaglobulinemic individual. The patient probably represents a case of the X-linked lymphoproliferative syndrome. The unique feature of the present case is the demonstration of Epstein-Barr virus-specific T-cell memory. The significance of this finding and the variable expression of this syndrome in two members of the same family are discussed.

KEY WORDS: Hypogammaglobulinemia; Epstein-Barr virus; X-linked lymphoproliferative syndrome.

INTRODUCTION

Infectious mononucleosis (IM) is a usually self-limiting lymphoproliferative disease caused by the Epstein–Barr (EB) virus (1). The virus is regularly found in the throat washings of acute-phase patients and may indeed still be detected there long after clinical symptoms and disease-related laboratory findings, such as atypical lymphocytes, hypergammaglobulinemia, and heterophil antibody positivity, have subsided (2). In vitro EB virus infects human B-cell populations activating the synthesis of IgM, IgG, and IgA (3) and “immortalizing” these cells into continuously growing lymphoblastoid cell lines (4). These processes of polyclonal B-cell activation and proliferation are also seen in vivo during the acute phase of IM, accompanied by a vigorous T-cell response encompassing both suppressor (5) and cytotoxic (6) components and by humoral responses to the virus capsid antigen (VCA) and to the early antigen (EA).

Recovery from IM is associated with a fall in the number of virus-infected B cells in the blood, by the disappearance of demonstrable suppressor and cytotoxic activities from the circulating T-cell pool, and by the stabilization of anti-VCA, disappearance of anti-EA, and development of anti-EB nuclear antigen (EBNA) antibody titers (7). The EB virus carrier state thus established in convalescent individuals is also accompanied by the development of stable levels of EB virus-specific cytotoxic T-cell precursors (memory T cells) in the circulation; this activity can be monitored in vitro by measuring the capacity of the T cells to be reactivated in EB virus-infected blood mononuclear cell cultures to cause the regression of outgrowth of the nascent virus-transformed B-cell line (8, 9). Occasionally primary EB virus infection may cause an unusually severe IM leading either to permanent agammaglobulinemia or to uncontrolled lymphoproliferative disease-lymphoma (10, 11). This is seen most dramatically in the male children of families with a history of the X-linked lymphoproliferative syndrome (12); affected males suffer from a complex immunodeficiency with predisposes them in particular to severe, often fatal, EB virus infections. In this report

1Department of Medicine and Immunology, Trinity College, Dublin 2, Ireland.
2To whom correspondence should be addressed at the Department of Immunology, Regional Hospital, Galway, Ireland.
3Department of Pathology, University of Bristol, The Medical School, University Walk, Bristol, England.
4Second Department of Surgery, Kumanoto Medical School, Kumanoto, Japan.
5Department of Pathology and Laboratory Medicine, University of Nebraska Medical Center, Omaha, Nebraska 68105.
the case of a young man who presented with pneumonia and infectious mononucleosis and who apparently simultaneously developed hypogamaglobulinemia is described.

CASE REPORT

A 17-year-old male (ML) presented in November 1978 with fever, sore throat, headache, cough, and general malaise of 1 week’s duration. His previous history included one bout of pneumonia and occasional sinusitis, while in childhood he had measles, mumps, and chickenpox. He had been vaccinated without ill effects against tuberculosis, smallpox, poliomyelitis, diphtheria, tetanus, and pertussis. A male sibling had died 7 years previously at the age of 6 years with encephalitis following infectious mononucleosis. The patient’s mother has asthma but the extended family history is otherwise unremarkable. Physical examination revealed a moderately distressed young man with an inflamed throat and decreased air entry into both upper lobes. Radiological examination confirmed the presence of consolidation in these areas. Enlarged lymph nodes were noted in the cervical and axillary areas. A marked neutrophil leukocytosis was present, a throat swab grew *Haemophilus influenzae*, and a diagnosis of bacterial pneumonia was made. During the following week he responded to penicillin and cloxacillin but the lymphadenopathy became more pronounced. A monospot test (Ortho Diagnostics, Raritan, NJ) for infectious mononucleosis became positive and this was confirmed by the Paul-Bunyell test.

LABORATORY INVESTIGATIONS

As a matter of routine, peripheral blood total and differential white-cell counts were carried out daily. Serum immunoglobulin levels were estimated using Hoechst antisera (Marburg, West Germany) to human immunoglobulins G, A, and M in a Behring Laser nephelometer. These were repeated at regular intervals over the next few weeks and months. The monospot test was also repeated at regular intervals. Sensitivity to delayed-type hypersensitivity (DTH) skin test antigens was assayed by the Mantoux technique using 0.1 ml of antigen solution, purified protein derivative of *M. tuberculosis* (PPD). Tuberculin PPD (Statens Seruminstitut, Copenhagen), 10 TU, and streptokinase/streptodornase (SK/SD) (Varidase, Lederle Laboratories, Pearl River, NY), 50 units/ml. The skin tests were read at 48 hr. Peripheral blood count mononuclear cells (PBMC) were obtained by isopycnic centrifugation on Ficoll/Hypaque (Pharmacia). T lymphocytes were identified using a standard E-rosetting assay and monoclonal antisera obtained from Ortho (OKT 3 for total T lymphocytes, OKT 4 for T helper cells, and OKT 8 for suppressor T cells). B lymphocytes were identified by immunofluorescent staining of surface immunoglobulin using fluorescein-conjugated antihuman G + A + M (Hoechst). A bone marrow aspirate was also performed and a detailed search was made for plasma cells. In vitro lymphocyte proliferation was studied using phytohemagglutinin M (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM) in the range of doses previously described (13). Triplicate cultures were performed and the mean response was recorded. Cells from an age-matched control were cultured simultaneously. Serum antibodies to VCA (14) and to EA (15) were determined by indirect immunofluorescence. For the detection of antibodies to VCA, a P3HR-1 cell line was maintained at 33°C in RPMI 1640 plus 10% fetal calf serum (Microbiological Associates, Bethesda, MD), 100 μg/ml penicillin, and 100 μg/ml streptomycin (GIBCO, Grand Island, NY) for 2 weeks. The smears contained approximately 10% VCA-positive cells. Fluorescein-conjugated (FITC) anti-human IgG and IgM (μ-chain specific) were obtained from Hyland Diagnostic Laboratories (Costa Mesa, CA) and Dakopatts (Denmark), respectively. Raji cells exposed to EBV from spent media of P3HR 1 cultures were used for anti-EA determinations. The virus was adjusted to yield 10% positive cells after 48 hr at 37°C in the presence of 20 μg Ara C (Sigma, St. Louis, MO). Raji cells grown at 37°C for 3–4 days were used for anti-EBNA tests (16). FITC-conjugated caprine antibody to human Bla/B1c (Hyland Laboratories) was diluted 1:40 before use.

For the assay of EB virus-specific memory T-cell (cytotoxic precursor) activity, PBMC were separated as before and a fraction of this population was further separated into T-cell and T cell-depleted (TD) components by E rosetting, the rosetted T cells being rescued by lysis of the sheep erythrocytes at 4°C in a 0.75% NH₄Cl solution in 0.016 M Tris buffer, pH 7.25, as previously described (17). Both PBMC and TD-cell populations were exposed to EB virus (a 10× concentrate from the culture supernatant of the B95-8 cell line) before seeding into 0.2-ml microtest plate wells at various initial