Journal of Clinical Virology 57 (2013) 165–168

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Case report

Mumps virus encephalomyelitis in a 19-year old male patient with an undefined severe combined immunodeficiency post-haematopoietic bone marrow transplantation: A rare fatal complication

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ARTICLE INFO

Article history:
Received 22 November 2012
Received in revised form 31 January 2013
Accepted 4 February 2013

Keywords:
Mumps paramyxovirus
Encephalomyelitis
Transplantation
Combined immunodeficiency

ABSTRACT

We describe a rare case of fatal mumps encephalomyelitis occurring in 19-year old male following matched unrelated donor peripheral blood haematopoietic stem cell transplantation (HSCT). The indication for HSCT was for an undefined form of severe combined immunodeficiency (SCID). Molecular typing of the mumps viral RNA isolated from neural tissue indicated that the infection was acquired at the time of a mumps outbreak in England and Wales that occurred between 2004 and 2006. This case highlights the importance of considering mumps in the differential diagnosis of central nervous system infection in highly immunosuppressed patients.

1. Why this case is important?

The mumps virus (MuV) is a single-stranded, non-segmented, negative sense RNA virus of the genus *Rubulavirus* in the *Paramyxoviridae* family.[1] Infection typically follows a benign course, causing parotiditis and less frequently, orchiditis, oophoritis, aseptic meningitis, pancreatitis and sensorineural hearing loss.[1] 30% of infections are asymptomatic.[2] Before the introduction of mumps vaccine, MuV was a common cause of CNS infection,[3,4] but since the introduction of vaccination programmes, CNS complications declined and sequelae are usually self-limiting and benign.[5] While mumps meningitis usually has a benign course and outcome,[6] mortality and long-term morbidity occurs in 1–5% of encephalitis cases.[3] Unlike CMV, EBV, HHV-6 and respiratory viruses, serious pathology due to MuV is extremely rare in allogeneic HSCT recipients. This case highlights the importance of considering unusual viral aetiology and the possibility of environmental pathogen exposure in the differential diagnosis of encephomyelitis in the severely immunocompromised.

2. Case report

2.1. Case description

The patient was born at term after uncomplicated pregnancy and delivery. His early development was normal. He received full infant vaccinations including measles, mumps and rubella. At age three and a half he suffered from a severe bacterial pneumonia. His immunoglobulin levels were normal (IgG 13.8 g/L, IgA 0.9 g/L, IgM 0.5 g/L) at this stage. Following persistent symptoms of respiratory infection and recurrent otitis media, he was shown to have developed bronchiectasis. Repeat immunoglobulin levels at age five years showed an IgA 0.2 g/L (0.5–2.4) and IgG subclass estimations showed (IgG1 11.49 g/L (3.6–7.3), IgG2 0.55 g/L (1.4–4.5), IgG3 0.15 g/L (0.3–1.1) and IgG4 < 0.02 g/L (0.1–1.0)). Repeat investigations showed confirmed these abnormalities. In view of the rapid deterioration in pulmonary status, immunoglobulin treatment was commenced without waiting for further studies of vaccine antigen responses. There was no family history of immunodeficiency.

Further investigation revealed a reversed CD4:CD8 ratio with normal total T cell number and T cell proliferative response to phytohaemagglutinin (PHA) and anti-CD3 stimulation. CD40 ligand deficiency was excluded by genetic analysis. Sweat and ciliary function was normal.

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http://dx.doi.org/10.1016/j.jcv.2013.02.003

An initial diagnosis of undefined hypogammaglobulinaemia was made but despite regular, and prompt initial immunoglobulin replacement, his childhood was complicated by extensive molluscum contagiosum, chronic otitis media, recurrent oral candidiasis, chronic cryptosporidium-induced cholangiopathy and bronchiectasis. His growth was impaired with height and weight both at the 0.4th centile. The frequency of infections increased despite increased immunoglobulin dosing and T cell numbers fell; particularly CD4 cell numbers. Protein losing enteropathy was considered very unlikely in view of serum albumin levels always remaining normal (37–45 g/L). The diagnosis was revised to combined immunodeficiency of undefined molecular subtype and at 15.5 years he was referred for consideration of allogeneic HSCT. At this stage his PHA response was depressed, as was his proliferative response to candida antigen (5761 cpm versus 28,442 cpm in a healthy control).

His sibling was not HLA-compatible but a fully HLA-matched (10/10 antigen) unrelated male donor was identified. In February 2003, aged 16.75 years, he received an unrelated donor peripheral blood HSCT (cell dose WCC 4.23×10^8/kg, CD34 6.39×10^6/kg CD3 44.8×10^6/kg) using Campath (1 mg/kg), Fludarabine (150 mg/m^2) and Melphalan (140 mg/m^2) conditioning with cyclosporin A for Graft-versus-Host-Disease (GvHD) prophylaxis. The peri-transplant period was complicated by intestinal and biliary cryptosporidiosis treated with paromomycin, azithromycin and nitazoxanide.

Cyclosporin was withdrawn over five months post HSCT with no GvHD. Despite good post-transplant engraftment (chimerism at six months showed 93% of mononuclear cells and 100% of granulocytes were donor origin), immune reconstitution was poor; with a CD3 T cell count 160/μl (normal 1100–2250/μl).

Seven months post-transplant he developed recurrent, severe direct antiglobulin test (DAT) positive (IgG, C3) autoimmune haemolytic anaemia (AIHA) which presented as massive intravascular haemolysis, resulting in Hb 30 g/L. He was treated with pulsed methylprednisolone, rituximab and intensive packed red cell transfusion support. The haemolysis stabilised, but immune reconstitution remained significantly delayed with very low T cell counts (CD3 170/μl, CD4 50/μl, CD8 12/μl) despite near full donor chimerism. 18 months post HSCT he was well and attended university from October 2004. He continued to receive regular immunoglobulin replacement achieving good levels of IgG.

At 24 months post HSCT, he developed right shoulder discomfort and altered sensation radiating from his shoulder to fifth digit. A magnetic resonance imaging (MRI) spine was normal. Six weeks later, he experienced similar left sided symptoms associated with severe neck pain and reduced right lower limb power. A repeat MRI spine revealed central increased signal within the spinal cord from C5-T1, in keeping with an inflammatory subacute myelopathy. At this stage, a pre-infusion IgG level was low at 3.9 g/L, and post-infusion IgG 8.8 g/L.

Cerebrospinal fluid (CSF) analysis revealed no white cells, 49 red cells/mm,[3] and normal glucose and protein levels. CSF analysis by Polymerase Chain Reaction (PCR) was negative for adenoviruses, herpes viruses (herpes simplex, varicella zoster, cytomegalovirus, Epstein–Barr virus, human herpes virus 6) and mumps virus. An empirical trial of methylprednisolone with IV aciclovir (10 mg/kg tds) was of no benefit.

A few days later he developed right-sided partial seizures. An EEG revealed unusual fast epileptic activity arising from a left cortical parietal focus. A repeat MRI Brain was normal. His seizures became generalised and more frequent. He became aphasic and only intermittent communication was possible. He was discharged home with palliative support and died a few days later, 2 years and 3 months after transplantation.

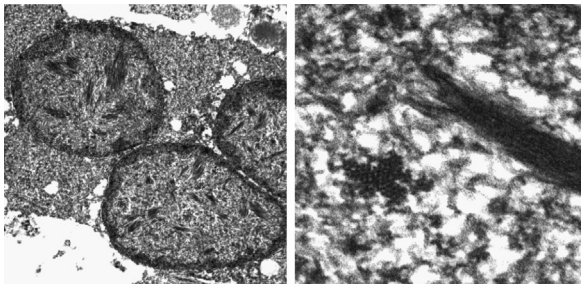

Fig. 1. Intranuclear viral inclusions at low (left) and high (right) magnification. There is a degree of degradation artefact in this post mortem sample.

A post mortem examination found no macroscopic leptomeningeal thickening, haemorrhage or inflammation. In the left parietal lobe there was punctate haemorrhage and congested vessels that was not present on the right. There was no oedematous change, with the gyri and sulci of normal width. There was no periventricular softening or grey discolouration typical of demyelination.

Microscopically in the cerebrum, there were patchy perivascular cortical and subcortical aggregates of macrophages, lymphocytes and astrocytes. There were scattered eosinophilic inclusions present that appeared viral in nature. The inclusions appeared intranuclear with the chromatin pushed to the periphery of the nucleus. The white matter was unaffected and there was no leptomeningeal inflammation. Temporal and cerebellar cortices were unaffected and without inclusions. Almost complete neuronal destruction of two spinal cord sections was found, with dramatic macrophage infiltration and many inclusions. Inclusions were located in astrocytic cells, microglia and diffusely throughout the parenchyma. Other cervical cord sections revealed similar, but less prominent changes. Subsequent electron microscopy confirmed that the viral inclusion bodies were seen within the nucleus (Fig. 1), and that the changes were most likely caused by a paramyxovirus.

The spinal cord tissue was analysed by PCR for the pathogens listed above and JC and BK polyomaviruses. Only MuV RNA, genotype C, was detected and confirmed in the CSF collected at post-mortem (Virus Reference Department, Colindale, London).

Cervical spinal cord sections were de-waxed and following microwave antigen retrieval, a monoclonal antibody that recognises the nucleoprotein of mumps virus (N93-51/01) was used. Specific binding sites were immuno-detected as previously described.[7] Extensive cytoplasmic and intranuclear mumps virus nucleoprotein was demonstrated within the spinal cord and in the neuropil and axonal processes (Fig. 2). Neurons were the predominant infected cell type but infection of glial cells was also observed. Control sections from uninfected spinal cord were consistently negative when used for immunohistochemistry with this monoclonal antibody. Furthermore, omission of the primary antibody or replacement with mouse isotype serum resulted in absence of immunoreactivity. Access was only available to cord sections for immunohistochemistry, and we were therefore unable to fully map the distribution of the virus throughout the CNS.

2.2. Other similar and contrasting cases in the literature

To the best of our knowledge, this is only the second case of fatal MuV CNS infection post HSCT and the first adult case. The first patient was a 16-month old infant who developed meningoencephalitis peri-transplantation. The infant had been vaccinated against MuV several months previously.[8] The authors considered the vaccine strain to be the likely cause.