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Enteroviral meningoencephalitis as complication of Rituximab therapy in a patient treated for diffuse large B-cell lymphoma

The occurrence of an enteroviral encephalitis during Rituximab therapy in a patient with diffuse large B-cell lymphoma has been recently reported (Kiani-Alikhan *et al*, 2009). We recently diagnosed a similar case in our department. Because neurological complications of Rituximab therapy are rare and mostly attributed to reactivation of latent John Cunningham (JC) polyoma virus (Carson *et al*, 2009), we believe it is important to report other potential harmful complications of this treatment.

A 61-year-old female was treated in our department of haematology for a stage IVB diffuse B-cell lymphoma with an International Prognostic Index Score of 3. Eight cycles of standard immunochemotherapy with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone (R-CHOP) and intrathecal injection of methotrexate for the first three cycles were administered. This resulted in a complete metabolic remission on positron emission tomography-restaging after four cycles and at the end of the treatment.

Four months after completing therapy, the patient was hospitalized for neurological symptoms including confusion, ataxia and a cerebellar syndrome, without fever. Computed tomography brain scan was normal. Cerebrospinal fluid (CSF) examination showed $0{\cdot}039 \times 10^9$ leucocytes/l with 49% lymphocytes, elevated proteins at 0·591 g/l and normal glucose. There was no evidence of cerebro-meningeal infiltration by the lymphoma based on cytology, immunophenotyping and molecular analyses of the CSF. Microbiological cultures of the CSF were negative. Cryptococcal antigen was not present. Qualitative and quantitative Polymerase Chain Reaction (PCR) did not detect Aspergillus, cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zona virus (VZV), JC polyoma virus, enterovirus, toxoplasma, or borrelia burgdorferri. Because of a positive serology for HSV-1 (very high titre of IgG and complement fixation), she was treated with intravenous acyclovir (10 mg/kg tid) for 14 d. She partially recovered and was discharged from the hospital.

Two months later, she was hospitalized twice for persistent neurological symptoms including confusion, ataxia, cerebellar syndrome and dysphasia. A brain magnetic resonance imaging (MRI) scan showed tiny T2 hyperintense lesions in the periventricular and subcortical regions (Fig 1). An electroencephalogram confirmed a diffuse encephalopathy. Repeated lumbar punctures showed elevated leucocyte count and proteinorachy. This time, enterovirus RNA was detected in the CSF by Reverse Transcription (RT)-PCR. This was confirmed on a second sample taken few days later. Our patient was thus diagnosed with an enterovirus-associated encephalitis occurring after immunosuppressive treatment with Rituximab. She was treated with intravenous immunoglobulins (IVIg) (0·5 g/kg once a month), which resulted in a marked neurological improvement.

Our case illustrates that the diagnosis of enterovirus-induced meningoencephalitis is often difficult to make. Clinical symptoms and radiological abnormalities are not specific. The MRI scan of the brain may be normal early in the course of infection, particularly in immunocompromized patients in whom host responses can be reduced and delayed (Ganjoo *et al*, 2009). The diagnosis can be made by demonstrating the presence of enteroviral RNA by RT-PCR in CSF or in neurosurgical biopsies. The virus can also be looked for in stool, respiratory tract or blood samples.

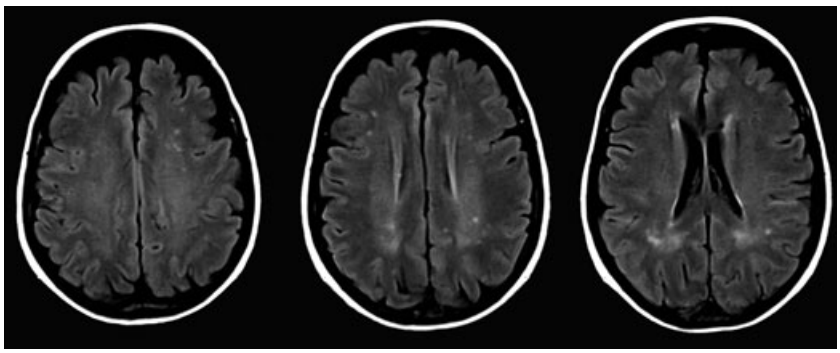

Fig 1. MRI T2 Flair – Tiny T2 hyperintense lesions in the periventricular and subcortical regions.

There are only five reported cases of enteroviral meningoencephalitis following Rituximab therapy (Table I). Four of the five patients were treated with Rituximab for lymphoma and the remaining patient for idiopathic thrombocytopenic purpura. In all cases, Rituximab was associated with immunosuppressive or cytotoxic drugs and three patients had also received an autologous stem cell transplant. The time between Rituximab treatment and neurological manifestations was variable in each case, ranging from symptoms appearing during therapy to 11 months after completion.

In contrast with other viral infections, enterovirus infection is controlled mainly by neutralizing antibodies (Padate & Keidan, 2006). The first cases of enteroviral meningoencephalitis were reported in patients suffering from congenital

Table I. Cases of Rituximab-associated enterovirus meningoencephalitis reported in the literature.

	Underlying disease and prior treatment	Delay between Rituximab and symptoms	MRI	IgG at the time of enterovirus diagnosis	Treatment and outcome
Case 1 (Quartier *et al*, 2003)	Immune thrombocytopenic purpura, treated by ASCT, Rituximab, Prednisolone and Dapsone	11 months	Diffuse white matter abnormalities	3·2g/l (N: 5·4–16·1 g/l)	High dose IVIg and pleconaril. Clinical improvement with residual learning and behavioural disabilities
Case 2 (Archimbaud *et al*, 2003; Quartier *et al*, 2003)	Follicular lymphoma, treated by cyclophosphamide, adriamycin, teniposide, prednisone, IFN-α and rituximab at relapse	6 months	Asymmetrical signal enhancement of the right parietal meninges and myelitis	5·5 g/l (N: 5·4–16·1 g/l)	High dose IVIg and pleconaril. Clinical improvement
Case 3 (Padate & Keidan, 2006)	Waldenström macroglobulinaemia with transformation into DLBCL, treated by Radiotherapy, Fludarabine and R-CHOP	7 months	NR	3·6 g/l (N: 6–13 g/l)	Ganciclovir, acyclovir and high-dose IVIg. Slow neurological recovery, but death due to intercurrent infection
Case 4 (Ganjoo *et al*, 2009)	DLBCL, treated by R-CHOP, ASCT and R-ICE at relapse	NR	Diffuse lesions in cerebellum, thalami and basal ganglia	4·2 g/l (N: NR)	High-dose IVIg. Death due to relapse of lymphoma
Case 5 (Kiani-Alikhan *et al*, 2009)	DLBCL, treated by R-CHOP and IT MTX	During treatment	Enhanced signals in the posterior part of the left temporal lobe	NR	High-dose IVIg Neurological deterioration and death.
Case 6 Our case	DLBCL, treated by R-CHOP and IT MTX	4 months	Tiny lesions in the periventricular and subcortical regions	7·37 g/l (N: 6·80–14·45 g/l)	High-dose IVIg Neurological improvement

MRI, magnetic resonance imaging; ASCT, autologous stem cell transplantation; IVig, intravenous immunoglobulins; IFN-α, alpha interféron; DLBCL, diffuse large B-cell lymphoma; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone; NR, not reported; R-ICE: Rituximab-ifosfamide, carboplatin and etoposide; IT MTX, intrathecal administration of methotrexate.

agammaglobulinaemia (Quartier *et al*, 2000). Rituximab is a chimeric anti-CD20 monoclonal antibody. Its administration leads to profound B-cell lymphopenia and long-lasting antibody deficiency for 6–12 months. However, a reduced level of IgG could only be found in three of the five cases reported (cases 1, 3 and 4 in Table I). In our patient, IgG levels were at the lower end of the normal range.

IVigs are the only option that is currently available for the treatment of enteroviral meningoencephalitis. IVigs contain neutralizing antibodies directed against commons serotypes of enterovirus (Cheng *et al*, 2008). This treatment has been reported to be efficious in congenital agammaglobulinaemia, but responses are variable and a consensus on dosage and duration of treatment is lacking (Cheng *et al*, 2008; Quartier *et al*, 2000; Webster, 2005). Two of the patients with Rituximab-associated enterovirus encephalitis also received pleconaril, an anti-enteroviral agent. This drug is no longer available (Webster, 2005). Monotherapy with IVIg failed to improve the outcome in three patients.

Rituximab is now recognized as a standard agent in the treatment for B-cell lymphoma and its use expands to a number of other diseases. It is usually well tolerated. Nevertheless, severe neurological infectious complications have been recently reported. Progressive multifocal leucoencephalopathy due to JC polyoma virus after Rituximab therapy is a well described complication. It is now suggested that enteroviral meningoencephalitis can also occur after this type of treatment. Hence, we would draw attention to this potential harmful and life-threatening complication of this widely used therapy. Enteroviral RNA should be looked for in CSF samples of patients presenting with neurological symptoms after anti-CD20 therapy and early treatment with IVIg is recommended.

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