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CASE REPORT

Enteroviral encephalitis in a patient with a marginal zone lymphoma treated with rituximab

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ABSTRACT

A 64-year-old woman with a progressive marginal zone lymphoma for which she had received induction therapy with six courses of rituximab and fludarabine presented with fever while receiving maintenance therapy with rituximab. In addition to the fever she complained of nausea, vomiting, weight loss and fatigue. After an extensive diagnostic procedure no cause was found for the fever. Finally, additional testing showed a positive polymerase chain reaction (PCR) for enterovirus in the cerebrospinal fluid and faeces. Because the immunoglobulin G level of our patient was 4.06 g/l (normal values 5.2 to 16 g/l), she was treated with intravenous immunoglobulins (IVIg) weekly with the goal to maintain an IgG level above 10 g/l. This resulted in a significant rise in anti-enteroviral antibodies from 10 IE/ml to 106 IE/ml. One month after treatment with IVIg, while withholding the rituximab, the PCR for enterovirus on faeces was negative and antibodies to the enterovirus in the serum had returned to normal levels. Rituximab can cause a prolonged B-cell deficiency resulting in hypogammaglobulinaemia. We believe that treatment with ritxumab may have played a significant role in the development of this rare central nervous system infection.

What was known on this topic?
Rituximab can induce a long-lasting depletion of B cells which results in hypogammaglobulinaemia. Several case reports describe severe opportunistic infections in patients treated with rituximab in combination with immunosuppressive agents or chemotherapy. Enteroviral encephalitis after treatment with rituximab has been described in several case reports before.

What does this add?
Rituximab is part of the standard therapy for patients with B-cell lymphomas and is usually well tolerated. However, rituximab can cause a prolonged B-cell deficiency. In this case report we describe a patient with enteroviral encephalitis after therapy with rituximab. We propose treatment with rituximab may have predisposed our patient. To our knowledge our patient is the first patient with enteroviral encephalitis to be successfully treated with intravenous immunoglobulins. With the increasing use of rituximab we recommend clinical awareness for enterovirus infections in these patients, if no other nonspecific signs can be found.

KEYWORDS

B cells, enteroviral encephalitis, hypogammaglobulinaemia, marginal zone lymphoma, rituximab

INTRODUCTION

Severe enteroviral infections are mainly observed in patients with congenital immunodeficiencies. Most viral infections are controlled by the cellular immune system. However, enteroviruses are generally controlled by neutralising antibodies. Rituximab is a chimeric anti-CD20 molecule and induces a long-lasting depletion of peripheral B cells which may result in hypogammaglobulinaemia. We describe a patient with marginal zone lymphoma and enteroviral encephalitis after treatment with rituximab.

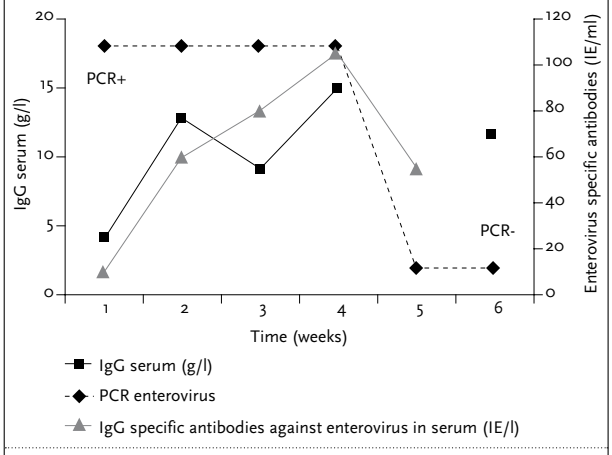
CASE REPORT

A 64-year-old female with a marginal zone lymphoma presented at our hospital with fever, nausea, vomiting, weight loss and fatigue. One month earlier she was admitted to the internal medicine department with fever caused by an upper respiratory infection. Her general medical history included extirpation of the uterus and a hemithyroidectomy. The haematological history noted a stage IV marginal zone lymphoma for which she had been treated three years before with eight cycles of R-CVP (rituximab 375 mg/m^2 day 1, cyclophosphamide 750 mg/m^2 day 1, vincristine 1.4 mg/m^2 day 1 and prednisone 40 mg/m^2 day 1-5) which resulted in a partial remission. Approximately 18 months before, the lymphoma became progressive and therefore our patient was treated with fludarabine (25 mg/m^2) and rituximab (375 mg/m^2) induction for six courses, followed by rituximab 375 mg/m^2 every three months as maintenance therapy for the next two years until one month before presentation. On admission, the patient received levothyroxin (0.125 mg/day), mirtazapin (30 mg/day), movicolon (2 sachets daily) and metoclopramide (10 mg in case of complaints of nausea). The patient was not in acute distress, her blood pressure was 98/59 mmHg, heart rate 109 beats/min and her temperature was 37.3 °C. At physical examination no abnormalities were found. During admission the patient's temperature varied between 37.3 and 40 °C. Laboratory findings revealed a haemoglobin of 8.4 mmol/l (7.5 to 10 mmol/l), a platelet count of 150 x 10^9/l (150 to 400 x 10^9/l) and a white blood cell count of 5.1 x 10^9/l (4.3 to 10 x 10^9/l) with lymphopenia of 0.5 x 10^9/l (1 to 4 x 10^9/l). Renal and liver functions were unremarkable. Our differential diagnosis included infection, progression of the lymphoma, autoimmune disease or drug fever. After admission a diagnostic procedure was performed. A chest-X-ray, an X-orthopantogram, MRI cerebrum and gastroscopy revealed no abnormalities. CT scanning of thorax and abdomen showed some pleural effusion but no other abnormalities pointing to residual marginal zone lymphoma. A PET scan was performed and showed an increased uptake of FDG in the thoracic region most probably due to local tension of the pectoral muscles. Besides depletion of B cells (2%), bone marrow investigation showed no signs of infection or recurrence of lymphoma. Cultures of urine and blood were repeatedly negative. Serological tests on Epstein-Barr virus (EBV), Cytomegalovirus (CMV), *Mycoplasma pneumoniae*, *Chlamydia trachomatis* and human immunodeficiency virus (HIV) revealed an EBV infection in the past. Because of persistent complaints of nausea and vomiting we also performed a cerebrospinal fluid puncture to exclude cerebral localisation of the lymphoma. The number of cells and protein was increased, further cytological investigation revealed pleiocytosis consisting of 90% of T cells, 0.3% of B cells and 9.7% of granulocytes. There was no evidence of marginal lymphoma cells. Extensive tests showed a positive polymerase chain reaction (PCR) for an enterovirus in the cerebrospinal fluid. The PCR for enterovirus was also positive on the patient's faeces. At that time, the immunoglobulin G of our patient was 4.06 g/l (5.2 to 16 g/l). She was treated with nonspecific intravenous immunoglobulins (40 g) once a week which resulted in an increase of specific antibodies against the enterovirus from 10 IE/ml to 106 IE/ml. The method used to measure enterovirus specific antibodies is a commercially available test from Serion Immundiagnostica & Institut Virion\ Serion GmbH, which is located in Würzburg, Germany (product number: Enterovirus IgG quantitativ (ESR133G)). Our goal was to keep the immunoglobulin G above 10 g/l (*figure 1*). Follow-up consisted of weekly PCRs on faeces and serological testing of the blood serum (*figure 1*). One month after starting treatment with IVIg the IgG level of our patient was normal and the enterovirus could no longer be found by PCR on the faeces. The level of antibodies against the virus in blood serum had returned to normal levels. She is still being treated with IVIg once monthly until one year after the last rituximab infusion. Clinically she is doing well without symptoms and no other signs of progression of the lymphoma.

DISCUSSION

To our knowledge we present the first patient with enteroviral encephalitis following treatment with rituximab

Figure 1.



The gray line represents IgG level in time. Treatment with intravenous immunoglobulins started on T=0 and was repeated weekly for the first month. The black line represents IgG specific enterovirus antibodies. After treatment with intravenous immunoglobulins enteroviral specific antibodies levels rise from 10 IE/ml to 106 IE/ml. The dotted line represents results of the weekly performed PCRs on the faeces. The patient is currently treated with IVIg monthly until one year after the last exposure to rituximab.

who has been successfully treated with IVIg. The human enteroviruses are classified into five sub-genera based on differences in host range and pathogenicity.[1] Enterovirus infection can occur in all age groups, although infections are mostly seen in infants and children. The virus is transmitted from person to person through ingestion of faecally contaminated material. Infection with an enterovirus can lead to a wide spectrum of clinical manifestations. More than 90% of the non-polio enteroviruses are asymptomatic or give undifferentiated fever.[2] Most viral infections are controlled by the cellular immune system. Enteroviruses, however, cause an infection that is controlled mainly by neutralising antibodies. Severe enterovirus infections have been described in patients with hereditary or acquired defects in B-lymphocyte function (X-linked agammaglobulinaemia, common variable immunodeficiency).[3] The enteroviruses can cause persistent central nervous infections in these patients. Clinical symptoms in immunocompromised patients can be mild or even absent and include headache, lethargy, papilloedema, seizure disorders, motor weakness, tremors and ataxia. Symptoms can fluctuate in severity, they can progress or disappear.

Since the beginning of the 1980s, patients with congenital agammaglobulinaemias are treated with intravenous immunoglobulins (IVIg). This treatment appears to prevent chronic enterovirus infections.[4] Successful treatment with IVIg in hypogammaglobulinaemic patients with enteroviral meningoencephalitis has been reported.[4,5] Several case reports describe the occurrence of meningoencephalitis following treatment with rituximab.[6-11] Rituximab is a chimeric anti-CD 20 molecule and induces a rapid and long-lasting depletion of the peripheral B-cell pool, which can last for up to 24 months.[8] Padate *et al.* describe a case of enteroviral meningo-encephalitis in a patient with non-Hodgkin's lymphoma after therapy with rituximab.[6] This patient was treated with IVIg weekly to maintain immunoglobulin G at 10 g/l. At first the patient responded symptomatically; unfortunately, his neurological situation deteriorated and the patient died.[6]

Rituximab is usually well tolerated and is part of the standard therapeutic regimen in most B-cell lymphomas.[12,13] However, several case reports have documented severe and opportunistic infections in patients treated with rituximab combined with chemotherapy or immunosuppressive agents.[6,8,14,15] One of these opportunistic infections may be an enterovirus infection. This infection may be accompanied by nonspecific signs such as fever, lethargy and fatigue. Because enterovirus infections are usually encountered in adults who lack B cells and because the pleiocytosis of the cerebrospinal fluid consisted mainly of T cells we do not think that the pretreatment with fludarabine was causative for the enterovirus infection. We propose that hypogammaglobulinaemia due to rituximab predisposed our patient for developing enteroviral encephalitis. With the increasing use of rituximab we therefore recommend screening for enterovirus infections in these patients, if no other nonspecific signs can be found.

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