Mild encephalopathy with a reversible splenial lesion syndrome (MERS) Is this a new side effect of Rituximab?

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March 07, 2024

Abstract

Mild encephalitis/encephalopathy with a reversible splenial lesion syndrome (MERS) is a rare clinico-radiological entity. Its occurrence after Rituximab (RTX) has never been described. We report the first case of MERS following RTX in a patient treated for IgG4 related disease (IgG4-RD). It was about a 33-year-old patient diagnosed since 2017, with an IgG4-RD. This diagnosis was made in front of a prolonged fever, sicca syndrome, hepatic damage and renal pseudotumor associated to a high level of IGg4 at 2.8 g/l with suggestive renal histology. The patient was treated with corticosteroid therapy with persistence of renal impairment and nephrotic syndrome that's why RTX has been indicated. The patient received his first dose of RTX and presented few hours after, neurological and respiratory impairments. An infectious investigation comprising a SARS CoV-2 PCR and viral PCRs (VZV, Herpes and CMV) on cerebrospinal fluid (CSF) were negative. The HBV, HCV, HIV, Parvo B19, CMV, EBV, Herpes, Mycoplasma and syphilis serologies as well as Legionella antigenuria were also negative. The patient had received methylprednisone boli, intravenous immunoglobulin's associated with sodium valproate with good evolution. The diagnosis of MERS induced by RTX is likely. However the viral aetiology is not excluded.

Introduction

Mild encephalitis/encephalopathy with a reversible splenial lesion syndrome (MERS) is a rare clinical-radiological syndrome. It was first identified by Carlos Garcia-Monco **[1]** in 2011. The most common neurological symptoms are behavioral changes, altered consciousness and seizures **[2].** The diagnosis is based on Brain magnetic resonance imagings (MRIs) showing a transient anomalies mainly in the corpus callosum or sometimes extending to adjacent parenchyma **[1].** This syndrome mostly recovers without treatment **[1].** Biotherapy was reported to be efficient in MERS in some cases. **[3, 4]** This syndrome was reported in patients with viral infections, particularly rotavirus, herpes simplex virus, adenovirus, coxsackie virus, echoviruses, mumps, influenza A/B virus, and recently SARS CoV-2 **[5-12].** In few cases MERS was induced by some drugs such ipilimumab **[13]** and mumps vaccination **[14].** Here, we describe an original case of MERS appearing few hours after RTX treatment in a patient with IgG4-RD.

Case report

It was about a 33-year-old man followed since 2017 for IgG4 related disease. The diagnosis was retained in front of glandular involvement with xerostomia and xerophtalmia, hypergammaglobulinemia at 28g/L with IgG level at 23g/L and IGg4 level at 2.9 g/L, hepatic involvement with cytolysis, cholestasis and positive anti smooth muscles antibodies (ASMA). Radiologic findings were highly suggestive of malignancy. Therefore, the patient underwent right nephrectomy with the presence of IgG4 at direct immunofluorescence technique (DIFT) at the histology.

The patient was treated by corticosteroid therapy at a dose of 0.6 mg/kg/day for 2 months then progressive decrease with improvement in glandular and hepatic involvement. Six months after treatment initiation, the patient exhibited an edema of the lower limbs with hematuria. Biological tests showed proteinuria at 15 ng/24H with a creatinine value at 413µmol/l. Thus, an impure nephrotic syndrome was retained and the patient was prescribed RTX as this complication was thought to be a corticosteroid-resistant IgG4-RD manifestation.

The patient was hospitalized to receive RTX cure. On admission, his temperature was 37°C without obvious infectious foci. The pre-therapeutic assessment had shown a CRP at 14 IU, an ESR at 2min, the absence of hyperleukocytosis, negative SARSCoV-2 PCR and sterile ECBU culture. The Natremia was normal at 142mmol/l and the AANs were negative. The chest scanner was without abnormalities.

The patient received his first RTX cure at a dose of 1g. During the course of this later treatment, he manifested a headach. Pressure blood measurement showed a hypertensive peak at 150/80mmHg which regressed spontaneously. Six hours after the end of the treatment, the patient described paresthesias in the left lower limb with ataxia on walking. He presented also, a fever peak at 40°C with a rapid alteration of consciousness, a state of confusion, vomiting with myoclonus and tremulation without motor or sensory deficit and with normal osteotendinous reflexes. The patient became polypneic at 28cycles per minute with crackling rales at lung bases.

A lumbar puncture was performed showing a clear fluid, presence of 100 white elements with 94 lymphocytes, proteinorrachia at 0.8g/L with normal glycorrhachia at 4mmol/l.

Two hours later he presented a status epilepticus requiring intensive care with intubation and mechanical ventilation. A cerebral angio-MRI was performed showing high signal intensity on T2 weightned images and diffusion weighted images **(figure 1).**

A second SARSCoV-2 PCR was done and was negative. Viral and bacterial multiplex PCRs on cerebrospinal fluid were negative. The infectious tests (HBV, HCV, HIV, Parvo B19, CMV, EBV, Herpes, Mycoplasma and syphilis serologies as well as Legionella antigenuria) were negative. ECBU and blood culture test are steriles.

The patient received a bolus of methylprednisone (15mg/Kg/day) for 3 days with intravenous immunoglobulin cures associated with sodium valproate and he was extubated 48 hours later with a calm awakening and a gradual recovery of his state of consciousness. The diagnosis of MERS induced by RTX was most likely.

Discussion

We reported herein the first case of MERS occurding after RTX. This diagnosis was retained in front of multiple symptoms appeared post treatment and suggestive neurologic radiologic anomalies.

MERS is characterized by a reversible lesion with homogenously reduced diffusion in the corpus callosum. It usually develops in children between the ages of 0 and 16 years and occasionally in adults

[15].

The clinical symptoms of MERS syndrome are nonspecific and diverse. The most common manifestation is fever which was the prodromal symptom in our patient **[16].** Fever may precede or accompanies neurological symptoms. Other general clinical symptoms including headache and digestive tract disturbances (vomiting and diarrhea)**[10, 17]** have been also reported. Consciousness disturbance, seizures, behavior changes, drowsiness, confusion, acute urinary retention, and delirium may also be the common neurological symptoms associated with MERS **[10; 18, 19, 20].** In our case, gastro-intestinal involvement and consciousness disturbance were predominant.

Typically, MRI features show reversible hyperintense signals on T2- weighted images, fluid-attenuated inversion recovery images (FLAIR), and diffusion-weighted images (DWI) in the splenium of the corpus callosum (SCC) (classified in MERS type I) **[16].** Sometimes, radiologic abnomalies can extend to other areas of the

corpus callosum and adjacent periventricular white matter in a symmetrical pattern (classified in MERS type II). Our patient was a MERS type II case.

Yuan et al, in their review reported that the total of 29 patients recovered completely within a month **[6, 19].** In rare cases, patients, especially those with type II lesions on MRI, may develop neurological sequelae and lesions may persist on MRI for months even if their size diminishes **[21].**

Several mechanisms have been proposed for the pathogenesis of MERS but this is still unclear. There are several hypotheses, including intramyelinic edema **[18],** hyponatemia **[17],**and oxidative stress **[22],** neuroaxonal damage**[23],** autoimmune processes **[24],** and cytotoxic edema **[25].** The possible explanation for this is intramyelinic edema resulting from separation of myelin layers**[26, 27]** and local infiltration of inflammatory cells

[17, 18].

Moreover, most cases of reversible lesions demonstrate the evidence that cytotoxic edema of the SCC is an important mechanism in this syndrome**[28].** Miyata R et al **[16],** reported that patients with MERS has an elevated IL-6 and IL-10 levels in CSF. Cytotoxic edema in the neurons, astrocytes, and oligodendrocytes of the SCC, caused by cytokines, may offer the best explanation. Recently, these lesions have been called cytotoxic lesions of the corpus callosum or CLOCC lesions **[28, 29].** This could explain the elevated white cells in the CSF as it is the case of our patient. A recent review study **[19]** found that more than half (15/23) cases had elevated white cells in the CSF. Even if we take all these hypotheses into account, MERS still be a rare syndrome with unclear pathogenesis and none of the existing hypotheses may explain why MERS specially involves the site splenium.

In addition, serum sodium levels were significantly lower in patients with MERS than in age matched controls. These data support the hypothesis that a transient cerebral edema may develop as a result of hyponatremia **[17].**

RTX is a murine/human-chimeric monoclonal antibody that depletes CD20+ B cells through both cell-mediated and complement mediated cytotoxic effects **[30].** It is widely used in malignancy and immune-mediated diseases in combination with corticosteroids and other immunosuppressive drugs.

RTX is also effective for both induction therapy and treatment of relapses in IgG4-RD specially in nephrologic flare refractory to corticosteroids **[31].** Its administration rarely causes serious neurologic adverse events. However, it was reported to lead to complement activation, cell lysis and subsequent massive release of cytokines, culminating in cytokine release syndrome and systemic inflammatory response syndrome **[32-35].** This could, in part, explain the early development of MERS after rituximab in our patient. But MERS induced by Rituximab has never been reported before.

However, Posterior reversible encephalopathy syndrome (PRES), which may be a differential diagnoses for MERS, has been reported to be related to RTX **[3].**

PRES is a rare clinical disorder which has nearly clinical symptoms to MERS. It manifests also with headache, convulsions, altered level of consciousness and reversible cerebral edema. It is also a reversible disorder that requires rapid diagnosis by demonstrating the presence of characteristic vasogenic edema on brain MRI in the appropriate clinical context [36, 37].

Progressive multifocal leukoencephalopathy (LEMP) after RTX, which is a rare opportunistic infection due to reactivation of JC virus into the central nervous system, is described **[38].**

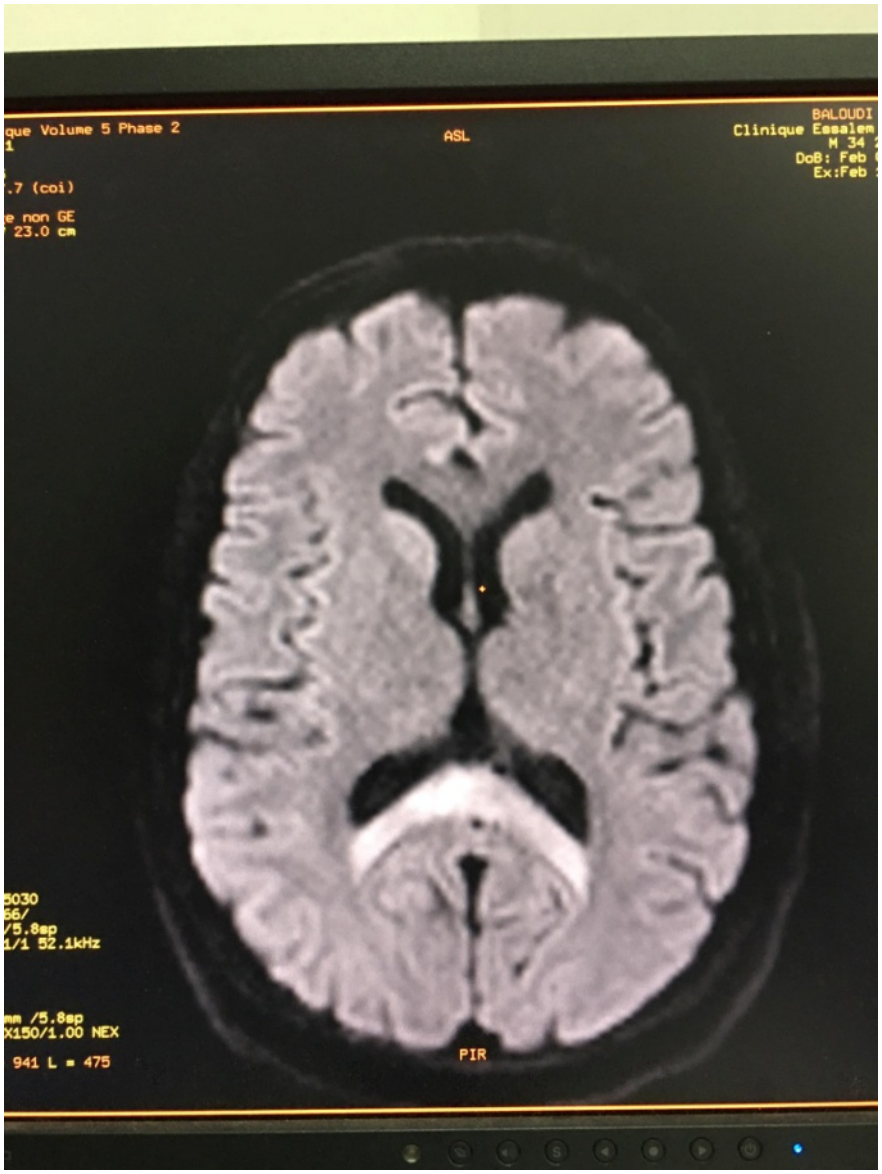
Acute disseminated encephalomyelitis (ADEM) is being the main differential radiologic diagnosis of MERS **[39]** but RTX is effective for this disease **[40].**

The neurological manifestations presented by the patient cannot also be related to his underlying disease. IgG4-related disease can involve nearly any organ system, including the central and peripheral nervous systems but MERS has never been reported **[41].**

Furthermore, MERS is a rare disease and evidence on the therapeutic approaches is currently not yet available. Methylprednisolone pulse therapy and IVIG were prescribed in MERS patients without any evidence of efficacy of these treatments. However, many patients without methylprednisolone pulse therapy or IVIG recovered clinically completely, which suggests that those treatments may not be necessary **[42].** Our patient was treated by methylprednisolone pulse therapy and IVIG as we had a severe neurological involvement and we were face an auto immune disease (IgG4-RD).

Conclusion

We reported a case of an adult onset MERS after RTX cure. Taken together with the previously reported cases, we suggest that MERS in adults is an entity with a broad clinico-radiological spectrum and the prognosis is good. The early recognition of MERS can avoid unnecessary treatments and provide reassurance about good outcomes.



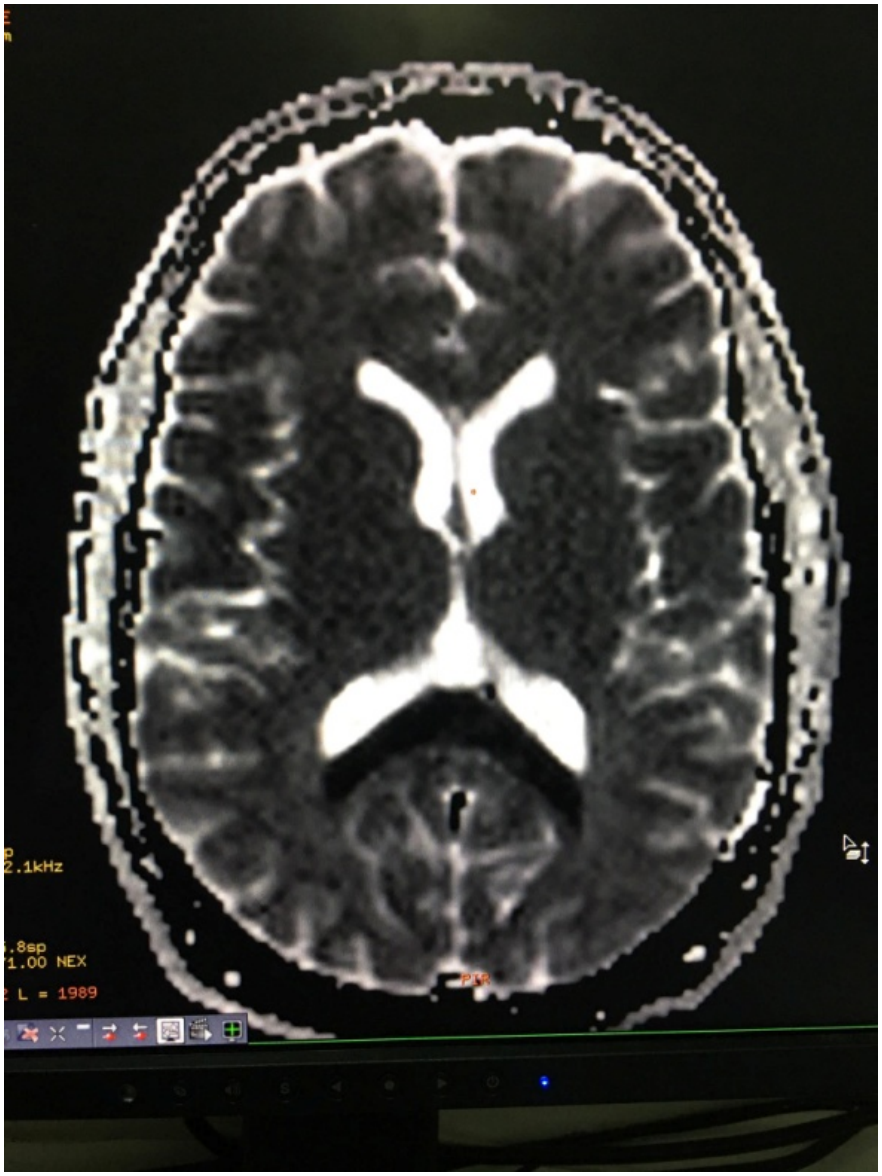


Figure 1: A cerebral angio-MRI was performed showing high signal intensity on T2 weightned images and diffusion weighted images.

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