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Posterior Reversible Encephalopathy Syndrome after a First Injection of Cyclophosphamide: A Case Report

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Abstract

Posterior reversible encephalopathy syndrome is a clinical radiological syndrome, characterized by acute headache, altered consciousness, seizures and hypertension. The most frequent causes are hypertensive encephalopathy, eclampsia and some immunosuppressive therapies. Here, we describe a 75-year-old man with high blood pressure and anti-neutrophil cytoplasmic antibody associated vasculitis with crescentic glomerulonephritis who was treated with cyclophosphamide bolus and corticoids. Symptoms of posterior reversible encephalopathy syndrome have appeared during a hypertensive crisis, 3 days after cyclophosphamide infusion. Cyclophosphamide was stopped and rituximab therapy introduced. The patient recovered promptly. There are only a few reports of posterior reversible encephalopathy syndrome where cyclophosphamide is the only one culprit and they all concern patients with renal disease.

Keywords

Posterior reversible encephalopathy syndrome; Cyclophosphamide; Adverse effect; Renal disease

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinical radiological syndrome which could be induced by pre-eclampsia, transplantation, autoimmune disease (systemic lupus erythematosus, Wegener's granulomatosis, systemic sclerosis), abrupt arterial hypertension (which is probably one of the most important), impaired renal function or drugs (anticalcineurin, chemotherapie) [1-5]. Some atypical cases were also reported in a weightlifter patient after an intensive gym session or as a rare association with a polyarteritis nodosa [6,7]. Renal disease seems to be a risk factor of PRES, as seen in many case reports of PRES in patients, in particular in pediatric population, with acute glomerulonephritis, lupus nephritis or, nephrotic syndrome or small vessel vasculitis [8-10].

Furthermore, although PRES has been commonly associated with chemotherapies (e.g. CHOP) [11], there are only a few reports of PRES where CYC is the only one culprit. We presented here a case of PRES appearing after a first infusion of CYC injection in a patient with crescentic glomerulonephritis.

Case Presentation

A 75-year-old French man presented in hospital on June 26th 2013 for general weakness, myalgia, inflammation and fever. He had no medical history apart from hyperlipidemia treated with statin. His bodyweight was 64 kg. Renal function was normal (85 µmol/l) in early June, and creatininemia was 105 µmol/l at entry. The patient then developed a rapidly progressive glomerulonephritis (creatininemia was 212 µmol/l on July 05th) associated with ANCA positivity. The patient was initially treated with corticoids (prednisone 1 mg/kg on the July 4th and three methylprednisolone bolus (500 mg) on the July 9th, 10th, and 11th) and he received a first intravenous injection of 500 mg cyclophosphamide (CYC-Endoxan®) on July 12th. Renal biopsy confirmed the diagnosis of anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis with crescentic glomerulonephritis. An atrial fibrillation was also diagnosed on July 9th (day of biopsy). Sinus rhythm was restored with amiodarone loading dose and no anticoagulation was introduced due to recent renal biopsy puncture. Atrial fibrillation resumed on 12th and low dose calcium heparin was introduced because of recent renal biopsy. Amiodarone was given again, but atrial fibrillation remained. No trans-esophageal echocardiography was performed. On July 15th (3 days after CYC infusion), the patient presented a generalized tonico-clonic seizure and a right-sided hemibody motor deficit. A moderate hypertension was noted (164/91 mmHg) comparative to early July (128/69 mmHg on July 2nd). There was no neurological harbinger (headache, visual disturbance, confusion). He was transferred in Neurologic Intensive Care Unit for 3 days. On clinical examination, the patient had a blurred vision, psycho-motor slowdown, right hemiparesis without language disturbance and ataxia of the left hemibody.

The MRI examination showed multiple bilateral deep cerebral infarctions (MCA territory) and images consistent with posterior reversible encephalopathy syndrome (PRES) with widespread abnormalities in the white matter of left parietal region and cerebellar hemispheres (Figure 1). There was no argument for a cerebral vasculitis. Blood cultures were negative. There was no urinary tract infection. Lumbar puncture contained 2 nucleated elements, normal glucose, and CSF proteins were 0.5 g/l, 93 red blood cells and no germ on direct examination. The electroencephalogram (EEG) showed nonspecific diffuse slow waves. Levetiracetam was given (250

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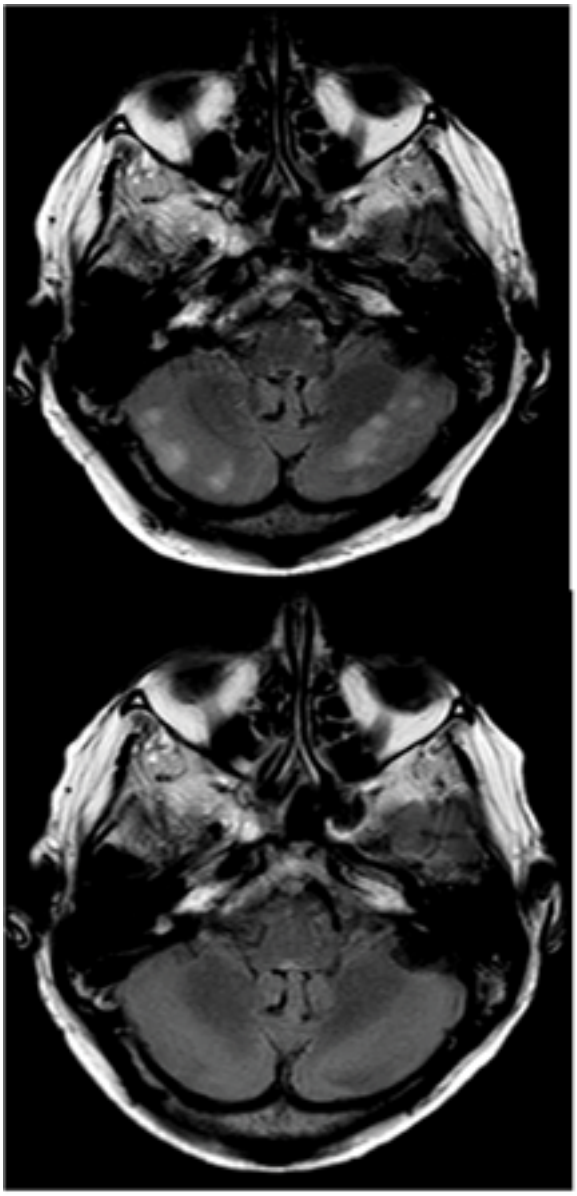

Figure 1: MRI (fluid attenuated inversion recovery): acute cerebellar vasogenic oedema involving bilateral temporo occipital and cerebellar regions consistent with PRES.

mg twice a day) for 2 days and anticoagulation was increased. Of note because of high blood pressure (174/85 mmHg), amlodipine was started on July 10th. On 15th, urapidil was added, and furthermore nebivolol was introduced on 19th.

The CYC was suspected to induce the PRES and not re-administrated. The MRI control on July 24th showed regression of PRES related lesions (Figure 2). Compared with previous MRI, no new ischemic lesion was noted. Rituximab (653 mg) was introduced 20 days after the CYC injection on August 1st and was well tolerated as well as the 3 following injections (August 8th, 14th and 21th). The patient recovered promptly: no other neurological sign was observed after the switch. Heart rate was regular and no atrial fibrillation recurrence was noted. He came home the day after the first Rituximab administration, on August 2nd.

Discussion

Pathophysiology of PRES remains uncertain but for [12] who described firstly in 1996 this syndrome, a breakdown of cerebral auto-regulation due to hypertensive encephalopathy is evoked, leading to disruption of the blood-brain barrier with fluid transudation and hemorrhages [12]. Other authors observed PRES in infection, sepsis, shock, preeclampsia patients or in cytotoxic treated patients and suspected that circulating toxins vasospasm which causes a decrease in blood flow and subsequent ischemia leading to edema [13-16].

In our case, atrial fibrillation appeared simultaneously and could not be treated with anticoagulation immediately because of recent renal biopsy, but was responsible for ischemic cerebral infarctions at the same time. Explorations did not show any argument for an infection or an

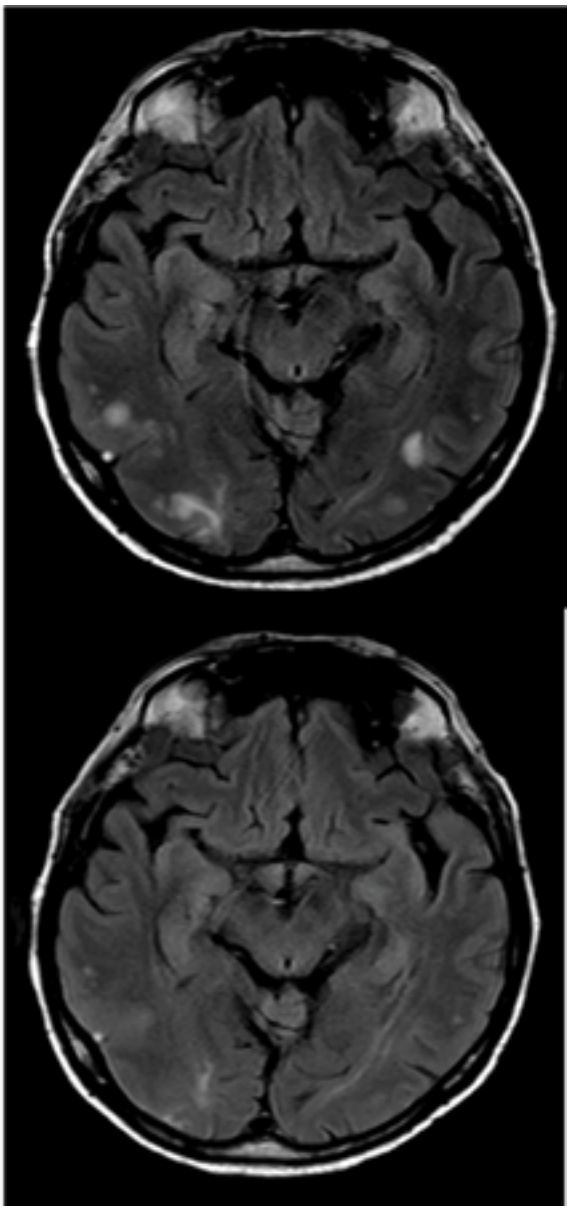

Figure 2: Follow up MRI at day 14 (fluid attenuated inversion recovery): dramatic reduction of vasogenic oedema with only persistence of a mild hypersignal of the right.

immune disease, especially a cerebral vasculitis. As regards drugs: PRES associated with amiodarone is not reported in literature. When the PRES appeared in 2013, literature search did not bring cases of PRES associated with corticoids only and it was not suspected, contrary to CYC. Furthermore, although some studies have suggested an interaction between corticoids and CYC, others had refuted it [1]. Currently, some authors described PRES appearing 3 and 4 days after starting pulse intravenous methylprednisolone (30 mg/kg/day for 3 or 5 days following case) in patients with autoimmune hemolytic anemia and systemic lupus erythematosus [17, 18].

In patients with renal failure, it appears that intravenous administration of CYC is associated with decrease plasma clearance of CYC, resulting in an increase of systemic drug exposure and an enhanced toxicity, notably hematological toxicity or infection [19]. Regarding the neurotoxicity of CYC, there are few descriptions in literature compared with others chemotherapies (5-fluorouracil, cisplatin, vincristine). Otherwise, pharmacokinetics of CYC's metabolites does not explain PRES occurrence: the metabolites had cytotoxic properties but crossed less easily the hemato-encephalic barrier and literature did not demonstrate their neurotoxicity [20]. Considering the drug etiology of PRES, in particular with chemotherapy, there are only a few reports of PRES where CYC is the only one culprit and they almost concern patients with renal disease. Compared with our case where PRES symptoms appeared three days after the first CYC infusion, in the cases of literature the time to onset were variable between two days and one month.

Recently, Jayaweera et al. described the case of a 33-year-old Sri Lanka woman with a childhood history of nephritic syndrome who was treated with methylprednisolone (15 mg/kg/day) for 3 days and 500 mg of intravenous CYC in front of active lupus nephritis diagnosis [21]. Two weeks later, she received a second dose of CYC in keeping with the treatment guidelines of the Euro-Lupus Nephritis Trial [22] which was complicated 4 hours after the end of the CYC infusion by PRES with recurrent generalized tonic-clonic seizures, loss of conscience (Glasgow coma scale 7/15) but normal blood pressure. Her level of consciousness and PRES symptoms promptly resolved under 48 hours.

Abenza-Abildua et al. described the case of a 27-year-old man with hypertension and glomerulonephritis caused by Goodpasture syndrome [23] treated with oral CYC (150 mg/day), prednisone (30 mg/day), calcium supplements and dialysis who presented a PRES one month after CYC introduction and resolved under 2 days with symptomatic treatment. Previously, Primavera et al. have described four other cases of PRES in patients, aged from 22 to 30-year-old treated by CYC for renal disease [24] (Wegener's granulomatosis or nephritis secondary to systemic lupus erythematosus). In the first case, the patient received 2 days of prednisone and 5 days of oral treatment by CYC (750 mg/day) for glomerulonephritis. In the second case, the patient received intravenous CYC (unknown dose). In the third case, the patient received 2 days of intravenous CYC (500 mg/per dose). All three patients presented a similar symptomatology with headache, recurrent seizures, visual blurring, altered mental function, high creatinine serum (between 320 and 840 µmol/l) and high blood pressure (up to 220/150 mmHg). PRES diagnosis was made respectively 11 days, 7 days and in the 2 days after the beginning of CYC. Neurological examination was normal, respectively, in 3, 4 and 10 days after the first signs. The fourth case appeared unusual since the patient had a previous history of 6 years CYC (dose unknown) treatment for lupus nephritis secondary to SLE before her PRES diagnosis.

Jenanne et al. succinctly described a case of PRES which occurred 23 days after conditioning with fludarabine and CYC in a 17-year-old girl with chronic myeloid leukemia that transformed to acute myeloid leukemia who undergone a blood stem cell transplantation [25]. CYC which was over the therapeutic range was replaced by mycophenolate mofetil leading to a prompt resolution.

In summary, CYC is an established treatment in autoimmune nephropathy. His safety profile is well-known and do not include PRES. In our case, severe renal failure, systemic active vasculitis, high blood pressure and atrial fibrillation with ischemic cerebral infarctions may have contributed to cerebral damages and development of PRES, which may be the results of several physiopathologic events. But the 3 days onset time after CYC injection is consistent with other reported cases, and highly suggestive of its involvement. Literature does not allow confirming the hypothesis of a direct role of CYC or its metabolites in the onset of PRES. Contrary to CYC, the active CYC's metabolites do not penetrate into the brain and neurotoxicity is not expected nor described in literature. The corticoids may also contribute to the development of PRES and could not be totally excluded of the culprits.

Physicians should keep at mind this diagnostic that must be suspected in every patient, including in patient with autoimmune disease, treated with CYC in front of neurologic symptoms.

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