Case Report

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 that 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 present 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 creatinemia 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 methylpredisolone 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 antiocoagulation 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. Lvetiracetam was given (250

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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 21st). 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
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 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.

References

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