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Case Report

Posterior reversible encephalopathy syndrome and Wernicke encephalopathy in patient with acute graft-versus-host disease

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ABSTRACT

Graft-versus-host disease (GVHD) is an immune triggered process leading to severe immune dysregulation and organ dysfunction until death and it is one of the worst medical complications after a transplant. Patients with GVHD may have several neurological alterations: during this acute severe phase there is coexistence of various and nonspecific neurological symptoms. We are reporting a case of a 53 year old woman with severe GVHD after bone marrow transplant with acute neurological signs and symptoms. MRI study showed findings consistent with Posterior reversible encephalopathy syndrome and Wernicke encephalopathy.

Introduction

Graft-versus-host disease (GVHD) and graft failure are the most medically feared complications following bone marrow transplant. GVHD is an immune triggered process, leading to severe immune dysregulation and organ dysfunction; it is the second leading cause of death, after disease relapse, in patients undergoing Allogeneic Stem Cell Transplantation (ASCT) [1].

We describe the case of an adult patient, who underwent ASCT and 2 months later developed severe acute

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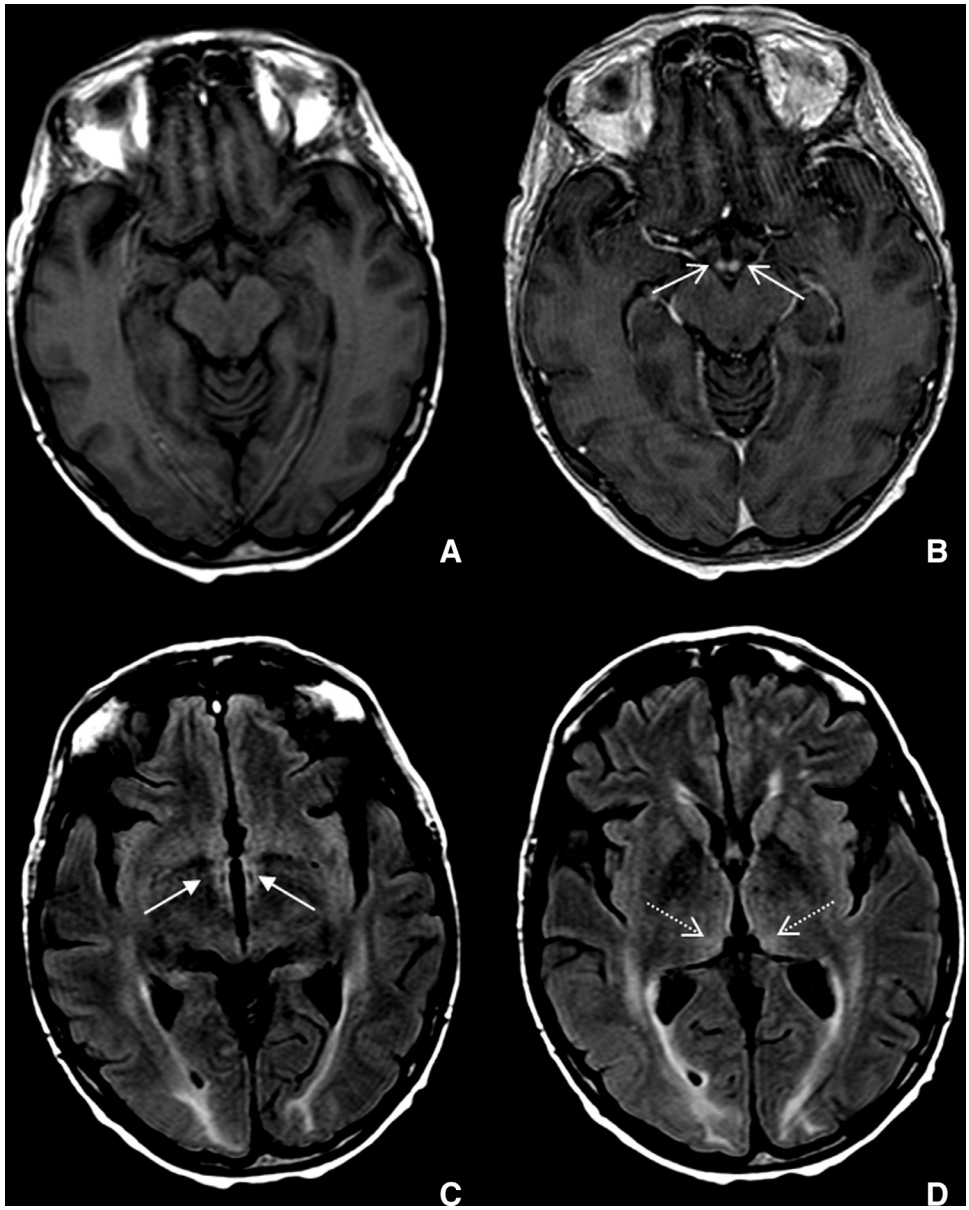

Fig. 1 – Wernicke Encephalopathy signs at MR examination. T1 Turbo Spin Eco (A) and T1 Fast Field Echo (B) after administration of gadolinium-based contrast agent, T2 FLAIR (C and D). To note the intense enhancing of mammillary bodies (open arrows in B) and the mild T2 hyperintensity to the gray matter around the third ventricle (close arrows in C) and in the thalamic pulvinar (dotted arrows in D).

GVHD with associated Posterior reversible encephalopathy syndrome (PRES) and Wernicke encephalopathy.

Case report

A 53-year-old woman, previously affected by acute lymphoid leukemia was treated with polychemotherapy and after 8 months she underwent to ASCT; prophylaxis therapy with Cyclosporine, Methotrexate, Basiliximab, Mycophenolate mofetil, and GCSF was performed to avoid GVHD.

Two months after the transplant, the patient went to the emergency room for extensive erythroderma, acholic stools, hyperchromic urine, hypertensive status, biliary vomiting (bilirubin: 20 mg/dL), and dyspnea.

Computed Tomography exam showed bilateral pleural effusion and calico-pyelic dilatation: diuretic and oxygen therapy were established.

The patient was confused and suffering from alternating drowsiness and psychomotor agitation, disorganized behavior, and seizures. Neurological examination documented spontaneous movements of the eyeballs and vertical nystagmus; no cranial nerves or side deficit were detected. The patient was in alteration of consciousness appearing lethargic. The EEG showed slow wave activity, with paroxysmal notes, in fronto-temporal regions in particular on the right side. For

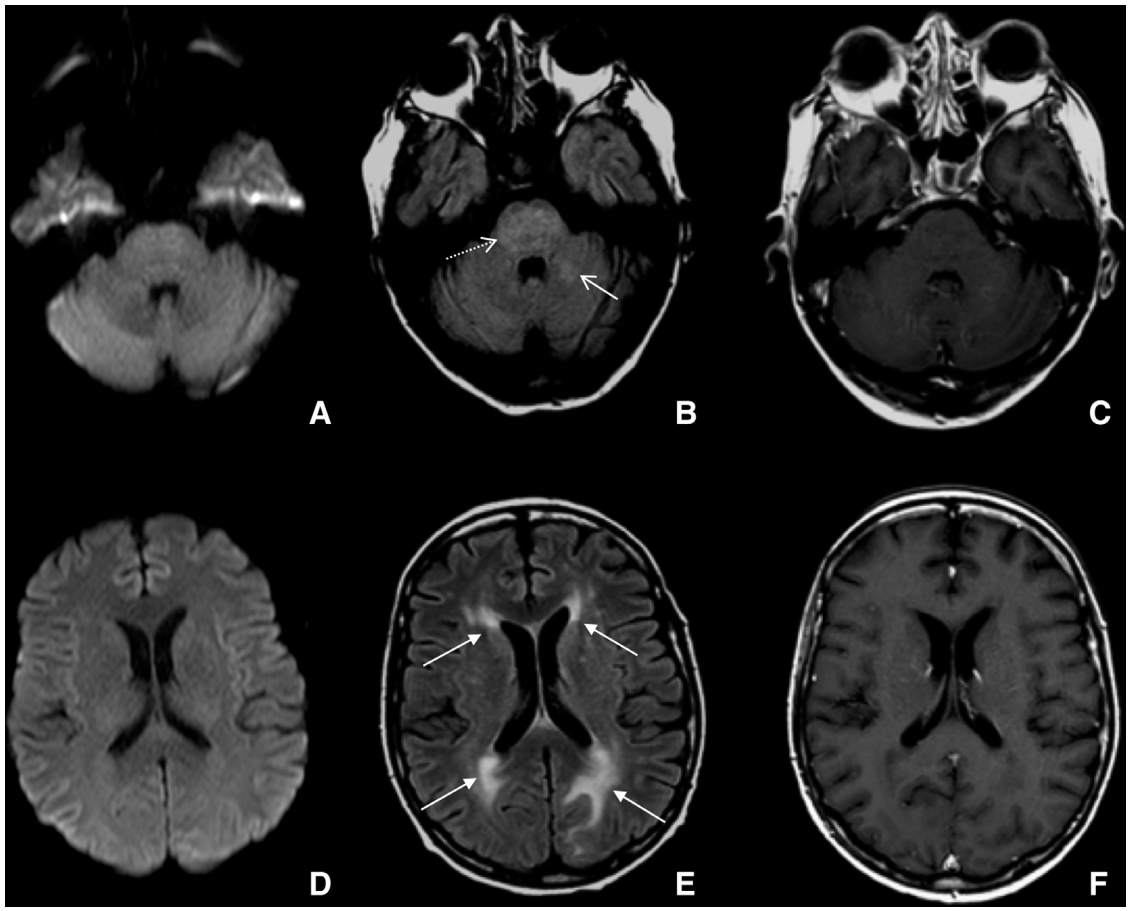

Fig. 2 – Posterior Reversible Encephalopathy Syndrome signs at MR examination. Diffusion weighted imaging (A and B), T2-FLAIR (C and D), T1 after administration gadolinium-based contrast agent (E and F). The exam showed T2-hyperintensity in the pons (short open arrow in C), left *brachium pontis* (long open arrow in C), and in the periventricular and subcortical white matter (close arrows in D). No enhancing or anomalies on the Diffusion Weighted Imaging were detected. These findings are highly suggestive for PRES.

these reasons brain magnetic resonance imaging (MRI) was planned.

The MRI showed T2 hyperintensities of subcortical parieto-occipital white matter bilaterally and in the left precentral frontal gyrus; involvement of deep white matter and infratentorial structures was also detected, in particular in pons with no enhancement after administration of contrast agent; Diffusion weighted imaging (DWI) showed no anomalies (Fig. 1). These findings, considering the patient's clinical features (hypertensive status and neurological alterations) and the administration of Cyclosporine, were suggestive for severe PRES with Superior Frontal Sulcus Pattern.

Moreover, MRI showed symmetric T2 and T2-FLAIR hyperintensity in the periaqueductal gray matter, around the third ventricle and in mammillary bodies with the latter characterized by marked enhancement after administration of gadolinium-based contrast enhancement (Fig. 2). The described MRI alterations, together to the gastrointestinal symptoms and mucositis related to polychemotherapy, as well as the blood level of thiamine was 30 nmol/L (normal value: 75-225 nmol/L), were consisted with Wernicke encephalopathy. Therefore, therapy with thiamine infusion (2000 u/die) was started. Furthermore, after the interruption of cyclosporine administration, the clinical signs of PRES gradually improved and, together with the simultaneous administration of thiamine, an improvement in neurological symptoms was observed. The above-mentioned signs and symptoms were therefore consistent with severe acute GVHD associated to PRES and Wernicke encephalopathy.

The follow-up MRI, performed 2 weeks after, showed reduction of T2-hyperintensities in the parieto-occipital lobes, in the left precentral frontal gyrus and in the deep white matter; however, the contrast enhancement of mammillary bodies persisted (Fig. 3).

Discussion

PRES was first described in 1996 by Hinchey et al.; it is characterized by headache, confusion, seizures, and visual loss and may occur in different etiologies but predominantly appears in malignant hypertension, eclampsia, and medical therapy [2]; moreover, PRES is quite common in patients

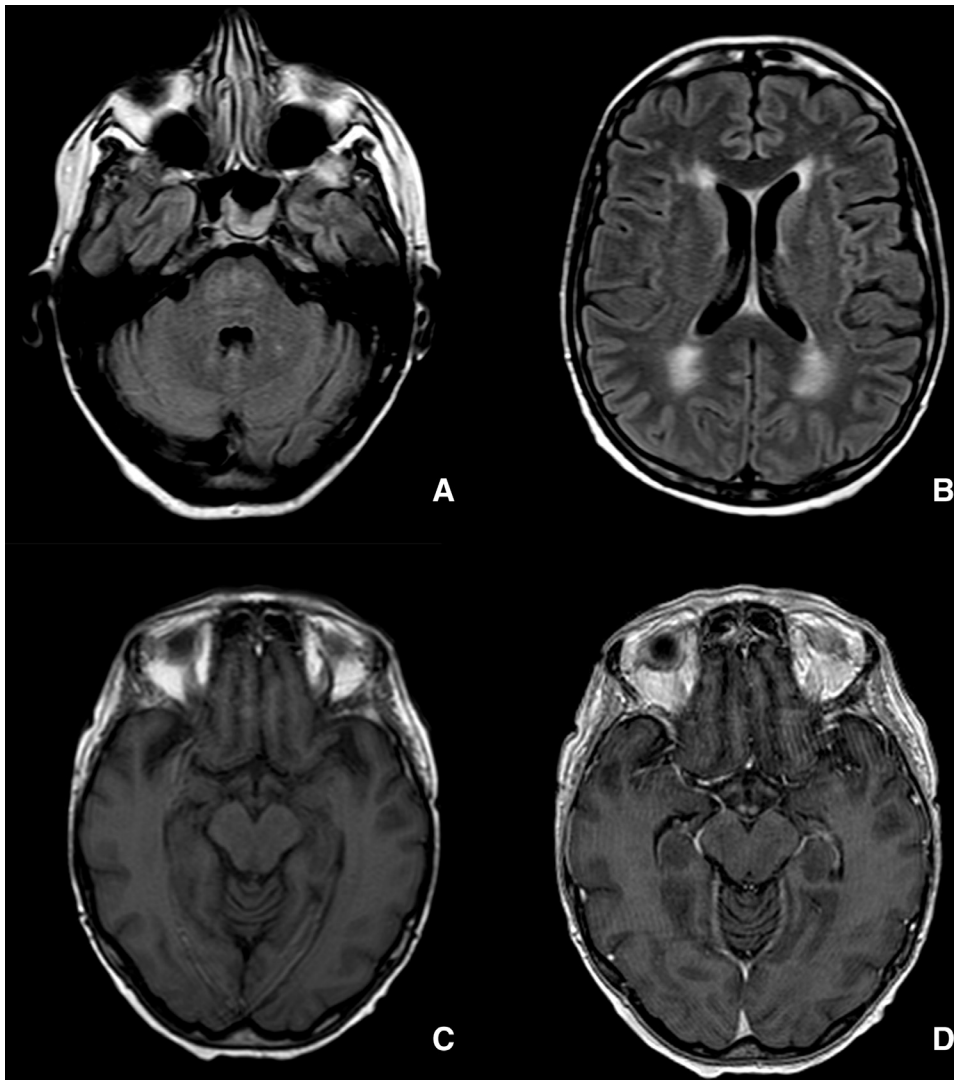

Fig. 3 – MRI at discharge. T2-FLAIR (A, B), T1 Turbo Spin Echo (C), and T1 Fast Field Echo on axial plane after gadolinium-based contrast agent administration (D). The MRI at discharge showed reduction of T2-hyperintensity of the parieto-occipital white matter while persisted the contrast enhancement of mammillary bodies.

treated with calcineurin inhibitors after hematopoietic stem cell transplantation [3,4]. PRES is a hypertensive encephalopathy which is related to inability of intracranial posterior circulation to autoregulate in response to acute changes in blood pressure.

Several theories have been proposed for PRES pathophysiology, but none of them has been fully confirmed: nowadays there are 2 widely accepted theories. The first is related to a failure of the cerebrovascular autoregulatory mechanism, with consequent vasodilatation, hyper-perfusion, and vasogenic brain edema. The second theory describes a "vasculopathy" pattern with consequent diffuse or focal vasospasms or even alternating the areas of vascular spasms and dilatation, and hypo-perfusion [5]. PRES is typically characterized by neurological symptoms as headache, visual disturbances, altered mental state, seizures, and hypertension.

The main radiological features of PRES with MRI are T2 hyperintensities in the subcortical parieto-occipital white matter, with involvement of basal ganglia, pons, and cerebellum, without restriction on DWI and variable patchy enhancement; however, atypical MRI patterns are common too.

Even though PRES is resolved with the treatment of the precipitating causes, in some cases PRES can progress until to permanent cerebral injury and neurological deficit, especially in patients with brain microbleeds and enhancement at MRI [3,6].

Other clinical conditions might have similar MRI findings. In particular, stroke, hypoglycemia, and the epilepticus status. Stroke and hypoxic conditions are characterized by the restriction of DWI and reduction of the apparent diffusion coefficient (ADC) related to the cytotoxic edema while PRES shows usually increased of ADC which reflect the underlying vasogenic edema [3,7]. Also, the hypoglycemic encephalopa-

thy is characterized by restricted diffusion and low ADC value but these alterations are in the cortex, basal ganglia, and hippocampi; rare is the involvement of the subcortical and deep white matter [8]. The loss of consciousness after status epilepticus have to be excluded; usually patients with status epilepticus showed transient unilateral gyral edema associated with increased representation of the specific arterial vector at MR angiographic images; quite common is the involvement of ipsilateral thalamus [9,10].

Wernicke encephalopathy is uncommon as severe neurological syndrome due to thiamine deficiency. It is characterized by sudden onset of altered consciousness, ophthalmoplegia, and ataxia; however, this classic clinical triad appears only in small cases, making this condition misdiagnosed. Wernicke encephalopathy prevalence comes mainly from autopsy studies with rates ranging between 1% and 3%, and this result shows that the diagnosis of Wernicke encephalopathy is often made only postmortem and less than 20% of the patients obtain the right diagnosis during life [11].

Thiamine is a coenzyme which plays a central role in neurons. Deficiency of thiamine lead to decreased levels of alpha-keto-glutarate, acetate, citrate, acetylcholine and accumulation of toxic intermediates (lactate and alanine), reduction in pH, and cerebral lactic acidosis [12].

The most common cause of thiamine deficiency is chronic alcohol abuse. Other conditions are malnutrition or decreased thiamine absorption after gastrointestinal surgical procedures (including gastric bypass surgery, gastrojejunostomy, gastrectomy, and colectomy), therapy with intragastric balloon, terminal tumor, chemical therapy, allogenic stem cell transplantation, AIDS, parenteral nutrition, hyperalimentation, prolonged intravenous glucose infusion, hyperemesis gravidarum, anorexia, hemodialysis, pancreatitis, wrong formula feeding as well as gastrointestinal mucositis [12]. The typical neuroradiological signs of acute Wernicke encephalopathy in MRI are T2 and T2 FLAIR bilateral and symmetrical hyperintensities occurring in gray matter area of CNS as mammillary bodies, anterior and medial nuclei of thalamus, periventricular gray matter, inferior and superior colliculi, and occasionally cerebellum. In these areas, the maintenance of cellular osmotic gradients is considered to be strictly related to thiamine levels [13]. Contrast enhancement can also be seen in the same regions, most commonly of the mammillary bodies.

The MRI of Wernicke encephalopathy may mimic the subacute necrotizing encephalomyelopathy (Leigh syndrome) which is a neurological syndrome occurring in children, characterized by psychomotor regression or delay, ataxia, ophthalmoplegia, and facial nerve disorders due to damage of mitochondrial DNA: however, even though the subacute necrotizing encephalomyelopathy affect mainly the periaqueductal grey matter, the brainstem and the putamen, the Leigh syndrome doesn't affect the mammillary bodies. Moreover, the Metronidazole-induced encephalopathy has similar MRI findings to the Wernicke encephalopathy but the first is associated with abnormal signal intensities in the dentate nuclei, vestibular, abducens, red nuclei, and splenium [14].

Wernicke encephalopathy prognosis is extremely variable from the complete remission to irreversible clinical manifestations: only prompt acknowledgment of clinical symptoms and radiological signs guarantees an early diagnosis allowing to start a prompt administration of thiamine. Often, clinical manifestations of Wernicke encephalopathy regress rapidly after the beginning of the therapy, even though residual deficits may persist; clinical progression cannot be excluded if treatment is not timely.

Conclusion

Our case confirms the usefulness of MRI in patients with acute GVHD and neurological signs. Due to the nonspecific neurological symptoms and/or simultaneous coexistence of various severe neurological syndromes, MRI is the most important and effective tool for early diagnosis allowing a prompt treatment to avoid irreversible brain damage.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2019.05.024.

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