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Case report

PRES-like leukoencephalopathy presenting with status epilepticus associated with Brentuximab Vedotin treatment

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Abstract. Posterior Reversible Encephalopathy Syndrome (PRES) is characterized by acute neurological symptoms with typical imaging features, primarily in the territories of the brain supplied by the posterior circulation, probably due to vasogenic edema. Both clinical and imaging features are generally reversible. We report a 13-year-old girl affected by Nodular Sclerosis Classical Hodgkin Lymphoma stage IIIB into complete remission, with a recurrence and autologous bone-marrow transplantation, who has been treated with an anti-CD30 monoclonal antibody, brentuximab-vedotin. The girl has suddenly presented a convulsive status epilepticus, that needed intubation and sedation. Therefore, an IV therapy with levetiracetam was started. Furthermore, the girl has presented high blood pressure and reduced kidney function. Brain MRI demonstrated a diffuse PRES-like disease, that went into regression after the first week. After another week, the girl presented a new prolonged generalized tonic clonic convulsive episode, that needed intubation and sedation and an association of clobazam and levetiracetam: a new brain MRI showed a recurrence of PRES-like lesions in addition to some signs of leukoencephalopathy with brain lactate accumulation on 1H-MRS, due to cerebral energetic failure. The girl also presented a refractory arterial hypertension. After 45 days of ICU hospitalization the patient has been discharged and followed up with neurological examinations. Brain MRI and brain 1H-MRS, 5 months after patient's discharge, showed incomplete regression of cerebral white matter signal abnormalities with MRS normalization. (www.actabiomedica.it)

Key words: Atypical PRES, Brentuximab-Vedotin, Status Epilepticus, leukoencephalopathy

Background

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinical syndrome characterized by acute neurological symptoms (1, 2) with typical imaging features, primarily in the territories of the brain supplied by the posterior circulation (3). PRES evolves over few hours and the most common symptoms are headache, disturbed vision and altered mental state, with a wide range of severity degree. Although seizures, that generally are multiple and take origin by the occipital regions (3), are often a manifestation of PRES, convulsive Status Epilepticus (SE) is not a typical sign of initial presentation. Usually, it presents with a nonconvulsive Status Epilepticus, defined as impaired consciousness for 30 to 60 minutes, characterized by a positive electroencephalography without convulsion, but with different cognitive features. A prompt recog-

nition and an early treatment with antiepileptic drugs are extremely important, because delays can cause irreversible damages or *exitus* (3, 4). Status epilepticus is defined by the International League Against Epilepsy (ILAE) as a condition resulting from the failure of the mechanism responsible for seizure termination or from the initiation of mechanisms which lead to prolonged seizures, able to determine long-term consequences (5). Risk factors for SE may be renal failure and history of epilepsy (3).

Case presentation

We report a 13-year-old girl was diagnosed with Nodular Sclerosis Classical Hodgkin Lymphoma stage IIIB. After a chemotherapy cycle with a regimen COPP/ABV the lymphoma went into remission. One year after, the girl was diagnosed with a recurrence of the tumor and has been treated with a chemotherapy cycle with OPPA and IEP regimens and an autologous bone-marrow transplantation, performed after a FEAM conditioning regimen.

After the transplantation, a maintenance treatment with brentuximab-vedotin (BV), a newly approved monoclonal anti-CD30 antibody, has been undertaken at a dose of 1.8 mg/kg IV every three weeks, for a total of four doses. The research of JC virus before BV start was normal.

During the maintenance treatment with BV, the girl has shown a creatinine increase, without hematuria nor proteinuria, and a progressive anemia, that has needed a blood transfusion, and a thrombocytopenia, that has needed a steroid therapy (at the dose of 1 mg/kg). Two months later, the patient presented at ER with severe headache and vomiting, followed by convulsive status epilepticus, characterized by incoming, tonic-clonic, generalized seizures.

She was admitted to ICU when the status epilepticus was interrupted with Propofol and intravenous midazolam. She was centralized to our ICU department, and she started intravenous treatment with levetiracetam (30 mg/kg/die). The continuous electroencephalogram-monitoring showed a burst suppression pattern.

The girl has begun an antibiotic (ceftriaxone 2 gr/die IV) and antiviral therapy (acyclovir 30 mg/kg/die IV), due to the suspect of meningoencephalitis. After a few days, the antibiotic and antiviral treatment was withdrawn after the negative CSF (cerebrospinal fluid) result. JCV DNA research on CSF was also negative. Brain MRI revealed multiple focal hyperintensities on FLAIR images, scattered into the cerebellar cortex, temporo-occipital cortex and frontal cortex, with normal DWI and with diffuse leptomeningeal enhancement (Fig.1). A 7-days follow-up MRI revealed the almost complete resolution of the cortical signal abnormalities and the complete reversal of leptomeningeal enhancement. It was then decided to extubate the girl and start a NIV support. In a few hours, the girl presented a prolonged seizure, so she has been again sedated and intubated and a clobazam therapy (0.25 mg/kg/die) was added.

The following brain MRI control showed recurrence of PRES-like cortical lesions and diffuse subcortical cerebral leukopathy. Single-voxel 1H-MRS of the affected white matter demonstrated an abnormal lactate accumulation which was referred to the cerebral energetic imbalance, induced by brain hypoxemia (Fig.2).

Next to the neurological conditions of the patient, there has been a systemic involvement, characterized by refractory hypertension, that has been treated with furosemide (6 mg/kg/die), carvedilol (1 mg/kg/die), amlodipine (0.6 mg/kg/die) and valsartan (2,7 mg/kg/die), with partial resolution of the condition; reduction of ventricular function (with a EF of 30-35% and mild elevation of proBNP) and mild mitral failure; increase of creatinine and BUN with a chronic kidney disease; pancytopenia that have requested a IVIG treatment (400-600 mg/kg), steroid treatment (metilprednisolone 1 mg/kg) and many platelet and red cells transfusions. After 45 days of ICU hospitalization the patient was discharged.

In the last MRI, performed 5 months later, leukoencephalopathy was improved and spectroscopy normalized (Fig.3).

Nowadays, after 8 months since the recovery, the neurologic exam and the electroencephalogram are normal. The girl has reduced levetiracetam until she stopped it, maintaining only clobazam treatment.

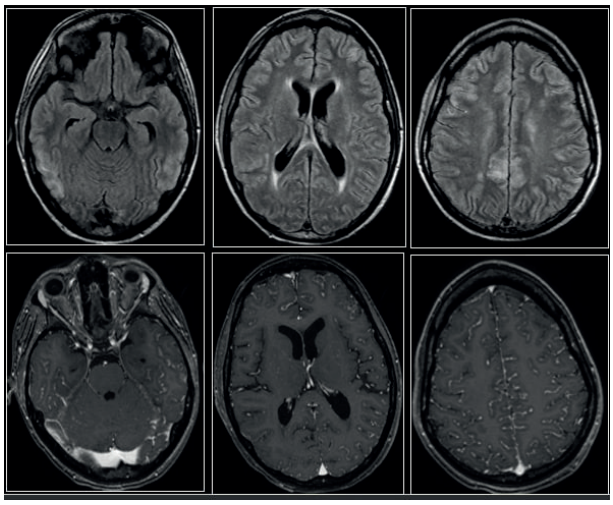

Figure 1.

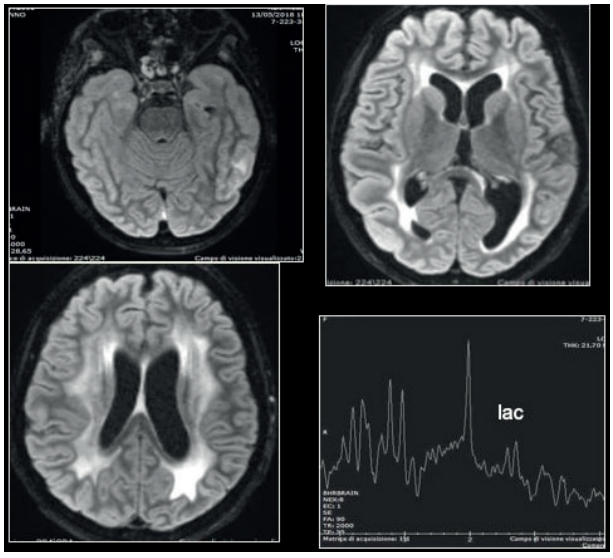

Figure 2.

Discussion

The cause and the pathophysiology of PRES remain controversial: two competing theories exist, both of which entail blood-brain barrier dysfunction, leading to the development of cerebral vasogenic edema.

According to the first theory, a rapid increase in blood pressure overcomes the cerebral vessels' autoregulatory mechanism with cerebral hyper-perfusion. This condition lead to an injury to the capillary bed and consequential vasogenic edema (6). On the basis of this theory, the sympathetic innervation, which has the abil-

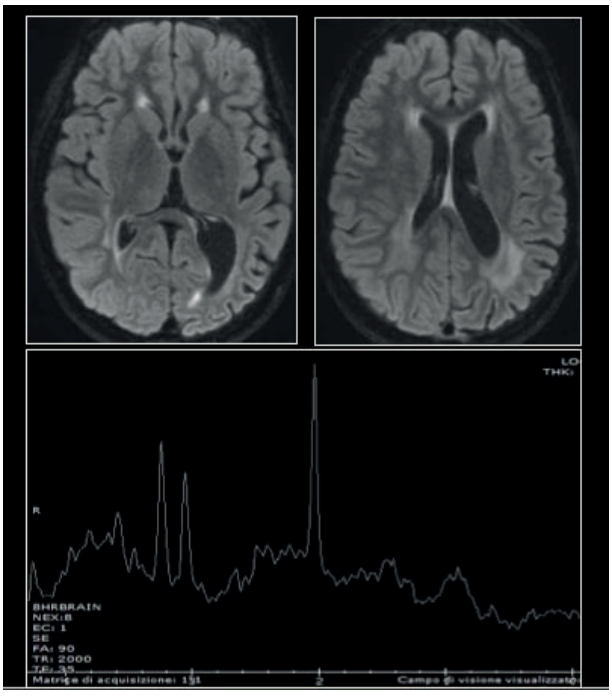

Figure 3.

ity to increase the upper limit of autoregulation, is less represented in the vertebrobasilar circulation compared with the carotid system (7).

Whereas hypertension/hyper-perfusion theory has been the most popular, a second immune-based pathogenetic theory, also common to other pathologies of neurological and neurosurgical interest, takes into account T-cell and endothelial cell activation, resulting in leukocyte trafficking and vasoconstriction that leads to cerebral hypoperfusion (6, 8-14). In this condition, the edema could be related to the cytotoxicity of immunosuppressive therapies, infections or autoimmune diseases, that may induce the activation of the vascular endothelial growth factor, causing vasogenic edema (7). Some authors have hypothesized that systemic hypertension couldbe a reactive and protective response rather than a cause of PRES because of the ability to improve perfusion and reduce cerebral edema (6).

The diagnosis of PRES is made by recognition of the clinical features and it is supported by the use of neuroimaging and electroencephalography, while ruling out other possible infectious/toxic and vascular etiologies (15-20). Brain CT and MRI may emphasize vasogenic edema, with a more consistent affection of white matter than the gray one (21). Lesions are usually hemi-

spheric and bilaterally symmetric (21) and they commonly involve occipital lobes. Atypical and more severe patterns can see the affection of frontal lobes, inferior temporooccipital region and the cerebellum (22).

The typical symptom presentation of PRES evolves over few hours and the most common symptoms are headache, disturbed vision and altered mental state, with a sporadic seizure usually starting from posterior region of the brain associated with visual symptoms. The status epilepticus is rare, and typically non-convulsive. Our patient, after a complete remission Hodgkin lymphoma, atypically showed a sudden unexpected convulsive status epilepticus, only preceded with headache and vomit. Moreover, our patient presented an atypical MRI presentation with cortical involvement of superior frontal, parietal and occipital temporal lobes, and a high leptomeningeal enhancement. The spectrum of imaging findings in PRES is wide (23). Although PRES is classically characterized by symmetric parieto-occipital oedema, there are large series of PRES cases publications which demonstrate that brain oedema may occur, in higher incidence, in the other cerebral lobes, in cerebellum, in basal ganglia and brainstem (21).

The incidence of contrast enhancement in PRES is not well known because many studies lack of contrast use, since its administration is not necessary to diagnose PRES. Moreover, contrast-enhancement in PRES is transient, like in this case, and it is determined by prompt impairment of the blood-brain-barrier or by a transitory leptomeningeal vasodilatation. Even more atypical in our patients is the prolonged and relapsing course of the loss of the cerebral arteries autoregulation, which resulted in a condition of brain energy impairment, as demonstrated by spectroscopy.

Moreover, in our patient leukoencephalopathy was partially reversed; PRES is typically characterized by a complete regression of the neuroradiological alterations to, but this may occur later than expected. Finally, at our knowledge this is the first paediatric case reported in literature with a leukoencephalopathy PRES-like presented with status epilepticus related to brentuximab therapy.

Brentuximab-Vedotin (BV) is an anti-CD30 monoclonal antibody-drug, conjugated with monomethyl-auristatin E, an anti-mitotic microtubule inhibitor, approved for the treatment of anaplastic large cell and Hodgkin lymphomas.

In 2014 some authors reported 5 patients with PML (Progressive multifocal leukoencephalopathy) associated with BV therapy and JC virus. Subsequently Von Geldern et al. published a 38-year-old patient affected by anaplastic cutaneous T-cell lymphoma, refractory to other treatment options, treated with brentuximab (24, 25). However, several different immune-modulating monoclonal antibodies, altering the normal immune function or immune surveillance and used for the treatment of many neuro-oncological pathologies, have been associated with PML (26-30). Taking into account the second pathogenetic theory of PRES (vasogenic edema due to the T-cells and endothelial activation and leukocyte trafficking), BV should have altered the T-cell activation, bringing to a relative immunosuppressive condition with depletion of CD30 expressing activated T-cells; this condition, in association with the primary hypertensive status, could have contributed to the generation of the clinical and neuroradiological features of our patient, configuring an atypical PRES. This hypothesis needs further observations. Moreover, it is noteworthy to see that literature does not mention any case of PRES presenting Status Epilepticus, associated with a BV therapy: only cases of patients in Bevacizumab therapy, a monoclonal antibody against vascular endothelial growth factor, are described (31).

Conclusion

We report the first patient with atypical PRES started with convulsant status epilepticus after treatment with Brentuximab Vedotin. This association needs further investigations to prevent the possibility of this side effects in patient that will go under this treatment.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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