



Case Report

Nonconvulsive status epilepticus secondary to paclitaxel administration[☆]Ignacio Illán-Gala^{a,*}, Francisco Javier Díaz de Terán^a, Pablo Alonso^{a,b}, María-José Aguilar-Amat^{a,b}^a Department of Neurology, Hospital Universitario La Paz, Universidad Autónoma de Madrid, Spain^b Reference Unit of Refractory Epilepsy, Spain

ARTICLE INFO

Article history:

Received 8 November 2014

Received in revised form 29 November 2014

Accepted 5 December 2014

Available online xxxx

Keywords:

Paclitaxel

Cremophor

Seizure

Toxicity

Adverse effect

ABSTRACT

Nonconvulsive status epilepticus (NCSE) can be triggered by metabolic disturbances and drugs in adults without previous epilepsy. We present the case of a 51-year-old woman without previous history of epilepsy and recently diagnosed with infiltrating lobular breast carcinoma. Following the administration of paclitaxel–cremophor, she presented a striking disinhibited behavior with episodic spatial disorientation, emotional indifference, and irritability. Urgent EEG was consistent with NCSE. Clinical improvement and resolution of EEG abnormalities were observed following the administration of intravenous levetiracetam and lacosamide. Other causes of NCSE were ruled out, and antiepileptic drugs were slowly tapered off without new episodes of abnormal behavior after three months of follow-up. We have reported the first case of NCSE secondary to paclitaxel–cremophor. Neurologists and oncologists should consider NCSE as an unusual complication of treatment with paclitaxel–cremophor in patients without a history of epilepsy.

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1. Introduction

Nonconvulsive status epilepticus (NCSE) can be triggered by metabolic disturbances and drugs in adults without previous epilepsy. With patients with cancer in particular, some chemotherapeutic agents have been associated with encephalopathy and seizures, complicating the diagnostic approach in the context of behavioral changes. We report a case of NCSE closely related to the administration of paclitaxel–cremophor and conduct a review of the literature to explore this relationship.

2. Case report

A 51-year-old woman presented to our emergency department, accompanied by relatives worried about her strange behavior. She had no medical history other than breast cancer diagnosed at the pN1a stage (HER2 negative), which was successfully treated with local radiotherapy and chemotherapy during the last year. She took no regular medication other than previous treatments for cancer, which included four cycles of cytarabine and etoposide without significant adverse effects. However, paclitaxel formulated with the micelle-forming vehicle cremophor was started eight days before the first symptoms. Since

then, the family reported episodes of disorientation, difficulty recognizing close persons, and striking disinhibited behavior. The patient performed compulsive shopping, spending her savings; showed socially inappropriate behavior, including inappropriate laughing on several occasions; and was nearly struck by a vehicle because of her careless attitude. The day before being admitted to the emergency department, the patient attended her follow-up consultation in oncology. Relatives were informed that she started to undress in the waiting room and demanded to speak to her doctor immediately. The patient behaved aggressively and left the hospital without being evaluated. When asked about these latest incidents, the patient affirmed remembering them, considering them very amusing. Her family convinced her to seek medical attention.

During the examination at the emergency room, she did not seem concerned about the situation. Physical examination was uninformative. She was cooperative and oriented, her language was fluent and appropriate, and she was able to respond to simple commands. The rest of the neurological examination was normal. Routine laboratory tests ruled out infectious or metabolic disorders, and computed tomography of the brain was unremarkable. An urgent electroencephalogram (EEG) was performed (Fig. 1A) showing continuous generalized sharp-wave activity consistent with the diagnosis of nonconvulsive status epilepticus (NCSE) alternating with occasional bilateral-prominent frontal activity (Fig. 1B).

No changes were observed after the administration of 4 mg of intravenous diazepam. Afterwards, 1000 mg of levetiracetam was administered with a marked improvement of the electroencephalographic trace but without complete resolution of EEG abnormalities. Finally, although clinical assessment was hindered by patient sleepiness,

[☆] All authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

* Corresponding author at: Department of Neurology, Hospital Universitario La Paz, Paseo de la Castellana 261, 28046, Madrid, Spain. Tel.: +34 91 7277444; fax: +34 913581403.

E-mail address: ignacio.illan@gmail.com (I. Illán-Gala).

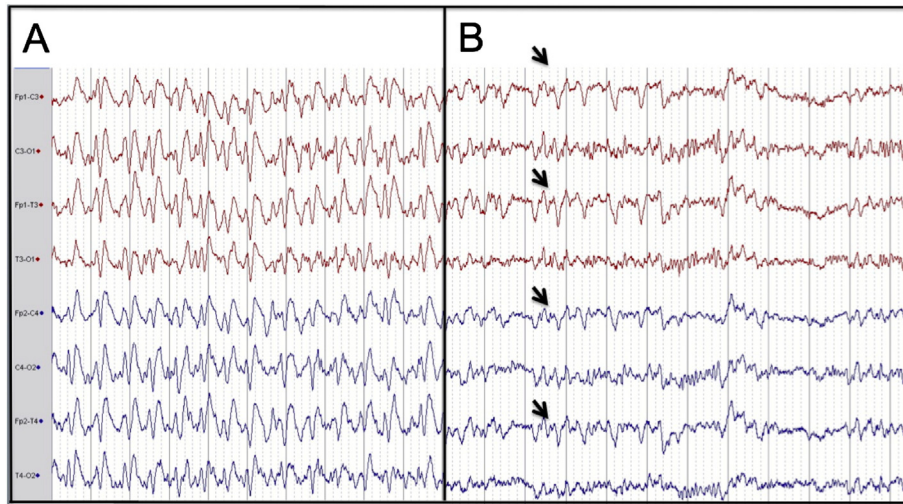


Fig. 1. Urgent EEG after admittance. (A) Urgent EEG showing the existence of bilateral continuous sharp-wave frontal activity consistent with nonconvulsive status epilepticus. (B) The same EEG showing intermittent burst of sharp waves of frontal-predominant distribution (black arrows). Horizontal bars = 1 s. Sensibility: 50 μ V (1 mm vertical).

clinical and electroencephalographic improvement was achieved with the administration of 200 mg of intravenous lacosamide. The patient was admitted to the neurology ward, and a complete study of de novo status epilepticus in the patient without epilepsy was performed. Laboratory data did not show any abnormalities. Antibodies directed against surface and intraneuronal antigens were negative, and magnetic resonance imaging, including DWI sequence and contrast administration, was unremarkable. A nontraumatic lumbar puncture was performed within the first 24 h of admission, and spinal fluid did not show any abnormality. Neither tumoral cells nor oligoclonal bands were detected. Forty-eight hours later, a new EEG was performed, showing complete normalization of the trace with the exception of occasional left temporal bursts of low amplitude sharp waves (Fig. 2).

The patient declared feeling very ashamed of her acts from the past few days, being able to remember the majority of them. Serial EEG was normal, and treatment with lacosamide was first discontinued while levetiracetam was slowly tapered off, without new episodes of abnormal behavior after three months of follow-up. Treatment with paclitaxel was discontinued.

A total of three cases corresponding to seizures (GTCS in all cases) and 11 to acute encephalopathy secondary to paclitaxel administration

were identified in our review. No previous cases of NCSE secondary to paclitaxel were identified.

3. Discussion

We have described, to our knowledge, the first case of nonconvulsive status epilepticus secondary to the administration of paclitaxel and cremophor (for further details, see Supplementary information). Paclitaxel is a chemotherapeutic agent commonly prescribed to treat a wide variety of solid tumors in addition to breast cancer. It promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. It is known to cause peripheral neurotoxicity, but central nervous system toxicity has been rarely described, in contrast to other chemotherapeutic agents such as ifosfamide, probably because of its difficulties crossing the blood–brain barrier. However, it has been reported as a cause of GTCS and acute encephalopathy [1]. Moreover, cremophor, a micelle-forming agent associated with paclitaxel, is considered a neurotoxic agent. In fact, it has been associated with GTCS, EEG burst suppression patterns, and axonal swelling in rats [2]. We used the Naranjo Adverse Drug Reaction Probability Scale to determine the probability of an association between paclitaxel–cremophor

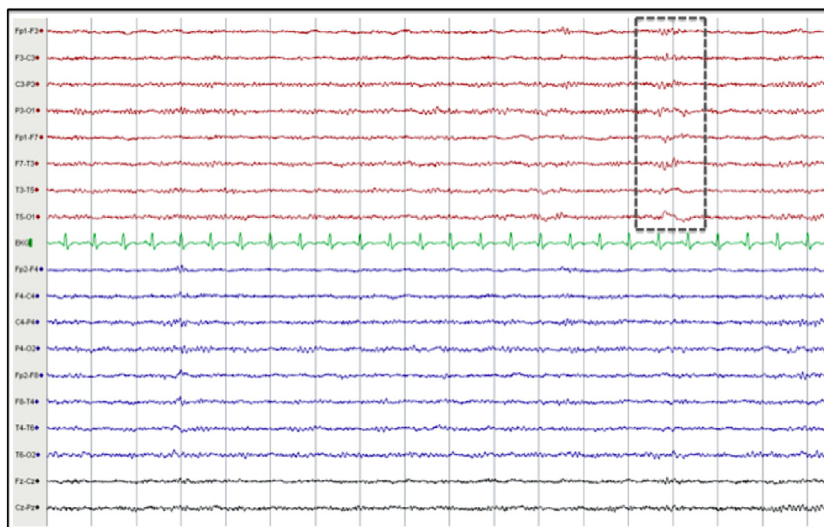


Fig. 2. Control EEG performed 48 h after the start of treatment. Control EEG, 48-hours posttreatment start, showing complete normalization of the trace with the exception of low-voltage transient sharp-wave activity on the left hemisphere (dotted box). Horizontal bars = 1 s, Vertical: 100 μ V/cm.

and NCSE [3]. The score for our patient was seven, indicating that the association was probable.

Nonconvulsive status epilepticus can be divided into generalized or focal according to clinical and EEG features [4]. Even though absence status (AE) is associated with idiopathic general epilepsies, it may also present “de novo” in adults without epilepsy, and differentiating from frontal focal NCSE (FNCSE) can be challenging, if not impossible [4]. De novo late AE may present as in the described case, in a middle-aged adult with abnormal behavior, slight cognitive disturbances, and a preserved level of consciousness. Moreover, FNCSE is a largely unrecognized form of status epilepticus often resistant to antiepileptic therapy. In the described case, three antiepileptic drugs were required for seizure termination on EEG monitoring. Patients may show striking frontal semiology and are otherwise able to perform normal-living activities. Interestingly, O'Connor reported a case of a delayed GTCS related to paclitaxel treatment with frontal-predominant spike-wave activity on EEG. However, this patient did not show clinical features consistent with NCSE [2].

Both neurologists and oncologists should be aware of this unusual complication of treatment with paclitaxel and cremophor in patients with no history of epilepsy.

Acknowledgments

We would like to thank Hao Yiu for his revision of this manuscript.

Disclosure of conflicts of interest

None of the authors has any conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ebcr.2014.12.001>.

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