Brain Radiotherapy during Treatment with Anticonvulsant Therapy as a Trigger for Toxic Epidermal Necrolysis

GIULIO METRO¹, SIMONA PINO¹, DOMENICA PELLEGRINI¹, GIORGIO SACERDOTI² and ALESSANDRA FABI¹

¹Department of Medical Oncology, Regina Elena National Cancer Institute, Rome; ²Department of Dermatology, S. Gallicano Institute, Rome, Italy

Abstract. Toxic epidermal necrolysis (TEN) is a severe mucocutaneous syndrome that can be occasionally caused by anticonvulsant drugs. In some cases, cranial irradiation may act as a precipitating factor. Thus, in cancer patients who suffer from brain metastases and are administered antiepileptic drugs for seizure prophylaxis, the risk of developing TEN after receiving palliative brain radiotherapy cannot be ignored. We report the case of a young patient with non-small cell lung cancer (NSCLC) treated with prophylactic phenobarbital who developed TEN within a few days of completing cranial radiotherapy for brain metastases. To minimize the risk of TEN in patients undergoing brain radiotherapy, prophylactic anticonvulsant therapy is recommended only after an accurate measurement of the true benefits. Alternatively, discontinuation of antiepileptic treatment before the initiation of brain radiotherapy, or the use of anticonvulsants associated with a lower risk of developing cutaneous reactions might be considered.

Toxic epidermal necrolysis (TEN) is a rare and severe cutaneous syndrome which is usually drug related. Among various compounds, aromatic anticonvulsant drugs (e.g. phenobarbital, phenytoin, carbamazepine) are recognized as the most common cause of this disorder (1), which is often associated with a multisystemic involvement called anticonvulsant hypersensitivity syndrome (AHS) (2).

Cranial irradiation in patients receiving anticonvulsants for prophylaxis of epileptic attacks might act as a precipitating factor in the development of TEN for reasons not yet elucidated. Our case is that of an advanced non-small cell lung cancer (NSCLC) patient on anticonvulsant prophylaxis with phenobarbital who developed TEN immediately after completing cranial irradiation for multiple supra- and sub-tentorial brain metastases. Treatment and follow-up are also discussed, focusing on the importance of adopting measures to avoid the risk of TEN.

Case Report

A 41-year-old white male, with a smoking history of 25 packets/year, was diagnosed in our institution with adenocarcinoma of the right lung (T3), metastatic to both lungs. A magnetic resonance of the brain revealed a 15-mm left parietal metastasis surrounded by abundant oedema associated with two sub-centimetric lesions in the same area. A cerebellum lesion of 5 mm was also present. Since a focal seizure was the revealing symptom of his disease, oral phenobarbital at a daily dose of 100 mg for secondary prophylaxis of epileptic attacks was initiated and palliative whole brain radiotherapy (30 Gray in 12 fractions, 2.5 Gray per fraction) was delivered before the start of any systemic treatment. On day 30 of anticonvulsant therapy, 3 days after the completion of whole brain radiotherapy, the patient was admitted to our hospital for the development of fever, malaise, stomatitis, odynophagia, dysuria and painful and pruritic erythematous rash covering the skin of the skull, chest and back (Figures 1, 2). A few days later, bullous lesions of the skin appeared, firstly confined to the scalp, but then also involving the upper chest, back, palms and soles (Figure 3). Physical examination also showed conjunctival keratitis and skin exfoliative rash of the genitalia and axilllas. The erythematous rash progressed rapidly into blistering and denuding areas covering more than 30% of the estimated body surface area. Cytological examination of cutaneous lesions obtained by scraping revealed the presence of squamous cells, keratin lamellas and a number of inflammation cells. Laboratory tests were in the normal range of values with the exception of a slight increase in serum ALT and γGT levels and a moderate increase in serum bilirubin. Cytological examination of cutaneous lesions obtained by scraping revealed the presence of squamous cells, keratin lamellas and a number of inflammation cells. Laboratory tests were in the normal range of values with the exception of a slight increase in serum ALT and γGT levels and a moderate increase in serum bilirubin.

Correspondence to: Alessandra Fabi, MD, Regina Elena National Cancer Institute, Division of Medical Oncology A, Via Elio Chianesi, 53, 00144, Rome, Italy. Tel: +39 06 52665144-6919, Fax: +39 06 52665637, e-mail: alessandra.fabi@virgilio.it

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decrease in serum total protein value (on day 16 of admission they were respectively 239 U/L, 243 U/L and 5.3 g/dl). Such clinical presentation matched the diagnosis of toxic epidermal necrolysis (TEN) prompting us to immediate discontinuation of phenobarbital in view of the fact that such a syndrome could be related to the anticonvulsant drug. Despite no evidence supported the effectiveness of high-dose corticosteroids in TEN, the patient was managed with an intravenous bolus of high-dose corticosteroids (methylprednisolone 80 mg bid) and broad-spectrum antibiotic therapy. In addition, antiseptic measures were adopted and the patient also received vigorous hydration. Symptoms like pruritus and pain were treated with oral anti-histamines and intravenous opiates. From day 25 of admission, skin lesions underwent a slow but progressive re-epithelisation process with no appearance of new blistering and the administration of corticosteroids was slowly reduced. Ten days later, on improved general condition, with a physical examination showing exfoliated areas confined only to the skull, the patient was discharged. Two weeks later, the patient was judged able to receive systemic treatment and chemotherapy with carboplatin and gemcitabine was initiated.

Discussion

TEN is a rare syndrome defined as a mucocutaneous reaction involving more than one third of the body surface area (3), which is often part of a multisystemic disorder. It is a potentially fatal syndrome whose rate of mortality exceeds 30% (4). The mechanism by which aromatic anticonvulsants can lead to TEN is probably related to a defect in their metabolism. More specifically, as they are converted via cytochrome P-450 to reactive toxic aromatic epoxide intermediates, called arene oxides, it has been postulated that patients developing anticonvulsant induced TEN lack epoxide hydrolases which are the enzymes responsible for detoxification of arene oxides. As a consequence, the binding of these toxic compounds to macromolecules might
elicit an immunological cell mediated response directed against epidermis and mucous membranes eventually leading to cell necrosis (5).

Interestingly, no cases of TEN have been described with radiotherapy as the only determinant. The reason why brain radiotherapy might represent a trigger for TEN in patients receiving aromatic anticonvulsant drugs for seizure prophylaxis is unknown. Nevertheless, the temporal relationship between the completion of brain radiotherapy and the onset of TEN supports the role played by cranial irradiation as a precipitating factor for development of TEN (6). Furthermore, all reported cases of TEN in patients receiving anticonvulsants and radiotherapy involved patients who had received cranial irradiation (6).

In general, all aromatic antiepileptics in association with brain irradiation can lead to TEN, although the majority of cases have been described with the antiepileptic phenytoin (7). Despite the presence of an in vitro test capable of assessing the risk of developing an AHS (8), in our opinion such risk in patients undergoing brain radiotherapy can be minimized by carefully selecting patients to be treated with prophylactic anticonvulsants. No evidence supports the routine prescription of seizure prophylaxis in cancer patients with metastatic brain tumors and no history of seizures (9, 10). Other authors suggest the use of prophylaxis of epileptic attacks only in patients suffering from brain metastases from melanoma (11). In our opinion, if patients have to receive cranial radiotherapy, anticonvulsants should be given only to those who strongly need prophylactic anticonvulsant therapy, as was the case of our patient in whom a seizure was the initial symptom of his disease. Interestingly, the reported cases of TEN induced by antiepileptic drugs and radiotherapy have some characteristics in common, with the majority of reports involving men who are in their fourth or fifth decade of life (6). Nevertheless, in the attempt to reduce the risk of TEN, treatment with aromatic anticonvulsant therapy might be temporarily discontinued in view of treating a patient with whole brain radiotherapy. Alternatively, treatment could be shifted to non-aromatic anticonvulsants, such as valproic acid, which have been reported to carry a lower risk of developing cutaneous reactions (12).

The importance of the early recognition of signs and symptoms of TEN needs to be emphasized. The early discontinuation of the anticonvulsant drug in case of TEN is of crucial importance for a more favorable prognosis of this disorder, which is often fatal.

References


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