EMPACT Syndrome - Erythema Multiform Due to Phenytoin Associated to Cranial Radio Therapy: Case Report and Review of the Literature

Tomás Reinert¹*, Marília Ferreira², Jaqueline Fonini², Roberta Castilhos³ and Marcelo Mattana⁴

¹Department of Medical Oncology, Instituto De Vita / CEPESG, Caxias do Sul, Brazil.
²School of Medicine, Universidade de Caxias do Sul (UCS), Caxias do Sul, Brazil.
³Department of Dermatology, School of Medicine, Universidade de Caxias do Sul (UCS), Caxias do Sul, Brazil.
⁴Department of Neurology, School of Medicine, Universidade de Caxias do Sul (UCS), Caxias do Sul, Brazil.

Authors’ contributions

This work was carried out in collaboration between all authors. Authors TR, MF and JF were involved in patient care during admission. Author RC provided dermatological consultation. Author MM provided neurological consultation. Authors TR, MF and JF wrote the first draft of the manuscript and managed the literature search. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JCTI/2015/18387

Editor(s):
(1) Nicole Riddle, Department of Pathology, The University of Texas Health Science Center (UTHSCSA), USA.

Reviewers:
(1) Celso Eduardo Olivier, Department of allergy and immunology, Instituto Alergoimuno de Americana, Brazil.
(2) Cuneyt Tetlikurt, Pulmonary Diseases Department, Istanbul University, Turkey.

Complete Peer review History: http://www.sciencedomain.org/review-history.php?id=1106&id=43&aid=9615

Received 20th April 2015
Accepted 8th May 2015
Published 6th June 2015

ABSTRACT

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis are rare and severe cutaneous syndrome that are usually drug related. Aromatic oral anticonvulsants (e.g.: phenobarbital, phenytoin, carbamazepine) are recognized as the most common cause of these disorders. Cranial irradiation in patients receiving anticonvulsants might act as a precipitating factor in the development of these severe cutaneous drug reactions for reasons not yet elucidated. The most common presentation is an erythematous macular eruption on the scalp within the radiation field that extends to the trunk, eventually disseminating to involve mucus membranes and

*Corresponding author: Email: masreinert@hotmail.com;
extremities. Investigators have named this syndrome “Erythema Multiforme associated with Phenyltoin And Cranial radiation Therapy” (EMPACT). We report a case of a patient with advanced non-small cell lung cancer on phenytoin prophylaxis that developed severe EMPACT syndrome after completing cranial irradiation for brain metastasis. Pathogenesis and management are discussed, with special interest on the importance of adopting measures to decrease the risk of this complication.

Keywords: Antiepileptic drugs; radiotherapy; stevens-Johnsons syndrome; toxic epidermal necrolysis; EMPACT syndrome; rash.

1. INTRODUCTION

Radiotherapy is a frequently prescribed treatment for patients with central nervous system (CNS) metastasis. This treatment is generally well tolerated, with the most common side effect being a mild and reversible irritation of cutaneous and mucous surfaces. Patients in need of brain irradiation are often treated concurrently with prophylactic anti-epileptic drugs (AED), and it might act as a precipitating factor in the development of severe skin toxicity syndromes for reasons not yet elucidated.

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life-threatening mucocutaneous syndromes, often induced by medications. The medications most frequently associated to these disorders are aromatic oral anticonvulsants (e.g.: phenobarbital, phenytoin, carbamazepine) [1]. Epidermal necrosis causes erosions of the mucous membranes, extensive detachment of the epidermis and severe constitutional symptoms. The EMPACT Syndrome is characterized by a reaction specifically triggered by concomitant use of phenytoin with cranial radiation, and is characterized by multiforme lesions starting at the radiation spot that irradiates to the torso, eventually disseminating to involve mucus membranes and extremities [2]. There are not substantial data about the prevalence and pathogenesis of this disorder. The early discontinuation of the anticonvulsant drug and adequate clinical support of critical importance for a more favorable prognosis, which is often fatal.

2. PRESENTATION OF CASE

A 64-year-old female on treatment for metastatic lung cancer presented with fever and painful skin lesion with redness, edema and bullous lesions over the scalp (Fig. 1). She was diagnosed with brain metastasis 5 weeks before the admission and had received whole-brain radiation therapy (WBRT) as well as phenytoin 100 mg three times daily for secondary prophylaxis of seizures. The skin reaction developed one the last week of WBRT (radiation dose of 30Gy) and on the 42nd day after starting phenytoin. It is noteworthy that the patient tolerated phenytoin treatment alone without any toxicity prior to starting radiotherapy.

Other than anticonvulsant medication, she was using only a single anti-hypertensive drug. She had a history of smoking and was diagnosed with metastatic lung cancer eight months before admission. She received palliative chemotherapy (six cycles of carboplatin and paclitaxel) and achieved stable disease. Prior to the admission she had an ambulatory performance status (Karnofsky 70%).

The desquamating erythematous cutaneous eruptions were originally confined only to areas of skin corresponding to the radiation field, along the scalp and on the top of the ears. On the fourth day of admission, further extension of the disease was observed with the development of conjunctival congestion, pruritic maculopapular rash on trunk and erosion of lips. Oral and genital mucosal sites had erosions and ulcerations. Moreover, the patient developed keratitis and conjunctival lesions. The reaction gradually became more intense, leading to erythematous cutaneous eruption with vesicles and sloughing of the skin (Fig. 1). Finally, sheet-like loss of epidermis and raised flaccid blisters occurred (Fig. 2). The patient reported intense pain.

After admission, we discontinued phenytoin and started intravenous fluid replacement, nutrition support, antimicrobial prophylaxis and moderate-dose opiates. Corticosteroids (intravenous dexamethasone 16 mg/d) were started, even though their effectiveness has never been demonstrated in prospective controlled trials for TEN and SJS treatment. During the hospitalization, there was a progressive clinical deterioration and the patient died on the 18th day, in consequence of a septic shock caused by a respiratory tract infection.
3. DISCUSSION

Drug-induced hypersensitivity syndrome is a systemic autoimmune disorder that results in mucocutaneous disease. Its presentation ranges from a mild rash to life-threatening skin and mucosal loss, with different nomenclature depending on the extension and severity of the symptoms [3]. The acronym EMPACT (E: erythema; M: multiforme; associated with P: phenytoin; A: and; C: cranial, radiation; T: therapy) was first described by Ahmed et al. in 2004 [4]. Although the pathophysiology of this syndrome is still unclear, evidence suggest that radiotherapy increases the potential for adverse reactions caused by the anticonvulsant. The lesions usually begin in the radiation spot and tend to be more severe over there.

Fig. 1a. Patient on admission

Fig. 1b. Patient on admission
Fig. 2a. Patient on the 8th day

Fig. 2b. Patient on the 8th day 2

Fig. 2c. Patient on the 8th day
vascular permeability leading to the entrance of radiation induced kinins may increase the shows that mediators such as histamine and proposed for the EMPACT syndrome. Evidence drugs

Intensification of stimulation of T cells induced by carbamazepine and barbiturates be associated to this pathology are phenytoin, hundred different compounds have been initiation of ther

epidermis rash that may result in detachment of the patient may experience p extensive keratinocyte apoptosis full clinical signs together with the histological Diagnosis of EMPACT syndrome is detailed in Table 1. The incidence of toxic epidermal necrolysis is estimated at 0.4 to 1.2 cases per million person-years and of SJS, at 1 to 6 cases per million person-years [5]. On the other hand, the incidence of EMPACT syndrome is still unknown. In the largest published series of patient using AED during cranial therapy, only one of 289 patients developed EM. However, milder rashes occurred in 18% of patients exposed to AEDs, being 22% exposed to phenytoin, compared with the expected rate of 5-10%. Probably radiation was not the cause of these reactions, since most of the mild drug rashes occurred before the initiation of radiotherapy [6].

SJS can occur after the administration of different medications, after viral infections and cancer and is characterized by severe cutaneous manifestations of hypersensitivity reaction to immune complexes. Nowadays SJS is considered part of the Toxic Epidermal Necrolysis (SJS-TEN) and not a part of Erythema Multiforme spectrum as considered before. To consider the TEN diagnosis, 30% of epidermal detachment must occur. When only 10-30% of epidermal detachment occurs, it is considered transitional SJS-TEN [7]. EM is characterized by mucosal erosions and specific skin lesions in its standard (typical targets, with or without blisters) with a symetrically distribution and preferably acral.

Diagnosis of SJS-TEN spectrum is based on clinical signs together with the histological analysis of a skin biopsy, which shows typical full-thickness epidermal necrolysis due to extensive keratinocyte apoptosis. Initially, the patient may experience prodrome of fever, malaise and involvement of mucous membranes, and it can evolve to heterogeneous bullous skin rash that may result in detachment of the epidermis [8]. Drug-induced SJS and TEN typically begin one to three weeks after the initiation of therapy. Although more than a hundred different compounds have been implicated in these syndromes, the most likely to be associated to this pathology are phenytoin, carbamazepine and barbiturates [1].

Intensification of stimulation of T cells induced by drugs and radiotherapy is the first mechanism proposed for the EMPACT syndrome. Evidence shows that mediators such as histamine and radiation induced kinins may increase the vascular permeability leading to the entrance of the new antigen in the circulation. To reinforce this hypothesis, it is known that certain human leukocyte antigen (HLA) types are sometimes associated with increased risk of SJS, including HLA B1502 [9]. An alternative mechanism by which aromatic anticonvulsants can lead to SJS/TEN is related to a metabolism defect, because they are converted via cytochrome P450 to reactive toxic aromatic epoxide intermediates, called arene oxides. Patients developing anticonvulsant induced TEN may lack epoxide hydrolases which are the enzymes responsible for detoxification of arene oxides and therefore turn out to be more vulnerable to the development of this syndrome. Consequently, the binding of these toxic compounds to macromolecules may elicit an immunological cell mediated response directed against epidermis and mucous membranes eventually leading to cell necrosis [10]. Radiation contribute to the development of symptoms because it helps to produce a preferential depletion of suppressor on T cells, thereby stimulating increased clonal expansion of sensitized cells.

The reason why brain irradiation might represent a trigger for these syndromes in patients receiving aromatic anticonvulsant drug for seizure prophylaxis is still unknown [11]. Interestingly, no cases of SJS/TEN have been described with radiotherapy as the only determinant [12]. Nevertheless, EMPACT acronym may not cover the full spectrum of the syndrome because it suggests that the syndrome is associated only with cranial irradiation with concurrent phenytoin administration, but cases with the same clinical presentation have been described after radiation to different parts of the body [13-14]. Notwithstanding, the clear temporal relationship between radiation treatment and the onset of the skin reaction supports that radiotherapy could be a precipitating factor for the development of EMPACT syndrome [15].

The first step in the prevention of this potentially devastating complication is a careful consideration of the risks and benefits of the use of prophylactic anticonvulsants, particularly phenytoin, and on the indication of WBRT. Therefore, it is postulated that the routine use of postoperative anticonvulsants is not recommended in seizure-naïve patients with newly diagnosed primary or secondary brain tumors, especially in light of a significant risk of serious adverse effects and problematic drug interactions [16-17].
Table 1. Definition

<table>
<thead>
<tr>
<th>Steven Johnson Syndrome (SJS) – also called Erythema multiforme major</th>
<th>Cutaneous lesions of erythematous papules, vesicles, bullae, or iris lesions covering &lt;10% of the body surface. Common presence of mucosal lesions and conjunctivitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transition TEN/SJS</td>
<td>SJS with lesions covering 10-30% of the body surface. Frequent presence of mucosal lesions and ophthalmological manifestations.</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis (TEN) – also called Lyell syndrome</td>
<td>SJS with lesions covering &gt;30% of the body surface. Frequent presence of mucosal lesions and ophthalmological manifestations. Severe life-threatening condition.</td>
</tr>
<tr>
<td>Erythema multiforme (EM) – also called Erythema multiforme minor</td>
<td>Localized skin eruptions, usually on the lower extremities, that begin to heal in 7 days. Characteristic skin lesions (typical targets, with or without blisters), of symmetric distribution and preferably acral.</td>
</tr>
<tr>
<td>EMPACT</td>
<td>SJS-TEN like syndrome triggered specifically by concomitant use of oral anticonvulsant drug with cranial radiation.</td>
</tr>
</tbody>
</table>

Another way to prevent this syndrome is to consider gabapentin and valproate as a substitute AED for a suspected sensitive patient while undergoing radiation treatment, since carbamazepine and barbiturates have shown cross-sensitivity with phenytoin [13]. But is also important to consider that gabapentin-related SJS reactions, however, have been reported in the literature [18]. Another possibility is the use of Levetiracetam, which is a newer AED with fewer side effects and essentially no drug interaction. Levetiracetam is not known to produce EM, SJS or TEN when administered alone or with concurrent radiation therapy, and the safety and feasibility of switching patients from phenytoin to levetiracetam monotherapy for seizure prophylaxis in cancer patients have been demonstrated [13]. Because of these predictable complications, some worldwide renowned neuro-oncological centers have changed their institutional protocols and now recommend the use of valproate or levetiracetam for seizure prophylaxis in patients who may expect to receive brain radiation therapy in the near course of their care [19].

Another factor to be considered is that genetic predisposition plays a significant role in pathogenesis of cutaneous adverse drug reactions. Based on pharmacogenomics studies that could identify specific biomarkers, physicians could be guided in order to optimize drug selection and dosing, as well as to avoid adverse drug reactions. One of the best characterized examples is the association between HLA-B*1502 and development of carbamazepine-induced SJS [20]. Advances in the understanding of the interaction between drugs and the major histocompatibility complex (MHC) could be used to inform drug design and drive pre-clinical toxicity programs to improve drug safety [21].

WBRT has been the most indicated therapy for patients with metastasis to the SNC and is associated with increases in the median survival of these patients to approximately 4 to 6 months, It is also associated with several acute and long-term toxicities, such as skin reactions, alopecia and neurocognitive impairment [22]. Development of stereotactic radiosurgery (SRS), which is a more precise, less toxic and more convenient method, which led to the identification of a group of patients with limited cranial metastasis who can be adequately treated with focal therapies only, withholding WBRT until progression [23].

The Score of Toxic Epidermal Necrosis (SCORTEN) scale is a severity-of-illness scale that can be used to determine the mortality rate of an individual patient [24]. Although it was initially developed for patients with SJS and TEN, it has been validated and used for patients with burns and other exfoliative disorders [3]. The average reported mortality rate of SJS is 1-5%, and of TEN is 25-35%. Elderly patients and those with a large surface area of epidermal detachment can present with higher scores. More than 50% of patients surviving TEN suffer from long-term sequelae of the disease [8].

A precise recognition of these situations from the beginning of symptoms is of utmost importance in order to intervene as soon as possible and prevent a worst prognosis. Optimal management of patients with established EMPACT syndrome should be held in an acute burn or intensive care unit. Treatment should include prompt
discontinuation of the anticonvulsant, initiation of systemic corticosteroids, intensive local treatment, IV hydration and medication for pain. For patients with extensive skin involvement involving loss of epidermis, it is very important to prevent infection, facilitate reepithelialization and control fluid balance. There is no strong evidence yet regarding the use of intravenous immunoglobulin for patients with SJS and TEN, which have shown mixed results and prospective controlled trials are lacking. Successful treatment appears to be dose dependent with early treatment recommended [25]. Other medications have been studied and found beneficial on case reports and small series, including IV infliximab, cyclosporine, and IV N-acetyl cysteine [3].

4. CONCLUSION

EMPACT syndrome is a rare and life-threatening cutaneous hypersensitivity syndrome characterized by a reaction triggered by concomitant use of phenytoin with cranial radiation. Physicians should be aware of these complications while evaluating risks and benefits of prescribing prophylactic anticonvulsants and WBRT. Pharmacogenomics studies may allow better understanding of pathogenesis and provide biomarkers for treatment selection. The immediate care involves identification and cessation of the medication, followed by appropriate skin care and intensive medical care when indicated.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICS APPROVAL

All authors declare that written informed consent was obtained from the patient for publication of the accompanying case report and images.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


© 2015 Reinert et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=1106&id=43&aid=9615

88