An Adverse Impact of Concurrent Cranial Irradiation Therapy and Phenytoin-Erythema Multiforme, Phenytoin, and Cranial Irradiation Therapy Syndrome

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Abstract

Prophylactic antiepileptics, especially phenytoin, are very commonly prescribed post brain tumor excision. Its concomitant use with radiotherapy (RT) increases its adverse effect profile and leads to skin lesions ranging from erythema multiforme, maculopapular eruption to SJS/TEN. Erythema multiforme, phenytoin and cranial irradiation therapy (EMPACT) syndrome is the term that describes this reaction. Herein, we report a case of EMPACT syndrome in a 32-year-old woman, receiving targeted RT and prophylactic antiepileptics post astrocytoma excision. The patient developed facial swelling more over the right side and blanchable erythematous maculopapular rash with atypical target lesions all over the body. These lesions were seen 1½ months post prophylactic phenytoin treatment and 7 days after targeted RT of the right frontal area. Immediate cessation of phenytoin, alternative antiepileptics, and systemic corticosteroids aided in complete recovery. EMPACT syndrome is a rare, but serious complication and clinicians should be made aware of this entity.

Keywords: Cranial irradiation therapy, cutaneous hypersensitivity, erythema multiforme

Introduction

Erythema multiforme, phenytoin, and cranial irradiation therapy syndrome (EMPACT syndrome) was first proposed by Ahmed *et al*. in 2004.[1] Higher risk of severe adverse drug reactions was reported in patients receiving cranial irradiation therapy and phenytoin, which suggested that anticonvulsants coupled with radiotherapy (RT) increase the adverse reaction potential of the anticonvulsant.[2,3] Here, we describe an interesting case of a patient with astrocytoma post excision, who developed erythema multiforme lesions while on prophylactic antiepileptics drugs (AED) and targeted RT. Over the past two decades, more than 30 such cases have been described.

Case Report

A 32-year-old woman presented with a history of fever, swelling of the face and eyelids, and itchy raised red rashes all over the body since 1 day. She had undergone surgical excision of right frontal diffuse astrocytoma (Grade 2) 1½ months back and postsurgery was started on prophylactic phenytoin 300 mg once a day and levetiracetam 750 mg twice a day for 1½ months. She was also treated with targeted RT over the right frontal area of the scalp 7 weeks after the surgery for 5 consecutive days. She developed the aforementioned symptoms 1 day after stopping RT.

On examination, she was found to be febrile and tachycardic. Erythema and edema of the face and eyelids were noted which were more pronounced over the right side [Figures 1 and 2]. Few pinpoint petechiae were noted over the hard palate [Figure 3]. Erythematous maculopapular blanchable rashes were present over the

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neck and trunk, and atypical target lesions were seen over her bilateral upper and lower limbs including palms and soles [Figures 4–6]. Conjunctival and genital mucosa were not involved. Nikolsky sign was negative. There was no lymphadenopathy. Rest of the systemic findings were within normal limits. Following the findings, a provisional diagnosis of drug reaction (drug reaction with eosinophilia and systemic symptoms) and erythema multiforme was made.

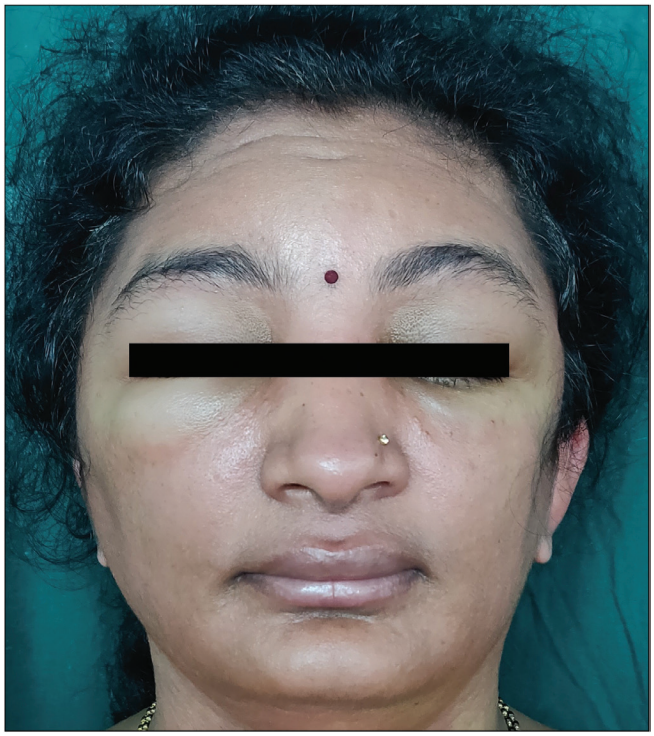

Figure 1: Edema and erythema noted over face which is more pronounced over the right side

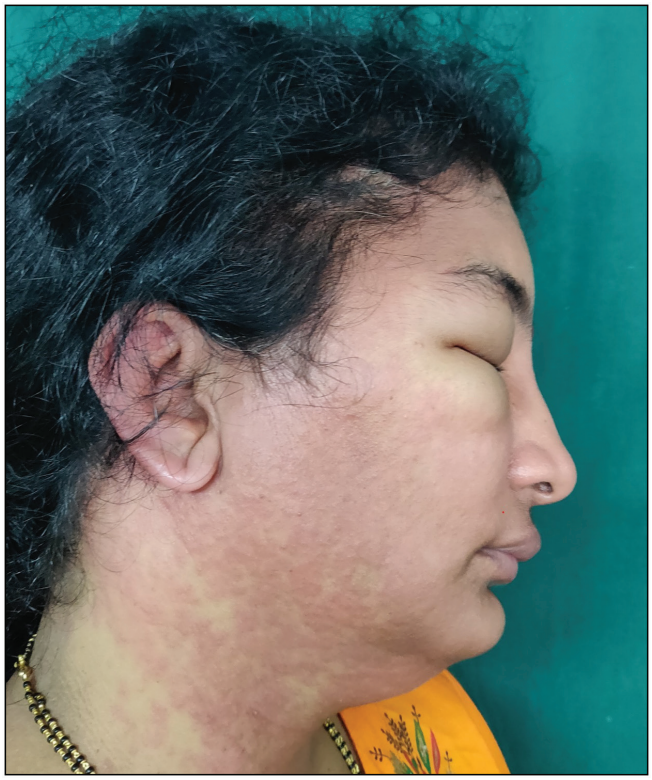

Figure 2: Erythema and edema noted over right ear

Routine blood tests showed a 10% increase in eosinophil count. Liver function tests were minimally deranged. Peripheral smear revealed relative neutrophilia. RegiSCAR criteria for DRESS were not met hence ruled out. Skin biopsy from the forearm revealed epidermal spongiosis, apoptosis of keratinocytes, few necrotic keratinocytes in the basal layer, tagging of lymphocytes along the dermoepidermal junction, edema of the superficial dermis with perivascular lymphocytic infiltrate, and extravasated erythrocytes suggestive of erythema multiforme. [Figure 7].

A neurology reference was sought for change of AEDs, following which safer alternative anticonvulsants were started. On admission, a high dose of corticosteroids was initiated but because of the persisting facial edema and periorbital puffiness, on physician's recommendation, a single dose of injection adrenaline 0.5cc intramuscularly was administered. Over the ensuing 7 days, systemic corticosteroids were tapered, resolution of the lesions occurred, and the patient was discharged from the hospital. A clinicopathological diagnosis of erythema multiforme was made, and a history of concurrent phenytoin treatment with RT aided in the ultimate diagnosis of EMPACT syndrome.

Discussion

Erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis are acute, life-threatening mucocutaneous syndromes frequently triggered by medications. Aromatic oral anticonvulsants (e.g., phenobarbital, phenytoin, and carbamazepine) are the drugs most frequently associated with these disorders.[4]

The important points to be considered in the diagnosis of EMPACT syndrome are as follows: lesions first start on radiation-exposed areas and then spread to the rest of the body, duration between the initial RT-AEDS and onset of skin rash is between 1 and 2 months. Finally, the lesions rapidly improved following the discontinuation of phenytoin.[5,6] In our case, the skin lesions developed over the radiation-exposed head area and gradually spread over the rest of the body, 1½ months following phenytoin treatment and 7 days post initiating RT. Tablet phenytoin and levetiracetam were immediately withheld and the patient was started on tablet lacosamide 100mg twice a day and clobazam 10mg once a day, following which the patient recovered well.

Ahmed *et al.* studied a case series of EMPACT syndrome wherein 16 (73%) of 22 individuals developed Stevens–Johnson syndrome, while the rest had erythema

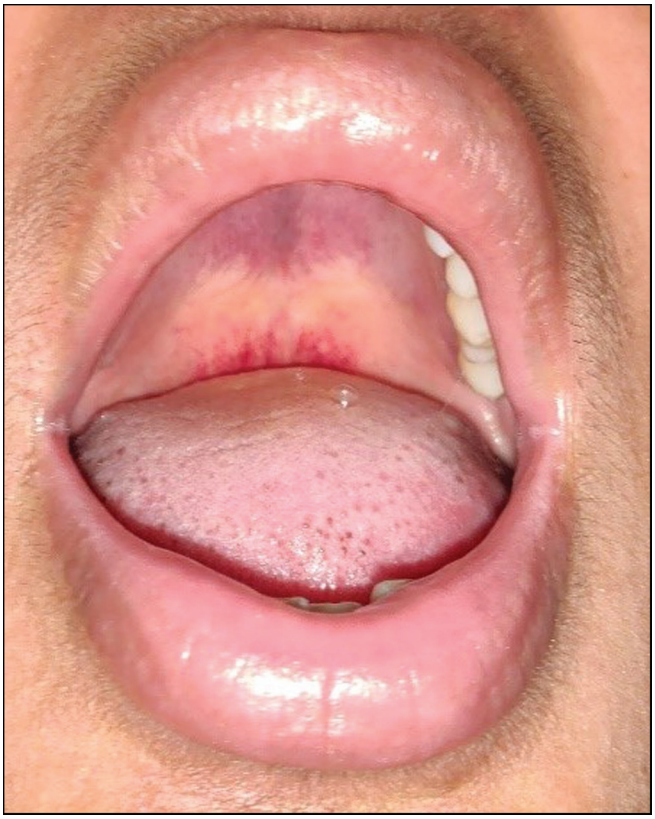

Figure 3: Few pin point petechiae noted over the hard palate

multiforme.[1] Delattre *et al*. described eight patients who developed erythema multiforme or Stevens–Johnson syndrome after receiving combination whole-brain radiation therapy and phenytoin.[7] Kazanci *et al*. reported a patient who developed erythema multiforme after administration of cranial irradiation and phenytoin treatment post temporal glial tumor excision.[8]

Radiation disrupts the metabolism of phenytoin and anticonvulsant medications. Normally, phenytoin and other anticonvulsants stimulate microsomal cytochrome 450(CYP)3A, resulting in oxidative intermediates that are then detoxified by epoxide hydrolase. A deficiency of this enzyme leads to increased intermediate metabolites, inhibits T-suppressor lymphocytes, and eventually activates an immune response leading to skin manifestations.[9,10] We present this report to emphasize the importance of close monitoring in patients receiving irradiation and drugs that induce cytochrome P 450.

EMPACT syndrome is an uncommon and potentially fatal form of cutaneous hypersensitivity. Clinicians should exercise caution while treating patients receiving phenytoin and radiation, and complications that arise should be managed aggressively. To lower the patient's morbidity profile, early detection, withdrawal of the offending medicine, safer AEDs, and active care are essential.

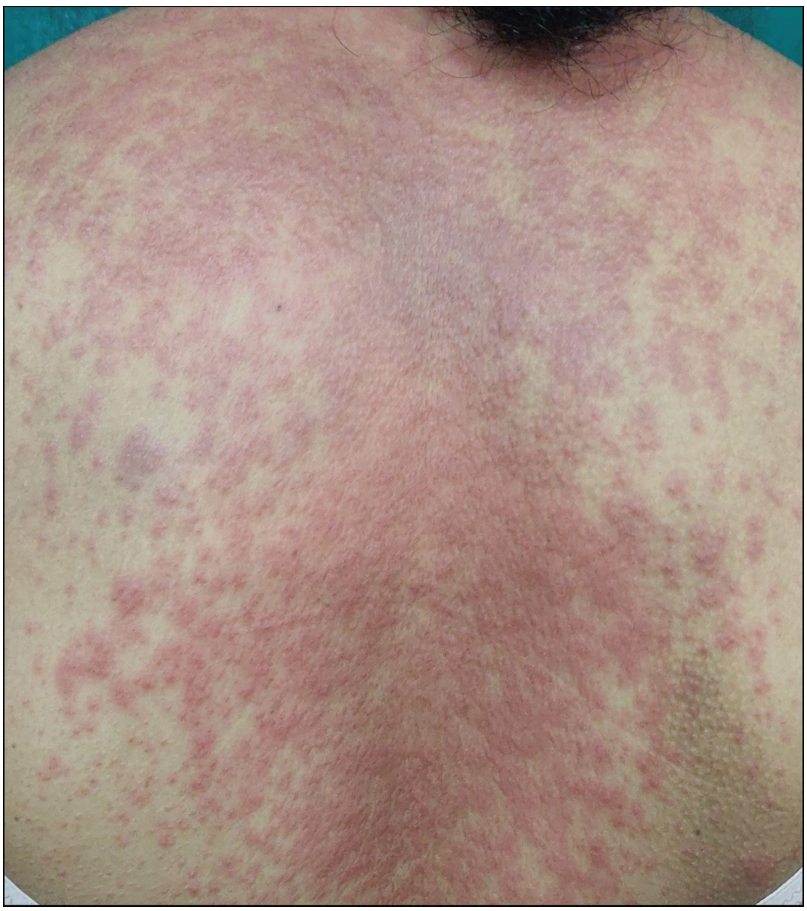

Figure 4: Erythematous maculopapular blanchable rashes with atypical target lesions noted over upper back

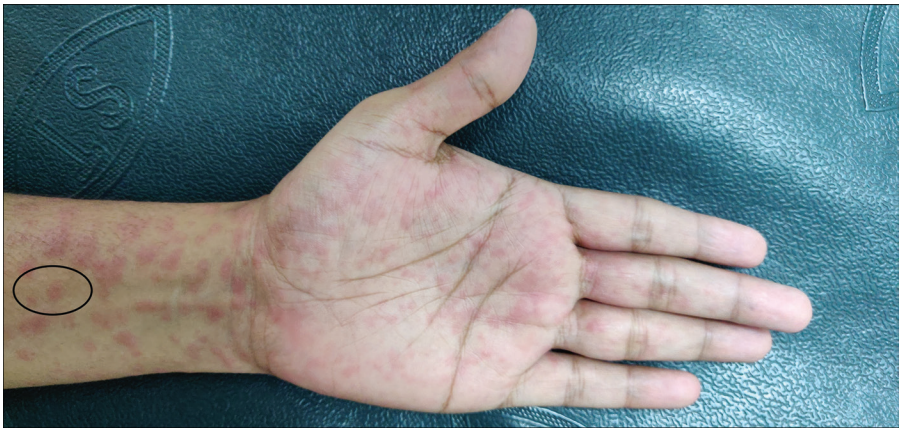

Figure 5: Erythematous maculopapular rashes with atypical target lesions over palms and forearms (see marked target lesions)

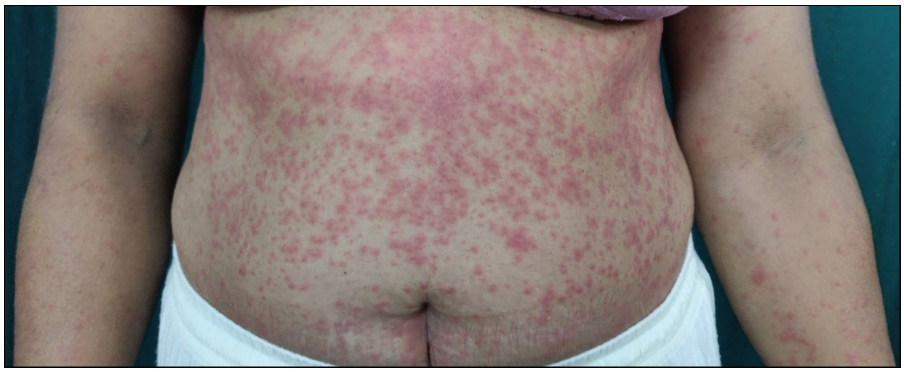

Figure 6: Erythematous rashes with few atypical target lesions over abdomen

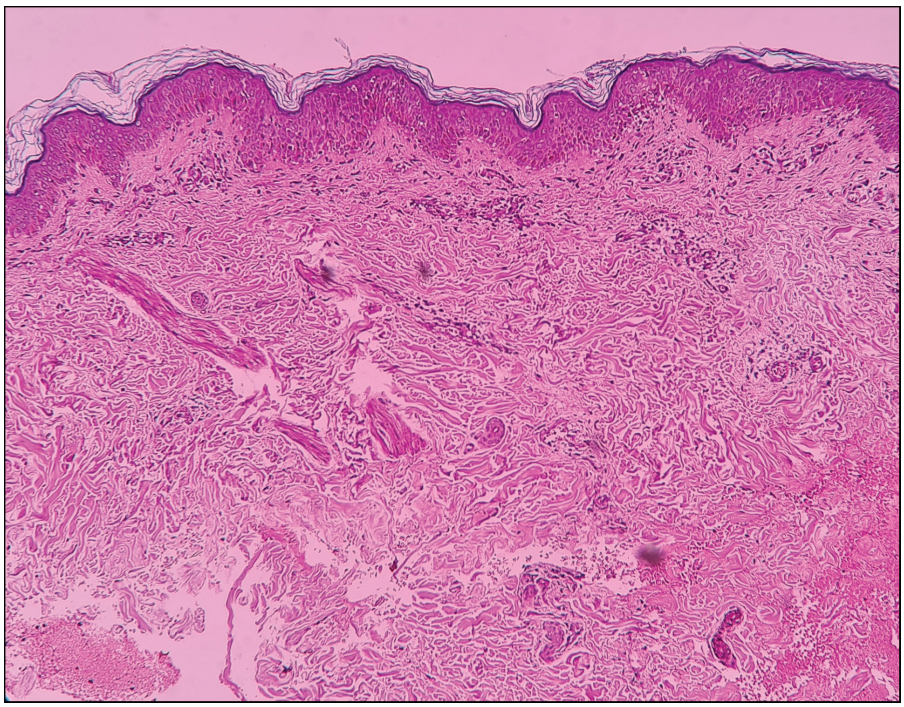

Figure 7: Epidermal spongiosis, edema of superficial dermis with perivascular lymphocytic infiltrate (H and E, ×10)

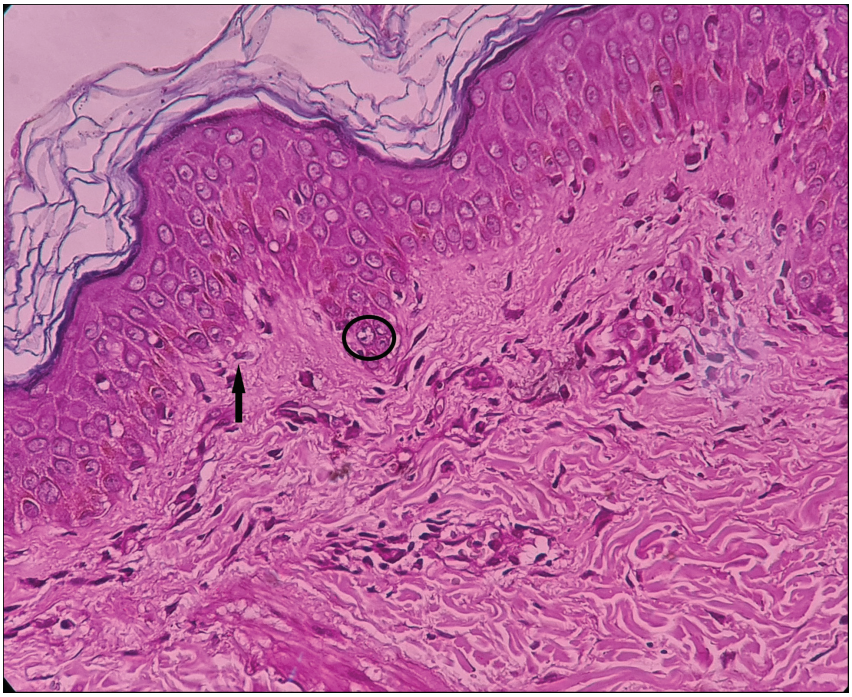

Figure 8: Few necrotic keratinocytes in basal layer (marked in black circle), tagging of lymphocytes along the dermoepidermal junction (black arrow) (H and E, ×40)

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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