

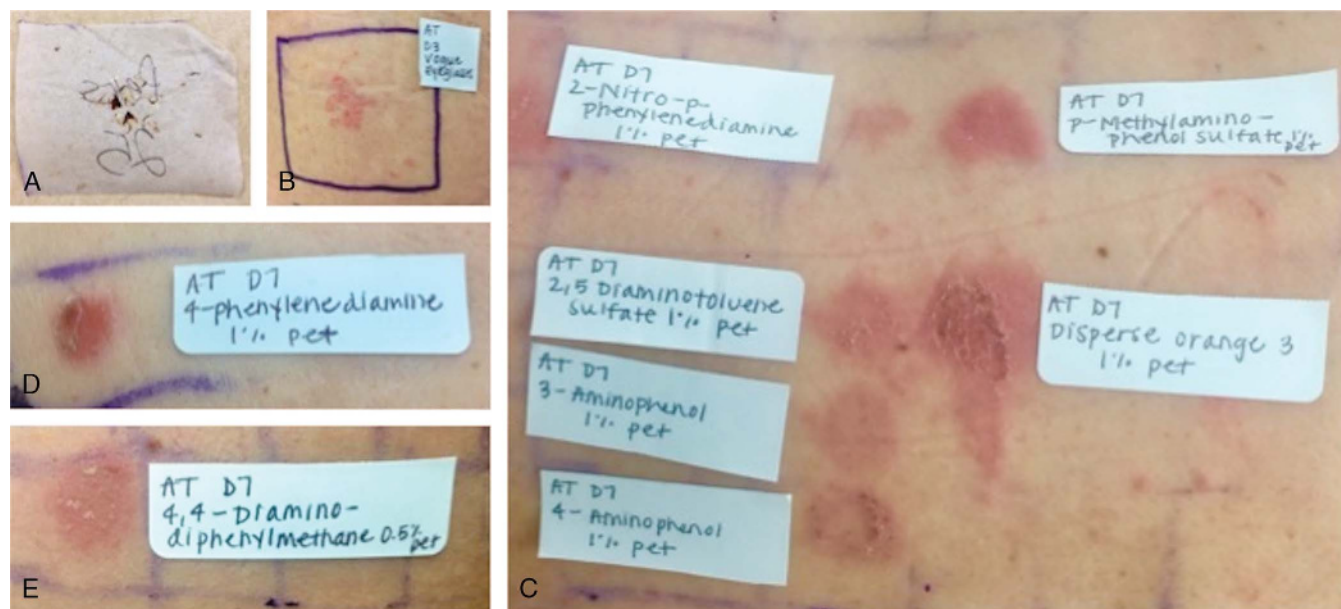


Figure 2. Photographs of (A) patch test to the patient's eyeglasses with (B) patch test results to eyeglasses on day 3. C, Photographs of day 7 patch test results from top left to bottom right, respectively, to 2-nitro-*p*-phenylenediamine, 2,5-diaminotoluene sulfate, 3-aminophenol, 4-aminophenol, *p*-methylaminophenol sulfate, and disperse orange no. 3. Photographs of day 7 patch test results to (D) 4-phenylenediamine and (E) DDM.

PEARL

4,4-Diaminodiphenylmethane can cause eyeglass-associated allergic contact dermatitis, frequently cross-reacting with PPD.

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EMPACT Syndrome in a Patient Treated With Phenobarbital

Luigia Panariello, MD, Maria Carmela Annunziata, MD, Gabriella Fabbrocini, MD, Maurizio Lo Presti, MD, and Mario Delfino, MD

PRECÍS

EMPACT syndrome is a rare clinical entity typically associated with phenytoin and cranial radiotherapy. We report a case that occurred in a patient on phenobarbital therapy.

DISCUSSION

EMPACT syndrome is a rare clinical entity characterized by “Erythema Multiforme associated with Phenytoin And Cranial radiation Therapy.”¹ It is characterized by erythema multiforme-like lesions, which develop in patients affected by brain metastasis, who are treated with cranial radiotherapy and phenytoin. The eruption typically starts at the cranial radiation site and subsequently spreads for a few days to involve extensive areas of the body.

To date, more than 30 cases of EMPACT syndrome have been described in the literature, all of which developed in patients under phenytoin treatment.² In 2013, we described the first 2 cases of EMPACT syndrome arising in patients treated with phenobarbital instead of phenytoin.³

Herein, we report another case of EMPACT syndrome that occurred in a patient on phenobarbital therapy.

A 41-year-old woman came to our dermatology outpatient clinic for an erythematous macular eruption with epidermal detachment and positive Nikolsky sign, involving the whole cutaneous surface, with palms and soles spared. These manifestations were associated with conjunctival hyperemia and erosions of the lips and oral mucosa (Fig. 1).

From the Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Italy.

Address reprint requests to Luigia Panariello, MD, Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Via S Pansini 5, 80131 Naples, Italy. E-mail: luigia.panariello@gmail.com.

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Figure 1. The patient at first visit.



Figure 2. The patient after 40 days of therapy.

The patient experienced lung cancer with brain metastases and was under therapy with afatinib and phenobarbital. She underwent whole-brain radiation therapy with a total dosage of 38 Gy to treat brain metastases.

Three days after discontinuation of the radiation therapy, she developed the rash, which was initially localized on the scalp and, during the following 4 days, spread to 90% of the skin surface.

The patient was hospitalized with a presumptive diagnosis of EMPACT syndrome. Results of virology tests for herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, and hepatitis B and C viruses were negative.

The neurologist consulted recommended discontinuation of phenobarbital and its replacement with levetiracetam.

After the exclusion of an infectious etiology, the patient was begun on therapy with steroids (prednisone 50 mg/d plus dexamethasone sodium phosphate 4 mg per 1 mL/d) resulting in complete resolution of manifestations after 40 days (Fig. 2).

The pathogenesis of EMPACT syndrome is still unclear. Radiation can alter anticonvulsant drug metabolism. Phenytoin induces microsomal cytochrome 450 3A, producing oxidative intermediates that are subsequently detoxified by epoxide hydrolase. The association of phenytoin and radiation therapy can lead to a deficiency of this enzyme, so oxidative intermediates cannot be metabolized. These intermediates are directly toxic to cells, and they can bind to cell macromolecules, behaving like haptens.³ These mechanisms can stimulate a secondary immune response. Because barbiturate detoxification too is mediated by epoxide hydrolases, this might also explain how phenobarbital can be responsible for EMPACT syndrome.

On the basis of our reports, it is important to alert physicians about the risk of developing EMPACT syndrome in patients treated with antiepileptic drugs who start radiotherapy. An alternative therapy for seizure prevention should be considered, such as gabapentin or levetiracetam, neither of which is metabolized by this detoxification pathway.

An interaction among dermatologists, oncologists, and radiotherapists is fundamental to prevent this type of reactions, to facilitate prompt diagnosis and therapy, and ultimately to help elucidate its pathogenesis.

ZEBRA

This is the third case described of EMPACT syndrome caused by phenobarbital, indicating that phenytoin is not the only anti-convulsant responsible for this syndrome.

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