

Erythema multiforme associated with prophylactic use of phenytoin during cranial radiation therapy

LEANDRO A. BARBOSA AND CARLOS ROBERTO V. TEIXEIRA

The concurrent use of anticonvulsant therapy and cranial irradiation is very common in cancer patients. Cranial irradiation is widely used for patients with brain metastasis, and the occurrence of seizures in these patients leads to the administration of anticonvulsant therapy. Erythema multiforme (EM) is a skin reaction that may occur in patients receiving concurrent cranial irradiation and phenytoin therapy.

Patients with EM may have the minor or major form of the disease.¹ Patients with EM minor typically have self-limited target-like lesions on the extensor surfaces of extremities that are often associated with an underlying infection (commonly herpes simplex) or a hypersensitivity reaction to a medication (e.g., sulfonamides, penicillins, anticonvulsants).² Patients with EM major present with typical raised or atypical flat target lesions, purpuric macules, and epidermal detachment.³ Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN) are considered to be major forms of EM.

We report the case of a patient who developed EM after concurrent

Purpose. A case of erythema multiforme associated with prophylactic use of phenytoin during cranial radiation therapy is reported.

Summary. A 60-year-old woman with intraductal adenocarcinoma of the breast and cerebral metastasis who had an implanted central venous catheter arrived at the hospital for the treatment of cerebral metastasis. She underwent whole brain irradiation and was given a total dose of 3750 cGy over 15 fractional doses spaced over three weeks. At the beginning of cranial radiation therapy, prophylactic oral ranitidine, oral dexamethasone, and oral phenytoin were initiated to prevent seizures. After 30 days of continuous prophylactic phenytoin and cranial radiation therapy, the patient developed an episode of coughing with yellow sputum, mucositis, and a minor skin reaction that was diagnosed in the emergency department as radiotherapy-associated lesions. After 2 days, the patient returned to the hospital with severe mucositis and an erythematous macular eruption on the

scalp and auricular region within the radiation field. These were believed to be due to the radiation therapy, and the patient was subsequently hospitalized. The eruption dramatically extended over the next day, with itching micropapular urticarial lesions over large areas of the face, trunk, and genital region. The condition had worsened by the next day, with erythematous eruptions on the whole body (including the extremities), skin detachment, and vesicular lesions on the eyelids. The patient was then diagnosed toxic epidermal necrolysis.

Conclusion. A patient with intraductal adenocarcinoma of the breast and cerebral metastasis developed erythema multiforme after receiving concurrent phenytoin and radiation therapy.

Index terms: Anticonvulsants; Dexamethasone; Erythema multiforme; Neoplasm metastasis; Phenytoin; Radiation; Ranitidine; Seizures; Toxicity

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administration of cranial irradiation and phenytoin.

Case report

A 60-year-old woman with in-

traductal adenocarcinoma of the breast and cerebral metastasis who had a total implanted central venous catheter arrived at our hospital for treatment of cerebral metastasis. She

LEANDRO A. BARBOSA, PH.D., M.SC., is Pharmacist, Pharmacy Service, Hospitals of Cancer III and IV; and CARLOS ROBERTO V. TEIXEIRA, M.D., is Oncologist, Oncology Clinic, Hospital of Cancer III, National Cancer Institute, Rio de Janeiro, Brazil.

Address correspondence to Dr. Barbosa at the Instituto Nacional de Câncer, Setor de Farmácia HCIII/HCIV, Rua Visconde de Santa Isabel 274, 20560-120 Rio de Janeiro, Brazil (leaugust@yahoo.com.br).

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underwent whole brain irradiation and was given a total dose of 3750 cGy over 15 fractional doses spaced over three weeks. At the beginning of cranial radiation therapy, a course of prophylactic ranitidine 300 mg p.o. daily, dexamethasone 8 mg p.o. daily, and phenytoin 300 mg p.o. daily was administered. The patient continued to receive phenytoin for the entire duration of her cranial radiation therapy. After the completion of her radiation therapy, the patient developed an episode of coughing with yellow sputum, mucositis, and a minor skin reaction that was diagnosed as radiotherapy-associated lesions. The patient was discharged from the hospital and told to continue with her phenytoin regimen.

After two days, the patient returned with severe mucositis and an erythematous macular eruption on the scalp and auricular region within the radiation field for which she was hospitalized. The eruption dramatically extended over the next day to large areas on the face, trunk, and genital region. The patient received topical sulfur for scabies and fluconazole 200 mg i.v. daily for a fungal infection but did not respond to either regimen.

The condition had worsened by the next day with erythematous eruptions on the whole body (including the extremities), skin detachment, and vesicular lesions on the eyelids, which led to the diagnosis of TEN. Of the patient's medications, phenytoin was the only agent known to cause SJS or TEN and was discontinued immediately. The patient's score on the Naranjo et al.⁴ adverse-reaction probability scale was 4, demonstrating a possible association between the reaction and phenytoin use.

Dexamethasone 16 mg i.v. daily and promethazine 50 mg i.v. daily were administered for symptomatic control. The oral mucositis was treated with nystatin and cefepime 4 g i.v. daily. A few days later, the development of a systemic infection

with fever prompted the addition of vancomycin 2 g i.v. daily and the initiation of supportive care using i.v. fluids and enteral nutrition. Because of the persistent nature of the infection, a catheter-associated source was suspected, and the total implanted central venous catheter was removed. This resulted in rapid improvement of the patient's status, with subsequent disappearance of the signs of the infection.

The patient's condition further improved over the ensuing three weeks, and she was discharged from the hospital soon thereafter.

Discussion

Several cases of EM associated with phenytoin and radiation therapy have been described in the literature.⁵⁻¹¹ The association of cutaneous reactions with radiation therapy is a well-recognized phenomenon; acute radiation dermatitis is usually dose dependent and consists of EM limited to the radiation field.¹² Likewise, skin reactions to phenytoin are common, and phenytoin is known to cause SJS and TEN.¹³⁻¹⁵

The mechanism of phenytoin-induced SJS or TEN has not been completely elucidated, but a combination of metabolic and immunologic factors may be involved. The risk of developing these skin reactions is greater during the first weeks of phenytoin therapy.^{13,14} In addition, the molecular structure of phenytoin is similar to that of other anticonvulsants known to cause SJS or TEN, such as carbamazepine and phenobarbital. The aromatic chain in the chemical structure of these agents undergoes a particular detoxification pathway mediated by epoxide hydrolases. Anticonvulsants that do not cause SJS or TEN (e.g., gabapentin) are not metabolized by this detoxification pathway.¹⁵

The prophylactic use of anticonvulsants after brain surgery or during cranial irradiation is very common. Retrospective studies have demon-

strated that 20% of patients with intracranial malignancies who undergo brain surgery or radiation therapy develop seizures.¹⁶ However, according to recent guidelines, anticonvulsants are not effective in preventing first seizures in patients with newly diagnosed brain tumors.¹⁷ Given the lack of efficacy and potential adverse effects, anticonvulsants should not be used routinely for seizure prophylaxis in these patients. In patients with brain tumors who are treated with anticonvulsants, the dosage should be tapered and the drug discontinued after the first postoperative week if the patient has not had a seizure.¹⁷ This is particularly recommended for those patients who are medically stable but have anticonvulsant-related adverse effects.

Conclusion

A patient with intraductal adenocarcinoma of the breast and cerebral metastasis developed erythema multiforme after receiving concurrent phenytoin and radiation therapy.

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