Phenytoin Induced Erythema Multiforme after Cranial Radiation Therapy

Atilla Kazanci, M.D., Ismail Hakki Tekkök, M.D.

Department of Neurosurgery, Ankara Atatürk Education and Research Hospital, Ankara, Turkey

INTRODUCTION

The prophylactic use of phenytoin during and after brain surgery and cranial irradiation is a common measure in brain tumor therapy. Phenytoin has been associated with a variety of adverse skin reactions including urticaria, erythroderma, erythema multiforme (EM), Stevens-Johnson syndrome, and toxic epidermal necrolysis. EM associated with phenytoin and cranial radiation therapy (EMC) is a rare specific entity among patients with brain tumors receiving radiation therapy while on prophylactic anti-convulsant therapy. Herein we report a 41-year-old female patient with left temporal glioblastoma who underwent surgery and then received whole brain radiation therapy and chemotherapy. After 24 days of continuous prophylactic phenytoin therapy, the patient developed minor skin reactions and 2 days later the patient returned with generalized erythematous and itchy maculopapular rash involving neck, chest, face, trunk, and extremities. There was significant periorbital and perioral edema. Painful mucosal lesions consisting of oral and palatal erosions also occurred and prevented oral intake significantly. Phenytoin was discontinued gradually. Systemic administration of corticosteroids combined with topical usage of steroids for oral lesions resulted in complete resolution of eruptions in 3 weeks. All cutaneous lesions in patients with phenytoin usage with the radiotherapy must be evaluated with suspicion for EM.

Key Words: Cranial Radiotherapy · Erythema Multiforme · Phenytoin.

CASE REPORT

A 41-year-old female patient with left temporal lobe WHO grade IV glioblastoma multiforme underwent surgery on the first day after admitting to our hospital (Fig. 1). The patient was given 300 mg/day of phenytoin and 16 mg/day dexamethasone before the surgery. Upon initial diagnosis of glioblastoma multiforme (GBM) after maximal surgical resection, the patient underwent radiotherapy, and concomitant and adjuvant chemotherapy with temozolomide. She continued taking phenytoin and tapering dosage of dexamethasone. In patients receiving phenytoin as a prophylactic anti-epileptic therapy, anti-epileptics must be administered with caution, and all cutaneous reactions developing subsequently within the radiation site must be promptly evaluated with a high index of suspicion for erythema multiforme.

Herein we report the case of a patient who developed EM after administration of cranial irradiation and phenytoin treatment.

Key Words: Cranial Radiotherapy · Erythema Multiforme · Phenytoin.
derwent whole brain radiation therapy and was given a total dose of 6000 cGy over 5 days per week in doses of 2.0 Gy fractions spaced over 6 weeks. The patient underwent chemotherapy with temozolomide 130 mg/day for 42 days. After 1 month without chemotherapy she was given 6 cycles of 300 mg/day temozolomide for 5 days.

After completing radiation therapy and tapering of dexamethasone on the 24th day of continuous prophylactic phenytoin therapy the patient developed minor skin reactions on the scalp within the radiation field especially on left temporal side. The maculopapular eruption generalized within a few days to involve the neck, face, trunk and extremities (Fig. 2). Edema on the lips, mucosal lesions consisting of oral erosions, conjunctival suffusion and periorbital edema also evolved. Laboratory serology included a normal blood cell differential with 12% monocytes, 1.9% eosinophils. Transaminase levels were mildly elevated-aspartate aminotransferase 49 U/L and alanine aminotransferase 57 U/L. Anti-nuclear antibody (ANA), anti-double stranded DNA (Anti-dsDNA), anti-extractable nuclear antigen (Anti-ENA), anti-neutrophil cytoplasmic antibody (ANCA) were negative and serum immunoglobulin levels were normal. The was no clinical and/or laboratory evidence of a infection or an autoimmune disease.

Dermatological consultation was sought and a diagnosis of phenytoin induced EM was considered. Phenytoin was discontinued and patient received intravenous corticosteroid that was tapered over 4 days. The patient was also given topical corticosteroid for oral ulcerations. On the 6th day of discontinuation of phenytoin patient had temporal lobe seizure and levetiracetam 2000 mg/day and carbamezapine 400 mg/day was initiated for seizure prophylaxis. Over the following 1 week resolution of the mucocutaneous lesions occured and the patient completely recovered within 3 weeks after stopping phenytoin.

**DISCUSSION**

EM is a mucocutaneous reaction associated with several precipitating factors that include infections and various drugs such as sulfonamides, penicillinle, anti-convulsants, allopurinol and anti-inflammatory drugs. EM typically presents with self-limited targetoid lesions on the extensor surfaces of extremities but skin lesions range from skin rashes to a progressive mucocutaneous disease.

Phenytoin is commonly prescribed as a prophylactic anti-convulsant in patients with intracranial malignancies. Phenytoin induced skin reactions ranging from urticaria to toxic epidermal necrolysis has been reported several times. Skin reactions associated with anti-convulsant therapy mainly occur during the first few days to 8 weeks of anti-convulsant drug administration. As in our case skin lesions occured 24 days after continuous prophylactic phenytoin therapy.

A generalized hypersensitivity has also been described in approximatley 10% of patients receiving phenytoin that consists of fever, arthralgias, peripheral eosinophilia, generalized lymphadenopathy and hepatosplenomegaly. This hypersensitivity reaction frequently associated with aromatic anti-convulsants such as phenytoin, phenobarbital and carbamezapine. Anti-convulsants are converted to reactive metabolites and induce cytochrome P450 3A and produce oxidative reactive intermediates that may be implicated in hypersensitivity reactions and then these metabolites excreted from kidney via another hepatic enzyme epoxide hydrolase. Imbalance between the formation of metabolites and enzymatic detoxification leads to accumulation of metabolites causes them to bind with celluller macromolecules resulting in a toxic role in type 4 hypersensitivity reactions. Baba et al. suggested that hypersensitiv-
tions but EM lesions on the irradiation area with phe-nytoin treatment commenced more than 2 months before irra-
diation might promote the development of a hypersensitivity reaction to phenytoin that may be more evident patients receive a tapering dosage of steroids. \(^1\)

Ahmed et al. \(^2\) recently used definition EMPACT (E : erythema M : multiforme associated with P : phenytoin and C : cranial radiation T : therapy) to best describe this disorder. Ahmed et al. reviewed 24 patients which had taken phenytoin for variable time periods (mean 40 days) the lesions developed within the port site during the radiation treatments or soon after its completion. In literature many cases, as in our case, the skin rashes and eruptions first occur in the irradiation area which may result in misdiagnosis as a normal radiation reaction and this may cause delaying the diagnosis of EM lesions and more severe syndromes. \(^2,4,6,8,10\) In literature as in our case not only skin eruptions but EM lesions on the irradiation area with phenytoin treatment was described as diagnostic criteria for EMPACT. \(^4\) It is also reported that the incidence of this syndrome is much more frequent in cases where phenytoin was administered less than 2 months prior to start of radiotherapy, compared to cases where treatment commenced more than 2 months before ir-

The optimal treatment for EM is not well defined. Phenytoin should be discontinued immediately and high dose intravenous steroid applicationresolve dermal lesions. For the oral mucosal lesions topical steroid is necessary. \(^2,4,6,8,10,13\) If the lesions are more severe like Stevens-Johnson syndrome or toxic epidermal necrolysis symptomatic treatment should be applied si-
milar to that used for burns. Metabolic and electrolyte im-

**Conclusion**

The prophylactic use of anti-convulsants after brain surgery or during cranial irradiation is very common. In patients receiving phenytoin as a prophylactic anti-convulsant who have also treated with radiotherapy EM is a relatively rare adverse situation. The physician must be aware of the anti-convulsant hypersensitivity syndrome when combined with radiotherapy and all cutaneous reactions developing subsequently within the radiation field must be evaluated with the suspicion of EM. In patients with disseminated rashes phenytoin administration should be discontinued immediately and intravenous steroid treatment should be given and if necessary symptomatic and supportive treatment should be started similar to that given to patients with burns.

**References**

1. Ahmed I, Reichenberg J, Lucas A, Shehan JM: Erythema multiforme associated with phenytoin and cranial radiation therapy: a report of three patients and review of the literature. Int J Dermatol 43: 67-73, 2004
2. Arif H, Buchsbaum R, Weintraub D, Koyfman S, Salas-Humara C, Bazil CW, et al.: Comparison and predictors of rash associated with 15 antiepileptic drugs. Neurology 68: 1700-1709, 2007
3. Baba M, Karakaş M, Aksungur VL, Homan S, Homan Y, Acul MA, et al.: The anticonvulsant hypersensitivity syndrome. J Eur Acad Dermatol Venereol 17: 399-401, 2003
4. Barbosa LA, Teixeira CR: Erythema multiforme associated with prophylactic use of phenytoin during cranial radiation therapy. Am J Health Syst Pharm 65: 1048-1050, 2008
5. Lin MS, Dai YS, Pwu RF, Chen YH, Chang NC: Risk estimates for drugs suspected of being associated with Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control study. Intern Med J 35: 188-190, 2005
6. Mamoun HJ, Purrh AC, Lefftner JS: Allergic skin reactions to anticonvulsant medications in patients receiving cranial radiation ther-

**Onkologie** 27: 389-392, 2004

11. Pelekanos J, Camfield P, Camfield C, Gordon K: Allergic rash due to antiepileptic drugs: clinical features and management. Epilepsia 32: 554-559, 1991
12. Roujeau JC, Kelly JP, Naldi L, Rayna B, Stern RM, Anderson T, et al.: Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 333: 1600-1607, 1995
13. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R: Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. Lancet 353: 2190-2194, 1999

14. Welykyj S, Gradini R, Nakao J, Massa M: Carbamazepine-induced eruption histologically mimicking mycosis fungoides. J Cutan Pathol 17: 111-116, 1990

15. Wöhrl S, Loewe R, Pickl WE, Stingl G, Wagner SN: EMPACT syndrome. J Dtsch Dermatol Ges 3: 39-43, 2005