

CASE REPORTS

Toxic Epidermal Necrolysis Induced by Phenytoin and Whole Brain Radiotherapy

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Abstract. Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been associated with some drugs, particularly anticonvulsants such as phenytoin. Some authors have pointed out an increased risk of TEN/SJS when phenytoin is associated with whole brain radiotherapy. We report a patient diagnosed with breast adenocarcinoma and brain metastases that was on treatment with phenytoin and, shortly after receiving whole brain radiotherapy, developed toxic epidermal necrolysis.

Key words: phenytoin, whole brain radiotherapy, toxic epidermal necrolysis, Stevens-Johnson syndrome, anticonvulsants.

NECROLISIS EPIDÉRMICA TÓXICA INDUCIDA POR FENITOÍNA Y RADIOTERAPIA HOLOCRAANEAL

Resumen. Los cuadros de necrosis epidérmica tóxica (NET)-síndrome de Stevens-Johnson (SSJ) se han asociado al consumo de algunos fármacos, en especial a la toma de antiepilépticos como fenitoína. Algunos autores han planteado un incremento en el riesgo de padecer NET/SSJ cuando la fenitoína se asocia con radioterapia craneal. Se presenta el caso de una paciente diagnosticada de adenocarcinoma de mama con metástasis cerebrales en tratamiento con fenitoína que poco después de recibir radioterapia cerebral presenta un cuadro de NET.

Palabras clave: fenitoína, radioterapia holocraneal, necrosis epidérmica tóxica, síndrome de Stevens-Johnson, antiepilépticos.

Introduction

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are 2 forms of a disease characterized by an intense inflammatory reaction of the skin that gives rise to blistering and erythematous plaques, frequently also affecting the ocular and oral mucosa, and the general condition of the patient through fever and malaise. The only difference between them is the extent of skin involvement: TEN affects greater than 30% of the skin surface and SJS less than 10%. The disease is rare

(0.4-6 cases per million persons per year)¹ but carries a significant morbidity and mortality.

The most common cause of these conditions is the administration of drugs²: on some occasions, this may be medication that is taken for a short period of time, such as antibiotics (co-trimoxazole, aminopenicillins, quinolones, or cephalosporins); in other cases, the causative medication is of prolonged use, with the first 2 months of treatment being the period of highest risk. The most notable drugs in the latter group include anticonvulsants^{3,4} such as phenytoin,⁵ lamotrigine,⁶ carbamazepine,⁷ and phenobarbital.

In 1988, Delattre et al⁸ published an article describing 8 patients with TEN-SJS who had all received phenytoin and cranial radiotherapy; this led to the initial suggestion that these 2 factors could favor the onset of this skin disorder. Since that time, around 30 cases have been published in which these 2 concomitant circumstances were present in patients with TEN/SJS.⁹

We present a new case of TEN in a woman with brain metastases who received whole-brain radiotherapy while on treatment with phenytoin.

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Figure 1. Appearance of the head and neck. Widespread erythematous lesions, some with blistering. Intense palpebral edema. Hemorrhagic ulcerated lesions on the lips.



Figure 2. Appearance of the trunk. Extensive erythematous plaques with epidermal blisters containing a clear fluid and detachment of the skin.



Figure 3. Appearance of the back. Bullae with detachment of the skin.

Case Description

The patient was a 76-year-old woman who had been diagnosed 8 years earlier with adenocarcinoma of the breast, for which she underwent radical mastectomy with axillary dissection. Two months before the present admission, she was diagnosed with brain metastases. Treatment was started at that time with dexamethasone (12 mg/d), phenytoin (300 mg/d), and omeprazole (20 mg/d), and it was decided to perform whole-brain radiotherapy. Two weeks after receiving the first session of radiotherapy, the patient developed widespread, pruritic, erythematous, papular lesions predominantly affecting the back and scalp, with dissemination to the palms, and with intense inflammation of the eyes and mouth.

On physical examination, the patient presented a temperature of 38°C and a blood pressure of 110/50 mm Hg. There were widespread erythematous lesions, some of them with blisters. On examination of the head and neck, intense palpebral edema was observed bilaterally and there were hemorrhagic ulcerated lesions on the ocular and oral mucosas (Figure 1). Extensive erythematous plaques were present over the rest of the body (more than 30% of the body surface), with epidermal blisters containing a clear fluid, and detachment of the skin, particularly over the back (Figures 2 and 3). Important findings in the blood tests were a white cell count of 5300 (74.3% neutrophils), hemoglobin of 12.6 g/dL, and a platelet count of 222 000. Apart from the presence of hypoalbuminemia, biochemical parameters were within the normal range. The patient was admitted to hospital with a diagnosis of TEN, probably secondary to phenytoin.

During the first few days following admission, the lesions showed signs of superinfection, and a purulent greenish exudate was observed from which *Pseudomonas aeruginosa* and polymicrobial flora were isolated on successive cultures.

She was treated with ceftazidime and later with amoxicillin-clavulanic acid, in association with 40 mg intravenous methylprednisolone every 8 hours, as treatment for the skin lesions, along with intravenous fluids and morphine chloride. The clinical course was slow but favorable, with detachment of large areas of skin. The patient was discharged after 1 month with no cutaneous or mucosal sequelae. All serological studies for Epstein-Barr virus, Herpes simplex 1 and 2, *Mycoplasma pneumoniae*, varicella zoster, and adenoviruses were negative.

Discussion

In the past 20 years, isolated cases of TEN-SJS have been reported in patients with brain tumors (primary or metastatic) soon after receiving cranial radiotherapy while

on treatment with anticonvulsants, particularly phenytoin,¹⁰⁻¹⁴ but also with phenobarbital^{15,16} and carbamazepine.¹⁷

At the end of the nineties, this led some authors to question whether there was a real increase in the risk of suffering TEN-SJS among patients treated with these anticonvulsants who received whole brain radiotherapy.^{18,19} Subsequently, in 2004, Ahmed et al²⁰ performed a literature review of all cases published (24) and proposed the acronym EMPACT (erythema multiforme associated with phenytoin and cranial radiation therapy) to refer to this entity.

Although the pathogenesis of these lesions is unknown, a number of hypotheses have been put forward²¹: first, radiation therapy could induce the deficit of an enzyme (epoxide hydroxylase) responsible for eliminating toxic metabolites of phenytoin and, secondly, it could also affect the pool of suppressor T lymphocytes.

Although it is not thought that corticosteroids or inhibitors of gastric acid secretion (anti-H2 or proton pump inhibitors) are etiological factors in these syndromes, it is true that the majority of these patients are receiving dexamethasone and inhibitors of gastric acid secretion (omeprazole) in addition to radiation therapy and phenytoin, as in our case.²²

For all the above reasons, the choice of anticonvulsant treatment in patients with brain tumors must be individualized, and in those patients in whom it is decided to use one of these anticonvulsants (phenytoin, carbamazepine, or phenobarbital), special attention must be paid to the possible onset of skin lesions. The therapeutic alternatives include gabapentine and valproic acid.

Conflicts of Interest

The authors declare no conflicts of interest.

References

- Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med.* 1994; 331:1272-85.
- Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* 1995; 333:1600-7.
- 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.* 1999;353:2190-4.
- Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology.* 2005;64: 1134-8.
- Scheinfeld N. Phenytoin in cutaneous medicine: its uses, mechanisms and side effects. *Dermatol Online J.* 2003;9:6.
- Fein JD, Hamann KL. Images in clinical medicine. Stevens-Johnson syndrome. *N Engl J Med.* 2005;352:1696.
- Devi K, George S, Criton S, Suja V, Sridevi PK. Carbamazepine – the commonest cause of toxic epidermal necrolysis and Stevens-Johnson syndrome: a study of 7 years. *Indian J Dermatol Venereol Leprol.* 2005;71(5):325-8.
- Delattre JY, Safai B, Posner JB. Erythema multiforme and Stevens-Johnson syndrome in patients receiving cranial irradiation and phenytoin. *Neurology.* 1988;38(2):194-8.
- Gómez-Criado MS, Ayani I, León-Colombo T, Ramos ML, Reneses MJ. Síndrome de Stevens-Johnson, necrolisis epidérmica tóxica y fenitoína. Factores asociados a un aumento del riesgo. *Rev Neurol* 2004;38:1056-60.
- Khafaga YM, Jamshed A, Allam AA, Mourad WA, Ezzat A, Al Eisa A, et al. Stevens-Johnson syndrome in patients on phenytoin and cranial radiotherapy. *Acta Oncol.* 1999;38: 111-6.
- Eralp Y, Aydinler A, Tas F, Saip P, Topuz E. Stevens-Johnson syndrome in a patient receiving anticonvulsant therapy during cranial irradiation. *Am J Clin Oncol.* 2001; 24:347-50.
- Pérez-Hortez C, García-Almagro D, Urrutia S, Schoendorf C, López-Barrantes O. Dos casos de necrolisis epidérmica tóxica localizada asociada a radioterapia. *Actas Dermosifiliogr.* 2003;94:475-8.
- Oner Dinçbas F, Yoruk S, Demirkesen C, Uzel O, Koca S. Toxic epidermal necrolysis after cranial radiotherapy and phenytoin treatment. *Onkologie.* 2004;27(4):389-92.
- Cockey GH, Amann ST, Reents SB, Lynch JW Jr. Stevens-Johnson syndrome resulting from whole-brain radiation and phenytoin. *Am J Clin Oncol.* 1996;19(1):32-4.
- Duncan KO, Tigelaar RE, Bolognia JL. Stevens-Johnson syndrome limited to multiple sites of radiation therapy in a patient receiving phenobarbital. *J Am Acad Dermatol.* 1999; 40(3):493-6.
- Vincenzi B, Santini D, Grilli C, La Cesa A, Dianzani C, Tonini G. Complications of therapy in cancer patients: Case 3. Toxic epidermal necrolysis induced by oral phenobarbital and whole-brain radiotherapy in a breast cancer patient. *J Clin Oncol.* 2004;22:4649-51.
- Hoang-Xuan K, Delattre JY, Poisson M. Stevens-Johnson syndrome in a patient receiving cranial irradiation and carbamazepine. *Neurology.* 1990;40:1144-5.
- Micali G, Linthicum K, Han N, West DP. Increased risk of erythema multiforme major with combination anticonvulsant and radiation therapies. *Pharmacotherapy.* 1999;19: 223-7.
- Aguir D, Pazo R, Durán I, Terrasa J, Arrivi A, Manzano H, et al. Toxic epidermal necrolysis in patients receiving anticonvulsants and cranial irradiation: a risk to consider. *J Neurooncol.* 2004;66:345-50.
- 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.* 2004;43:67-73.
- Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. *Arch Intern Med.* 1995;155:2285-90.
- Cohen AD, Reichental E, Halevy S. Phenytoin-induced severe cutaneous drug reactions: suspected interactions with corticosteroids and H2-blockers. *Isr Med Assoc J.* 1999;1: 95-7.