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CLINICAL-PATIENT STUDIES

Stevens-Johnson syndrome in children receiving phenobarbital therapy and cranial radiotherapy

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Abstract Stevens-Johnson syndrome (SJS) is a severe cutaneous eruption that most often appears as an adverse reaction to medication. In this report, we present two children with brain tumour who developed SJS while receiving cranial irradiation and anticonvulsant therapy with phenobarbital. Concomitant application of these two therapies may play an important role in the occurrence of the disease.

Keywords Stevens-Johnson syndrome · Erythema multiforme major · Cranial irradiation · Anticonvulsant therapy

Introduction

Seizure prophylaxis is a common measure in oncologic patients with brain masses [1–3]. Phenytoin and phenobarbital are the most widely used anticonvulsants for seizure prophylaxis. Stevens-Johnson syndrome (SJS) or Erythema multiforme major (EMM) is a mucocutaneous bullous form of erythema multiforme reaction resulting from hypersensitivity to a variety of agents including most anticonvulsants [4]. There are few reports about Stevens-Johnson syndrome that can develop in patients treated with cranial irradiation and phenobarbital, especially in pediatric patients.

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Case report

Case A

A 6-year-old male patient with diagnosis of medulloblastoma underwent, following surgery and chemotherapy, craniospinal irradiation. He had never suffered of seizures. Prophylactic therapy with phenobarbital (4 mg/kg/day) was started. On the 26th day of irradiation, widespread maculopapular eruptions and rashes including lips were observed. The dermal lesions progressed to bullae and subsequently toxic epidermal necrolysis covering <10% of the whole body surface developed. No association with viral infections (including human herpesvirus-6, parvovirus B19, adenovirus, coxsackievirus, measles, EBV) was detected. The extensive involvement of the oral mucosa with conjunctivitis and synechiae of the eyelids, facial swelling, and extension of the rash over the trunk and shoulders with bullous detachment of less than 10% of the total body surface strongly suggested SJS. The immediate cessation of anticonvulsant therapy, combined with administration of systemic corticosteroids along with intensive local treatment and pain medications, resulted in complete resolution of the skin eruption.

Case B

A 7-year-old female patient with medulloblastoma. As the previous patient, she underwent surgery and chemotherapy, and finally craniospinal irradiation was performed. Phenobarbital (4 mg/kg/day) was administered as prophylactic

treatment too. On the 28th day of irradiation, a similar cutaneous manifestation appeared and covered the whole body surface. No viral infection was detected. A diagnosis of SJS was made. Supportive and symptomatic treatment with antiseptic measures, hydration and broad-spectrum antibiotics were started (Fig 1)

Discussion

Intracranial tumors account for 24% of all pediatric malignancies in children younger than age 14 years. New-onset seizures and epilepsy represent particularly common comorbidities of brain tumors. Physicians often administer anticonvulsant medication prophylactically to patients with brain tumors, despite the lack of definitive evidence that prophylactic anticonvulsant therapy is effective in preventing first seizures [1–4].

Typical anticonvulsant-induced side effects, including cognitive impairment, myelosuppression, liver dysfunction, and dermatologic reactions (ranging from minor rashes to life-threatening SJS), appear to occur more frequently in patients with brain tumors than in other patient groups, although direct comparison studies have not been published. There is still controversy about whether all anticonvulsants are associated with SJS and toxic epidermal necrolysis (TEN). SJS and TEN are closely related severe, acute mucocutaneous reactions that are mostly elicited by drugs. Both SJS and TEN have been observed in patients receiving antiepileptic drugs and concomitant radiotherapy. Generally, the risk of severe cutaneous manifestations is confined to the start of antiepileptic therapy, within 8 weeks [5].

There has been conflicting evidence on the role of radiotherapy in the increased risk of severe drug reactions. Although various authors have emphasized the augmented rate of severe mucocutaneous reactions caused by anticonvulsants given during radiotherapy and suggested discontinuing the prophylactic use of such drugs in patients with no history of seizures, others have argued in favour of prophylactic anticonvulsants. There is increasing anecdotal [6–12] support in the literature for a synergistic effect between anticonvulsant medications (AEDs) and cranial radiotherapy that can result in the life-threatening SJS or TEN. Most of them had been were receiving phenytoin together with the cranial irradiation. Usually, cases with detachment of less than 10% of the epidermis are classified as SJS and those with more than 30% as TEN [13]. The pathogenesis of the disorder is probably immunologic.

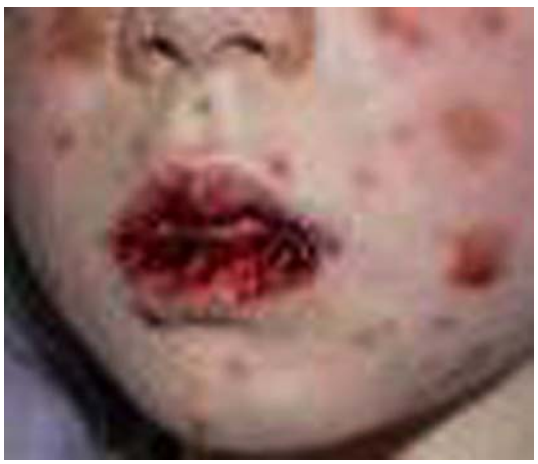

Fig. 1 cutaneous manifestations in patient 1

Most recently, the acronym EMPACT (Erythema Multiforme associated with Phenytoin And Cranial radiation Therapy) was proposed to specifically describe this syndrome [14–15]. According to the authors, EMPACT should be classified as a specific entity among the EEM-like drug reactions as it only appears after radiotherapy and seizure prophylaxis with the anticonvulsant phenytoin. The reaction, or its severity, has no relationship to the phenytoin or radiation therapy dosage, or to the histological type of brain tumor. Also, EMM has no apparent age or gender predisposition in association with phenytoin-radiation therapy. Thus this is a clinical phenomenon that occurs with unusual frequency in patients with brain tumor who undergo radiation therapy while taking phenytoin. Phenytoin and other anticonvulsants such as phenobarbital and carbamazepine induce cytochrome P450 3A and produce oxidative reactive intermediates that may be implicated in hypersensitivity reactions such as EMM. Both carbamazepine and barbiturates have shown cross-sensitivity with phenytoin.

The incidence of these complications has not been well studied among pediatric patients with brain tumors. The available evidence suggests, in addition, that prophylactic administration of anticonvulsant medications does not provide substantial benefit (i.e., a risk reduction of 26% or more for seizure-free survival), whereas anticonvulsant-associated side effects are especially common and occasionally life-threatening.

In 24 months we encountered two patients with intracranial tumors who developed the SJS. Both occurred shortly after use of phenobarbital and brain radiation therapy. While the association is uncommon, our experience suggest that the routine use of a prophylactic anticonvulsant in the absence of a history of seizures may not be warranted if the patient is candidate to receive cranial radiotherapy. In addition, patients under anticonvulsants with radiotherapy should be educated to recognize early signs of cutaneous reactions consistent with the SJS or TEN in order to withdraw the anticonvulsant at the early clinical presentation of the cutaneous complications.

References

1. Forsyth PA, Weaver S, Fulton D, Brasher PMA, Sutherland G et al (2003) Prophylactic anticonvulsants in patients with brain tumour. Can J Neurol Sci 30(2):106–112
2. Sirven J, Wingerchuk DM, Drazkowski JF, Lyons MK, Zimmerman RS (2004) Seizure prophylaxis in patients with brain tumors: a meta-analysis. Mayo Clin Proc 79(12):1489–1494
3. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY et al (2000) Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 54(10):1886–1893
4. Kelly JP, Auquier A, Rzany B, Naldi L, Bastuji-Garin S et al (1995) An international collaborative case-control study of severe cutaneous adverse reactions (SCAR). Design and methods. J Clin Epidemiol 48(9):1099–1108
5. Rzany B, Correia O, Kelly J, Naldi L, Auquier A, Stern R (1999) Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Lancet 353(9171):2190–2194
6. Oner Dincbas F, Yoruk S, Demirkesen C, Uzel O, Koca S (2004) Toxic epidermal necrolysis after cranial radiotherapy and phenytoin treatment. Onkologie 27(4):389–392
7. Gomez-Criado MS, Ayani I, Leon-Colombo T, Ramos ML, Reneses MJ (2004) Stevens-Johnson syndrome, toxic epidermal necrolysis and phenytoin. Factors linked to a higher risk. Rev Neurol 38(11):1056–1060
8. Eralp Y, Aydiner A, Tas F, Saip P, Topuz E (2001) Stevens-Johnson syndrome in a patient receiving anticonvulsant therapy during cranial irradiation. Am J Clin Oncol 24(4):347–350
9. Aguiar D, Pazo R, Duran I, Terrasa J, Arrivi A et al (2004) Toxic epidermal necrolysis in patients receiving anticonvulsants and cranial irradiation: a risk to consider. J Neurooncol 66(3):345–350
10. Dincbas FO, Yörük S, Demirkesen C, Uzel O, Koca S (2004) Toxic epidermal necrolysis after cranial radiotherapy and phenytoin treatment. Onkologie 27:389–392
11. Aydin F, Cokluk C, Senturk N, Aydin K, Canturk MT, Turanli AY (2006) Stevens-Johnson syndrome in two patients treated with cranial irradiation and phenytoin. J Eur Acad Dermatol Venereol 20:588
12. Khafaga YM, Jamshed A, Allam AA, Mourad WA, Ezzat A, Al Eisa A, Gray AJ, Schultz H (1999) Related articles, links Stevens-Johnson syndrome in patients on phenytoin and cranial radiotherapy. Acta Oncol 38(1):111–116
13. Bastuji-Garin S, Rzany B, Stern RS et al (1993) Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 129:92–96
14. Ahmed I, Reichenberg J, Lucas A, Shehan JM (2004) Erythema multiforme associated with phenytoin and cranial radiation therapy: a report of three patients and review of the literature. Int J Dermatol 43(1):67–73
15. Wohrl S, Loewe R, Pickl WF, Stingl G, Wagner SN (2005) EMPACT syndrome. J Dtsch Dermatol Ges 3(1):39–43