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Stevens-Johnson Syndrome and Epidermal Necrolysis after Administration of Sodium Phenytoin with Cranial Irradiation

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TOXIC EPIDERMAL necrolysis is a severe form of the Stevens-Johnson syndrome [1], characterised by generalised erythema and bullous formation followed by detachment of the skin, which may be extensive. We report 4 cases of this dermatological syndrome believed to be due to an interaction between phenytoin and local irradiation to the brain.

A 53-year-old white male was admitted to our clinic with the diagnosis of non-operable glioblastoma multiforme. He had been on Na phenytoin 200 mg/day and phenobarbital 100 mg/day for seizure prophylaxis and paramethazone 36 mg/day, when he started cranial irradiation. After receiving 4660 cGy he developed intense skin erythema which originated from the skull and subsequently disseminated over the entire body.

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Phenytoin and phenobarbital were discontinued and paramethazone was switched over to methylprednisolone 48 mg/day. The skin lesions progressed to extensive bullous formation followed by epidermal necrolysis which encompassed approximately 40% of the body surface area. Methylprednisolone was increased to 200 mg/day and after 2 months of intensive management of fluid and electrolyte imbalances and of high grade fevers with broad spectrum antibiotics, the patient's condition improved with gradual skin re-epithelialisation. Over the past 3 years, 3 similar cases were recorded in our institution and are presented in Table 1.

Epidermal necrolysis due to phenytoin ingestion, although rare, has been reported [2-5]. Local irradiation has also been associated with the syndrome [6-9]. It seems likely that the combination of both factors may act in synergy for the development of the syndrome. From the University of Helsinki, in 1 year, 4 patients developed Stevens-Johnson syndrome, after receiving phenytoin and local irradiation to the brain [10]. In 1988, Delattre and associates from MSKCC reported 8 similar cases in 14 months [11]. In all of our cases, the skin lesions began from the primary site of irradiation and subsequently propagated to the rest of the body. Another characteristic was the time elapsed from the onset of the skin rash to the actual recognition of the syndrome (about 5 to 7 days).

The pathogenesis of the syndrome remains unknown. Immunologic mechanisms have been implicated. Others believe that a disruption of the hypothalamic pituitary axis during cranial irradiation may be the causative factor [10]. The concomitant use of other medication, such as phenobarbital and ranitidine by our patients raises the question whether these agents might play a role in the pathogenesis of the syndrome.

The severity of the syndrome mandates its early recognition and institution of therapy as soon as possible. This is achieved only by a high level of suspicion on part of the physician. We, therefore, recommend that the appearance of a skin eruption in

Table 1. Presentation of 4 patients with extensive skin eruption including characteristics, management and final outcome

Case	1	2	3	4
Sex	Male	Male	Male	Male
Age	53	45	44	48
Other medication	Paramethasone, ranitidine	Dexamethasone, ranitidine	Cortisone	Cortisone
Phenytoin dose (mg/day)	200	200	200	200
Primary tumour	Glioma	NSCLC	NSCLC	NSCLC
Radiation field	Brain	Brain, mediastinum	Brain	Brain
Onset of rash	Skull	Skull, thorax	Skull	Skull
Type of rash	Toxic epidermolysis	Stevens-Johnson	Toxic epidermolysis	Toxic epidermolysis
Extension of rash	Skull, conjunctivae, oral mucosa, upper body, genitalia	Skull, conjunctivae, oral mucosa, oesophagus, upper limbs	Skull, conjunctivae, oropharyngeal mucosa, upper body, genitalia	
Interval from first phenytoin dose to the onset of the rash	> 30 days	32 days	—	> 30 days
Interval from the initiation of RT to the onset of the rash	30 days	30 days	25 days	> 30 days
Therapy	Discontinuation of phenytoin, increase methyl prednisolone	Discontinuation of phenytoin, increase prednisolone	Discontinuation of phenytoin, continue cortisone	Discontinue phenytoin, add cortisone
Restoration of skin damage	2 months	45 days	42 days	44 days

NSCLC = non-small cell lung cancer, RT = radiotherapy.

the irradiated field of a patient receiving phenytoin should be followed closely and, upon signs of extension, both radiation therapy and phenytoin should be discontinued and high-dose steroids instituted.

1. Rasmussen JE. Causes, diagnosis and management of toxic epidermal necrolysis. *Comprehensive Ther* 1990, 16, 3-6.
2. Tucker MS, Fitzharris JW. Dilantin induced erythema multiforme major: Report of a case with liver and kidney involvement. *J Am Osteopath Assoc* 1985, 85, 511-514.
3. Patterson R, et al. Erythema multiforme and Stevens-Johnson Syndrome. Descriptive and Therapeutic Controversy. *Chest* 1990, 98, 331-336.
4. Chan HL, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol* 1990, 126, 43-47.
5. Sheretz EF, Jegasothy BV, Lazarus GS. Phenytoin Hypersensitivity reaction presenting with toxic epidermal necrolysis and severe hepatitis. *J Am Acad Dermatol* 1984, 12, 178-181.
6. Howell WR, Knight AL, Scruggs HJ. Stevens-Johnson syndrome after radiotherapy. *South Med J* 1990, 83, 681-683.
7. Nawalkha PL, Mathur NK, Malhotra HC. Severe erythema multiforme (Stevens-Johnson syndrome) following telecobalt therapy. *Br J Radiol* 1971, 45, 768-769.
8. Lowe L, Camiel ML. Exanthem complicating neoplastic disease. *Am J Roentgenol Rad Ther* 1940, 43, 587-596.
9. Davis J, Pack G. Erythema multiforme following deep X-ray therapy. *Arch Dermatol Syph* 1952, 66, 41-48.
10. Maiche A, Teerenhovi L. Stevens-Johnson syndrome in patients receiving radiation therapy. *Lancet* 1985, 45, 8445.
11. Delattre JH, Safai B, Posner JB. Erythema multiforme and Stevens-Johnson syndrome in patients receiving cranial irradiation and phenytoin. *Neurology* 1988, 38, 194-198.