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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. 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

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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.

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Shifts in Respiratory and Upper Digestive Tract Cancer in Eastern Austria

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In Eastern Austria, from 1960 to 1989, mortality in males from buccopharyngeal cancer (ICD 140–149) rose steadily whereas lung cancer mortality declined, both trends resulting from a double wave shaped cohort effect [1, 2]. The complex site larynx showed only slight cohort-related trends of regional mortality [2]. Cases diagnosed at our institution, however, covering one fourth of regional incidence, suggested a rise of hypopharynx carcinoma and a decrease of laryngeal, especially glottic carcinoma [3]. Age-specific patterns showed similarities between hypopharynx carcinoma and buccopharyngeal cancer, and between larynx carcinoma and lung cancer, respectively [1, 3]. The Eastern Austrian ratio of buccopharynx cancer by lung cancer, in number of deaths, and the hospital-based ratio

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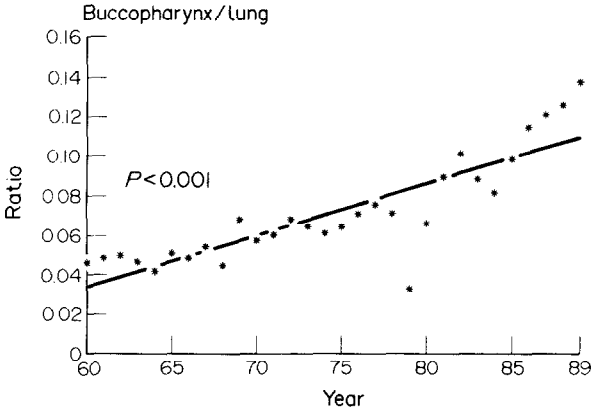

Fig. 1. Ratio of buccopharynx cancer (n = 2805) by lung cancer (n = 40346), males, deaths, Eastern Austria 1960–1989.

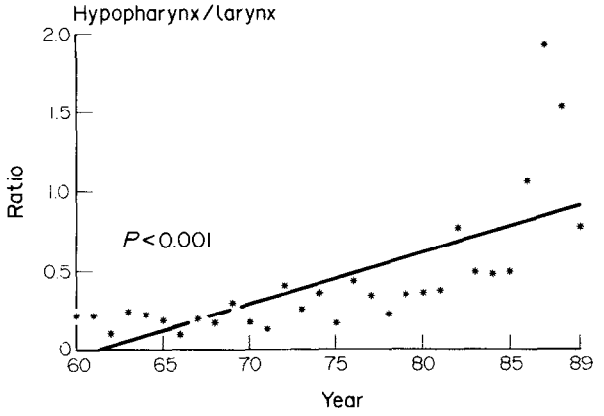

Fig. 2. Ratio of hypopharynx carcinoma (n = 334) by larynx carcinoma (n = 1048), males, Department of Otorhinolaryngology 1, University of Vienna 1960–1989.

of hypopharynx carcinoma by larynx carcinoma, have been increasing continuously (Figs 1 and 2). Thus substituting precise, yet not strictly representative hospital data to regional statistics, strikingly parallel developments emerge: hypopharynx carcinoma resembled buccopharyngeal cancer, and larynx carcinoma resembled lung cancer. Increase obviously did not affect sites of the respiratory tract subject to the classical risk factor of inhalative smoking, but rather affected sites with a more complex aetiological background, notably interactions of tobacco and alcohol [4–6].

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