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Is phenytoin contraindicated in patients receiving cranial irradiation?

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SUMMARY

Three recent publications have reported the development of erythema multiforme and Stevens–Johnson syndrome in patients receiving cranial irradiation and sodium phenytoin. Some authors have recommended that patients receiving whole brain radiation therapy and who have had seizures should not be prescribed phenytoin but an alternative anticonvulsant. This article reviews the current literature pertaining to the development of this potentially lethal complication in patients receiving whole brain radiation and phenytoin, with reference to the single recorded case of Stevens–Johnson syndrome in a patient receiving cranial irradiation and phenytoin in Auckland, New Zealand. While the clinical picture in the 16 patients reported in the literature and the current case report differed from the classical form of erythema multiforme, a similar pattern of presentation and outcome appeared in all patients reviewed, suggesting that the combination of phenytoin, cranial irradiation and the gradual reduction of concomitant steroids seem to lead to the development of erythema multiforme and/or Stevens–Johnson syndrome. The data presented, although sparse, suggest that phenytoin should not be prescribed in patients receiving cranial irradiation.

Key words: *cranial irradiation; erythema multiforme; phenytoin.*

INTRODUCTION

Erythema multiforme syndrome is a characteristic response of the skin and mucous membranes secondary to a number of aetiological factors including hydantoins such as sodium phenytoin.[1–3] Pathologically, erythema multiforme consists of an acute lymphohistiocytic inflammatory infiltrate around blood vessels that may lead to degenerative changes in the endothelial cells of the capillaries and marked papillary–dermal oedema.[3–5] Rarely, the disease progresses to a severe form characterized by bullous formation with generalized erythema, exfoliation of the skin, organ involvement and possibly systemic shock, known as Stevens–Johnson syndrome.[3] This may be unrelenting and fatal in its outcome. Classical forms of erythema multiforme and Stevens–Johnson syndrome have been reported to complicate treatment both with phenytoin and radiation therapy separately.[6–15] Three recent publications have reported the development of these two syndromes in patients receiving phenytoin and radiation therapy concomitantly, presenting with a clinical picture that differs from the classical form of erythema multiforme syndrome.[16–18] This study reviews the current literature pertaining to this uncommon complication with reference to the single recorded case of Stevens–Johnson syndrome in a patient receiving cranial irradiation and phenytoin, presenting in Auckland, New Zealand.

CASE REPORT

A 55 year old Caucasian female underwent mastectomy for an early stage carcinoma of the right breast 6 years ago. She presented 3 years following surgery with grand mal seizures and was placed on phenytoin, 300 mg *nocte* and dexamethasone 16 mg daily. Computed tomography (CT) scan of the whole brain had shown multiple cerebral metastases. Other staging investigations had shown evidence of bone metastases. The patient was prescribed tamoxifen 20 mg daily. She commenced palliative whole brain irradiation therapy using 6 MV photon energy with parallel opposed fields. After 7 × 2.25 Gy fractions a gradual dose reduction of dexamethasone was commenced. The patient at that stage was well and was tolerating her treatment without untoward effects. After 11 fractions the patient developed a grade 1 (RTOG) cutaneous reaction

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involving her scalp. The patient had been on phenytoin for 30 days. Two days later the patient re-presented with periorbital oedema, conjunctivitis, a severe erythematous reaction of the scalp extending onto the forehead and involving the external auditory canal and posteriorly along the neck. It was associated with a generalized maculo-papular eruption, oliguria and hypotension, and a fever of 40°C. The patient was dehydrated and had multiple small benign-feeling nodes. There was no evidence of systemic organ involvement on examination. Phenytoin and tamoxifen were immediately withdrawn, but the cutaneous lesions continued to progress involving all of the head and neck, trunk and extremities including the back of the palms, associated with the development of target-like lesions (Figs 1,2). The patient developed bilateral purulent conjunctivitis and folliculitis, complicated by oral candidiasis. Cultures of the cutaneous lesions and multiple sites including eyes, lips and throat were negative for bacterial and viral organisms. Serology for various viral infective organisms was also negative. High dose combination antibiotics including flucloxacillin and gentamicin, prescribed empirically, did not retard the progression of the cutaneous changes. The patient developed diffuse epidermal sloughing. A lesion from the left lower limb was biopsied (Fig. 3). Histology of the dermis showed a predominantly superficial perivascular infiltrate of lymphocytes, histiocytes and a few eosinophils and oedema of the papillary dermis. The epidermis showed mild oedema and inflammatory

Fig. 2 Generalized rash with target lesions evident, particularly lateral to the umbilicus of the same patient shown in Fig. 1. Note right mastectomy scar.

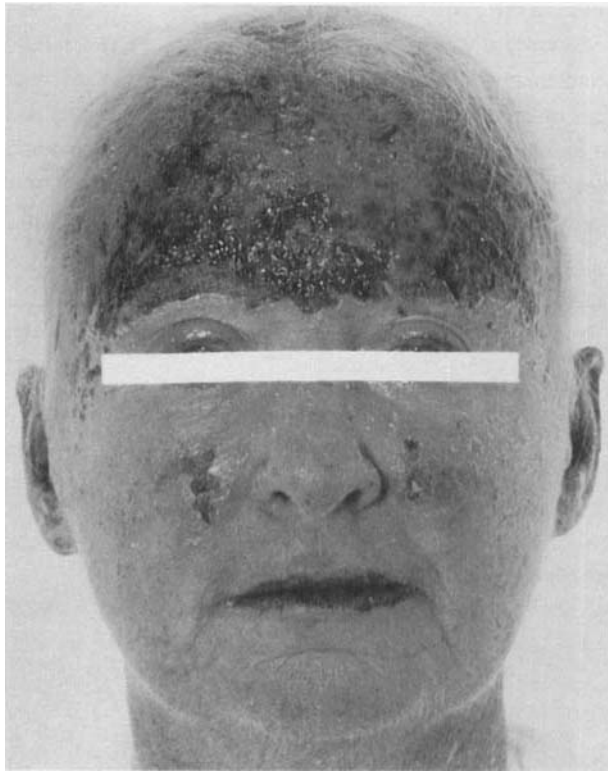

Fig. 1 Erythema, desquamation and ulceration particularly prominent within the radiated field on the patient's scalp.

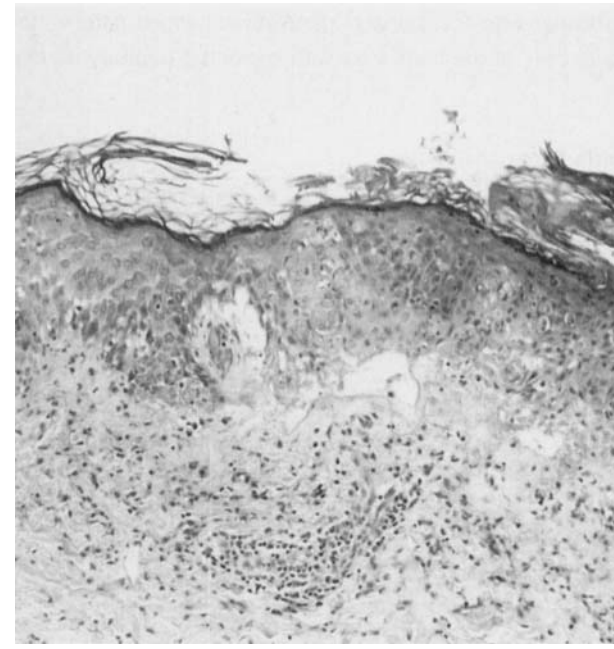

Fig. 3 Skin biopsy showing features of dermal/epidermal erythema multiforme (HE × 500).

cell infiltration (exocytosis) with scattered necrotic keratinocytes, appearances classical for mixed dermal/epidermal type erythema multiforme.

Because of the extensive desquamation and mucositis involving the oral cavity and other mucosal surfaces with severe peri-orbital and oral oedema, the patient required intensive care. In view of recurrent seizures the patient was commenced on alternative anticonvulsant medication with sodium valproate 600 mg twice daily. Intensive management, including fluid and electrolyte replacement, was required over a period of 5 days. The patient's condition gradually improved and the skin eventually re-epithelialized over a period of 6 weeks. She did not require any form of skin grafting or surgical repair. Her only persisting complication was that of impaired hearing, which resolved following complete re-epithelialization of the skin and the external auditory canals.

Radiotherapy to the whole brain was not resumed and the patient was eventually discharged home on sodium valproate 600 mg twice daily and placed on a gradual reducing dose of dexamethasone.

DISCUSSION

Erythema multiforme syndrome is characterized by typical clinical and pathological appearances of the skin and mucosa and occasionally is complicated by systemic organ involvement. A number of aetiological factors have been associated with this condition; these include infectious agents, drugs (including hydantoins such as phenytoin), and radiation therapy. It may also occur as a paraneoplastic phenomenon. In 50% of cases no aetiology is determined. The association with malignancy is rare.[1-3,5] Pathologically, there is an acute lymphohistiocytic inflammatory infiltrate surrounding blood vessels associated with occasional degenerative changes in the endothelial cells of the capillaries with a marked papillary/dermal oedema (Fig. 3). Evidence of an immunologic disorder has been reported.[3-5,16]

Stevens–Johnson syndrome is a severe form of erythema multiforme characterized by generalized erythema and bullous formation with exfoliation of skin and mucosal surfaces, accompanied by constitutional symptoms and occasionally systemic organ involvement. This syndrome can be life-threatening.[3,15] Whilst a number of authors have reported the association of these syndromes separately with phenytoin[6-9] or radiation therapy,[10-15] only three publications have reported the incidence of erythema multiforme or Stevens–Johnson syndrome when cranial radiation therapy is prescribed to a patient receiving phenytoin (Table 1).[16-18] The pathogenesis of this disorder is controversial but is believed to be associated with an immunologic disorder.[16] Some authors suggest that disruption of the hypothalamic-pituitary axis following cranial radiation is also contributory.[17]

All three associated factors, that is, the cerebral tumour/s, radiation therapy and phenytoin are associated with a decrease in the number of circulating T lymphocytes, and a decrease in the lymphocyte transformation response to mitogens.[16] This impairment of T suppressor cells might allow for the full development of a hypersensitivity reaction to phenytoin, which would be made more evident as the patient is placed on a reducing dose of steroids. Phenytoin is also known to reduce the bio-availability of dexamethasone, which may well worsen the sensitivity reaction.[19] Other authors have also suggested that phenytoin hypersensitivity reactions may be due to an excess of cytotoxic T cell subtypes.[16,20]

Clinically, erythema multiforme presents with a characteristic symmetrical distribution, and a predilection for the extensor areas of the distal part of the limbs, the back of the hands and the dorsa of the feet with frequent involvement of palms and soles. Involvement of mucosal membranes is also common,

Table 1. Reported cases

Author	No	Sex	RT field	Interval (days)		Type of reaction		Dose reduction of steroids	Treatment	Recovery (weeks)
				1st Phenytoin dose	1st RT dose	EM	SJS			
Maiche *et al.* (1985)[18]	4	—	Whole brain	—	—	—	4	—	Increase steroids Discontinuation of phenytoin & RT	—
Delattre *et al.* (1988)[16]	8	3M 5F	Whole brain	24–35	25–30	5	3	Yes	Increase steroids Discontinuation of phenytoin & RT	2–8 (1 > 52)
Janinis *et al.* (1993)[17]	4	M	Whole brain	30–32	25 ⩾ 30	3	1	?Yes	Increase steroids Discontinuation of phenytoin & RT	6–7
Borg *et al.* (1994)	1	F	Whole brain	30	7	—	1	Yes	Increase steroids Discontinuation of phenytoin & RT	6

RT, radiotherapy; M, male; F, female; EM, erythema multiforme; SJS, Stevens–Johnson syndrome.

particularly the oral cavity. In this situation, lesions initially present as vesicles or bullae that ulcerate and are associated with oedema and crusting. The syndrome may progress to its more severe form with severe toxaemia, fever and systemic involvement (lungs, liver and kidneys).[6,15] The primary lesions of the skin are termed 'target' lesions (Fig. 1) presenting as bright red lesions associated with induration and pale, ulcerated centres. The central area may contain a bulla. In the milder form the skin reactions typical of erythema multiforme usually resolve spontaneously even in the presence of malignant disease or, if due to a known aetiological cause, after removal or treatment of the known cause.[3-5] Systemic corticosteroids have often been employed in the treatment of this condition. Unlike the classical picture associated with erythema multiforme from other causes, this syndrome, as reported by Delattre *et al.*, Maiche *et al.*, and Janinis *et al.* and as seen in our case report, always began within the irradiated field on the scalp.[16-18] Most patients were on a tapering dose of steroids, and the cutaneous and/or systemic lesions progressed despite immediate discontinuation of phenytoin and radiotherapy and in spite of the use of increasing doses of steroids. The early involvement of the scalp suggests that the syndrome may be preceeded by an early radiation cutaneous reaction. Biopsy is essential to confirm the clinical diagnosis and to exclude malignant cutaneous involvement or infective causes. Patients developing this syndrome were all shown to have normal therapeutic serial phenytoin levels (where these were undertaken).[16-18] In previous reports there was no correlation between the histological type of cerebral tumour or the radiation dose received by the patient (Table 2). The clinical presentation of the case reported here is similar to other cases, particularly with regards to the distribution of the lesions, the similar delay between the commencement of phenytoin and the development of the rash (approximately 30 days), the delay between the first radiation therapy dose and the onset of the rash (20 days), and the similar time to recovery (6–8 weeks; Table 1). Although there are no reported fatalities, the severity of the syndrome is of concern; our patient developed shock with oliguria and hypotension requiring several days in intensive care, whilst others have reported organ involvement and complications associated with re-epithelialization of the involved area.[16] One of the cases reported by Delattre *et al.* underwent a left lower lid splitting procedure for secondary adhesions of the left lid to the globe and had persistent difficulty in opening his eyes.[16] This patient was also reported to have difficulty in walking and in his ability to use his upper limbs as a result of tenderness, retractions and severe pain. Therefore, prompt diagnosis and treatment with cessation of radiation therapy and phenytoin are strongly recommended.

Whether phenytoin should be completely avoided in patients receiving cranial irradiation, as suggested by some authors, is controversial.[16,21] Other anticonvulsants are associated with their own side-effects. Sodium valproate, which is often used as an alternative therapy in our department, is known to be associated with liver toxicity.[3,16] The use of anticonvulsants as prophylaxis is also controversial. It would seem inappropriate to place patients receiving cranial irradiation on prophylactic anticonvulsant therapy in the absence of a history of seizures.[1,21] Some 20% of patients with metastatic cerebral tumours have been reported to suffer from seizures, with a higher incidence in patients with metastatic melanoma and primary gliomas. Some authors also report a high incidence of seizures in the latter patients following surgery.[1,16,21] To avoid the risk of developing erythema multiforme syndrome, the use of anticonvulsants, usually over prolonged periods of time (with the associated problems of compliance, side-effects and drug interaction, particularly with dexamethasone), should therefore only be prescribed to patients with a history of seizures.

Table 2. Primary tumour

Author	Tumour	No.
Maiche *et al.* (1985)[18]	Glioma	3
	Lung carcinoma	1
Delattre *et al.* (1988)[16]	Breast carcinoma	3
	Lung carcinoma	3
	Germinoma	1
	Glioma	1
Janinis *et al.* (1993)[17]	Lung carcinoma	3
	Glioma	1
Borg *et al.* (1994)	Breast carcinoma	1

There are very few reports suggesting an increase in the severity of this syndrome when patients are on concomitant chemotherapy but similar cutaneous reactions have been reported with certain chemotherapeutic drugs.[5]

In summary, physicians caring for patients receiving cranial irradiation and phenytoin should have a high index of suspicion and be able to recognize the development of erythema multiforme and/or Stevens–Johnson syndrome in their initial phase. The latter complication in particular is life-threatening and these lesions should be treated promptly and appropriately in a combined clinical setting in consultation with dermatologists and infectious disease specialists. Both cranial irradiation and phenytoin should be withdrawn promptly and an alternative anticonvulsant therapy used. Prompt cessation of the two latter treatment modalities may not necessarily prevent further progression of the disease. Furthermore, these patients may well require either further radiation therapy at some future date or alternative treatment for their cerebral malignancy. Tapering steroids more gradually over a prolonged period of time may also help to limit the severity of erythema multiforme syndrome.

Therefore, it may well be appropriate to avoid the use of phenytoin in patients receiving whole brain irradiation therapy although this drug remains the drug of choice in patients requiring anticonvulsant medication in most centres.

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