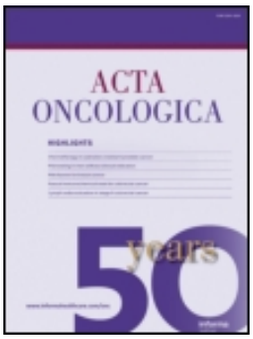

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Stevens–Johnson Syndrome in Patients on Phenytoin and Cranial Radiotherapy

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The use of phenytoin as a prophylactic anticonvulsant after brain surgery, particularly for brain tumors, is a common practice, regardless of whether the patient has a previous history of convulsions. This treatment policy assumes that the benefits exceed the risks. Four cases are described of adverse reactions to phenytoin during the concomitant use of cranial radiotherapy. In one patient this proved fatal. There is increasing anecdotal support in the literature for a synergistic effect between phenytoin therapy and cranial radiotherapy that can result in the life-threatening Stevens–Johnson syndrome. While the association is uncommon, four cases within 24 months in one department suggest that the routine use of postoperative phenytoin as a prophylactic anticonvulsant in the absence of a history of seizures may not be warranted, particularly if the patient is to receive cranial radiotherapy.

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Recent studies have shown that Stevens–Johnson syndrome (SJS) and toxic epidermal necrosis (TEN) can be distinguished from erythema multiforme (EM) based on the etiology, clinical presentation, as well as on the histopathologic picture (1–4). Erythema multiforme major (EMM) is an acute skin eruption with distinct clinical and pathological features. It is associated with numerous factors, drugs and herpes simplex virus (HSV) being the most frequent causes. The classical distribution of skin lesions in EMM is symmetrical and confined to the face and extremities with a predilection for extensor surfaces. They appear as erythematous macules that may progress to typical target lesions in the form of raised edematous papules with or without mucosal involvement. The target lesions are defined as individual lesions less than 3 cm in diameter with a regular round shape, well-defined border and having at least three different zones; two concentric rings around a central disk (2).

SJS is characterized by atypical target lesions accompanied by widespread blisters involving the face, trunk and extremities, in association with ocular and mucous membrane manifestations.

TEN is a severe form of the disease that might overlap with SJS, and both disorders are drug-induced. In many series, over 90% of TEN cases have a probable drug cause (5, 6). This is characterized by severe cutaneous blistering and extensive detachment of the epidermis. In both SJS and TEN the predominance of an extensive necrotic pattern of the epidermis in the histologic picture was observed (3). The condition may be accompanied by constitutional symptoms and visceral involvement and there is a risk of a fatal outcome (7–9). TEN is associated with a mortality rate of 20–66% and the more extensive the blisters, the higher the morbidity and mortality (5).

The appearance of this syndrome in patients undergoing radiotherapy is rare (8, 10). Recently, this condition has been increasingly recognized in patients on anticonvulsant drugs and cranial radiation (7, 10–12). We present four cases, which demonstrate the risk of using phenytoin in patients receiving cranial radiotherapy.

CASE 1

A 22-year-old male patient presented in August 1994 with a 2 months' history of headache, nausea, vomiting, diplopia and occasional transient loss of consciousness. Over the last month he had noticed weakness in his left side. Neurological examination showed bilateral VI nerve palsy, temporal hemianopia and left hemiparesis (grade 3/5). A CT scan of the brain showed a large right temporal lesion extending to the thalamus, mid-brain and corpus

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callosum. A stereotactic biopsy of the lesion was unsuccessful. Craniotomy and debulking of the tumor was undertaken on 10 August and the histology showed glioblastoma multiforme. After surgery the patient was put on 100 mg phenytoin three times daily and dexamethasone 2 mg/8 h.

The patient was then started on postoperative radiation and adjuvant chemotherapy. Radiation therapy treatment was given between 11 September and 8 October 1994, using a linear accelerator and a three-field technique to treat the tumor-bearing area with a safety margin. He received a radiation dose of 50 Gy in 20 fractions over 4 weeks. Chemotherapy was started on 3 October (BCNU 80 mg/m.sq.)

On 6 October, the patient developed a mild maculopapular rash on the face which progressed and necessitated hospital admission three days later. At the time of admission the patient had a fever (39.7°C), and on examination there was conjunctivitis with periorbital edema and extensive oral and mucosal ulcerations. The maculopapular rash was intense and involved the neck, trunk and upper extremities. A complete blood count showed thrombocytopenia. Liver function tests and renal profile were normal. Serum phenytoin level was 7.3 mg/L (therapeutic range 10–20 mg/L). Blood cultures and serology for cytomegalovirus, viral hepatitis A, B and C were negative. A biopsy was done on a skin lesion and this showed inflammatory cellular changes with perivascular mixed inflammatory infiltrate and extensive necrosis of the epidermis that involved predominantly the basal layer. These histological features were consistent with TEN/SJS. Phenytoin was discontinued and the patient was put on intravenous fluids, corticosteroids, acyclovir and vancomycin. He went into a state of shock and died on 11 October 1994.

CASE 2

A 56-year-old woman was seen with a 4-month history of double vision and partial hearing loss in the left ear. On physical examination she was found to have right III, IV and VI cranial nerve palsy with no other neurological anomalies. A CT scan of the brain showed a destructive lesion of the base of the skull involving the sphenoid sinus and extending into the nasopharynx. A craniotomy with partial excision of the tumor was carried out on 8 March 1995. The histopathological examination of the tumor showed chondrosarcoma. After surgery the patient was treated prophylactically on phenytoin 100 mg 8/h.

The patient began radiotherapy treatment on 3 April 1995 on an 18 MV linear accelerator. The plan was to deliver a radiation dose of 50 Gy in 25 fractions over 5 weeks, treating the tumor with a safety margin using a three-field technique. On 10 April, just one week after the start of radiation treatment, the patient became febrile (38.3°C) and displayed symptoms that suggested a urinary tract infection, for which reason she was started on amoxicillin 500 mg t.i.d. She developed a maculopapular rash on the face on 19 April, by which time she had received 20 Gy of radiation to the tumor. The rash was attributed to amoxicillin, which was promptly stopped and radiation treatment was suspended to allow resolution of the skin lesions. The patient was hospitalized on 22 April as the rash had become generalized with bullae formation. The patient also had fever, conjunctivitis and severe mucositis (Fig. 1). Phenytoin was then discontinued and sodium valproate 500 mg b.i.d. was started. Oral swab, blood and urine cultures did not grow any pathogens. CBC, renal profile and liver function tests were normal apart from elevated GGT 529 U/L (normal range 5–55 U/L). Serum phenytoin levels were not measured. A biopsy was taken from the right forearm lesion and histologic examination revealed a superficial perivascular inflammatory infiltrate consisting mainly of neutrophils, with absence of the lichenoid pattern and excytosis usually seen in EMM. The most prominent histologic feature was focal epidermal necrosis that was out of proportion to the inflammatory infiltrate. These findings were consistent with SJS/TEN (Figs. 2 and 3). The patient was given corticosteroid treatment and her condition gradually improved, the skin lesions cleared and the fever subsided. The patient was discharged from the hospital after 7 days and restarted on radiotherapy without any further problems. When seen at follow-up in July 1995, she was in good health.

CASE 3

A 41-year-old female presented in June 1997 with a 2 months' history of right-sided weakness, headache and repeated seizures. Neurological examination showed right hemiplegia. Magnetic resonance imaging (MRI) of the brain showed three separate lesions in the trigone of the lateral ventricle, parasagittal and left frontal region. She

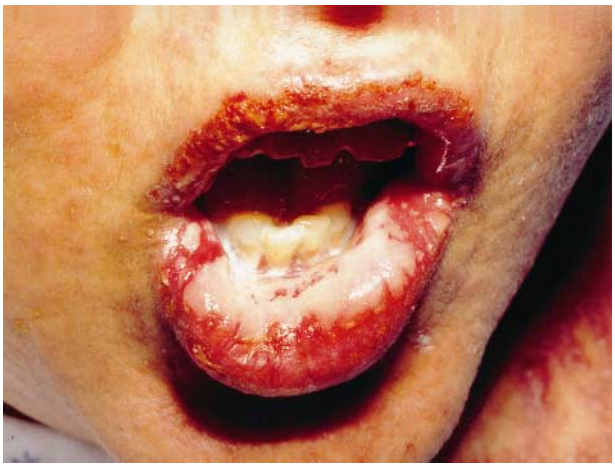

Fig. 1. Close-up of oral mucosa and lips: severe mucosal reaction and ulceration (case 2).

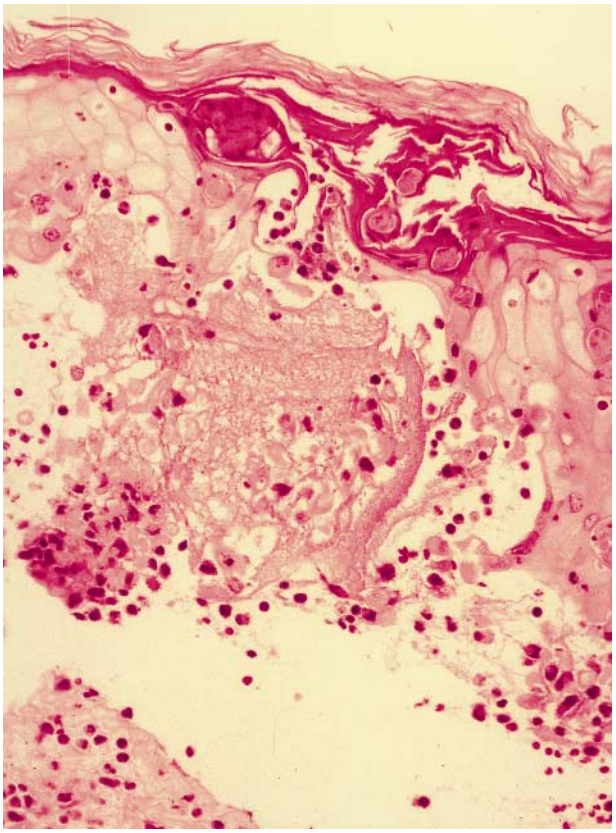

Fig. 2. Histologic findings from a skin biopsy showing predominant areas of focal epidermal necrosis with a mild perivascular inflammatory infiltrate, consistent with Stevens–Johnson syndrome (SJS).

underwent craniotomy and biopsy on 1 June 1 1997 and the histology revealed glioblastoma multiforme (multifocal). After surgery The patient was started on phenytoin, 100 mg three times daily. From 8 June to 5 July 1997 she received palliative radiation to the entire brain at 45 Gy using parallel-opposed fields. Two days after completion of radiotherapy, the patient presented with a generalized skin rash of acute onset. On examination, she was febrile and toxic, and had extensive bullous erythema involving the face, scalp neck and trunk regions. There were severe ulcerative mucosal lesions of the mouth that interfered with feeding. She had a purulent discharge from both ears. The patient was admitted to hospital and put on IV fluids, antibiotics, low-dose steroids and subcutaneous morphine/midazolam infusion. The serum phenytoin level was below the therapeutic range, blood cultures and serum virology tests were negative. Phenytoin was discontinued. A biopsy of an abdominal skin lesion showed that the histological features were consistent with SJS. The patient's condition gradually improved with clearance of the skin and mucosal lesions and she was discharged from hospital 3 weeks later.

CASE 4

A 45-year-old female with a 4-month history of headache, nausea and progressive right-sided body weakness but no history of seizures was found to have a right hemiplegia. A CT scan of the brain showed a space-occupying lesion in the left parieto–occipital region. Partial tumor excision was carried out in May 1997 at an outside hospital and the pathology revealed glioblastoma multiforme. She was admitted for further surgery at our hospital on 28 June 1997, for excision of residual tumor, and the histologic diagnosis was confirmed.

The patient was started on postoperative prophylactic phenytoin, 200 mg twice a day. The postoperative course was complicated by infection of the bone flap and a third operation was carried out for removal of the infected flap. She then started radiation therapy to the whole brain and received a total dose of 45 Gy. Three weeks from the start of her radiation treatment, on 28 July, the patient developed a generalized maculopapular rash with widespread blisters, periorbital edema, purulent discharge from both ears, and extensive oral mucosal ulcerative lesions. The phenytoin level was within the therapeutic range. The clinical diagnosis of SJS was made and phenytoin discontinued. A skin biopsy was not done. The patient was started on antibiotics and low-dose decadron (2 mg twice/

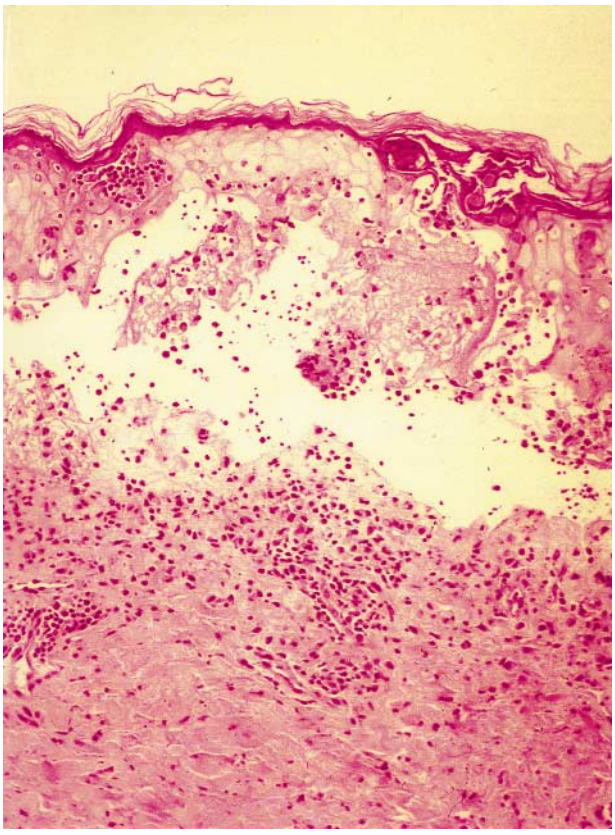

Fig. 3. Low power view shows epidermal separation with a subepidermal blister (case 2).

day). The course of the disease was mild and the patient's condition rapidly improved. She was discharged 7 days after admission and continued her radiation treatment without any further problems.

DISCUSSION

There is no universally acceptable definition to differentiate between EM, EMM, SJS and TEN (2). In the past 30 years, it was thought that these were all parts of a spectrum of a single disease at various evolutionary phases, and with varying degrees of severity, rather than separate clinical entities. TEN was thus considered the most severe form of the disease within the spectrum. It was first described by Leyll in 1956, as a syndrome characterized by extensive necrosis and detachment of the epidermis, associated with constitutional symptoms and serious complications. It was notoriously described to have a mortality rate between 20% and 66% and potentially disabling ocular sequelae in survivors (4).

Recent reports suggest that EM, SJS and TEN could be separated as two distinct clinical disorders with similar mucosal reactions but different patterns of cutaneous lesions (1–4). The findings suggested that typical papular target lesions, distributed on the extremities and face, characterize herpes-induced EMM, whereas flat atypical target lesions or purpuric macules, with widespread distribution on the trunk, face and extremities were characteristic of drug-induced SJS.

Two large population-based studies, were carried out to estimate the incidence of EM, SJS, and TEN requiring hospitalization, and to identify possible drug therapies associated with these reactions (5, 6). In these studies, a uniform set of diagnostic criteria was used to differentiate between these different entities, based on type and size of the skin lesions (bullae, typical or atypical target lesions > 3 cm vs. < 3 cm), extent of skin involvement ($> 20\%$ vs. $< 20\%$ of body area) and presence or absence of mucosal lesions. In some other studies, these distinctions were also based, in addition to this, on histologic findings. EMM skin lesions were associated with a predominantly inflammatory pattern with deep perivascular inflammatory infiltrate and exocytosis, while in SJS/TEN detailed histologic analysis revealed a predominantly necrotic pattern, with major epidermal necrosis, fewer dermal inflammatory changes and less exocytosis (3). This clinico-histologic correlation was highly significant statistically. All these studies however, have the limitation of being retrospective, based on a review of clinical photographs and hospital records rather than prospective clinical assessment of patients (3–6). Consequently, these different patterns may in fact represent evolutionary stages of the same disease, and the histopathologic changes might have depended mainly on the age of the lesions and the site of biopsy.

The patients presented in this report had constitutional symptoms, atypical skin target lesions, ocular and mucosal involvement on which the diagnosis of SJS/TEN was based. In 3 out of 4 cases the diagnosis was confirmed by histologic diagnosis which showed the typical features of epidermal necrosis with a mild to moderate perivascular inflammatory infiltrate. This was also supported by the negative viral serology in our cases.

Whereas EM, SJS and TEN are all caused by drug therapies, EMM has many other causes unrelated to drug therapy (1, 6). The common etiological factors for EMM are classified as iatrogenic, infectious and idiopathic (6, 13–15). The antibiotics most frequently implicated are sulfonamides, penicillins, tetracycline, erythromycin, and cephalosporins. Antituberculous treatment, anticonvulsants, butazones and antibiotics were also reported to induce TEN (14, 15). Skin reactions occur in 5 to 10% of patients receiving phenytoin, but SJS is an uncommon association (15). Some recent studies suggest that TEN, SJS and other adverse drug reactions (ADRs) might also have a metabolic basis (16). It has been hypothesized that cutaneous ADRs to sulfonamide and anticonvulsant drugs may be linked to a highly specific defect in the detoxification of drug-reactive metabolites. Others suggested a probable immune-mediated mechanism, and many authors have proposed that these patients be treated with immunosuppressive drugs (17, 18). In both immune and metabolic-based hypotheses a genetic susceptibility is suspected: in fact an association between TEN and certain HLA subtypes has been reported (19).

Radiation as a cause of SJS and TEN has also been described (9–11). The possible causes of SJS in cases 1, 3 and 4 included both phenytoin and radiation, whereas in case 2 penicillin, phenytoin and radiation have to be considered. It is unlikely that amoxicillin was the cause, as the rash improved only after cessation of phenytoin and radiation. In case 1, BCNU was used. Although this agent may sometimes cause some skin reactions (facial flushing, burning sensation and skin hyperpigmentation), there are no reports of BCNU as a cause of EM or SJS. We believe that the combination of phenytoin and radiation in these four patients resulted in the development of SJS.

The clinical evaluation of the agent causing ADRs, may be complicated by factors such as simultaneous exposure to several drugs, drug interactions, and variability of the latent period between delivery of the offending agent and the appearance of the reaction. Timing is a key clinical feature to consider: in our patients the time interval from starting phenytoin and radiation and the appearance of the rash is similar to that given in other reports (10). All four patients were put on phenytoin postoperatively, and radiation treatment was started at weeks 3–4 after surgery. In 3 patients, the skin and

mucosal lesions appeared at 3–4 weeks from the start of radiation; in case 2 the rash was observed after the first week of radiation. The use of postoperative steroids in case 1 may have resulted in a longer latent time interval and some delay in the onset of reactions in this patient. In all but case 2, the onset of reactions developed at a time when patients had been on anticonvulsant treatment for 5–7 weeks or longer, making phenytoin alone as a causative agent unlikely. Although this possibility cannot be completely ruled out, yet ADRs usually develop 2–3 weeks after intake of the offending drug, and it is uncommon for patients to develop these reactions later then a month (6). In all four patients the possibility of viral infections being the underlying etiology was excluded by negative serology screening.

The serum phenytoin level was checked in 3 of these 4 patients, and was found below or within the therapeutic range, at the time of occurrence of SJS. The reaction is apparently not dose related, and abrupt discontinuation of phenytoin does not necessarily alter the course once the reaction has begun. The SJS course was fulminant and severe in 3 patients, one of whom died (case 1), and was mild in one patient (case 4).

The clinical course of the reactions in these four patients supports the possible combined effect of phenytoin and cranial irradiation as a causative agent of SJS. Furthermore, in cases 2 and 3 radiotherapy was resumed, after changing to an anticonvulsant other than phenytoin, without exacerbating the skin lesions.

The pathogenesis of SJS in patients receiving combined radiotherapy and phenytoin remains obscure. A number of hypotheses have been advanced to explain the possible mechanisms. While some authors suggested that irradiation of the hypothalamic–pituitary axis could be a triggering mechanism for skin reactions in patients on drugs known to cause SJS (12, 20), others proposed that immunosuppression following radiotherapy may somehow facilitate the development of a hypersensitivity reaction to phenytoin (11, 17). In our view perhaps it is the combination of radiation, steroids and phenytoin, each affecting the immune system in its own way to create an environment where the patient is at increased risk of developing SJS. In the majority of the previously reported cases receiving cranial irradiation and phenytoin, steroids were also being administered (13). Recent studies show that long-term steroid therapy may delay the onset of the reaction, but does not halt its progression (18).

Finally, the routine use of anticonvulsants after brain surgery seems to be a variable practice. The indication was doubtful in our cases. In case 1 there was a history of recurrent transient loss of consciousness, which may have been epileptic in nature. In case 3, there was a clear history of seizures, whereas in cases 2 and 4 there was nothing to suggest a history of convulsions.

CONCLUSION

Stevens–Johnson syndrome can occur in patients receiving cranial radiotherapy and phenytoin and this complication can be fatal. Care should be taken with patients who are given phenytoin during cranial radiotherapy and both radiation and phenytoin should be discontinued at the first sign of EM. We suggest that the practice of routine use of phenytoin following brain surgery should be re-evaluated, since the treatment may be neither essential nor without side effects.

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