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Case Report

Toxic epidermal necrolysis in a breast cancer patient treated with whole brain radiotherapy and phenytoin: Should phenytoin have been used?

乳癌患者接受全腦放射治療出現中毒性表皮壞死症：苯妥英納應否使用？

H Ranu, SM Pang

Phenytoin is commonly used as a prophylactic anticonvulsant for intracranial malignancies. Many of these patients also receive concurrent cranial radiotherapy. There are increasing numbers of reports suggesting possible synergism between phenytoin therapy and cranial radiotherapy leading to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Phenytoin should be used with caution and all cutaneous reactions must be promptly evaluated and reported. We report a case of TEN in a patient receiving phenytoin that appeared shortly after the end of cranial irradiation for brain metastases from breast cancer. The pathogenesis and implications are briefly discussed.

苯妥英鈉常用於顱內惡性腫瘤作預防性抗驚厥藥。很多這類病人同時接受顱放射治療。越來越多報導顯示苯妥英鈉與顱放射治療會有引起史蒂芬強森症候群及中毒性表皮壞死症的連合作用。應小心應用苯妥英鈉，所有皮膚反應必須及時評估及報導。我們報導一例苯妥英鈉應用病人於乳癌腦轉移的腦放射治療後期發生中毒性表皮壞死症，並對其發病機理及意義作簡略討論。

Keywords: Cutaneous drug eruptions, Phenytoin, Prophylactic anticonvulsants, Toxic epidermal necrolysis, Whole brain radiotherapy

關鍵詞：藥疹，苯妥英鈉，預防性抗驚厥藥，中毒性表皮壞死症，全腦放射治療

Introduction

Toxic epidermal necrolysis (TEN) is an acute and life-threatening mucocutaneous disease that is almost always related to exposure to drugs and has an average mortality of 25-35%. Other rare associations include vaccinations, exposure to industrial chemicals and *Mycoplasma pneumoniae* infection. The drugs most frequently implicated are sulpha drugs such as trimethoprim/sulphamethoxazole and sulphasalazine, allopurinol, non-steroidal anti-inflammatory drugs and anticonvulsants. Toxic epidermal necrolysis is characterised clinically by a rapidly progressive, severe vesicobullous eruption causing necrotic and haemorrhagic bullous lesions of the skin and mucous membranes. This progresses to

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generalised erythema with extensive detachment of the epidermis. Characteristic histopathology includes subepidermal oedema, bullae formation and confluent necrosis of the epidermis.[1] We highlight here the combination of phenytoin and intracranial radiation therapy as a risk factor for this skin disorder.

Case report

A 43-year-old Chinese lady was diagnosed with locally advanced carcinoma of the left breast in October 2005. She underwent neoadjuvant chemotherapy with three cycles of doxorubicin and cyclophosphamide with reduction in size of the breast mass, followed by wide excision with axillary clearance. Histology showed a 5 cm residual invasive ductal carcinoma that was negative for oestrogen and progesterone receptors but strongly positive for cerb-B2 (3+); 25 out of the 28 lymph nodes were positive. She was undergoing adjuvant weekly paclitaxel and trastuzumab when she developed solitary metastases to contralateral right cervical lymph nodes confirmed on fine needle aspiration. She was then switched to vinorelbine, cisplatin and trastuzumab followed by consolidative radiotherapy to the left breast and bilateral supraclavicular fossae. However, there was progression of the nodal disease in the right supraclavicular fossa in August 2006 and she was switched to capecitabine to which she did not respond. Then she was enrolled into a clinical trial using capecitabine and lapatinib.

During the 5th cycle of lapatinib and capecitabine, she was admitted following a generalised tonic-clonic seizure. Computed tomography of the brain revealed a frontal lobe mass suggestive of cerebral metastasis. She was commenced on phenytoin and dexamethasone. Five days later, whole brain radiotherapy (WBRT) was commenced. On the third day after the completion of WBRT (i.e. 23 days after the first dose of phenytoin and 19 days after the initiation of radiotherapy), she developed fever, malaise, and a rapidly progressing vesicobullous eruption. There was a confluent erythematous exanthem observed over the irradiated areas (Figures 1 & 2) i.e. the scalp, neck and upper chest, which progressed rapidly into painful blistering and denudation of the skin. There was associated oral mucositis, haemorrhagic cheilitis and conjunctivitis. Within two days, the eruption progressed to involve the upper abdomen and back. The estimated body surface area affected was 30% with approximately 15% epidermal detachment. Phenytoin was discontinued on admission and a skin biopsy was performed on the upper back. Histopathological examination of the biopsy specimen revealed confluent foci of epidermal necrosis and sub-epidermal bulla formation with the presence of apoptotic keratinocytes. There was a moderate perivascular lymphocytic infiltrate (Figure 3). These findings were consistent with toxic epidermal necrolysis.

She was started on intravenous corticosteroids. Intravenous vancomycin and piperacillin/tazobactam were administered. The patient was managed with strict antiseptic measures. She was put on regular morphine for pain control. The blisters were punctured and saline compresses were applied. Supportive topical care and pain medication was also provided. New blisters continued to appear daily. Her fever continued to spike and she became increasingly breathless. Radiographs of the chest showed bilateral pleural effusions. Blood cultures were negative. Subsequently new blisters ceased to appear with gradual improvement of her skin condition following discontinuation of phenytoin and administration of intravenous steroids. However, she continued to deteriorate and succumbed on day 6 of the illness.

Discussion

Phenytoin is well known for its frequent dermatological side effects. In 1983, Rapp et al reported a 19.4% incidence of cutaneous side

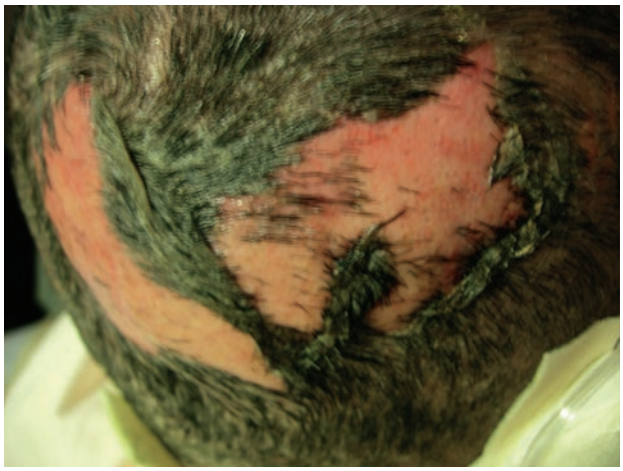

Figure 1. Occipital scalp of the patient on day 4 of rash. Blistering and denudation noted in the radiation field. The lesions subsequently spread to non-irradiated sites.

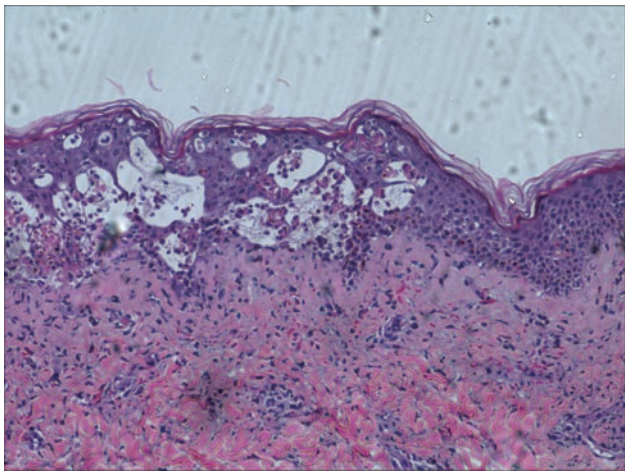

Figure 3. Epidermal necrosis, bulla formation and presence of necrotic keratinocytes. (H&E, Original magnification x 10).

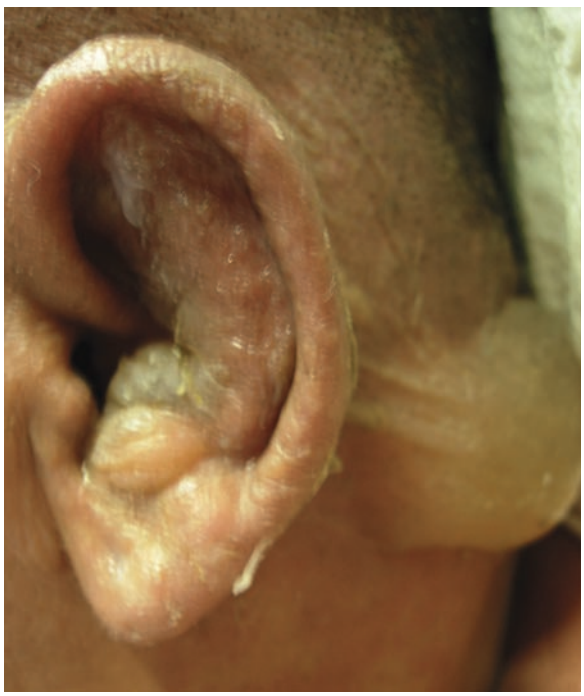

Figure 2. Tense blisters on an erythematous base over the left ear.

effects in 124 patients with brain metastases receiving phenytoin for seizure prophylaxis.[2] In 1988, Delattre et al were the first to report the occurrence of erythema multiforme major in patients with brain metastases undergoing cranial irradiation with phenytoin for seizure prophylaxis.[3] Most recently, Chung et al showed that the allele HLA-B*1502 was a predictor in the Taiwanese population for the development of SJS/TEN subsequent to carbamazepine, an anticonvulsant that is closely related structurally to phenytoin.[4] Our patient had concurrent radiotherapy with phenytoin. Several reports have shown the association of ionizing brain irradiation with development of toxic epidermal necrolysis. In most of these reports, the onset of the eruption have been associated with concurrent anticonvulsant therapy (phenytoin, phenobarbital or carbamazepine).[5]

The onset of illness was acute in our patient and the interval between introduction of the drug and formation of the rash was approximately three weeks. Serum indirect immunofluorescence to skin antigens was negative. The mechanism of irradiation-associated epidermal necrolysis is unclear. Relapses of pemphigus, pemphigoid and paraneoplastic pemphigus evoked by ionizing radiation suggests an autoimmune mechanism.[6] The eruption in these patients showed a predilection for sites of previous irradiation as in our patient where the rash started on the irradiated

sites but progressed to involve other non-irradiated areas.[7,8] A number of hypotheses have been advanced to explain the possible mechanisms. 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/TEN. [9] Others proposed that the impairment or depletion of suppressor T-cells following radiotherapy may facilitate the development of a hypersensitivity reaction to phenytoin.

There are more than 30 reported cases of SJS/TEN with the use of anticonvulsants and radiotherapy and 90% of them were receiving phenytoin together with cranial radiotherapy. One characteristic feature in all these patients is that the cutaneous eruption typically begins on and around the irradiated areas and subsequently progresses to the rest of the body.

A consensus classification defines the main difference between SJS and TEN as being the degree of epidermal detachment, being less than 10% and more than 30% respectively. Among the cases reported of SJS/TEN in patients receiving anticonvulsants and radiotherapy, only eight cases were of TEN (not SJS). Our case report is the ninth. Patients were usually in the fourth or fifth decade of life. In all cases the eruption began over the irradiated areas. The median time-lapse between initiation of radiotherapy and the onset of rash was 3-4 weeks and our patient was no exception.

In this case, the use of phenytoin was indicated as the patient initially presented with a tonic-clonic seizure. Differing opinions exist regarding the use of prophylactic anticonvulsant therapy in patients with intracranial tumours whether primary or metastatic, who do not present with seizure. Cohen et al retrospectively studied 195 patients with various intracranial metastases and observed that only 10% developed late seizures. They found no significant improvement in seizure prevention with prophylactic anticonvulsants.[10]

We highlight this case to raise awareness of the possibility of this potentially serious complication for patients undergoing cranial radiotherapy while on phenytoin. Routine use of anticonvulsants as primary prophylaxis against seizures in patients with brain tumours should be discouraged due to lack of supporting evidence. For patients with brain metastases already on phenytoin, WBRT should not be withheld, but clinicians should take extra care to monitor the skin condition of these patients both during and after such treatment.

We suggest substituting anticonvulsants like phenytoin with sodium valproate which hardly ever causes SJS or TEN. Since cranial irradiation alone can cause SJS it is unwise to use an anticonvulsant like phenytoin that is also notorious in causing SJS/TEN. With this case report we would like to urge physicians to adopt a more discerning approach in choosing an anticonvulsant for the treatment of patients undergoing cranial irradiation with strict avoidance of phenytoin.

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