Toxic epidermal necrolysis in a patient receiving concurrent phenytoin and whole brain and thoracic radiotherapy

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ABSTRACT

إن انحلال البشرة السمي هو متلازمة فرط الحساسية – النوع الرابع الناجم عن الأدوية والذي ينتج عن الأدوية المضادة للصرع خصوصاً مضادات الصرع الأروماتية مثل الفينيتوين. يتلقى أكثر المرضى المصابين بنقائل الدماغ العلاج الإشعاعي للدماغ بأكمله مع تدابير مضادات الوذمة ومضادات الصرع للوقاية أو السيطرة على الأعراض. ويعد الفينيتوين من أكثر الأدوية استخداماً. في مجموعة من المرضى، العلاج الاشعاعي للجمجمة يعد بمثابة عامل مساعد مع مضادات الصرع لتطور انحلال البشرة السمي. نستعرض في هذا التقرير حالة مريض يبلغ من العمر 54 عام مصاب بسرطان الرئة النقيلي غير صغير الخلايا وعولج بالعلاج التلطيفي للدماغ كله والعلاج الاشعاعي للنصف مع الفينيتوين المصاحب والذي بدأ من داخل بوابات الإشعاع وانتشر لاحقاً. على الرغم من أن المضاعفات نادرة ولكنها خطيرة، والتي اشتملت على تجنب استخدام الفينيتوين بالتزامن مع العلاج الإشعاعي، لتحل محل الفينيتوين مع أحدث مضادات الصرع، والتعرف المبكر، والتحكم بالأعراض والوعي بهذه المضاعفات المحتملة استعرضت جميعها في هذه التقرير.

Toxic epidermal necrolysis (TEN) is a severe drug induced type IV hypersensitivity syndrome that can be caused by anticonvulsant drugs, especially the aromatic anticonvulsants such as phenytoin. Most patients with brain metastasis receive whole brain radiotherapy along with anti-edema measures and anticonvulsants either as prophylactic or for symptom control; phenytoin being the most commonly used drug. In a subset of patients, cranial irradiation may act as a precipitating factor along with anticonvulsants for the development of TEN. We report a 54-year-old patient with metastatic non-small cell lung cancer treated with palliative whole brain and mediastinal radiotherapy with concurrent phenytoin-developing TEN, which started within the radiation portals with subsequent generalization. Though a rare, but serious complication, avoidance of the use of phenytoin concurrent with radiotherapy, replacing phenytoin with newer anticonvulsants, early recognition, aggressive management and awareness of this possible complication has been implied upon in this report.

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Steven Johnson Syndrome (SJS), Steven Johnson Syndrome-toxic epidermal necrolysis (SJS-TEN), and toxic epidermal necrolysis (TEN) are a spectrum of type IV hypersensitivity drug-induced disorders, which are characterized by blisters and epidermal detachment resulting from epidermal necrosis in the absence of substantial dermal inflammation often associated with anticonvulsant medications.[1,2] Patients with brain metastasis, irrespective of the primary tumor location are often symptomatic. They require active treatment in the form of palliative radiotherapy to the whole brain and symptomatic management, which includes anti-edema measures with systemic steroids and use of anticonvulsants either for seizure control or prophylactic use. Phenytoin is the most common drug used for seizure control. A subgroup of patients receiving this combination of whole brain radiotherapy and phenytoin develop severe cutaneous hypersensitive drug reaction that may manifest as SJS-TEN spectrum of systemic syndrome.[3,4] In this report, we describe one case of TEN developing in a patient with metastatic lung cancer receiving palliative whole brain and thoracic radiotherapy (RT) with concurrent phenytoin, emphasizing the need for anticipation, early recognition, and aggressive management of this potentially fatal medical emergency.

Case Report. A 54-year-old male patient presented with a history of shortness of breath and multiple episodes of seizure of one week duration. On evaluation, he was diagnosed with right lung non-small cell lung cancer (squamous cell carcinoma) with metastasis to brain and superior vena caval syndrome (stage IV). He was started on tab phenytoin 300 mg at bedtime and anti-edema measures with steroids (tab dexamethasone 8 mg 3 times daily during RT and tapered over 2 weeks post RT). He received palliative RT to the mediastinum and whole brain with a total dose of 20 Gray in 5 fractions over one week with Co-60 gamma rays. Two weeks post radiotherapy, his general condition improved and he received one cycle of palliative chemotherapy with paclitaxel-carboplatin combination. Nearly 3 weeks after completing the RT, he presented with painful, erythematous lesions in the scalp, which subsequently generalized. During examination, he was afebrile with pulse rate 98/min, respiratory rate 28/min, blood pressure 109/83 mm Hg, and features of mild dehydration. Examination of the skin revealed erythematous, tender macules over the scalp, face, trunk, and limbs with areas of confluent epidermal detachment and blistering involving almost 30% of his body surface area (**Figure 1**). Conjunctivitis, hemorrhagic crusting on lips, erosions over buccal and nasal mucosa and over the glans penis were noted, strongly suggesting TEN caused by phenytoin. Hemogram and biochemical parameters were normal except for hyponatremia. Phenytoin was immediately discontinued, and he was managed with intravenous fluid replacement, electrolyte correction, systemic antibiotics, steroids (dexamethasone 16 mg/day tapered at 2 mg/day over one week), and local skin care with antibiotic and antifungal dressings. After primary supportive care, his condition worsened and he died due to septicemia on the seventh day of hospital admission.

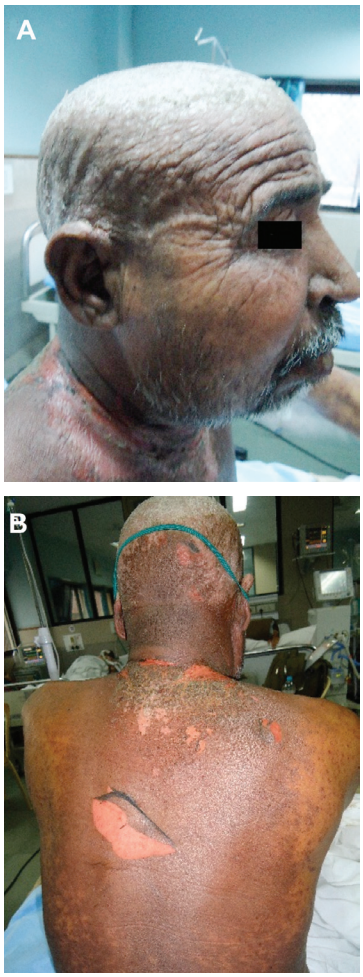

Figure 1 - An image showing areas of: **A)** dusky eruptions over the entire scalp; **B)** extensive epidermal detachment over the scalp, nape of the neck, and upper back.

Discussion. Patients with TEN, initially present with acute onset, painful skin lesions, fever >39°C (102.2°F), sore throat, oral and ocular mucosal complications, with rapidly spreading confluent and extensive epidermal detachment, dehydration, dyselectrolytemia, which rapidly evolves into systemic disease with 25-35% mortality.[2] The risk of death of patients with TEN can be accurately predicted by TEN specific severity-of-illness score, which considers 7 independent risk factors such as age >40 years, malignancy, heart rate >120/ min, initial percentage of epidermal detatchment over 10%, serum urea >10 mmol/litre, serum glucose >14 mmol/litre, and bicarbonate <20 mmol/litre.

Aromatic anticonvulsants such as phenytoin, phenobarbitone, carbamazapine are not only among the common drugs inducing this reaction, but also considered as a high risk agents especially in new users.[2] Phenytoin is the most common anticonvulsant used for seizure control and for prophylactic use in the brain metastasis setting. Its risk of inducing TEN is approximately 8.3 per 10,000 new users and usually occurs within 8 weeks of drug use.[3]

Radiation alone has to date not resulted in SJS-TEN syndrome. However, concurrent use of whole brain RT and phenytoin has been shown to induce cutaneous type IV hypersensitivity drug reactions as erythema multiforme (EM), SJS or TEN.[4-6] The first case was reported by Delattre et al[4] in an individual who received

radiation therapy while using phenytoin for seizure prophylaxis and developed EM. A special nomenclature of erythema multiforme associated with phenytoin and cranial radiation therapy (EMPACT) syndrome has been given to EM developing due to concurrent use of phenytoin and cranial RT, which begin as dusky macules in the RT portal, later spreading to other regions evolving as an eruptive disorder with systemic involvement.[5,6]

Though the pathogenesis is largely unknown, it is postulated that it is an immunologically mediated type IV hypersensitivity to phenytoin and its metabolites, which is augmented by the concurrent use of RT.[7] Though most of the EM-SJS-TEN syndromes were described in patients receiving aromatic anticonvulsants concurrent with late whole brain RT, there have been reports describing the occurrence of similar lesions in the non-cranial RT sites when anticonvulsants are given concurrently.[8] The illustrative case also shows similar clinical behavior. But, it has to be noted that in all these reports there was a component of concurrent whole brain RT, which must also act as a trigger for the development of lesions in other RT sites.

This hypersensitivity reaction has also been reported in patients with non-small cell lung cancer undergoing combination chemotherapy with carboplatin-pemetrexed regimen. Thus, in the illustrative case, carboplatin based chemotherapy might also be a potential trigger behind development of TEN.[9]

Management should be aggressive under the intensive care unit and immediate cessation of the offending drug. Fluid, and electrolyte replacement, systemic steroids, antibiotics, and local wound care, should be included. A high dose of corticosteroids instituted early within TEN (24-48 hours) halts the hypersensitivity reaction and prevents further tissue damage. However, a rapid tapering followed by withdrawal within 2 weeks is recommended to prevent increased mortality from sepsis, gastrointestinal bleed, and delayed wound healing.[10]

In conclusion, although SJS-TEN syndrome associated with concurrent use of phenytoin and cranial RT is a rare clinical scenario, this is a potential complication with significant mortality. Hence, the use of phenytoin should be avoided during RT, and if indicated, phenytoin can be replaced with other anticonvulsants such as sodium valproate, benzodiazepines or the newer antiepileptic drugs such as gabapentin and topiramate. In patients receiving phenytoin and concurrent whole brain radiation, complications should be anticipated and managed aggressively.

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