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EMPACT syndrome: limited evidence despite a high-risk cohort

Andrew J. Bishop,

Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York 10065, USA

Maria Chang,

Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York 10065, USA

Mario E. Lacouture, and

Department of Medicine, Dermatology Service, Memorial Sloan-Kettering Cancer Center, New York 10065, USA

Christopher A. Barker

Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York 10065, USA

Christopher A. Barker: barker@mskcc.org

Abstract

Serious dermatologic adverse events such as erythema multiforme (EM) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) have been reported in patients receiving antiepileptic drugs (AEDs) and cranial radiotherapy (RT). Given the frequency of AED-associated rashes and the infrequency of serious dermatologic adverse events after cranial RT, we sought to further assess the prevalence of cutaneous eruptions in patients receiving an AED before and after cranial RT. We reviewed medical records of patients taking AEDs while undergoing RT for a high-grade glioma and recorded demographic, disease, and treatment parameters, as well as the development of rashes. Rashes were found in 19 % of patients taking AEDs. Phenytoin was most commonly implicated (93 %) in rash formation compared with other AEDs ($P < 0.0001$), both before and during RT. Most rashes (76 %) occurred before starting RT ($P < 0.0001$). However, of those during RT, most were associated with phenytoin compared with other AEDs ($P = 0.002$). One case of SJS was noted in a patient receiving phenytoin prior to RT. While rashes were slightly less prevalent in patients receiving temozolomide compared with those not receiving temozolomide (3.4 vs 4.8 %), this difference was not statistically significant ($P = 0.65$). Rashes are relatively common in patients receiving AEDs, with the highest incidence associated with phenytoin. However, the risk of serious dermatologic events is low. There did not appear to be an association between the receipt of cranial radiotherapy and the development of AED-associated rash with phenytoin or other AEDs.

Correspondence to: Christopher A. Barker, barker@mskcc.org.

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Conflict of interest None.

Keywords

Antiepileptic drug; Radiotherapy; Stevens-Johnson syndrome; Toxic epidermal necrolysis; EMPACT syndrome; Rash

Introduction

Antiepileptic drugs (AEDs) and radiotherapy (RT) are both commonly used in the management of patients with brain tumors [1, 2]. Each of these treatments can be associated with dermatologic adverse events. In the case of AEDs, dermatologic adverse events often manifest as cutaneous eruptions without clear anatomic predilection, and can be life-threatening [3]. In contrast, radiotherapy-related dermatologic adverse events typically occur within the irradiated area of skin, and are typically not life-threatening [4].

Almost 20 years ago, investigators reported on a group of patients experiencing life-threatening cutaneous eruptions (erythema multiforme [EM] and Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS/TEN]) in patients with brain tumors. These eruptions originated on the scalp of patients receiving whole brain radiotherapy. All of the patients started taking the AED drug phenytoin prior to radiotherapy [5]. Since then, numerous case reports and small case series have been published of patients that developed serious rashes, namely, EM or SJS/TEN, shortly after receiving phenytoin (or other AEDs) and cranial radiotherapy. Investigators have dubbed this syndrome “erythema multiforme associated with phenytoin and cranial radiation therapy” (EMPACT), and define it as an erythematous macular eruption on the scalp within the radiation field, eventually disseminating to involve cutaneous and mucous membranes [6–14].

The contribution of cranial radiotherapy to the development of cutaneous eruptions outside the irradiated skin, such as that seen in the EMPACT syndrome, is unclear. Because of the limited nature of prior studies of the EMPACT syndrome, we sought to systematically evaluate the risk of cutaneous eruptions in a large cohort of patients undergoing cranial radiotherapy and taking an AED. In this cohort, we analyzed the prevalence of cutaneous eruptions before and during RT. In addition, we investigated whether tumor grade or concurrent use of immunosuppressive chemotherapy affected the risk of developing cutaneous eruptions. Finally, we quantified the risk of developing a life-threatening dermatologic event, such as EM and SJS/TEN.

Materials and methods

Patients

With institutional review board approval, electronic institutional databases were used to identify eligible patients for analysis. Patients with a histologic diagnosis of a high-grade primary brain tumor (anaplastic astrocytoma [AA], a grade III glioma or glioblastoma [GBM], a grade IV glioma) confirmed by a neuropathologist at our institution were eligible for study. Patients must have been diagnosed between 1987 and 2007, and have undergone cranial radiotherapy. Finally, patients must have been taking an AED during radiotherapy.

Patient characteristics were recorded and included: age at diagnosis, date of first seizure, AED use, and occurrence of rash. Recorded treatment characteristics included RT technique and use and type of chemotherapy during RT.

All cutaneous eruptions documented while on an AED were coded as an AED-associated rash unless the medical record specifically noted a more definitive cause that was unlikely to be related to the AED. Rash timing in relation to the start of RT was defined as either before or during RT. AED regimens, both prior to and during RT, were recorded with particular attention to the AED in use at the time of cutaneous eruption.

Statistical analysis

Descriptive statistics were performed by calculating the prevalence of AED-associated rashes in patients prior to initiating and during RT. Categorical data was statistically analyzed using Fisher's exact test to calculate a two-tailed *P* value. Further analysis was performed using an exact analogue of McNemar's test. The Kaplan–Meier method was used to calculate survival times defined from the start of RT to the first occurrence of the considered event. Log-rank tests were used to assess the equality of the survival function. Analyses were carried out using WinSTAT® for Microsoft Excel (Version 2009.1).

Results

Cohort characteristics

Five hundred ninety-four patients met criteria for analysis. Table 1 presents patient as well as treatment and AED characteristics. Median age was 57 years (range: 6–89); the majority of the patients were male ($n = 400$; 67 %) and the most common histologic diagnosis was GBM ($n = 482$; 81 %). Additionally, while not standard in the modern era, many patients were on oral dexamethasone in this cohort at the time of RT ($n = 483$; 81 %).

A wide variety of techniques were used for cranial irradiation. As noted in Table 1, the two most common modalities were three-dimensional conformal RT ($n = 245$; 41 %) and intensity-modulated RT (IMRT; $n = 171$; 29 %). The majority of patients did not receive any concurrent chemotherapy ($n = 355$; 60 %), with only 29 % of patients receiving concurrent temozolomide (TMZ). The other 11 % of patients receiving chemotherapy received a variety of drugs in various combinations including carmustine, lomustine, procarbazine, vincristine, and cisplatin.

Phenytoin was the most common AED used ($n = 341$; 57 %) during RT. Levetiracetam was used in the more recent era and overall was the second most commonly used AED ($n = 119$; 20 %). Despite modern recommendations against the use of prophylactic AEDs, 44 % of patients on an AED during RT did not have a history of a seizure.

Prevalence of AED-associated rash

Rashes associated with AEDs were relatively common, occurring in 19 % ($n = 110$) of patients. Of the patients with an AED-associated rash, 76 % of them occurred prior to RT and 24 % during RT (Table 2).

Of those that exhibited a systemic rash, the prevalence was most commonly associated with use of phenytoin ($P < 0.0001$) compared with other AEDs. Rash occurred in 72 patients (86 %) prior to starting RT and 23 (89 %) during RT who were only taking phenytoin ($P < 0.0001$) (Table 3). Additionally, nine patients (11 %) had a rash prior to RT when taking phenytoin in combination with another AEDs. The other AED that was associated with a rash prior to and during RT was carbamazepine ($n = 3$ [4 %] and $n = 2$ [8 %], respectively). There was only one rash that was documented as SJS; this occurred before cranial RT began and was attributed to phenytoin. Among patients who had a seizure prior to RT, 73 % of the rashes occurred in patients who were on the AED less than 8 weeks.

Steroid use was not associated with rash prevalence. There was no statistical correlation between steroid use and rashes before treatment ($P = 0.113$), during RT ($P = 0.150$), or either before and during RT ($P = 0.474$).

An AED-associated rash was statistically more likely to occur before RT than during ($P < 0.0001$). This risk of AED-associated rash occurring before RT was present for patients with GBM ($P < 0.0001$) and anaplastic astrocytoma ($P = 0.0035$). However, of AED-associated rashes that occurred during RT, most were associated with phenytoin compared with other AEDs ($P = 0.002$). Among patients treated with TMZ during RT, AED-associated rashes appeared less prevalent (3.4 %) than in patients who did not receive concurrent chemotherapy (4.8 %), but this was not statistically significant ($P = 0.65$).

Outcomes

The median survival was 14 months (range, 0–241), in a cohort dominated by GBM histology (81 %). There was no difference among patients who had a rash ($n = 110$) compared with those that never had a rash ($n = 488$) (17 vs 14 months, respectively; $P = 0.66$). A rash before RT did not significantly impact survival (18 months) compared with no rash before treatment (14 months) ($P = 0.17$). Similarly, during RT, survival was not influenced by a rash during treatment (12 vs 14 months; $P = 0.32$).

Discussion

Our retrospective analysis evaluated a large patient population at risk for EMPACT syndrome. Of the nearly 600 patients undergoing cranial RT while taking an AED, there was a large proportion that exhibited an AED-associated rash (19 %). However, we found a significantly higher prevalence of AED-associated rashes prior to RT, not during RT. Furthermore, the one case of SJS occurred before RT started while the patient was taking phenytoin. Therefore, our cohort analysis did not reveal evidence to suggest an association of cranial RT with the development of a serious rash in patients taking an AED.

EMPACT syndrome is a rare clinical entity developing in patients treated with cranial RT and phenytoin, with over 30 described cases [9]. When searching for an association of rashes among all AEDs and RT, sixty-one cases are identified. Furthermore, a recent review reported 151 evaluable EM-like cases associating any medication with RT [11].

The pathophysiology that results in EMPACT syndrome is only partially understood. Drugs are recognized as the etiologic factor in the majority of cases, yet how they induce epidermal necrosis is unknown. Cytotoxic T cells likely play an important role in the process. CD8 + lymphocytes were recently isolated from blister fluid and reacted without restimulation against the parent drug; they also reacted by killing autologous lymphocytes and keratinocytes [15]. T cell activation requires interactions between T-cell receptors and drug antigen presenting cells. Hapten-receptor affinity is increased in certain populations, suggesting a genetic predisposition for SJS/TEN due to increased interactions with certain medications [16, 17].

With only a limited understanding of the pathogenesis of SJS/TEN, the immunological mechanisms resulting in EMPACT syndrome remain elusive. A type IV hypersensitivity reaction to AEDs (i.e., phenytoin) likely contributes since it has a role in SJS/TEN. Several AEDs and their metabolites have immunogenic properties including activation of populations of T-cells and downregulation of T-suppressor cells [18, 19]. This immunogenicity may be compounded by RT enhancing a primary antibody response that is believed to further deplete the T-suppressor lymphocyte pool [20]. The end result is a greater clonal expansion of sensitized T-lymphocytes without feedback inhibition, which could explain the EM reaction in phenytoin-sensitized patients who receive RT.

Based on the hypothesis that T-cell interactions help drive SJS/TEN, we examined the influence TMZ had on our population. TMZ is an oral alkylating agent used to treat high-grade gliomas and is known to induce lymphopenia. In a recent report Iversen et al. showed that TMZ decreases CD4 T-cell populations and alters the proportions of CD8 T-cell populations. Despite observing a slightly lower prevalence of rashes in patients receiving TMZ (3.4 vs 4.8 %), the small number of patients and events observed limit our ability to conclude that TMZ modifies the risk of AED-associated rash.

Radiation has been shown to influence cytokine expression patterns by increasing levels of tumor necrosis factor, intercellular adhesion molecule-I, and mRNA in mice models. These elevated levels could induce cellular autoimmunity catalyzing the immunogenic response within the RT field before spreading systemically [20, 21]. Others have suggested that a deficiency in epoxide hydrolase enzyme induced by the phenytoin-radiation combination may be a contributing mechanism. Oxidative intermediates produced by phenytoin and typically detoxified by epoxide hydrolase may accumulate as a result of the enzyme deficiency and act as haptens, triggering secondary immune responses [20, 22]. Less popular proposed mechanisms include radiation to the hypothalamic-hypophyseal axis triggering skin reactions and phenytoin possibly sensitizing the skin to photons [22, 23]. Neither theory has substantiated evidence. However, perhaps a combination of these primary and secondary immune mechanisms may explain the observed EM-like reaction between AEDs and cranial radiation.

The alternative explanation is that SJS/TEN occurs in patients undergoing anticonvulsant treatment and cranial RT solely because of AED use, which is a medication well-documented to be implicated in EM-like reactions. The suggestion that the combination of RT with AEDs results in SJS/TEN is based more on anecdotal reports than on scientific

evidence. Our large cohort analysis of a population at risk for EMPACT syndrome did not find evidence to validate a high incidence of this clinical syndrome. This was supported by a case-control study that did not find any significance in the relative risks of SJS/TEN associated with AEDs in the presence or absence of RT [6].

Interestingly, a recent review identified a subset of patients in the literature who had a EM-like rash in response to a medication, yet had skin sparing of previously irradiated skin while rash developed on all other parts of the body [24]. There are several cases reporting absent systemic rashes within RT fields both in the acute and long-term setting [25, 26]. Perhaps the absent skin reaction within the irradiated field is due to radiation-induced local immunosuppression by depletion of lymphocyte subsets, or by dermoepidermal cell alterations and changes to the cutaneous microvasculature. These conflicting data question the validity of the proposed association between cranial RT and AEDs in rash formation. Furthermore, if there was a true association between RT and EM-inducing medications, would there not be more cited cases involving RT to other anatomic sites due to additional medications that can precipitate SJS/TEN?

There are possible reasons why we did not observe a higher prevalence of AED-associated rashes in patients after starting RT. Most of the cases of EMPACT syndromes reported have described patients undergoing whole brain RT for brain metastases, a technique that exposes more of the skin and scalp to RT. In the present cohort, few received whole brain RT. Over the last few decades, RT for brain tumors has become increasingly conformal, and this may explain why reports of EMPACT syndrome are becoming less frequent in recent years. Or perhaps earlier case reports were confounded by other allergens. Previously, CT with high osmolality iodinated contrast (and its associated risk of dermatologic adverse events in approximately 10 % of patients) was the primary form of neuroimaging [27].

Another alternative possibility as to why an association was not observed is based on the fact that many of the reported cases are in patients with brain metastases and our cohort was comprised of patients with primary high-grade gliomas. Perhaps there is an inherent immune dysfunction in patients with brain metastases, one that permits metastases and a systemic reaction to persist unchecked. Finally, many of the patients previously diagnosed with the EMPACT syndrome have been relatively young (median age of 46 years in the previously reported cases presented in the Supplemental Table). Patients in the present cohort were a median of 57 years old. If the EMPACT syndrome is an immunologically mediated disorder, immunosenescence may contribute to our observation that AED-associated rash was not more common after patients initiated RT.

In an attempt to overcome the limitations that influenced much of the literature on this topic, we selected a high-risk population to analyze for the prevalence of EMPACT syndrome. While this is the largest cohort of patients evaluated for EMPACT syndrome, it is retrospective, which opens up the analysis to inherent bias found in all retrospective analyses. One major limitation of the study was that a control cohort was not identified for comparison. An AED-alone control group does not exist since RT remains standard of care for high-grade gliomas. Similarly, an RT cohort without AED use is biased since rash prevalence is less likely to be recorded in the medical chart without a notable cause.

For this study, the inciting medication of the rash was documented as determined by the treating physicians; however, an additional limitation is the possibility of confounding medications influencing rash formation. While these limitations are important to note when interpreting the results, they provide the best evidence to suggest no clear association exists between cranial RT and phenytoin. An alternative argument may be that, despite evaluating a large at-risk cohort, perhaps this syndrome is rare enough that it was not captured by this series.

Conclusions

To date, this is the most comprehensive evaluation of the prevalence of dermatologic adverse events in a population receiving cranial RT and AEDs. This analysis did not show an increased prevalence in patients receiving RT and phenytoin but rather observed a statistically significant increased prevalence of AED-induced rash prior to starting RT. Previous reports noting this association may have been confounded by the use of other culprits or simply by the AED as the sole precipitant. If in fact EMPACT is a true clinical syndrome, reports of it will likely remain limited to case reports and literature reviews.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient characteristics

	Patients (<i>n</i> = 594)	%
OS		
Median	14 months	
Range	0–241	
Median RTOG RPA score	4	
Age (range)	6–89	
Sex		
Male	400	67.3
Female	194	32.7
Histology		
GBM	482	81.1
AA	112	18.9
Steroid use		
Yes	483	81.3
No	97	16.3
Unknown	14	2.4
Seizure history		
Yes	333	56.1
No	260	43.8
Unknown	1	0.2
Primary AED during RT		
Phenytoin	341	57.4
Levetiracetam	119	20.0
Valproic acid	48	8.1
Carbamazapine	38	6.4
Phenobarbital	24	4.0
Other	24	4.0
Cranial RT		
2D PBRT	78	13.1
3D CRT	245	41.2
IMRT	171	28.8
WBRT	32	5.4
Other	31	5.2
Unknown	37	6.2
Systemic therapy		
Concurrent TMZ	174	29.3
Concurrent chemotherapy	65	10.9
No concurrent therapy	355	59.8
Rash		
No	484	81.5

	Patients (<i>n</i> = 594)	%
Yes	110	18.5
Before RT	84	76.4
During RT	26	23.6

OS overall survival, *RTOG RPA* radiation therapy oncology group recursive partitioning analysis, *GBM* glioblastoma multiforme, *AA* anaplastic astrocytoma, *AED* anti-epileptic drug, *RT* radiation therapy, *2D PBRT* 2-dimensional partial brain radiation therapy, *3D CRT* 3-dimensional conformal radiation therapy, *IMRT* intensity modulated radiation therapy, *WBRT* whole-brain radiation therapy TMZ

Table 2

Rash prevalence based on histology

	Rash before RT	Rash during RT	P value
All patients	84	28	<0.0001
Glioblastoma multiforme	65	22	<0.0001
Anaplastic astrocytoma	19	4	0.0035

RT radiation therapy

Table 3

Rash prevalence based on anti-epileptic drug

	Rash before RT (<i>n</i> = 84)		Rash during RT (<i>n</i> = 26)		<i>P</i> value
		%		%	
Phenytoin alone	72	85.7	23	88.5	<0.0001
Other AEDs (without phenytoin)	3	3.6	3	11.5	0.683
Carbamazepine alone	3	3.6	2	7.7	1.0
Gabapentin alone	0	0.0	1	3.8	1.0
Phenytoin with other AED	9	10.7	0	0.0	0.008
Carbamazepine with phenytoin	6	7.1	0	0.0	
Phenobarbital with phenytoin	2	2.4	0	0.0	
Levetiracetam with phenytoin	1	1.2	0	0.0	

RT radiation therapy, *AED* anti-epileptic drug