Turkish Journal of Emergency Medicine 16 (2016) 176–178

Contents lists available at ScienceDirect

Turkish Journal of Emergency Medicine

journal homepage: http://www.elsevier.com/locate/TJEM

Case report

Is this a simple drug eruption to be discharged?

Mucahit Emet [a], Ilker Akbas [a, *], Esra Senturk [a], Omer Faruk Elmas [b], Sahin Aslan [a]

[a] Ataturk University Education and Research Hospital, Department of Emergency Medicine, Erzurum, Turkey
[b] Ataturk University Education and Research Hospital, Department of Dermatology, Erzurum, Turkey

ARTICLE INFO

Article history:
Received 9 March 2016
Accepted 23 May 2016
Available online 14 June 2016

Keywords:
Erythema multiforme
Phenytoin
Cranial radiation
Skin
Emergency

ABSTRACT

'Erythema Multiforme associated with Phenytoin And Cranial radiation Therapy' (EMPACT) is a very rare clinic situation and classified in EM-like drug reactions. It can be easily misdiagnosed as acute urticaria or drug eruption in ED. Initial symptoms may resemble a simple skin problem, but diagnosing and early hospitalization of the patients can be lifesaving. Here, we present a man with renal cell cancer and brain metastases who admitted to ED due to fever and generalized rash. His skin lesions beginning from his head and spreading through the torso appeared four days after the end of radiotherapy (11 days after the initial dose of both radiation and oral phenytoin). Inspection showed erythematous lesions on the scalp, neck, torso and arms. These lesions had desquomative character on the scalp. Erythematous maculopapular lesions with the tendency of fusion were also visible on the chest, abdomen, back, on the flexor areas of the arm, forearm and femoral region. Laboratory studies showed normal complete blood counts, high creatinine kinase, creatinine kinase-MB, gamma-glutamyl transpeptidase, aspartate aminotransferase, lactate dehydrogenase, albumin and total protein. After discontinuation of phenytoin and giving H1, H2 receptor blockers and steroid intravenously, he was discharged two weeks later with full recovery.

Copyright © 2016 The Emergency Medicine Association of Turkey. Production and hosting by Elsevier B.V. on behalf of the Owner. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

'Erythema Multiforme associated with Phenytoin And Cranial radiation Therapy' (EMPACT), first introduced by Ahmed et al in 2004,[1] is erythema multiforme (EM) in patients who takes cranial radiotherapy accompanying with phenytoin medication. The reason is thought as the increase in adverse effect of the anticonvulsant due to radiotherapy.[2]

In this syndrome, the patients can be presented in a wide range of clinical spectrum from a simple erythema multiforme to complex toxic epidermal necrolysis (TEN).[3] Mortality is closely associated with the therapy given and the severity of TEN. Leading causes of mortality are sepsis and multiorgan failure.[2,3] Other important complications are pulmonary embolism, renal failure, fluid-electrolyte imbalance, thrombocytopenia and leukopenia.[3]

Here, we present a man with renal cell cancer and brain metastases who admitted to the emergency department (ED) due to fever and generalized rash. Emergency physicians should be aware of this syndrome before giving the decision of discharge.

2. Case presentation

A 41-year-old man admitted to our ED due to malaise, fever, sores in the mouth and generalized rash. His anamnesis revealed that the diagnosis of renal cell cancer was put three years ago and then he had a nephrectomy operation from the right. Because of brain metastases, he had been given full brain radiotherapy 20 days ago. Concurrent phenytoin sodium (Epanutin©, Pfizer, Turkey) was given to the patient 300 mg daily for seizure prophylaxis. He had also hypothyroidism for 10 years and on levothyroxine 0.1 mg/day. Generalized rash beginning from his head and spreading through the torso appeared four days after the end of radiotherapy (11 days after the initial dose of both radiation and oral phenytoin). He had treated in dermatology unit of a state hospital with the diagnoses of drug eruption and/or acute urticaria.

During his hospitalization, he had also taken imipenem 500 mg/days intravenously for three days due to prediagnosis of hospital

* Corresponding author. Ataturk Universitesi Tip Fakultesi Hastanesi, Acil Tip Anabilim Dali, Yakutiye, Erzurum, Turkey. Tel.: +90 0544 422 28 80.
E-mail address: akbasilker@gmail.com (I. Akbas).

Peer review under responsibility of The Emergency Medicine Association of Turkey.

http://dx.doi.org/10.1016/j.tjem.2016.05.002

2452-2473/Copyright © 2016 The Emergency Medicine Association of Turkey. Production and hosting by Elsevier B.V. on behalf of the Owner. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

acquired infection. Since his complaints did not resolved but alleviated, he was discharged voluntarily and had admitted our ED.

His initial vital signs were within normal limits. Inspection showed erythematous lesions on the scalp, neck, torso and arms (Fig 1). These lesions had desquamative character on the scalp. Erythematous maculopapular lesions with the tendency of fusion were also visible on the chest, abdomen, back, on the flexor areas of the arm, forearm and femoral region. Oral mucosa was dehydrated and aphthous lesions were remarkable in the oropharynx with crust on the lips. His other physical examination signs were unremarkable.

Laboratory studies showed normal complete blood counts, high creatinine kinase (138 U/L, range: 1–24), creatinine kinase-MB (127 U/L, range: 1–171), gamma-glutamyl transpeptidase (107 U/L, range: 1–55), aspartate aminotransferase (52 U/L, range: 1–50), lactate dehydrogenase (692 U/L, range: 1–247), albumin (2,9 g/dl, range: 3,5-5,2) and total protein (5,5 g/dl, range: 6,6–8,8). Hepatobiliary ultrasound showed paraaortic and paracaval lymphadenopathies. We stopped phenytoin, gave H1 and H2 receptor blockers as well as steroid intravenously in ED and hospitalized him in dermatology clinic with the diagnosis of EMPACT. There, he was given daily levetiracetam 500 mg for seizure prophylaxis, H1 and H2 receptor blockers and prednisolone 80 mg additional to fluid and supportive treatment. He was discharged two weeks later with full recovery of the skin lesions.

3. Discussion

EMPACT syndrome is a very rare clinic situation and classified in EM-like drug reactions. About thirty cases have been described so far.[1,2,4] No correlation was found between size and severity of cutaneous eruptions and the dose of phenytoin or radiation therapy, or the origin or size of intracranial malignancy.[3,5] In previous case reports, associated cancers were glioblastoma multiforme, glioma, astrocytoma or tumors with brain metastases like lung cancer, breast cancer, germinoma, melanoma, angiosarcoma, chondrosarcoma or bronchial carcinoma. However, nothing yet reported about renal cell cancer as it was in our case.[2]

It is known that phenytoin use may cause a wide range of cutaneous lesions with the leading sign of examatous eruptions (8.5%–19%). EM is far rarer.[1,6] Differential diagnosis is important. Acute radiation dermatitis due to radiotherapy is dose dependent and limited in the radiation exposured skin area.[1] Dermatological lesions occur at the same time in phenytoin induced drug eruption, however in EMPACT, rash begins from the area where radiotherapy was given and spreads through the whole body the following days. The duration of cutaneous lesions after radiotherapy is typically between 7 and 35 (mean 23) days in EMPACT. A fast improvement can be achieved with just stopping phenytoin.[1,3] In our case, the rash had begun from the head through the torso 11 days after the first radiation.

Pathophysiologic mechanism of EMPACT is not yet clear. Many mechanisms were asserted in the pathway of phenytoin metabolism. Animal studies showed that radiation to brain may cause a rise in cellular autoimmunity by upregulating mRNA expression of immunologic cytokines in rats.[5] Radiation may also induce a defect in epoxide hydrolase, an enzyme that breaks down the drug, causing accumulation of oxidative metabolites.[2,5] Additionally, phenytoin and its metabolites can activate CD4, CD8 T-cells and diminish the functions of T-suppressor, NK and B cells.[7,8] These changes in immune system may lead to form autoantibodies causing cutaneous phenytoin reactions.[2] Phenytoin induced type 4 hypersensitivity is another mechanism to be blamed.[2]

Discontinue of phenytoin is the main point of the initial treatment. Although the efficacy of the systemic therapeutic agents is controversial, high dose steroid and intravenous immunoglobulin-G can be used. Plasmapheresis, cyclosporine and cyclophosphamide are other alternative curative regimens.[3] We used high dose steroid and supportive treatment in our patient. Gabapentin and levetiracetam are preferable for prevention of seizures instead of

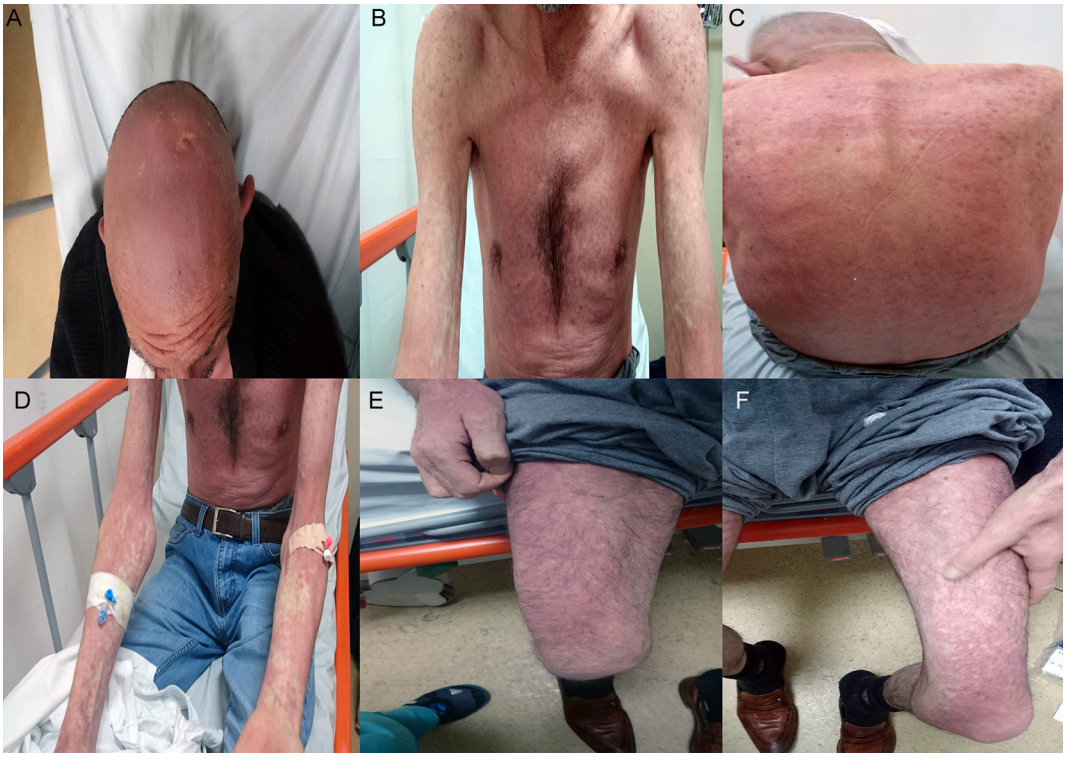

Fig. 1. Erythematous maculopapular desquomative lesions with the tendency of fusion on the scalp (A), torso (B, C) and extremities (D, E, F).

phenytoin. Especially levetiracetam is a better choice to avoid skin lesions as other anti-epileptic drugs like phenobarbital, valproic acid, and carbamazepine had been associated with EM. Additionally, both carbamazepine and barbiturates may cause cross-reactions in patients that are sensitive to phenytoin as they share same aromatic chain in their chemical structure.[1,2,5]

4. Conclusion

In conclusion, a case of EMPACT syndrome can be easily misdiagnosed as acute urticaria or drug eruption in ED. Phenytoin and cranial radiotherapy concomitance is frequent but reported EMPACT cases are rare may be because the clinicians do not give attention to this concordance. Initial symptoms may resemble a simple skin problem, but diagnosing and early hospitalization of patients with this syndrome can be lifesaving.

Conflicts of interest

None.

Acknowledgment

None.

References

1. Ahmed I, Reichenberg J, Lucas A, Shehan JM. Erythema multiforme associated with phenytoin and cranial radiation therapy: a report of three patients and review of the literature. *Int J Dermatol*. 2004;43:67–73.
2. Aydogan K, Vatansever S, Adim SB, Saricaoglu H. Empact syndrome: a case report and review of the literature. *Int J Dermatol*. 2010;49:945–949.
3. Bilgili SG, Calka O, Karadag AS, Burakgazi AZ. EMPACT syndrome. *Cutan Ocul Toxicol*. 2011;30:328–330.
4. Bishop AJ, Chang M, Lacouture ME, Barker CA. EMPACT syndrome: limited evidence despite a high-risk cohort. *J Neurooncol*. 2014;119:129–134.
5. Fabbrocini G, Panariello L, Pensabene M, et al. EMPACT syndrome associated with phenobarbital. *Dermatitis*. 2013;24:37–39.
6. Silverman AK, Fairley J, Wong RC. Cutaneous and immunologic reactions to phenytoin. *J Am Acad Dermatol*. 1988;18:721–741.
7. Mauri-Hellweg D, Bettens F, Mauri D, Brander C, Hunziker T, Pichler WJ. Activation of drug-specific CD4+ and CD8+ T cells in individuals allergic to sulfonamides, phenytoin, and carbamazepine. *J Immunol*. 1995;155:462–472.
8. Basaran N, Hincal F, Kansu E, Ciger A. Humoral and cellular immune parameters in untreated and phenytoin-or carbamazepine-treated epileptic patients. *Int J Immunopharmacol*. 1994;16:1071–1077.