Toxic epidermal necrolysis after radiotherapy for pleomorphic liposarcoma

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Abstract

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are life-threatening, cutaneous reactions often associated with culprit drugs. A growing body of knowledge has deepened our understanding of the pathophysiology and clarified mechanisms such as drug-specific cytotoxicity mediated by T-cells, genetic linkage with HLA and non-HLA genes, TCR restriction, and cytotoxicity mechanisms. Physicians should broadly consider the etiology of SJS/TEN in order to better understand treatment strategies as well as identify which patients may be at risk for developing this condition. Mechanisms for how radiotherapy and rare malignancies may contribute to the development of TEN and SJS have been proposed.

Keywords: toxic epidermal necrolysis, TEN, pleomorphic liposarcoma, liposarcoma, radiotherapy, radiation therapy

Introduction

Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and SJS/TEN overlap comprise a spectrum of life-threatening, blistering, mucocutaneous disease. Toxic epidermal necrolysis is the rarest, representing the greatest amount of body surface area involvement. The majority of cases are attributed to drug reactions. We report a case of TEN in the setting of radiation therapy for a pleomorphic liposarcoma.

Case Synopsis

A 52-year-old man, with a recent diagnosis of pleomorphic liposarcoma, presented to the emergency department (ED) with a progressive rash and fever while undergoing neoadjuvant radiation therapy. He was scheduled to complete 30 sessions of radiotherapy, 5 days per week. Two days after his 18th treatment he noted erythema and pain at his radiation site, which spread as a morbilliform rash across his body. Despite being started on prednisone 60mg daily by his primary care physician, he developed oral mucosal erosions, difficulty swallowing, and hemoptysis prompting referral to the ED. His only other medications were long-standing: lorazepam 0.5mg as needed for sleep and anxiety, senna and polyethylene glycol as needed for constipation, and ibuprofen 200mg as needed for pain.

Physical examination at the time of evaluation revealed a surgical scar on the left lateral back with overlying blistering and detached skin, diffuse pink-red macules over face and torso, dusky-centered papules over the lower extremities, superficial erosions of the soft palate, and vesicles of his lips (**Figure 1**). There was a positive Nikolsky sign. No appreciable cervical lymphadenopathy or scleral injection were present.

Given these findings, he was suspected to have Stevens Johnson syndrome/Toxic epidermal necrolysis (SJS/TEN) and a SCORTEN (SCORE of Toxic epidermal necrolysis) of 3 given his age over 40 years, body surface area detached >10%, and an

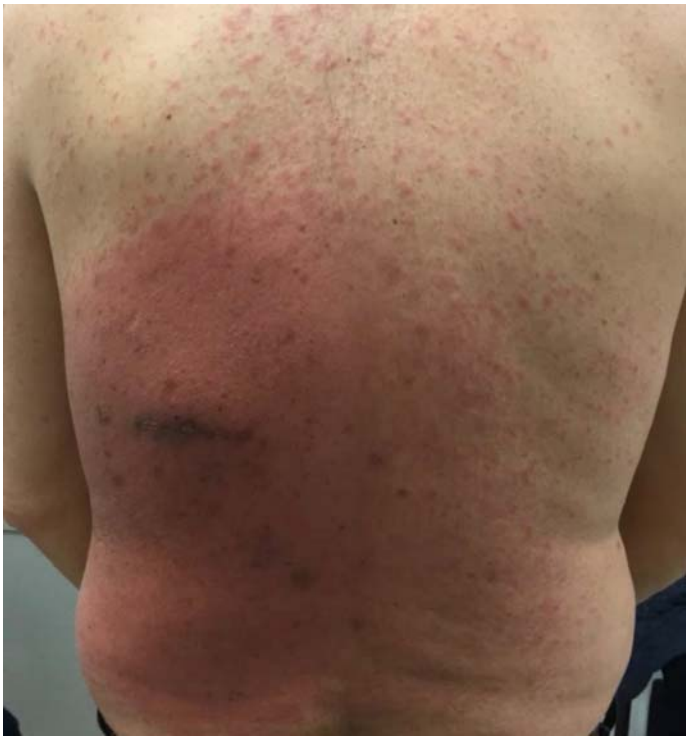

Figure 1. *Early clinical presentation. Morbiliform rash covering back.*

associated malignancy. Therapy was promptly initiated with oral cyclosporine. A regimen of 3mg/kg/d for 10 days followed by 2mg/kg/d for 10 days, and finally, 1mg/kg/d for 10 days was recommended [1]. Herpes simplex viruses (HSV) 1 and 2 IgM and *Mycoplasma pneumoniae* IgM titers were negative.

During the course of his hospitalization, the eruption continued to progress to his distal extremities, genitalia, eyes ears, and face with involvement of over 30% of his body surface area (**Figure 2**). He received rigorous wound care in the burn center unit and was discharged on hospital day 11.

The patient followed up with a surgical oncologist for definitive removal of his pleomorphic liposarcoma. Approximately 6 weeks following his discharge from the hospital he underwent radical resection of his pleomorphic liposarcoma on the back with reconstruction by the plastic surgery team.

The pathology report revealed negative margins, four mitotic figures per 10 high power fields, and no lymphovascular invasion. Immunohistochemistry was focally positive for S100, focally weak-positive for SMA, negative for CK cocktail, CD24, myogenin, and desmin. Cytogenetics were negative for *MDM2* amplification.

Case Discussion

The mechanism of SJS and TEN is largely believed to be immune-mediated [2]. Over the last decade, the understanding of the pathophysiology of SJS and TEN has improved with the investigation and clarification of mechanisms such as drug-specific cytotoxicity mediated by T-cells, genetic linkage with HLA and non-HLA genes, TCR restriction, and cytotoxicity mechanisms [3]. The mechanisms for autoimmune and viral-induced forms of epidermal necrolysis not related to medication require further investigation [3]. In addition, there are multiple hypotheses for how radiation therapy may contribute to the development of SJS/TEN. For example, one hypothesis is that radiation may cause inhibition or deficiency of enzymes such as

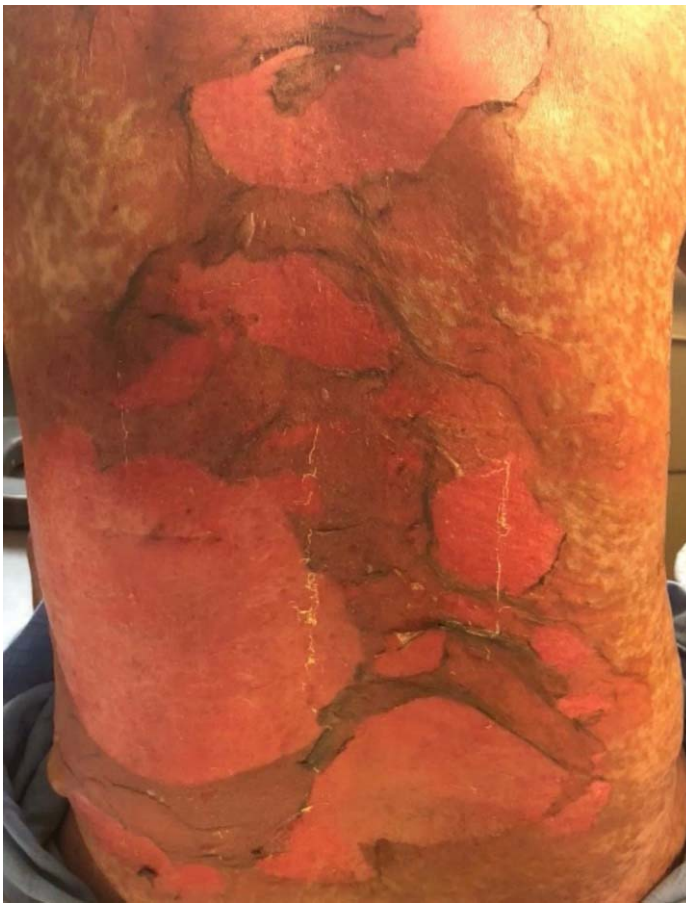

Figure 2. *Desquamation and progression to toxic epidermal necrolysis. Extension of affected body surface area along with sloughing skin and positive Nikolsky sign.*

cytochrome P450, which would prevent the biotransformation of reactive metabolites and allow them to act as haptens that induce an immunologic response [4]. Another hypothesis is that SJS/TEN may develop after radiation owing to the release of antigenic factors as tumor cells are killed [5]. Additionally, radiation therapy is known to cause trauma to the skin and produce cutaneous reactions such as dermatitis.

Although there are reported cases of TEN in patients receiving radiotherapy, the eruptions reported have occurred with concurrent use of anti-epileptic or chemotherapeutic agents. The only recent change in medication our patient noted was increased use of ibuprofen 200mg, which he had only been taking as needed. Stevens-Johnson syndrome/toxic epidermal necrolysis is not frequently reported in patients exposed to radiation therapy alone and similarly to this case, it is often difficult to ascertain if there is a culprit drug [3] There are reports of EM, SJS, and SJS/TEN overlap occurring with radiation alone, although many cases involved culprit medications as well [6]. In the majority of cases in irradiated patients, the rash originated at the site of radiation, much like in our patient [6, 7]. A gentleman receiving radiation therapy for non-small cell lung cancer even developed EM localized to his radiation port [7].

Toxic epidermal necrolysis has also been documented in the setting of infections and autoimmune disease [2, 3]. *Mycoplasma pneumoniae* infections have been associated with SJS and TEN in cases without culprit drugs [2]. The incidence of TEN is 1000-fold higher in patients with HIV than the general population [2]. The possibility of an autoimmune mechanism has led some authors to call for a distinction between a toxic and "non-toxic" form of epidermal necrolysis [3]. Several cases of TEN without a culprit drug have also been reported in the setting of an autoimmune condition [3]. In a UK-based epidemiological study identifying risk factors for developing SJS/TEN (acknowledging that drug intake could be a confounding factor in some cases), lupus erythematosus, a well-established auto-immune disease, was associated with SJS/TEN with an odds ratio of 16.0 [3].

In the same study, active cancer was also identified as a risk factor with an odds-ratio of 2.01 [3]. The potential for this rare malignancy to be involved in the etiology of this patient's TEN should certainly be considered. Pleomorphic liposarcomas are rare high-grade tumors capable of metastasis [8]. In a study of undifferentiated pleomorphic liposarcoma of the extremity and trunk specifically, Keung et al. demonstrated a trend towards increasing density of tumor immune infiltrate after radiotherapy, including CD3, CD4, CD8, FOXP3, and PD-L1 expression [9]. Other cases of cutaneous reactions including SJS, have been reported after the utilization of nivolumab and pembrolizumab, which are programmed cell death receptor-1 (PD-1) antibodies, suggesting that the increased expression of PD-L1 and CD8+ cells can contribute to the development of erythema multiforme and SJS [10-12]. Accentuation of the SJS in areas where the radiation therapy was administered has also been demonstrated in patients receiving anti-PD1 immunotherapy both after and during radiation therapy for squamous cell carcinomas of the head and neck [11, 12].

Conclusion

The potential for this rare malignancy to be involved in the etiology of this patient's TEN should certainly be considered. This case reminds us that although SJS/TEN is often associated with a drug, our understanding of it is not yet complete. Physicians should broadly consider the etiology of SJS/TEN — a cutaneous reaction with multiple mechanisms at play — in order to better understand treatment strategies as well as predict which patients may be at risk for developing this condition.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Lee HY, Fook-Chong S, Koh HY, Thirumoorthy T, Pang SM. Cyclosporine treatment for Stevens-Johnson syndrome/toxic epidermal necrolysis: Retrospective analysis of a cohort treated in a specialized referral center. *J Am Acad Dermatol*. 2017;76:106-13. [PMID: 27717620].
2. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet J Rare Dis*. 2010;5:39. [PMID: 21162721].
3. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current Perspectives on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. *Clin Rev Allergy Immunol*. 2018;54:147-76. [PMID: 29188475].
4. Ridgway HB, Miech DJ. Erythema multiforme (Stevens-Johnson syndrome) following deep radiation therapy. *Cutis*. 1993;51:463-4. [PMID: 8519192].
5. Dumas M, Hua C, Hotz C, et al. Epidermal necrolysis and autoimmune diseases: two more observations supporting the concept that 'toxic' epidermal necrolysis can be 'non-toxic'. *J Eur Acad Dermatol Venereol*. 2018;32:e360-e1. [PMID: 29524279].
6. Vern-Gross TZ, Kowal-Vern A. Erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis syndrome in patients undergoing radiation therapy: a literature review. *Am J Clin Oncol*. 2014;37:506-13. [PMID: 22892429].
7. Chodkiewicz HM, Cohen PR. Radiation port erythema multiforme: erythema multiforme localized to the radiation port in a patient with non-small cell lung cancer. *Skinmed*. 2012;10:390-2. [PMID: 23346669].
8. Ghadimi MP, Liu P, Peng T, et al. Pleomorphic liposarcoma: clinical observations and molecular variables. *Cancer*. 2011;117:5359-69. [PMID: 21598240].
9. Keung EZ, Tsai JW, Ali AM, et al. Analysis of the immune infiltrate in undifferentiated pleomorphic sarcoma of the extremity and trunk in
response to radiotherapy: Rationale for combination neoadjuvant immune checkpoint inhibition and radiotherapy. *Oncoimmunology*. 2018;7:e1385689. [PMID: 29308306].
10. Vivar KL, Deschaine M, Messina J, et al. Epidermal programmed cell death-ligand 1 expression in TEN associated with nivolumab therapy. *J Cutan Pathol*. 2017;44:381-4. [PMID: 28000240].
11. Shah KM, Rancour EA, Al-Omari A, Rahnama-Moghadam S. Striking enhancement at the site of radiation for nivolumab-induced Stevens-Johnson syndrome. *Dermatol Online J*. 2018;24. [PMID: 30142712].
12. Saw S, Lee HY, Ng QS. Pembrolizumab-induced Stevens-Johnson syndrome in non-melanoma patients. *Eur J Cancer*. 2017;81:237-9. [PMID: 28438440].