Clinical, Cosmetic and Investigational Dermatology

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CASE REPORT

Diffuse Erythematous Follicular Eruption Induced by Pegylated Liposomal Doxorubicin

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Abstract: Pegylated liposomal doxorubicin (PLD) is a form of doxorubicin enclosed in pegylated liposomes and is associated with a high risk of mucocutaneous side effects. The most common cutaneous side effect is hand-foot syndrome, whereas other cutaneous reactions are rarely reported. The pathogenesis of PLD-induced cutaneous reaction is not yet clear. It is presumed that PLD could discharge through sweat or damaged vessels and impair keratinocytes in the basal layer or hair follicles as well as induce lymphocytic inflammation. We report a relatively rare of PLD-induced cutaneous reaction presented as diffuse follicular rashes and intertrigo-like dermatitis. A 56-year-old man, with leiomyosarcoma, developed pruritic and painful follicular erythematous papules with scaling on the trunk and limbs after receiving three cycles of PLD. The patient discontinued the use of PLD because of pain and exacerbation of the eruptions, and then the rashes gradually disappeared. This case highlights the potential pathogenesis underlying this unusual cutaneous reaction related to Pegylated Liposomal Doxorubicin.

Keywords: pegylated liposomal doxorubicin, diffuse follicular rash, intertrigo-like dermatitis

Introduction

Pegylated liposome doxorubicin (PLD) is an anthracycline drug and a form of doxorubicin encapsulated in pegylated liposomes. It is associated with a high risk of mucocutaneous side effects, especially hand-foot syndrome. Other cutaneous reaction, such as intertrigo-like dermatitis, diffuse follicular rash, melanotic macules, maculopapular rash or recall phenomenon are less common.[1,2] The pathogenesis of PLD-induced cutaneous reaction is not yet clear. Some studies have found that that PLD could be excreted through sweat or penetrate through the damaged vessels and induce lymphocytic inflammation associated with keratinocyte apoptosis.[3–8] Here we report a case of diffuse follicular rashes and intertrigo-like dermatitis induced by PLD, which mainly affected the area with frequent friction and abundant sweet glands, suggesting the potential pathogenesis underlying this unusual cutaneous reaction.

Case Report

A 56-year-old male presented with pruritic and painful rashes on the trunk and limbs for 40 days. He was diagnosed with leiomyosarcoma and underwent posterior mediastinal tumor resection 1 year ago. Ten months ago, he started treatment with PLD (80 mg) and dacarbazine (2g) intravenously every 4 weeks. Shortly after the third cycle, diffuse pruritic rashes occurred on the trunk and limbs, especially on the axilla. After the fourth cycle, the rashes aggravated but gradually disappeared after the end of chemotherapy. Seven months ago, the chemotherapy was replaced with Gemcitabine (2g) and paclitaxel (500mg), but was quitted due to obvious numbness and pain of hands and feet. Three months ago, he was treated with PLD (80 mg) and dacarbazine (2g) again. Three days after the third cycle, the patient developed pruritic rashes on the abdomen and thighs similar to those in the previous treatment of PLD and dacarbazine. After the fourth cycle, the eruption became more extensive, pruritic, and painful.

Received: 24 November 2024
Accepted: 8 February 2025
Published: 16 April 2025

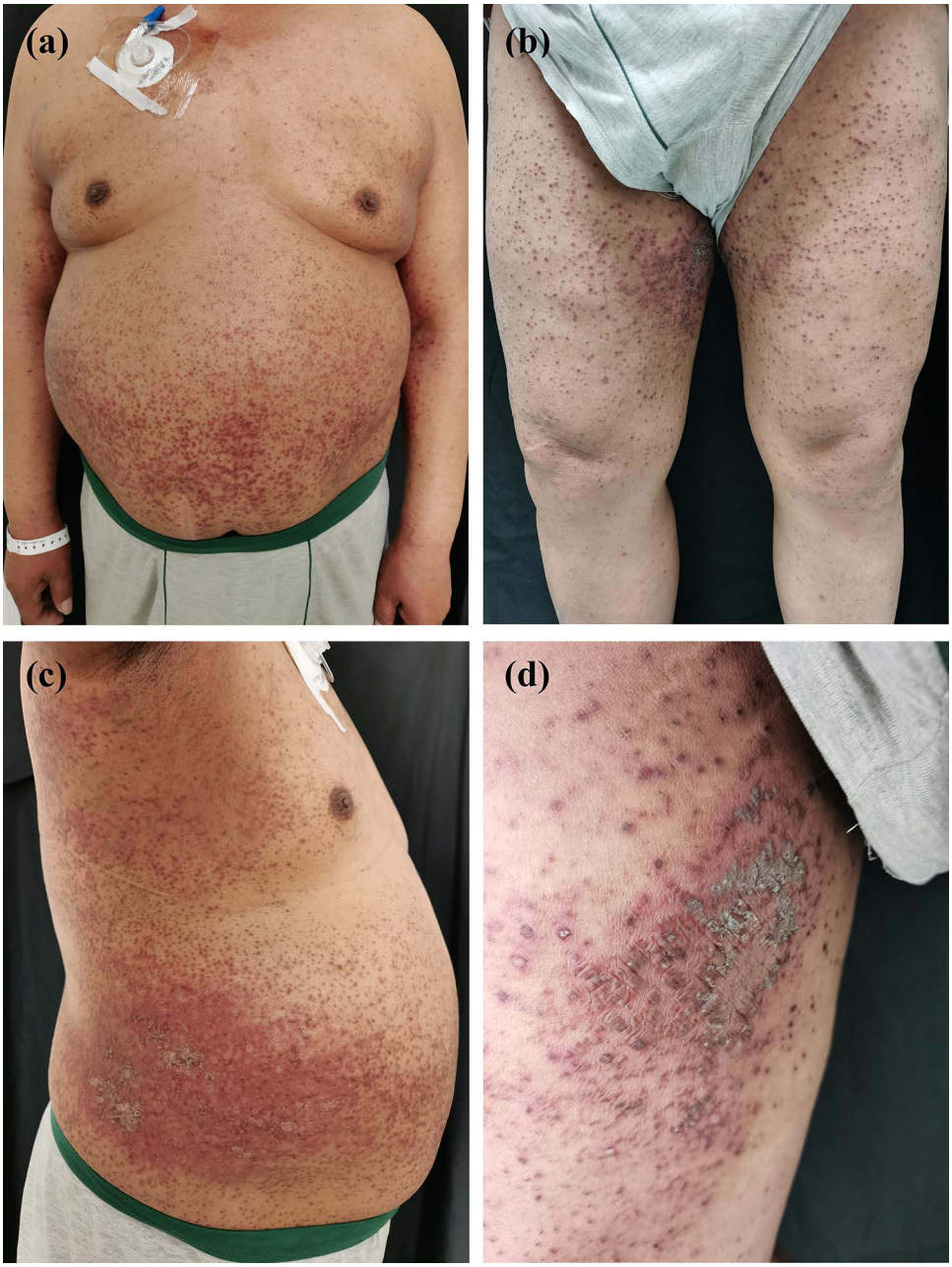

Figure 1 Clinical picture. (**a** and **b**) Innumerable reddish and brown folliculocentric papules distributed on the trunk and extremities. Some fused into plaque with scaling on (**c**) the lateral abdomen and (**d**) the inner thighs.

Clinical examination revealed innumerable reddish and brown folliculocentric papules on the trunk and extremities (Figure 1a and b). Some fused into plaque with scaling on (Figure 1c) the lateral abdomen and (Figure 1d) the inner thighs. The rashes were pruritic and painful and caused a decline in quality of life and limitation of daily activities (toxicity grade 3, according to the basic scale from the Common Terminology Criteria for Adverse Events, version 5). The patient had the conditions of a higher body mass index (BMI, 33.8) than normal range and hypertension.

Laboratory findings revealed declined complement C1q (134 mg/L), immunoglobulin A (0.69 g/L), immunoglobulin G (4.85 g/L) and immunoglobulin M (0.30 g/L). A skin biopsy specimen was obtained from the abdomen, and the histopathological findings revealed revealed apoptotic keratinocytes in epidermis (Figure 2a), dilated and proliferated small vessels, and perivascular lymphocytic infiltrate in dermis (Figure 2b).

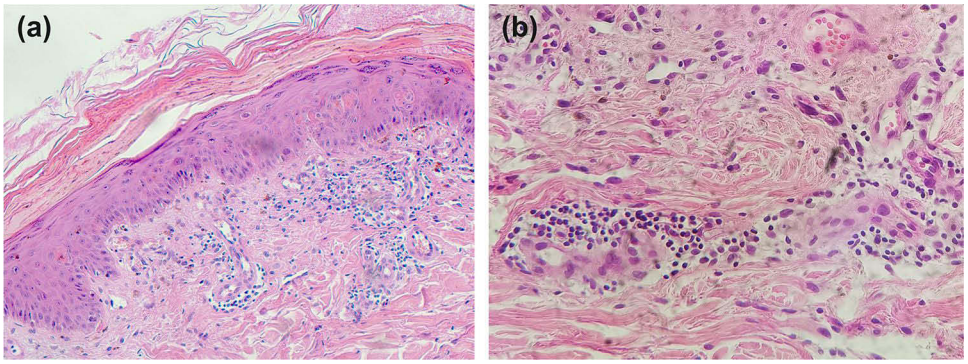

Figure 2 Histopathological findings. (**a**) Hyperkeratosis, parakeratosis, and apoptotic keratinocytes were observed in epidermis (H&E, magnification: ×200). (**b**) Dilated and proliferated small vessels and perivascular lymphocytic infiltrate were observed in the dermis (H&E, magnification: ×400).

Treatment with systemic compound glycyrrhizin and topical steroids was given but the effect was limited. The patient discontinued the use of PLD because of pain and exacerbation of the eruptions, and then the rashes gradually disappeared.

Discussion

Pegylated liposome doxorubicin (PLD) is an anthracycline drug and a form of doxorubicin encapsulated in pegylated liposomes. It is associated with a high risk of mucocutaneous side effects, especially hand-foot syndrome. Other cutaneous reaction, such as intertrigo-like dermatitis, diffuse follicular rash, melanotic macules, maculopapular rash or recall phenomenon are less common.[1,2] Here we report a case of diffuse follicular rashes and intertrigo-like dermatitis induced by PLD, suggesting the potential pathogenesis underlying this unusual cutaneous reaction.

The pathogenesis of PLD-induced mucocutaneous adverse reaction is not yet clear. Studies have indicated that PLD can be excreted through sweat or penetrate through the damaged vessels and then impair keratinocytes. Jacobi et al[3] found that the hydrophilic liposomal coating increased the accumulation of PLD in the ducts of eccrine glands, resulting in drug excretion to the corneum layer through sweat. Local microtrauma and vasodilatation may also result in the extravasation of the molecule.[4] Yokomichi et al[5] found that doxorubicin can react with copper ions in the skin to produce reactive oxygen species, which can release interleukin (IL)-1β, IL-1α and IL-6 and induce keratinocyte apoptosis. PLD-induced cutaneous eruptions may result from direct cytotoxicity to keratinocytes, which is supported by the dose-dependent cutaneous symptoms and histological findings of vacuolar degeneration and dyskeratosis.[6,7] However, based on the delayed presentation of cutaneous toxicity and the discovery of lymphocytic inflammation associated with apoptotic keratinocytes, Skelton et al[8] proposed an immunological mechanism of host-vs.-altered-host reaction as a cause of PLD-induced eruption. These studies indicated that PLD-induced eruption can be prevented and treated by avoiding friction and trauma, reducing sweat secretion, and inhibiting inflammatory reactions.

Diffuse follicular eruptions induced by PLD are rarely reported.[1,2,6,9] Time to eruption onset has varied from shortly after the first infusion to 3 weeks after the completion of therapy.[6] Herein, we describe a case of diffuse follicular rashes accompanied by intertrigo-like dermatitis, which occurred 3 days after the third circle of PLD. In the previous reports, the follicular eruptions were limited in distribution, asymptomatic and relieved by continuous treatment.[1,2] However, the rashes in this case were extensive in distribution, pruritus and painful, CTCAE 3 grade, and have unique appearance. In addition to the erythematous folliculocentric rashes, normal colored folliculocentric skin with a central black dot was also seen within the abdominal erythema. Hairless body parts such as palms, soles and abdominal scars were all unaffected. These specific rashes suggested the key role of hair follicles in the pathogenesis. In addition, the intertrigo-like eruptions were caused by the confluence of follicular rashes and were mainly located on lateral abdomen, inguinal area, and the axilla. These body parts have frequent friction, vasodilatation tendency and abundant sweet glands, which are considered related to the pathogenesis. Several risk factors such as immune status, obesity, perspiration, and racial differences may contribute to severe intertrigo-like eruptions.[10]

The histopathological discovery also suggests the potential pathogenesis underlying this unusual cutaneous reaction. In addition to vacuolar degeneration and apoptotic keratinocytes in epidermis,[6,7] dyskeratotic cells in the follicular epithelium

and perifollicular lymphocytic inflammation were also observed.[2,6,9] It is presumed that PLD can damage keratinocytes in the basal layer or hair follicles and thus induce lymphocytic inflammation. Unfortunately, there were no hair follicles seen in our biopsy specimen, so the keratinocytes damage in the basal layer or hair follicles is not clear. It is presumed that PLD can cause keratinocytes apoptosis and induce lymphocytic inflammation by the host-vs.-altered-host reaction.[9] The keratinocytes in hair follicles or the basal layer may have different sensitivity to PLD between individuals, thus resulting in different cutaneous reaction. In addition, the histopathological discovery of significant perivascular lymphocytic infiltrate in dermis suggests that the extravasation of PLD from damaged cutaneous vessels may result in perivascular inflammation.

In conclusion, we report a rare case of cutaneous reaction induced by PLD. PLD can discharge through sweat or the damaged vessels and then impair keratinocytes in the basal layer or hair follicles as well as induce lymphocytic inflammation. Methods including avoiding friction, reducing perspiration, and inhibiting inflammation, may help to prevent and treat PLD-induced eruption. More studies are needed to further clarify the mechanism of this unique drug eruption.

Data Sharing Statement

The data generated in the present study may be requested from the corresponding author.

Ethics Approval and Consent to Participate

Institutional approval was not required to publish the case details.

Patient Consent for Publication

The patients in this manuscript have given written informed consent to publication of their case details.

Acknowledgments

We thank the patient for agreeing to have this case published.

Funding

This study was supported by Natural Science Foundation of Beijing Municipality (No. 7222195).

Disclosure

All authors report no conflicts of interest in this work.

References

1. Lotem M, Hubert A, Lyass O, et al. Skin toxic effects of polyethylene glycol-coated liposomal doxorubicin. *Arch Dermatol*. 2000;136:1475–1480. doi:10.1001/archderm.136.12.1475
2. Cady FM, Kneuper-Hall R, Metcalf JS. Histologic patterns of polyethylene glycol-liposomal doxorubicin-related cutaneous eruptions. *Am J Dermatopathol*. 2006;28:168–172. doi:10.1097/01.dad.0000199880.71481.0f
3. Jacobi U, Waibler E, Schulze P, et al. Release of doxorubicin in sweat: first step to induce the palmar-plantar erythrodysesthesia syndrome? *Ann Oncol*. 2005;16(7):1210–1211. doi:10.1093/annonc/mdi204
4. Miller KK, Gorcey L, McLellan BN. Chemotherapy-induced hand-foot syndrome and nail changes: a review of clinical presentation, etiology, pathogenesis, and management. *J Am Acad Dermatol*. 2014;71(4):787–794. doi:10.1016/j.jaad.2014.03.019
5. Yokomichi N, Nagasawa T, Coler-Reilly A, et al. Pathogenesis of hand-foot syndrome induced by PEG-modified liposomal Doxorubicin. *Hum Cell*. 2013;26(1):8–18. doi:10.1007/s13577-012-0057-0
6. Dai J, Micheletti R, Rosenbach M, Chu EY. Striking follicular eruption to pegylated liposomal doxorubicin. *Am J Dermatopathol*. 2014;36(7):590–591. doi:10.1097/DAD.0000000000000077
7. English JC III, Toney R, Patterson JW. Intertriginous epidermal dysmaturation from pegylated liposomal doxorubicin. *J Cutan Pathol*. 2003;30:591–595. doi:10.1034/j.1600-0560.2003.00113.x
8. Skelton H, Linstrum J, Smith K. Host-vs.-altered-host eruptions in patients on liposomal doxorubicin. *J Cutan Pathol*. 2002;29(3):148–153. doi:10.1034/j.1600-0560.2002.290304.x
9. Seghers AC, Tey HL, Tee SI, Cao T, Chong WS. Pegylated liposomal doxorubicin-induced miliaria crystallina and lichenoid follicular eruption. *Indian J Dermatol Venereol Leprol*. 2018;84(1):121. doi:10.4103/0378-6323.206233
10. Totsuka M, Watanabe Y, Asai C, et al. Case of severe bullous erythema including intertrigo-like eruptions with angioedema induced by pegylated liposomal doxorubicin. *J Dermatol*. 2019;46(6):535–539. doi:10.1111/1346-8138.14895