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Bullous Pemphigoid Induced by Doxycycline: Case Report and Literature Review

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Abstract

Bullous pemphigoid (BP) is the most prevalent autoimmune sub-epidermal blistering disease that affects mainly the elderly and could lead to serious morbidity. It has numerous risk factors and triggers, including an aging population with several comorbidities and drug exposure. In the published paper, we reported a case about a 32 years old male patient with unknown medical conditions who presented with erythematous patches and plaques on the scalp, face, and trunk with scattered blisters two weeks after initiating doxycycline treatment for folliculitis. The exact pathogenesis of the drug-reaction in drug-associated bullous pemphigoid (DABP) remains controversial. In conclusion, it is crucial for clinicians to be aware of DABP when prescribing doxycycline. The purpose of this case report is to raise awareness of the possible association between bullous pemphigoid and doxycycline.

Keywords

Bullous Pemphigoid, Doxycycline, Drug-Associated Bullous Pemphigoid

1. Introduction

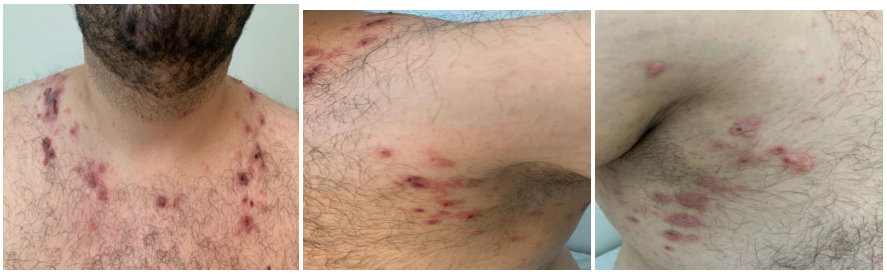
Bullous pemphigoid (BP) stands out as the most prevalent autoimmune sub-epidermal blistering disease, predominantly affecting elderly with a generalized pruritic bullous eruption and can lead to serious morbidity. This autoimmune condition is characterized by a humoral and cellular immune response targeting two well-defined self-antigens: BP antigen 180 and BP antigen 230 [1]. The diagnosis is based on examining the blister edge, conducting direct immunofluorescence (DIF) on adjacent skin, and performing histopathologic analysis indi-

cating detachment at the dermo-epidermal junction (DEJ) with eosinophilic infiltration in the dermis. Linear deposition of IgG and complement component 3 (C3) at the DEJ is revealed through DIF. Additional diagnostic methods, including indirect immunofluorescence on human skin, enzyme-linked immunosorbent assay (ELISA) utilizing recombinant proteins BP180 and BP230, and immunoblotting on keratinocyte extracts, serve to validate and support the diagnosis of BP [2].

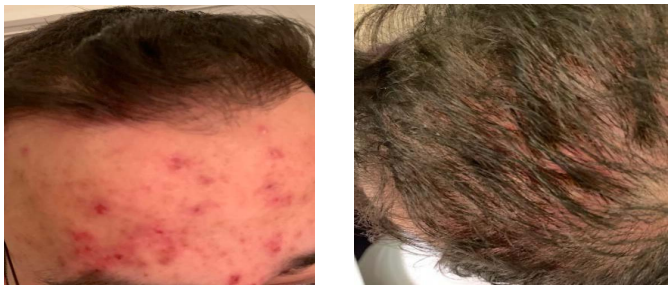
The incidence of BP has increased over the past decades due to a combination of factors, including an aging population with several comorbidities, drug exposure that may potentially trigger the condition, and advancements in diagnosis techniques [3]. The etiopathogenesis of BP remains largely elusive, encompassing broad predisposing factors like aging, human leukocyte antigen genes, and various triggers such as drugs, physical factors, vaccines, ultraviolet (UV) radiation, trauma, transplantations, surgical procedures, and infections [2]. The term "drug-associated bullous pemphigoid" (DABP) refers to cases displaying clinical, immunopathological, or histological characteristics comparable to idiopathic BP and linked to specific drug ingestion or topical application [4]. Identification of potential triggers is essential for prognosis enhancement. In spite of the substantial studies conducted on bullous disorders, no particular antibodies for drug-induced bullous pemphigoid (DIBP) have been identified [5] [6]. In this context, we present an unusual case of new-onset BP induced by Doxycycline, underscoring the significance of recognizing drug-induced variants and the need for further exploration in understanding their mechanisms.

2. Case Report

A 32 years old male, unknown chronic diseases presented to the clinic with scattered blisters on erythematous patches and plaques on scalp, face and trunk two weeks after initiating doxycycline 100 mg for one month to treat folliculitis (**Figure 1**). No additional medications were taken. Mucosal involvement was not detected. The patient had not undergone recent surgery, received vaccinations, or experienced infections in the preceding months. Trauma or prolonged sun exposure was also not reported. Skin biopsy was taken and revealed sub-epidermal non acantholytic blister. Blister cavity is filled with fibrin and many eosinophils and neutrophils. The adjacent skin reveals occasional collection of eosinophils at dermo-epidermal junction in the papillary dermis and in dermal vessels. The infiltrate of eosinophils and lymphocytes noted in dermis below the blister and peri-vascularity containing mostly lymphocytes (**Figure 2**). Direct immunofluorescent revealed deposition of C3 & IgM in linear serrated pattern in basement membrane. The diagnosis of BP induced by Doxycycline was established, leading to the termination of Doxycycline tablets. The patient received treatment with topical Clobetasol cream and a short course of prednisolone 40 mg for two weeks, resulting in noticeable improvement. Patient underwent follow-up after three months, six months and a year with full remission. He was educated to not use

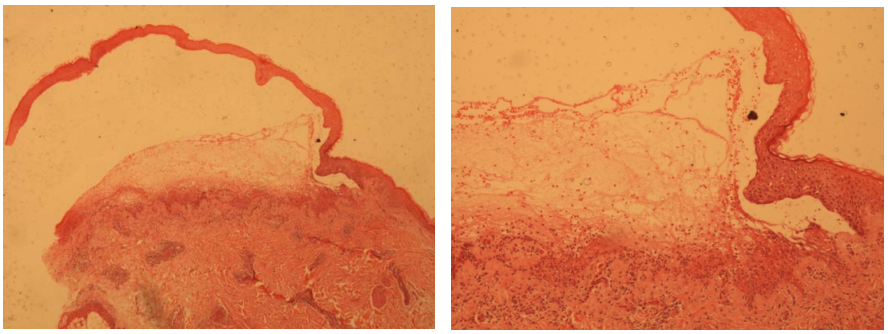


(a)

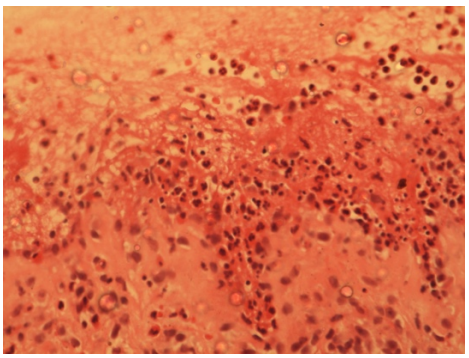


(b) (c)

Figure 1. Illustrates the examination findings of scattered blisters on erythematous patches and plaques with few crusted erosions observed on the (a) trunk, (b) face, and (c) scalp.



(a) (b)



(c)

Figure 2. Illustrates histopathology images stained with Hematoxylin & Eosin. (a) Unilocular sub-epidermal non-acantholytic blister (HE 4 × 10), (b) Blister cavity filled with fibrin, eosinophils & neutrophils (HE 10 × 10) and (c) Eosinophils, neutrophils and fibrin in the blister cavity (HE 40 × 10).

doxycycline for possible recurrence.

3. Discussion

In a recent multicentric "pragmatic" trial, there was evidence suggesting that initial doxycycline treatment might offer satisfactory blister control and a better safety profile compared to oral prednisolone [7]. Due to its anti-inflammatory properties, doxycycline is frequently included in the multi-drug management of BP; however, it is believed to be the offending drug in this case [8]. The pathogenesis of the drug-reaction in DABP remains to be elucidated and often difficult to understand. Drugs may trigger an immune response in genetically predisposed individuals, altering antigenic properties of the epidermal basement membrane zone (BMZ). This can occur through drug binding to BMZ molecules, acting as new antigens, or modifying molecules and revealing hidden epitopes, which then stimulate an immune response [4]. Supporting this, Patsatsi *et al.* found higher anti-BP180NC16A auto-antibodies levels in patients taking systemic medications before disease onset, indicating drug-associated epitope spreading compared to those not taking any medications [9]. According to another theory, medicines may, in some individuals, unintentionally produce immunological reorganization or dysregulation, which could subsequently inactivate endogenous regulatory mechanisms which may influence a potential disease phenotype [10]. It is possible for medications to be misinterpreted for microbial antigens since many of them interact by binding to micro RNA and other transcriptional and translational regulators in a manner similar to that of a virus [11]. In susceptible individual, the immune system misidentifying medications may activate CD4+ T cells and trigger the autoimmune cascade [12]. The medications known to trigger BP include diuretics, antibiotics, calcium channel blockers, angiotensin-converting-enzyme inhibitors, NSAIDs, β-blockers, salicylates, and others. Drug-induced BP has been commonly associated with antibiotics, especially in younger patients who are not typically affected by BP. Diverse antibiotics were reported to induce BP including penicillins, cephalosporines, quinolones, nitroimidazoles, actinomycin, levofloxacin, ciprofloxacin, Metronidazole and annamycin [2] [4]. The exact mechanisms behind the BP induced by antibiotics are not fully understood, and there are several theories proposed. One theory suggests that antibiotics with a sulfhydryl group, like penicillin, penicillamine, amoxicillin, and cephalosporins, may disrupt the immune system and impair the function of T-cells suppressors. This can lead to the release of autoantibodies. Thiol drugs may also directly damage the dermo-epidermal junction, exposing new antigens to the immune system. Another theory involves antibiotics with a phenol ring, such as cephalosporin, acting as a hapten and triggering the production of antibodies targeting the DEJ [13]. In a case report involving levofloxacin, researchers suggest that a type IV hypersensitivity reaction mediated by T-cells could explain the association between the drug and BP onset [14]. In context of our case study, we discovered that one of the most often prescribed antibiotics in dermatology

clinics that may cause BP is doxycycline. Although the underlying pathophysiology is not reported in literature and not comprehended yet. Sanchez's reported a case highlighted the role of doxycycline-induced phototoxicity in BP development [15] [16]. Despite the fact, this association differs from our reported case.

4. Conclusion

Our scientific understanding of BP, the primary autoimmune bullous disorder, has seen a significant advancement in recent years. However, the pathogenesis of the drug-reaction in DABP remains controversial. The purpose of this case report is to raise awareness of the possible association between bullous pemphigoid and doxycycline. Nonetheless, clinicians should employ a degree of suspicion for DABP when prescribing doxycycline. The presented case underscores the need for further investigations to understand the underlying mechanism. Continued vigilance and reporting of such cases are essential for advancing our knowledge and ensuring optimal patient care in the context of drug-induced dermatologic reactions.

Statement of Ethics

Consent to participate statement: informed consent was obtained from participant.

Author Contributions

Dr. Mishal provides and writes the case scenario and final review. Dr. Rahaf writes case discussion and review. Dr. Sohail and Dr. Abdulrahman skin histopathology report and pictures.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Bernard, P. and Antonicelli, F. (2017) Bullous Pemphigoid: A Review of Its Diagnosis, Associations and Treatment. *American Journal of Clinical Dermatology*, **18**, 513-528. https://doi.org/10.1007/s40257-017-0264-2

[2] Moro, F., Fania, L., Sinagra, J.L.M., Salemme, A. and Di Zenzo, G. (2020) Bullous Pemphigoid: Trigger and Predisposing Factors. *Biomolecules*, **10**, 1432. https://doi.org/10.3390/biom10101432

[3] Miyamoto, D., Santi, C.G., Aoki, V. and Maruta, C.W. (2019) Bullous Pemphigoid. *Anais Brasileiros de Dermatologia*, **94**, 133-146. https://doi.org/10.1590/abd1806-4841.20199007

[4] Verheyden, M.J., Bilgic, A. and Murrell, D.F. (2020) A Systematic Review of Drug-Induced Pemphigoid. *Actadermato-Venereologica*, **100**, adv00224. https://doi.org/10.2340/00015555-3457

[5] Smith, E.P., Taylor, T.B., Meyer, L.J. and Zone, J.J. (1993) Antigen Identification in

Drug-Induced Bullous Pemphigoid. *Journal of the American Academy of Dermatology*, **29**, 879-882. https://doi.org/10.1016/0190-9622(93)70262-R

[6] Kashihara, M., Danno, K., Miyachi, Y., Horiguchi, Y. and Imamura, S. (1984) Bullous Pemphigoid-Like Lesions Induced by Phenacetin. Report of a Case and an Immunopathologic Study. *Archives of Dermatology*, **120**, 1196-1199. https://doi.org/10.1001/archderm.1984.01650450078023

[7] Bolognia, J., Schaffer, J.V. and Cerroni, L. (2018) Dermatology. 4th Edition, Elsevier.

[8] Williams, H.C., Wojnarowska, F., Kirtschig, G., Mason, J., Godec, T.R., Schmidt, E., Chalmers, J.R., Childs, M., Walton, S., Harman, K., Chapman, A., Whitham, D., Nunn, A.J., UK Dermatology Clinical Trials Network BLISTER Study Group (2017) Doxycycline versus Prednisolone as an Initial Treatment Strategy for Bullous Pemphigoid: A Pragmatic, Non-Inferiority, Randomised Controlled Trial. *Lancet* (*London*, *England*), **389**, 1630-1638. https://doi.org/10.1016/S0140-6736(17)30560-3

[9] Patsatsi, A., Vyzantiadis, T.A., Chrysomallis, F., Devliotou-Panagiotidou, D. and Sotiriadis, D. (2009) Medication History of a Series of Patients with Bullous Pemphigoid from Northern Greece—Observations and Discussion. *International Journal of Dermatology*, **48**, 132-135. https://doi.org/10.1111/j.1365-4632.2009.03839.x

[10] Newport, M.J., Goetghebuer, T. and Marchant, A. (2005) Hunting for Immune Response Regulatory Genes: Vaccination Studies in Infant Twins. *Expert Review of Vaccines,* **4**, 739-746. https://doi.org/10.1586/14760584.4.5.739

[11] Baum, H., Butler, P., Davies, H., Sternberg, M.J. and Burroughs, A.K. (1993) Autoimmune Disease and Molecular Mimicry: An Hypothesis. *Trends in Biochemical Sciences*, **18**, 140-144. https://doi.org/10.1016/0968-0004(93)90022-F

[12] Bowman, C. and Delrieu, O. (2009) Immunogenetics of Drug-Induced Skin Blistering Disorders. Part I: Perspective. *Pharmacogenomics*, **10**, 601-621. https://doi.org/10.2217/pgs.09.11

[13] Cozzani, E., Chinazzo, C., Burlando, M., Romagnoli, M. and Parodi, A. (2016) Ciprofloxacin as a Trigger for Bullous Pemphigoid: The Second Case in the Literature. *American Journal of Therapeutics*, **23**, e1202-e1204. https://doi.org/10.1097/MJT.0000000000000283

[14] Ma, H.J., Hu, R., Jia, C.Y., Yang, Y. and Song, L.J. (2012) Case of Drug-Induced Bullous Pemphigoid by Levofloxacin. *The Journal of Dermatology*, **39**, 1086-1087. https://doi.org/10.1111/j.1346-8138.2012.01636.x

[15] Sanchez, I.I., Yale, K. and Lee, B.A. (2023) A Case of Bullous Pemphigoid Provoked by Doxycycline-Induced Phototoxicity. *JAAD Case Reports*, **37**, 41-44. https://doi.org/10.1016/j.jdcr.2023.05.005

[16] Lim, D.S. and Murphy, G.M. (2003) High-Level Ultraviolet A Photoprotection Is Needed to Prevent Doxycycline Phototoxicity: Lessons Learned in East Timor. *The British Journal of Dermatology*, **149**, 213-214. https://doi.org/10.1046/j.1365-2133.2003.05389.x