www.jsstd.org

Journal of Skin and Sexually Transmitted Diseases

Review Article

Anti-p200 pemphigoid: A review

Vattiyamveetil Sajeela Rasheed[1]

[1]Department of Dermatology, Abeer Alnoor Poly Clinic, Al Qusais, Dubai, United Arab Emirates.

***Corresponding author:**
Vattiyam Veetil Sajeela Rasheed, Department of Dermatology, Abeer Alnoor Poly Clinic, Al Qusais, Dubai, United Arab Emirates.

sajeelarasheed@gmail.com

Received: 19 April 2021
Accepted: 23 May 2021
EPub Ahead of Print: 03 July 2021
Published: 14 April 2023

DOI
10.25259/JSSTD_35_2021

Quick Response Code:

ABSTRACT

Anti-p200 pemphigoid, initially described in 1996, is a subepidermal autoimmune blistering disease. It is manifested as tense blisters, mostly in an acral distribution, and is accompanied by mucosal involvement in more than half the cases. The disease is produced by circulating autoantibodies directed against the dermal antigen of 200-kDa, the exact identity of which remains unknown. This review focuses on the clinical features, immunopathogenesis, and diagnosis of anti-p200 pemphigoid.

Keywords: Anti-p200 pemphigoid, Subepidermal blistering disease, Autoimmune, Clinical features, Immunopathogenesis, Diagnosis

INTRODUCTION

Autoimmune vesiculobullous diseases are characterized by circulating and tissue bound antibodies directed against various structural components of basement membrane zone of skin. In 1953, Lever reported the existence of bullous pemphigoid (BP) as a separate entity from pemphigus based on the observation of subepidermal spilt in the former.[1] Linear IgA bullous dermatosis (LABD), epidermolysis bullosa acquisita (EBA), herpes gestationis, and cicatricial pemphigoid were subsequently described as autoimmune blistering diseases that manifest a subepidermal split. Despite having subepidermal separation, as the common histopathology feature, these conditions showed variability in presentation, which was expected since the target antigen for the pathogenic antibody varied.

In 1996, Zillikens *et al.* reported a novel autoimmune blistering disease, which was precipitated by circulating antibodies directed against the dermal antigen of 200-kDa.[2] The antibodies bound to dermal side of salt split skin, indicating that the target antigen was localized to the lower lamina lucida.[2] This disease, named anti-p200 pemphigoid, though rare, was subsequently reported from different parts of the world.[3-5]

The observed rarity of the condition could partly be due to the lack of facility to diagnose the condition in all centers. This review deals with the pathogenesis, clinical features, diagnosis, treatment options, and prognosis of anti-p200 pemphigoid.

EPIDEMIOLOGY

Goletz *et al.* reported that the incidence of anti-p200 pemphigoid could be higher than what is reported since many patients with anti-p200 pemphigoid might have been misdiagnosed as EBA.[6] Most of the reports of anti-p200 pemphigoid have come from Japan, followed by France,

Germany, Netherlands, USA, India, and a few other countries.[4,6-8] Most of the affected were in their sixties which was younger than the common age group for BP.[4] A clear male predilection (75%) is documented in the literature.[4,6] Many previous authors have noted a definite association between anti-p200 pemphigoid and psoriasis.[4,6] Kridin and Ahmed, in their systematic review on anti-p200 pemphigoid, reported a prevalence of 6.4% for psoriasis in non- Japanese anti-p200 pemphigoid patients, while it was 56.4% among Japanese patients with anti-p200 pemphigoid.[4]

IMMUNOPATHOGENESIS

As already mentioned, the disease is caused by autoantibodies directed against a 200-kDa protein located within the lower lamina lucida of the basement membrane zone. Shimanovich *et al*. identified p200 as an acidic non-collagenous N-linked glycoprotein of the lower lamina lucida.[9] Both epidermal keratinocytes and dermal fibroblasts synthesize p200 antigen.[6] Dainichi using an immunoblot assay reported that the sera of 90% of anti-p200 pemphigoid patients reacted to C-terminus of recombinant laminin γ1 and proposed the name "anti-laminin gamma-1 pemphigoid."[10] ELISA technique that can detect anti-laminin γ1 antibodies is available, but has less sensitivity.[11] Laminin γ1 belongs to a family of extracellular matrix glycoproteins that are the major noncollagenous constituents of basement membranes.[12] The autoantibodies to p200 antigen and laminin gamma-1 belong to IgG4 subclass.[6] Goletz *et al*. suggested that the diagnosis of anti-laminin gamma-1 pemphigoid should be limited to patients who show reactivity against laminin-γ1 since all patients with anti-p200 pemphigoid do not show reactivity against laminin-γ1.[6] Subsequently, it was reported that the antibodies detected in the sera of anti-p200 pemphigoid patients are pathogenic, but the pathogenicity is not fully mediated by anti-laminin γ1 antibodies. Hence, the exact molecular identity of the autoantigen remains unknown.[13] A week reactivity against BP180, BP230, laminin 332, and type VII collagen is observed in about 25% of anti-p200 pemphigoid cases, which is attributed to intermolecular epitope spreading.[6] A similar observation is made by Holtsche *et al*.[14]

The exact reason for the unique association noted between anti-p200 pemphigoid and psoriasis is not yet elucidated. It is proposed that the extracellular matrix in psoriatic skin resembles the senescent extracellular matrix, probably due to the accelerated cell cycle time and turnover of epidermal keratinocytes. The alteration in the distribution and amount of proteins in the basement membrane zone brought out by this accelerated senescence increases the antigenicity of basement membrane zone proteins. This, in turn, increases the chance of an autoimmune response against the components of the basement membrane zone, which might contribute to the development of anti-p200 pemphigoid and other autoimmune vesiculobullous diseases associated with psoriasis.[4,15,16]

CLINICAL FEATURES

There are wide variations in the observed clinical features of anti-p200 pemphigoid. A systematic review by Kridin and Ahmed (1900–2018) after analyzing 113 patients reported in 68 articles documented that 45/113 (39.8%) patients showed resemblance to BP. In 45 cases, resemblance to another clinical entity was not mentioned. In the remaining patients, the clinical features resembled LABD, EBA, dermatitis herpetiformis, and mucous membrane pemphigoid.[4]

Others have noted lesions that mimicked pompholyx and pemphigus herpetiformis.[5,17] Bullae and/or vesicles are seen in all the patients.[4] Urticarial plaques, erosions on trunk and extremities, targetoid lesions, and lesions resembling annular erythema are the other documented cutaneous lesions.[2,4,6] Meijer *et al*. in a retrospective study of 12 patients found predominantly tense blisters on hands and feet, resembling dyshidrosiform pemphigoid.[7] Wozniak *et al*. reported a 52-year-old woman who developed oral erosions and erythema gyratum repens like skin lesions as features of anti-p200 pemphigoid that appeared following intake of oral penicillin for prolonged cough.[18] The most common site of involvement as observed in various studies is extremities (95.1%), followed by trunk (70.7%).[4] Palmoplantar (51.4%) and cephalic involvement (40.3%) is noted frequently.[3,4] Kridin and Ahmed reported generalized cutaneous involvement in a significant proportion of cases.[4] Scarring and milia formation though less common (15.7%), were more frequent than the same noted in BP (3.4%).[4,19] Furukawa *et al*. reported one case of anti-p200 pemphigoid who showed clinical features that fulfilled the criteria for EBA. The patient showed tense blisters on trauma prone sites, involvement of the oral mucosa, and nail dystrophy. The skin lesions healed with atrophic scars and formation of milia.[20] Immunoblotting revealed circulating IgG antibodies directed against both the 200-kDa antigen and the 290-kDa EBA antigen.[20] McCarty *et al*. have reported pathergy phenomenon in a patient with anti-p200 pemphigoid.[21]

Literature supports involvement of oral and genital mucosae.[2,4] Although there are no reports of patients presenting with lesions confined to mucosae, the frequency of mucosal involvement in the affected is higher (20–38.5%) than the same noted in BP (17.1%).[4,6,18,22] Patients of Japanese origin showed less frequent mucosal involvement in comparison to the remaining patients in the systematic review by Kirdin and Ahmed.[4] The review found psoriasis as the most common coexisting dermatosis and it preceded anti-p200 pemphigoid on most occasions. Different patients had chronic plaque psoriasis, psoriatic erythroderma, and

pustular psoriasis. Similar observations were made by others as well.[4,6] As already mentioned, the association between anti-p200 pemphigoid and psoriasis is mostly seen in Japanese patients.[6] Concomitant malignancies reported in anti-p200 pemphigoid include metastatic clear cell carcinoma of ovary, metastatic esophageal adenocarcinoma, and uterine adenocarcinoma.[23-25] IgA nephropathy and glomerulonephritis leading to end stage kidney disease, autosomal recessive congenital ichthyosis, polyarteritis nodosa, ulcerative colitis, and esophagitis are the other comorbidities reported in association with anti-p200 pemphigoid.[4]

DIAGNOSIS

A systematic review of 113 patients concluded that the possibility of anti-p200 pemphigoid should be considered when a subepidermal autoimmune blistering disease manifests with a predominantly acral and cephalic distribution along with mucosal involvement, especially when the affected individual belongs to an age group younger than the average age documented in BP.[4] A confirmed diagnosis needs investigations, some of which are available only in limited centers.

Histopathology

Histopathology cannot distinguish anti-p200 pemphigoid from other subepidermal blistering diseases. In majority of cases, the biopsy specimens show subepidermal blistering and a moderate to dense dermal infiltrate composed mainly of neutrophils or neutrophils and eosinophils. A predominantly eosinophilic infiltrate was observed less frequently. Other less commonly reported findings include microabscess formation in papillary dermis adjacent to blister cavity and eosinophilic and neutrophilic spongiosis.[4,26]

Immunofluorescence

Direct immunofluorescence (DIF) of perilesonal skin shows deposition of IgG and C3 in the majority.[26] A combination of IgA, IgG, and C3 or IgG or C3 alone is reported infrequently.[4,26] Wozniak *et al*. had reported a patient with anti-p200 pemphigoid with IgA antibodies directed against 200-kDa antigen located within the lower lamina lucida. The antigen corresponded to laminin γ1.[5] DIF cannot distinguish anti-p200 pemphigoid from BP or mucous membrane pemphigoid [Figure 1].

A linear n-serrated pattern is found in DIF for all sub-epidermal blistering diseases that show deposition of immunoreactants in hemidesmosomes, lamina lucida, or lamina densa.[7,27] Consistent with the localization of anti-p200 immunodeposits along the lower lamina lucida and upper lamina densa, anti-p200 pemphigoid also shows a n-serrated pattern.[7,27] BP and mucous membrane pemphigoid also show n-serration pattern on DIF. EBA in contrast, shows a linear u-serrated pattern that is as expected considering the localization of type VII collagen in the sublamina densa zone.[7] A similar serration pattern is observed in bullous systemic lupus erythematosus also.[7]

On indirect immunofluorescence (IIF) microscopy on 1 mol/l NaCL-salt split skin, anti-p200 pemphigoid shows binding of immunoreactants to the dermal side of the spilt.[7] A few cases of anti-p200 pemphigoid showed binding of immunoreactants to both roof and floor of salt split skin.[4] The floor pattern binding places anti-p200 pemphigoid along with EBA and anti-laminin 332 mucous membrane pemphigoid [Figures 2a and b].[4,7] The salt split study distinguishes anti-p200 pemphigoid from BP, which shows a roof pattern binding on most occasions.[27]

Demonstration of reactivity to 200-kDa protein in human dermal extract on immunoblot analysis is the confirmatory diagnostic test that distinguishes anti-p200 pemphigoid from EBA and anti-laminin 332 mucous membrane pemphigoid, the other diseases that show floor pattern binding on salt split skin.[4,7] Distinguishing anti-p200 pemphigoid from EBA and anti-laminin 332 mucous membrane pemphigoid is important since the response to treatment and further evaluation required differ in these conditions.[7] EBA shows poor response to treatment. Anti-laminin 332 pemphigoid needs oncological screening since it is known to be associated with malignancy.[6,7] However, the facility for immunoblot analysis for 200-kDa protein in

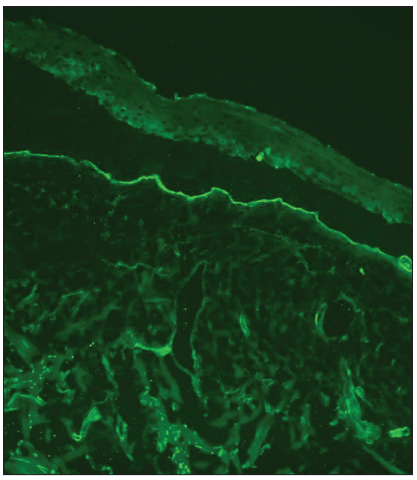
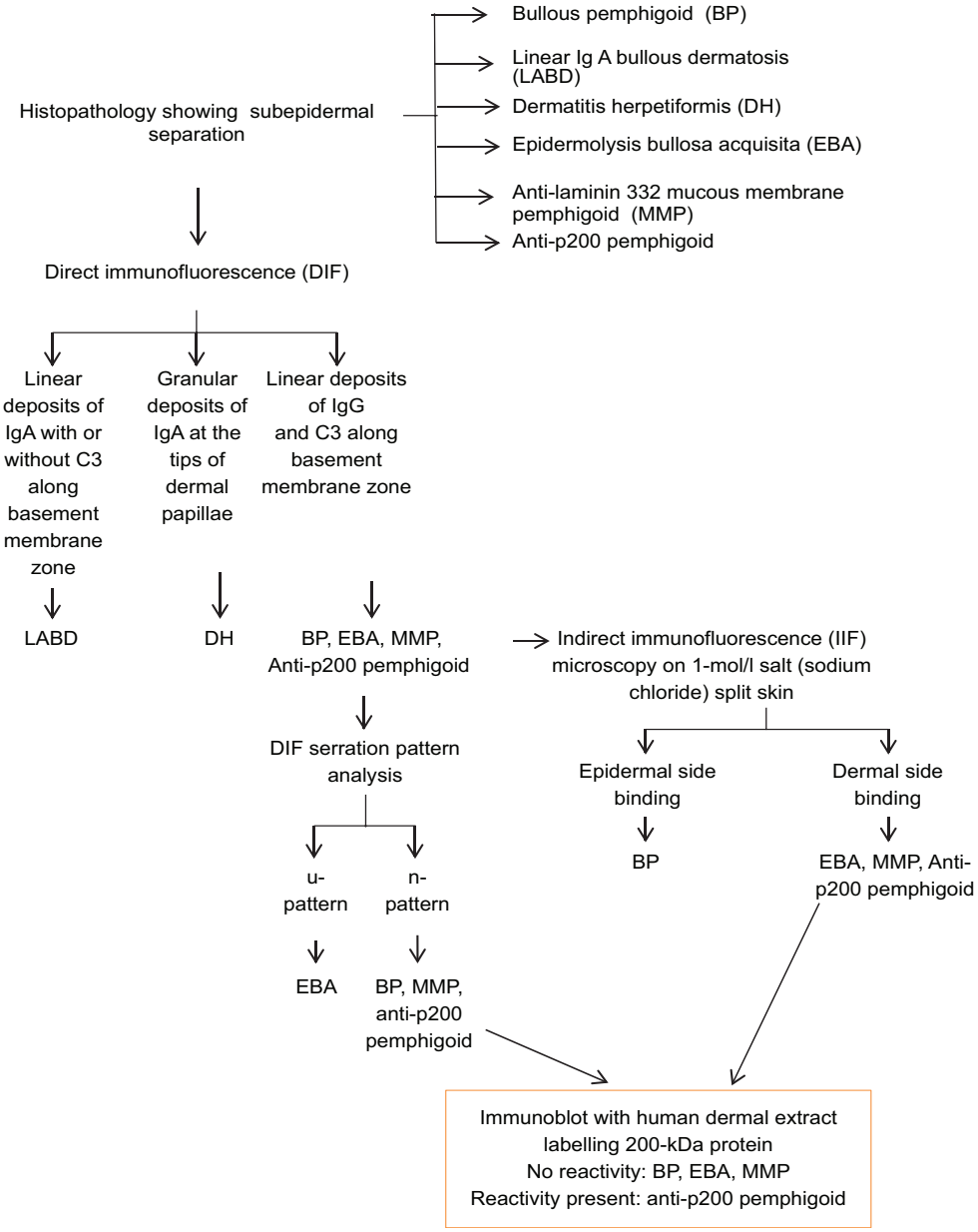


Figure 1: Direct immunofluorescence microscopy on the perilesional skin of a tense bulla from a patient with vesiculobullous disease showing IgG positive immunoreactants on the dermal side of the bulla. Indirect immunofluorescence microscopy on salt split skin is needed to confirm the finding (Image courtesy - Dr. K. P. Aravindan, MD Pathology, Medical Director, Microhealth Reference Lab, Kozhikode, Kerala, India).

Flow Chart 1: Diagnostic algorithm for common vesiculobullous diseases manifesting subepidermal clefting on histopathology.



human dermal extract is available only in a few specialized centers.[7]

IIF microscopy knock out analysis using patient's sera on substrates of recessive dystrophic hereditary epidermolysis bullosa skin that lacks type VII collagen and Herlitz type junctional epidermolysis bullosa skin that lacks laminin-332, may help to differentiate anti-p200 pemphigoid [Figure 2c] from EBA [Figure 2d] and anti-laminin 332 pemphigoid respectively. If a floor pattern binding is observed in salt split study, and further IIF on skin sections from recessive dystrophic hereditary epidermolysis bullosa fails to show reactivity, the diagnosis points to EBA. Since the serum from EBA patients shows pathogenic antibodies to type VII collagen, which is lacking in recessive dystrophic hereditary epidermolysis bullosa. Similarly floor pattern binding is observed in salt split study and if IIF on skin from Herlitz type junctional epidermolysis bullosa fails to show reactivity, then anti-laminin 332 pemphigoid should be considered since Herlitz type junctional epidermolysis bullosa lacks laminin 332. If floor pattern binding is visualized in salt split study and immunoreactivity along basement membrane zone is observed in both the skin sections from recessive dystrophic and Herlitz type junctional hereditary epidermolysis bullosa, then the probable diagnosis is anti-p200 pemphigoid.[7] However, the major difficulty with this diagnostic modality is

the difficulty in procuring enough of skin substrates of these rare types of epidermolysis bullosa. A negative ELISA for type VII collagen can also help to rule out EBA.[27]

On most occasions, the diagnosis may have to rely on clinical features, histopathology, DIF, IIF on salt split skin, and DIF serration pattern analysis [Flow Chart 1].[7,27]

TREATMENT

No standard treatment guidelines are available for anti-p200 pemphigoid. The treatment options include high potency topical steroids, systemic steroids (0.5 mg/kg/day as starting dose), and dapsone (100 mg daily).[5,6] Doxycycline, azathioprine, cyclosporine, colchicine, intravenous immunoglobulin, and ustekinumab are the other treatment options tried.[6] Anti-p200 pemphigoid is documented to show a better prognosis than EBA and on most occasions than BP, but a more severe prognosis than previously suspected is also suggested.[6,28]

CONCLUSION

Anti-p200 pemphigoid, (considered as a rare, subepidermal autoimmune blistering disease) is likely to be more common than currently believed. The failure to differentiate the condition from EBA and BP (due to lack of facility and due to the unfamiliarity with the condition among medical practitioners) could be the reason for the reported low incidence.

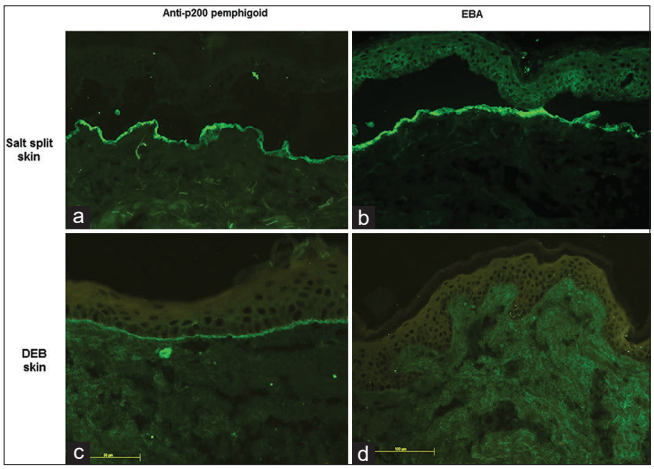


Figure 2: Indirect immunofluorescence microscopy on salt-split skin showing floor binding pattern in (a) anti-p200 pemphigoid, (b) epidermolysis bullosa acquisita (EBA), Modified indirect immunofluorescence microscopy using patient's sera and recessive dystrophic epidermolysis bullosa (DEB) skin as a substrate showing (c) persistent basement membrane zone staining in anti-p200 pemphigoid, (d) absence of basement membrane zone staining in EBA (fluorescein isothiocyanate, ×200). Goyal N, Rao R, Shenoi SD, Pai S, Kumar P, Bhogal BS, *et al*. Epidermolysis bullosa acquisita and anti-p200 pemphigoid as major subepidermal autoimmune bullous diseases diagnosed by floor binding on indirect immunofluorescence microscopy using human salt-split skin. Indian J Dermatol Venereol Leprol 2017;83:550-5. (Image courtesy – IJDVL).

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Lever WF. Pemphigus. Medicine (Baltimore) 1953;32:1-123.
2. Zillikens D, Kawahara Y, Ishiko A, Shimizu H, Mayer J, Rank CV, *et al*. A novel subepiderrnal blistering disease with autoantibodies to a 200-kDa antigen of the basement membrane zone. J Invest Dermatol 1996;106:1333-8.
3. Lerberghe LV, Lasek A, Gosset P, Jouen F, Modiano P. Anti p-200 pemphigoid responding to dapsone. Dermatol Sin 2014;32:51-4.
4. Kridin K, Ahmed AR. Anti P-200 pemphigoid: A systematic review. Front Immunol 2019;10:2466.
5. Wozniak K, Hashimoto T, Fakuda S, Ohyama B, Ishii N, Koga H, *et al*. IgA anti-p200 pemphigoid. Arch Dermatol 2011;147:1306-10.
6. Goletz S, Hashimoto T, Zillikens D, Schmidt E. Anti-p200 pemhigoid. J Am Acad Dermatol 2014;71:185-91.
7. Meijer JM, Diercks GF, Schmidt E, Pas HH, Jonkman MF. Diagnostic value and practicability of serration pattern analysis by direct immunofluorescence microscopy in pemphigoid diseases. JAMA Dermatol 2016;152:897-904.
8. Goyal N, Rao R, Shenoi SD, Pai S, Kumar P, Bhogal BS, *et al*. Epidermolysis bullosa acquisita and anti-p200 pemphigoid as major subepidermal autoimmune bullous diseases diagnosed by floor binding on indirect immunofluorescence microscopy using human salt-split skin. Indian J Dermatol Venereol Leprol 2017;83:550-5.
9. Shimanovich I, Hirako Y, Sitaru C, Hashimoto T, Brocker EB, Butt E, *et al*. The autoantigen of anti-p200 pemphigoid is an acidic noncollagenous N-linked glycoprotein of the cutaneous basement membrane. J Invest Dermatol 2003;121:1402-8.
10. Dainichi T, Kurono S, Ohyama B, Ishii N, Sanzen N, Hayashi M, *et al*. Anti-laminin gamma-1 pemphigoid. Proc Natl Acad Sci U S A 2009;106:2800-5.
11. Groth S, Recke A, Vafia K, Ludwig RJ, Hashimoto T, Zillikens D, *et al*. Development of a simple enzyme-linked immunosorbent assay for the detection of autoantibodies in anti-p200 pemphigoid. Br J Dermatol 2011;164:76-82.
12. Ido H, Ito S, Taniguchi Y, Hayashi M, Sato-Nishiuchi R, Sanzen N, *et al*. Laminin isoforms containing the gamma 3

chain are unable to bind to integrins due to the absence of the glutamic acid residue conserved in the C-terminal regions of the gamma1 and gamma2 chains. J Biol Chem 2008;283:28149-57.
13. Vafia K, Groth S, Beckmann T, Hirose M, Dworschak J, Recke A, *et al*. Pathogenicity of autoantibodies in anti-p200 pemphigoid. PLoS One 2012;7:e41769.
14. Holtsche M, Goletz S, von Gerog A, van Beek N, Hubner F, Pigors M, *et al*. Serologic characterization of anti-p200 pemphigoid: Epitope spreading as a common phenomenon. J Am Acad Dermatol 2020;84:1155-7.
15. Watanabe M, Natsuga K, Nishie W, Kobayashi Y, Donati G, Suzuki S, *et al*. Type XVII collagen coordinates proliferation in the interfollicular epidermis. Elife 2017;6:e26635.
16. Dainichi T, Kabashima K. Interaction of psoriasis and bullous diseases. Front Med 2018;5:222.
17. Dilling A, Rose C, Hashimoto T, Zillikens D, Shimanovich I. Anti-p200 pemphigoid: A novel autoimmune subepidermal blistering disease. J Dermatol 2007;34:1-8.
18. Wozniak K, Kowalewsky C, Hashimoto T, Ishi N, Glinska-Wielochowska M, Schwartz RA. Penicillin-induced anti-p200 pemphigoid: An unusual morphology. Acta Derm Venereol 2006;86:443-6.
19. Della Torre R, Combescure C, Cortés B, Marazza G, Beltraminelli H, Naldi L, *et al*. Clinical presentation and diagnostic delay in bullous pemphigoid: A prospective nationwide cohort. Br J Dermatol 2012;167:1111-7.
20. Furukawa H, Miura T, Takahashi M, Nakamura K, Kaneko F, Ishii F, *et al*. A case of anti-p200 pemphigoid with autoantibodies against both a novel 200-kD dermal antigen and the 290-kD epidermolysis bullosa acquisita antigen. Dermatology 2004;209:145-8.
21. McCarty M, Zillikens D, Fivenson D. Anti-p200 pemphigoid (anti-laminin-γ1 pemphigoid) demonstrating pathergy. Int J Womens Dermatol 2015;1:173-4.
22. Kridin K, Bergman R. Assessment of the prevalence of mucosal involvement in bullous pemphigoid. JAMA Dermatol 2019;155:166-71.
23. Mitsuya J, Hara H, Ito K, Ishii N, Hashimoto T, Terui T. Metastatic ovarian carcinoma-associated subepidermal blistering disease with autoantibodies to both the p200 dermal antigen and the g2 subunit of laminin 5 showing unusual clinical features. Br J Dermatol 2008;158:1354-7.
24. Goetze S, Dumke AK, Zillikens D, Hipler UC, Elsner P. Anti-p200/laminin gamma1 pemphigoid associated with metastatic oesophageal cancer. J Eur Acad Dermatol Venereol 2017;31:e219-21.
25. Hayashi M, Okamura K, Ujiie H, Iwata H, Suzuki T. Case of anti-p200 pemphigoid accompanying uterine malignancy. J Dermatol 2018;45:e341-2.
26. Rose C, Weyers W, Denisjuk N, Hellen U, Zillikens D, Shimanovich I. Histopathology of anti-p200 pemphigoid. Am J Dermatopathol 2007;29:119-24.
27. Jindal A, Rao R, Bhogal B. Advanced diagnostic techniques in autoimmune bullous diseases. Indian J Dermatol 2017;62:268-78.
28. Amber KT, Murrell DF, Schmidt E, Joly P, Borradori L. Autoimmune subepidermal bullous diseases of the skin and mucosae: Clinical features, diagnosis, and management. Clin Rev Allergy Immunol 2018;54:26-51.

How to cite this article: Rasheed VS. Anti-p200 pemphigoid: A review. J Skin Sex Transm Dis 2023;5:22-7.