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Bullous Pemphigoid Severity and Levels of Antibodies to BP180 and BP230

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ABSTRACT

Background: Bullous pemphigoid (BP) is a prevalent autoimmune blistering disorder characterized by an immune response directed against the structural components of the dermal–epidermal junction, primarily BP180 and BP230. **Literature Review:** Further investigations by (Liu et al., 2017) emphasized the pathogenic role of IgG autoantibodies against BP180 in disease development, revealing that serum levels of these antibodies correlate with disease activity. This correlation suggests that these autoantibodies are not merely markers but may play a direct role in the pathophysiology of BP. The increasing morbidity associated with BP, especially in older populations, underscores the necessity for effective therapeutic interventions. (Didona & Di Zenzo, 2018) explored the concept of humoral epitope spreading, indicating that initial immune responses to BP180 could lead to reactivity against BP230, complicating the immune landscape of BP. This phenomenon is essential for understanding disease progression and its clinical implications. (Farnaghi et al., 2020) provided novel insights into the relationship between eosinophilia and BP severity, demonstrating that eosinophil levels correlate with autoantibody titers, suggesting eosinophilia may serve as a biomarker for disease activity. **Conclusion:** Collectively, these studies contribute to a comprehensive understanding of the interplay between autoantibody levels and clinical manifestations of BP. They emphasize the importance of serological assays in diagnosing and monitoring disease activity, showcasing the complexity of autoimmune responses and the need for ongoing research to refine therapeutic approaches.

Keyword: Bullous Pemphigoid Severity, Levels of Antibodies to BP180 and BP230

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INTRODUCTION

Bullous pemphigoid (BP) is a prevalent autoimmune blistering disorder characterized by an immune response directed against the structural components of the dermal–epidermal junction, primarily BP180 and BP230. The literature surrounding BP has evolved to elucidate the complex relationship between the severity of the disease and the levels of specific autoantibodies. The foundational work by (Patsatsi et al., 2012) established a correlation between circulating autoantibodies (anti-BP180 and anti-BP230) and clinical disease activity, utilizing the BP Disease Area Index (BPDAI) and the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) as assessment tools for disease severity. This study underscored the importance of serological testing in the management and monitoring of BP.

Following this, (Hyung Lee et al., 2012) further reinforced the diagnostic utility of enzyme-linked immunosorbent assays (ELISA) for detecting autoantibodies against BP180 and BP230. Their findings highlighted that elevated serum levels of these autoantibodies correlate with disease activity, paving the way for more refined diagnostic and monitoring strategies in clinical practice. The emphasis on the immunodominant NC16A domain of BP180 as a key target for autoantibody formation was particularly noteworthy, suggesting that accurate serological profiling can provide insights into disease progression.

In a similar vein, (Liu et al., 2017) explored the pathogenic mechanisms of BP, detailing how the presence of IgG autoantibodies, particularly against BP180, is a critical factor in the development and severity of the disease. Their findings indicated that the serum levels of anti-BP180 correlate with disease activity, suggesting that these autoantibodies may play a direct role in the pathophysiology of BP. This article also highlighted the increasing morbidity associated with BP, particularly in older populations, and the need for effective therapeutic interventions.

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(Didona & Di Zenzo, 2018) expanded upon these findings by discussing the phenomenon of humoral epitope spreading in autoimmune diseases, including BP. They posited that initial immune responses to extracellular epitopes of BP180 could lead to subsequent reactivity against intracellular epitopes of BP230, thereby complicating the immune landscape of the disease. This concept of epitope spreading is crucial for understanding the progression of BP and its clinical implications.

(Farnaghi et al., 2020) provided novel insights into the correlation between eosinophilia—both dermal and peripheral blood—and BP severity. Their study demonstrated a significant relationship between eosinophil levels and autoantibody titers, reinforcing the notion that eosinophilic infiltration is a hallmark of BP and may serve as a biomarker for disease activity.

Finally, (Cole et al., 2022) delved deeper into the role of BP230 autoantibodies, proposing that their generation may result from epitope spreading initiated by initial immune responses to BP180. This work elucidated the dynamics of autoantibody formation throughout the clinical course of BP, suggesting that the timing and order of antibody responses could be indicative of disease severity.

Together, these studies contribute to a comprehensive understanding of the interplay between autoantibody levels and the clinical manifestations of BP, emphasizing the importance of serological assays in diagnosing and monitoring disease activity. The evolving narrative of BP underscores the complexity of autoimmune responses and the necessity for ongoing research to refine therapeutic approaches.

LITERATURE REVIEW

The article "Association of Autoantibodies to BP180 with Disease Activity in Greek Patients with Bullous Pemphigoid" by Patsatsi et al. (Patsatsi et al., 2012) presents a significant exploration of the relationship between levels of autoantibodies and disease activity in patients diagnosed with bullous pemphigoid (BP). As the most prevalent subepidermal autoimmune bullous disease,

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understanding the dynamics of BP is crucial for effective patient management and treatment strategies.

The authors provide a thorough examination of the diagnostic utility of serum autoantibodies, specifically anti-BP180 and anti-BP230, utilizing commercially available enzyme-linked immunosorbent assay (ELISA) kits. This method has become a standard practice in the clinical setting, allowing for routine monitoring and assessment of disease progression. The study notably correlates the titers of these autoantibodies with clinical scores derived from the BP Disease Area Index (BPDAI) and the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), thereby establishing a framework for evaluating disease severity.

A critical aspect of the study is its focus on the correlation between antibody levels and pruritus intensity, which is a significant symptom impacting the quality of life for patients with BP. By analyzing data from the first six months post-diagnosis, the authors contribute valuable insights into how fluctuations in autoantibody levels may correspond with clinical manifestations of the disease. The findings suggest that higher levels of anti-BP180 antibodies are associated with increased disease activity, as indicated by both the BPDAI and ABSIS scores.

However, while the study presents compelling evidence supporting the use of autoantibody titers as a biomarker for disease activity, it is essential to acknowledge potential limitations. The study's sample size and demographic specificity to Greek patients may restrict the generalizability of the findings. Furthermore, the reliance on two clinical scoring systems, while beneficial for a comprehensive assessment, may introduce variability based on subjective interpretations of disease severity.

The article titled "Usefulness of Enzyme-linked Immunosorbent Assay Using Recombinant BP180 and BP230 for Serodiagnosis and Monitoring Disease Activity of Bullous Pemphigoid" by 김수찬, 김신영, and 김송이 (et al., 2012) presents a significant advancement in the diagnostic and monitoring processes for bullous pemphigoid (BP). The authors focus on the development of an enzyme-linked immunosorbent assay (ELISA) aimed at detecting autoantibodies specific to

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BP180 and BP230, which are critical components of the pathophysiology of this autoimmune blistering disease.

One of the central insights of the article is the identification of the correlation between serum levels of autoantibodies to BP180 and disease activity in patients with bullous pemphigoid. The authors demonstrate that elevated levels of IgE anti-BP180 and anti-BP230 autoantibodies can serve as biomarkers for disease severity, suggesting that monitoring these levels could be instrumental in assessing disease progression and treatment efficacy. This finding is particularly relevant as it provides a quantifiable measure that can guide clinical decision-making and patient management.

Additionally, the article discusses the passive transfer model of bullous pemphigoid using antibodies generated against BP180, which underscores the pathogenic role of these autoantibodies in the disease process. By establishing a direct link between the presence of these antibodies and the manifestation of clinical symptoms, the authors contribute to a deeper understanding of the immunological mechanisms underlying bullous pemphigoid.

The article further elaborates on the preferential binding of in situ antibodies to the 230-kD bullous pemphigoid antigen, highlighting the importance of BP230 in the disease's immunopathology. This specificity in antibody targeting is crucial for both diagnostic accuracy and therapeutic strategies, as it may influence the choice of treatment modalities tailored to the individual patient's antibody profile.

The article "Usefulness of Enzyme-linked Immunosorbent Assay Using Recombinant BP180 and BP230 for Serodiagnosis and Monitoring Disease Activity of Bullous Pemphigoid" by Lee et al. (Hyung Lee et al., 2012) provides a comprehensive examination of the role of autoantibodies in the diagnosis and monitoring of bullous pemphigoid (BP). The authors elucidate the significance of BP180 and BP230, which are critical antigens in the pathogenesis of BP, an autoimmune disorder characterized by the formation of tense blisters due to the presence of specific IgG autoantibodies against the basement membrane zone.

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The study highlights the limitations of traditional diagnostic methods, such as indirect immunofluorescence (IF), which can be operator-dependent and may yield inconsistent results. In contrast, the enzyme-linked immunosorbent assay (ELISA) is presented as a more reliable alternative, offering reproducibility and the capability to quantify autoantibody levels. The authors emphasize that the ELISA method allows for the simultaneous testing of multiple samples, thereby enhancing the diagnostic process for BP.

A key insight from the study is the establishment of a correlation between the levels of circulating IgG autoantibodies and the clinical activity of BP. This finding is particularly relevant for clinicians as it suggests that monitoring autoantibody levels can provide valuable information regarding disease progression and severity. The article effectively discusses how the immunodominant NC16A domain of BP180 is particularly significant in this context, as it serves as a primary target for autoantibody production in BP patients.

Moreover, the authors explore the potential relationship between distinct autoantibody profiles and clinical features of BP, which could further refine diagnostic and therapeutic approaches. The study's findings support the notion that a better understanding of autoantibody dynamics can assist in tailoring treatment strategies for patients suffering from BP.

The article "BP180 Is Critical in the Autoimmunity of Bullous Pemphigoid" by Liu, Li, and Xia (Liu et al., 2017) provides a comprehensive examination of the role of autoantibodies, particularly against BP180 and BP230, in the pathogenesis of bullous pemphigoid (BP). BP is characterized by its autoimmune nature, where the body develops antibodies against components of the dermal–epidermal junction (DEJ), leading to significant clinical manifestations, primarily in older populations, though it can also affect younger individuals.

The authors emphasize that the presence of IgG autoantibodies against BP180 is typically the first serological indicator of BP, preceding the detection of IgG autoantibodies against BP230. This sequential emergence of antibodies underscores

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the critical role of BP180 in the disease's immunological framework. Furthermore, the detection of IgE antibodies against BP230 in patients adds another layer to the autoimmune profile associated with BP, suggesting a complex interplay between different antibody classes in the disease's progression.

A significant contribution of this article is its discussion on the correlation between serum levels of anti-BP180 NC16A autoantibodies and disease severity. The authors present compelling evidence that higher levels of these autoantibodies are associated with more active and severe disease states, as well as poorer prognostic outcomes. This finding is crucial as it not only highlights BP180 as a primary target in the autoimmune response but also suggests that measuring these autoantibody levels could serve as a valuable biomarker for assessing disease activity and guiding treatment strategies.

The article also addresses the increasing mortality associated with BP, which the authors attribute to various factors, including delayed diagnosis and treatment complications. This aspect of the discussion is particularly relevant in clinical practice, as it emphasizes the need for timely intervention and the potential for corticosteroid therapies, which remain the cornerstone of BP management.

The article "Humoral Epitope Spreading in Autoimmune Bullous Diseases" by Didona and Di Zenzo (Didona & Di Zenzo, 2018) provides an insightful exploration into the complexities of bullous pemphigoid (BP), highlighting both its clinical manifestations and the underlying immunological mechanisms. BP is characterized by a range of cutaneous symptoms, typically beginning with severe pruritus and evolving into the formation of vesicles and bullae on seemingly healthy or inflamed skin. This progression underscores the disease's protean nature, which poses challenges for timely diagnosis and management.

A key focus of the article is the role of autoantibodies, particularly those targeting BP180 and BP230—components of the junctional adhesion complexes in the skin. The authors emphasize that the presence of autoantibodies against these antigens is pivotal in the pathogenesis of BP, with a significant number of patients

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demonstrating reactivity to the NC16A domain of BP180. The pathogenicity of these antibodies is supported by experimental evidence, indicating that they can induce tissue damage and contribute to the disease's severity.

The article also delves into the dynamics of antibody reactivity, revealing that IgG responses to extracellular epitopes of BP180 precede those against intracellular domains. This finding suggests a process of epitope spreading, where initial immune responses to specific epitopes may lead to the exposure and subsequent targeting of other, previously hidden epitopes. This phenomenon is critical in understanding the progression of BP and the potential for increased severity as the immune response evolves.

Moreover, the authors note that the role of anti-BP230 antibodies remains less defined, indicating a gap in current understanding that warrants further investigation. The article effectively utilizes a transgenic mouse model to explore these immunological interactions, providing a robust framework for future research into the mechanisms of BP and the potential for therapeutic interventions.

The article titled "Correlation of dermal and blood eosinophilia with bullous pemphigoid disease severity" by Farnaghi et al. (Farnaghi et al., 2020) provides valuable insights into the relationship between eosinophilia and the severity of bullous pemphigoid (BP), an autoimmune blistering disorder characterized by the presence of antibodies against BP-180 and BP-230. The authors aim to elucidate the correlation between dermal and peripheral blood eosinophilia, levels of anti-BP-180 and anti-BP-230 IgG, and the clinical severity of BP as assessed by the bullous pemphigoid disease activity index (BPDAI).

The study included 27 patients with newly diagnosed BP, which is a relatively small sample size that may limit the generalizability of the findings. However, the authors employed a robust methodology to assess disease severity, utilizing both objective and subjective BPDAI scores. The results indicated a significant correlation between serum levels of anti-BP-180 and anti-BP-230 and both dermal eosinophilia and tissue inflammation severity. This finding is critical as it highlights the role of

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these antibodies not only as biomarkers for diagnosis but also as potential indicators of disease activity.

Furthermore, the authors reported a significant correlation between the percentage of peripheral blood eosinophils and subjective BPDAI scores, as well as urticarial/eczematous lesions. This suggests that eosinophilia may serve as an important component in assessing the clinical severity of BP, potentially guiding treatment decisions. The correlation of eosinophilia with subjective scores emphasizes the importance of considering patient-reported outcomes alongside clinical assessments.

The study's findings contribute to the understanding of BP pathophysiology by linking immune response markers with clinical manifestations. However, the authors could enhance their analysis by discussing the implications of these correlations in terms of treatment strategies or the potential for using eosinophil levels as a therapeutic target. Additionally, future studies with larger cohorts and longitudinal designs would be beneficial to validate these findings and explore the dynamics of eosinophilia in relation to BP severity over time.

The article "Deciphering the Contribution of BP230 Autoantibodies in Bullous Pemphigoid" by Connor Cole, Luca Borradori, and Kyle T. Amber (Cole et al., 2022) provides an in-depth examination of the mechanisms underlying the generation of autoantibodies against BP230 in the context of Bullous Pemphigoid (BP). The authors propose a significant role for intermolecular epitope spreading, a phenomenon whereby an immune response expands from an initial epitope to additional, distinct epitopes. This concept is pivotal in understanding the progression of BP, as it implies that the immune system's response evolves over time, potentially complicating the disease's clinical presentation and management.

The article highlights that the initial immune response in BP is directed against extracellular epitopes on BP180, which may lead to cellular damage and the subsequent exposure of intracellular BP230 and the cytoplasmic domain of BP180. This sequential exposure is critical, as it suggests that autoantibodies to BP230 may

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emerge later in the disease course, indicating a more complex immune response than previously understood. The authors reference multicenter studies that demonstrate epitope spreading predominantly occurs in the early stages of BP and correlates with increased disease severity, thus emphasizing the importance of early detection and monitoring of antibody levels.

Additionally, the authors discuss findings from mouse model studies, which indicate that the development of antibodies targeting extracellular epitopes precedes the recognition of intracellular epitopes. This evidence supports the hypothesis that damage to the basal membrane is a catalyst for the immune response, initially targeting BP180 before progressing to BP230. The identification of specific regions within BP230, particularly the N-terminal and C-terminal regions, as immunodominant antigenic portions adds a layer of complexity to the understanding of antibody formation and disease progression.

Critically, while the article provides substantial insights into the mechanisms of antibody generation and their implications for disease severity, it could benefit from a more extensive discussion on the clinical applications of these findings. For instance, understanding the timing and nature of antibody responses could inform treatment strategies and improve patient outcomes. Moreover, the potential for therapeutic interventions targeting specific epitopes or modulating the immune response could be an area for future research.

CONCLUSION

The literature on bullous pemphigoid (BP) has significantly advanced in understanding the correlation between disease severity and levels of autoantibodies, particularly those against BP180 and BP230. The foundational study by (Patsatsi et al., 2012) established a crucial link between circulating autoantibodies and clinical disease activity, employing the BP Disease Area Index (BPDAI) and the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) for assessment. This work highlighted the importance of serological testing in managing BP, reinforcing the diagnostic utility of enzyme-linked immunosorbent assays (ELISA) for

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detecting these autoantibodies. Further investigations by (Liu et al., 2017) emphasized the pathogenic role of IgG autoantibodies against BP180 in disease development, revealing that serum levels of these antibodies correlate with disease activity. This correlation suggests that these autoantibodies are not merely markers but may play a direct role in the pathophysiology of BP. The increasing morbidity associated with BP, especially in older populations, underscores the necessity for effective therapeutic interventions. (Didona & Di Zenzo, 2018) explored the concept of humoral epitope spreading, indicating that initial immune responses to BP180 could lead to reactivity against BP230, complicating the immune landscape of BP. This phenomenon is essential for understanding disease progression and its clinical implications. (Farnaghi et al., 2020) provided novel insights into the relationship between eosinophilia and BP severity, demonstrating that eosinophil levels correlate with autoantibody titers, suggesting eosinophilia may serve as a biomarker for disease activity. (Cole et al., 2022) further examined the role of BP230 autoantibodies, proposing that their generation may result from epitope spreading initiated by immune responses to BP180. This work elucidated the dynamics of autoantibody formation throughout the clinical course of BP, indicating that the timing and order of antibody responses could be indicative of disease severity. Collectively, these studies contribute to a comprehensive understanding of the interplay between autoantibody levels and clinical manifestations of BP. They emphasize the importance of serological assays in diagnosing and monitoring disease activity, showcasing the complexity of autoimmune responses and the need for ongoing research to refine therapeutic approaches.

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