Association between *Auto-Immune Bullous Disease* and *Interstitial Pneumonia*

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ABSTRACT

Numerous inflammatory, neoplastic, and genetic skin disorders are associated with interstitial lung disease (ILD), a fibrosing inflammation of lung parenchyma with significant morbidity and mortality. There is inconsistent data regarding the association between bullous pemphigoid and pneumonia. This article details the clinical manifestations of bullous pemphigoid (BP) and pemphigus vulgaris (PV) associated with interstitial pneumonia, specific diagnostic strategies, underlying mechanistic connections, and possible treatments.

Keywords: Bullous pemphigoid, interstitial lung disease, pemphigus vulgaris.

ABSTRAK

Banyak kelainan kulit inflamasi, neoplastik, dan genetik dikaitkan dengan penyakit pneumonia interstisial (ILD) berupa peradangan fibrosa parenkim paru dengan morbiditas dan mortalitas yang signifikan. Data hubungan antara infeksi pneumonia dan pemfigoid bulosa masih belum konsisten. Tinjauan literatur ini menjelaskan manifestasi klinis dari pemfigus bulosa (BP) dan pemfigus vulgaris (PV) yang terkait dengan pneumonia interstisial, strategi diagnostik spesifik, hubungan mekanistik yang mendasari, dan pengobatan yang mungkin diberikan. **Enggar Yusrina Hasyyati, Caprisia Tiaravicka Hasanah, Prajnamita Manindya El Farah, Inas Khoirunnisa. Asosiasi *Auto-Immune Bullous Disease* dengan *Interstitial Pneumonia*.**

Kata Kunci: Pemfigoid bulosa, penyakit pneumonia interstisial, *pemphigus vulgaris*.

INTRODUCTION

Research has found a correlation between auto-immune bullous illness and interstitial pneumonia.[1] Nevertheless, published literature on the association between autoimmune bullous disease and interstitial pneumonia is still restricted.[2] The objective of this study is to investigate the association by evaluating the clinical symptoms, applying specialized diagnostic approaches, investigating the underlying cellular associations, and considering potential therapeutic interventions.

AUTO-IMMUNE BULLOUS DISEASE

Auto-immune blistering dermatoses (AIBD) are potentially lethal, chronic relapsing disorders affecting skin and mucous membranes, mainly associated with IgG autoantibodies against distinct adhesion proteins of the epidermis or basement membrane zone.[3] Direct immunofluorescence (DIF) microscopy of a perilesional biopsy is the gold standard for detecting autoantibodies or complement components for AIBD diagnosis.[4] AIBD groups consist of pemphigus vulgaris, dermatitis herpetiformis, bullous pemphigoid, mucous membrane pemphigoid, and pemphigus foliaceus.[5]

Bullous pemphigoid (BP) is an autoimmune blistering skin disease, mainly in the elderly. It is characterized by generalized pruritic urticarial plaques and tense subepithelial blisters.[6] Histopathology studies with hematoxylin-eosin staining showed subepithelial bullous dermatitis with numerous eosinophils as well as perivascular chronic inflammation rich in eosinophils.[7] Pemphigus vulgaris (PV) is characterized by flaccid blisters and erosions of the skin and mucous membranes due to the intra-epidermal separation of keratinocytes. Autoantibodies specific for desmosomal (desmoglein 1 and desmoglein 3) and potentially additional non-desmosomal (thyroid peroxidase, thyroglobulin, and more) moieties lead to a breakdown of intercellular adhesion structures responsible for epithelial integrity.[8] Corticosteroids remain the mainstay of the treatment plan for bullous-pemphigoid and pemphigus vulgaris.[9]

INTERSTITIAL PNEUMONIA

Interstitial lung disease (ILD) is a collective term representing a diverse group of lung conditions characterized by the presence of non-infective infiltrates, most commonly in the pulmonary interstitium and alveoli, which in certain cases manifest as architectural distortion and irreversible fibrosis.[10] These

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conditions vary in their etiology, clinical pathways, severity, and prognosis.[11] Some conditions resolve completely without pharmacological intervention, whereas others, such as idiopathic pulmonary fibrosis (IPF) and non-IPF progressive fibrosing (PF) ILDs, inexorably progress to respiratory failure and premature mortality despite treatment.[10]

AUTOIMMUNE PATOPHYSIOLOGY AND INTERSTITIAL PNEUMONIA PATOPHYSIOLOGY

Lung disorders associated with linear IgA/IgG bullous dermatosis are extremely rare.[12] This immunologic reaction might contribute to the progression of interstitial pneumonia. Immune complexes have been reported to occur with interstitial pneumonias in patients with collagen vascular diseases, such as systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, and polymyositis/dermatomyositis.[13] Rarely does bullous pemphigoid affect mucous membranes, as in the airway. Two cases of diffuse alveolar hemorrhage-associated lung diseases linked to bullous pemphigoid were documented.[14] Yoshioka stated that linear deposition of IgG and C3 along the basement membrane of the alveoli was shown by direct immunofluorescence in bullous pemphigoid-associated interstitial pneumonia.[11] Further investigation may thus be needed regarding the immune complex in bullous pemphigoid.

LITERATURE SEARCH

This article was based on a literature search published from 2013 to 2023, through the PubMed, Google Scholar, and Cochrane databases with the keywords "associated" AND "autoimmune" OR "bullous" AND "pneumonia". The categories were: book and documents, clinical trial, meta-analysis, RCT, review, and systematic review. In the initial stage, 372 articles were obtained. Forty three articles were included for review, and 4 studies were critically appraised (**Figure**).

RESULT

Yoshioka reports a 73-year-old woman with bullous eruptions after a 1-month history of dry cough and dyspnea. Both oral antihistamines and steroid ointments were not effective. Subepidermal blisters with lymphocyte infiltrates were visible on chest CT scans. IgG and C3 were detected by direct immunofluorescence along the bronchial basal lamina. Subepidermal blisters with lymphocyte infiltrates were visible in a skin biopsy sample, and a circulating IgG autoantibody bound the basement membrane of the labial mucosa. Prednisolone 40 mg/d was administered to treat nonspecific interstitial pneumonia. Both cutaneous and pulmonary lesions improved and have been stable for 2.2 years on a maintenance dose of prednisolone 10 mg/dL.[11]

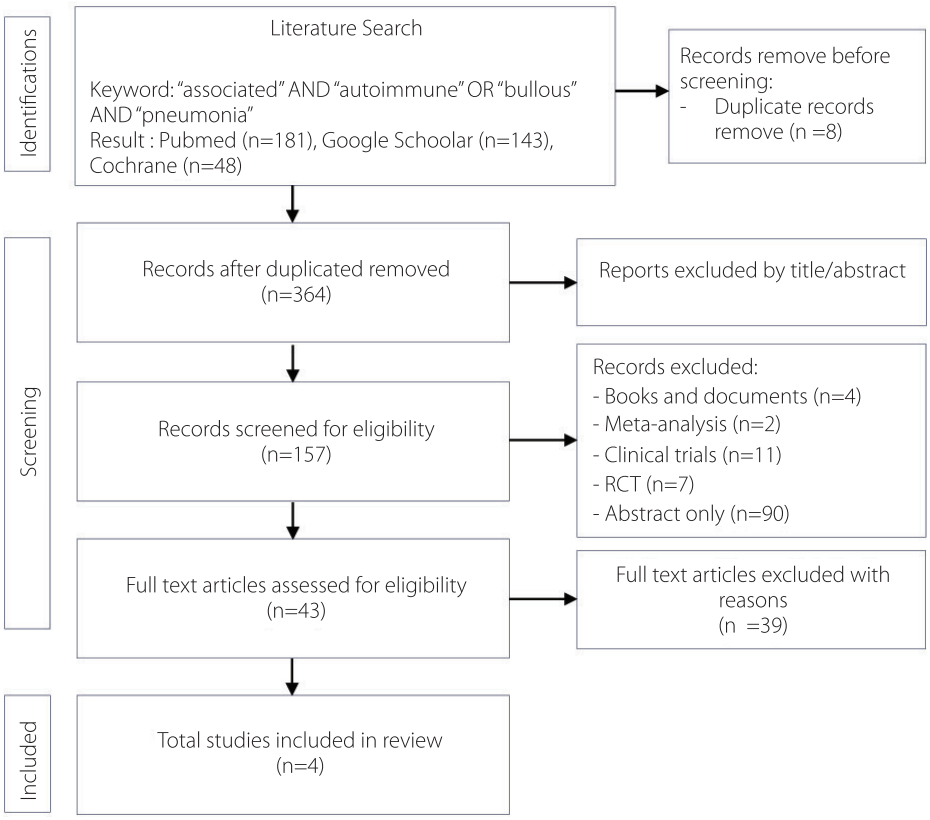

Figure. Flow of literature search.

Waki, *et al,* (2019) report a Japanese woman in her sixties with skin blisters, pyrexia, and a dry cough. Physical examination showed tight blisters, erosions, and oedematous erythema in the trunk and extremities. CT indicated patchy ground-glass opacity in the right lung fields, consistent with the diffuse alveolar damage pattern of interstitial pneumonia. Histopathological analysis confirmed subepidermal blistering, and direct immunofluorescence analysis identified weak linear IgG deposition and strong linear C3 deposition in the base membrane zone. A transbronchial lung biopsy's histopathological analysis indicated few inflammatory cells invading the bronchioles and only small changes in the alveolar septa. Methylprednisolone 1000 mg/day for 3 days quickly alleviated cutaneous and lung symptoms after the diagnosis of bullous pemphigoid accompanied by interstitial pneumonia. This situation indicates that interstitial pneumonia was associated with BP180, expressed by lung stem cells, detected as an antigen by immunocompetent cells in interstitial pneumonia.[15]

Bai, *et al,* (2012) reported that a 53-year-old Chinese woman developed extensive bullae and severe erosion over a period of six weeks. Direct immunofluorescence (DIF), indirect immunofluorescence (IIF), and histology confirm the diagnosis of PV. The lesions recovered quickly with prednisone 1 mg/kg/d. She resumed oral prednisone twice, but experienced two relapses. Complete erythema, blisters, erosions, crusts, and thrush were all visible at physical examination. Serum C-reactive protein, ferritin, procalcitonin, anti-Dsg1, anti-Dsg3, IIF, CD4 and CD8 T lymphocyte counts, as well as 1-3-b-D glucan, were all raised. No CMV, herpes simplex, or mycoplasma pneumonia antibodies were identified. Fever and cough were reduced after one week of intravenous methylprednisolone,

Table. Reported cases of bullous pemphigoid associated with interstitial pneumonia.

Case	Author	Year	Age/Sex	AIBD onset	Clinical Features	Laboratory Finding	Treatment	Response to Treatment
1	Yoshioka, et al.	2011	73 yo/F	8 months	▪ Fine crackles detected bilaterally on chest auscultation ▪ Tense blister, erosions on the trunk and extremities	▪ Biopsy specimen from a skin lesion: subepidermal blisters with lymphocyte infiltrates in the dermis and inside the blister cavity ▪ Histopathologic findings of alveolar septal thickening and inflammatory cell infiltration in the transbronchial lung biopsy specimens ▪ Indirect immunofluorescence showed a circulating IgG autoantibody that bound the basement membrane ▪ Direct immunofluorescence showed linear deposition of IgG and C3 along the basement membrane of the alveolar epithelium	Prednisone 40 mg/dL	Complete regression in 2 years
2	Waki, et al.	2019	65 yo/F	2 weeks	▪ Pyrexia ▪ Dry cough ▪ Tense blisters, erosions and oedematous erythema on the trunk and extremities	▪ Computed tomography: patchy ground-glass opacity in the right lung fields compatible with the diffuse alveolar damage pattern of interstitial pneumonia ▪ Histopathological examination: subepidermal blistering ▪ Direct immunofluorescence: weak linear deposition of IgG and strong linear deposition of C3 in the basement membrane zone ▪ Histopathological examination of transbronchial lung biopsy: minimal changes in the alveolar septa and few inflammatory cells infiltrating the bronchioles	Methyl-prednisolone 1000 mg/day for 3 days rapidly improved skin and pulmonary symptoms, followed by prednisolone 1 mg/kg/day.	Complete regression
3	Bai, et al.	2013	53 yo/F	8 months	▪ Extensive erythema, blisters, erosions, crust on the head, trunk, proximal upper limbs, with thrush and erosions in the oral cavity ▪ Nikolsky sign + ▪ Fever ▪ Cough ▪ Dyspnea	▪ High-resolution computed tomography (HRCT): multiple ground glass opacification and reticular opacities of bilateral lung fields	Methyl-prednisolone 80 mg/day oral	Relapsed one year later after treatment discontinuation. Remission was achieved in two weeks with oral methyl-prednisolone 24 mg/day.
4	Kakugawa, et al.	2013	76 yo/M		▪ Dyspnea ▪ Bullous eruptions on the skin of the trunk and extremities	▪ Direct immunofluorescence of a skin biopsy: the linear deposition of immunglobulin A (IgA), IgG, and C3 along the basement membrane. ▪ Chest computed tomography: bronchoalveolar lavage and transbronchial lung biopsy findings suggested nonspecific interstitial pneumonia. ▪ Direct immunofluorescence of the lung biopsy specimens: a deposition of IgA, IgG, and C3 along the epithelial cell membranes and basement membranes of the bronchioles and alveoli		


but dyspnea and hypoxemia continued. Because of economic limitations, the patient asked to be discharged after two months of oral methylprednisolone. PV relapsed after corticosteroid withdrawal. The patient had remission after taking oral MPd for two weeks.[2]

Kakugawa, *et al,* reported a 76-year-old male with interstitial lung disease after suffering persistent dyspnea with effort. He also experienced the recurrence of the bullous eruptions on his trunk and limbs previously attributed to vesicular pemphigoid. Direct immunofluorescence of a skin biopsy showed linear deposition of immunoglobulin A (IgA), immunoglobulin G (IgG), and C3 along the basement membrane, indicating a definite diagnosis of linear IgA/IgG bullous dermatosis. Results from bronchoalveolar lavage, transbronchial lung biopsy, and chest computed tomography suggested nonspecific interstitial pneumonia. Fluorescence microscopy-based direct immunofluorescence of lung biopsy tissues revealed the deposition of IgA, IgG, and C3 along the epithelial cell membranes and basement membranes of the bronchioles and alveoli.[16]

CONCLUSION

Numerous inflammatory, neoplastic, and genetic skin disorders are associated with interstitial lung disease (ILD). AIBDs-associated ILD occurs when AIBDs relapse or are not controlled. It responds well to systemic corticosteroids, and has a relatively better prognosis. Clinicians should be aware that interstitial pneumonia may be a pulmonary manifestation of bullous pemphigoid.

Conflict of Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Author Contributions

EY contributed to the concept of this review, CT collected relevant resources, PM performed statistical analysis, and IK wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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