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Pulmonary Alveolar Proteinosis Secondary to Chronic Ethylene Oxide Occupational Inhalation

Mesleki olarak Kronik Etilen Oksit İnhalasyonuna Sekonder Pulmoner Alveolar Proteinozis

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ABSTRACT

In this case report, a 40-year-old male patient with a persistent and productive cough lasting over 2 weeks, accompanied by dyspnea, who received an anti-tuberculosis drug regimen for 12 months without any clinical improvement at a different hospital before being referred to Persahabatan Central General Hospital was presented. In-depth clinical, and radiological investigations, the periodic acid-Schiff (PAS)-positive related to pulmonary alveolar proteinosis (PAP) confirmed through transbronchial biopsy (TBB). PAP is a rare lung disease with exceptionally low prevalence and incidence, Notably, the patient's occupational environment played a crucial role in the diagnosis, as we identified occupational PAP secondary to chronic inhalation of ethylene oxide in a poorly ventilated work setting and inadequate respiratory protection. The patient was administered inhaled filgrastim (1 vial) at four intervals over 30 days, yielding favorable and satisfactory clinical as well as radiological outcomes.
Keywords: Chronic ethylene oxide; pulmonary alveolar proteinosis; pulmonary lavage; transbronchial biopsy.

ÖZ

Bu olgu sunumunda, 2 haftadan uzun süredir devam eden inatçı ve prodüktif öksürüğün yanı sıra nefes darlığı şikayeti olan, Persahabatan Merkez Genel Hastanesi'ne sevk edilmeden önce farklı bir hastanede 12 ay boyunca anti-tüberküloz ilaç tedavisi alan ve herhangi bir klinik iyileşme göstermeyen 40 yaşında bir erkek hasta sunulmaktadır. Ayrıntılı klinik ve radyolojik incelemelerde, pulmoner alveoler proteinozis (PAP) ile ilişkili periyodik asit-Schiff (PAS) pozitifliği, transbronşiyal biyopsi (TBB) ile doğrulandı. PAP son derece düşük prevalansı ve insidansı olan nadir bir akciğer hastalığıdır. Yetersiz havalandırılan bir çalışma ortamında ve yetersiz solunum korumasıyla kronik etilen oksit inhalasyonuna ikincil olarak mesleki PAP belirlediğimiz hastada, özellikle hastanın mesleki ortamı tanıda çok önemli bir rol oynadı.
Hastaya 30 gün boyunca dört aralıkla inhale filgrastim (1 şişe) uygulandı ve olumlu ve tatmin edici klinik ve radyolojik sonuçlar elde edildi.
Anahtar kelimeler: Kronik etilen oksit; pulmoner alveoler proteinözis; pulmoner lavaj; transbronşiyal biyopsi.

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INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare and intriguing lung disorder where the delicate equilibrium of surfactant clearance and production is disrupted (1). Approximately 90% of PAP cases stem from the autoimmune variant, while secondary PAP accounts for 4%, congenital PAP for 1%, and the remaining 5% consists of undetermined PAP-like diseases (1). Autoimmune PAP is triggered by IgG anti-granulocyte macrophage colony stimulating factor (anti-GM-CSF) antibodies,

which lead to a decline in functional alveolar macrophages. On the other hand, secondary PAP lacks these antibodies but still experiences a reduction in effective alveolar macrophages (2). However, diagnosing PAP resulting from chronic ethylene oxide (ETD) occupational inhalation is exceedingly rare, making this case report particularly noteworthy. This case report aimed to present a PAP case secondary to ETD occupational inhalation.

CASE REPORT

A 40-year-old male with a history of 5 pack-years of tobacco use, presented with a productive cough for more than 2 weeks followed by shortness of breath (mMRC 3). He received an anti-tuberculosis drug regimen for 12 months without any clinical improvement at a previous hospital, before being referred to Persahabatan Central General Hospital. The patient has been screened for pulmonary tuberculosis yielding non-specific chest x-ray results with negative acid-fast bacilli (AFB) on sputum. On clinical examination, he was found to have clubbed fingers with oxygen saturation at rest breathing air of 80%, and late inspiratory crackles in the middle and lower fields of both lungs. A pulmonary function test was not conducted due to pandemic-related reasons. A repeated chest x-ray for evaluation and a contrast thorax computed tomography (CT) scan were obtained, showing an appearance of interstitial lung disease. Bronchoalveolar lavage (BAL) revealed the appearance of thoracic epithelial cells, leukocytes, and macrophages with a red blood cell background. Parenchymal lung tissue biopsy from transbronchial biopsy (TBB) revealed the appearance of alveolar space containing amorphous eosinophilic material (Figure 1). This histopathologic pattern was suggestive of PAP. Autoimmune marker tests including ANA, dsDNA, and RF showed negative results, and the IgG anti-GM-CSF test was not performed in Indonesia due to its unavailability.

The patient worked as a medical stem sterilizer with exposure to ETD for 6 months without adequate respiratory protection, thus leaving significant symptoms such as an irritative cough and conjunctival inflammation during and after work. There's no exposure to other agents. However, the patient didn't experience any difference in symptom severity whether he was at work or in a non-work environment. Based on comprehensive studies and his detailed work history, the diagnosis pointed towards secondary alveolar proteinosis attributed to chronic ETD exposure. Exposure avoidance has been carried out by the patient for 3 months but there was no clinical improvement. Due to the unavailability of GM-CSF in Indonesia, the patient underwent a treatment regimen consisting of four rounds of inhaled 1 vial filgrastim, a granulocyte colony stimulating factor (G-CSF), at 30-day intervals, resulting in favorable clinical and radiological outcomes (Figure 2). The treatment was well-tolerated and clinical improvement was achieved after 4 months. Cough and dyspnea decreased (mMRC 1), and oxygen saturation increased to 96%.

DISCUSSION

Pulmonary alveolar proteinosis (PAP) stands as a rare pulmonary disorder characterized by surfactant accumulation within the alveoli failure of clearance rather than increased production. This condition may manifest congenitally, secondary to other conditions, or linked to autoimmune factors. The clinical presentation of PAP can vary ranging from mild to severe and the symptoms are often not specific. The most common complaints include dyspnea and cough, reported in 39% and 21% of the patients respectively. Physical examination findings are often unremarkable, but cyanosis (25% to 30%), clubbing (30%), or inspiratory crackles (50%) may exhibit in some patients (1,2). The patient presented dyspnea, cough, clubbing, and inspiratory crackles.

Pulmonary function testing is not obligatory for the diagnosis of PAP, and it is not a specific indication for this condition. Chest radiography may reveal bilateral alveolar opacities in a perihilar and basilar distribution without an air-bronchogram (2). On CT, PAP often displays a fascinating pattern known as "crazy paving" featuring intralobular thickening and diffuse ground-glass opacities. When there

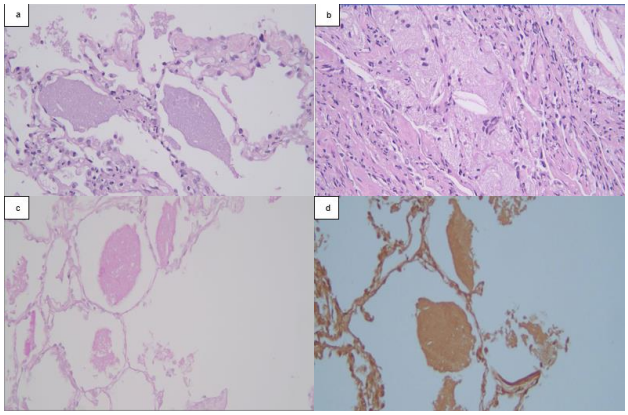

Figure 1. a,b) Haematoxylin & Eosin stain, the alveolar wall was relatively not thickened and the stroma was fibrotic and mildly infiltrated by leukocytes, **c)** periodic acid-Schiff stain, lumen filled with eosinophilic, **d)** Congo red stain was negative

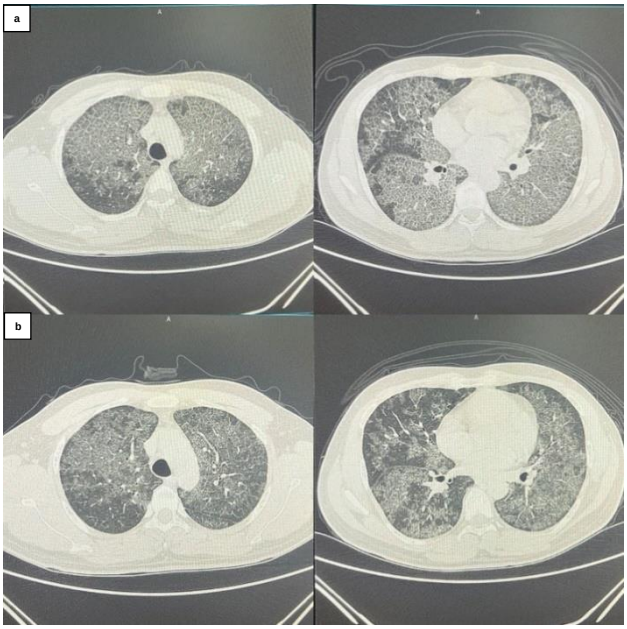

Figure 2. Axial view of thoracic computed tomography scan **a)** before and **b)** after granulocyte colony-stimulating factor (G-CSF) inhalation

is a suspicion of PAP, the gold standard for diagnosis is bronchoscopy with BAL. The lavage fluid often appears milky and opaque, and the cytological examination of BALF reveals large foamy macrophages with amorphous material that stains positive for periodic acid-Schiff (PAS) stain (2). A pulmonary function test was not conducted due to pandemic-related reasons. BAL revealed unspecific results, while TBB showed PAS-positive related to PAP.

Secondary PAP has been linked to various environmental exposures such as silica, talc, cement, kaolin, aluminum, titanium, indium, and cellulose. Studies from Japan and Korea have reported significant exposure rates in PAP, with 23% and 53% respectively (2,3). Raul et al. (4) and Li et al. (5) reported a case of PAP secondary to occupational inhaled exposure to chlorine and aluminum dust. ETD is an inhalation toxin that can induce various effects, including irritation of the eyes, skin, and mucous membranes (6). The patient's history of chronic ETD exposure at work left significant symptoms. There was no exposure to other agents. The patient didn't experience any difference in symptom severity whether he was at work or in a non-work environment. It suggests a potential association between exposure and the development of PAP. Additionally, exposure avoidance has been carried out by the patient for 3 months but there was no clinical improvement, and autoimmune marker tests showed negative results, although the IgG anti-GM-CSF test wasn't performed in Indonesia due to its unavailability.

Ndlovu et al. (7) reported a case of PAP diagnosis after re-evaluation for chronic cough unresponsive to empirical antituberculosis therapy. 4 of 7 patients were misdiagnosed with pulmonary tuberculosis before a diagnosis of PAP was made (8). As seen in previous cases, our patient was also treated with an anti-tuberculosis drug for 12 months without any clinical improvement at a different hospital before being referred to Persahabatan Central General Hospital. It could be misdiagnosed as tuberculosis because the symptoms of PAP can vary and are often not specific.

In exploring alternative therapies, clinical trials of GM-CSF replacement therapy have shown a positive response in 48% of a small group of 25 patients. Similarly, a trial involving 12 patients using inhaled GM-CSF revealed improvement in 91% of cases (2,9). In a fascinating study by Pamuk et al. (10), they explored G-CSF therapy in PAP patients with acute lymphoid leukemia. The use of G-CSF remarkably accelerated the patient's recovery leading to the disappearance of fever, a decrease in acute phase reactants, and the resolution of pulmonary infiltrates.

G-CSF is more commonly used than GM-CSF accounting for over >95% of the usage of molecularly cloned myeloid hematopoietic growth factors. This preference for G-CSF might be attributed to its wider usage and familiarity among physicians (11). In our study, we creatively employed inhaled filgrastim (G-CSF) by administering one vial four times over a 30-day interval due to drug limitations in Indonesia. The results were remarkable as the patient experienced significant clinical and radiological improvement demonstrating the effectiveness of this method. Further studies with larger sample sizes are necessary to make significant advancements in the future.

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