



Case report

The effectiveness of N-acetylcysteine for an adult case of pulmonary alveolar proteinosis: A case report

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ARTICLE INFO

Keywords:

Pulmonary alveolar proteinosis
N-acetylcysteine
Antioxidant treatment

ABSTRACT

Introduction: Pulmonary alveolar proteinosis is a rare disease that is characterized by accumulation of surfactant and phospholipids in the pulmonary alveoli. The current mainstay of treatment is whole lung lavage. There have been rare reports that have revealed the effectiveness of N-acetylcysteine on a secondary PAP.

Case presentation: A 45-year old man complained of shortness of breath and a productive cough with white sputum. He inhaled stone powder as an occupational hazard. CT scan of his chest radiograph showed ground glass changes superimposed on a reticular pattern as the so-called 'crazy paving' pattern. Lung biopsy revealed alveolar proteinaceous material with positive PAS stain. He eventually was diagnosed as PAP. He refused a whole lung lavage therapy, so the patient was rendered N-acetylcysteine as an antioxidant, enhanced immunotherapy and anti-infective treatment. His clinical symptoms and radiological manifestation improved gradually. No substantial adverse reactions were reported.

Conclusions: Persistent oral N-acetylcysteine may be an alternative treatment option for secondary PAP.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease with an estimated incidence of 0.1 cases per 100,000 persons [1], and is characterized by the alveolar accumulation of proteinaceous substance [2]. Its diagnosis requires positive periodic acid-Schiff stain (PAS) of histological tissue [3]. The HRCT crazy paving presentation should alert the clinicians of the rare disease. The prognosis is variable ranging from spontaneous remission to terminal respiratory failure [4]. According to the pathological characteristics, the disease is divided into the following three forms: "congenital PAP", "secondary PAP" and "idiopathic or acquired PAP", which accounts for 90% of all cases [5]. Secondary PAP occurs usually due to toxic substances exposure such as dust, silica as well as stone powder and infections (including tuberculosis, nocardiosis, and pneumocystosis), together with hematologic malignancies and allogeneic stem cell transplantation [6,7].

Up to now, no consensus has been reached on the treatment of PAP patients. Each medical establishment has its own experience and treatment plan for PAP patients. Whole lung lavage (WLL) is the golden treatment option for symptomatic PAP [8]. Although repeated whole lung lavage may alleviate symptoms, it does not actually stop the progression of the underlying disease [9]. Also, the whole lung lavage requires general anesthesia [10], which may be a challenge because it may exacerbate dyspnea. Noninvasive therapeutic options are gradually

welcomed such as granulocyte-macrophage colony-stimulating factor (GM-CSF) supplementation, rituximab [11] and plasmapheresis [12]. At present, related reports on the efficacy of N-acetylcysteine for PAP are still rare. Here we describe a case of secondary PAP successfully treated with oral N-acetylcysteine.

2. Case presentation

A 45-year old man, with contact history of stone powder, presented progressive dyspnea and an intermittent cough with white sputum. He never smoked, but inhaled stone powder as an occupational hazard. His vital signs showed body temperature of 36.6 °C, blood pressure of 130/80 mmHg, heart rate of 67 beats/min. His respiratory examination revealed moist rale in two lower lung. His laboratory tests showed normal complete blood counts, inflammatory markers and rheumatic immune index. An arterial blood gas analysis presented a significant hypoxia with partial pressure of oxygen (PaO₂) 64 mmHg and impaired diffusion with alveolar-arterial oxygen partial difference (PA-aDO₂) 42 mmHg, carbon monoxide diffusion capacity (DLCO) was 49%. High resolution CT scan (HRCT) of his chest demonstrated interstitial shadows bilaterally, an appearance known as the 'crazy-paving' pattern. Basing on his stone powder exposure and imaging findings, the preliminary diagnose was PAP. So surgical lung biopsy was arranged, and the result showed excessive pinkish protein-like substances in periodic

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<https://doi.org/10.1016/j.rmcr.2019.100883>

Received 8 March 2019; Received in revised form 11 June 2019; Accepted 11 June 2019

Available online 14 June 2019

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acid-Schiff (PAS) stain. The lung lavage fluid yielded negative results for fungus, bacteria, mycobacteria, and parasites. Simultaneously, we excluded the following probable diagnosis [13]: 1) Bronchioloalveolar carcinoma (BAC), 2) Infectious pneumonia, 3) rheumatism 4) Pulmonary edema 5) Diffuse alveolar haemorrhage (DAH). Eventually, he was diagnosed with PAP.

Before admission, the patient underwent a WLL, but the symptoms and blood gas analysis related parameters had no improvement. We suggested repeated WLL, but he refused our suggestion because he was anxious about complications and medical expenses, so we chose conservative treatment. The patient was rendered anti-infective therapy including moxifloxacin and clarithromycin, enhanced immunotherapy including thymopentin and antioxidant therapy including N-acetylcysteine.

Two weeks later, his symptoms had obvious improvement. However, repeat chest CT scan showed no obvious resolution of the bilateral lesions. More than one month later, repeat chest CT scan showed slight resolution of the lesions. After discharge, he received scheduled checkup examination at our outpatient clinic. His chest CT scan after treatment for five months showed significant improvement. He received continuous N-acetylcysteine treatment for 17 months without disease progression. No serious adverse events related with N-acetylcysteine were identified.

3. Discussion

PAP is characterized by the accumulation of surfactant lipids and proteins in the alveoli typically due to alveolar macrophage dysfunction. Approximately 90% of the PAP cases are associated with antibodies against GM-CSF [14]. The remaining 10% are either congenital or secondary PAP.

At present, the pathogenesis of PAP is still largely uncertain. Some patients may develop irreversible interstitial lung disease or pulmonary fibrosis, although imaging examination may not recognize these changes [15].

Fatigue, cough, dyspnea and subsequently respiratory failure are common clinical presentations. However, one third of PAP patients are asymptomatic. Physical examination is often unremarkable [6]. Lack of specific clinical symptom and sign make it easy to ignore the diagnosis.

The diagnosis of PAP is based on radiographic findings on HRCT and pathological/cytological results. Positive PAS staining of histological tissue is the gold standard for diagnosis. Clinically, a crazy paving pattern on CT imaging is a highly characteristic manifestation of PAP [16], although extensive differential diagnosis should be excluded, such as left heart failure, pneumonia, alveolar haemorrhage, pulmonary adenocarcinoma, carcinomatous lymphangitis and immunologic diseases.

Autoimmune PAP is characterized by the presence of anti-GM-CSF antibodies. For patients with autoimmune PAP, there have been multiple treatment options including WLL, GM-CSF supplementation [17], rituximab [18], plasmapheresis [19–21]. However, whole lung lavage is effective in almost 85% of patients [22], 15% of patients do not respond and 10% of patients require repeated WLL [23–29]. There is still no consensus on the safety and efficacy of rituximab and plasmapheresis [30].

For secondary PAP, it is important to stop exposure and treat primary disease. Secondary PAP occurs in several diseases which may reduce alveolar macrophage numbers or function and affect clearance of alveolar surfactants. WLL may be ineffective for patients with prolonged or extensive exposure, because other pathologies may have developed such as fibrosis [31]. However, N-acetylcysteine increases the synthesis of glutathione, which is a potent antioxidant and an important protective agent in the cell. Another, glutathione is necessary to maintain the integrity of cell function and morphology, can prevent the cell from being damaged by oxygen free radicals and various toxic substances and decrease the fibrotic response [32].

The treatment efficacy of N-acetylcysteine has been reported in other diseases such as IPF. However, for PAP patients N-acetylcysteine has not been the commonly chosen treatment option [33,34]. One study reported the effectiveness of intra-tracheal drip-infusion of N-acetylcysteine in PAP [35].

At present, it still is uncertain that how N-acetylcysteine affects the mechanism of PAP. We hypothesize that N-acetylcysteine may lead to functional changes of alveolar macrophages, protect the cells from being damaged by various toxic substances, and probably by improving the secretion and absorption of surfactant [36]. The delayed imaging improvement could be due to the time needed to restore the ability of alveolar macrophages to clear alveolar surfactants [37].

It is careful to conclude N-acetylcysteine may be the main reason for the improvement of symptoms. An estimated 7.9% of PAP patients may tend into remission spontaneously [38]. Spontaneous improvement mainly occurs in patients with PaO₂ > 70 mmHg, PA-aDO₂ < 40 mmHg or higher DLCO [36,39]. However, the patient reported in the study had lower PaO₂ and DLCO, higher PA-aDO₂. Another, within a short time his symptoms improved after initiating N-acetylcysteine. Hence, we reasonably conclude that N-acetylcysteine may contribute to the remission of PAP.

In conclusion, N-acetylcysteine might be beneficial in patients with secondary PAP. However, we still need collect more samples to evaluate the treatment efficacy of N-acetylcysteine in this very rare disease.

Compliance with ethical standards.

Conflicts of interest

We have no conflict of interest in this study.

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