Granulocyte Macrophage Colony Stimulating Factor Therapy for Pulmonary Alveolar Proteinosis

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Abstract

We report a case of 58 year old female diagnosed with Pulmonary Alveolar Proteinosis (PAP) with recurrence of PAP after 5 repeated whole lung lavage, responding to subcutaneous injections of Granulocyte Macrophage Colony Stimulating Factor therapy (GM-CSF). Thus indicating that GM-CSF therapy is a promising alternative in those requiring repeated whole lung lavage.

Introduction

PAP is a rare disease characterised by accumulation of surfactant protein in the alveoli impending the gas exchange. Idiopathic adult PAP is an autoimmune disorder characterized by circulating anti-Gm-cSF antibodies and dysfunction in Gm-cSF signalling, which results in an abnormal surfactant clearance from the alveoli.1 As WLL may give symptomatic relief but not correct the underlying defect, by supplementing GM-CSF, progression of the disease can be curtailed.2 Hence GM-CSF therapy following WLL is a promising alternative in symptomatic patient of Pulmonary Alveolar Proteinosis requiring repeated WLL. The case is being reported because of the successful remission of our patient with the GM-CSF therapy. However response to GM-CSF is better when used after rather than before WLL.

Case Report

We report a case of 58 year old female presented to us in May 2008. Her illness started 4 years ago with intermittent cough with milky white sputum and breathlessness which was progressive in nature and aggravated in May 2008. She was evaluated at another hospital with HRCT chest showing bilateral ‘crazy paving’ pattern suggestive of PAP (Figure 1) and Video assisted thoracoscopic Lung biopsy showed eosinophilic granular infiltrates in the alveoli (Figure 2) confirming the diagnosis of PAP. She had past history of hypertension since last 10 years and history of tuberculosis at the age of 6 yrs and 46 yrs and had taken complete anti tuberculosis treatment. No other co-morbid illness and no history of drug intake or exposure to toxic fumes or inorganic dust.

On examination she was tachypnoeic with respiratory rate of 32/min, Heart rate: 84/min, SPO2: 84% on room air and was 91% on 6 litres/min of supplemental oxygen via face mask. Respiratory system examination revealed bilateral fine crackles. No other significant finding was found on clinical examination. Her complete blood count was normal. LDH: 891, ABG: respiratory alkalosis (PH-7.5, PCO2-28.3, PO2-54, HCO3-23), sputum was negative for acid fast bacilli. She was treated with WLL. Right lung was lavaged with 8.5 litres and left lung with 6 litres of normal saline using double lumen endotracheal tube. The lavage fluid was milky white and showed sediments settled at the bottom of the container (Figure 3). Lavage fluid showed eosinophilic material with granular appearance and Periodic acid shiff (PAS) stain positive and was negative for malignant cells, Acid fast bacilli and fungal elements. Significant improvement was noted post WLL. In a follow up period of 2 years, she showed improvement over 1 year and then gradual worsening of the symptoms over next year. In February 2010 she had to undergo right side WLL with 5.5 litres of normal saline with 1cc heparin+ 10cc sodabicarbonate + 600 mg acetylcysteine added to each litre of normal saline, but this time her symptoms worsened within 2 months so her PET scan was done which showed no evidence of malignancy or tuberculosis. She refused WLL and so was started on symptomatic treatment and home oxygen therapy due to severe hypoaxia. Her daily activities got restricted to her room with 24 hrs oxygen requirement and worsening of breathlessness and orthopnoea. She was started on subcutaneous injection of GM-CSF 250 mcg daily. She responded to the therapy within 8 weeks in form of oxygen requirement only during exertion, decrease in hypoaxia, increase in daily activities and marked decrease in breathlessness. Follow up was done with ABG, LDH levels, Pulmonary function test (PFT) with Lung volumes and diffusion capacity of lung, 6 min walk test (6MWT). After 3 months the clinical and radiological improvement was seen but she was symptomatic so we decided to do another bilateral WLL and increased her dose of GM-CSF to 500 mcg (9 mcg/day) daily. Over a follow up period of 1 year she had showed marked clinical and radiological improvement with normal CBC and LDH levels, improvement in PFT and 6MWT. She is now doing all her activities without oxygen, no breathlessness on exertion, no cough. She did not require WLL in last 1 year. Her ABG:PH-7.4,PCO2-38.4,PO2-82.2,HCO3-24.6,LDH:205L,PFT:Severe obstruction with moderate restriction, air trapping and moderate reduction in diffusion capacity. Chest x-ray and HRCT has shown marked improvement (Figures 4 and 5).

Discussion

Pulmonary alveolar lipoproteinosis (PAP) is a syndrome characterized by progressive accumulation of surfactant phospholipids and proteins within alveoli and terminal airways. Surfactant is expelled in the form of the film as small aggregates that are taken up by both type II cells and alveolar macrophages. While type II cells are capable of recycling surfactant, alveolar macrophages catabolise both surfactant lipids and surfactant

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proteins, a process regulated by GM-CSF. There are three distinct types of PAP described as congenital, acquired and secondary each with variable etiology, course, treatment and outcome. Primary PAP (also referred to as acquired, autoimmune or idiopathic PAP is the most common form of PAP (>90%) results from decreased surfactant clearance by alveolar macrophages.

The GM-CSF receptors (Diagram 1) are present on surface of alveolar macrophages has 2 units, 1) α chain (binding unit) 2. Common βc chain (signal transduction unit). GM-CSF initiated signalling plays unique roles in alveolar macrophage function and pulmonary homeostasis like terminal differentiation and survival of macrophages, surfactant catabolism and recycling, etc. A specific Ab against GM-CSF (anti- GM-CSF autoantibody) in the lungs is related to a decreased GM-CSF pathway activity (Diagram 2). The functions of alveolar macrophages are inhibited when neutralizing GM-CSF autoantibodies bind to GM-CSF and block its binding to the α chain of the GM-CSF receptor, and prevent assembly of the GM-CSF–receptor complex and thus the function of alveolar macrophage. Thus, inhibition of GM-CSF binding to its receptor by autoantibodies results in decreased clearance of surfactant from the alveolar spaces, the hallmark of pulmonary alveolar proteinosis. The clinical course of pulmonary alveolar proteinosis falls into 2 categories, either a spontaneous remission or a progressive deterioration in condition resulting in high mortality rates. Lab studies usually done are 1) Surfactant analysis :Levels of surfactant B may be determined from bronchoalveolar lavage (BAL) fluid; Elevated levels of surfactant proteins A and D (SP-A,SP-D) and low levels of SP-B are usually found and have been observed in patients with PAP. 2) Lactate dehydrogenase (LDH) measurement :The serum LDH level may be elevated or at the upper limit of the normal range. Individual case reports suggest that serial LDH measurements may be useful to track the severity of disease. 3) ABG analysis: compensated respiratory alkalosis secondary to hyperventilation. 4) Latex agglutination test: Autoantibodies (neutralizing IgG antibody against GM-CSF) are detected in patients with acquired PAP Test and has 100% sensitivity.
and 98% specificity for diagnosis. A definitive diagnosis of pulmonary alveolar proteinosis is most often based on tissue examination obtained by either transbronchial lung biopsy or open lung biopsy. Sequential whole-lung lavage (WLL) is the treatment of choice till now. WLL is an invasive procedure that requires general anaesthesia and double-lumen endotracheal intubation. WLL does not correct the underlying defect in PAP.

A results of a prospective, open-label clinical trial of daily subcutaneous GM-CSF therapy in a group of adult 25 patients, with idiopathic PAP, 12 of 25 patients (48%) with moderate symptomatic disease who completed the trial, administration of GM-CSF showed improvement in clinical condition and quality of life. In this trial patients were treated with recombinant human yeast-derived GM-CSF administered subcutaneously once daily for 3 months. The starting dose was 250 mcg/d, which was progressively increased to 5mcg/kg/d for the second month of study, and to 9 mcg/kg/d for the third month. After the patient received therapy for 3 months, if the clinical response was still suboptimal and the patient was tolerating therapy, the patient underwent further dose escalation from 9 to 18 mcg/kg/d (i.e. 12 mcg/kg/d at 3 months, 15 mcg/kg/d at 4 months, and 18 mcg/kg/d at 5 months). If the patient had an adequate response based on above-mentioned criteria, that dose was continued from 3 to 12 months. The side effects were minor and included injection-site edema, erythema, and malaise.

In analyzing the subsequent data at the Cleveland Clinic Foundation in 2004, 21 out of 25 patients enrolled completed a trial of GM-CSF escalated to effect. Nine patients (43%) did not achieve clinical, radiological or functional improvement, while 12 patients (57%) had a good clinical response. There have been an additional seven published case reports of subcutaneous GM-CSF with six of them responding to the therapy. One case report of clinically successful treatment of PAP with GM-CSF described a profound reduction in GM-CSF neutralizing autoantibodies (both serum and BAL) and improvement in alveolar macrophage morphology and function.

Taken together, all these articles demonstrate an overall response rate of 17/33 (52%, 95% confidence interval 34–69%) to GM-CSF. The other mode of giving GM-CSF is in aerosole form through nebulisation. As per the British thoracic society (BTS) protocol, bilateral WLL first to clear as much disease as possible and re-check for organisms in the BAL and then start on GM-CSF protocol (through an advanced nebulizer). First dose in hospital, subsequent at home then 250 ugm GM-CSF in 1 ml saline via I-Neb once a day for 4 days, then 4 days “rest”. Repeat 250 ugm daily x 4 days then 4 days “rest”. Repeat for 3 months then re-assess. Stable or improved – continue for further 3 months and review. No improvement – double the dose to 500 ugm and re-assess. So far 11 out of 11 have improved and BTS have continued treatment for variable periods until they have been able to slowly wean it off. A smaller cohort of patients have been reported in a paper from the Mayo Clinic in the USA in which 11 out of 12 PAP patients responded to inhaled aerosol GM-CSF. Hence any patient of Pulmonary alveolar lipoproteinosis, requiring repeated whole lung lavage should be treated with GM-CSF replacement therapy.

References

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