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Mycophenolate mofetil (MMF) in Pulmonary Hypertension

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Abstract:

Pulmonary arterial hypertension is a vascular disease which is characterized by abnormal proliferation of smooth muscle cells leading to occlusion of pulmonary arterioles, right ventricular hypertrophy and death. Interstitial lung diseases are a diverse group of diseases mainly characterized by inflammation and fibrosis of the pulmonary interstitium. The association of pulmonary hypertension and interstitial lung disease is well known. Increased morbidity and mortality was observed when pulmonary hypertension presents in a patient with interstitial lung disease. The management of pulmonary hypertension in interstitial lung disease is a challenge. We report a case of 60 year old female with severe pulmonary hypertension and interstitial lung disease, who was treated with mycophenolate mofetil along with steroid and antihypertensive drug. Mycophenolate mofetil reduced nocturnal oxygen requirement to 50% after 6 months of treatment and resulted in discontinuation of oxygen therapy after one year of treatment. Profound improvement in pulmonary arterial hypertension and little improvement in interstitial lung disease were observed with no adverse effects.

Key words: Interstitial Lung Diseases, Mycophenolic Acid, Pulmonary Hypertension, Right Ventricular Hypertrophy, Vascular Diseases.

Introduction

Pulmonary arterial hypertension (PAH) is a vascular disease which is characterized by abnormal proliferation of smooth muscle cells (SMCs) leading to occlusion of pulmonary arterioles, right ventricular (RV) hypertrophy and death [1].

PAH is associated with connective tissue diseases such as systemic lupus erythrematosis (SLE) and scleroderma, human immunodeficiency virus infection and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes). Asymmetric neointimal hyperplasia in small pulmonary arteries and arterioles is one of the pathological outputs of PAH. The detectable levels of antinuclear antibody and elevated level of serum pro-inflammatory cytokines (IL-1 and IL-6)

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have been observed in primary PAH patients, which indicate inflammation and autoimmunity plays role in the development of PAH [2].

MMF acts by inhibition of inosine monophosphate dehydrogenase (IMPDH) which is a key enzyme in "de novo" synthesis of purine nucleotides. B and T lymphocytes are dependent in this pathway for DNA synthesis, MMF inhibits their proliferation [3]. Anti-inflammatory, anti-proliferating activity makes MMF as an attractive candidate drug for the treatment of fibrotic lung diseases of different causes [4]. A preclinical study reported that, MMF therapy can alleviate thickening of pulmonary arterial walls and inhibit abnormal vascular remodeling, suggesting wide potential of MMF in the treatment of human PAH [5]. In present case, patient had pulmonary hypertension and interstitial lung disease. Association of pulmonary hypertension and interstitial lung disease increases morbidity and mortality [6,7]. In this case, use of MMF as a supportive therapy in management of pulmonary hypertension and interstitial lung disease is presented.

Case Report

A 60 year old female patient was on treatment with methotrexate hydroxychloroquine and sulfasalazine (Salazopyrin) from 2006 for rheumatoid arthritis. In 2012, she had progressive breathlessness with dry cough. She was suspected to be suffering from interstitial lung disease which was later confirmed with Computed Tomography (CT) of chest. She also had progressive pulmonary arterial hypertension (PAH). A high-resolution CT of lung was performed on inspiratory and expiratory phases of respiration. Subtle septal thickening was noted in the periphery of both lobes and lung bases as early interstitial lung disease, evidence of small airway obstructive disease with mildly enlarged lymph nodes and prominent pulmonary artery. Patient was not able to perform pulmonary function tests. Her peripheral capillary oxygen saturation (SPO_2) was 82% at rest without oxygen and improved to 95% with oxygen. Arterial blood gas analysis showed PO_2 35 mmHg and PCO_2 30 mmHg with pH 7.35 and bicarbonate 18 meq/L. Patient was advised methyl-prednisolone 1 mg/kg and azathioprine. Dose of azathioprine was 50 mg initially then it was increased to 100 mg. Sildenafil (50 mg twice daily), nifedipine (30 mg once a day) and nocturnal oxygen were given along with this treatment. This treatment was continued for 2-3 months. Patient suffered with loose stool and abdominal pain due to azathioprine. Mycophenolate was started at dose of 500 mg once a day increased to 1.5 gm daily instead of azathioprine to avoid these side effects. After 5 months of treatment, the 2-D Doppler echocardiography was carried out. It revealed that, right ventricle and left ventricle was in normal size. Left ventricle systolic function was normal and left ventricular ejection fraction (LVEF) was 60%. Doppler echocardiography was repeated after 15 months of treatment. The Doppler echocardiogram demonstrated sclerotic aortic valve and right ventricular systolic pressure (RVSP) of 60 mmHg. The dilation of right atrium and right ventricle was detected. Left atrium and left ventricle appeared normal. Left ventricular ejection fraction was maintained at 60%. After 22 months, high-resolution CT of thorax (slice thickness of 1 mm) showed diffuse patchy ground glass haziness in both lung fields, reticular infiltrates with inner lobular septal thickening noted in both lobes suggestive of diffuse interstitial lung disease.

After 2.5 years of treatment, her BP was 140/90 mmHg, pulse rate 100 beats per minutes. The respiratory rate was 18/min. The echocardiogram with Doppler ultrasonography revealed trivial tricuspid regurgitation and right ventricular systolic pressure (RVSP) of 45 mmHg. The concentric left ventricle hypertrophy and LV diastolic dysfunction was observed. Left atrium, right atrium and right ventricles appeared normal.

Left ventricular ejection fraction was measured 80%. Moderate hypertrophy was observed as inter-ventricular septum (IVS) and posterior wall (PW) thickness calculated 14 mm. Aspirin 75 mg once a day was prescribed to patient in addition to previous treatment.

Discussion

Pulmonary hypertension is defined as mean pulmonary artery pressure of more than 25 mmHg at rest or more than 30 mmHg with exercise in the absence of a demonstrable cause. Normal pulmonary artery systolic pressure at rest is 18 to 25 mm Hg [8,9]. Pulmonary hypertension was diagnosed with electrocardiography (ECG), pulmonary function testing, chest radiography, perfusion lung scanning, chest CT, echocardiography, cardiac catheterization, lung biopsy or histopathology [10]. Echocardiography is a noninvasive tool to provide information regarding contractility, ejection faction, wall motion abnormalities, and biventricular interaction in patients. Presence of right ventricle (RV) failure is highly useful tool for judgment of pulmonary hypertension [8]. Interstitial lung disease accounts for more than 200 etiologies. It is also associated with pulmonary hypertension. Increase in diagnosis of interstitial lung disease is possible because of the help of recent advance diagnostic tools [11]. Connective tissue disease related interstitial lung disease was generally treated with glucocorticoids. Immunomodulatory agents like cyclophosphamide or azathioprine were added with steroid therapy which serve as steroid sparing agents [12]. In present case, patient had interstitial lung disease and pulmonary hypertension. To treat pulmonary hypertension, nifedipine 30 mg was prescribed (the maximum dose was tolerated by her) along with sildenafil 50 mg twice a day. Methyl-prednisolone 1 mg/kg and azathioprine 50 mg initially, which was increased to 100 mg for treating connective tissue disease related interstitial lung disease. Nocturnal oxygen was also provided along with these treatments. Patient showed improvement in breathlessness with steroid therapy and sildenafil during the initial few months. Due to adverse effect like loose stools and abdominal pain azathioprine was replaced with mycophenolate mofetil. Mycophenolate mofetil was prescribed because patient denied taking cyclophosphamide. Interestingly after starting mycophenolate mofetil, in next 6 months requirement for nocturnal oxygen reduced to 50% and oxygen therapy was not at all required after one year. Though patient showed improvement in breathlessness with steroid therapy and sildenafil treatment, nocturnal oxygen requirement was not reduced initially this was seen after starting mycophenolate mofetil treatment. Pulmonary artery hypertension was severe in this case having 65 mm Hg as shown by echocardiogram, which was attenuated to 45 mmHg by mycophenolate mofetil along with methyl prednisolone, sildenafil and nifedipine. At present patient has grade 1-2 breathlessness and SPO_2 92 mmHg at rest. Right atrium and right ventricle were found normal.

Radical improvement in pulmonary pressure may be significantly contributed by mycophenolate mofetil. Improvement in thickening of pulmonary arterial walls and inhibition of abnormal vascular remodeling may be probable mechanism of mycophenolate mofetil in reducing pulmonary arterial hypertension [5]. In a preclinical study, MMF effectively decreased right ventricle systolic pressure and right ventricular hypertrophy and reduced the medial thickness of pulmonary arteries. MMF significantly decreased the number of proliferating cell nuclear antigen (PCNA)-positive cells, infiltration of macrophages and expression of P-selectin and interleukin-6 on the endothelium of pulmonary arteries. Anti-inflammatory and anti-proliferative properties of MMF may be cause of attenuation of the development of PAH [1]. Previous literature reported that, mycophenolate mofetil was seemed to be safe and well tolerated in patients

with connective tissue related interstitial lung disease [12]. Tzouvelekis *et al*. reported that MMF was safe but failed to show a beneficial effect in idiopathic pulmonary fibrosis patients [4]. Profound improvement in pulmonary arterial hypertension and little improvement in interstitial lung disease were seen, with no adverse effect.

Conclusion

Mycophenolate mofetil along with methyl prednisolone, sildenafil and nifedipine showed promising improvement in patient with pulmonary hypertension associated with interstitial lung disease.

References

1. Suzuki C, Takahashi M, Morimoto H, Izawa A, Ise H, Hongo M, *et al*. Mycophenolate mofetil attenuates pulmonary arterial hypertension in rats. Biochem Biophys Res Commun. 2006;349(2):781-788.
2. Humbert M, Monti G, Brenot F, Sitbon O, Portier A, Grangeot-Keros L, *et al*. Increased interleukin-1 and interleukin-6 serum concentrations in severe primary pulmonary hypertension. Am J Respir Crit Care Med. 1995;151(5):1628-1631.
3. Zamora AC, Wolters PJ, Collard HR, Connolly MK, Elicker BM, Webb WR, *et al*. Use of mycophenolate mofetil to treat scleroderma-associated interstitial lung disease. Respir Med. 2008;102(1):150-155.
4. Tzouvelekis A, Galanopoulos N, Bouros E, Kolios G, Zacharis G, Ntolios P, *et al*. Effect and Safety of Mycophenolate Mofetil or Sodium in Systemic Sclerosis-Associated Interstitial Lung Disease: A Meta-Analysis. Pulmonary Medicine. 2012;2012: 143637.
5. Zheng Y, Li M, Zhang Y, Shi X, Li L, Jin M. The effects and mechanisms of Mycophenolate mofetil on pulmonary arterial hypertension in rats. Rheumatol Int. 2010;30(3):341-348.
6. Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. Eur Respir J. 2008;31(6):1357-1367.
7. Nations JA, Nathan SD. Pulmonary Hypertension in Interstitial Lung Disease Diagnosis and Management. Clin Pulm Med. 2009;16:252-257.
8. Harsoor SS, Joshi S. Anaesthetic management of parturient with primary pulmonary hypertension posted for caesarean section - A Case Report. Indian J Anaesth. 2005:49(3):223-225.
9. Nauser TD, Stites SW. Diagnosis and Treatment of Pulmonary Hypertension. Am Fam Physician. 2001;63:1789-1798.
10. Loyd JE, Phillips JA III. Heritable Pulmonary Arterial Hypertension. *In*: Pagon RA, Adam MP, Ardinger HH, *et al*. (editors). GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1485/. Accessed on August 03, 2015.
11. Palat P, Parmar HD. Recent trends in interstitial lung disease: Study of 25 cases. Int J Med Sci Public Health. 2013;2(1):52-55.
12. Swigris JJ, Olson AL, Fischer A, Lynch DA, Cosgrove GP, Frankel SK, *et al*. Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. Chest. 2006;130(1):30-36.