Rituximab for Salvage Therapy of Refractory Hypersensitivity Pneumonitis

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ABSTRACT

Introduction: Hypersensitivity pneumonitis is a complex syndrome characterized by non-Immunoglobulin E-mediated inflammation of lung parenchyma in response to an antigen.

Case Report: A 60-year-old white man presented with acute onset of hypoxia, dyspnea, and nonproductive cough. After extensive workup, he was diagnosed with hypersensitivity pneumonitis. We present the case of a patient with refractory hypersensitivity pneumonitis not responsive to standard immunosuppressive therapy, who was successfully treated with rituximab.

Discussion: Hypersensitivity pneumonitis is a multifaceted syndrome characterized by an exaggerated immune-mediated response to an antigen. Currently, the most common treatment for an acute exacerbation of the syndrome is withdrawal of the offending antigen and systemic corticosteroids. However, despite their widespread use, the efficacy of steroids in treating acute hypersensitivity pneumonitis is poor.

Conclusion: Rituximab could be considered as a salvage therapy in cases of severe hypersensitivity pneumonitis unresponsive to standard therapy, especially in patients with high risk of death.

INTRODUCTION

Hypersensitivity pneumonitis is a multifaceted syndrome characterized by an immune-mediated response to an antigen. It can be divided into 2 categories: acute/inflammatory and chronic/fibrotic,[1] often progressing from acute/inflammatory to chronic/fibrotic after repeated exposure to the offending antigen. Diagnosis can be difficult as it often mimics other pulmonary diseases and is misdiagnosed as idiopathic pulmonary fibrosis or idiopathic interstitial pneumonia.[1] Clinical diagnosis of hypersensitivity pneumonitis can be made based on history, clinical features, imaging, or bronchoalveolar lavage. Classically, a definite diagnosis requires histopathological confirmation,[1] which can be risky for a critically ill patient. Recently, Salisbury et al developed and validated a new point-based model that allows radiologic diagnosis with high confidence when supported by clinical presentation, history, and lack of alternate diagnoses.[2] Standard treatment consists of systemic corticosteroids and withdrawal of the offending antigen. Despite their historically established use, the efficacy of steroids in treating acute hypersensitivity pneumonitis is poor. As the search for better treatment continues, 2 studies have shown success with rituximab, a B-cell depleting anti-CD20 monoclonal antibody for treatment of refractory hypersensitivity pneumonitis.[3,4]

We present a case report of a patient with refractory hypersensitivity pneumonitis not responsive to standard immunosuppressive therapy, who was successfully treated with rituximab.

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CASE REPORT

A 60-year-old white man presented to the Emergency Department (ED) with complaints of nonproductive cough, chest tightness, and dyspnea found to be hypoxic. Cardiac workup, including electrocardiogram (ECG), echocardiogram, and troponins, was

negative. Computed tomography (CT) angiogram of the chest was negative for pulmonary embolism but revealed patchy bilateral ground glass opacities with subpleural sparing and no lobar consolidation. The patient initially was treated with antibiotics for community-acquired pneumonia. Thorough infectious workup was negative; a repeat CT scan was suggestive of atypical pneumonia or interstitial process such as hypersensitivity pneumonitis. Further history revealed he had 2 pet cockatiels at home. He was started on prednisone 60mg daily, improved, was discharged and advised to remove the birds.

Six months later, the patient again presented to the ED with worsening dyspnea, nonproductive cough, and was found to be hypoxic, requiring noninvasive mechanical ventilation. Cardiac workup, including ECG, B-type natriuretic peptide test, echocardiogram, and cardiac enzymes, was negative. CT chest revealed bilateral interstitial infiltrates with crazy paving pattern. Thorough infectious workup was initiated, and antibiotic therapy was started until all cultures were found negative. Further history revealed no fevers, exposure to sick contacts, or recent travel, but the patient had not removed the birds from his house. Clinical diagnosis of acute exacerbation of refractory hypersensitivity pneumonitis was made based on previous exposure, CT evidence, and negative cardiac and infectious workup. Systemic steroids were initiated for treatment of acute hypersensitivity pneumonitis exacerbation.

Despite treatment, the patient developed worsening hypoxic respiratory failure requiring mechanical ventilation on intensive care unit day #5. Bronchoscopy was performed with fungal, bacterial, and viral studies negative. Flow cytometry showed CD4/CD8 ratio of 1.8:1. However, the patient had been removed from antigen for 5 days and received 5 days of steroids, invalidating the CD4/CD8 result. Repeat CT scan showed worsening diffuse airspace consolidation without chronic interstitial findings. Due to his worsening clinical status and profound hypoxia, lung biopsy was entertained but ultimately not obtained. Despite treatment with steroids, he continued to decline as evidenced by increasing hypoxemia, requiring increasing level of fraction of inspired oxygen (FiO2) via ventilator. Due to the patient's inability to consent, consent was obtained from his family for off-label use of rituximab for treatment of refractory hypersensitivity pneumonitis. He was treated with rituximab 1000 mg IV x1 followed by a second dose 1000 mg IV 2 weeks later. The patient rapidly improved within 5 days after the first dose of rituximab and was successfully extubated. He was discharged home requiring 2 L supplemental oxygen 2 weeks after the first dose of rituximab. Prior to his discharge, his family removed all the birds, and thoroughly cleaned and repainted the house. Follow-up spirometry showed improvement in pulmonary function. As of this writing, he has been followed in our pulmonary clinic, with stable pulmonary function tests for more than a year. (See Table.)

Table. Pulmonary Function Test

	2 Weeks	2 Months	6 Months	9 Months	12 Months
FVC	48%	52%	51%	64%	64%
FEV_1	54%	55%	50%	65%	66%
FEV_1/FVC ratio	85%	79%	76%	76%	77%
DLCO	33%	33%	34%	38%	41%

Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second of expiration; DLCO, diffusing capacity of the lungs for carbon monoxide.

DISCUSSION

Hypersensitivity pneumonitis is an autoimmune response causing inflammation of the lung parenchyma, alveoli, and terminal airways after exposure to an antigen in genetically susceptible individuals.[5]

Its pathogenesis is not fully understood, and it is thought that both humoral and cell-mediated immune responses play a role in lung damage associated with hypersensitivity pneumonitis.[6-8] Soluble antigens and immunoglobulin G antibodies form following exposure to the antigen forming a complex. This triggers the complement cascade, causing macrophage activation. Alveolar macrophages secrete cytokines and chemokines, attracting neutrophils to the alveoli and small airways.[3] Patients with hypersensitivity pneumonitis also have an increased number of CD8 lymphocytes. It is thought to be mediated by a decrease in apoptosis, resulting in a decreased CD4+/CD8+ ratio.[7] Additionally, large amounts of cytokines, such as tumor necrosis factor (TNF)-α and Interleukin-1 (IL-1), are released from macrophages, causing an upregulation of intracellular adhesion molecule-1.[7]

Prognosis, outcomes, and disease trajectory of patients diagnosed with hypersensitivity pneumonitis are highly variable and can vary based on causative antigen. In addition, traditional treatment with high-dose steroids often fails. Currently, the most common treatment is systemic corticosteroids and withdrawal of the offending antigen.[1,6] Steroids seem to accelerate initial recovery, but they do not alter long-term course. Additionally, steroids do not target the inflammatory cascade that drives the disease.

In our case, we considered not only rituximab, but also previously described cyclosporine and cyclophosphamide. Both have been attempted in treatment of refractory hypersensitivity pneumonitis, but their published track record has been either unconvincing or counterproductive.[9-11] In one case series of 100 patients diagnosed with chronic hypersensitivity pneumonitis, 14 patients developed an acute exacerbation and were treated with high-dose systemic corticosteroids with or without cyclosporine or cyclophosphamide. Out of those 14 patients, 12 died of respiratory failure within 1 month after the onset of the acute exacerbation.[8] On the other hand, azathioprine or mycophenolate have been shown to be successful only in chronic, rather than acute, cases.[12-13]

The mechanism through which rituximab interferes with the

progression of fibrosis is not understood. Hypersensitivity pneumonitis pathophysiology involves an accelerated immune response involving mostly T lymphocytes. Rituximab has a high affinity for CD20; rapidly depletes B cells from circulation, thus blocking autoantibody production; acts directly on antibody dependent cellular cytotoxicity; and is involved in complement mediated cell death and signaling apoptosis.[4,14] It has also been described to attenuate T lymphocyte ratio abnormalities.[15] Because of that, its action could potentially affect both the humoral as well as cell-mediated components.

CONCLUSION

In cases of severe hypersensitivity pneumonitis unresponsive to standard therapy, we think rituximab could be considered as a salvage therapy, especially in patients with high risk of death.

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REFERENCES

1. Vasakova M, Morell F, Walsh S, et al. Hypersensitivity pneumonitis: perspectives in diagnosis and management. *Am J Respir Crit Care Med.* 2017;196(6):680-689. doi:10.1164/rccm.201611-2201PP

2. Salisbury M, Gross B, Chughtai A, et al. Development and validation of a radiological diagnosis model for hypersensitivity pneumonitis. *Eur Respir J.* 2018;52:1800443. doi:10.1183/13993003.00443-2018.

3. Miyazaki Y, Tateishi T, Akashi T, et al. Clinical predictors and histologic appearance of acute exacbations in chronic hypersensitivity pneumonitis. *Chest.* 2008;134(6):1265-1270. doi:10.1378/chest.08-0866.

4. Keir G, Maher T, Ming D, et al. Rituximab in severe, treatment-refractory interstitial lung disease. *Respirology*. 2014;19(3):353-359. doi:10.1111/resp.12214

5. Spagnolo P, Rossi G, Cavazza A, et al. Hypersensitivity Pneumonitis: a comprehensive review. *J Investig Allergol Clin Immunol*. 2015;25(4):237-250.

6. Selman M, Buendía-Roldán I. Immunopathy, diagnosis, and management of hypersensitivity pneumonitis. *Semin Respir Crit Care Med*. 2012;33(5):543-554. doi: 10.1055/s-0032-1325163.

7. Selman M, Pardo A, King T. Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. *Am J Respir Crit Care Med*. 2012;186(4):314-324. doi:10.1164/rccm.201203-0513CI.

8. Girard M, Israël-Assayag E, Cormier Y. Pathogenesis of hypersensitivity pneumonitis. *Curr Opin Allergy Clin Immunol*. 2004;4(2):93-98.

9. Gupta S, Mahipal A. Fatal pulmonary toxicity after single dose of cyclophosphamide. *Pharmacotherapy*. 2007; 27(4):616-618. doi:10.1592/phco.27.4.616

10. Hamada K, Nagal S, Kitaichi M, et al. Cyclophosphamide-induced late-onset lung disease. *Intern Med*. 2003; 42(1):82-87.

11. Roelofs P, Klinkhamer P, Gooszen H. Hypersensitivity pneumonitis probably caused by cyclosporine. A case report. *Respir Med.* 1998;92(12):1368-1370.

12. Morisset J, Johannson K, Vittinghoff E, et al. Use of mycophenolate mofetil or azathioprine for management of chronic hypersensitivity pneumonitis. *Chest*. 2017; 151(3):619-625. doi:10.1016/j.chest.2016.10.029

13. Adegunsoye A, Oldham J, Fernandez Perez E, et al. Outcomes of immunosuppressive therapy in chronic hypersensitivity pneumonitis. *ERJ Open Res.* 2017; 3(3):00016-2017. doi:10.1183/23120541.00016-2017

14. Lioté H, Lioté F, Séroussi B, Mayaud C, Cadranel J. Rituximab-induced lung disease: a systematic literature review. *Eur Respir J.* 2010;35(3):681-687. doi:10.1183/09031936.00080209

15. Stasi R, Del Poeta G, Stipa E, et al. Response to B-cell-depleting therapy with rituximab reverts the abnormalities of T-cell subsets in patients with idiopathic thrombocytopenic purpura. *Blood*. 2007; 110(8):2924-2930. doi:10.1182/blood-2007-02-068999

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