CLINICAL VIGNETTE

Uncontrolled Asthma in a Patient with Primary Ciliary Dyskinesia Treated Successfully with Omalizumab

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Primary cilia dyskinesia (PCD) is an autosomal recessive genetic disorder characterized by recurrent and chronic infections of the upper and lower respiratory tracts due to impaired mucociliary clearance. Severely reduced lung function is observed in adults with PCD with 98% developing bronchiectasis and 38% with severe lung disease with forced expiratory volume in 1 second (FEV1) <40% of predicted.[1] The goal of respiratory management is to improve any lung function deficit and limit subsequent disease progression. Treatment focuses on aggressive control of infections and airway clearance therapy. Bilateral lung transplantation is an option for end-stage respiratory failure.

Although rarely reported, patients with PCD can have co-existing asthma.[2] This is analogous to cystic fibrosis (CF) patients who wheeze as result of underlying asthma and are referred to as "CF asthma."[3] These patients are treated in accordance to asthma guidelines.

Omalizumab is a high affinity recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody against immunoglobulin E (IgE).[4] It is approved for treatment of moderate to severe persistent uncontrolled asthma in patients who are 12 years of age and older and have a total serum IgE level 30-700 IU/ml. Omalizumab binds to the third constant domain of the IgE heavy chain, forming complexes with free IgEs and preventing their interactions with receptors. When added to existing therapy, treatment with omalizumab is effective in improving symptoms and reducing frequency of exacerbation and inhaled corticosteroids.[5] We report a patient with known PCD and asthma who presented with symptoms consistent with infections and natural course of PCD but were in fact due to uncontrolled asthma and successfully treated with omalizumab.

Our patient is a 58-year-old female with PCD and progressive respiratory complications who presented for shortness of breath. Her pulmonary manifestations included recurrent infections leading to diffuse bronchiectasis with peribronchial thickening and mucoid impactions. She also has chronic sinusitis with associated headaches. Her upper and lower airway symptoms were thought due to natural progression of PCD. She has been treated with numerous antibiotics without significant improvement. She continued to have significant coughing, shortness of breath, and wheezing. These symptoms severely compromised her quality of life. Due to her significant lung disease, she was considered for lung transplantation. Of note, she also underwent right upper lobectomy at age 49 for a right upper lobe nodule suspicious for lung cancer. Final biopsy showed only benign tissue, notable for immotile cilia syndrome. In addition to her significant structural lung disease, she is atopic with allergic rhinitis and asthma since childhood. Her medications included scheduled nebulized albuterol and ipratropium, nebulized tobramycin, nebulized budesonide, and montelukast. Physical exam on her initial appointment showed diminished breath sounds with coarse rhonchi and diffuse wheezing. Initial pulmonary function test showed: FEV1 0.39 L (16%) and forced vital capacity (FVC) 1.03 L (33%). After bronchodilation, FEV1 improved to 0.44 L or 12% change, and she had improved breath sounds on physical exam. Initial total IgE 2 was 125 IU/ml. Fraction of exhaled nitric oxide (FeNO) was 8ppb, which would suggest less likely allergic inflammation but was thought to be lowered due to PCD.[6]

At the time of presentation, she was already maximized on airway clearance treatment for PCD. She was treated with various courses of antibiotics for infection without improvement for the year prior to her initial visit. Her pulmonary function test revealed a component of obstruction with reversible airway hyper-responsiveness. Her physical exam suggested response to bronchodilator. Therefore, despite PCD being the dominant disease pathology, she likely had a component of uncontrolled asthma. She was already maximized on beta2 agonist and inhaled corticosteroids with elevated total IgE, suggesting a component of allergic asthma. She was started on omalizumab 300mg subcutaneous on a monthly basis. Within 2-3 month of starting omalizumab, she reported significant improvement in symptomatic shortness of breath and appetite. At the time of this report, approximately 2 years after starting omalizumab, pulmonary function test shows: FEV1 0.45 L (19%), FVC 1.36 L (45%), FEV1/FVC 33, and FEF25-75 0.20 (9%). After bronchodilation, FEV1 improved to 0.49L or 10% change. She has overall improvement in FEV1 combined with improved symptoms of shortness of breath.

Discussion

Due to disorder of motile cilia, PCD patients have variable decline in pulmonary function. While the majority of their respiratory symptoms are likely due to structural lung damage related to recurrent infections, other etiologies for shortness of

breath such as concomitant asthma should not be overlooked. Asthma effects 7.7% of US adults and 9.4% of US children.[7] PCD effects approximately 1 in 15,000 births.[8] Although there is no estimation of asthma prevalence in PCD patients, in theory, similar proportion of PCD patients should have concomitant asthma. In addition, analogous to CF, PCD leads to similar airway mucosal edema and wall destruction secondary to chronic infection and inflammation, mechanical obstruction related to abnormal mucoid clearance, and smooth muscle contraction due to stimulation by host inflammatory mediators. This pathogenesis of airway likely leads to worsening of underlying bronchial hyper-responsiveness in PCD patients with concomitant asthma. Therefore, in addition to focusing on airway clearance therapy and aggressive infection treatment, recognizing underlying asthma is an important component of treatment.

In addition, atopy is one of the strongest risk factors for developing asthma.[9] Many asthmatic patients have elevated IgE levels due to sensitization to inhalant allergens. Allergic asthma that can be treated successfully with omalizumab therapy should be considered in patients with PCD. Traditionally, inhaled corticosteroids and a beta2 agonist have been the cornerstone to PCD patients with asthma. Although efficacy of omalizumab as add-on therapy in asthma treatment is well accepted, use of omalizumab in patients with concurrent asthma and underlying severe lung disease has not been widely reported. There are case reports of omalizumab for allergic bronchopulmonary aspergillosis (ABPA) treatment in cystic fibrosis patients.[10] To our knowledge, there are no previous reported cases of PCD and concurrent asthma treated successfully with omalizumab. Although our patient had mild improvement in FEV1 after treatment with omalizumab, she experienced significant clinical improvement in dyspnea. This greatly improved her quality of life in the setting of chronic disease.

In summary, recognizing concomitant asthma in selective PCD patients is important. Use of omalizumab in treatment of allergic asthma as add-on therapy should be considered in patients with elevated total IgE level, even in the setting of significant structural lung disease.

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