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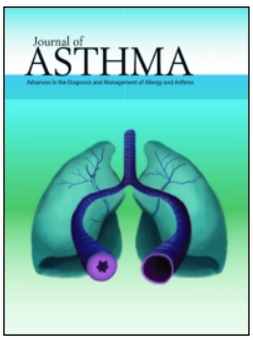

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Recurrent Asthma Exacerbations: Co-existing Asthma and Common Variable Immunodeficiency

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Abstract

Introduction: Common variable immunodeficiency is characterised by impaired B-cell differentiation and defective immunoglobulin production manifesting as recurrent respiratory tract infections. While the condition can masquerade as asthma, late diagnosis of CVID in known asthmatic is rarely reported.

Case Study: We present the case of a 43-year-old lady with recurrent episodes of wheeze, cough, sinusitis and multiple lower respiratory tract infections. transiently responsive to antibiotics and steroids. These episodes had been occurring for many years and she had a longstanding clinical diagnosis of asthma.

Results: As part of her work up for recurrent respiratory tract infections a CT thorax was performed and demonstrated bronchiectasis. Further tests including Immunoglobulin levels revealed critically low IgG, IgM, and IgA levels. Immunoglobulin replacement therapy was commenced with a reduction in exacerbation frequency and severity, and objective improvement of asthma control. Subsequent lung function tests demonstrated reversible airflow limitation (obstructive lung function with 13% reversibility in FEV_1 post-bronchodilator) consistent with asthma.

Conclusion: Our case illustrates the importance of searching for alternate and co-existent diagnoses in patients diagnosed with asthma who are unresponsive to conventional therapy. We believe that serum immunoglobulin measurement should form a component of such a workup.

Keywords immunodeficiency, asthma, bronchiectasis, immunoglobulins, lower respiratory tract infections, spirometry.

Introduction

Common variable immunodeficiency (CVID) disorders are heterogenous disorders characterised by recurrent bacterial infections and impaired B-cell differentiation leading to defective immunoglobulin production (1). Common pulmonary manifestations include recurrent respiratory tract infections, obstructive lung disease, bronchiectasis, granulomatous or interstitial lung disease, or neoplasia (2).

The age of onset of CVID is variable. Although in general the diagnosis is made between the age of 20 and 40 years, up to 20% of cases are diagnosed before the age of twenty years old (2–4). However, due to the heterogenous nature of the disease, the diagnosis is often delayed (in a recent European report, the delay was approximately 4 to 5 years). (3, 5)

Clinical manifestations of asthma and CVID can be very similar. Both conditions are characterized by cough, sputum production, recurrent upper and lower respiratory tract infections over years leading to bronchiectasis. Given the similarities in clinical manifestations, CVID can masquerade as asthma (6). Reports have suggested a higher prevalence of asthma in CVID patients but with limited information pertaining to lung disease specifics including lung function (7). A further study reported an increased prevalence of bronchial hyperresponsiveness (BHR) and bronchial asthma in CVID patients compared to the general population (8). Our case study, highlights the rarely described and often late diagnosed co-existence of CVID in a patient with a long-standing clinical history of asthma.

Case Study

A43-year-old female with a long-standing presumptive, clinical diagnosis of asthma was referred to a dedicated asthma clinic in our institution; an academic, tertiary referral center. She had a history of recurrent episodes of wheeze, productive cough, sinusitis and lower respiratory tract infections. Over the preceding three-year period, she had had six lower respiratory tract infections per year requiring antibiotics, nebulized bronchodilators and oral steroids with transient improvement of her symptoms. She had been hospitalized on three occasions during this time at another institution.

She didn't have either seasonal allergic rhinitis or eczema, and reported no obvious triggers for her asthma apart from recurrent infection. She had a background history of recurrent respiratory and urinary tract infections since childhood, small left kidney (7.7 cm) with an area of cortical loss related to a urinary tract infection in early childhood. She was an ex-smoker with a 10-pack year history of smoking. At the time of referral to the asthma clinic her regular medications were; Budesonide/Formoterol 400/12 mcg twice daily, and Salbutamol as required.

Pulmonary function testing was undertaken. Spirometry demonstrated FEV_1 of 2.25 liters (73% of predicted) increasing to 2.54 liters post bronchodilator. FEV_1/FVC ratio was obstructive and her $MMEF_{75-25}$ was 28% predicted. Findings were consistent with a diagnosis of asthma although her transfer factor was mildly reduced at 70% of predicted. Her eosinophil levels were within normal ranges, IgE levels were undetectable (total IgE level < 2.0 IU/ml – normal range 0–81 IU/ml), and a panel of allergen-specific IgE were negative. Her alpha-1 anti-trypsin level was normal.

Initial workup confirmed the diagnosis of asthma. Despite optimal medical management of asthma, she continued to have persistent symptoms and recurrent exacerbations. She had good inhaler technique and self-reported compliance with therapy.

Results

A CT Thorax revealed evidence of bronchiectasis with diffuse airway thickening affecting both lower lobes, right middle lobe and lingual, and multiple foci of small airways mucoid impaction with distal centrilobular nodularity (see image 1). Multiple sputum cultures during the episodes of acute lower respiratory tract infections grew a fully sensitive Haemophilus influenzae. Further investigations were ordered given poor asthma control and recurrent infections. Bronchoscopy with bronchoalveolar lavage culture was positive for an encapsulated organism (*Haemophilus influenzae*), no evidence of airway fungal infection was evident on bronchoalveolar lavage culture and no virus demonstrated on BAL PCR. Measurement of serum immunoglobulin levels showed reductions in IgG, IgM and IgA levels. Viral screening including testing for Human Immunodeficiency Virus, Hepatitis B and C, and EBV were negative. Her serum albumin level was normal (44 g/L), with no evidence of proteinuria or protein losing enteropathy and no paraprotein band was seen on serum

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protein electrophoresis. Peripheral blood eosinophil and neutrophil counts, CD3 and CD19 lymphocyte counts (Lymphocyte Subpopulations) were normal.

She was referred to an immunologist for further assessment.

Given the typical presentation, extremely low Immunoglobulins levels (IgG, IgM, and IgA), absence of evidence of severe T cell deficiency, and exclusion of secondary causes of immunoglobulin deficiency, the diagnosis of CVID was made without proceeding for vaccination and functional antibody responses testing (2, 9).

She was started on intravenous immunoglobulin therapy (Hygvia; 40 gm every 4 weeks) with good response (Table1). Following initiation of immunoglobulin replacement treatment, the frequency of exacerbation requiring systemic antibiotic and steroid reduced from six to less than two per year. No subsequent exacerbations required hospitalization in the year following initiation of immunoglobulins replacement. Her Asthma Control Questionnaire (ACQ-7) score improved from 1.7 pre-immunoglobulin therapy to 0.7 post therapy.

Discussion

This case highlights the potential co-existence of CVID and asthma. Our patient had been treated for her asthma with conventional asthma medications in the community for years. She had recurrent sinusitis, otitis media, and recurrent lower respiratory tract infections that required multiple courses of antibiotics and at times hospitalization for management of pneumonia.

At review in the asthma clinic, her phenotypic features and investigations including lung function tests were consistent with the diagnosis of asthma. However, her Asthma control remained poor and she continued to have frequent exacerbations despite attempts to optimize the medical management of her asthma.

Further investigations revealed evidence of respiratory infection with an encapsulated organism (*Haemophilus influenzae* on both bronchoalveolar lavage, and sputum samples), and immunoglobulin levels were markedly decreased (IgG, IgM, and IgA levels) suggesting the co-existence of a primary immunodeficiency state. Further investigations supported the concurrent diagnosis of CVID and asthma in our patient.

Clinical manifestations of asthma and immunodeficiency syndromes can be very similar. Furthermore, multiple previous studies have investigated the impact of short-term glucocorticoids on serum immunoglobulins. It has been shown that short term treatment with moderate to high dose glucocorticoids may result in decreases in serum IgG of 10–20%, but IgM levels haven't been shown to be impacted (10–13). Delay in the diagnosis of CVID in asthmatic patients may plausibly be due to some cases of immunoglobulin deficiency being attributed to steroid use. In general, a delay in the diagnosis of immunodeficiency syndromes is common, with an average of five to seven years between onset of symptoms and diagnosis.

Conclusion

We believe that our case supports the need to measure serum immunoglobulins as part of the diagnostic workup and evaluation of patients with recurrent respiratory tract infections and bronchiectasis, but additionally, highlights the need to consider immunodeficiency in asthmatics who fail to respond to conventional inhaler therapy.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

A written consent from the patient was given prior to drafting the case report, the case subject acknowledged that personal details will not be included, cannot be identified via the paper, and we have fully anonymized the study case.

Disclosure of interest

The authors report no conflicts of interest.

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Table 1 Immunoglobulin levels before and 6 months after treatment with Immunoglobulins.

Class	Value (g/L) Pre-Immunoglobulin Treatment	Value (g/L) Post Immunoglobulin Treatment (6 months)	Normal Range (g/L)
Immunoglobulin G	0.81	8.75	6-16
Immunoglobulin A	<0.1	<0.10	0.8-2.8
Immunoglobulin M	0.48	0.34	0.5-1.9

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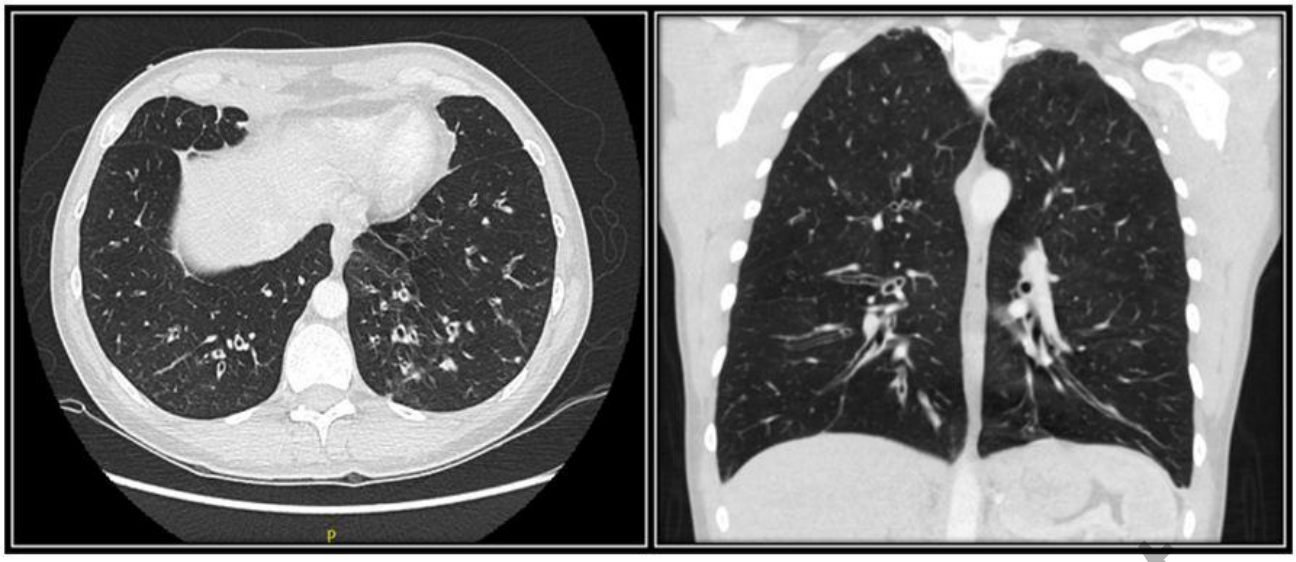

Image 1. Contrast CT Thorax showing diffuse airway thickening and bronchiectasis, multiple foci of small airways mucoid impaction with distal centrilobular nodularity.

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