

A RARE CASE OF HYPER IGE SYNDROME

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INTRODUCTION

This is the story of an eight-year, 10-month-old girl, who presented to the Paediatric Service at the Red Cross War Memorial Children's Hospital at the age of 20 months with a history of eczema since birth, recurrent superficial and deep-seated skin infections, and multiple severe viral and bacterial pneumonias. Laboratory analysis displayed a persistent eosinophilia, significantly elevated serum total IgE and evidence of food-specific IgE-mediated sensitisations. Genetic studies for mutations and deletions in the STAT3, DOCK8 and Tyk2 gene for Hyper IgE syndrome were negative. Currently, she has interstitial lung disease with features of reversible lower airway obstruction, primary immunodeficiency with abnormal immunoglobulin levels, low vaccine responses and recurrent infections. She is on maximal therapy for her asthma and receiving intravenous immunoglobulin monthly, and Omalizumab injections fortnightly. A good clinical response has been achieved since these latter two therapies were started.

HISTORY AND SYMPTOMATOLOGY

Patient LN first presented to a tertiary healthcare facility at the age of almost two years with a severe lower respiratory tract infection. However, she has had a history of lower airway obstruction treated at primary facilities since the age of seven months. She also has had mild eczema since birth, which was managed adequately on topical treatment. She was commenced on inhaled corticosteroids and short-acting beta 2 agonists at this point, and her treatment has been gradually upscaled to maximal therapy including daily oral steroids due to the continued lack of asthma control.

At two years of age she was diagnosed with zygomycosis (*Rhizopus* species) of the hand, requiring IV antifungal therapy for six weeks. Numerous admissions took place over the next few years for infections, including viral and bacterial pneumonias, superficial and deep-seated fungal infections, and status asthmaticus. Several of these episodes were life-threatening and required ventilator support in the intensive care unit. At the age of four years, a long-acting B2 agonist (LABA) was added to her treatment and she was being treated with regular pulses of steroids.

Her current therapy includes:

1. High dose inhaled steroids (ciclesonide), LABA (formoterol);
2. Montelukast;
3. Theophylline;
4. Azithromycin – 250 mg 3 times weekly;
5. Chloroquine;
6. Prednisone – 1 mg/kg daily;

7. Monthly intravenous immunoglobulin (IVIG) replacement therapy;
8. Two-weekly omalizumab.

OTHER RELEVANT HISTORY

The patient was HIV-exposed, but confirmed negative, with a normal birth history and no history of consanguinity. There was no significant family history of asthma or allergy. She was breastfed, eats a normal family diet and has never had any reactions to food despite elevated specific IgEs. She avoids peanuts, tree nuts and sesame since having been advised by doctors, but has had no reactions.

EXAMINATION FINDINGS

Physical examination is that of a well-grown girl with increased body mass index secondary to chronic steroid use. She is cushingoid, with coarse facial features, normal dentition and no high-arched palate or increased nasal width. Skin manifestations include well-controlled eczema and persistent molluscum contagiosum. No significant skeletal or connective tissue abnormalities are present and she has never suffered bone fractures. There is normal neurology. Over the years she has progressively developed chronic hyperinflation and digital clubbing.

Results of workup include:

- HIV-negative;
- TB-negative;
- lymphocyte subsets normal;
- IgG Subclass normal;
- IgM raised;
- Low vaccine response to pertussis, diphtheria and

tetanus. Re-immunised and raised, but six weeks later, low again;

- Th17 cells high;
- Interstitial changes on chest radiography with intermittent hyperinflation;
- Chronic bronchitis with increased goblet cells on lung biopsy;
- Non-specific small nodules with nodular and fibrotic changes on computed tomography;
- Normal sweat test;
- Normal milk scan;
- Aspergillus IgE always low, alternaria 15.1 kU/ℓ.

Allergy workup:

- Specific IgE to egg > 100 kU/ℓ, milk 67 kU/ℓ, peanut 67 kU/ℓ and wheat 22 kU/ℓ;
- SPT to egg 13 mm, milk 7 mm, peanut 11 mm, wheat 0 mm;
- ISAC foods:
 - High-level peanut sensitisation, soy, egg (conalbumin predominantly)
 - Kiwi (cross-reacts with alternaria), other LTPs
 - Low levels to milk, wheat, fish
- ISAC aeroallergens:
 - Multi-sensitisation, especially HDM, cat and mouse lipocalin, alternaria
 - Low levels to Bermuda and Timothy grass and storage mites.

Total IgE levels have ranged between 6,604 and 45,436 kU/ℓ.

SUMMARY OF PROBLEMS

Miss LN is an eight-year-old girl with structural lung disease with reversible lower airway obstruction, immune dysfunction with significantly elevated serum total IgE, multiple aeroallergen sensitisations and steroid dependence. These features are highly suggestive of Hyper IgE Syndrome.

DISCUSSION

Hyper IgE Syndrome (HIES) is a rare primary immunodeficiency characterised by recurrent eczema, skin abscesses, lung infections, eosinophilia and high serum levels of IgE. Multiple forms of HIES have been described, the most common being an autosomal dominant (AD or type 1) and an autosomal recessive (AR or type 2) form. These two forms share overlapping clinical and laboratory features, including eczema, recurrent infections, skin abscesses, high IgE level and increased eosinophil number.¹ However, they also exhibit distinct clinical manifestations, courses and outcomes.

Most autosomal dominant HIES have been found to be due to mutations in STAT3 (Signal Transducer and Activator of Transcription 3), whereas DOCK8 (Dedicator of Cytokinesis 8) mutations have been identified in patients

with autosomal recessive HIES (AR-HIES). Patients with AD-HIES also exhibit distinct dental, skeletal and connective tissue abnormalities not found in patients with AR-HIES. The condition is thought to be rare, although the exact prevalence is unknown. Approximately 200 cases have been described in the literature. STAT3 mutations have been found in many ethnic groups with an equal gender distribution.

Therapy of HIES remains largely supportive. Antibiotic prophylaxis is frequently used as prophylaxis against recurrent respiratory infections. Treatment for these infections, when they occur, should be started promptly. Given that patients with HIES suffer from significant eczema and skin infections and that the compromised skin offers a portal of entry to pathogens to cause deep seated infections, skin care and prompt treatment of skin infections is an important component of HIES management.

Poor antibody responses to vaccination in both AD- and AR-HIES lend support to the use of immunoglobulin replacement therapy in those patients. The role of interferon-gamma, granulocyte-colony stimulating factor or other immune modulators in HIES is, however, still under debate.

THE ROLE OF OMALIZUMAB IN HYPER IgE SYNDROME

Omalizumab is a recombinant DNA-derived humanised IgG1k monoclonal antibody that specifically binds to free IgE in the blood and interstitial fluid and to a membrane-bound form of IgE on the surface of mIgE-expressing B lymphocytes. It does not bind to IgE that is already bound by the high affinity IgE receptor (FcεRI) on the surface of mast cells, basophils and antigen-presenting dendritic cells. It is indicated as an add-on therapy in the management of severe asthma with evidence of allergic sensitisation and an IgE level of up to 1,500 IU/ml (= 1,500 kU/ℓ) in children of 6–12 years and in adults. There has been evidence to support the use of Omalizumab in patients with total IgEs > 1,500 kU/ℓ and demonstrable improvement in skin manifestations as well as general clinical outcomes in these patients.²

Omalizumab inhibits the binding of IgE to FcεRI on mast cells and basophils by binding to an antigenic epitope on IgE that overlaps with the site to which FcεRI binds and reducing free IgE. Free IgE binds to cell surface FcεRI and is available to bind antigen.

An additional dramatic effect, which was not foreseen when anti-IgE therapy was designed and which was discovered during clinical trials, is that as the free IgE in patients is depleted by omalizumab, the FcεRI receptors on basophils, mast cells and dendritic cells are gradually down-regulated with somewhat different kinetics, rendering those cells much less sensitive to the stimulation by allergens.^{5,6,7} In this regard, therapeutic anti-IgE antibodies represent

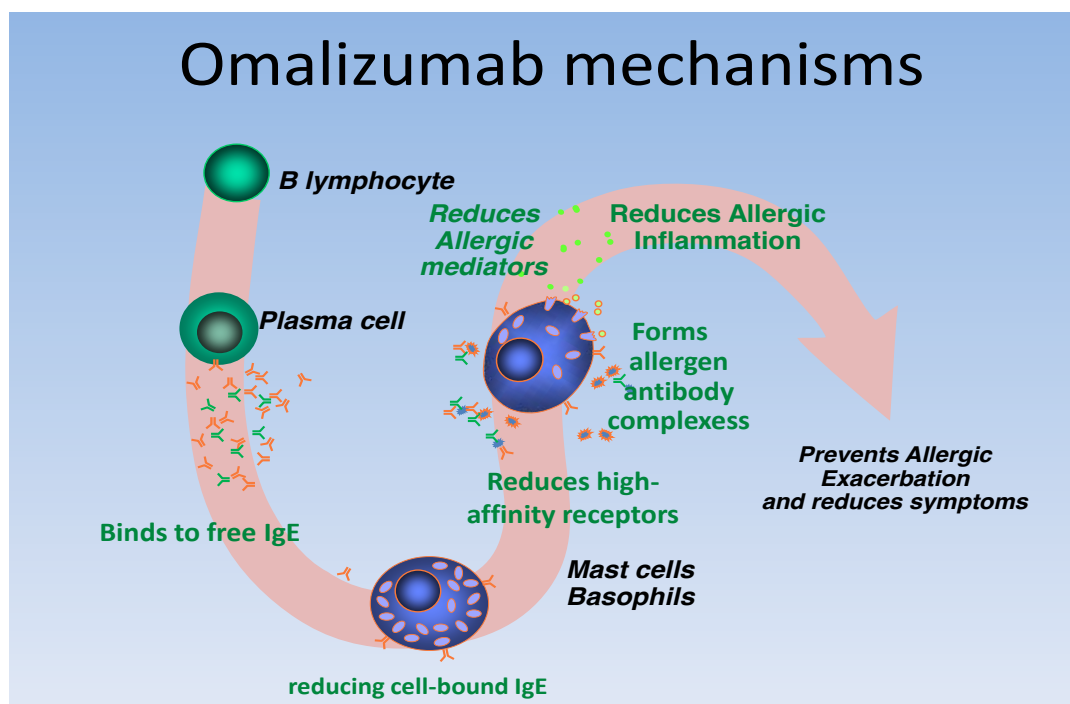


Figure 1: Multiple mechanisms of omalizumab resulting in reduced allergic inflammation

a new class of potent mast cell stabilisers⁸ providing the fundamental mechanism for omalizumab's effects on various allergic and non-allergic diseases involving mast cell degranulation. Many investigators have identified or elucidated a host of pharmacological effects, which help bring down the inflammatory status in the omalizumab-treated patients.⁹ An additional mechanism is the formation of allergen–antibody complexes with 'mopping up' of antigen, an effect that is independent of the initial IgE concentration.

The evidence for omalizumab therapy in allergic asthma and urticaria is striking; however, clinical trials are still warranted to determine its therapeutic benefit in Hyper IgE Syndrome. Case reports have shown improvement with the off-label use of omalizumab in HIES but mainly with skin manifestations.^{9,10}

Measurement of total IgE is not recommended as a monitoring tool for omalizumab as total IgE (comprising free IgE and omalizumab-bound complexes) rises following initiation of therapy with omalizumab as part of a normal response.¹¹ Despite a fall in the free IgE, the formation of IgE-omalizumab complexes contributes to measured total IgE leading to an initial apparent rise in total IgE concentrations. During omalizumab therapy production decreases over time and then equilibrates at a lower level.¹² Therefore, after the initial accumulation, total IgE levels decrease as the production is reduced. We therefore await a transition in levels during her ongoing therapy.

Following ten months of IVIG and six months of omalizumab (300 mg twice daily), our patient has presented with fewer

exacerbations requiring ICU, less daytime symptoms, and lower steroid dose requirements. Despite the fact that many of the measured parameters, including frequency of night symptoms, PEFR and FeNO have remained unchanged, she is now able to attend school, has spent less time in hospital, and requires lower doses of oral steroids, which has reduced the side-effects she is experiencing. After initiation of these two therapies significant clinical improvement was noted, however, it is difficult to establish if one mode of therapy individually, or both in combination have led to the clinical improvement.

A deterioration in her clinical course after October coincided with the holiday season, a change in school routine as well as medication times.

CONCLUSION

This patient has proved a great challenge to the Allergy Service at Red Cross Hospital, with a history of recurrent and prolonged hospital admissions for chest infections and hyper-reactivity, as well as skin infections. The most interesting aspect concerning the clinical picture is that the patient has textbook features of Hyper IgE syndrome, but negative genetic studies. The question is whether she is a highly atopic child with a 'hyper-IgE-like' syndrome, or whether she has Hyper IgE syndrome with an undescribed mutation.

In the past year she has resumed school and begun to participate in more age appropriate activities. She is currently completing her seventh month on anti-IgE therapy and we are eagerly monitoring her ongoing progress.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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