Interesting cases in fungal asthma

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Fungal asthma

• Broadly defined as the presence of fungal sensitization or fungal allergy in patients with asthma

• Fungal sensitization: immune-mediated response to a fungus, without evidence of inflammation or tissue damage

• Fungal allergy: immune-mediated inflammatory response to a fungus, sometimes associated with tissue damage
Fungal asthma

Denning DW et al. Clin Transl Allergy 2014, 4: 14
Agarwal R. Curr Allergy Asthma Rep 2011; 11: 403-413
# Diagnosis of fungal asthma

<table>
<thead>
<tr>
<th>Aspergillus fumigatus associated asthma (AFAA)</th>
<th>Allergic bronchopulmonary aspergillosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled asthma</td>
<td>Asthma</td>
</tr>
<tr>
<td>Elevated <em>A. fumigatus</em> (or other fungus) specific IgE (&gt;0.35 kUA/L)</td>
<td><em>A. fumigatus</em> specific IgE &gt;0.35 kUA/L</td>
</tr>
<tr>
<td>Total IgE &lt;500 IU/mL</td>
<td>Total IgE &gt;1000 IU/mL</td>
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<tr>
<td><strong>Severe asthma with fungal sensitization (SAFS)</strong></td>
<td>Elevated <em>A. fumigatus</em> specific IgG (&gt;27 mg&lt;sub&gt;A&lt;/sub&gt;/L)</td>
</tr>
<tr>
<td>Severe asthma</td>
<td>Transient or fixed pulmonary opacities</td>
</tr>
<tr>
<td>Elevated <em>A. fumigatus</em> (or other fungus)-specific IgE (&gt;0.35 kUA/L)</td>
<td>Total eosinophil count &gt;500 cells/µL</td>
</tr>
<tr>
<td>Total IgE 500-1000 IU/mL</td>
<td>HRCT of the chest</td>
</tr>
<tr>
<td>Normal <em>A. fumigatus</em> specific IgG (&lt;27 mg&lt;sub&gt;A&lt;/sub&gt;/L)</td>
<td>ABPA-S (normal HRCT chest)</td>
</tr>
<tr>
<td></td>
<td>ABPA-B (bronchiectasis)</td>
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<td>ABPA-HAM (high attenuation mucus)</td>
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</table>
Case 1

• 22-year old woman with history of asthma since 5 years, worsened for the last 1 year
• No history of fever, hemoptysis, weight loss
• Treated with a combination of inhaled steroids (budesonide 400 µg/d), long-acting β-2 agonists (LABA; formoterol 24 µg/d) and montelukast (10 mg/d)
• Treated for pneumonia twice in the past
Case 1

• Chest radiograph: fleeting pulmonary opacities
• *A. fumigatus*-specific IgE: 0.1 kUA/L
• Total IgE: 84 IU/mL
• *Aspergillus* skin test: negative
• *A. fumigatus*-specific IgG: 10 mgA/L
• *Aspergillus* precipitins: negative
• Eosinophil count: 840 cells/µL

• Sputum culture: *A. fumigatus*
• HRCT Chest:
Case 1
Case 1

• Flexible bronchoscopy:
  • Normal airway anatomy
  • Excess secretions
• Bronchoalveolar lavage: 
  *A.fumigatus*
• Post-bronchoscopy sputum: 
  *A.fumigatus*

• Diagnosed as ABPA 
  (eosinophilia, persistent growth of *A.fumigatus*, high attenuation mucus)
• Good response to oral glucocorticoids
Case 2

- 60-year old woman
- History of asthma since 26 years, treated with a combination of inhaled steroids (fluticasone 250 µg/d) and LABA (salmeterol 50 µg/d)
- Presented with fever and hemoptysis of 2 weeks duration
- Chest radiograph: LLL consolidation
- Treated with oral antibiotics (augmentin), no response
- Referred to our clinic
Case 2

- HRCT Chest: LLL consolidation
- Sputum culture: no growth of any organism
- CT-guided FNAC:
  - Cytology: acute inflammation, eosinophils
  - Cultures: sterile
Case 2

- *A. fumigatus*-specific IgE: 89 kUA/L
- Total IgE: 201 IU/mL
- *Aspergillus* skin test: negative
- *A. fumigatus*-specific IgG: 18 mgA/L
- *Aspergillus* precipitins: negative
- Eosinophil count: 280 cells/µL
Case 2

- Treated with itraconazole 400 mg/d for four months
- Good response
- Af-IgE: 89 -> 15.6 -> 0.6 kUA/L
<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td><strong>Asthma</strong></td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><em>A. fumigatus</em> specific IgE &gt;0.35 kUA/L</td>
<td>x</td>
<td>✔</td>
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<tr>
<td>Total IgE &gt; 1000 IU/mL</td>
<td>x</td>
<td>x</td>
</tr>
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<td>x</td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>Bronchiectasis</td>
<td>✔</td>
<td>X</td>
</tr>
<tr>
<td>High-attenuation mucus</td>
<td>✔</td>
<td>X</td>
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</table>
ABPA with normal IgE (total)

- Prior glucocorticoid therapy
- Very early ABPA
- Rituximab (anti CD20) therapy
- Patient has a very low IgE to begin with
  - For e.g. the IgE is 10-20 IU/mL. Despite a 10-20 fold rise it would be less than 200-400 IU/mL
- Any criteria or range for a population would generally cover only 95% of the population
  - It is expected that several individuals would not meet a criteria

Dorsaneo D et al. Ped Asthma Allergy Immunol 2004; 17: 146-150
Maiz L et al. J Allergy Clin Immunol 1997; 100: 431-432
Case 3

• 56-year old woman
• History of asthma since 22 years
• No history of fever, hemoptysis
• Treated with a combination of inhaled steroids (budesonide 400 µg/d) and LABA (formoterol 24 µg/d)
• Referred to our chest clinic for workup of fleeting pulmonary opacities
Case 3

- Chest radiograph: fleeting pulmonary opacities
- *A. fumigatus*-specific IgE: 60.3 kUA/L
- Total IgE: 12,546 IU/mL
- *A. fumigatus* skin test: positive
- *A. fumigatus*-specific IgG: 92 mgA/L
- *A. fumigatus* precipitins: positive
- Eosinophil count: 240 cells/µL
- HRCT chest: bronchiectasis, high-attenuation mucus

- Sputum culture: *A. flavus*
- *A. flavus*-specific IgE: 75.7 kUA/L
- *A. flavus* skin test: positive
- *A. flavus* precipitins: positive
Case 3

• Classic findings of ABPA (raised A.\textit{fumigatus} specific IgE, A.\textit{fumigatus} skin test positive, A.\textit{fumigatus} precipitins present)

• However, \textit{A.flavus} culture positive and \textit{A.flavus}-specific IgE greater than \textit{A.fumigatus}-specific IgE

• Co-sensitization or Cross-reactivity (ABPA or ABPM)
Cross-reactivity

• Phenomenon where the IgE antibody recognizes, binds, and induces an immune response to similar allergenic molecules (homologues) present in different species

• IgE crossreactivity often occurs between
  • allergenic molecules in closely related species or
  • between well preserved molecules with similar function present in widely different species that belong to the same protein family
Co-sensitization

• Genuine sensitization to more than one allergen source, where the sensitization is not due to cross-reactivity

• The presence of cross-reactivity can be discerned by performing qualitative IgE inhibition tests or by identifying the amino-acid sequence responsible for cross-reactivity

Canonica GW et al. World Allergy Organ J 2013; 6: 17
van Kampen V et al. Int Arch Allergy Immunol 2015; 166: 63-70
Sensitization to *A. flavus* in ABPA

- 53 subjects with a mean (SD) age of 34.2 (12.8) years were included
- Sensitization to *A.flavus* was seen in 51 (96.2%) subjects; 49 (92.5%), 21 (39.6%) and 12 (22.6%) instances on fungal-specific IgE, skin prick test and precipitins, respectively
- Sputum culture was positive in 18 (33.9%; *A.flavus* [n=12], *A.fumigatus* [n=6]) subjects
- ABPM due to *A.flavus* was diagnosed in 16 (30.2%) subjects
- More likely to have high-attenuation mucus and a trend towards higher occurrence of sinusitis, compared to ABPA
- Future work will correlate the role of component-resolved diagnostics in differentiating between the two entities

Sehgal IS et al. Med Mycol 2018; In press
Case 4

• 32-year old man
• History of asthma since 25 years
• No history of fever, hemoptysis
• Diagnosed as ABPA at another hospital
• Referred to our chest clinic for recurrent asthma and ABPA exacerbations and glucocorticoid-dependent ABPA
Case 4

- Chest radiograph: fleeting pulmonary opacities
- *A. fumigatus* specific IgE: 98 kUA/L
- Total IgE: 4300 IU/mL
- *A. fumigatus* skin test: positive
- *A. fumigatus* specific IgG: 42 mgA/L
- *A. fumigatus* precipitins: positive
- Eosinophil count: 986 cells/µL
- HRCT chest: extensive bronchiectasis involving all lobes
- Sputum culture: no organism
- FEV₁ 1.1 liters (42% predicted)
Case 4

- Was being treated with prednisolone (20 mg/d), itraconazole (400 mg/d), inhaled steroids (budesonide 1600 µg/d), LABA (formoterol 24 µg/d), theophylline (400 mg/d) and montelukast (10 mg/d)
- Had significant steroid-related adverse effects (weight gain, cushingoid facies, acne, skin striae)
- We increased the dose of prednisolone to 50 mg/d and changed itraconazole to voriconazole (400 mg/d) as he had significant anorexia and fatigue
- Despite this, the patient experienced two asthma exacerbations over the next two months
Case 4

• Also, the IgE decreased to only 3900 IU/mL (10%) after 2 months with no significant improvement in symptoms

• Subsequently, the patient received intravenous methylprednisolone pulse 1 gm/day for 3 days. All other therapies were continued

• The patient again landed in emergency with another asthma exacerbation

• Prednisolone was increased to 60 mg/day and omalizumab 375 mg s.c every two weeks was initiated
Case 4

- The patient had another mild asthma exacerbation in the next month which was managed with nebulized bronchodilators.
- There was only mild improvement in symptoms initially.
- However, there was no exacerbation over the next 4 months.
- We could taper his steroids and voriconazole over the next 4 months.

- After 8 months of omalizumab therapy, the patient was off prednisolone, montelukast, voriconazole and theophylline.
- For the first time in 8 years, the patient was off any oral medication.
Treatment of ABPA

• Glucocorticoids are the most effective anti-inflammatory agents

• **Regime 1 (Low [medium] dose regimen):** prednisolone 0.5 mg/kg/day x 1-2 weeks, then on alternate days for 6-8 weeks. Then taper by 5-10 mg q2 weeks and discontinue

• **Regime 2 (High-dose regimen):** prednisolone, 0.75 mg/kg for 6 weeks, 0.5 mg/kg for 6 weeks, taper by 5 mg q6 weeks. Continued for at least 6-12 months

A randomised trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating asthma

Ritesh Agarwal¹, Ashutosh N. Aggarwal¹, Sahajal Dhooria¹, Inderpal Singh Sehgal¹, Mandeep Garg², Biman Saikia³, Digambar Behera¹ and Arunaloke Chakrabarti⁴

Glucocorticoids in ABPA

- 92 subjects (high-dose n=44, medium-dose n=48)
- Numbers of subjects with exacerbation after 1-year and glucocorticoid-dependent ABPA after 2-years similar in the two groups
- Improvement in lung function and time to first exacerbation similar in the two groups
- Side-effects significantly higher in the high-dose group
- About 12% of patients treated with the low (medium) dose protocol do not respond and require higher doses

Azoles in ABPA

• 55 steroid-dependent ABPA: itraconazole 400 mg/day vs. placebo
  • Difference between 2 groups was significant in composite outcome
    • Reduction in steroid by ≥50%
    • Decrease in IgE by ≥25%
    • At least one [increase in exercise tolerance by ≥25%, improvement by ≥25% in PFTs, resolution of infiltrates]
  • No significance when each outcome examined separately

• 29 ‘clinically stable’ ABPA randomized to receive itraconazole or placebo (1/3rd already on steroids)
  • Use of itraconazole led to a decline in sputum inflammatory markers, serum IgE levels and number of exacerbations warranting glucocorticoid

Wark PA et al. J Allergy Clin Immunol 2003; 111: 952-957
Other therapies

• Newer azoles (voriconazole, posaconazole), aerosolized amphotericin
  • Reserved in patients with no (or poor) response with itraconazole or encounter adverse effects with itraconazole

• Pulse doses of methylprednisolone
  • Refractory ABPA exacerbations
  • Along with azoles to decrease the adverse effects associated with daily oral steroids

Sehgal IS et al. J Postgrad Med 2014; 60: 41-45
Sehgal IS et al. Eur Respir Rev 2014; 23: 149-152
Omalizumab

13 patients with chronic ABPA randomized to 4-month treatment with omalizumab (750 mg monthly) or placebo

- Exacerbations occurred less frequently
- Mean FeNO decreased
- Basophil sensitivity to *A. fumigatus* decreased significantly after omalizumab but not after placebo

**Clinical Efficacy and Immunologic Effects of Omalizumab in Allergic Bronchopulmonary Aspergillosis**

Astrid L. Voskamp, MSc², Andrew Gillman, FRACP⁴, Karen Symons, RN⁵, Alessandra Sandrini, MD, PhD⁶, Jennifer M. Rolland, PhD⁴, Robyn E. O’Hehir, FRACP, PhD⁴, and Jo A. Douglass, MD, FRACP⁴ Melbourne, Australia

Mepolizumab

- Mepolizumab - additional and effective treatment option for severe ABPA resistant to corticosteroids, antifungal therapy, and omalizumab

- It also demonstrates a potentially synergistic effect of using mepolizumab with omalizumab


Clinical Communications

Combination omalizumab and mepolizumab therapy for refractory allergic bronchopulmonary aspergillosis

Matthew C. Altman, MD\textsuperscript{a,b}, Jake Lenington, MD\textsuperscript{a}, Steve Bronson, RN\textsuperscript{a}, and Andrew G. Ayars, MD\textsuperscript{a,b}
Treatment protocol

Active ABPA (stage 1)

Initiate therapy with corticosteroids: 3-6 months

Followup: chest radiograph, spirometry, serum total IgE q8 weeks

Response (stage 2) | Remission (stage 4)

Exacerbation (stage 3): Steroids plus itraconazole for 6 months

Treatment-dependent (stage 5)

Long term therapy: azoles, low-dose glucocorticoids, methylprednisolone pulses, nebulized amphotericin B, omalizumab

Agarwal R. Mycopathologia 2014; 178: 447-56
Our experience with omalizumab

- We have used omalizumab in only 8 cases
- 7 of the 8 have shown good response
- Response generally occurs after 4 months, and is maintained till you continue omalizumab
Case 5

• A 21-year old male previously treated twice for tuberculosis with empiric anti-tuberculosis treatment presented with cough, recurrent hemoptysis, low grade fever and wheezing since 8 months

• Six months prior to presentation, he had a history of acute onset chest pain (spontaneous pneumothorax) requiring placement of intercostal tube
Case 5

- Diagnosed as chronic pulmonary aspergillosis (CPA) complicating ABPA and started on oral itraconazole (400 mg/day)
- Serum itraconazole levels after 2 weeks were 1.24 µg/mL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. fumigatus-specific IgE</td>
<td>61.7 KUA/L</td>
</tr>
<tr>
<td>A. fumigatus-specific IgG</td>
<td>182 mgA/L</td>
</tr>
<tr>
<td>Total IgE</td>
<td>19,366 IU</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td>350 cells/µL</td>
</tr>
<tr>
<td>Aspergillus skin test</td>
<td>22 mm</td>
</tr>
<tr>
<td>Serum precipitins</td>
<td>++</td>
</tr>
<tr>
<td>Serum galactomannan</td>
<td>0.49</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>A. fumigatus</td>
</tr>
<tr>
<td>FVC</td>
<td>2.37 litres</td>
</tr>
<tr>
<td>FEV 1</td>
<td>2.17 litres</td>
</tr>
<tr>
<td>FEV1:FVC ratio</td>
<td>91.6</td>
</tr>
</tbody>
</table>
Case 5

- At 6 months he had clinical (except hemoptysis) and serological response
- Itraconazole was stopped

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>A. fumigatus</em>-specific IgE</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>A. fumigatus</em>-specific IgG</td>
<td>35 mgA/L</td>
<td>26 mgA/L</td>
</tr>
<tr>
<td>Total IgE</td>
<td>11,160 IU</td>
<td>6,911 IU</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Aspergillus</em> skin test</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serum precipitins</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Serum galactomannan</td>
<td>0.39</td>
<td>0.30</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>-</td>
<td>2.87</td>
</tr>
<tr>
<td>FEV1</td>
<td>-</td>
<td>2.84</td>
</tr>
<tr>
<td>FEV1:FVC ratio</td>
<td>-</td>
<td>99</td>
</tr>
</tbody>
</table>
Case 5

- Six months after stopping treatment he again presented with low grade fever, hemoptysis, worsening breathlessness
- Total IgE (19,994 IU/mL), \textit{A. fumigatus}-specific IgG (84 mgA/L)
- Again started on itraconazole; there was partial response, however fever and breathlessness persisted (serum itraconazole levels, 1.4 µg/mL)
- IgE had declined to 15,441 IU/mL after 2 months
- Oral glucocorticoids were added
- At 6-month follow up, symptomatically better, total IgE (8,720 IU/mL)
Case 5

Before starting glucocorticoids

After glucocorticoids and itraconazole
CPA complicating ABPA

• The diagnosis of CPA complicating ABPA is difficult
• The diagnostic hallmark for CPA is *A. fumigatus*-specific IgG, which is also seen in ABPA
• Detection of *Aspergillus* spp. by culture, antigen or molecular testing is encountered in both the conditions

• Thus, the diagnosis of CPA-ABPA is primarily based on serial radiology, clinical and serological findings
• Nodules (some with cavitation), lobar shrinkage with indrawing of extrapleural fat, aspergillomas and bilateral pleural thickening are characteristic for CPA complicating ABPA

CPA complicating ABPA

- Treatment also offers certain challenges
- Oral triazoles are the treatment of choice for CPA; glucocorticoids are contraindicated
- Oral glucocorticoids are the treatment of choice for ABPA; itraconazole monotherapy is also beneficial in about 88% of cases
- Thus in CPA complicating ABPA, itraconazole controls both ABPA and CPA
- However, glucocorticoids might be required in ABPA-CPA, and they are not contraindicated in ABPA-CPA

Denning DW et al. Eur Respir J 2016; 47: 45-68
Agarwal R et al. Chest 2018; In press
ABPA with aspergilloma has been treated with glucocorticoids alone. Hence, patients with ABPA-CPA may require glucocorticoids for control of disease activity.

References:
- Rosenberg IL et al. Chest 1984; 85: 123-125
- Agarwal AK et al. Asian Pac J Allergy Immunol 1996; 14: 5-8
Summary

• Fungal asthma can have varied presentations

• While the hallmark of the diagnosis of allergic bronchopulmonary mycosis is raised total IgE, it can be normal in some individuals

• The role of the different fungi in causing allergic mycosis depends on the geographic locale

• In patients with allergic bronchopulmonary mycosis, more than one fungi may be allergenic. Molecular-based allergy diagnostics may help in clarifying the role of a particular fungi
Summary

• More evidence and experience is required with newer treatments like omalizumab (and mepolizumab)

• Long-standing allergic bronchopulmonary mycosis can be complicated by CPA, which may be difficult to diagnose and treat