CASE REPORT

Necrotising pneumonia and bronchiectasis in a previously healthy 30-year-old man

David G Blauvelt,¹ Angela Castellanos,¹ Theodore A Stern,² Alberto Puig²

¹Harvard Medical School, Boston, Massachusetts, USA
²Massachusetts General Hospital, Boston, Massachusetts, USA

Correspondence to

David G Blauvelt,
 david.g.blauvelt@gmail.com

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SUMMARY

We present a case of a previously healthy 30-year-old man who presented with a necrotising pneumonia and bronchiectasis. His infectious workup revealed a *Staphylococcus aureus* pneumonia. Since bronchiectasis and necrotising pneumonia are unusual findings in an otherwise healthy person, further investigation was pursued. His workup revealed non-classic cystic fibrosis (CF) and allergic bronchopulmonary aspergillosis (ABPA). This case discusses the differential diagnosis of bronchiectasis, the diagnosis and treatment of ABPA, and the role of CF mutations in the pathogenesis of ABPA.

BACKGROUND

Pneumonia is one of the most common reasons for hospitalisation among all age groups. Most community-acquired pneumonias require no further workup to search for an underlying predisposition to lung infections. However, the following case describes a previously healthy man who developed a severe necrotising pneumonia. The significant nature of his illness prompted a search for a susceptibility to severe pulmonary infections. His workup illustrates a collaborative effort between various medical disciplines, including infectious disease, pulmonology and allergy/immunology.

CASE PRESENTATION

A 30-year-old man was well until 6 days prior to admission, when he developed fever, night sweats, malaise and cough. Over the next few days, his symptoms worsened, and he had temperatures up to 103°F. Two days prior to admission, his cough became productive of thick, green-brown sputum with occasional blood streaks. His coughing fits increased in severity and often induced vomiting. The morning of admission, he awoke with moderately severe right-sided chest pain, which was exacerbated by inspiration or coughing.

The patient had no significant medical history except for seasonal allergic rhinitis and an intermittent, mildly productive cough that had worsened over the past year. He denied a history of asthma or childhood infections. He was up-to-date with all vaccinations (including influenza), and he had no known sick contacts or recent travel. The patient had never smoked cigarettes. He admitted to occasional use of alcohol and marijuana, but denied other drug use.

On examination, the patient was afebrile and had an oxygen saturation of 99% on room air. However, he was ill-appearing and looked to be in

significant pain with coughing and breathing. Examination of his chest revealed right lateral chest wall pain at rest that was non-reproducible with palpation. Auscultation of his lungs revealed diminished breath sounds throughout the entire right lung and the upper left lung field. He also had increased fremitus and egophony over the right upper and middle lung fields as well as over the left upper lung field.

INVESTIGATIONS

His initial laboratory studies were notable for a white cell count of 17 500 cells/mm³. A chest radiograph (figure 1) showed an airspace opacity in the right upper lobe with multiple lucencies and possible air fluid levels. It also showed a confluent airspace opacity in the left perihilar region. A CT scan (figure 2) showed bilateral upper lobe consolidative opacities with evidence of necrosis and central bronchiectasis. Empiric antibiotic therapy with azithromycin (for atypical bacteria), vancomycin (for methicillin-resistant *Staphylococcus aureus* (MRSA)) and piperacillin/tazobactam (to cover most typical organisms, anaerobes, and Gram-negative rods) was initiated. Sputum fungal stains and cultures were negative, as were a HIV test and a respiratory viral panel (influenza, adenovirus, parainfluenza, and respiratory syncytial virus). He had three separate sputum samples that were negative for acid-fast bacilli and had a negative tuberculosis purified protein derivative skin

Figure 1 Radiograph of the chest. A posteroanterior chest radiograph was obtained on initial presentation. It showed a right upper lobe airspace opacity with multiple lucencies (arrows). It also demonstrated a left perihilar opacity.

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Figure 2 CT scan of the chest. A CT scan was obtained following the initial chest radiograph. It showed bilateral consolidative opacities consistent with a necrotising pneumonia. There was also evidence of centrally distributed bronchiectasis (arrow).

test. The infectious aetiology was confirmed when sputum culture grew abundant, MSSA. Our patient's antibiotic regimen was subsequently narrowed. Azithromycin, vancomycin and piperacillin/tazobactam were all discontinued, and he was started on intravenous cefazolin. He improved significantly during his hospital stay, and he left the hospital on day 7 with a 14-day course of cefazolin.

DIFFERENTIAL DIAGNOSIS

Our patient presented with the signs and symptoms of a severe, bilateral pneumonia with necrosis and bronchiectasis on CT. Thus, two diagnostic challenges were apparent: the infectious aetiology of his acute pneumonia and his underlying susceptibility that caused his bronchiectasis and predisposed him to a severe pneumonia. The acute cause of his pneumonia was discovered relatively quickly, when his sputum culture grew *S. aureus*. However, bronchiectasis was an unusual finding in a young, non-smoking, otherwise healthy individual.

Bronchiectasis involves an irreversible dilation of the bronchial tree caused by destruction of the surrounding supportive muscle and elastic tissue.¹ It is a result of the breakdown of the lung's intrinsic defense system. In a normal lung, inhaled pathogens, toxins and allergens are first trapped in mucus that coats the airways. Cilia then mechanically remove the mucus from the lungs. The second line of defense includes antibodies and immunological cells (eg, neutrophils, macrophages and T-cells), which work to destroy immunogens that make it to the lower airways.

Bronchiectasis arises when one of these defenses is locally or systemically compromised, whether from impaired mucus

drainage or a defect in host immunity. In this context, the lung becomes vulnerable to infection and inflammation, resulting in destruction of the supportive stroma of the lung and irreversible airway dilation. These dilated airways then impede mucus drainage because of an inability to generate sufficient pressure to mobilise secretions. This further increases their vulnerability to infection, resulting in a vicious cycle of infection, inflammation, destruction and further dilation (figure 3A).² Bronchiectasis thus begets further bronchiectasis. Using this framework, the aetiologies of bronchiectasis can be categorised by their primary effect on this cycle (figure 3B).

OUTCOME AND FOLLOW-UP

Our patient improved rapidly with antibiotic therapy. At a follow-up appointment 2 weeks after discharge, his symptoms had nearly resolved. A 3-week follow-up CT scan also showed near complete resolution of his pulmonary consolidations, though the bronchiectasis was persistent. As an outpatient, he had a comprehensive work-up to discover the aetiology of his bronchiectasis.

He was found to be heterozygous for the cystic fibrosis (CF) $\Delta F508$ mutation as well as two other CF mutations of unknown clinical significance. His chloride sweat test was interpreted as being borderline (right arm: 51, 50; left arm: 56, 51), and he was noted to have intact vas deferens. In addition, he was found to have an elevated IgE of 1290 IU/mL, a peripheral eosinophilia of 950 cells/mm³, and serum precipitating antibodies against *Aspergillus*. These initial findings were concerning for allergic bronchopulmonary aspergillosis (ABPA) as a cause for his bronchiectasis.

Our patient met five of the major diagnostic criteria for ABPA (box 1)³ based on his initial work-up and had additional tests sent to evaluate whether he met the other criteria. He had never been diagnosed with asthma, which is an important component of the ABPA diagnosis. However, it was thought that he may have had undiagnosed asthma, so he was sent for pulmonary function tests after his pneumonia had resolved. His forced expiratory volume over 1 second to forced vital capacity ratio was 0.71, improving to 0.77 after bronchodilator administration. This was consistent with a mild, partially reversible obstructive process. He was referred to an allergist for skin-prick testing, which showed positive reactivity to *Aspergillus fumigatus* at 15×32 mm. Finally, he had his *Aspergillus*-specific IgE and IgG antibody levels measured, which revealed elevated indices of 3.3 and 4.18 respectively.

On the basis of his diagnostic work-up, his bronchiectasis was thought to be due to a combination of non-classic CF and ABPA. He was started on a budesonide/formoterol inhaler. He also received fungal allergen immunotherapy. These treatments were well tolerated, and he has remained healthy without recurrence of pneumonia.

DISCUSSION

ABPA is an immunological pulmonary disorder that typically presents with poorly-controlled asthma, pulmonary infiltrates, and central bronchiectasis, and classically affects patients with asthma and CF. It affects 1–2% of patients with asthma⁴ and 2% of patients with CF.⁵ Worldwide, it is thought to affect over four million people, though due to under-reporting and under-diagnosis, accurate epidemiological data are limited.⁶

The pathogenesis of ABPA is incompletely understood, but thought to be a complex hypersensitivity reaction to the fungus, *A. fumigatus*. It begins with inhalation of spores from *A. fumigatus*, which are ubiquitous throughout the environment. These spores

Figure 3 The pathogenesis of bronchiectasis. (A) Schematic showing the cycle of bronchiectasis. Dilation of the airways leads to impaired drainage, which in turn increases the chance of infection, causing inflammation, ultimately resulting in further airway dilation. (B) Causes of bronchiectasis categorised by the primary mechanism in which they affect the cycle of bronchiectasis.

are immunologically inert due to their surface proteins, called hydrophobins.⁷ However, in patients unable to clear the spores (such as in patients with CF and asthma), the spores can then germinate into hyphae. Normally, the immune cells quickly destroy these hyphae without triggering a larger inflammatory response. However, if the host has an immunological defect, the hyphae persist and eventually release proteases that trigger secretion of proinflammatory cytokines by respiratory epithelial cells.⁸ In addition, these proteases directly damage lung parenchyma, leading to further inflammation. Together, these processes cause a runaway inflammatory cascade, mediated by an enhanced type 2 helper T cell (Th2) response, ultimately leading to the clinical features of ABPA.⁹

Limited data exist about the link between *S. aureus* pneumonia and ABPA. *S. aureus* pneumonia is a common infection in patients with CF, isolated in nearly 70% of them.¹⁰ However, it is found in less than 10% of patients with non-CF

bronchiectasis.¹¹ A study by Shah *et al*¹² investigated *S. aureus* pulmonary infections in 86 patients with non-CF bronchiectasis. They found that *S. aureus* infection in these patients was significantly associated with ABPA and non-classic CF. These findings suggest that ABPA and non-classic CF should be strongly considered in patients with bronchiectasis found to have *S. aureus* in their sputum.

One of the unusual aspects of this case was the absence of severe asthma in our patient. Asthma is a major diagnostic criterion for ABPA, so the lack of an asthma history made it difficult to diagnose ABPA. It is important to note that occasionally, ABPA can be found in patients without clinical evidence of asthma.¹³ Furthermore, our patient was found to be heterozygous for several CF mutations, which likely contributed to his development of ABPA. A meta-analysis by Agarwal *et al*¹⁴ found an increased prevalence of CF transmembrane conductance regulator (CFTR) mutations in patients without clinical CF with

Box 1 Major diagnostic criteria for allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis major diagnostic criteria
Minimal essential diagnostic criteria

- ▶ History of asthma
- ▶ CT evidence of bronchiectasis*
- ▶ Immediate skin test reactivity to *Aspergillus* antigens
- ▶ Serum IgE concentration >417 IU/mL (1000 ng/mL)
- ▶ *Aspergillus fumigatus* specific IgE and IgG index >2

Other major diagnostic criteria

- ▶ Lung infiltrates on radiograph or CT
- ▶ Serum precipitating antibodies
- ▶ Peripheral blood eosinophil count >500 cells/mm³

*If there is no evidence of bronchiectasis, a diagnosis of seropositive allergic bronchopulmonary aspergillosis is made.

ABPA versus non-ABPA controls. It has been shown that CFTR mutations cause an enhanced Th2 response to *A. fumigatus*, suggesting that even in the absence of classic CF disease, CFTR mutations may contribute to the pathogenesis of ABPA.^{15 16} Thus, while our patient presented without clinically apparent asthma or CF, the combination of subclinical forms of both diseases explained the development of ABPA.

Another notable aspect of the case was the use of fungal allergen immunotherapy, an emerging treatment for ABPA. The traditional treatment of ABPA consists of glucocorticoids and antifungal agents.¹⁷ Allergen immunotherapy consists of exposing the patient to increasing doses of fungal allergen extracts to hyposensitise the patient to the allergens. While high-quality clinical trials evaluating fungal allergen immunotherapy in ABPA do not exist, there is some evidence that immunotherapy is efficacious in some fungal allergies.¹⁸ Fungal allergen immunother-

apy is not generally recommended as first-line treatment of ABPA, though it can be considered for patients who are candidates for immunotherapy for concurrent asthma or allergic rhinitis.¹⁹

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Learning points

- ▶ *Staphylococcus aureus* infection should be suspected in the setting of a severe necrotising pneumonia.
- ▶ Bronchiectasis in a young, otherwise healthy individual is abnormal and requires further investigation.
- ▶ Allergic bronchopulmonary aspergillosis (ABPA) is an important cause of bronchiectasis in young individuals. It is classically found in severe asthmatics, but it may be found in those with subclinical asthma, especially if they have one or more cystic fibrosis transmembrane conductance regulator (CFTR) mutations.
- ▶ There may be a link between ABPA, non-classic CF, and an increased risk of *S. aureus* pneumonia.
- ▶ Fungal allergen immunotherapy is an emerging treatment for ABPA, though its efficacy needs further investigation.

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