ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS – A PREDICTOR FOR WORSE OUTCOME IN CYSTIC FIBROSIS PATIENTS (CASE REPORT)

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Summary

Allergic Bronchopulmonary Aspergillosis (ABPA) is a disease primarily occurring in patients with asthma or Cystic Fibrosis (CF) and develops from sensitization with allergens from Aspergillus fumigatus (Af) present in the environment. It is manifested by wheezing, pulmonary infiltrates and bronchiectasis and fibrosis. Immunological manifestations are peripheral blood eosinophilia, immediate cutaneous reactivity to Af antigen, elevated total serum Ig E, precipitating antibody to Af, and increased serum IL2 receptor concentrations.

The diagnosis of ABPA in CF may be difficult and often delayed because of overlaping of diagnostic criteria with common manifestations in CF. The typical presentation of ABPA in CF is with wheezing, new pulmonary infiltrates, a rise in total serum IgE and specific Ig E to A fumigatus, with a fall in pulmonary function. Early diagnosis and treatment aiming to suppress the inflammation is however important to prevent irreversible lung damage.

This is a case report of 11 years and 7 months old boy diagnosed with CF at the age of 4 months but started to be followed up on a regular basis at the age of 9 years.

By the time of first presentation in our clinic he had a poor nutritional status and a poor lung function. Partial recovery followed after including him in standardized treatment regimens . He presented in January 2006 with a severe pulmonary exacerbation diagnosed as ABPA. Decision making and treatment options are disscussed.

Key words: Allergic bronchopulmonary aspergillosis, cystic fibrosis, lung function

Introduction

Allergic Bronchopulmonary Aspergillosis (ABPA) develops from sensitization with allergens from Aspergillus fumigatus present in the environment. ABPA is a disease primarily occurring in patients with asthma (1-2%) or Cystic Fibrosis (CF) (2-15%).

It is manifested by wheezing, pulmonary infiltrates and bronchiectasis and fibrosis. Some immunological manifestations are peripheral blood eosinophilia, immediate cutaneous reactivity to Af antigen, elevated total serum Ig E, precipitating antibody to Af, and increased serum IL2 receptor concentrations.

The diagnosis of ABPA in CF is usually difficult and may be often delayed because many of the diagnostic criteria overlap with common manifestations in CF. The typical presentation of ABPA in CF is with wheezing, new pulmonary infiltrates, a rise in total serum IgE and specific Ig E to A fumigatus, with a fall in pulmonary function.

The hyphae of Af that grow saprophytically in the bronchial lumen result in persistent bronchial inflammation leading to proximal bronchiectasis.

Early diagnosis and treatment aiming to suppress the inflammation is however important to prevent irreversible lung damage.

A consensus guideline on management of ABPA in CF has been published recently (1).The mainstay of treatment is oral corticosteroid therapy, but this need to be continued for several months and may be associated with significant adverse effects. It seems reasonable as well to attempt to reduce the burden of A fumigatus in the respiratory tract (2). Studies of Itrakonazole in CF uncontrolled setting (3) and in randomized trials in adults with asthma and ABPA (4) have shown evidence of benefit, including the ability to reduce steroid dosage.

Case presentation

We describe one case with CF and ABPA with difficult decision making regarding treatment options.

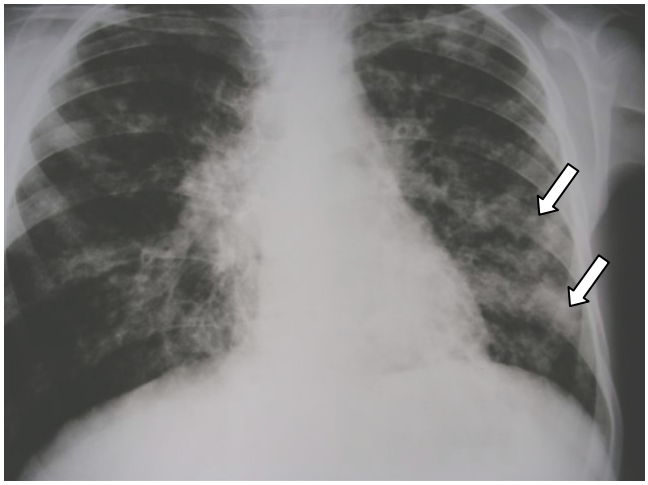
A 11 years and 8 months old boy was admitted on the 15th of January 2006 in the Children's Hospital of Brasov for frequent coughing, brown sputum plugs, exertional dyspnoea, left-sided chest pain, fatigue, respiratory disstress. The patient was known as having CF, homozigot for del F508 mutation, diagnosed at the age of 3 months.He was unfortunately followed up and treated on a regular basis only starting with the age of 9 years.

His actual status was of severe pulmonary involvement with extensive bronchiectasis, low lung function (FEV1 50-60%pred), satisfactory nutritional status (BMI 16). During the 3 years prior to his current consultation, the patient has been admitted to the Children's Hospital of Brasov on several occasions for pulmonary exacerbations. He is chronically infected with Staphylococcus aureus, intermittently colonized with Pseudomonas aeruginosa.

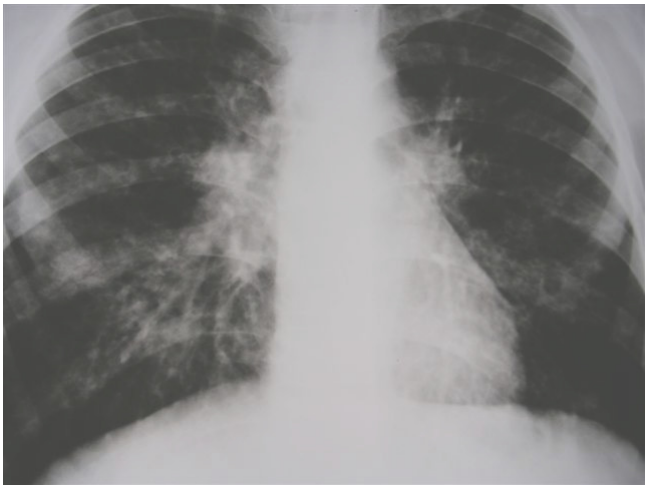
The onset of symptoms goes back to December 2005 when he experienced a pulmonary exacerbation with intense coughing and brown sputum. He had a short course of iv Cefuroxime followed by oral Ciprofloxacin with attenuation of symptoms.

The actual episode started 4 days before the hospital admission with frequent coughing, minor hemoptizia and brown sputum plugs, exertional dyspnoea, no appetite.

On clinical examination, he was found to have a weight of 31 kg, height 138 cm, afebrile, dyspnoeic, with frequent cough and perioral cyanosis, wheezing, small amounts of brown sputum, some crackels over the left hemithorax. Oxigen saturation was 90%. The chest X-ray showed bronchiectasis in the upper and lower lobes, new patchy infiltrates in the left lower lobe, right mucus hilar impaction (fig.1), compared to his last examionation (fig.2).



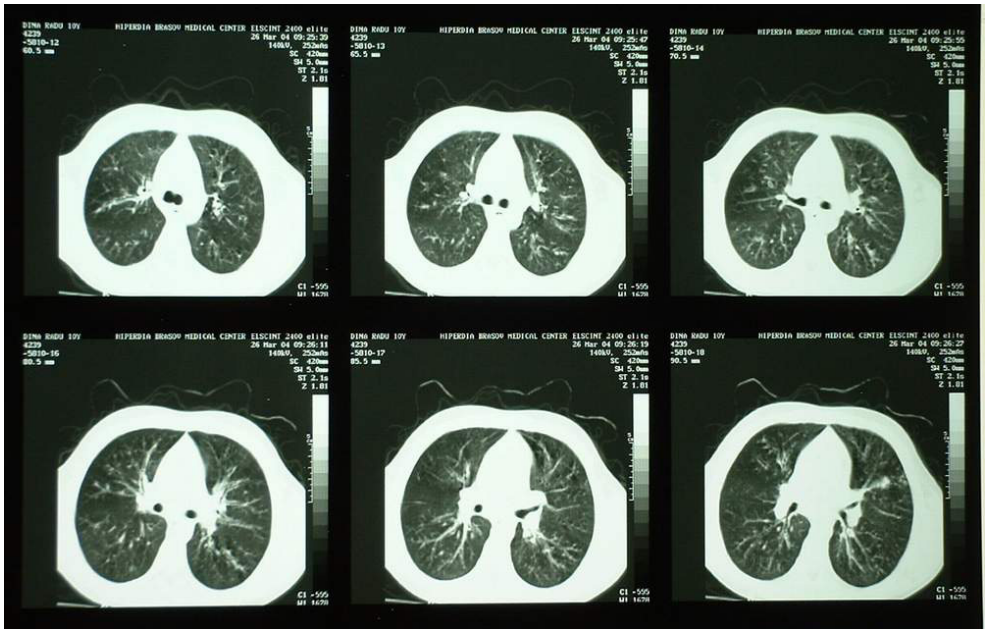
Chest x-ray January 2006 (fig.1).



Chest x-ray November 2005 (fig.2).

The CT scan confirmed the extensive bronchiectasis, bronchial wall thickening and mucus plugging, air trapping and new infiltarates in the left lower lobe.

There was a significant worsening of CT scores compsre with last CT performed in 2003 (see fig.3).

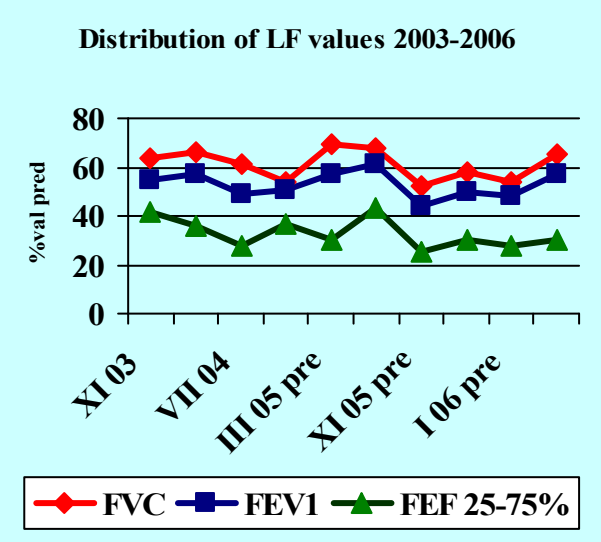


CT aspect in 2003 (fig.3).

The laboratory data were: WBC 14 600/mmc, 61%granulocytes, Hb 11.9 g/dl, ESR 68 mm/h, CRP 24mg/l, IgG 368 IU/ml; IgM 600 IU/ml. The sputum cultuture showed *Aspergillus fumigatus*, there was no growth of other bacteria.

Spirometry: FVC 1.26 (54%pred), FEV1 0.98(48% pred); FEF 25-75% 0.80 (28% pred).

In order to show variation of lung function over time, we attach the following graph:



Other laboratory findings regarding glicaemic and hepatic status were normal (regular annual OGTT normal)

Conssidering the clinical symptoms, the new infiltrates on the chest x-ray, sudden decline of lung function and positive sputum culture for *A fumigatus*, there was a high suspicion for ABPA. Skin prick test for *Af* was positive, total serum IgE were 13 579 IU/ml ans IgE to *Af* >100chiroU/l (ref values<0.35 chiroU/l).

At this stage, the patient encountered sufficient diagnostic criteria for ABPA. This determined us to start treatment with Prednisolone 2 mg/kg/day for the first 2 weeks followed by 1 mg/kg/day 1 week and 1 week of alternate day therapy. Dose was tappered to 15 mg/day alternate day till present. Itrakonazole capsules 200mg/day was associated for 6 weeks along Pulmozyme, physiotherapy and hypercaloric diet.

After the first 5 weeks of treatment the total serum IgE dropped to 8 300 IU/ml, the clinical status significantly improved, there was ocasional coughing with clear sputum, diminished infiltrates on the chest x-ray, lung function increased with ~7%. There were no adverse reactions from corticosteroid and antifungic therapy.

Disscussions

Out of 25 CF patients followed up during a 7 years period in the Children's Hospital of Brasov, only 3 were colonised with *Af* and one had ABPA. All 3 patients had lower levels of lung function and didn't beneffit from early treatment and follow up.

ABPA occurred in a patient with severe lung disease, with already important lung tissue scarring and who unfortunately didn't benefit from regularly follow up and treatment from diagnosis till the age of 9 years.

The patient also had a former exacerbation during November 2005 (2 months before the actual episode), with particular infiltrates on his x-ray, but no evidence of *Af* in the sputum, positive response to antistaphylococcal therapy. There were several exacerbations when he experienced wheezing , probably showing an asthmatic pattern of response to different viral triggers.

In this particular case,the short term outcome seems to be somehow favorable, but is well known that ABPA negatively influences the pulmonary status in CF, which will be. at a certain moment a marker for a worser outlook.

Chronic infection with *Staph. aureus* seemed to be a risk factor for the developing of ABPA in this patient, more so being a determinant of extensive bronchiectasis. This could allow (as mentioned in some reports) colonisation by fungi, paticularly the thermotolerant *A. fumigatus.*

Interestingly, this patient probably was colonised with *Af* following heavy rains and floods that were encountered in the county region where he lives, during the rainy season of last summer.

It has been shown that there are much higher air counts of moulds during summer-autumn season; the hypothesis hat increased humidity, coupled with higher winds may trigger increased spore production and dissemination.

It is mentioned that the proof of efficiency of corticosteroid therapy in ABPA is demonstrated when total serum IgE decrease more than 50% of the initial value, which is still not our case.It seems that there is still a long way to go regarding corticosteroid thearpy (probably several months) in terms of reducing the level of allergic response to *Af.*

Knowing that the bioavailability of Itrakonazole capsules is low in CF and being in the situation of very high values of total serum IgE even after 2 months of corticosteroid therapy, it seems reasonable to try to atempt reducing the burden of *Af* antigen in this patients' airways; measntime hoping to be able to reduce the doses of Prednisolone.

Vorikonazole (Vfend – Pfizer), as mentioned in the literature, even an expensive alternative, could offer a better treatment option for a patient with altered lung function, extensive bronchiectasis and very important allergic response to *Af.*

Decision making on using this antifungal agent along prolonged corticosteroid therapy, will depend on hospital policy and judging of benefits for the patient.

The question that remains is which treatment would be the best choice for this child who has already a severe impairment of lung function. It has to be considered the effect of prolonged treatment with prednisolone that apparently doesn't work as expected (only a small reduction in total serum IgE) and its adverse effects on glucose tolerance and osteopenia. In this respect, it would seem reasonable to try to attempt treatment with Vorikonazole in a supervised hospital setting, at least in order to lowering the burden of *Af* antigen response and try to restore residual lung function.

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