Unusual presentation of more common disease/injury

A rare *CFTR* intronic mutation related to a mild CF disease in a 12-year-old girlNadia Nathan,¹ Emmanuelle Girodon,² Annick Clement,¹ Harriet Corvol¹¹Department of Pediatric Pulmonology, AP-HP Hôpital Armand Trousseau, Paris, France – INSERM UMR S-938²Department of Biochemistry-Genetics, AP-HP, Groupe hospitalier Henri Mondor, Créteil, France - INSERM, U955 équipe 11

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Summary

We report the case of a 12-year-old girl with an allergic bronchopulmonary aspergillosis (ABPA), intermediate sweat chloride tests and one cystic fibrosis (CF)-causing mutation, p.Phe508del. After extensive screening of the CF transmembrane regulator (*CFTR*) gene, she finally was found to carry a rare deep intronic mutation (c.872-1110_1113delGAAT), which confirmed the atypical mild CF disease. Although a classical steroid treatment did not allow the healing of the ABPA, an omalizumab therapy led to a long-term recovery. This case emphasises the need to search for rare *CFTR* gene mutations as far as possible when a CF disease is evoked. Moreover, it also highlights that although omalizumab is not yet recognised as a classical ABPA treatment in CF, it should be considered as an alternative therapy in steroid-resistant patients.

BACKGROUND

Atypical presentations of cystic fibrosis (CF) are not rare and the physician must search for rare CF transmembrane regulator (*CFTR*) gene mutations as far as possible when the disease is evoked. We report the case of a young girl presenting with persistent cough and extensive bilateral alveolar pneumonia consistent with an allergic bronchopulmonary aspergillosis (ABPA) and no digestive disease.

CASE PRESENTATION

A 12-year-old girl was referred to our outpatient clinic for a persistent cough since 3 months. She was born on normal term, being the only child of a non-relative couple. No familial diseases were known and both parents had French origins. Her height and weight growths were normal and she had no other medical records. At the time she was born, no neonatal CF screening was done in France. She was following a normal scholar course and was playing several different sports (athletics, swimming and gymnastics).

At her first visit, her height and weight were on the 50th centile, the auscultation revealed diffuse crackles. The chest radiography showed bilateral alveolar opacities of the upper right lobe and of the lingula. She was treated by several oral antibiotics courses (cephalosporin and macrolides) with no improvement after 2 months.

INVESTIGATIONS

The high-resolution (HR) thoracic CT-scan revealed bilateral lobar collapses and diffuse bronchiectasis (figure 1). Lung function and blood gas were slightly below normal values as shown in table 1. A bronchoscopy was then performed, that showed a diffuse airway inflammation and mucus plugging in the lingular bronchus. The analysis of the extracted mucus revealed 3×10^2 *Aspergillus fumigatus*. The blood cytology showed a hypereosinophilia (1.35×10^9 /litre), with high total immunoglobulin (Ig) E

level (2406 kUI/l) and elevated *A. fumigatus* specific IgE level. The *A. fumigatus* skin test and serology were positive. These criteria confirmed an ABPA and we searched for a causal aetiology.

DIFFERENTIAL DIAGNOSIS

ABPA has been described mostly in severe asthma, immune deficiencies and CF. Our patient had no asthma history and no immune deficiency was found. The sweat chloride test (Gibson and Cooke) was intermediate with 43–45 mmol/l of chloride level. The faecal elastase level was normal. Testing for 30 frequent *CFTR* gene mutations revealed only one mutation, c.1521_1523del, p.Phe508del (F508del). Further, extensive screening of *CFTR* coding regions did not reveal any other mutation. The nasal potential difference showed very low baseline values (–71 and –67 mV) with an important inhibition of Na transport by amiloride (46.2 and 48.3 mV) but a normal chloride transport. The search for epithelial sodium channel (ENaC) gene mutations was negative. Finally, based on recent publications, we looked for the *CFTR* deep intronic mutation c.870-1110_1113delGAAT mutation: its presence in the patient, in compound heterozygosity with c.1521_1523del, p.Phe508del, confirmed the atypical CF disease.

TREATMENT

The patient was treated by oral itraconazole and 2 mg/kg/day oral steroids for 2 months followed by a 6-month decrease. As she was still presenting an active ABPA after this treatment, omalizumab was started.

OUTCOME AND FOLLOW-UP

Omalizumab allowed the resolution of the cough after 1 month, as well as the negatization of *A. fumigatus* in the sputum and the negatization of the serology. After a 1-year treatment, the thoracic HRCT scan showed

Figure 1 High-resolution thoracic CT (HRCT). (A and B) First thoracic HRCT showing bilateral alveolar condensation of the upper lobes and moderated diffuse bronchiectasis. (C) Thoracic HRCT after 1 year treatment of the allergic bronchopulmonary aspergillosis showing bilateral large cystic bronchiectasis in place of the alveolar consolidations.

bilateral large cystic bronchiectasis in place of the alveolar consolidations and an improvement of the other diffuse bronchiectasis (figure 1). Two years after omalizumab was stopped, the patient was still free of ABPA. She had still no pancreatic and liver diseases, and her respiratory function tests and blood gases were normal (table 1). During all the follow-up, she pursued a normal scholar course and several sports.

DISCUSSION

ABPA is a complex clinical entity that results from an allergic immune response to *A fumigatus* most often occurring in patients with asthma or CF. Primary diagnosis criteria include asthma, radiological evidence of pulmonary

Table 1 Lung function tests evolution

	At presentation	After 1 year of omalizumab treatment	Two years after omalizumab treatment was stopped
Age, years	12	13.5	15.5
Weight, kg	35	42	49
Height, cm	153	156	158
FVC, l (%)	2.02 (70)	2.5 (78)	2.76 (89)
FEV1, l/s (%)	1.78 (74)	2.49 (93)	2.38 (90)
FEF 25–75, l/s (%)	2.19 (75)	3.77 (117)	2.93 (88)
Arterial	73	93	94
PaO ₂ , mm Hg			
Arterial PaCO ₂ , mm Hg	40	35	36

FEF 25–75, forced expiratory flow 25–75% (these three values are given in litres or l/s and in percentage of expected value); FEV1, forced expiratory volume at 1 s; FVC, forced vital capacity.

infiltration, positive skin test to *A fumigatus*, hypereosinophilia, positive *A fumigatus* serology, elevated total and/or *A fumigatus*-specific IgE level and central bronchiectasis. A diagnosis of ABPA is nearly certain, as in our case, when six of these eight criteria are fulfilled.¹

Oral steroids remain the mainstay ABPA treatment and are mostly used with an initial high daily dose for 4–12 weeks, followed by a slow and long decrease of 3–12 months. Corticosteroids are usually associated with an antifungal therapy as ketoconazole, itraconazole and newly voriconazole, considered as corticosteroid-sparing agents. More recently, omalizumab, a monoclonal antibody directed against IgE, has been shown in adults to also benefit the corticoid-dependent or resistant patients.^{2–4} Until now it has not yet been recommended, especially in children. Interestingly, in our case, this treatment allowed a complete long-term healing of the ABPA that was initially resistant to a long-term corticoid treatment associated with itraconazole.

This case highlights that the diagnosis of ABPA must incite physicians to request extensive *CFTR* testing, even if the CF neonatal screening was negative. Sweat chloride tests have to be performed in first intention, although some rare CF mutations are associated with normal or intermediate sweat chloride values.⁵ More than 1900 *CFTR* gene sequence variations have been reported so far in patients with CF- and *CFTR*-related disorders (www.genet.sickkids.on.ca/cftr/app). As in our case, the 30 most frequent CF mutations are first tested and an extensive analysis should be further discussed depending on the clinical evaluation. Still, extensive screening of the *CFTR* gene coding regions may be negative, as was the case in our patient. In such situations, search for splicing defects in deep intronic regions, possibly by studying messenger RNA (mRNA) obtained from nasal epithelial cells, should be considered, as recently evidenced.^{6,7} In our patient, the recently described intron 7 c.870-1113_1110delGAAT mutation was specifically screened for and identified, which led to confirm the diagnosis of atypical CF. This deletion of 4 base pairs (bp) was shown to be associated with an insertion of a new exon of 97bp in the mRNA between exons 7 and 8, which contains a premature stop codon. It was first described in three Italian patients having classical CF. A French collaborative study in

patients suspected to have CF and who had no or only one known CF mutation led to identify 17 patients presenting CF or a CFTR-related disorder.⁶ Fourteen of them were originated from France or Italy, and geographic origin was unknown for the others. Among the 17 patients, four had a normal or intermediate sweat test and none of them presented an ABPA. The severity of the disease was extremely variable, from a severe, typical CF with pancreatic insufficiency and *Pseudomonas aeruginosa* colonisation, to asymptomatic presentations. The fertility was also reported to be variable. Our young patient showed a mild lung CF disease with diffuse bronchiectasis and preserved lung function, chronic rhinitis, pancreatic sufficiency. Her fertility status is not known yet.

Learning points

- The diagnosis of allergic bronchopulmonary aspergillosis (ABPA) in children must encourage physicians to search for cystic fibrosis (CF).
- Extensive analysis of the CF transmembrane regulator (CFTR) gene, including search for rare intronic splicing mutations has to be performed before excluding a CF diagnosis.
- Omalizumab could be considered as an alternative therapy for cortico-resistant ABPA in CF children.

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Competing interest None.

Patient consent Obtained.

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