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Case report

Nasal polyposis in atypical cystic fibrosis: A case report

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ABSTRACT

Cystic fibrosis (CF) is one of the most common inherited life-shortening diseases with an incidence of 1:2.500–3500 and a carrier frequency of 4–5% [1]. It is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, which encodes a protein expressed in the apical membrane of exocrine epithelial cells, resulting in changes to the fluid and electrolytes on cell surface. More than 1500 mutations have been described so far in the CFTR gene, grouped in 5 classes on the basis of the impact on protein synthesis or activity [2].

In the last years a mounting number of reports described patients that did not meet all diagnostic criteria for CF [4]; in particular, atypical or nonclassic CF is characterized by normal or borderline sweat test, pancreatic sufficiency and a monosymptomatic phenotype; the most studied forms are: congenital bilateral absence of vasa deferentes, acute or chronic recurrent pancreatitis, idiopathic bronciectasis [5]. These patients typically bear a severe and a mild (classes 4–5) CFTR mutation, the latter being dominant [6].

The involvement of upper airways is observed in up to 100% of classic CF patients, including recurrent sinusitis and rhinitis. Nasal polyps are present in 6–48% of overall CF patients and in 5–15.2% of less than 10 years old CF patients.

Surgery is required for syntomatic polyps. It is the second most common class of operations performed on CF patients. In spite of the best of operations CF patients will have recurrence, because of systemic disease.

We describe a patient diagnosed as "atypical CF" on the basis of persisting chronic rhinosinusitis, that showed a very rare CFTR genotype.

1. Introduction

Cystic fibrosis (CF) is one of the most common inherited life-shortening diseases with an incidence of 1:2.500–3500 and a carrier frequency of 4–5% [1]. It is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, which encodes a protein expressed in the apical membrane of exocrine epithelial cells, resulting in changes to the fluid and electrolytes on cell surface. More than 1500 mutations have been described so far in the CFTR gene, grouped in 5 classes on the basis of the impact on protein synthesis or activity [2].

The genotype of classic CF patients typically includes two severe (classes 1–3) mutations [3]. The prevalent clinical features are chronic sinopulmonary disease, exocrine pancreatic insufficiency and increased sweat electrolytes levels. Within chronic sinopulmonary disease, chronic sinusitis, nasal polyps and hypertrophy of inferior turbinates with nasal airway obstruction are typical signs of CF. Sweat chloride levels are invariably above 60 mmol/L.

In the last years a mounting number of reports described patients that did not meet all diagnostic criteria for CF [4]; in particular, atypical or nonclassic CF is characterized by normal or borderline sweat test, pancreatic sufficiency and a monosymptomatic phenotype; the most studied forms are: congenital bilateral absence of vasa deferentes, acute or chronic recurrent pancreatitis, idiopathic bronciectasis [5]. These patients typically bear a severe and a mild (classes 4–5) CFTR mutation, the latter being dominant [6].

Another group includes CFTR related diseases, characterized by respiratory symptoms as chronic sinusitis, allergic bronchopulmonary aspergillosis, asthma; a higher occurrence of CFTR mutations is described in such diseases, but more than a single gene and environmental factors are involved in the pathogensis of such disorders.

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The involvement of upper airways is observed in up to 100% of classic CF patients, including recurrent sinusitis and rhinitis. Nasal polyps are present in 6–48% of overall CF patients and in 5–15.2% of less than 10 years old CF patients. Surgery is required for syntomatic polyps. It is the second most common class of operations performed on CF patients. In spite of the best of operations CF patients will have recurrence, because of systemic disease.

We describe a patient diagnosed as "atypical CF" on the basis of persisting chronic rhinosinusitis, that showed a very rare CFTR genotype.

2. Case report

S.M., female, current age 9-year old, was admitted to Otorhinolaryngology Department of our institution for nasal obstruction assessment. There was family history of atopy. At the age of 4 years, the girl developed a severe acute lung disease associated to allergic asthma requiring hospitalization. Respiratory symptoms improved with regular treatment with inhaled steroids and bronchodilators until she was 8 years old, when she started suffering from nasal obstruction, unresponsive to medical treatment. She underwent adenoidectomy at 8 years and 6 months. Four months later, the girl presented oral breathing, nasal obstruction, snoring, a runny nose with thick yellowish secretions and occasional headache. On physical examination, the child was in regular health status, hydrated, with no fever, cyanosis, digital clubbing or respiratory discomfort. Chest examination did not reveal snoring or pathological murmurs. Anthropometric parameters were in the normal range for age. Rhinoscopy showed purulent secretions and polyps obstructing whole bilateral nasal cavities. At oroscopy we detected post-nasal dripping. The presence of eosinophilia among the inflowing cells was revealed. Positive result of skin test-overreactivity to home dust acarid antigens and high level of total IgE in serum were ascertained. No chest X-ray abnormality was found. Paranasal sinus computed tomography (CT) scan with axial and coronal views without contrast detected pansinusitis and a polyp in each nasal cavity obstructing osteomeatal complex. CT images revealed a complete opacity of maxillary and ethmoid sinuses with heterogeneous density associated to sinuses expansion, some degree of decalcification and erosion of right orbital medial wall (Fig. 1). Surgical procedures included a combination of maxillary antrostomy, anterior and posterior ethmoidectomy and adenoidectomy was performed. Histopathology revealed intact surface epithelium made up of respiratory epithelium. The stroma was markedly edematous and was infiltrated by chronic inflammatory cells, predominantly eosinophils, plasma cells, and lymphocytes. On the basis of the history of atopy and the histopathologic features of the polyps, an allergic etiology was strongly hypothesized.

However, given the higher frequency of CFTR mutations in patients with polyps, particularly when recurrent and destructive CF was suspected and a sweat chloride test was carried out. Mean sweat chloride levels was 42 mmol/L. Molecular testing for a panel of CFTR mutations by reverse dot-blot technique (Innogenetics, Gent, Belgium) was negative. However, given the clinical history and the borderline result of the sweat test, the whole coding regions of CFTR was tested by sequencing analysis, and the L636P/P499A genotype was identified.

3. Discussion

We describe a 9 years old girl with a history of chronic involvement of upper airways, borderline sweat test and a CFTR genotype with two mutations. She may be classified as "atypical CF". Some clinical and genetic features of the patient warrant a comment.

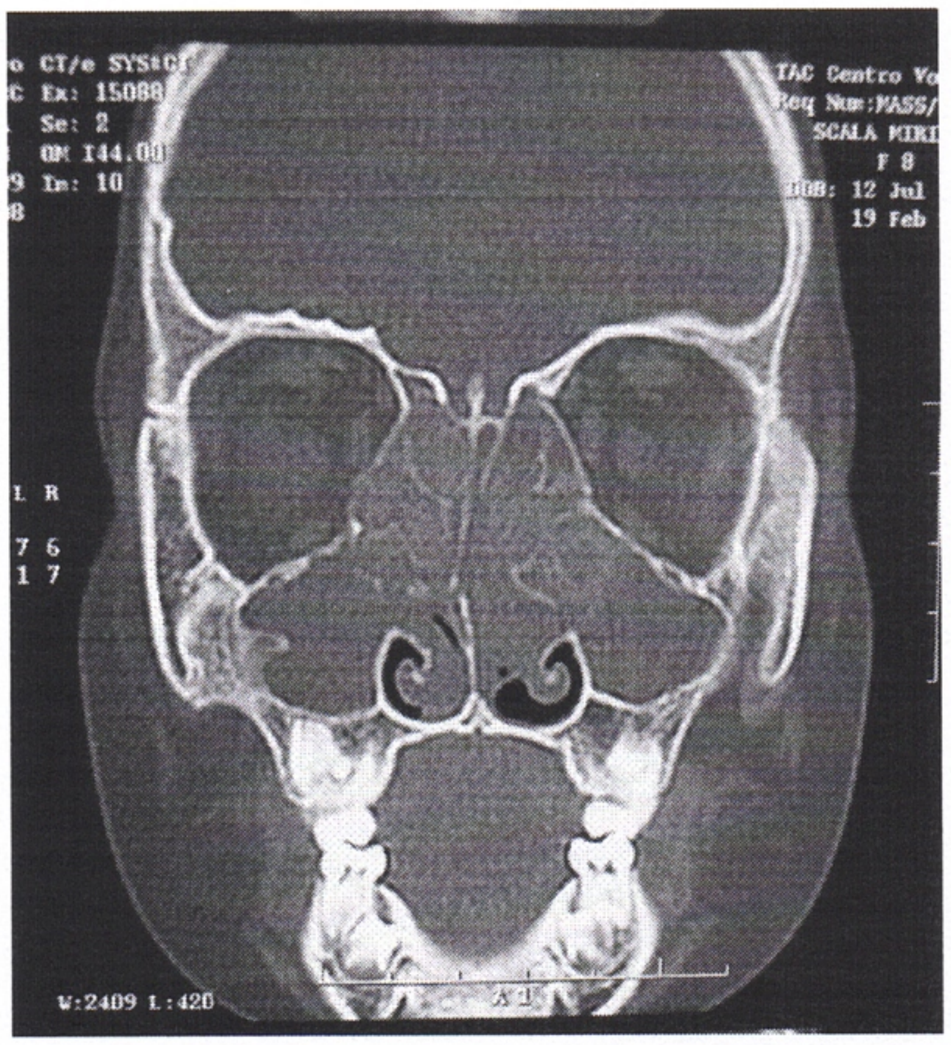

Fig. 1. Paranasal sinus computed tomography (C.T) shows massive polyposis completely obstructing bilateral nasal cavities, maxillary and ethmoid sinuses.

The clinical history revealed the involvement of upper airway since the first years of life, i.e., an acute lung disease at the age of 4 years old that required hospitalization, nasal obstruction, and signs of chronic rhinosinusitis at the age of 8 years old and, finally, nasal polyposis that required surgery. The presence of allergic asthma since the age of 4 years old, the improvement of respiratory symptoms after steroids and bronchodilators therapy, the subsequent results of histopathological features suggested an allergic etiology, and delayed diagnosis of CF. On the other hand, the relationships between asthma and CF are still controversial.

Furthermore, only in recent years atypical forms of CF and CFTR related diseases have been clearly classified and defined, modifying the current opinion that CF is a severe disease, and that the sweat test is invariably altered in CF patients. As a consequence of the wide spectrum of clinical phenotypes of atypical CF, i.e., (congenital bilateral absence of vasa deferentes, recurrent pancreatitis, disseminated bronchiectasis, biliary cirrhosis, asthma, allergic bronchopulmonary aspergillosis and others) a variety of physicians with different specialisations are today potentially involved in CF, but in their mind CF remains a severe disease, and sweat chloride test remains the lone predictive test for CF diagnosis or exclusion.

On the contrary, the presence of nasal polyps, the chronic involvement of upper airways and the borderline results for sweat test prompted us to ask for molecular analysis for CFTR also using the "second level" approach of the whole gene sequencing, that confirmed the diagnosis of atypical CF. It must be underlined that the respiratory involvement in atypical CF and in CFTR related diseases usually appears at a late age while in our patient these symptoms appeared early, and that rhinosinusitis may be due to a miriad of other ethiologies, including still unknown genetic factors [7].

Going to molecular analysis, the patient bears a very particular genotype, i.e., L636P/P499A, that at the best of our knowledge has not been previously identified in CF nor atypical CF patients. Both the mutations are rare, in fact none of them was identified in 371 CF patients from Southern Italy studied by our group [8] nor in about 100 atypical CF patients from the same ethnic group (unpublished data). The P499A was previously identified in a patient bearing CBAVD that had on the other allele the severe

mutation W1282X; thus, P499A should be a mild mutation [9]. Similarly, the L636P has been identified so far only in a patient with normal sweat chloride and diffuse bronchiectasis, another atypical CF form (www.genet.sickkids.on.ca).

Both mutations are not routinely tested, even because most panels of mutations screen only for severe CFTR mutations; none of the commercial kits detects the two mutations identified in our patient [10]. This strongly confirms that only scanning procedures can be used for molecular analysis in patients bearing atypical CF.

4. Conclusion

An updated clinical assessment of symptoms compatible with diagnosis of "atypical CF" could permit an early detection of disease and the access to Specialized Medical Care improving morbidity and mortality. Although chronic rhinosinusitis with or without polyps does not always mean CF, it is recommended a strict otolaryngology investigation of chronic untreated sinusits/polyps not otherwise explained by the most common causative disease. If CF or "atypical CF" is suspected, in addition to sweat test, molecular analysis with the scanning of the whole CFTR gene is recommended.

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