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The c.3274T> C mutation in the *CFTR* gene results in bronchiectasis and loss of lung function in a 44-year-old Peruvian woman: A very rare condition

Mutación c.3274T> C en el gen CFTR provocando bronquiectasias y pérdida de la función pulmonar en una mujer peruana de 44 años: una condición muy rara

Samuel Pecho-Silva[1,2,*], **Ana C. Navarro-Solsol**[3,#]

Abstract

CF is an autosomal recessive disease, requiring mutations to be present in both alleles in the CF transmembrane conductance regulatory gene (*CFTR*). The c.3274T> C (p.Tyr1092His) mutation is not registered in the “CFTR2 project” database, but it is registered in The Human Gene Mutation Database. Neither are the two DNAAF4 c.1177C> T (p.Leu393Phe) and DNAAF5 c.1195G> A (p.Glu399Lys) mutations found in the "CFTR Project", and their clinical consequences are currently uncertain. Here, we report the case of a Peruvian woman presenting this mutation, bronchiectasis and loss of lung function and provide a review of the literature.

Keywords: cystic fibrosis, bronchiectasis, C.3274T> C mutation.

Resumen

La FQ es una enfermedad autosómica recesiva que requiere la presencia de mutaciones en ambos alelos del gen regulador de la conductancia transmembrana de la FQ (CFTR). La mutación c.3274T> C (p.Tyr1092His) no está registrada en la base de datos del “proyecto CFTR2”, pero está registrada en la base de datos de mutaciones de genes humanos. Ademas otras dos mutaciones DNAAF4 c.1177C> T (p.Leu393Phe) y DNAAF5 c.1195G> A (p.Glu399Lys) encontradas en el "Proyecto CFTR", son actualmente inciertas en sus consecuencias clínicas. A continuación, presentamos el caso de una mujer peruana que presenta esta mutación, bronquiectasias y pérdida de función pulmonar y se proporciona una revisión de la literatura.

Palabras clave: fibrosis quistica, bronquiectasias, mutacion c.3274T>C.

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Introduction

In 2019, about 80,000 patients were registered as having cystic fibrosis (CF) in the United States and Europe (1). The clinical diagnosis of CF during adulthood is a difficult because: 1) the vast majority of patients do not undergo neonatal screening, especially in Peru; 2) systemic manifestations are usually infrequent; and 3) bronchiectasis-like lung lesions and chronic respiratory symptoms due to functional compromise are usually considered as pulmonary tuberculosis or as secondary lesions (2). The latter is very frequent in countries such as Peru where the prevalence of tuberculosis is high. Adults with CF may have a residual function of the gene involved in CF, and thus, the sweat chloride test with pilocarpine (gold standard test) is usually not positive, leading to indeterminate results (3,4), making molecular biology studies necessary to achieve a definitive diagnosis (1,5).

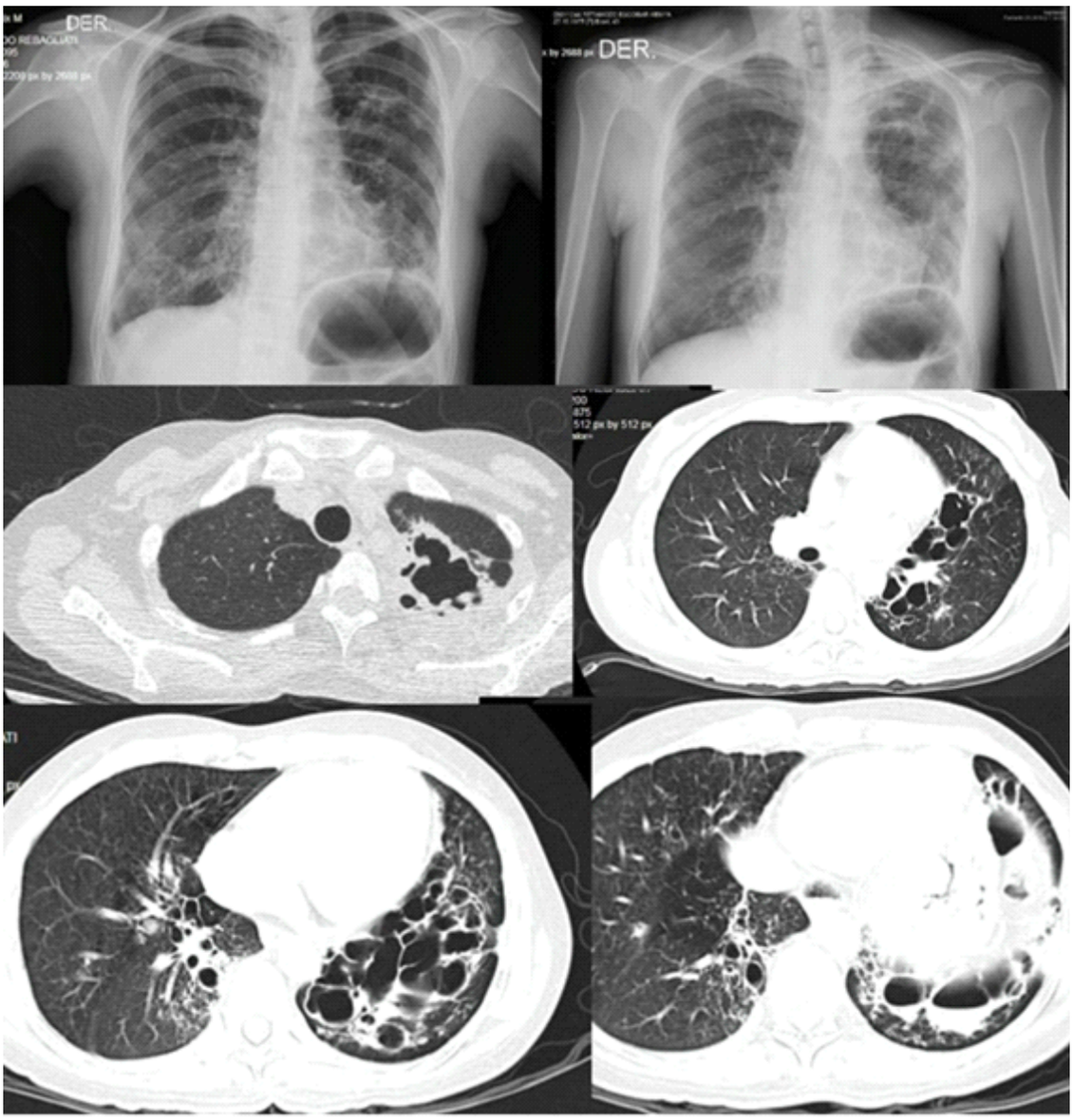
CF is an autosomal recessive disease, requiring mutations to be present in both alleles in the CF transmembrane conductance regulatory gene (*CFTR*). More than 2,000 mutations have been described in this gene, but only 412 mutations have been fully characterized (6). The different variations in mutations can be classified as: a) CF-causing variants, b) pathogenic variants of variable clinical significance, c) non-disease-causing variants, and d) variants of uncertain significance (3,4). The most frequent mutation worldwide is delta F508, although its presence varies considerably between races and regions. Here, we report the case of a peruvian woman who gave her consent presenting this mutation and provide a review of the literature.

Case Report

The patient was a 44-year-old woman, a native of the Department of Huancavelica (3,676 meters above sea level) in the Peruvian highlands, presenting nearly 40 years of respiratory symptoms including: cough, phlegm, and dyspnea. At the age of 30, she was diagnosed with a pulmonary sequela due to untreated tuberculosis after several previous radiographs showed lung lesions of the bronchiectasis type. For several years, only sputum samples were requested in search of M. tuberculosis, all of which were negative. The general examinations did not show striking alterations. Chest tomography showed initially diffuse bilateral cystic bronchiectasis that was later located predominantly in the upper and lower left lobe and the lower right lobe (Figure 1). The paranasal sinuses showed no alterations. No fungal microorganism was isolated.

On referral to our unit, and after obtaining informed consent from the patient, the following analyses were made to determine the cause of bronchiec-

Figure 1. Comparative chest X-Ray: 2014 (upper left corner) and 2019 (upper right corner). Computed tomography of the chest (2019): bilateral cystic bronchiectasis that was later located predominantly in the upper and lower left lobe and the lower right lobe



tasis: immunoglobulins, aspergillus antibodies, antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) targeting myeloperoxidase (MPO) and proteinase 3 (Pr3), native anti-DNA antibodies, extractable nuclear antigen (ENA) autoimmunity profile, procalcitonin, C-reactive protein (CRP) and blood count, all of them were normal. The functional study using spirometry and plethysmography showed a very severe obstructive disorder (forced expiratory volume in one second [FEV1] of 38%) with a decrease in forced vital capacity (FVC) of 44% without response to bronchodilators associated with a severe increase in residual volume (RV: 160%) and functional residual capacity (FRC: 180%) with normal total lung capacity (TLC: 118%) and severe decrease in the diffusion capacity of carbonmonoxide (DLCO: 27%). In the 6-minute walk test the patient walked 400 meters (adequate for her age) with a resting saturation of 94% and a minimum saturation during the test of 88%.

With respect to specific examinations for the study of CF, 4 chloride sweat tests were carried out using the pilocarpine method. All the results were within the indeterminate range (30 - 60 mmol / L): 41, 37, 44 and 42 mmol / L, respectively, which is unusual in infectious bronchiectasis. Although more useful in neonates and children, a serum immunoreactive trypsin test was also performed: 764 ng / mL (very high). In May, 2016 a genetic study for CF carried out by massive sequencing and found the presence of the c.3274T> C mutation (*p.Tyr1092His*) in one of the alleles of the CFTR gene; this first study evaluated 24 mutations of this gene. A second genetic study conducted in 2019 evaluated 36 genes related to CF, immunodeficiencies, and primary ciliary dyskinesia found the same c.3274T>

C mutation (*p.Tyr1092His*) in one of the alleles of the CFTR gene. Additionally, the presence of heterozygosity of the *DNAAF4 c.1177C> T* (*p.Leu393Phe*) and *DNAAF5 c.1195G> A* (*p.Glu399Lys*) was found; the first mutation is not present in the database (https://gnomad.broadinstitute.org/) and the second has a frequency in the population of 0.00003605%, and neither mutation has known clinical correlation.

A blood count was performed on March 5, 2020, showing a leukocyte count of 14,900 / mm3 and CRP level of 53.6 mg / L. Two blood cultures was negative. The growth of *Pseudomonas aeruginosa* in sputum culture was found to be sensitive to piperacillin / tazobactam, third and fourth generation cephalosporins, carbapenems, aztreonam and fluoroquinolones with intermediate sensitivity to colistin, and therefore, antibiotic treatment was initiated with ceftazidime 2 g every 8 hours intravenous plus amikacin 750 mg every 24 hours also intravenous and nebulized colistin every 12 hours for 28 days. Azithromycin at 500 mg was also started 3 times per week. Sputum cultures taken on March 18 and 28, 2020 showed no bacterial growth and the patient remains stable.

Discussion

There are many more mutations or variants that can affect the course, the clinical manifestations, and the severity of the disease (7-10). The diagnosis of CF with molecular biology techniques is based on the recommendations of the "Cystic Fibrosis Foundation" that uses the "*CFTR2 project database*" (11-13). Little is known about the mutation in exon 20 of the CFTR gene located on chromosome 7q31.2 known as c.3274T> C (p.Tyr1092His or y1092h) and identified in the *HGMD* (*The Human Gene Mutation Database*) with the code *Cm972958*.

According to *ClinVar* (*www.ncbi.nlm.nih.gov/clinvar/variation/495930/*), this mutation is classified as a variant of uncertain significance.

The *c.3274T> C* (*p.Tyr1092His*) mutation is not registered in the "*CFTR2 project*" database, but it is registered in the *HGMD* database. Neither are the two DNAAF4 c.1177C> T (p.Leu393Phe) and DNAAF5 c.1195G> A (p.Glu399Lys) mutations found in the "*CFTR Project*", and their clinical consequences are currently uncertain. The c.3274T> C (p.Tyr1092His) mutation has been found on a Caucasian chromosome in the United States. This mutation was also found in a 9-year-old patient diagnosed with asthma in which 2 chloride sweat tests were also undetermined: 58 and 52 mmol / L respectively, and sputum cultures were negative for Staphylococci and Pseudomonas. In Europe, the c.3274T> C mutation (p.Tyr1092His) was found in only one out of a total of 62 patients with CF evaluated in Italy and was reported as accompanying a CF-causing mutation or variant (14,15).

We believe that the *c.3274T*> C (*p.Tyr1092His*) mutation, together with the *DNAAF4 c.1177C*> T (*p.Leu393Phe*) and *DNAAF5 c.1195G> A* (*p.Glu399Lys*) mutations, are responsible for the clinical and functional manifestations and the progressive pulmonary lesions observed in the tomography of our patient. We also believe that they are the cause of the alterations of the biomarkers in chloride sweat tests and serum immuno reactive trypsin. Globally, the *c.3274T> C* (*p.Tyr1092His*) mutations has only been previously reported in 3 patients: two with CF and one with asthma. Although the present case did not involve CF, the genetic background of the patient is likely to underly the cause of her disease. The findings of this case suggest the need to study the presence of possible mutations in cases of suspected CF or bronchiectasis of unknown cause.

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Contribution of the authors

All authors participated in the entire research process.

Interest conflict

We declare no conflict of interest.

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