CASE REPORT

Can we change a genetically determined future?

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SUMMARY

We describe the clinical evolution of the first patient diagnosed with a severe α-1 antitrypsin (AAT) deficiency caused by a rare null allele (Q0Ourém), over the past 18 years. We highlight the clinical course of the disease as well as the evolution of the pulmonary function tests from initial diagnosis and the benefits of augmentation therapy for this specific condition. We report the case of a 43-year-old man with exertion dyspnoea who was observed in our pulmonology unit. The unexpected findings in the complementary examinations led us to diagnose AAT deficiency and to the discovery of a new mutation with the SERPIN A1 gene (hence named Q0Ourém) responsible for the disease. Augmentation therapy was initiated, as is the protocol in this condition. Eighteen years after the diagnosis, the patient is clinically stable, fully autonomous and maintaining an acceptable quality of life, despite severe obstructive lung disease.

BACKGROUND

α-1 Antitrypsin (AAT) deficiency is one of the most common genetic conditions in European descent populations and can result from a variety of mutations with distinct functional consequences.[1] A common point is the loss of anti-elastasic activity, fundamental to protect lung tissue against the action of neutrophils. Null alleles are rare and their consequences are less predictable.[2] AAT deficiency is probably often overlooked, but should not be ruled out, particularly if the clinical context is suggestive, as adequate treatment and follow-up can truly alter a genetically determined future.

CASE PRESENTATION

We describe the case of a 43-year-old Caucasian man, born and residing in central Portugal (in the village of Ourém), who worked in building construction.

In the first consultation, the patient gave a history of dyspnoea, dry cough (daily) and wheezing (more occasionally) starting 2 years prior. All complaints were associated with moderate exertion (weight bearing, fast walking) and were predominantly nocturnal. Complaints had arisen 1 month after having started a part time job in an aviary. Symptoms were relieved by dawn, with resurgence in the evening, but progressive worsening of symptoms continued even after 6 months of cessation of occupational activity.

The patient had been previously treated with Betamethasone tablets, 2 mg, once daily with improvement of symptoms during treatment, but with relapse after stopping medication. Medication was switched to beclomethasone inhaler pressurised, 250 μg/dose twice daily associated with salbutamol pressurised inhaler, 100 μg/dose, as needed, with improvement, which he continued later as SOS in periods of increased intensity of symptoms.

With continuous exposure cessation, the patient's complaints (exertional dyspnoea, cough and wheezing) diminished, but normal health was never fully restored.

The patient's medical history included: diphtheria at the age of 7 years; present moderate alcohol consumption and a past smoking habit with 13 years of exposure (former smoker for 10 years of 12 pack-years) with no regular medication. There was no history of respiratory disease among his relatives.

Physical examination revealed a patient in good overall condition and nutrition, eupnoeic at rest. Aside from bilateral diminished breath sounds, heart and lung auscultation showed no other alterations. The remaining physical examination was normal.

INVESTIGATIONS

Pulmonary function tests (table 1) revealed severe obstruction with hyperinflation and reduced diffusing capacity for carbon monoxide (DLCO). Arterial blood gases in room air showed a slightly hypoxaemic respiratory insufficiency (PO2 79 mm Hg, PCO2 34.9 mm Hg). Laboratory evaluation revealed peripheral eosinophilia (536 eosinophils/mm^3), elevated haematocrit (46%) and elevated serum total IgE (100 UI/mL). Skin prick allergy tests were negative (for standardised aeroallergens, according to the recommendations of the European Academy of Asthma, Allergy and Clinical Immunology[3]) as well as aviary antigens. Chest X-ray showed classic signs of hyperinflation. Peripheral eosinophilia disappeared after one dose of mebendazole 100 mg (repeated 15 days later).

We diagnosed Chronic Obstructive Pulmonary Disease (COPD)—grade B (current GOLD—50% FEV1, MRC 2, low risk of exacerbations).[4] Owing to these changes (unexpected for age and mild exposure to risk factors), we decided to proceed with further investigation with a thorax CT scan, which showed changes consistent with panlobular emphysema predominantly in the lower lobes (figure 1).

Given the extent of findings consistent with extensive emphysema, but discrepant with the context of exposure, serum AAT measurements were performed. Serum levels <0.10 g/L led us to carry out immunoelectrophoresis phenotyping, which revealed a ZZ phenotype.

TREATMENT

After the initial diagnosis of AAT deficiency the patient was prescribed a salmeterol pressurised

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Table 1 Pulmonary function tests—evolution from the diagnosis to present time (performed according to the ATS criteria)

	Pulmonary function tests								
	At presentation			Before starting augmentation therapy (3 years after diagnosis)			Present time (after 15 years of augmentation therapy)		
	Measured	% of predicted	Post-BD*	Measured	% of predicted	Post-BD*	Measured	% of predicted	Post-BD*
FVC (mL)	4900	115	+3	5560	125	−2	5100	126	+8
FEV1 (mL)	1650	50	+10	1420	44	+7	1200	38	+10
FEV1/FVC	–	34	–	–	26	–	–	24	–
RV (mL)	3620	143	– 30	3560	147	–	3490	142	–
TLC (mL)	9200	140	–10	9120	149	–	8590	126	–
RV/TLC	–	40	–	–	39	–	–	41	–
DLCO	5.8 mmol/KPa/min	45	–	5.5 mmol/KPa/min	45	–	11.3 mL/mmHg/min	41	–
DLCO/VA (DLCO/L)	0.77	42	–	0.72	40	–	1.6	31	–

ATS, American Thoracic Society; BD, bronchodilator; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; VA, alveolar volume.
*After 400 μg of inhaled salbutamol.

inhaler, 50 μg/dose, twice daily, beclomethasone, pressurised inhaler, 250 μg/dose twice daily, aminophylline 225 mg tablets, twice daily and salbutamol 100 μg/dose for SOS situations.

He remained stable for about 18 months, maintaining mild exertion dyspnoea and cough with discrete mucus sputum. The patient continued working with mild limitation to heavier work and no limitation in his personal life.

As part of the evaluation protocol of patients with a ZZ phenotype, a complementary study was carried out with liver biopsy, which showed no morphological criteria compatible with the clinical diagnosis (figure 2).

In the absence of liver disease (being universal in patients with phenotype PiZZ), we decided to undertake a new genetic study, this time using genetic sequencing and not just immunoelectrophoresis. Genetic studies revealed the presence of a homozygous null allele (mutation L353fsX376) first described by S Seixas *et al*[1] and hence named Q0Ourém.

The patient maintained his background therapy for COPD (meanwhile he was prescribed with fluticasone propionate, 500 μg diskus, twice daily; salmeterol pressurised inhaler, 50 μg/dose, twice daily; Aminophylline 225 mg tablets twice daily; Tiotropium, HandiHaler, 18 μg, once daily and anti-flu vaccination yearly).

Three years after diagnosis, the patient presented with worsening dyspnoea on exertion and his pulmonary function tests had deteriorated (table 1).

Given the situation, and according to the established criteria,[2] we decided to start enzyme replacement treatment with human AAT, which the patient still continues monthly as an outpatient. He has never had allergic reactions or intolerance to the drug. Prior to the onset of treatment, the patient underwent hepatitis B, C and HIV tests, which he has continued on a regular basis; the results have always been negative.

OUTCOME AND FOLLOW-UP

Currently, the patient has been followed for 18 years in our unit, with monthly replacement of AAT in the past 15 years. Since then, he has had an average of one exacerbation every 1.5 years, and has only needed hospitalisation on four occasions. In May 2010, the patient presented with healthcare associated pneumonia with severe respiratory failure requiring hospitalisation in the intensive care unit and mechanical ventilation. At discharge, he had a pO_2 of 54 mm Hg, and therefore started with long term domiciliary oxygen therapy (1.5 L/min)

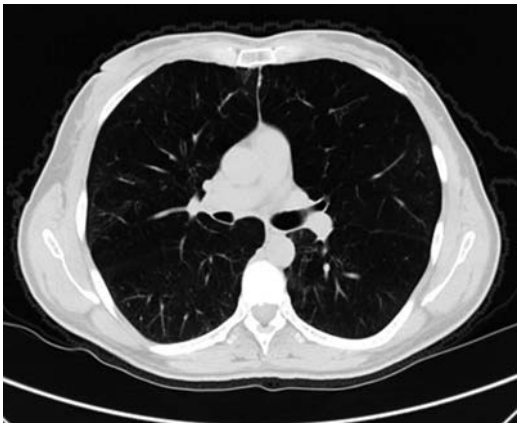

Figure 1 Sagittal section of thoracic CT scan: changes consistent with panlobular emphysema predominantly in the lower lobes.

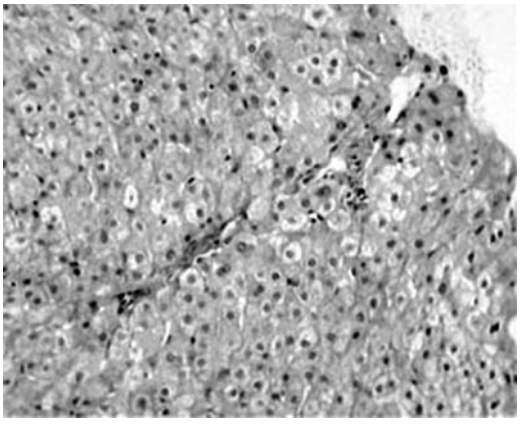

Figure 2 Liver biopsy: liver architecture preserved; liver cells positive for PAS and negative by diastase reaction—no morphological criteria compatible with the diagnosis of α1-antitrypsin deficiency ZZ phenotype.

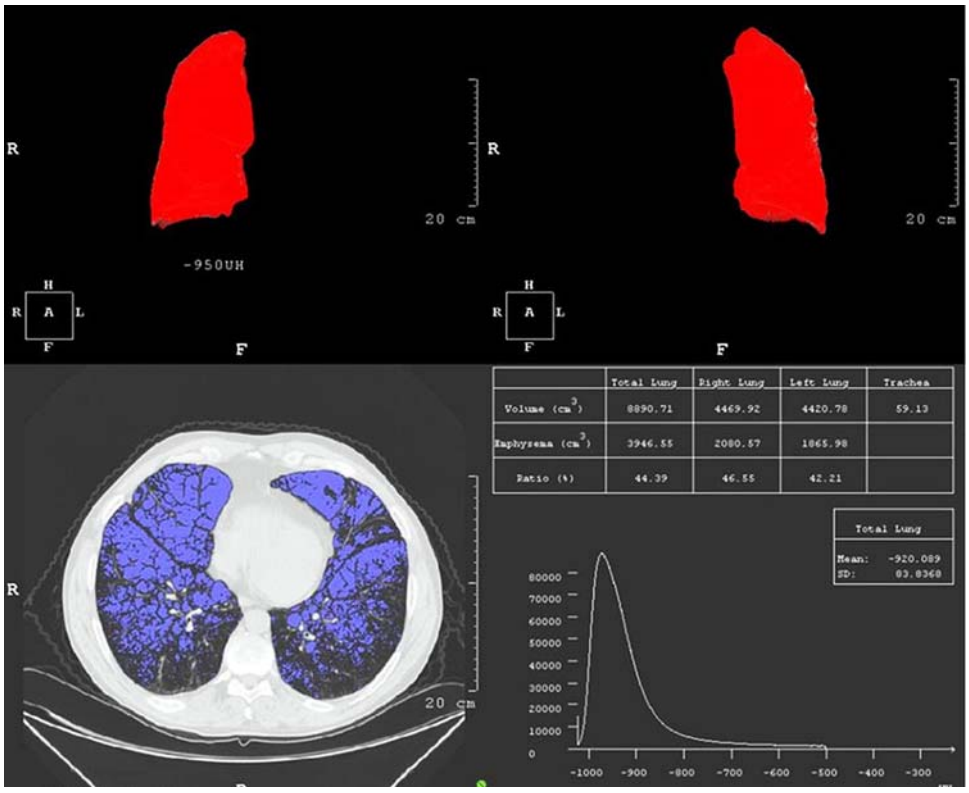

Figure 3 Thoracic CT scan with quantification of emphysema: In the top image, three-dimensional reconstruction of the lungs: red areas represent lung with a density equal to or less than −950 HU (Hounsfield units); the image below is a sagittal section presenting the same areas shown in blue. Total percentage of emphysema −44.39%.

with correction of hypoxaemia. Later emergence of essential hypertension, hyperuricaemia and hypercholesterolaemia, have been controlled. Thoracic CT scan with quantification of emphysema (13 years after diagnosis) revealed a total of 44.39% of emphysema (figure 3).

At the present time, the patient is clinically stable, fully autonomous and maintaining an acceptable quality of life despite severe impairment of lung function tests (table 1).

DISCUSSION

To the best of our knowledge, this is the first description of the clinical evolution of a patient with severe AAT deficiency caused by this specific null allele (Q0Ourém).

We highlight the need for a high clinical suspicion to pursue the correct diagnosis of this disease (which led us to question the first ZZ phenotype and drove us to perform full genetic sequencing, which ultimately allowed the correct identification of this mutation).

As expected, by the in vitro studies previously performed,[5] the disease seems to be restricted to the lung tissue, which is in agreement with the postulated mechanism of action of the mutation[1] (ie, known to produce a premature stop codon that leads to the formation of a truncated protein, which is still secreted by the hepatocytes, but rapidly degraded within the bloodstream and therefore will not be able to exert its protective effect). No hepatic lesions were observed in this patient (neither on diagnosis nor throughout the evolution of the disease).

The clinical findings and pulmonary function deterioration observed in this case are in agreement with the findings observed in other patients with this specific mutation[6] as well as in other patients with different null mutations described in previously published papers.[7 8] Augmentation therapy provided clinical improvement, even without functional enhancement (table 1), which is also in agreement with the majority of published papers regarding this type of therapy[2] (even though most of them are not null allele cases).

Learning points

- Chronic obstructive pulmonary disease (COPD) is a prevalent disease with significant implications for patients, including clinical, social and economic burdens. Smoking is the main risk factor but genetic determinants of COPD—SERPINA1 mutations—although much rarer, should not be set aside, particularly if the clinical and/or family history is compatible.
- The existence of null alleles is a rare phenomenon and pathophysiological consequences are less predictable.
- Genetic sequencing should be regarded as the gold standard in molecular characterisation of α1 antitrypsin deficiency (A1AT).
- Family screening is mandatory because it allows early intervention, particularly in changing risk factors such as smoking, early diagnosis and treatment, which are fundamental aspects in the prevention and treatment of COPD.
- The onset of A1AT augmentation therapy, when indicated, may provide an improvement in quality of life, with symptom relief and fewer exacerbations, thus contradicting a genetically determined bleak future.

The finding of this novel mutation prompted further evaluation.[1 6] This mutation is thought to have originated in the middle ages, in the region of Ourém, Portugal, and then geographically dispersed, being subsequently identified in other regions of mainland Portugal.

After the discovery of this new mutation, family screening was carried out. Screening of close relatives allowed the detection of four children carrying the mutation—four heterozygotes (3 MQ0 and 1 SQ0).[6] Evaluation of the other relatives showed seven individuals carrying the mutation (3 Q0 homozygous and 4 heterozygous). This family screening allowed an early intervention, especially in younger relatives (prevention of smoking or smoking cessation, genetic counselling and early diagnosis and treatment).

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