Delayed diagnosis of cystic fibrosis associated with R117H on a background of 7T polythymidine tract at intron 8

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Abstract

We report late diagnoses of cystic fibrosis (CF) in two men aged 61 and 65 years. At the time of presentation, both patients had significant pulmonary disease. In each case two CFTR gene mutations were identified, including R117H on a background of a poly T genotype of 7T/9T. Patients with two identified CFTR mutations which include the R117H/7T anomaly should be followed up routinely as they remain susceptible to severe lung disease.

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1. Introduction

Over 1000 CFTR mutations have been identified and classified into various functional classes according to the mechanisms by which they produce quantitative or qualitative changes in CFTR function. The amount of functioning CFTR appears to be related to clinical status with some ‘milder’ mutations presenting with congenital absence of vas with or without mild respiratory disease [1–4]. However the spectrum of mutations in the CFTR gene gives rise to a very variable clinical phenotype that may not be predictable from the genotype alone due to the influences of other factors such as the environment and the absence or presence of modulator genes.

We report late diagnoses of CF in two elderly men, both of whom had an R117H mutation on a background of a poly T genotype of 7T/9T.

1.1. Case 1

A 61-year-old man was admitted with a 7-month history of progressive weight loss, dyspnoea, cough and fever. There was no family history of cystic fibrosis (CF).

Ten years earlier, he had undergone an oesophagogastrectomy followed by chemotherapy for T3 N1 M0 oesophageal carcinoma. At the age of 27 years, he had been investigated for male infertility and was found to have obstructive azoospermia. On examination he was pyrexial and cachectic with significant muscle bulk loss. He had mild finger clubbing with coarse left basal crackles.

Chest radiograph (CXR) and computed tomography (CT) showed bronchiectasis with left lower lobe collapse and consolidation. Abdominal CT showed a fatty, atrophied pancreas. There was no evidence of tumour recurrence. Forced expiratory volume (FEV1) and Forced Vital capacity (FVC) were 2.18 l/s (60% predicted) and 3.0 l (65% predicted), respectively. Sputum and bronchoscopic lavage cultured Mycobacterium avium complex (MAC), Stenotrophomonas maltophilia, Acinetobacter xylosoxidans and Aspergillus fumigatus. C reactive protein, white blood cell count and plasma viscosity were elevated at 182 mg/l, 16 10⁹/l and 2.5, respectively.
The clinical history, radiological evidence of bronchiectasis, and significant pancreatic atrophy suggested CF. Sweat tests showed a sodium concentration of 62 and 55 mmol/l and chloride concentrations of 56 and 48 mmol/l. Genetic analysis demonstrated N1303K and R117H with a poly T genotype 9T/7T. Faecal pancreatic elastase was less than 15 µg/g and confirming pancreatic insufficiency. Following the introduction of nasogastric feeding and corticosteroids for possible cryptogenic organising pneumonia, he developed insulin dependent diabetes mellitus.

He was treated with broad spectrum intravenous antibiotics, oral steroids and 18 months triple therapy for MAC infection. Overnight nasogastric feeding was followed by the insertion of a jejunostomy feeding tube. A year following the diagnosis his weight had increased by 15 kg and he has regained a good exercise tolerance.

1.2. Case 2

A 64-year-old man presented with symptoms of progressive shortness of breath and increased chronic sputum production. As a child he had suffered from persistent cough, sinusitis and nasal polyps. He had been diagnosed with childhood asthma and then adult bronchiectasis. At the age of 40 years he had been forced to take early retirement on medical grounds. There was no family history of CF.

Chest X-ray and CT demonstrated predominately upper lobe bronchiectasis and right upper lobe fibrosis with volume loss. Sputum grew non-mucoid P. aeruginosa. He was pancreatic sufficient. CFTR genotype analysis revealed delta 508 and R117H with a poly T genotype 9T/7T.

Despite several courses of intravenous and nebulised antibiotics, he remained chronically infected with P. aeruginosa. He was commenced on long term nebulised colomycin, oral azithromycin and bronchodilator therapy. Sputum volume fell dramatically and lung function, exercise tolerance and general well-being improved.

2. Discussion

Doubts have been expressed over the diagnosis of cystic fibrosis in patients with R117H with a background 7T polythymidine tract at intron 8. This is because the R117H is an exon 4 missense mutation which affects exon 9 splicing and is influenced by the polythymidine sequence of intron 8 which precedes the splicing receptor site. This polythymidine tract is polymorphic with sequences of 5, 7 and 9 thymidines [5]. Because CFTR missing exon 9 splicing is non functional and exon-9 splicing is inversely proportional to the length of the thymidine sequences, the 9T variant allows normal reading of the gene while the 5T variant is considered to be a mild mutation with incomplete penetrance and is associated with the highest level of non-functional CFTR protein [5]. The commonest polymorphism is the seven thymidine (7T) variant [2,5]. The presence of R117H/DF508 on a background of 5T is associated with elevated or borderline sweat test, moderate lung disease, pancreatic exocrine sufficiency and male infertility while R117H/DF508 in association with 7T is associated with a normal, borderline or elevated sweat test and variable clinical presentation [1–4,6–8] R117H in association with 9T is very unusual but has been reported [5].

Some authors have suggested that R117H with a 7T allele should not be considered as a true mutation unless associated with a positive sweat test [9,10]. While R117H is associated with a broad phenotype, it is often associated with a normal or borderline sweat test despite the presence of sino pulmonary disease. Long term follow up studies of asymptomatic individuals are needed to clarify the risk of developing CF in this group of patients [6,11,12]. Taylor et al. reported the cases of three infants with DF508/R117H genotype on a 7T/9T background identified through routine screening. They had no sino pulmonary disease, normal pancreatic function and sweat test results which were not indicative of CF [13]. However on subsequent follow up two patients developed respiratory infections with typical CF pathogens including Staphylococcus aureus, Haemophilus influenzae and P. aeruginosa.

3. Conclusion

The presence of two CF mutations including R117H with a 7T allele can be associated with late presentation and severe lung disease. Patients with this genotype should be followed up, including sputum surveillance, to allow appropriate early intervention by the multidisciplinary team.

References


