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CFTR:F508d/A613T Mutation Is Associated With Recurrent Episodes of Pancreatitis

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Abstract: Pancreatic insufficiency (PI) is found in 85% of individuals with cystic fibrosis (CF). Of the remaining who are pancreatic sufficient (PS), there is potential for developing pancreatitis, and is described in ~20% of PS individuals. We report a case of a 17.5-year-old female presenting with acute recurrent pancreatitis (ARP) and PS, later diagnosed with CF. This is the first reported case of ARP in an individual with a *F508d/A613T* genotype. To date, there are only 6 other individuals with this genotype, and the mechanisms of it causing ARP and no overt respiratory symptoms of CF are unclear. Her diagnosis occurred 10 years after her initial presentation of pancreatitis, highlighting the importance of screening for CFTR mutations in the workup for ARP with no clear etiology.

Key Words: cystic fibrosis, pancreatic sufficiency, acute recurrent pancreatitis, delayed presentation

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease of the *CFTR* gene. Over 2000 *CFTR* mutations have been found to date,[1] with different CF genotypes having specific clinical phenotypes. Pancreatic insufficiency (PI) is found in 85% of individuals with CF. Of the remaining who are pancreatic sufficient (PS), there is potential for developing pancreatitis, reported in approximately 20% of PS individuals with CF.[2] We present a case of an adolescent female with delayed diagnosis of CF due to presentation of recurrent episodes of pancreatitis and no overt respiratory or other gastrointestinal (GI) symptoms.

CASE REPORT

A 17.5-year-old female with a past medical history significant for acute recurrent pancreatitis (ARP) was seen at the outpatient GI clinic. She was referred by the emergency department (ED) after presenting with a 1-week history of abdominal pain, nausea, steatorrhea, and a low-grade fever. She had a previous episode of pancreatitis requiring hospitalization for one week at the age of 7 years, with severe abdominal pain and elevated lipase and amylase (Table 1). Over the last 10 years, she had experienced monthly episodes of abdominal pain and steatorrhea that were self-managed with Tylenol and clear fluids. These episodes of pain were associated with an average of 6 missed school days per semester. Reported triggers include high-fat foods and alcohol. To limit recurrences, she recently switched to a vegan diet and restricted alcohol consumption. Her parents are of English/Scottish and Irish/Italian descent and nonconsanguineous. A paternal aunt had alcohol-related chronic pancreatitis; no known relatives had CF or lung disease. BMI was 25 kg/m^2 (85th centile) with weight at 86th percentile and height at 44th percentile. Respiratory and abdominal examinations were normal, and no digital clubbing was noted.

Further testing and imaging were obtained to determine the etiology of ARP and to evaluate for evidence of PI. She had normal laboratory results, including CBC, glucose, albumin, renal function, liver enzymes, bilirubin, calcium, triglycerides, inflammatory markers, and fat-soluble vitamins except a low vitamin D level (Table 1).

Abdominal ultrasound did not show radiographic signs of gallstones, pancreatitis, or complications.

Magnetic resonance cholangiopancreatography (MRCP) did not show pancreatic divisum, or annular pancreas. Fecal elastase at baseline was normal. IgG4 was slightly above normal range. Referral was sent to genetics to look for hereditary causes of pancreatitis; however, 1 week after the initial consultation, her sweat chloride test was performed and was elevated (Table 1). She was urgently referred to the CF clinic and underwent genetic testing for *CFTR* variants. Initial testing of common *CFTR* mutations revealed a single *CFTR F508d* mutation. This prompted further genetic sequencing which showed a second variant: *CFTR p.A613T* (*c.1837G>A*). Given age and diagnosis, her care was transferred to adult pulmonology and gastroenterology. She subsequently demonstrated normal pulmonary function tests and a normal lung CT.

DISCUSSION

Most CF patients are pancreatic insufficient[2]; however, certain mutations of the *CFTR* gene are associated with pancreatic sufficiency, which can present with features such as ARP and lack the common respiratory or GI complications.

A recent literature review highlighted 19 individuals who were initially diagnosed with chronic pancreatitis (CP) or ARP and subsequently had a CF diagnosis.[3] The average length of delay in CF diagnosis was 4 years, ranging from 0 to 15 years. In our patient, the time from her initial presentation of pancreatitis to a CF diagnosis was 10 years. To ensure timely diagnosis and management, we recommend testing for *CFTR* function be included in all patients with recurrent episodes of pancreatitis with no clear etiology. To this point, individuals with mutations that are predicted to be responsive to *CFTR* modulation may benefit from treatment with CFTR modulators in reducing episodes of pancreatitis.[4]

Risk factors for ARP in CF include pancreatic sufficiency. Our patient had a normal fecal elastase at baseline. She reported

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Written consent from the patient was obtained to publish this case report.

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TABLE 1. Select relevant patient laboratory tests with normal reference ranges

Laboratory test	Initial presentation (2010)	Emergency department presentation (2019)	GI clinic consultation (2019)	Cystic fibrosis clinic (2020)	Normal range
Amylase (U/L)	395	494	169		28–100
Lipase (U/L)	155	345	80		13–60
Calcium (mmol/L)	2.6		2.39		2.1–2.55
Triglycerides (mmol/L)	1.65		0.85		<1.7
CRP(mg/L)			2.2		<5
25-OH Vitamin D (nmol/L)			70		75–250
IgG4 (g/L)			2.25		0.11–1.57
Fecal elastase (mcg/L)			>500		>200
Sweat chloride (mmol/L)			104	98	<30 [30–59 (indeterminate)]
Pulmonary function test (%)				FEV1: 99 FVC: 95 FEV1/FVC: 92 TLC: 105 RV: 138 DC: 113	FEV1: 80–120 FVC: 80–120 FEV1/FVC: >75 TLC: 80–120 RV: 65–135 DC: 80–120

CRP = C-reactive protein; DC = diffusion capacity; FEV1, forced expiratory volume; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

steatorrhea with episodes of pain, which could be transient exocrine PI; however, she self-managed at home and did not seek medical attention, so it is uncertain if her baseline fecal elastase changed during these occurrences. She had other risk factors for ARP outside of PS CF that may have influenced the development of pancreatitis, including alcohol consumption and a BMI at 85th centile, which is considered overweight in pediatrics and females.

Of the different CF mutations reported by Baldwin et al[3] in patients presenting with ARP, no patient had a *CFTR*: *F508d/A613T* genotype. This is the first reported case of ARP in an individual with this genotype. The *CFTR F508d* mutation is the most common mutation found in individuals with CF, either as a homozygous recessive pair or as a part of a compound heterozygous genotype. In contrast, *CFTR:p.A613T*, a class II missense mutation,[5] has only been reported in 6 other individuals.[6] Given the reported phenotypes, it is reasonable to assume that *A613T* is associated with a mild genotype. Existing data demonstrate that mild mutations, as determined by PI prevalence scores (PIP), are more likely to develop pancreatitis.[7] Of note, class II mutations are typically associated with clinically severe disease; however, this does not appear to be the case in the reported individuals with *A613T* mutations. Further research is warranted to better understand the mechanism.

Our patient's CF diagnosis was made with the elevated sweat chloride,[8] and genetic testing was performed to determine the genotype. Initial testing revealed only a single *F508d* mutation.

Additional genetic sequencing was performed which detected the *A613T* mutation. While less diagnostically relevant for our patient, it is important to note that individuals with ARP and a single *CFTR* mutation and/or an intermediate sweat chloride should have additional genetic tests to detect rare variants to differentiate CF from *CFTR*-related disorders.[8]

Our case highlights the importance of screening for CF in individuals presenting with recurrent pancreatitis even if clinical signs of pulmonary disease and other typical features of CF are absent. Early detection in this case would have led to more timely management of symptoms through the involvement of an interprofessional health team, reduced hospital visits, and improved quality of life.

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