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DIABETIC Medicine

LETTER

Diabetic ketoacidosis as a unique initial presentation of cystic fibrosis

1 | BACKGROUND

Cystic fibrosis–related diabetes (CFRD) is an increasingly common complication of CF as life expectancy of people with the condition increases. The pathophysiology differs from type 1 and type 2 diabetes. In CFRD, there is a reduced and delayed insulin response to carbohydrates while basal insulin is often spared. Many people with CF have abnormally high glucose levels at intermediate time points of an oral glucose tolerance test despite meeting conventional criteria for normal glucose tolerance. This pattern of transient postprandial hyperglycaemia also means that a normal HbA1c in persons with CF does not reliably exclude CFRD.[1] Aggressive screening and early institution of insulin has been reported to be associated with reduced mortality, but there are differing opinions on whether good glycaemic control does modify the course of CF. For example, the rationale for treatment with insulin in CFRD may include reducing the impact on lung function and infection risk.[1,2] However, it is important to differentiate CFRD from other forms of diabetes as the insulin regime and treatment rationale are different.

2 | CASE PRESENTATION

A 45-year-old man presented to the emergency department with a two-to-three-week history of feeling unwell with nausea and vomiting. He also described unintentional weight loss of 15 kg over the preceding 3 months. He did not complain of polydipsia or polyuria.

He reported a history of depression and anxiety but no known history of diabetes or acute pancreatitis. His father had two brothers who died of pulmonary tuberculosis in childhood. There was no known family history of diabetes or hemochromatosis. The participant is a pharmacist, a non-smoker and stopped drinking alcohol 5 years previously.

Blood tests on admission are presented in Table 1.

After initial fluid resuscitation lactate was 1.3; acidosis persisted (pH 7.15) and ketones remained elevated. A chest X-ray demonstrated a left upper zone patchy opacification, indicative of an infective process, a normal right lung and normal cardiac shadow.

Computed tomography of the thorax, abdomen and pelvis (CT TAP) suggested a left upper lobe pneumonia. Calcification was noted in the pancreas indicative of chronic calcific pancreatitis of uncertain aetiology. The pancreas appeared atrophic with no acute changes identified (Figure 1).

2.1 | Diagnosis

The initial diagnosis was ketoacidosis precipitated by a lower respiratory tract infection in a participant without known diabetes. Based on the clinical presentation and history, it was thought that the participant most likely had autoimmune type 1 diabetes.

2.2 | Treatment

The participant was educated on diabetes and insulin administration and discharged on a basal bolus insulin regimen.

2.3 | Outcome and follow-up

At out-patient follow-up the participant's Hba1c was 6% (42 mmol/mol), anti-GAD antibodies and islet cell antibodies were undetectable, insulin was 1.2 μU/ml (2.6–24.9), and C-peptide levels were 0.38 ng/ml (1.1–4.4), with a glucose of 9.2 mmol/l. He reported frequent hypoglycaemic episodes on insulin glargine 11 units once daily and insulin aspart 2 units three times daily with meals. Even when taking 1–2 units of insulin aspart with a large

carbohydrate meal, he was apt to have hypoglycaemia postprandially. Anti-GAD antibody was repeated and was again undetectable.

It was felt that he may have entered a honeymoon period of type 1 diabetes. However, the participant revealed that his brother had recently been diagnosed with CF in his thirties when he and his wife were being investigated for primary infertility. The participant asked as to whether he too could have CF. He reported that throughout his life he experienced profuse sweating in hot environments and had experienced several near-syncopal episodes during exercise. He had undergone extensive investigation for these episodes with no cause found. He reported no pulmonary problems prior to his admission with ketoacidosis. He had never attempted to father a child.

Considering this new information in the setting of GAD antibody negative diabetes, a sweat test was performed. The sweat sodium level was 104 mmol/l (<60), supporting a diagnosis of CF. Genetic testing for CF was performed, and this demonstrated that the participant was heterozygous for pPhe508del and pARG117His variants with 5T variant in intron 8 (formally 5T/9T), confirming a diagnosis of CF. The participant reported significant diarrhoea and a faecal elastase was measured at <15 μg/g stool (<100 consistent with severe pancreatic exocrine insufficiency). Commencement of pancreatic enzyme replacement ameliorated his bowel symptoms. A repeat chest X-ray demonstrated almost complete clearing of the prior infection. Pulmonary function testing demonstrated a mildly obstructive pattern without significant reversibility, mildly increased residual volume and mildly reduced diffusion capacity.

During follow-up, the participant temporarily discontinued insulin due to tight control with frequent hypoglycaemia. As he moved residence, he has not been seen recently in our clinic but reports being well controlled on basal-bolus insulin.

TABLE 1 Laboratory values on admission

Test	At presentation	Reference range
Arterial pH	6.89	(7.32–7.43)
Glucose	38 mmol/l	(3.9–6.1)
$PC0_2$	4.7 mmol/l	(4.6–6.4)
Lactate	7.0 mmol/l	
HCO_3^-	2.8 mmol/l	(22–26)
Ketones	6.5 mmol/l	
HemoglobinA1c (HbA1c)	13.4% (123 mmol/mol)	(4.3–6) (23–42)
C-reactive protein	267 mg/l	(0–5)
Amylase	14 U/l	(28–100)
Sodium	131 mmol/l	(136–145)
Potassium	4.9 mmol/l	(3.5–5.1)
Urea	11.9 mmol/l	(2.8–8.1)
Creatinine	127 μmol/l	(59–104)
Phosphate	1.52 mmol/l	(0.81–1.45)

3 | DISCUSSION

CF is an autosomal recessive disorder caused by a mutation of the CF transmembrane conductance regulator (CFTR) gene. CF is the most common autosomal recessive condition in white populations with an incidence of 1 in 2500 live births. CF is caused by the presence on both alleles of at least one of 2000 known mutations in the CFTR gene. It is characterized by chronic pulmonary infections, pancreatic insufficiency, biliary cirrhosis, low BMI, male infertility and increasingly CFRD. In people with CF, the incidence of CFRD increases with increasing age with up to 50% of adults with CF developing CFRD by adulthood. It is characterized by insulin deficiency and periods of reduced insulin sensitivity. Postprandial hyperglycaemia with normal fasting glucose levels is the most frequently seen abnormality. CFRD has been reported to be associated with accelerated pulmonary function decline, poor nutritional status and excess mortality. The deleterious clinical outcomes associated with CFRD can start prior to the usual thresholds for diabetes being reached. Some guidelines, therefore, now recommend using continuous

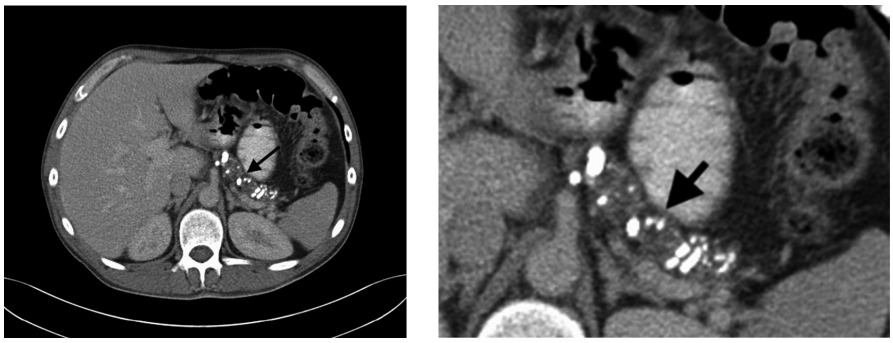

FIGURE 1 CT TAP demonstrating atrophic, extensively calcified pancreas (black arrow)

glucose monitoring to help identify dysglycaemia in patients with CF.[1]

The severity of disease in an individual with CF is determined by the least severe CF mutation they carry. In most white populations, F508del is the most common mutation, and patients homozygous for this mutation have severe disease. Our participant had one F508del, a 3 nucleotide deletion that removes the phenylalanine residue at position 508 of CFTR resulting in misfolding of the CFTR protein. The second mutation in our participant, R117H, is a missense mutation that can result in a wide variety of clinical features including pancreatic insufficiency, congenital bilateral absence of the vas deferens (CBAVD) and chronic pulmonary disease, but interestingly some patients have normal lung function and normal pancreatic function. The 5T variant in our participant is usually associated with a high level of non-functional CFTR, and it is perhaps surprising that he did not have more severe multi-organ involvement.[3] In recent years, CF screening programs have been developed across Europe; however this does not preclude the diagnosis of milder forms of CF in adulthood or the development of CFRD in cases of unknown CF diagnoses as screening programs can only test for a small subset of the approximately 2000 mutations associated with CF. In addition, there has been debate regarding whether R117H mutations should be included in new-born screening programs, so cases such as the one described here may not consistently be diagnosed at screening.[4]

Ketoacidosis is thought to be rare in people with CFRD, although ketoacidosis has previously been reported as the initial presentation of CFRD in a patient with known CF.[5] Our patient had a low C-peptide, in keeping with insulin deficiency, but his antibodies were negative suggesting that his diabetes was not autoimmune in origin. Intercurrent infection has been reported to be a cause of ketoacidosis in CFRD, and we believe that the lower respiratory tract infection, which the participant experienced, was the precipitant for his ketoacidosis. To our knowledge, this is the first case of a new diagnosis of CF following a first presentation of diabetes with ketoacidosis.

KEYWORDS

cystic fibrosis diagnosis, cystic fibrosis related diabetes, diabetes diagnosis, diabetic ketoacidosis

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CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

This study was not related to either human or animal experimentation.

INFORMED CONSENT

Informed consent was obtained from the participant included in the case report.

Michelle Sugrue
Anne Marie Liddy
John H. McDermott
Seamus Sreenan

Department of Diabetes and Endocrinology, Royal College of Surgeons in Ireland, Connolly Hospital, Blanchardstown, Ireland

Correspondence
Seamus Sreenan, Department of Diabetes and Endocrinology, Royal College of Surgeons in Ireland, Connolly Hospital, Blanchardstown, Dublin 15, Ireland.
Email: seamus.sreenan@hse.ie

ORCID

Seamus Sreenan https://orcid.org/0000-0003-2457-2612

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