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Case Report

Chronic Calcific Pancreatitis, Type IIIc Diabetes Mellitus: A Case Report from Chennai, India

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ABSTRACT

Diabetes Mellitus (DM) encompasses a spectrum of metabolic disorders, with type 3c DM, also known as pancreatogenic diabetes mellitus, arising secondary to pancreatic disease. Despite its prevalence, type 3c DM remains significantly underdiagnosed due to overlapping symptoms with type I and type II DM, complicating the differentiation process. This case report features a 53-year-old male patient who came with complaints of epigastric pain for the past 2 days. The patient is a known case of chronic pancreatitis, had elevated blood glucose, lipase, and liver enzyme level, and had a weight loss of about 15 kg in the last 10 years. CT Abdomen suggested chronic calcific pancreatitis with multiple intraductal calculi and mild central intrahepatic biliary radicle dilatation with mildly dilated common bile duct. From the above-mentioned evidence, the patient was diagnosed with Type 3c diabetes mellitus, which was initially misdiagnosed as Type 2 DM, benign biliary stricture of Common Bile Duct (CBD) and chronic calcific pancreatitis. The patient was treated with insulin and metformin for the hyperglycemic state. For chronic pancreatitis, ERCP was done and a stent was placed. Standardizing diagnostic criteria and increasing awareness among healthcare providers are essential steps toward improving the diagnosis and management of this often overlooked form of diabetes mellitus.

Keywords: Type 3c diabetes, Diabetes mellitus, Chronic pancreatitis, Pancreatogenic diabetes mellitus, Exocrine pancreatic insufficiency.

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INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disease characterized by persistent and recurrent hyperglycemia resulting from impaired insulin synthesis and insulin resistance, affecting more than 500 million people worldwide.[1] While type I and type II diabetes are well-known types of the disease, type3c remains significantly underdiagnosed despite being more prevalent than type I.[2] Based on standard classification criteria type I DM is characterized by the presence of autoantibodies and insulin requirements which are usually early in onset while type II diabetes is characterized by the absence of autoantibodies and insulin requirements and the presence of insulin resistance.[3] Type 3c diabetes mellitus, also termed pancreatogenic diabetes mellitus, refers to diabetes mellitus secondary to a condition or disease of the exocrine pancreas.[4] Among all diabetics, approximately 2% of all diabetic patients are diagnosed with type 3c DM.[2] The pathophysiology of pancreatogenic DM is multifactorial, various factors contributing to the mechanism include loss of mass of pancreatic cells, autoimmunity, local or systemic inflammatory response, genetic mutation in CFTR proteins, deficiency in fat-soluble vitamins such as A, D, E, and K, disruption in the insulin-incretin axis.[5] In type 3c diabetes, mechanisms such as inflammation, fibrosis, and hardening of endocrine tissue of the pancreas lead to the destruction of pancreatic acinar cells and islets of Langerhans.[1,5] This causes decreased insulin synthesis, reduced glucagon secretion by alpha cells, and decreased pancreatic polypeptide secretion from the PP cells causing hypoglycemia. Whereas hyperglycemia occurs by increased hepatic insulin resistance and decreased hepatic glucose production.[6] Patients with type 3c diabetes often have a history of pancreatitis, and can also develop it due to various genetic and non-genetic causes such as chronic pancreatitis (76%), hemochromatosis (8%), pancreatic cancer (9%), cystic fibrosis (4%), and previous pancreatic surgery (3%).[3] Chronic Pancreatitis (CP) refers to irreversible physiological alterations to the pancreas manifesting as persistent pain, dysglycemia, pancreatic insufficiency, and a higher risk of pancreatic cancer. The prevalence of type 3c diabetes in chronic pancreatitis accounts for about 70%. Causes of chronic pancreatitis include alcoholic pancreatitis, hereditary pancreatitis, autoimmune pancreatitis, traumatic pancreatitis, and pancreas divisum.[1] The risk of DM in chronic pancreatitis increases with an increase in the duration and severity of the disease.[5] Acute recurrent pancreatitis causes repeated parenchymal trauma leading to chronic pancreatitis,

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while severe episodes of acute pancreatitis can directly lead to the development of type 3c diabetes. Pancreatic insufficiency remains an early manifestation of type 3c diabetes while other major symptoms of type 3c diabetes include diarrhoea, abdominal pain, bloating, change inappetite, nausea, vomiting, and general fatigue. Apart from pancreatic disease, patients with type 3c DM may present similarly to those with type I and type II diabetes complicating the diagnosis and leading to misdiagnosis and mistreatment.[1,2]

CASE REPORT

A 53-year-old male patient came with complaints of epigastric pain (3/10) for the past 2 days. The patient also had a history of high-colored urine for the past 2 days and had been experiencing weight loss of about 15 kg in the past 10 years. The patient was initially treated in an outside hospital where USG (Ultrasonography) abdomen was done which suggested pancreatic intraductal calculi with the largest measuring 8 mm and atrophic pancreas and the patient's amylase and lipase levels were found to be elevated (Table 1). He is a known case of type II diabetes mellitus, Chronic pancreatitis, and dyslipidemia and has been taking T. metformin 500 mg BD, T. pancreatin 300 mg OD, and T. atorvas 40 mg HS respectively for the conditions. He underwent Cystoscopy+URSL (Ureteroscopic Lithotripsy) 20 years back and a DJ (Double J) Stent.

Computed Tomography (CT) abdomen suggested chronic calcific pancreatitis with multiple intraductal calculi and mild central intrahepatic biliary radicle dilatation with mildly dilated common bile duct. From the above-mentioned data, the patient was diagnosed to have acute on chronic calcific pancreatitis, benign biliary stricture of Common Bile Duct (CBD), and type 3c diabetes which was initially misdiagnosed as Type II diabetes mellitus. Endoscopic Retrograde Cholangiopancreatography (ERCP) was done and a stent was placed. The patient was prescribed pancreatin, pantoprazole, paracetamol, ondansetron, N-Acetyl Cysteine, atorvastatin, tramadol, and an antibiotic Sulbactam and cefoperazone combination. For the patient's hyperglycemic state, Insulin Aspart, regular insulin, Insulin Glargine, and metformin were prescribed (Table 2).

Once the patient's condition improved and he was in stable condition, he was discharged with antibiotic cefpodoxime and clavulanic acid, pantoprazole, pancreatin, silodosin, multivitamin, tramadol, and acetaminophen combination. Diabetic discharge medications include metformin 500 mg (1-0-1), insulin aspart (16U-14U-12U), and insulin glargine (0-0-16U). The review was scheduled at the Hepatology Outpatient Department (OPD), urology OPD, and internal medicine OPD.

Table 1: Laboratory investigations.

Parameter	Observed value	Normal value
Hematology		
Hemoglobin	14.7 g/dL	14-18 g/dL
RBC	5.3×10^6 cells/mm^3	$4.5\text{-}6\times10^6$ cells/ mm^3
PCV	46%	38-54%
MCV	87 fL	80-100 fL
TLC	10820↑	$4\text{-}10\times10^3$cells/ mm^3
Neutrophils	85.5%↑	40-60%
Lymphocytes	9.9%↓	20-40%
Eosinophils	0.3%	0-5%
Monocytes	4.1	4-8%
Basophils	0.2%	0-1%
Platelet	261000 cells/mm^3	1.5-4L cells/mm^3
Renal function test		
Serum Creatinine	0.76 mg/dL	0.8-1.3 mg/dL
Liver function test		
AST	234 U/L↑	0-40 U/L
ALT	362 U/L↑	0-30 U/L
ALP	241 U/L↑	50-160 U/L
Total Bilirubin	6.9 mg/dL↑	0.1-1.0 mg/dL
Direct Bilirubin	3.73 mg/dL↑	0.2-0.6 mg/dL
Albumin	4.3 g/dL	3.5-5.5 g/dL
Globulin	2.61 mg/dL	1.5- 3.5 g/dL
Albumin: Globulin ratio	1.7↑	1: 1
Prothrombin time	12.4s	11-14s
INR	1.02	0.9-1.2
Biochemistry		
CBG	312 mg/dL↑	70-140 mg/dL
Others		
CRP	5.3 mg/dL↑	0.3-1 mg/dL
Amylase	118U/L↑	30-110U/L
Lipase	250U/L↑	0-160U/L

DISCUSSION

Chronic Calcific Pancreatitis (CCP) is an inflammatory disease that affects the pancreas, causing calcification and scarring within the gland.[8] Individuals with chronic pancreatitis should be screened for blood glucose levels and HbA1c levels to assess diabetes. If diabetes is confirmed, further an autoimmune workup should be done to exclude late-onset type I DM.[4] CCP is one of the common causes for type 3c DM, which is often misdiagnosed or mislabelled. In this case, initially, the patient was incorrectly diagnosed with Type II diabetes mellitus. The patient

Table 2: Diabetic chart.

Time	Capillary Blood Glucose (CBG)	Drug	Dose
Day 1			
2 A.M	226 mg/dL	Monitoring	
6 A.M	236 mg/dL	Inj. Novorapid	4U
12 P.M	261 mg/dL	Monitoring	
6 P.M	309 mg/dL	T. metformin	500 mg
Day 2			
6 A.M	287 mg/dL	Inj. Actrapid	8U
12 P.M	358 mg/dL	Inj. Actrapid	8U
6 P.M	215 mg/dL	Monitoring	
Day 3			
6 A.M	185 mg/dL	Inj. Actrapid	4U
1 P.M	313 mg/dL	Inj. Actrapid	10U
6 P.M	260 mg/dL	Inj. Actrapid	10U
11 P.M	336 mg/dL	Inj. Actrapid	10U
Day 4			
6 A.M	177 mg/dL	Inj. Actrapid	8U
12 P.M	245 mg/dL	Inj. Actrapid	8U
6 P.M	276 mg/dL	Inj. Novorapid	8U
11 P.M	336 mg/dL	Inj. Lantus	8U
Day 5			
6 A.M	214 mg/dL	Inj. Novorapid	8U
12 P.M	336 mg/dL	Inj. Novorapid	15U

showed weight loss of about 15Kg in the last 10 years which is a sign of type IIIc diabetes, and the patient had chronic calcific pancreatitis which is a major risk factor for type IIIc diabetes and from the patient's USG report, the patient was later correctly diagnosed with Type IIIc diabetes. Hence, CT and MRI scans are recommended diagnostic tools for early detection of CCP.

The diagnosis of type 3c DM presents with greater challenges due to its potential overlapping and ambiguity in distinguishing it from other DM, however, it has a distinct clinical course, including poor glycemic control and a notable higher insulin need.[9] Longstanding cases of type I DM and type II DM also exhibit concurrent exocrine pancreatic insufficiency, further complicating diagnosis.[5] Additionally, individuals with diabetes face an elevated risk for acute and/ or chronic pancreatitis, with type II DM notably associated with a 1.86-2.89 times higher chance of developing acute pancreatitis based on an extensive retrospective analysis. Furthermore, a bidirectional relationship exists between acute pancreatitis and diabetes mellitus, where patients with acute pancreatitis can also develop type I and type II DM irrespective of exocrine pancreatic dysfunction.[5]

Uc *et al.* highlighted standardizing diagnostic criteria to differentiate type 3c diabetes from type I and type II as a critical research requirement.[7]

It has been found that about 40% of the inpatients with diabetes of the exocrine pancreas are misdiagnosed as type II DM. Currently, there are no available valid diagnostic criteria for type 3c DM.[9] Diagnostic parameters for type 3c include basic laboratory tests that are performed in type II DM:

Clinical symptoms of hyperglycemia.

Blood glucose ≥200 mg/dL.

Fasting glucose ≥126 mg/dL.

HbA1c > 6.5%.[5]

It is still up for debate, whether or not all the DM linked to pancreatic disease should be classified as type 3c DM. Ewald and Bretzel proposed standard diagnostic criteria, however these were criticized for being difficult to apply clinically.[6] The proposed criteria are represented in the Table 3.

Considering the differential criteria, type 3c presents with distinct characteristics compared to type II DM, including

Table 3: Diagnostic criteria.[6]

Major Criteria (All Must Be Fulfilled)
1. Evidence of exocrine pancreatic insufficiency.
(Faeces Elastase 1 (FE1) < 200_g/g or incorrect direct function testing).
2. Pathological pancreatic imaging.
(endoscopic ultrasound, magnetic resonance imaging, and computed tomography).
3. Absence of type I diabetes mellitus-associated autoimmune markers.
Minor Criteria
1. Impaired beta cell function (e.g., HOMA-B, C-peptide/glucose-ratio).
2. No excessive insulin resistance (e.g., HOMA-IR).
3. Impaired incretin secretion (e.g., GLP-1, pancreatic polypeptide).
4. Low serum levels of lipid-soluble vitamins (A, D, E, and K).

Source; American Diabetes Association.

a deficiency of Pancreatic Polypeptide (PP), whereas in the case of type II DM high levels of nutrients stimulated pancreatic polypeptide are seen.[2] Various pathological imaging parameters including endoscopy, MRI, and ultrasound can be used to differentiate type 3c DM from type I. Additionally, the absence of certain autoimmune markers associated with type 1 DM serves as a differentiating factor between type I DM and type 3c DM. Minor criteria that can further contribute to the differentiation of type I and type 3c DM include assessment of β-cell function, insulin resistance, abnormalities in incretin secretion, and lower levels of fat-soluble vitamins (A, D, E, K).[2] Patients with DM following chronic pancreatitis are subjected to retinopathy screening which revealed an increase in risk for microvascular changes in type 3c than type I and type II due to inadequate glycemic control.[5] In a study, type 3c DM patients had normal mean BMI and fewer macrovascular complications compared to type I DM and type II diabetes mellitus.[10]

The treatment approach for type 3c DM includes correction of both exocrine and endocrine pancreatic insufficiency.[5] Insulin therapy remains a cornerstone for the management of pancreatogenic pancreatitis, however, there is no established standard insulin regimen. caution is required while dosing insulin and monitoring due to the potential risk for hypoglycemia that exists from impaired glucagon function.[5] There is always a basic need to maintain glucose levels a little greater than the normal level to avoid hyperglycemia.[2]

Metformin emerges as a prominent first-line therapy for type 3C DM, offering various benefits such as a reduction in daily insulin requirements and exerting reduced risk for the development of pancreatic ductal adenocarcinoma. Additionally, it may increase GLP-1 levels and expression of pancreatic GLP-1 and GLP receptor genes and potentially prolong the survival rate of DM patients without pancreatic cancer metastasis.[9] Other pharmacological agents such as sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 analogues, and α- glycosidase inhibitors can also be used for the treatment of endocrine dysfunction.[5] Due to the potential risk for pancreatic damage, newer incretin-based agents such as glucagon-like peptide receptor agonists and dipeptidyl peptidase 4 inhibitors are contraindicated in type 3c patients.[9]

Type 3c patients are more prone to malabsorption secondary to pancreatic exocrine dysfunction than in type I and type II. hence, pancreatic enzyme and vitamin D supplements are provided to prevent malnutrition and osteoporosis.[9] In addition, the presence of malabsorption, alcohol consumption, and poor diet complicates the management of the disease.[6] Indeed, dietary management also plays an essential role in reducing the symptoms and complications associated with chronic pancreatitis, patients are advised to adhere to a diet rich in fiber and low in fat to alleviate symptoms of steatorrhea and prevent hyper-glycemia.[2]

CONCLUSION

Type 3c DM, arising from pancreatic disease, is often misdiagnosed or overlooked, contributing to poor patient outcomes. Patients with Chronic Pancreatitis (CP) face an elevated risk of developing diabetes, particularly with the development of pancreatic ductal calcification and exocrine insufficiency, indicating the progression of the disease. Accurate history taking, appropriate diagnostic tests, and recognizing various risk factors are essential identification for type 3c DM, which aids in timely detection and management, potentially reducing complications and mortality.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

PATIENT CONSENT

The patient has been informed about the publishing and assured that the information will only be used for scientific and research purposes and identity of the patient will not be disclosed.

ABBREVIATIONS

DM: Diabetes mellitus; **CP:** Chronic pancreatitis, **USG:** Ultrasonography; **URSL:** (Ureteroscopic Lithotripsy); **DJ:** Double J Stent; **CT:** Computed Tomography; **CBD:** Common Bile Duct; **ERCP:** Cholangiopancreatography; **OPD:** outpatient department; **CCP:** Chronic calcific pancreatitis; **DDP:** Dipeptidyl peptidase 4; **GLP:** Glucagon-like peptide.

SUMMARY

A 53-year-old male with a history of chronic pancreatitis, misdiagnosed as type II diabetes mellitus, and dyslipidemia presented in the hospital with chief complaints of epigastric pain, high-colored urine, and recent weight loss. Diagnostic imaging revealed chronic calcific pancreatitis with intraductal calculi and benign biliary stricture of the Common Bile Duct (CBD). Based on the subjective and objective evidence, the patient was diagnosed to have type 3c DM. He underwent ERCP with stent placement and was managed with a combination of medications including pancreatin, pantoprazole, paracetamol, ondansetron, N-Acetyl Cysteine, atorvastatin, tramadol, and antibiotics. Additionally, insulin therapy was initiated for hyperglycemia. Upon improvement, he was discharged with a regimen comprising cefpodoxime and clavulanic acid, pantoprazole, pancreatin, silodosin, multivitamin, tramadol, acetaminophen, metformin, insulin aspart, and insulin glargine. Follow-up appointments were scheduled in hepatology, urology, and internal medicine outpatient departments.

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