CASE REPORT

Diabetes Mellitus—Not Just Type 1 or Type 2 Anymore

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ABSTRACT

Introduction: Diabetes mellitus traditionally has been categorized as type 1 (insulin deficiency due to autoimmune destruction of islet cells) or type 2 (insulin resistance with the development of relative insulin deficiency). However, other pathophysiologic etiologies for diabetes must be considered in the evaluation of patients with new-onset diabetes.

Case Presentation: We report the case of a 50-year-old man with a diagnosis of type 2 diabetes mellitus who—despite appropriate pharmacotherapy—developed worsening hyperglycemia. Further investigation revealed the presence of metastatic pancreatic cancer.

Discussion: Although an association between pancreatic cancer and diabetes has been noted widely in the gastroenterology, oncology, and endocrine literature, a paucity of primary care literature on the topic exists. Features of predominant insulin deficiency and new onset of diabetes in a patient without family history of type 2 diabetes should raise suspicion for undetected/early-stage pancreatic cancer.

Conclusions: This case highlights the importance of considering all possible pathophysiologic etiologies when a patient has a new diagnosis of diabetes. Clinicians should consider the possibility of pancreatic cancer in patients with new-onset diabetes mellitus, especially when features not characteristic of type 2 diabetes are present. Understanding the relationship between diabetes and pancreatic cancer has the potential to improve early detection of pancreatic cancer and can provide an opportunity for early treatment and improved survival.

CASE PRESENTATION

A 50-year-old man came to our acute care clinic with a 5-day history of polyuria. He also was experiencing polydipsia and dry mouth. He recently had started antihypertensive therapy with losartan-hydrochlorothiazide, but with the onset of these symptoms, he had called his primary care clinician and the hydrochlorothiazide was discontinued. Despite this change in medications, his symptoms had worsened.

The patient had no family history of diabetes and no known comorbidities other than hypertension. His body mass index (BMI) was 29 kg/m², his serum glucose was 435 mg/dL, and his hemoglobin A₁c (HbA₁c) was 8.6%. A urinalysis showed 3+ glucose and 2+ ketones. He was diagnosed with type 2 diabetes mellitus and started on metformin 500 mg twice daily. He was scheduled to see his primary care clinician 2 days later.

At the initial follow-up appointment, the patient reported that he had minimal improvement in the dry mouth and polydipsia, and that he still had substantial polyuria. He had also lost 10 pounds. He was referred to a diabetes educator but declined. No changes were made in his medication, and he was advised to return to his primary care clinician’s office in 3 months with a repeat HbA₁c test.

Twelve days later, the patient again came to the acute care clinic reporting that he continued to have significant polyuria. Additional laboratory studies were repeated and he was again noted to have hyperglycemia. Glipizide was added to his regimen. He was prescribed a glucometer and advised to start monitoring his blood sugar concentrations at home.

Four days later, the patient saw his primary care clinician, who believed that a dental infection could be contributing to his uncontrolled diabetes, so he was started on antibiotics. No other changes were made in his therapy. He agreed to see a diabetes educator.

One month later, he called his primary care clinician’s office to report that his condition was deteriorating. He had experienced epigastric abdominal pain for several weeks and reported that he had lost 35 pounds since his original diagnosis of type 2 diabetes. He was referred to the Emergency Department for further evaluation. Urinalysis again showed 3+ glucose and 2+ ketones, and his alkaline phosphatase concentration was mildly elevated at 168 U/dL (normal
A computed tomography scan of the abdomen was obtained and showed a 7.8-cm mass in the body and tail of the pancreas, as well as hepatic and peritoneal metastases (Figure).

One week later the patient underwent a percutaneous biopsy of his pancreas, which revealed adenocarcinoma. Biopsy of an omental mass showed metastatic adenocarcinoma. He was referred to oncology, and treatment options were reviewed. He elected to start chemotherapy with folfirinox. He underwent placement of a port catheter and infusion of his first cycle of chemotherapy.

Three days later the patient went to an outside hospital with complaints of weakness, palpitations, and chest pain. An electrocardiogram revealed atrial fibrillation with a rate of 135 beats per minute. A diltiazem infusion was started, which improved his heart rate. Additional laboratory studies were obtained (Table 1, and a diagnosis of diabetic ketoacidosis (DKA) was considered. He was transferred to our center and underwent standard treatment for DKA. His metabolic abnormalities improved rapidly with intravenous fluid resuscitation and insulin therapy. He was maintained on a standard insulin regimen at discharge.

**DISCUSSION**

An association between diabetes mellitus and pancreatic adenocarcinoma was recognized as early as 1934. Since that time, multiple studies have been conducted to determine the relationship between these entities. Using the American Diabetes Association (ADA) criterion of fasting blood glucose concentration of > 126 mg/dL, Pannala et al reported that 47% of patients with pancreatic cancer have diabetes mellitus, closely mirroring a 2001 report by Chari et al (46%). However, the primary care literature rarely identifies the association of pancreatic cancer and new-onset diabetes mellitus.

A temporal association also has been described. In a large population-based study, Chari and colleagues found that in the 3 years after a new-onset diabetes diagnosis, patients have an 8-fold higher range 30-140 U/dL.)
risk of being diagnosed with pancreatic cancer compared with the general population. Diabetes associated with pancreatic cancer is typically new-onset, less than 24 months. In a meta-analysis of cohort studies, Ben et al reported a relative risk of 5.4 with diabetes of less than 1 year duration, with the relative risk decreasing to 1.5 for diabetes of greater than 5 years duration. Hence, new-onset diabetes should raise suspicion for undetected/early-stage pancreatic cancer. Gangi et al reported that diabetes occurs before radiological evidence of malignancy. Evidence of early derangements in glucose metabolism can provide a useful clinical tool for the early detection of pancreatic cancer before radiological diagnosis.

Diabetes caused by pancreatic cancer behaves differently than type 1 or type 2 diabetes mellitus. The underlying mechanism appears to be that pancreatic cancer itself induces diabetes in part by paraneoplastic phenomenon and in part by other less clear mechanisms. One of the obvious features related to diabetes with pancreatic cancer is weight loss at the time of diagnosis, as opposed to weight gain associated with type 2 diabetes mellitus. Furthermore, in pancreatic cancer-associated diabetes, fasting blood glucose levels become progressively higher as weight loss progresses, whereas in type 2 diabetes mellitus, weight loss leads to improved glycemic control. Pancreatic cancer causes beta cell dysfunction and insulin resistance similar to that seen in type 2 diabetes mellitus; however, the underlying molecular mechanisms have been postulated to be different. Higher levels of adrenomedullin are observed in pancreatic cancer patients than in patients with type 2 diabetes mellitus, in which decreased adiponectin and increased lectin levels play an important role in insulin resistance. Insulin resistance at the postreceptor level is observed with both types of diabetes, but differences have been reported in glycogen metabolism. Islet amyloid polypeptide has been reported to be responsible for the insulin resistance seen in pancreatic cancer, but that suggestion is controversial. Studies also have suggested relationships between pancreatic cancer and adipose inflammation and lipolysis, similar to those observed in type 2 diabetes mellitus. A comparison of the clinical and laboratory similarities and differences between type 2 diabetes mellitus and pancreatic cancer-associated diabetes mellitus (type 3c) is provided in Table 2.

Higher levels of circulating insulin and C-peptide levels observed in patients with pancreatic cancer support the fact that the cancer causes insulin resistance. One of the earliest postulated mechanisms was similar to the pathogenesis of diabetes in chronic pancreatitis, where the progressive destruction of healthy tissue and consequent beta cell loss led to worsening hyperglycemia, which can come into play at later stages of the disease. Tumor resection in pancreatic cancer results in resolution of diabetes in up to 60% of cases, further evidence that the tumor itself causes the diabetes mellitus.

Islet cell dysfunction also is believed to play a causative role in diabetes associated with pancreatic cancer. Cersosimo and colleagues demonstrated reduced insulin secretion in response to normal stimuli in patients with pancreatic cancer. Current evidence supports a paraneoplastic etiology, rather than a loss of a critical mass of islet cells, for the reduction of insulin release.

New-onset diabetes was significantly related to larger tumors and elevated levels of cancer antigen 19-9 (CA 19-9) but not to tumor location and presence of biliary obstruction. The ADA recognizes diabetes associated with exocrine pancreas as type 3c diabetes based on an etiological classification, an entity separate from type 1 and type 2, wherein type 3c is associated with neoplasia of exocrine pancreas. The biggest utility of understanding diabetes related to pancreatic cancer is the potential for early detection of pancreatic cancer before symptomatic or radiological diagnosis is possible. This, in turn, can provide opportunity for early resection of tumor and the possibility of improved survival. According to a 2015 American Cancer Society report, pancreatic cancer is the fourth-leading cause of cancer death in the United States. Five-year survival of pancreatic cancer (5%-8%) has been unchanged since 1975, primarily due to the lack of a better marker for early tumor detection.

**CONCLUSIONS**

The prevalence of diabetes is far higher than that of pancreatic cancer, so there is a need to develop a protocol to select and stratify patients with new-onset diabetes mellitus who should undergo screening for pancreatic cancer. One potential group should be patients with new-onset (<24 months) diabetes mellitus who have no family history that pancreatic cancer is associated with diabetes.
of diabetes, who have unexplained weight loss, and whose glycemic concentrations are poorly responsive to oral antidiabetic medications, as was the case for our patient. Although our focus has been on new-onset diabetes mellitus, another potential group should be patients with already diagnosed diabetes mellitus whose disease abruptly becomes more difficult to control.

Clinical management of type 3c diabetes mellitus poses noteworthy challenges, and conventional strategies used for managing type 2 diabetes might not be effective in patients with pancreatic cancer. However, appropriate therapy of patients with type 3c diabetes mellitus can prevent the development of potentially life-threatening conditions like diabetic ketoacidosis and decrease potential morbidity. Although 1-year survival is less than 30%, understanding the relationship between diabetes and pancreatic cancer has the potential to improve early detection of pancreatic cancer and can provide an opportunity for early treatment and improved survival.

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