Weight Loss With Rising Blood Glucose: Challenges in Distinguishing Conventional Type 2 Diabetes From Pancreatic Cancer–Associated Hyperglycemia

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Diabetes is both a risk factor for pancreatic cancer and a potential early warning sign of a growing tumor. Approximately 1% of people with diabetes who are ≥50 years of age will be diagnosed with pancreatic cancer within 3 years of first meeting the criteria for diabetes, a rate that is eight times higher than would have been expected for people of similar age and sex in the general population (1). Distinguishing typical diabetes from hyperglycemia associated with pancreatic cancer can be difficult. There is no validated, widely available, noninvasive test for pancreatic cancer, and, unlike colon and breast cancer, there is no standard screening process. Additionally, given its low prevalence compared with type 2 diabetes, pancreatic cancer is often low on the list of differential diagnoses when patients present with hyperglycemia. While the lifetime risk of diabetes in U.S. adults is estimated at ∼40% (2), the lifetime risk of pancreatic cancer is 1.7% (3). However, the prevalence of hyperglycemia in patients with pancreatic adenocarcinoma may be as high as 75% (4), indicating a relationship between pancreatic cancer and diabetes.

In many cases, hyperglycemia may precede detection of a tumor and be the first clinical indication of malignancy, so hyperglycemia can provide a critical clue to diagnosis if it prompts early evaluation. Although surgical resection of pancreatic cancer offers the best chance at a cure, some 80% of pancreatic tumors are not detected until they are unresectable. The transition of a growing pancreatic tumor from resectable to unresectable occurs over a period of ∼6 months before diagnosis, suggesting that detection even as little as 6 months earlier would lead to an increase in the resectability rate (5).

Case Presentation

A 56-year-old female recreational cyclist presented to her primary care provider (PCP) with postprandial hyperglycemia, new-onset upper abdominal pain worse with fatty meals, and weight loss.

She had a history of type 2 diabetes, with an A1C of 7.4% 3 years before presentation. At that time, she had a BMI of 36.5 kg/m^2 and subsequently lost 51 lb via lifestyle interventions, with a corresponding reduction in A1C to 5.0% and durable remission of diabetes.

At presentation, her A1C had risen to 6.1%, with associated postprandial glucose excursions into the 200-mg/dL range. Her fasting C-peptide concentration was 0.84 ng/mL and tests for pancreatic autoantibodies (GAD65, IA-2, and anti-insulin) were negative. Her PCP was initially concerned about gastritis and prescribed omeprazole. The patient had lost 23 lb in 11 weeks since the onset of abdominal pain, although this was thought to be explained by dietary modifications to address her gastritis. A DEXA body composition scan demonstrated that her weight loss had been entirely accounted for by loss of lean mass when compared with prior studies.

Four months after presentation, the patient reported that, despite a weight loss of an additional 5 lb, or a total of 28 lb since the abdominal pain began, a home A1C measurement was 6.4%, and she was recording fingerstick blood glucose values as high as 321 mg/dL. She was prescribed metformin.

Because of severe hyperglycemia from glycemic excursions, worsening abdominal pain, and pruritus, the patient presented to a local emergency department, where urinalysis revealed moderate bilirubin. In follow-up

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with the PCP, her A1C had risen to 7%, her serum C-peptide concentration was 1.39 ng/mL, and her blood glucose was 285 mg/dL. Insulin glargine 20 units daily was initiated. A *Helicobacter pylori* urea breath test was negative, and upper endoscopy was recommended. Given her high postprandial blood glucose levels, insulin aspart with meals was initiated, and metformin was discontinued because of abdominal pain and loose stools. Her fasting glucose levels and weight trends over time are shown in Figure 1.

The patient was subsequently noted by friends to appear jaundiced, and she presented to the emergency department, where an abdominal CT scan revealed a hypodense mass in the pancreatic head, highly concerning for malignancy, as well as several ill-defined lesions in the liver, enlarged lymph nodes, and small nodules in the lungs. She was admitted and received a biliary stent. The tumor was biopsied and found to be adenocarcinoma, which was deemed nonresectable, and she sought specialist care for her malignancy and diabetes.

Questions

1. When should pancreatic cancer be suspected in a patient with hyperglycemia?
2. How should hyperglycemia be evaluated and managed in patients with suspected pancreatic cancer?

Commentary

Distinguishing typical type 2 diabetes from tumor-related hyperglycemia can be challenging in clinical practice. This case highlights how difficult it is to make the connection between new-onset hyperglycemia and pancreatic cancer, as classic symptoms of cancer such as abdominal pain and weight loss can easily be attributed to other causes.

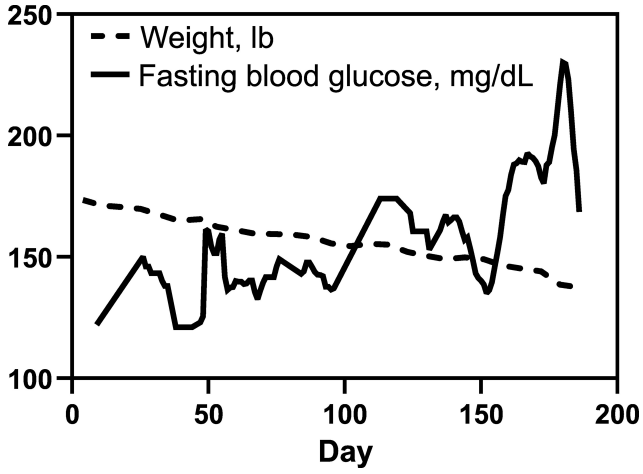

FIGURE 1 Weight and fasting blood glucose trends from day of initial presentation (day 0). Blood glucose trendline represents 7-day running average.

In certain clinical circumstances, new-onset diabetes or sudden and unexplained worsening of glucose control may be a red flag for possible underlying malignancy. As previously noted, ~75% of pancreatic cancer patients present with either diabetes or impaired glucose tolerance. In this case, significant postprandial glucose excursions appear not to have been reflected by the A1C, which remained mostly in the prediabetes range despite intermittent blood glucose readings >300 mg/dL. The mechanisms by which pancreatic cancer contribute to hyperglycemia are not fully understood but appear to include both an increase in insulin resistance and an impaired β-cell response (6).

Type 2 diabetes is a gradually progressive disease and does not typically advance as rapidly or dramatically as seen in this case, and the worsening in blood glucose despite significant weight loss and a healthy low-glycemic diet should suggest a possible secondary cause. Given that patients are often instructed to lose weight, this sign can be overlooked by both patients and clinicians, but successful weight loss—16% of body weight in this case—should have resulted in a significant improvement in glycemia. The onset of abdominal pain, although nonspecific, is also not typical of type 2 diabetes and, in the setting of unexplained worsening glycemia, should be investigated more aggressively.

Despite the established link between pancreatic cancer and new-onset diabetes, the American Diabetes Association recommends against routine evaluation for pancreatic cancer in patients without clinical signs or symptoms such as weight loss or abdominal pain (7), and the low prevalence of the disease paired with the current lack of a low-cost screening modality limits the practicality of widespread screening. Clinical tools such as the Enriching New-Onset Diabetes for Pancreatic Cancer (END-PAC) score have been developed to aid clinicians in identifying patients who may warrant further workup (8), but this score is not in widespread clinical use and requires knowledge of blood glucose values before the onset of diabetes, which may limit its practicality. In this case, the patient had a complete remission of diabetes for 3 years before her diagnosis of cancer, and, at the time of diabetes relapse, an END-PAC score would have been 9, suggesting a high risk of malignancy (although this score has not been validated in the setting of diabetes relapse). The glucagon-to-insulin ratio has been proposed as a method for discriminating pancreatic

cancer–associated hyperglycemia from type 2 diabetes (9), but the specificity of this approach is not adequate to be used in clinical practice, and this ratio was not determined in this patient. There is interest in developing better biomarkers to identify patients with new-onset hyperglycemia who are at high risk of pancreatic adenocarcinoma; a large clinical study is currently enrolling patients to determine the role of measuring carbohydrate antigen 19–9 and potentially other markers in this population (10), and Bluestar Genomics is developing a blood test to screen for pancreatic cancer based on DNA hydroxy-methylation signatures (11). For now, however, it is up to health care providers to clinically assess patients with a new diagnosis of diabetes or suddenly worsening diabetes for signs or symptoms of pancreatic cancer that warrant further evaluation.

In patients with suspected or confirmed pancreatic adenocarcinoma, it is important to recognize that the secretion of multiple islet hormones may be affected, with therapeutic implications. Extensive pancreatic destruction results in pancreatogenic, or type 3c, diabetes, which is characterized not only by decreased insulin production, but also by lower glucagon and pancreatic polypeptide levels (12). In terms of therapy, studies of particular antihyperglycemic agents, including incretin-based therapy (i.e., dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists), generally have been unable to establish a strong causal relationship between any agent and pancreatic cancer (13). It may be helpful to estimate insulin secretory function at the time of cancer diagnosis by measuring fasting or stimulated C-peptide level to assess the need for insulin therapy, although this can also be determined based on a patient's response to noninsulin therapy and the clinical scenario, as patients who are perioperative or have impaired renal or hepatic function may have limited therapeutic options. Note that patients with substantial metastatic liver involvement may have diminished gluconeogenic capacity and therefore may be prone to fasting hypoglycemia, and, rarely, paraneoplastic IGF-II production can result in noninsulin-mediated hypoglycemia (14), presenting management challenges.

In conclusion, risks of pancreatic cancer and diabetes are bidirectional; pancreatic cancer is a risk factor for new-onset diabetes, and longstanding type 2 diabetes is a risk factor for pancreatic cancer. Careful clinical assessment is critical at the time of diabetes diagnosis or a change in diabetes status that is characterized by atypical features such as unintentional weight loss, abdominal pain, or dramatic postprandial glucose excursions out of proportion to overall glycemic control, since early detection of pancreatic adenocarcinoma is likely to be lifesaving.

Clinical Pearls

- At the time of diabetes diagnosis, worsening blood glucose despite significant weight loss with negative pancreatic autoantibodies, particularly in patients >65 years of age, should prompt assessment for secondary causes, including pancreatic cancer.
- Abdominal pain in the context of new-onset or worsening diabetes should trigger expedient assessment.
- Patients with pancreatic cancer and hyperglycemia can be treated with standard diabetes therapy, although there may be high risk for hypoglycemia, particularly in patients with substantial pancreatic destruction or resection.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

L.J. drafted the initial manuscript. G.P.W. critically reviewed and revised the manuscript. G.P.W. is the guarantor of the work and, as such, had full access to all data in the case study and takes responsibility for the contents of this article.

REFERENCES

1. Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. Gastroenterology 2005;129:504–511

2. Gregg EW, Zhuo X, Cheng YJ, Albright AL, Narayan KMV, Thompson TJ. Trends in lifetime risk and years of life lost due to diabetes in the USA, 1985–2011: a modelling study. Lancet Diabetes Endocrinol 2014;2:867–874

3. National Cancer Institute Surveilance, Epidemiology, and End Results Program. Cancer stat facts: pancreatic cancer. Available from https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed 2 August 2022

4. Permert J, Ihse I, Jorfeldt L, von Schenck H, Arnqvist HJ, Larsson J. Pancreatic cancer is associated with impaired glucose metabolism. Eur J Surg 1993;159:101–107

5. Chari ST. Detecting early pancreatic cancer: problems and prospects. Semin Oncol 2007;34:284–294

6. Hart PA, Bellin MD, Andersen DK, et al.; Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC). Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol 2016;1:226–237

7. American Diabetes Association Professional Practice Committee. 4. Comprehensive medical evaluation and assessment of comorbidities: *Standards of Medical Care in Diabetes—2022*. Diabetes Care 2022;45(Suppl. 1):S46–S59

8. Sharma A, Kandlakunta H, Nagpal SJS, et al. Model to determine risk of pancreatic cancer in patients with new-onset diabetes. Gastroenterology 2018;155:730–739.e3

9. Kolb A, Rieder S, Born D, et al. Glucagon/insulin ratio as a potential biomarker for pancreatic cancer in patients with new-onset diabetes mellitus. Cancer Biol Ther 2009;8:1527–1533

10. ClinicalTrials.gov. A study to establish a new onset hyperglycemia and diabetes cohort (NOD). Available from https://clinicaltrials.gov/ct2/show/NCT03731637. Accessed 2 August 2022

11. ClinicalTrials.gov. EpiDetect study: clinical validation of a pancreatic cancer detection test in new-onset diabetes patients. Available from https://clinicaltrials.gov/ct2/show/NCT05188573. Accessed 2 August 2022

12. Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. Pancreatology 2011;11:279–294

13. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs: FDA and EMA assessment. N Engl J Med 2014;370:794–797

14. Dynkevich Y, Rother KI, Whitford I, et al. Tumors, IGF-2, and hypoglycemia: insights from the clinic, the laboratory, and the historical archive. Endocr Rev 2013;34:798–826