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Journal of Diabetes and Clinical Research Commentary

Atypical Diabetes Mellitus Presentation, an Early Warning of Pancreatic Carcinoma

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Abstract

Background: Diagnostic delay contributes to high mortality rates for pancreatic carcinoma. In 50-80% of patients with pancreatic carcinoma diabetes mellitus is present 1-3 years before the carcinoma is diagnosed. Primary care guidelines devote little attention to differentiating characteristics between diabetes mellitus due to pancreatic disease and other types.

Aim: This commentary, accompanying a previously published case-series, reflects on the reciprocal relationship between pancreatic carcinoma and diabetes mellitus. Increasing awareness of atypical signs in diabetes mellitus presentation/course might aid primary care physicians in identifying patients with possible underlying/co-existing pancreatic carcinoma, possible decreasing the diagnostic delay.

Take home message: Atypical course can be understood as the following: a) weight loss preceding the diagnosis 'diabetes mellitus type 2' that persists despite (adequate) treatment; b) the lack of accompanying metabolic characteristics such as dyslipidemia, hypertension, or obesity (common soil); and c) (sub-)acute deterioration of glycemic control that cannot be attributed to other factors.

Introduction

In 2020 we published a case-series detailing patients who died from pancreatic cancer [1] (Appendix). These three patients were diagnosed with new-onset type 2 mellitus or deterioration of pre-existing type 2 diabetes shortly before their pancreatic malignancy was detected. We reflected on some characteristics in their presentation and clinical course of their diabetes mellitus that were atypical and could suggest the need for further investigation. In the presented cases the diagnosis diabetes mellitus led not to the diagnosis of the underlying pancreatic carcinoma in such a timely manner that it contributed to survival.

We will try and summarize the key elements in their disease course that could be relevant for clinicians treating diabetes mellitus, especially in primary care. For this purpose, we will discuss the epidemiology of diabetes mellitus and pancreatic carcinoma, as well as factors contributing the diagnostic delay of and therefore the poor survival associated with pancreatic carcinoma. These factors include the limited consideration of diabetes mellitus due to pancreatic disease, classified as diabetes mellitus type 3c, in (primary care) guidelines, the reciprocal relationship between diabetes mellitus type 2 and pancreatic carcinoma and lastly characteristics of diabetes mellitus atypical for type 2 diabetes that, if present, should prompt reconsideration of diabetes type. By discussing this we hope to put (primary care) physicians on the alert for atypical signs in diabetes mellitus presentation/course, and in doing so we hope to aid them in identifying at least some patients suffering from pancreatic cancer at an earlier stage.

The Burden of Pancreatic Carcinoma

The number of incident cases and deaths due to pancreatic cancer have risen globally, with approximately 448,000 new cases and 441,000 deaths in 2017 [2]. Most cases of pancreatic cancer are only diagnosed when patients present with symptoms due to local invasion and metastases (e.g., back pain) [3]. Due to the disease

stage at presentation, only 10-15% of patients have a malignancy eligible for pancreatectomy. This is especially poignant considering that even in patients that underwent pancreaticoduodenectomy the 5-year survival is approximately 10-30%, depending on nodal status [4]. For patients with metastatic disease the 5-year survival rate is less than 10%. In contrast, in patients with (limited) local disease, 5-year survival can increase to more than 75%, if treated surgically [5].

In the light of these figures emphasis has been put on the need for preventative strategies, treatment methods, and screening programs suited for early detection [6]. Effort to identify possible screening methods, and whether and how to use them if identified, are still ongoing [6,7]. Most of these efforts, such as serological markers and imaging, are ill suited for primary care. Thus, leaving the general practitioner (GP) with no additional tools other than personal history, physical examination, and alertness, to identify this malignancy, that is often diagnosed too late. In this commentary, accompanying the case-series, we discuss the relationship between diabetes mellitus and pancreatic carcinoma. Additionally, will try and summarize the key elements in their disease course that could be relevant for (primary care) clinicians treating diabetes mellitus with regards to a possible co-existing pancreatic carcinoma.

Epidemiology of Diabetes and Pancreatic Disease

Globally, approximately 22.9 million people per year are diagnosed with type 2 diabetes mellitus [8]. Diabetes mellitus as a result of pancreatic disease is classified in international guidelines as diabetes mellitus type 3c [9,10]. Approximately 1-9% of all patients with diabetes mellitus have type 3c diabetes mellitus [11]. Diabetes mellitus type 3c encompasses a variety of etiologies, not all of them malignant. In 78.5% of patients with diabetes mellitus type 3c the underlying causes are acute, recurrent, or chronic pancreatitis. Other causes are haemochromatosis, cystic fibrosis, pancreatic agenesia, pancreatic trauma and pancreatectomy. Pancreatic carcinoma is estimated to be the cause of 1-14% of the cases of diabetes type 3c [11]. Familial pancreatic cancer accounts for 10% of patients with pancreatic carcer. Screening programs for familial associated pancreatic cancers are available, but these are not applicable for patients without known genetic burden [12].

Recognition of new-onset diabetes mellitus as being a type 3c is still uncommon [10,11]. Perhaps contributing to this is that the separate distinction of diabetes mellitus type 3c renders this type of diabetes mellitus as a pathophysiological distinct entity. In doing so, the ways in which symptoms in type 2 and type 3c diabetes mellitus overlap are insufficiently emphasized, possibly contributing to under recognition of type 3c diabetes mellitus. To our knowledge guidelines for primary care physicians usually devote little to no attention to possible (etiologic) variants, other than maturity-onset diabetes of the young' (MODY) or autoimmune diabetes mellitus with late presentation. The possibility of diabetes mellitus as an early manifestation of pancreatic carcinoma is neglected in most guidelines for general practice.

A Reciprocal Relationship between Diabetes Mellitus and Pancreatic Cancer

Another factor obfuscating the distinction between type 2 diabetes mellitus and type 3c, is the reciprocal relationship these two types share. Which in turn indicates a certain degree of similarity rather than difference. The relationship between diabetes mellitus and pancreatic cancer is complex and multi-factorial [9,10]. Over two-thirds of patients with pancreatic cancer have co-existing impaired glucose tolerance or diabetes mellitus [10]. Diabetes mellitus is associated with an increased risk of developing pancreatic carcinoma. However, pancreatic cancer can contribute to deterioration of existing diabetes mellitus, or even be the cause of new-onset diabetes mellitus [9-11,13]. This increased risk of pancreatic carcinoma is in part due to the manifestations of type 2 diabetes mellitus and pathophysiological common soil like obesity and physical inactivity [14]. Type 2 diabetes mellitus associated factors that predispose to the development of pancreatic cancer include weight gain, hyperinsulinemia and increased IGF-1 and -2 signaling [15,16]. Furthermore, glucose-lowering drugs such as insulin and metformin have been associated with, respectively, an increased and decreased risk of developing pancreatic cancer [9,17].

Epidemiological studies found a 1.5-2 times higher risk of developing pancreatic carcinoma in patients with type 2 diabetes mellitus, compared to non-diabetic controls [10]. In contrast, 50-80% of patients diagnosed with pancreatic cancer were diagnosed with diabetes mellitus 1-3 years before the co-existing/underlying carcinoma was diagnosed [13]. Interestingly, in patients diagnosed with pancreatic carcinoma, retrospective evaluation of CT-scans made 6 months or more prior to their diagnosis showed tumors that were either fully resectable or undetectable [18]. Given these intervals, the correct identification of diabetes mellitus presentation or clinical course as being atypical could contribute to survival [18].

The mechanisms underlying the reciprocal relationship between pancreatic cancer and diabetes mellitus are not yet fully elucidated. The development of diabetes mellitus in the, relatively short, phase preceding the diagnosis of pancreatic carcinoma, is regarded as being the result of a paraneoplastic phenomenon [10]. This is deemed

to be due to the tumor-mediated increase in cytokines, contributing to insulin-resistance [6,10,11]. Supporting this is the worsening of glucose-regulation in patients with other malignancies that lead to increased cytokine production [19]. Locally the pancreatic tumor can lead to destruction of β-cells, contributing to insulin deficiency [10]. Among some patients with pancreatic cancer and peripheral insulin resistance, removal of the tumor improved glucose metabolism, providing evidence that altered glucose metabolism may be a result of the tumor itself [20]. However, the reduction in tumor-mediated cytokine production due to resection of the tumor cannot be ruled out as the underlying mechanism in this case.

Atypical Presentation of Type 2 Diabetes

It is unclear whether criteria to distinguish type 2 diabetes mellitus as a result of a pancreatic carcinoma could be set. In our case series, all three patients were over 65 years. Two of them presented with new-onset diabetes mellitus, classified as being type 2, the other had long-standing, well-regulated type 2 diabetes mellitus, with acute unexplained deterioration of glycemic control and upper abdominal discomfort. All three lost weight, the two presenting with new-onset diabetes mellitus had lost 4-7 kg (9-16 pounds) at presentation, the patient with long-standing diabetes lost 5.7 kg (12 pounds). Weight loss persisted, despite (intensification of) glucose-lowering therapy. Additionally, the two patients with new-onset diabetes mellitus had no positive family history for type 2 diabetes mellitus and lacked any signs characteristic of metabolic syndrome (e.g., dyslipidemia).

Some characteristics in these abbreviated cases are atypical for the clinical course of type 2 diabetes mellitus. Firstly, history of recent weight loss at presentation is uncharacteristic for type 2 diabetes mellitus, given that weight loss generally leads to improved glucose-regulation [21]. Secondly, weight loss continuing after start of treatment is irregular, considering that adequate glucose-regulation generally leads to a negation of the catabolic state, and thus stabilization of bodyweight. The lack of a positive family history is not uncommon, and therefor ill-suited for distinguishing type 2 from type 3c diabetes mellitus [20]. Thirdly, (sub-)acute deterioration of previously well-regulated (long-standing) diabetes mellitus, without sufficient explanation should put treating physicians on the alert. Lastly, in 58-91% of cases, patients with type 2 diabetes mellitus suffer from metabolic dysregulation (e.g., dyslipidemia), as a result of the common soil shared with diabetes mellitus [22,23]. On their own, these characteristics might be unsubstantial, but taken together these deviations from the general clinical course should prompt reconsideration of diabetes type. In this way, the primary care physician might identify at least some patients suffering from pancreatic cancer at an earlier stage.

It must be emphasized that once contributing pancreatic disease is suspected, referral to secondary care is required for diagnostic work-up, since the diagnosis of pancreatic malignancy requires imaging (e.g., computed tomography).

Conclusion

Atypical presentation of type 2 diabetes mellitus should create an awareness between caregivers, of possible underlying disease. One of the possibilities is pancreatic cancer. In a primary care setting the options for detection are limited. Increasing awareness of and alertness for atypical signs in diabetes mellitus presentation could lead to earlier detection of a pancreatic tumor and decrease diagnostic delay. In doing so, more patients might be eligible for surgical resection, which is associated with better survival.

Atypical course can be understood as the following: a) weight loss preceding the diagnosis ‘diabetes mellitus type 2’ that persists despite (adequate) treatment; b) the lack of accompanying metabolic characteristics such as dyslipidemia, hypertension, or obesity (common soil); and c) (sub-)acute deterioration of glycemic control that cannot be attributed to other factors.

References

1. Holtrop R, Creyghton WM. Atypical presentation of type 2 diabetes mellitus: be aware of pancreatic carcinoma. Nederlands Tijdschrift Voor Geneeskunde. 2020 Sep 9;164.

2. Pourshams A, Sepanlou SG, Ikuta KS, Bisignano C, Safiri S, Roshandel G, et al. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. The Lancet Gastroenterology & Hepatology. 2019 Dec 1;4(12):934-47.

3. Porta M, Fabregat X, Malats N, Guarner L, Carrato A, de Miguel A, et al. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. Clinical and Translational Oncology. 2005 Jun 1;7(5):189-97.

4. Allen PJ, Kuk D, Fernandez-del Castillo C, Basturk O, Wolfgang CL, Cameron JL, et al. Multi-institutional validation study of the American Joint Commission on Cancer changes for T and N staging in patients with pancreatic adenocarcinoma. Annals of Surgery. 2017 Jan;265(1):185.

5. Canto MI. Screening and surveillance approaches in familial pancreatic cancer. Gastrointestinal Endoscopy Clinics of North America. 2008 Jul 1;18(3):535-53.

6. Kaur S, Baine MJ, Jain M, Sasson AR, Batra SK. Early diagnosis of pancreatic cancer: challenges and new developments. Biomarkers in Medicine. 2012 Oct;6(5):597-612.

7. Lucas AL, Kastrinos F. Screening for pancreatic cancer. Journal of the American Medical Association. 2019 Aug 6;322(5):407-8.

8. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Scientific Reports. 2020 Sep 8;10(1):1-1.

9. Andersen DK, Korc M, Petersen GM, Eibl G, Li D, Rickels MR, et al. Diabetes, Pancreatogenic Diabetes, and Pancreatic Cancer. Diabetes. 2017 May 1;66(5):1103-10.

10. Sah RP, Nagpal SJ, Mukhopadhyay D, Chari ST. New insights into pancreatic cancer-induced paraneoplastic diabetes. Nature Reviews Gastroenterology & hepatology. 2013 Jul;10(7):423-33.

11. Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. The lancet Gastroenterology & hepatology. 2016 Nov 1;1(3):226-37.

12. Benzel J, Fendrich V. Familial Pancreatic Cancer. Oncology Research and Treatment. 2018;41(10):611-618.

13. Chari ST, Leibson CL, Rabe KG, Timmons LJ, Ransom J, de Andrade M, et al. Pancreatic Cancer-Associated Diabetes Mellitus: Prevalence and Temporal Association With Diagnosis of Cancer. Gastroenterology. 2008 Jan 1;134(1):95–101.

14. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. Journal of the American Medical Association. 2001 Aug 22;286(8):921-9.

15. Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, Albanes D. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. Journal of the American Medical Association. 2005 Dec 14;294(22):2872-8.

16. Kolotkin RL, Andersen JR. A systematic review of reviews: exploring the relationship between obesity, weight loss and health-related quality of life. Clinical Obesity. 2017 Oct;7(5):273-89.

17. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology. 2009 Aug 1;137(2):482-8.

18. Gangi S, Fletcher JG, Nathan MA, Christensen JA, Harmsen WS, Crownhart BS, Chari ST. Time interval between abnormalities seen on CT and the clinical diagnosis of pancreatic cancer: retrospective review of CT scans obtained before diagnosis. American Journal of Roentgenology. 2004 Apr;182(4):897-903.

19. Wu Y, Liu Y, Dong Y, Vadgama J. Diabetes–associated dysregulated cytokines and cancer. Integrative Cancer Science and Therapeutics. 2016 Feb;3(1):370.

20. Permert J, Ihse I, Jorfeldt L, Von Schenck H, Arnquist HJ, Larsson J. Improved glucose metabolism after subtotal pancreatectomy for pancreatic cancer. British Journal of Surgery. 1993 Aug;80(8):1047-50.

21. Gummesson A, Nyman E, Knutsson M, Karpefors M. Effect of weight reduction on glycated haemoglobin in weight loss trials in patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2017 Sep;19(9):1295-305.

22. Nsiah K, Shang VO, Boateng KA, Mensah FO. Prevalence of metabolic syndrome in type 2 diabetes mellitus patients. International Journal of Applied and Basic Medical Research. 2015 May;5(2):133.

23. Ilanne-Parikka P, Eriksson JG, Lindström J, Hämäläinen H, Keinänen-Kiukaanniemi S, Laakso M, et al. Prevalence of the metabolic syndrome and its components: findings from a Finnish general population sample and the Diabetes Prevention Study cohort. Diabetes Care. 2004 Sep 1;27(9):2135-40.

Appendix

Patient A

A 72-year-old man, presented to his primary care physician with increased thirst, polyuria, and weight loss lasting several months. When the diagnosis of type 2 diabetes mellitus was made, he had lost 4 kg (8.8 pounds). Family history for type 2 diabetes mellitus was negative. He had a plasma fasting glucose (PFG) of 13.1 mmol/L (236 mg/dl), with a glycated hemoglobin (HbA1c) of 85 mmol/mol (9.9%). His lipid profile consisted of a total cholesterol (TC) of 3.9 mmol/L (151 mg/dl), high-denisty-lipoprotein (HDL)-cholesterol 1.38 mmol/L (53 mg/dl), low-density-lipoprotein (LDL)-cholesterol 1.9 mmol/L (74 mg/dl) and triglycerides of 1.4 mmol/L (124 mg/dl). His body-mass index (BMI) was 24.8 kg/m^2 (bodyweight: 87.5 kg, height 1.88 m). The patient reported no abdominal pain, no changes in appetite or stool.

The GP treated the patient, in accordance with the guidelines for type 2 diabetes mellitus of the Nederlands

Huisartsen Genootschap (Dutch College of General Practitioners; NHG), with metformine 500 miligrams (mg) twice daily and gliclazide retard 60 mg once daily. Following three months of treatment, the PFG was 6.5 mmol/L (117 mg/dl), with a HbA1c 47 mmol/mol (6.5%). However, weight loss continued to 79.6 kg (176 pounds), a near 8 kg (18 pounds) loss. Patient was referred to the specialist for internal diseases.

The internist ordered an endo-echograph of the pancreas. Showing a lesion with calcification in the pancreas head, as well as dilatation of the common bile duct and the pancreatic duct and its side-branches. Six months following the initial diagnosis of type 2 diabetes mellitus an abdominal CT was performed, showing a tumor with a diameter of 1 cm in the head of the pancreas, confirming the diagnosis of pancreatic carcinoma. There was no loco-regional lymphadenopathy, but regional invasive tumor growth was suspected.

After concluding that the tumor was inoperable, the patient withdrew from conventional treatment and opted for experimental treatment using graphene in Taiwan. A little over four months following the diagnosis of his pancreatic carcinoma the patient returned to his GP with progressive disease and icterus. A non-covered metal endoprostheses was placed. The patient's condition progressively worsened, resulting in his passing seven months after the diagnosis of pancreatic carcinoma was made.

Patient B

A 68-year-old male was treated for type 2 diabetes mellitus with metformin 1000 mg twice daily, gliclazide 80 mg thrice daily and 32 units of isophane insulin before. His identical twin was diagnosed with type 2 diabetes mellitus as well. In spite of adequate treatment, his HbA1c progressively worsened, from 62 mmol/mol (7.8%) to 81 mmol/mol (9.6%), over a four-year period. Glucose-lowering therapy was intensified by adding post-prandial short-acting insulin following every meal to the existing regimen.

A few months later the patient presented with overall malaise, fatigue and posture-dependent abdominal discomfort in the upper-left abdominal quadrant. He attributed his abdominal discomfort to his change in lipid-lowering therapy (rosuvastatin was switched for simvastatin). Additionally, he had lost weight from 77.1 (170 pounds) to 71.4 kg (157 pounds). Furthermore, he reported nausea, vomiting and recent discoloration of stool.

At physical examination, the patent was icteric and was pressure-sensitive in the epigastric region, in the absence of palpable masses. The GP referred the patient to the internist. Laboratory measurements revealed the following abnormalities: C-Reactieve Protein 81 mg/L, total bilirubin 33 μmol/l (1.9 mg/dl), direct bilirubin 14 μmol/l (0.8 mg/dl), and ALT 274 U/I. Gastroscopic evaluation revealed a duodenal ulcus, suspect of invasive growth originating from the pancreatic region. Abdominal CT revealed a large mass in the head of the pancreas, with invasive growth in the ventricular antrum and duodenal bulbous. Furthermore, the pancreatic and bile ducts were dilated, there was a radiological image of pancreatitis in the pancreatic corpus and tail, and minor loco-regional lymphadenopathy. Based on this the diagnosis pancreatic carcinoma was made. Following diagnosis, the patient's condition worsened steadily. The patient died in a hospice, two months after receiving the diagnosis of pancreatic carcinoma

Patient C

A 71-year-old male went to his GP for a medical check-up required for his driver's license renewal. He had a PFG of 8.2 mmol/L (148 mg/dl). He had no personal or family history of type 2 diabetes mellitus. The patient reported weight loss of approximately 7 kg (15 pounds) over a five-month period (bodyweight 81.3 kg, height: 1.82, BMI 24.5 kg/m2). He had no abdominal pain, nor icteric signs. Laboratory results followed a week later and revealed a fasting glucose of 12.2 mmol/L (220 mg/dl), HbA1c 82 mmol/L (9.7%), alkalic phosphate of 251 U/l, γ-GT 553 U/l, ALT 259 U/l, lactate dehydrogenase 270 U/l. In accordance with the NHG-guidelines for type 2 diabetes mellitus, the GP prescribed metformin 500 mg twice daily. On account of his liver test abnormalities, he underwent echography of the upper abdomen, the imagery of which was suspect for a carcinoma of the pancreas with vascular invasion.

A week following the diagnosis the patient developed an icterus, which necessitated the placement of an endoprosthesis. The patient died seven months following the diagnosis of pancreatic carcinoma.