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Caso Clínico

# Decompensated Diabetes Mellitus: Beyond Therapy Non-Compliance and Disease Progression

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A B S T R A C T

Decompensated diabetes mellitus is a common clinical event with variable severity. Clinicians should actively pursue the decompensating precipitant. Infections, vascular events, progression of beta cell dysfunction and poor adherence to treatment are among the most common causes. The authors report on a case of a 59-year-old male, with known type 2 diabetes that presented to the emergency department with severe hyperglycemia. Clinical case investigation revealed a pancreatic adenocarcinoma as the cause of the glycemic decompensation. The case is noteworthy for the rarity and severity of the clinical entity and reminds the busy clinician of this uncommon association.

*Palavras-chave:*
Adenocarcinoma
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## Diabetes Mellitus Descompensada: Para Além do Incumprimento Terapêutico e Progressão da Doença

R E S U M O

A diabetes *mellitus* descompensada é uma ocorrência comum na prática clínica com gravidade e consequências variadas. A causa da descompensação deverá ser sempre investigada, sendo mais frequentemente precipitada por infeções, eventos vasculares agudos, progressão da doença (falência da célula beta) e/ou incumprimento terapêutico. Os autores descrevem o caso de um doente de 59 anos com história conhecida de diabetes *mellitus* tipo 2 que recorreu ao Serviço de Urgência por hiperglicemia grave. A investigação revelou a presenca de um adenocarcinoma pancreático como a causa da descompensação glicémica. O caso é relevante pela raridade da neoplasia do pâncreas como causa da descompensação glicémica e serve para relembrar ao clínico esta rara associação.

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## Introduction

Diabetes mellitus (DM) is an exceedingly common disease with an estimated prevalence of 13.3% in the Portuguese population.[1] It is characterized by elevated blood glucose levels and is associated with micro and macrovascular complications. Acutely, diabetes may present with hyperglycemic emergencies namely diabetic ketoacidosis and hyperglycemic hyperosmolar state.[2]

Fortunately, the pharmacological armamentarium for glycemic control has significantly expanded in the last decade, being able to reduce the incidence of acute and chronic complications of DM.[2] Nevertheless, many patients still suffer from acute severe hyperglycemia that may not be totally preventable. Severe infections such as pneumonia, pyelonephritis and foot infections occur more frequently in diabetic patients. The cytokine release and stress state often generate a state of insulin resistance and acute hyperglycemia. Additionally, medications such as corticosteroids, second generation antipsychotics and pasireotide also negatively affect glycemic control. Finally, both acute vascular events and pancreatitis are also common causes of disease decompensation. Apart from these intercurrent illnesses, other factors may underlie decompensation, such as treatment non-compliance, namely omission of insulin therapy, which is unfortunately frequent.[3]

Disease progression is inevitable, being insulin therapy required in a significant number of patients with type 2 DM. Although new pharmacological agents have been shown to protect beta cells and delay its exhaustion, current treatment algorithms still recommend a step-wise approach once the treatment target is no longer obtained with the currently employed strategy.[2] As such, regular patient follow up is warranted in order to anticipate and prevent decompensation.[2]

Accelerated disease progression, refractory to non-insulin regimens, may occur and warrant investigation of an underlying cause. Neoplastic disease, namely pancreatic cancer, is a recognized cause of new onset severe hyperglycemia.[4] The authors report on a case of a diabetic patient presenting with severe hyperglycemia due to an underlying pancreatic adenocarcinoma.

## Case Report

A 59-year-old male, with past medical history of type 2 DM (diagnosed 5 years ago and without any macrovascular or microvascular complications), hypercholesterolemia, active smoking (40 pack-year) and cured hepatitis C infection, treated with metformin (1.5 g/day) and simvastatin (20 mg/day) presented to the emergency department with polyuria, polydipsia, vomiting and weight loss with 3 days duration. He also described 9% weight loss over the last 2 months. No abdominal pain, diarrhea, cough, dyspnea, urinary symptoms, skin changes were reported. Upon admission, the patient was hemodynamically stable, tachycardic, apiretic, eupneic, dehydrated and presented with a body mass index of 20.6 kg/m$^2$. Admission laboratory parameters are presented in Table 1.

Chest X-ray, electrocardiogram, serum lipase and cardiac enzymes were unremarkable. Vigorous intravenous hydration (normal saline with potassium supplements) and insulin infusion were given, which led to a clinical and biochemical improvement.

After hyperglycemic hyperosmolar state resolution, subcutaneous basal bolus insulin scheme was introduced, rendering the patient euglycemic with low insulin requirements (total daily insulin dose of 26 units). Admission hemoglobin A1c was 11.3% and C peptide of 2.5 ng/mL (RR 1.1-4.4 ng/mL). Urinary and blood cultures were negative and leucocyte count and renal function markers soon normalized with supportive care alone. As no obvious precipitant had been identified, an abdominal ultrasound was requested, which revealed a heterogeneous nodule in the pancreatic tail with irregular borders (Fig. 1). Abdominal contrast enhanced computed tomography CT) documented an isodense, non-enhancing pancreatic mass with 55x50 mm with celiac trunk and splenic vessel involvement (Fig. 2). Additionally, the lesion led to extrinsic duodenal compression with could also have explained the vomiting. Celiac and mesenteric lymph node and peritoneal involvement was also seen with no additional suspected metastat-

*Table 1.* Admission laboratory parameters

| Parameter | Admission | Reference range (RR) |
|---|---|---|
| Plasma Glucose (mg/dL) | 764 | 72-106 |
| Serum Osmolality (mosm/kg) | 334 | 285-295 |
| Creatinine (mg/dL) | 3.38 | 0.7-1.2 |
| Urea (mg/dL) | 138 | 13-43 |
| Sodium (mmol/L) | 121 | 135-145 |
| Potassium (mmol/L) | 3.87 | 3.5-4.5 |
| Chloride (mmol/L) | <60 | 98-107 |
| pH | 7.46 | 7.35-7.45 |
| Bicarbonate (mmol/L) | 49.1 | 21-28 |
| Base excess (mmol/L) | 25.3 | -2 to +3 |
| pCO2 (mmHg) | 49 | 35-45 |
| pO2 (mmHg) | 60 | 75-100 |
| Leucocytes (x109) | 22.2 | 4-10 |
| Neutrophils (%) | 88 | 40-80 |
| CRP (mg/dL) | 0.3 | <0.5 |
| Hemoglobin (g/dL) | 16.5 | 13-17 |

CRP – C-reactive protein

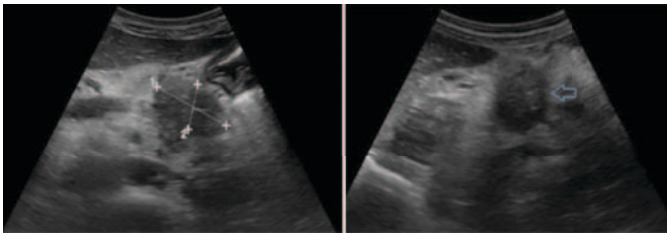

*Figure 1.* Abdominal ultrasound showing an hypoecogenic nodule with irregular borders and heterogeneous content in the pancreatic tail with 43x25 mm (blue arrow).

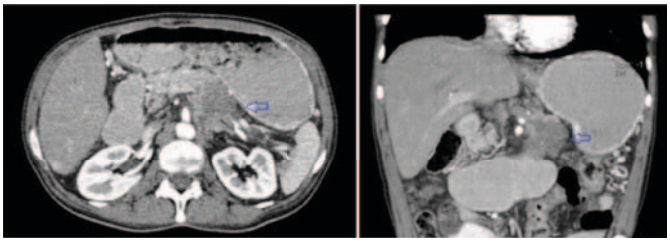

*Figure 2.* Abdominal CT scan after contrast enhancement showing a 55x50 mm hypocaptating mass, located in the transition from the pancreatic body to its tail (blue arrow). It has irregular borders and exhibits an exophytic growth pattern, involving the celiac trunk and splenic vein.

ic disease. Endoscopic ultrasound-guided biopsy was consistent with well differentiated pancreatic adenocarcinoma. Due to the advanced disease stage, palliative chemotherapy was proposed. The patient never began this treatment due to performance status deterioration. This fact led patient's demise within 1 month after initial diagnosis.

## Discussion

Pancreatic adenocarcinoma is the most common pancreatic malignancy, accounting for 85% of pancreatic cancers. It is a rare neoplasm, with an estimated incidence of 1 to 10 per 100 000 people.[5] A male gender predilection has been documented, and the median age at diagnosis is 71 years.[5] Risk factors include smoking, obesity, diabetes mellitus, chronic pancreatitis and some genetic syndromes such as hereditary pancreatitis, Peutz-Jeghers, Lynch, familial atypical multiple mole and melanoma, and hereditary breast and ovary cancer syndromes. The neoplastic masses often arise in the pancreatic head (60%-70%), less frequently affecting the body or tail (20%-25%).[6]

Despite being an aggressive malignancy, pancreatic adenocarcinomas usually have an initial subclinical course, becoming clinically evident late in the disease course due to space occupying effects or widespread metastatic disease.[7] Pancreatic head tumors may become symptomatic earlier than body/tail lesions, commonly giving rise to obstructive jaundice.[8] Regardless of the location, abdominal pain, anorexia, asthenia and weight loss herald more advanced disease and are associated with a dismal prognosis.[8]

No cost-effective screening protocols have been created due to the absence of a satisfactory biochemical early disease marker and unfeasibility of population-based imaging screening protocols for a rare disease.[9] Pannala R *et al* have purposed a promising screening protocol that still lacks validation.[4] Diagnosis may be suggested by ultrasound or cross sectional imaging, (CT-scan and magnetic resonance imaging) findings, being often confirmed by endoscopic ultrasound guided fine needle aspiration cytology, which has a high sensitivity and specificity for malignancy (85% and 98% respectively).[6,10] Tumour markers such as CA19-9 and CEA lack sensitivity and specificity and are not useful for diagnosis, being mostly used for follow up when elevated levels are seen in patients with known disease.[6]

Treatment relies on en bloq surgical removal, often requiring a pancreaticoduodenectomy (Whipple's procedure) by an experienced hepatobiliary surgeon. Due to the high rate of disease persistence and recurrence after surgery alone, adjuvant systemic chemotherapy and chemoradiotherapy are frequently employed to reduce risk of metastatic and locoregional disease, respectively.[6] Prognosis is dismal (5 year survival of 5%) due to the usual advanced stage at disease diagnosis (50% present with metastatic disease, 29% with locoregional spread and only 3% with disease confined to the pancreas), low rate of neoplasm resectability (<15%) and high rate of metastatic spread.[6,11]

Diabetes mellitus and pancreatic cancer seem to have a bidirectional interaction. On the one hand, diabetes has been considered a risk factor, with an estimated odds ratio of 1.8 for pancreatic malignancy.[4] In fact, up to 80% of patients with pancreatic cancer have diabetes.[12] However, the risk of pancreatic cancer among diabetics shows an inverse trend with diabetes duration, being the association highest for patients with diabetes with less than 2 years of duration.[4] On the other hand, pancreatic cancer may cause glucose intolerance and diabetes. The latter has been supported by many studies that further report glycemic profile improvement after effective tumor treatment.[4] The underlying mechanisms are not known, although evidence favors the presence of a humoral factor that gives rise to insulin resistance and beta-cell dysfunction, rather than pancreatic tissue destruction.[4]

Although new onset diabetes may herald the presence of pancreatic cancer, universal screening is not considered to be cost effective since the prevalence of pancreatic cancer is less than 1% in the newly diagnosed diabetic population.[13] Nevertheless, upon new onset diabetes or severe glycemic decompensation in a patient with previously controlled diabetes, the absence of diabetes risk factors or of a clear precipitant should always make the clinician consider the possibility of an underlying pancreatic malignancy.

**Take Home Messages:**

- Pancreatic cancer is a rare malignancy with a dismal prognosis.
- Pancreatic cancer and diabetes are bidirectionally related. Diabetes is a risk factor for pancreatic cancer and the latter is a known cause of diabetes.
- Most patients with pancreatic cancer suffer from diabetes (up to 80%).
- Less than 1% of patients with new onset diabetes have pancreatic cancer.
- Pancreatic neoplasm should be considered as a possible precipitant of hyperglycemic crisis in the absence of the usual culprits (infection, cardiovascular events, pancreatitis, treatment non-compliance) and in the presence of cancer risk factors.

## Responsabilidades Éticas

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## References

1. Observatório Nacional da Diabetes. Diabetes: Factos e Números - O Ano de 2015. Lisboa: OND; 2016.
2. American Diabetes Association, Standards of Medical Care in Diabetes. Diabetes Care. 2017; 40 (Suppl): S1-S135.
3. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009; 32:1335-43. doi: 10.2337/dc09-9032.
4. Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. Lancet Oncol. 2009;10:88-95. doi: 10.1016/S1470-2045(08)70337-1.

5. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69-90. doi: 10.3322/caac.20107.
6. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014;371:1039-49. doi: 10.1056/NEJMra140419
7. Modolell I, Guarner L, Malagelada JR. Vagaries of clinical presentation of pancreatic and biliary tract cancer. Ann Oncol. 1999;10:(Suppl 4):82-4.
8. 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. Clin Transl Oncol. 2005;7:189-97.
9. Li D. Diabetes and pancreatic cancer. Mol Carcinog. 2012;51:64-74. doi: 10.1002/mc.20771.
10. Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012;75:319-31. doi: 10.1016/j.gie.2011.08.049.
11. Berrino F, De Angelis R, Sant M, Rosso S, Lasota MB, Coebergh JW, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. Lancet Oncol. 2007;8:773–83.
12. Wang F, Herrington M, Larsson J, Permert J. The relationship between diabetes and pancreatic cancer. Mol Cancer. 2003;2:4.
13. Chari ST, Liebson CL, de Andrade M, Rabe KG, Ransom JE, Petersen GM. Probability of pancreatic cancer following diabetes: A population-based study. Gastroenterology. 2005;129:504–11. doi: 10.1016/j.gastro.2005.05.007.