Diabetes Could Be a Warning Sign of Pancreatic Cancer: A Case Report and Literature Review

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Received: December 13, 2019; Accepted: January 2, 2020; Published: January 16, 2020

Abstract: Pancreatic cancer (PC) is one of the deadliest cancers, representing the fourth leading cause of cancer death in the world; This high mortality is due to late symptom onset and because most of the cases of pancreatic cancer are stage IV at diagnosis, and hence not a candidate for curative resection. The following report will serve to emphasize the role of new-onset diabetes in certain patients as a warning sign necessitating further investigation for pancreatic cancer. It’s about a 46-years old man was admitted in hospital «service of forensic and penitentiary medicine » for jaundice associated with progressive asthenia, abdominal pain, and weight loss. He had been diagnosed with diabetes 4 weeks earlier by his GP. Despite lifestyle changes, he had been commenced on metformin after just 2 weeks due to poor glycaemic control. Physical examination showed a mass of the upper right quadrant on palpation. Computed tomography of the abdomen showing a solid mass of 55 mm in the head of the pancreas, hypodense in particular, with mild Wirsung and bile ducts dilatation, and the focal thrombi is found at the level of the 9 mm splenomerosaraic confluent, with hepatic secondary localization images. He was subsequently diagnosed with new-onset diabetes and metastatic pancreatic cancer. The treatment with basal insulin / bolus and anticoagulant therapy was instituted and after stabilization; the patient has been oriented for bilio-pancreatic derivation, and eventual biopsy in a specialized center, but unfortunately the patient died only a few weeks after. PC occurs with increased frequency in patients with type 2 diabetes mellitus (DM2) which is considered the third modifiable risk factor for pancreatic cancer after cigarette smoking and obesity. Although numerous studies have linked both entities since 1833 the mechanism behind this association are complex and not well understood by the moment.

Keywords: Diabetes, Pancreatic Cancer, Diagnosis, Warning Sign

1. Introduction

Pancreatic cancer is one of the most common cancers world-wide, with a 5-year survival rate of approximately [7%-8%], and for most patients, death occurs within 6 months after the diagnosis [1-4].

Despite decades of effort, there are still few early detection methods or effective treatments, and at diagnosis, most patients have locally advanced unresectable or metastatic lesions, rendering them Incurable, [5] PC is expected to become the second leading cause of cancer mortality by 2020 [2].

Diabetes is a multi-factorial and heterogeneous disease, which involves about 424 million people globally according to the latest statistics released by the International Diabetes Federation, this figure being expected to rise to 552 million by 2030 [6, 7].

Type 2 diabetes mellitus is likely the third modifiable risk factor for pancreatic cancer after cigarette smoking and obesity [2, 8-10].

The association between diabetes mellitus (DM) and pancreatic cancer has been known for over a century; This
association was supported by statistically significant relative risk near to 2 in several studies [11]. It is now well understood that while long-standing diabetes is an etiologic factor for pancreatic cancer, new-onset diabetes can be a manifestation of the cancer [12].

2. Materials and Methods

2.1. Illustrative Case Report

Case report
A 46-years old man was admitted in hospital «service of forensic and penitentiary medicine » for jaundice associated with progressive asthenia, abdominal pain, and weight loss. He had been diagnosed with diabetes 4 weeks earlier by his GP. Despite lifestyle changes, he had been commenced on metformin after just 2 weeks due to poor glycaemic control.
He was a smoker with a 15 pack-year and drank excessive amount of alcohol, weaned for a few years. Her family history was significant for type 2 diabetes and hypertension, but he denied a family history of any cancers.
Physical examination showed: weight, 63.0 kg; height, 168 cm; body mass index, 22 kg/m²; and blood pressure, 130/70 mmHg. His aspecific symptoms, such as weakness and weight loss was thought to be the consequences of diabetes. A mass of the upper right quadrant on palpation.
Laboratory Values:
Hemogram showed level of hemoglobin at 10.09 g/dl, with MCV at 81.8 fl and MCHC at 32.5 (NR 30-300), total leukocytes, 10,000 / mm³, and the level of platelets at 481 x 10⁹/L.
The erythrocyte sedimentation rate (ESR) was at 40 mm/hr, a C-reactive protein within the normal range, an elevated lactate dehydrogenase of 455 U/L (normal range, 120 to 240 U/L), and a serum calcium of 7 mg/dL. Renal function tests were normal (serum creatinine, 0.7 mg/dL; creatinine clearance, 102 mL/min); electrolytes showed a potassium of 7.0 mmol/L; electrolytes showed a sodium of 110 mmol/L; creatinine of 0.0 mg/dL.
Urinalysis showed trace amounts of glucose, normal urobilinogen, no protein or ketones, and pH 6.
Computed tomography of the abdomen showing a solid mass of 55 mm in the head of the pancreas, hypodense in particular, focal thrombi is found at the level of the 9 mm splenomersaric confluent, with hepatic secondary localization images (figure 1).

2.2. Management and Out-come

The treatment with basal insulin / bolus and anticoagulant therapy (Tinzaparin) was instituted and after stabilization; the patient has been oriented for bilio-pancreatic derivation. And eventual biopsy in a specialized center, but unfortunately the patient died only a few weeks after.

3. Discussion
Pancreatic cancer and diabetes have a complex bidirectional relationship (figure 2). A large proportion (varied between 50%–80% by studies) of pancreatic cancer patients have concurrent diabetes or impaired glucose tolerance [6, 8, 9, 12-19]. Diabetes or impaired glucose tolerance is present in more than 2/3rd of pancreatic cancer patients.
There have been numerous epidemiologic studies, both cohort and case-control, on the association between diabetes and pancreatic cancer. The studies have stratified the risk of cancer based on duration of diabetes. As is to be expected, a number of meta-analyses of these studies have been published (Everhart, Huxley Ben) [14]. The latest meta-analysis, in 2018 by Ji-Jun Zhang et al, includes 26 case-control studies published before October 2017 [1].
The early symptoms of pancreatic cancer, such as abdominal pain, weight loss, fatigue, jaundice, and nausea [2, 12, 20], are non specific and may occur late in the course of the disease.
It must be kept in mind that, although rare, PC might be the precipitating factor in diabetic keto-acidosis cases [21, 22].
As a result, pancreatic cancer is usually diagnosed at an advanced stage, frequently after the tumor has already metastasized [5, 15].
Both diabetes and cancer share a dramatic negative impact on both the expectancy and quality of life, and their parallel increase in rate of incidence has stimulated the scientific community to look for a relationship in terms of pathophysiological mechanisms and/or common environment. In 1957s, the pathologist E. T. Bell reported that patients...
suffering by glycosuria and hyperglycemia have an increased incidence of pancreatic carcinoma [7].

The mechanism of the association between DM and PC is mysterious but most hypothesized mechanisms underlying the association between T2DM and PC include hyperinsulinemia, insulin resistance (IR), elevated levels of circulating insulin-like growth factors (IGFs), hyperglycemia and chronic inflammation that influences tumor growth [6, 7, 23].

a) Hyperinsulinemia and insulin resistance

Insulin itself is a growth promoting hormone with mitogenic (but not mutagenic) effects and diabetes associated cancer cells express insulin and IGF-1 receptors which play a key role in cell growth and differentiation [6].

As previously stated, DM2 is a consequence of a deficiency of functional insulin. This deficiency can be due to a lack of production or lack of end-organ response to insulin. In 2004, Chari and colleagues showed that DM2 associated with PC is likely due to both decline in b-cell function and increased end-organ resistance [9].

b) Insulin-insulin like growth factor axis

Peripheral insulin resistance and hyperinsulinemia have been suggested to promote growth in pancreatic cancer cells. Insulin binds to the IGF1 (insulin-like growth factor 1) receptor and thereby increases the amount of available IGFBP1 (insulin-like growth factor binding protein 1), which in turn stimulates growth in exocrine PaC cells in an autocrine manner [24]. These receptors can stimulate cancer cell proliferation and survival and promote metastasis, thus favoring cancer progression [6, 7].

c) Hyperglycemia

Hyperglycaemia has been found to enhance proliferation, local invasiveness and metastatic potential in pancreatic cancer [23].

Moreover, hyperglycemia is responsible for induction of oxidative stress and DNA damage, which may trigger the first phases of tumorigenesis [7, 14].

Specifically the tumor within the pancreatic parenchyma, is more aggressive in a microenvironment combining hypoxia with hyperglycemia. High glucose levels can up-regulate HIF-1α expression, which promotes metastasis of pancreatic cancer [24]. Hyperglycemia aggravates microenvironment hypoxia and promotes the metastatic ability of pancreatic cancer in a hypoxic environment, pancreatic cancer cells express high levels of the hypoxia-inducible factor 1α (HIF-1α) [25].

d) Chronic inflammation

Inflammatory cytokines, ROS, and mediators of inflammatory pathways, such as cyclooxygenase-2 (COX2) and nuclear factor kappa B (NFκB) are associated with oncogene expression, silencing of tumor suppressor genes, and affect the cell cycle, all of which may facilitate pancreatic carcinogenesis [6].

Increased circulating levels of specific adipose tissue-derived cytokines have been reported to promote tumor cell growth (tumor necrosis factor-α [TNF-α], interleukin [IL]-6), enhance metastasis (TNF-α, IL-6, transforming growth factor [TGF]-β), increase angiogenesis (TNF-α, IL-17, TGF-β), and impair the function of macrophages and NK cells [7, 24].

Oxidative stress is another player tightly linked with inflammation and cancer risk in diabetes. The levels of all biomarkers of oxidative stress are usually increased in patients with diabetes, and oxidative stress can mediate damage to cell structures, including lipids and membranes, proteins, and especially DNA [7].

Type 2 diabetes or intratumoural leukocyte (macrophage, neutrophil or eosinophil) infiltration alone did not significantly influence pancreatic cancer prognosis. However, among cancer patients with T2D high macrophage or neutrophil tumour-infiltration was associated with a significant reduction in overall survival (adjusted hazard ratio [HR] 7.2; 95% CI 1.5e35.0 and HR 5.4; 95% CI 1.1e26.3, respectively) [3].

4. Conclusion

The prognosis of pancreatic cancer is quite poor and the case illustration underscores PC’s aggressive. Nature and the need for early detection. Currently, there are no validated means of screening for PC. Patients presenting with symptoms of PC, which are usually vague and non-specific.

References


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