Clinical case

Diabetes mellitus as an early symptom of pancreatic cancer diagnosed three years later

Diabète sucré : symptôme précoce d’un cancer pancréatique diagnostiqué trois ans plus tard

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Résumé


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Abstract

We present a case of a 40-year-old man with strong family history of diabetes. His pancreatic ultrasonography was normal at the discovery of his diabetes. Anti-pancreatic antibodies were negative. The patient was treated by insulin and continued to lose weight. His diabetes remained unstable during the follow-up. Three years later, a pancreatic adenocarcinoma was diagnosed which was locally advanced and could not be removed surgically. This observation argues among several mechanisms explaining diabetes in subjects with pancreatic cancer, in favor of tumor-derived diabetogenic substance and suggests that diabetes mellitus could reveal pancreatic cancer even in the presence of conventional risk factors of type 2 diabetes.

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Pancreatic cancer (PC) is becoming more frequently diagnosed accounting about 3000 new cases each year in France and about 32,000 new cases each year in the United States. As the prognosis of PC is known to be poor with an overall five-year survival rate not exceeding 5% [1], the identification of risk factors such as smoking, heavy alcohol consumption, family history of PC [2], diabetes mellitus (DM) [2,3], morbid obesity [4] and history of gestational diabetes [5] could have an impact on reducing PC morbidity and mortality. The association between DM and PC has long been recognized but this relationship remains complex and not yet well clear. About 80% of patients with PC have glucose intolerance or patent diabetes [6,7]. The occurrence of DM could be explained either by the gland destruction due to a large pancreatic tumor [8] or by dia-
betogenic hormones (such as glucagon, somatostatin) secreted by a pancreatic neuroendocrine tumor [9,10]. Some drugs used in the treatment of PC such as cisplatin have also hyperglycemic effect and hence could induce glucose intolerance [11]. Furthermore, long-standing DM could also be an etiologic factor for PC which could be added, according to Everhart and Wright, to the list of complications of diabetes [3]. On the other hand, there is growing evidence that new-onset diabetes is a direct consequence of PC, therefore, it may be considered as a symptom or early biomarker of PC [12]. We present the case of PC discovered three years after DM diagnosis in a patient with strong family history of type 2 diabetes and we discuss the possibility of a tumor-derived diabetogenic substance as a cause of DM.

1. Case report

A 40-year-old man was diagnosed with DM when he was 37. He had a strong familial history of DM but no signs of exocrine pancreatic disease in his relatives. He was a smoker and drank excessive amount of alcohol. He had no history of abdominal pain or jaundice. At the discovery of diabetes, he had a significant weight loss. Investigation of this weight loss did not show any increase of biochemical marker of chronic infection or neoplasia including CA 19-9. Chest X-Ray did not reveal any suspicious mass of neoplasia or tuberculosis. The transabdominal ultrasonography at diagnosis was normal particularly, in the pancreatic area. His BMI was at 22.4 kg/m² and transabdominal ultrasonography was therefore requested and showed a tumor of the head of the pancreas and coelomesenteric nodes. Serum CA 19-9 was greatly elevated (863.3 UI/L). Computed tomography confirmed the presence of pancreatic tumor which did not exceed 2 cm in diameter but which was locally advanced; hence, it was unresectable (Fig. 1). Palliative surgery was performed to improve obstructive signs. Histological diagnosis of infiltrative intraductal adenocarcinoma of the pancreas was made. Immunohistochemical analysis did not reveal any tumour-tissue marker of neuroendocrine tumor. Chemotherapy including gemcitabine and cisplatin was used. Before starting chemotherapy, potassium was within the normal range (4.6 mmol/L), fasting glucose level was 13.6 mmol/L and glycated hemoglobin (HbA1c) was 9.6%.

One week after the second chemotherapy cycle, the patient was admitted to hospital with vomiting and epigastric pain without fever or diarrhoea. On admission, random glucose was elevated at 19 mmol/L and electrolytes showed a very low potassium of 2.1 mmol/L, with a sodium of 138 mmol/L, plasma bicarbonate of 30 mmol/L, calcium of 2.30 mmol, urea of 3.0 mmol/L and creatinine of 53 μmol/L. Arterial blood gases confirmed the metabolic alkalosis with a pH of 7.55 and a pCO₂ of 35.6 mmHg. Liver function tests were at normal range. Urine analysis revealed ketosis. Control of glycaemia as well as improvement of symptoms was achieved with intravenous insulin and fluids. Nevertheless, hypokalaemia persisted (2.6 mmol/L) many weeks later. The department of medical oncology informed us that the patient died a few months later.

2. Discussion

DM in the case reported here, was diagnosed few years before PC diagnosis and no degenerative complications were found at its discovery. Furthermore, diabetes duration of three years is not enough to explain the PC development [13]. This led us to rule out the hypothesis that PC is a consequence of long-standing type 2 diabetes. Neuroendocrine origin of the pancreatic tumor was also ruled out, since no clinical or histological signs suggesting this etiology were found. In addition, the small size of the tumor argues against the possibility of a lack of insulin via tumor-induced beta-cell destruction [8]. The use of cisplatin would complicate the situation because it has been reported that among patients receiving cisplatin for their PC, about 5% developed diabetes [11]. Our patient was already diabetic, when he was treated by cisplatin. This drug can also be responsible for a poor insulin response to glucose stimuli, abnormal glucagon metabolism and an acute or chronic hypokaliemic metabolic alkalosis via nephrotoxic effects which may explain the metabolic disorders following cisplatin therapy in our patient [14].

The latest hypothesis that DM is a consequence of PC seems to be the most appropriate in this observation. Interestingly, in a recent study, an American group from Mayo clinic has shown that DM in more than half of diabetic patients with PC is new-onset (< 2 years) [15,16]. In their population-based study, Chari et al. showed that subjects with new-onset diabetes have a 8-fold higher likelihood of being diagnosed with PC within 3 years.
of first meeting of diabetes compared to general population [7]. Moreover, in PC-associated DM, glucose tolerance often resolved after tumor resection [15]. It has been also reported that PC could enhance hyperglycemia by increasing peripheral insulin resistance, suppressing insulin secretion, impairing proinsulin conversion and/or inducing chronic inflammation [2]. Taken into account the small size of tumor, these facts provide the strong evidence that a diabetogenic factor secreted by the pancreatic tumor is the only valid explanation in the case reported here. Katsumichi and Pour have recently demonstrated that islet amyloid polypeptide (or amylin), which is already known to reduce insulin secretion and which is increased in type 2 diabetes and inconstantly in PC, was rather reduced within tumor areas [12]. This seems to argue against the role of this peptide in glucose intolerance in PC patients. Of interest, Basso et al. identified, by using proteomic applications, a PC-derived 14-Aminoacid that they considered to be a putative diabetogenic factor by reducing glucose uptake in myoblasts [17]. The clinical application of this peptide should be confirmed in few years. These findings have led investigators to suggest that recognition of DM as an early manifestation of PC, well before the appearance of PC-specific clinical signs, could lead to the diagnosis of surgically resectable PC and hence with better prognosis [16]. Therefore, we are convinced that PC was present since the first meeting of DM in our patient; however biologic and radiological markers performed at that moment were insufficient to make the diagnosis of PC. Indeed, transabdominal ultrasonography has lower sensitivity compared to CT scan or MRI (55–90% versus 98%) [13] and hence misdiagnoses tumors smaller than 2 cm in diameter. In addition, several reports showed that CA 19-9, a tumour-associated antigen, despite its high sensitivity and specificity (70 and 80%, respectively) is not useful for screening asymptomatic populations for PC because of its very low positive predictive value [14].

These data raise the question of how to distinguish type 2 diabetes from PC-associated DM which needs more investigations to diagnose the tumor. It has been reported that PC rarely occurs in persons younger than 50 years, and the risk increases with age [1,13], therefore Damiano et al. suggested to carry out a pancreas CT scan or MRI on all patients over 50 years old presenting with unstable new-onset diabetes [13]. Our observation showed that this age threshold could not be formally recommended. Furthermore, previous investigators have suggested that patient with atypical diabetes with regard to a lack of family history of diabetes, absence of obesity, and a rapid progression to insulin dependence should be screened for PC [18]. In the case reported here, it is interesting to note that even in the presence of conventional risk factor of type 2 diabetes (i.e. strong family history of type 2 diabetes) new-onset DM was secondary to PC. Taken all these finding together, it is important to mention that although the incidence of PC in diabetic patients remains low (approximately 1% of subjects aged over 50 with new-onset DM) [7], it would be beneficial to screen PC in unstable newly-diagnosed diabetic patients (≤2 years), especially if other PC risk factors (i.e. smoking, alcohol consumption) in order to diagnose earlier PC at treatable stage.

3. Conclusion

Our case argues in favor of DM as an early symptom of PC probably by the tumor secretion of a diabetogenic substance. There is enough evidence now that new-onset diabetes may serve as a good tool of detection of early stage PC even in asymptomatic patients. We suggest that patients with unstable newly-diagnosed diabetes without type 1 diabetes criteria and even in the presence of conventional risk factors of type 2 diabetes should be screened by CT scan. This method could help to diagnose small cancers of the pancreas, which are more likely to be treatable. Further prospective large studies are needed to determine the clinical validity of this approach. The identification of a specific mediator of PC may facilitate screening in new-onset diabetes.

Conflicts of interest

The author(s) declare that there is no conflict of interest.

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References


