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New-onset diabetes mellitus type 2 treated with metformin- is it possible to slow the development of pancreatic cancer? - case report

New-onset DM2 and pancreatic cancer treated with metformin

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ABSTRACT

In this article, we present the case of an 87-year-old patient whose initial symptom of developing pancreatic cancer was newly diagnosed type 2 diabetes mellitus. She was treated with metformin, which, on the one hand, could slow the development of pancreatic cancer and, on the other hand, delayed a key cancer diagnosis. However, before the definitive diagnosis, the patient's symptoms were considered merely as side effects of metformin treatment, delaying the proper diagnosis. We consider that early diagnosis of pancreatic cancer remains a significant challenge. Often, the first symptom is newly diagnosed diabetes mellitus type 2. In this article, we aim to demonstrate the importance of being vigilant when diagnosing and treating diabetes mellitus with metformin. We also present the impact of metformin on the course of pancreatic cancer. Additionally, we emphasize the need to be attentive when patients complain of side effects of this medication, as they may often mask the development of pancreatic cancer.

Key words: pancreatic cancer; diabetes mellitus type 2; metformin; new-onset diabetes mellitus; cancer treatment; cancer diagnosis

INTRODUCTION

Pancreatic cancer is one of the most malignant tumors. By 2030, it is anticipated that pancreatic tumors will become one of the leading causes of cancer-related mortality [1]. Pancreatic neoplasia is a cancer of the elderly, with a median age of about 70 years old. Still, the 5-year survival rate for pancreatic cancer remains at only 11%. This is due to the fact that the majority of these tumors are diagnosed at a late stage, when metastases are present. Although if it is diagnosed at stage I the median survival is extended to 26 months. Diagnosis at stage IV results in a median survival of 4.8 months. [2] The identification of the disease is very difficult because the symptoms are not obvious. One of the first manifestations of

pancreatic cancer is new-onset diabetes mellitus type 2. Research shows that nearly 80% of patients with newly diagnosed pancreatic cancer also had newly diagnosed diabetes mellitus type 2 or glucose intolerance. Unfortunately, these diseases often have a negative prognostic impact on tumor remission [3]. The risk of pancreatic cancer increases by eight times for individuals over 50 who experience a new diagnosis of diabetes [4]. However, it is very easy to misrecognize elevated glucose blood level as the first symptom of cancer, because the manifestations of diabetes and tumor could be similar, for instance, vomiting, weakness, drowsiness, and also, of course, elevated glucose blood level. The correct diagnosis is particularly challenging, especially in the adult population with risk factors such as a family history of pancreatic cancer, obesity, diabetes, smoking, drinking alcohol, and pancreatitis [5]. Diabetes could be both the risk factor and the early manifestation of pancreatic cancer, which makes achieving an accurate diagnosis more challenging.

The first-choice readily available examination for detecting pancreatic cancer is computer tomography (CT). Early tumor detection is possible when CT is performed on patients at high risk for pancreatic neoplasia (for example with newly diagnosed diabetes). In this imaging examination, there may be very small changes, such as dilatation of the pancreatic duct or pancreatic atrophy. However, by spotting them on CT, the disease can be diagnosed even 3 to 36 months before the clinical stage of the tumor. It escalates the chances for radical surgery [2] and for the patient survey. Unfortunately, most people are diagnosed with an advanced stage of cancer, leaving palliative therapy as the only treatment option [6].

Metformin is the hypoglycaemic medication, that is used the most often in the treatment of diabetes mellitus type 2 nowadays. Most of the recent studies show that it also improves the treatment of pancreatic cancer. Metformin's effective hypoglycaemic impact might help lower the risk of pancreatic carcinogenesis [5].

In this case I will present a patient whose initial symptom was new-onset diabetes mellitus type 2, treated with metformin. While metformin may potentially slow the progression of cancer, it can also contribute to delaying accurate diagnosis.

CASE DESCRIPTION

The patient, an 87-year-old woman, in November, presented to the emergency department with dizziness lasting several days. At the time, she weighed about 63 kilograms. She had a medical history significant for hypertension, atherosclerosis, and osteoporosis, for

which she had been prescribed medications. The initial head CT scan showed no acute abnormalities. Urinalysis revealed bacteriuria without associated symptoms. Blood tests indicated elevated glucose levels. The patient was discharged with a prescription for further evaluation for diabetes mellitus.

After subsequent glucose testing, her primary care physician diagnosed diabetes mellitus type 2 and initiated metformin therapy- 500mg per day. However, the patient experienced worsening side effects over time, including nausea and vomiting. She also exhibited significant weight loss, exceeding 10 kg over six months, with an ongoing decline in weight and a waning appetite. Despite improvement in HbA1c levels from 6.7% to 6.4%, her glycaemic control worsened, and she started taking metformin irregularly.

In September, she developed increased persistent vomiting and diarrhea and decreased appetite, leading to multiple emergency department visits for electrolyte imbalances and fluid loss. In her blood tests, potassium level was 3.19 mmol/l and sodium level was 128,4 mmol/l. After several recurrent emergency department visits due to uncontrollable emesis, it was decided to perform an abdominal computer tomography scan. An abdominal CT scan revealed findings suggestive of a pancreatic head tumor, including cystic changes in the liver, dilated intrahepatic bile ducts, and dilation of the common bile duct without calcifications (Figure 1.). Additionally, the pancreas exhibited abnormal morphology, with dilation of the Virsung duct and infiltration around the superior mesenteric artery, consistent with pancreatic malignancy.

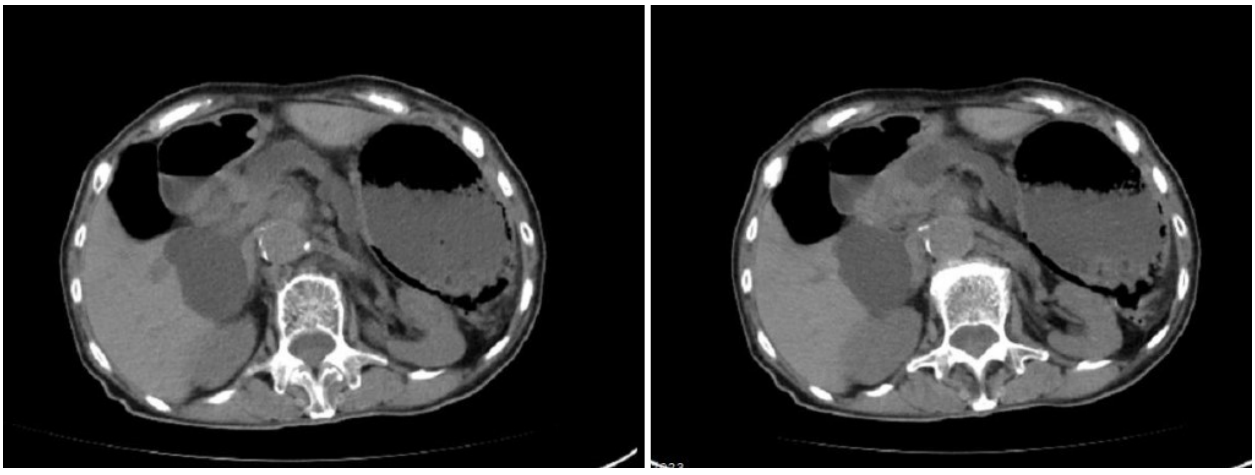

Figure 1.Pancreatic head tumor

It has been proposed to create bypass anastomoses (gastrointestinal and intestinal-jejunal) but due to the patient's cachexia, advanced age, and overall frailty, she declined further

treatment and surgical intervention. The patient was managed acutely with analgesic therapy, intravenous hydration, nutritional supplementation with nutridrinks, and attempts to reduce the frequency of vomiting. Unfortunately, she passed away one month later.

DISCUSSION

As we presented in our case pancreatic cancer and diabetes mellitus type 2 are inherently linked. Sometimes, diabetes can be the first symptom of cancer, while at other times, it serves as a risk factor for malignant changes. Retroactively establishing this connection can be challenging, especially in the elderly with newly diagnosed diabetes, as we presented in the described patient. It requires physicians to exercise greater vigilance when dealing with older, weakened patients with elevated blood sugar levels.

Metformin, a biguanide derivative, is still the most popular described oral glucose-lowering drug for the treatment of type 2 diabetes mellitus [7]. Its main mechanism of action against hyperglycemia is the inhibition of hepatic gluconeogenesis, which lowers the amount of glucose produced by the liver. Additionally, the medication increases the liver's sensitivity to insulin. It converts hepatocytes from a less energy-intensive catabolic pathway, such as glycolysis, to an anabolic one, such as gluconeogenesis. Additionally, metformin improves peripheral tissue insulin sensitivity by raising skeletal muscle and adipose tissue's absorption and consumption of glucose [7]. Furthermore, this medication reduces insulin resistance in addition to directly inhibiting the proliferation of certain cancer cells [1].

Recent studies have demonstrated the potential of metformin to exert inhibitory effects on tumor development. Although the precise mechanism of action of metformin in treating pancreatic cancer is not fully understood and ongoing studies have not consistently confirmed its therapeutic effect [8] on pancreatic tumors, decreasing blood sugar levels and tissue insulin resistance may have positive effects on the patient. Hyperglycemia and hyperinsulinemia influence the development of tumors, their malignancy, and invasiveness, as well as angiogenesis and immunomodulation [9]. These mechanisms operate through the gradual destruction of pancreatic beta cells, thereby increasing the risk of cancer development [10]. Insulin also reduces the synthesis of IGF-binding protein in the liver, thus increasing the risk of pancreatic cancer occurrence. Metformin can also reduce the weight of the patient, resulting in decreased synthesis of pro-inflammatory cytokines such as VEGF, TNF-alfa, and IL-6 [5,9]. We presented some of the anti-cancer effects of metformin in Figure 1 [1,5,7,8,9].

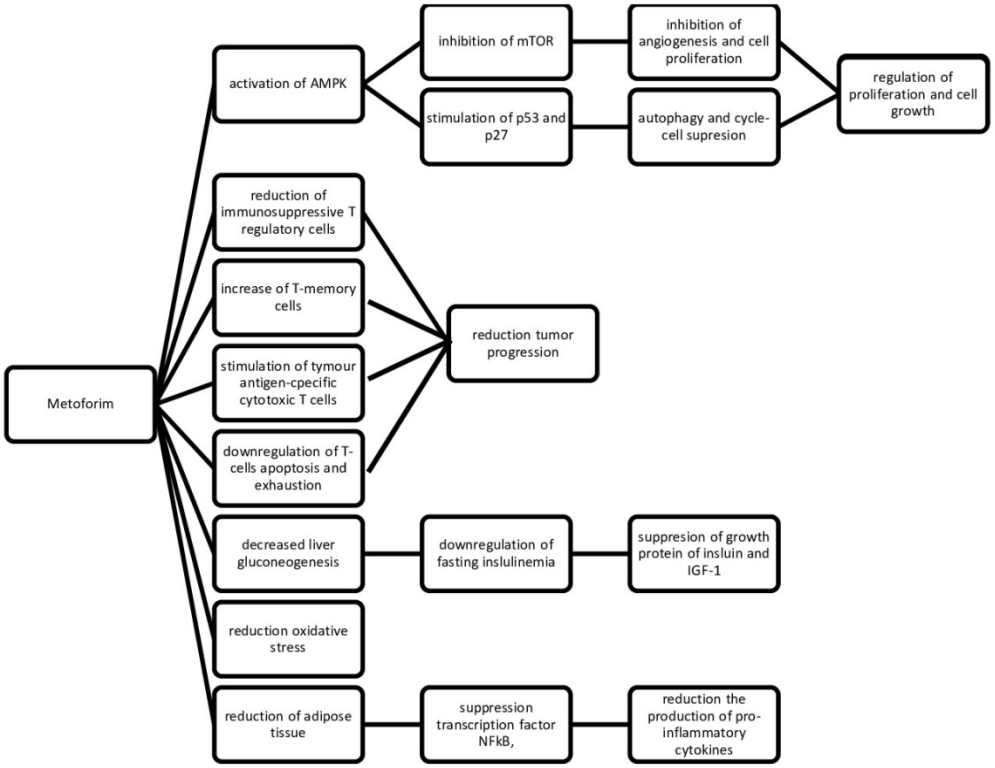

Figure 2. Certain anti-neoplastic effects of metformin. (AMPK- Adenosine monophosphate (AMP)-activated protein kinase; mTOR- mammalian target of rapamycin; IFG-1- insulin-like growth factor-1)

As the most commonly prescribed medication for diabetes management, metformin holds significant promise in the realm of cancer prevention and treatment. We may see the greatest impact of metformin on pancreatic cancer when it's used after surgery to reduce the chance of the cancer coming back (adjuvant therapy) or to prevent cancer from forming in the first place (chemoprevention)[11]. However, it is worth considering including metformin in the treatment of patients with diagnosed pancreatic cancer. Particularly, attention should be paid to those who have been controlling their existing diabetes with other medications.

Despite benefits of metformin, up to 25% of people experience side effects from this medication. 5% of them are unable to take metformin due to its poor tolerance. There are most

commonly nausea and diarrhea [12]. Unfortunately, the increased risk of side effects may particularly affect females and patients with reduced body mass. Regrettably, all of these symptoms have an adverse impact on their quality of life and could lead to inadequate medication dosing and lack of adherence [13]. It should also be remembered that although metformin is a well-tolerated drug in the majority of cases, it is contraindicated in some patients, including those with kidney failure or increased risk of lactic acidosis [10].

As mentioned above, insulin resistance can be treated with metformin. It occurs in both diabetes type 2 and pancreatic cancer. With appropriate diagnosis, it is important to note that the increased insulin resistance in tissues often coincides with weight gain in diabetes, whereas in the presence of pancreatic cancer, weight loss is observed [5,9,14]. However, it prompts us to ponder whether, in cases where new-onset type 2 diabetes coincides with weight loss, it might be careful to expand diagnostic investigations or heighten vigilance regarding the possibility of malignancy, particularly pancreatic cancer.

Newly diagnosed diabetes, especially in adults over 50 may indicate pancreatic cancer [5,9]. We want to highlight the importance of considering malignancy in patients presenting with elevated blood glucose levels. Peripheral insulin resistance typically appears early in the course of cancer, which could explain why diabetes can appear before signs of a pancreatic tumor [1]. Narrowing our focus exclusively on diabetes and its management may inadvertently mask the signs of growing pancreatic cancer.

The majority of individuals diagnosed with pancreatic cancer initially present with obstructive jaundice, and in rare instances, painless enlargement of the gallbladder. Patients with pancreatic cancer affecting the body or tail commonly experience epigastric pain, significant weight loss, detection of an abdominal mass upon palpation, and early satiety.

Nonetheless, a crucial distinction is the fact that diabetes mellitus in pancreatic cancer correlates with weight loss, while diabetes mellitus type 2 is linked to weight gain [5]. For this reason, elevated blood glucose levels in the elderly without previously diagnosed diabetes should serve as an alarming signal for physicians in the context of cancer, especially pancreatic cancer [5,9]. In diabetics with a weight loss of more than 5% of the body weight for 6 months, it is worth doing an abdominal CT and checking the pancreas [15].

However, metformin may protect diabetics type 2 from pancreatic cancer, according to retrospective meta-analyses [6]. Several examines have summarised that patients treated with

metformin for diabetes had a lower risk of developing pancreatic ductal adenocarcinoma than those without treatment with the drug [16]. Nevertheless, metformin does not affect high-grade tumors, while a little effect may have been seen in people with low-grade tumors. We still need more research on people with pancreatic cancer. However, due to its hypoglycaemic effect, metformin acts beneficially in both pancreatic cancer patients and those with diabetes. For sure, well-controlled diabetes can reduce the risk of developing pancreatic cancer [5].

CONCLUSION

We recommend careful consideration during the treatment of newly diagnosed type 2 diabetes in elderly individuals. Initiating metformin therapy, which has been shown to slow tumor development, is advisable. However, it is important to pay attention to whether the symptoms reported by the patient are side effects of metformin use or further signs of developing pancreatic cancer. An examination that can be performed in such cases is an abdominal computed tomography scan. This will allow us to detect pancreatic cancer development more quickly and efficiently, thereby increasing the chances of curing it.

ARTICLE INFORMATIONS

Author's contribution: Conceptualization, methodology, software, check, formal analysis, investigation, resources, data curation, writing - rough preparation, review and editing, visualization, supervision, project administration- Katarzyna Pochodowicz, Karolina Rogowska, Julia Zawistowska , Weronika Rutkowska-Kawalec , Jakub Kawalec , Angelina Lęgas , Joanna Smalira, Weronika Rogala, Bartosz Przybysz , Karolina Urbańska . All authors have read and agreed with the published version of the manuscript**.**

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