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Case Report

# Exenatide and Pancreatic Cancer: A Case Report and Review of Relevant Literature

Timothy L. Cannon[1]*, Melany B. Atkins[2], John F. Deeken[1], Haresh Mani[2], Svetlana Rassulova[1], Megan Kokon[1], Donald L. Trump[2]

[1]Inova Dwight and Martha Schar Cancer Institute

[2]Inova Fairfax Hospital

**Introduction:** Pancreatic cancer is the 4th most common cause of cancer death in the United States, and is associated with a 5 year survival rate of 5%. In recent years, epidemiological studies have raised the concern about a link between the use of antidiabetic drugs that act along the glucagon-like peptide pathway and the development of pancreatic cancer. Additionally, pre-clinical studies have suggested that GLP-1 pathway agents may promote the malignant progression of pancreatic intraepithelial (PanIN). Exenatide, which is a glucagon-like peptide -1 agonist (GLP-1), is among the most commonly used agents in this class.

**Case presentation:** The patient described in this case report presented with stage IV pancreatic cancer 5 years after the initiation of exanetide. The patient and her husband raised the question of an association between exanetide and her cancer. Unfortunately, her cancer was refractory to gemcitabine based therapy, and she succumbed to her disease shortly after diagnosis.

**Conclusion:** There is limited evidence to establish a link between this class of antidiabetic medication and pancreatic cancer. While there are preclinical studies that demonstrate a mechanism by which GLP-1 pathway drugs cause chronic pancreatitis and promotion of pancreatic oncogenesis, epidemiological studies are conflicting. However, most of these studies had a fairly brief follow up period (< 5 years), and the process of oncogenesis is likely to be protracted over several years. This case, occurring 5 years after the initiation of the agent, highlights the need for longer epidemiological studies. As of 2007, over 700,000 patients had already used exanetide. Given the high usage of these medications and the poor prognosis associated with pancreatic cancer, any association is important. Long term clinical studies, and preclinical studies that explore the question of associated deleterious somatic mutations in this population are indicated.

**Keywords**: pancreatic cancer; diabetes; glucagon-like peptide-1 agonists; GLP-1;PanIn (PanIN); intraepithelial neoplasia.

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**Consent**: We confirm that the patient has given the informed consent for the casereport to be published.



***Correspondence to:** Timothy L. Cannon, Inova Dwight and Martha Schar Cancer Institute, 8505 Arlington Blvd., Suite 100, Fairfax, VA 22031,United States; **Email**: timothy.cannon@inova.org

# Background

## Exenatide

Type II diabetes results from inadequate insulin secretion from β cells to compensate for resistance to insulin in peripheral tissues. This results in many adverse health effects – most involving vascular pathology – hypertension, cardiac and CNS disease, retinopathy, neuropathy and nephropathy. 20.8 million people in the U.S. have diabetes [1], and life expectancy of such individuals is 6 years less than people without diabetes [2]. Metformin is effective as monotherapy or as part of a combination with other oral antidiabetic agents at improving glycemic control [3, 4], but many patients become refractory to these agents, and glycemic control is lost.

Exendin-4 is a peptide isolated from the saliva of the Gila monster, a large venomous land lizard native to the southwestern United States [5]. Exendins have physiologic effects which mimic the effects of glucagon- like peptide-1 (GLP-1), such as augmenting insulin secretion. Exenatide is a synthetic version of exentin-4, and has significant sequence homology with glucagon like peptide-1 (GLP-1) [6]. Exenatide is more potent *in vivo* [7] and aids in glucose control by augmenting insulin secretion and decreasing glucagon secretion [8, 9]. It is given twice daily, and exerts its greatest impact on post-prandial glycemia, and has a less pronounced impact on fasting blood glucose [10]. Exenatide is cleared by the kidney, and not recommended for those with a creatinine clearance that is less than 30 ml/minute.

## Exenatide and Pancreatitis:

GLP-1 receptors are ubiquitous in the exocrine pancreas. In mouse models, stimulation of GLP-1 promotes ductal replication and induces acinar to ductal hyperplasia [11]. This, in turn, stimulates inflammation of the pancreas, resulting in the potential risk of pancreatitis.

There are several case reports of the association of acute pancreatitis, after initiation of antidiabetic drugs that act on the GLP-1 pathway [12]. These case reports involve both GLP-1 agonists and inhibitors of dipeptidyl peptidase-4 inhibitors (DPP-4), which degrades GLP-1. Complicating the analysis of the relationship between these drugs and case reports and small series of cases of pancreatitis is the clearly increased risk of pancreatitis in all diabetics, regardless of treatment.

Population-based analyses are inconsistent. Elashoff, et al. examined the US Food and Drug Administration (FDA) database for reported adverse events after the initiation of GLP-1 agonists or DPP-4 inhibitors between 2004 and 2009 [13]. Among the population taking antidiabetic drugs, a 6-fold increase in the incidence of reported pancreatitis was found. Similarly, Singh et al analyzed a large BCBS database between early 2005 and late 2008. For those receiving GLP-1 agonists there was a significantly increased risk of acute pancreatitis, even after adjusting for metformin use [14]. Other population based studies did not show a link. A large study from a privately insured database in 2012 [15], and a pooled analysis of 25 trials involving sitagliptin, did not find any statistically significant difference in the incidence of pancreatitis [16].

Though many of these studies have design flaws such as short follow up time and the stringent criteria for pancreatitis. Additionally, the negative studies have been largely manufacturer sponsored [17, 18, 19, 20].

## Exanetide and Pancreatic Cancer

Pancreatic cancer occurs by the accumulation of somatic mutations in the exocrine cells of the pancreas. As in colon and breast cancer, pancreatic cancer is the result of a transition through a series of morphological stages. Normal ductal tissue transforms into contained neoplastic lesions, such as pancreatic intraepithelial neoplasia (PanIN) or intraductal papillary mucinous neoplasia (IPMN). These, in turn, may become cancerous through the acquisition of somatic mutations. PanIN is a well-established

precursor of malignant pancreatic cancer, and has been associated with over 80% of pancreatic cancer diagnoses [21]. However, the rate of transformation from PanIN to pancreatic cancer is quite low, estimated to be 1% [22].

In murine models, GLP-1 infusion increases pancreatic duct proliferation and acinar-to-ductal metaplasia, both events that predispose to the development of malignancy [23, 11]. GLP-1 receptors are ubiquitous in the human pancreas. Gier et al demonstrated that treatment with 12 weeks of a GLP-1 analog, exendin, induced replication of pancreatic duct glands at four times the frequency of controls. Morphologically, the pancreas of the treated group developed features resembling low grade PanIN lesions. Additionally, exendin-4 infusion resulted in induction of pro-proliferative pathways, increased in CREB phosphorylation and cycle D1 expression [24].

PanIN lesions are quite common; approximately 75% of pancreata of individuals by age 55 demonstrate PanIN[25]. For those with preexisting PanIN lesions when they start a GLP-1 agonist such as exanetide, there is concern that the interaction between the drug and the GLP-1 receptors will promote transformation from premalignant lesions [26] to pancreatic cancer. Further characterization of this mechanism is made difficult by the relative inaccessibility of human pancreas tissue.

The difficulty with linking pancreatic cancer with exanetide in longitudinal studies lies in the relatively short time since its approval. Exanetide was initially approved in 2005 and hence less than a decade of history is available for analysis. The process of oncogenesis, possibly starting with intraepithelial neoplasia, and developing to symptomatic pancreatic cancer years later, may be too lengthy to allow definitive conclusions presently. The transformation from chronic pancreatitis to pancreatic cancer becomes progressively more likely with years of exposure [27].

A signal of correlation between exanetide and pancreatic cancer has been described in a few studies, but not seen in many others. Notably, Elashoff et al, noted 81 cases of pancreatic cancer in those on exanetide versus 13 cases in controls. This amounted to an odds ratio of 2.95 for use of exanetide and pancreatic cancer compared to control. Additionally, Sitagliptin (DPP-4 inhibitor), was found to have an odds ratio of 2.72 [13]. These results came via an analysis of FDA claims between early 2005 and late 2009.

A number of population based studies followed that were retrospective accounts, primarily from insurance databases. This includes the large pooled study of sitagliptin by Engel et al. Most of the negative studies involving exanetide were sponsored by Amylin Pharmaceuticals, the maker of Byetta® (exanetide) [17, 18, 19, 20], while the Engel study was sponsored by Merck. One exception was the study by Romley et al. which evaluated claims from beneficiaries enrolled between 2007-2009. There were 295 pancreatic cancer diagnoses in the cohort, and the diagnosis was not common in users of exanetide (0.81%) or non-users (0.70%).

Additionally, large prospective trials evaluating cardiovascular outcomes with GLP-1 pathway agents in type II diabetes did not show an increase in pancreatic cancer (SAVOR and EXAMINE). The SAVOR trial was a double blinded, randomized trial with 16,492 patients designed to evaluate cardiovascular outcomes. There were only 5 cases of pancreatic cancer observed in the treatment group, and 12 in the placebo arm. Importantly, the maximum follow up time in this study was 2.9 years, making this finding of questionable relevance.

In 2014, the FDA and European Medicines Agency (EMA) collaborated on a report of the data regarding pancreatic cancer and pancreatitis with use of GLP-1 agonists and DPP-4 antagonists [28]. They analyzed over 250 toxicology studies, and over 200 clinical trials. While they note that there is not enough information for a final conclusion, their findings were that no correlation between the use of these agents and pancreatic cancer could be assumed, based on the available data.

## Case Presentation

Ms. D is a 72 year old female with a history of poorly controlled diabetes who presented in July of 2014 with abdominal discomfort just above the umbilicus, slightly to the right of midline. The pain was crampy and intermittent. She had never experienced this type of pain before. Along with the pain, she was disturbed by progressive fatigue and a 15 pound weight loss over the prior one month.

Her past medical history included diabetes, with an average pre-meal glucose level ranging from 100 -200. She had no history of coronary artery disease or cerebrovascular events. She did not have a history of liver disease or pancreatitis. On physical exam, she was a pleasant female in no acute distress. Her body-mass index was over 30. Her abdominal exam was remarkable for right upper quadrant pain to deep palpation, but no peritoneal signs.

Given the new symptoms, she sought out the opinion of her primary care physician, who noted an elevated lipase. As her abdominal pain worsened, an MRI of her abdomen was ordered. There was at least 11 minimally T2 hyperintense lesions within the liver, which were hypointense to surrounding parenchyma on postcontrast images. There was a narrowing of the pancreatic duct in the head of the pancreas, and ill-definition of the pancreatic head with mild peripancreatic infiltrative changes. There was diffuse low T2 signal within the common bile duct wall with enhancement on the coronal postcontrast images. There was a slight irregularity of the common duct within its midportion. The impression of the radiologist was that of a possible primary pancreatic malignancy. At the time, cholangiocarcinoma was also thought to be a possibility. The patient had a CT scan, and the coronal views seemed to demonstrate a pancreatic head mass (see Figure 1).

**Figure 1** Coronal reformatted image from a noncontrast CT of the Abdomen. Ill-defined pancreatic head mass causing biliary and pancreatic ductal obstruction with a common bile duct stent in place is consistent with pancreatic adenocarcinoma (arrow). Innumerable hypodense hepatic lesions throughout the liver are consistent with hepatic metastatic disease.

In light of the imaging findings, a gastroenterology consult was ordered. She had an EGD with common bile duct brushing. This revealed rare malignant cells. They had enlarged hyperchromatic nuclei, irregular nuclear membranes and prominent nucleoli (see Figure 2).

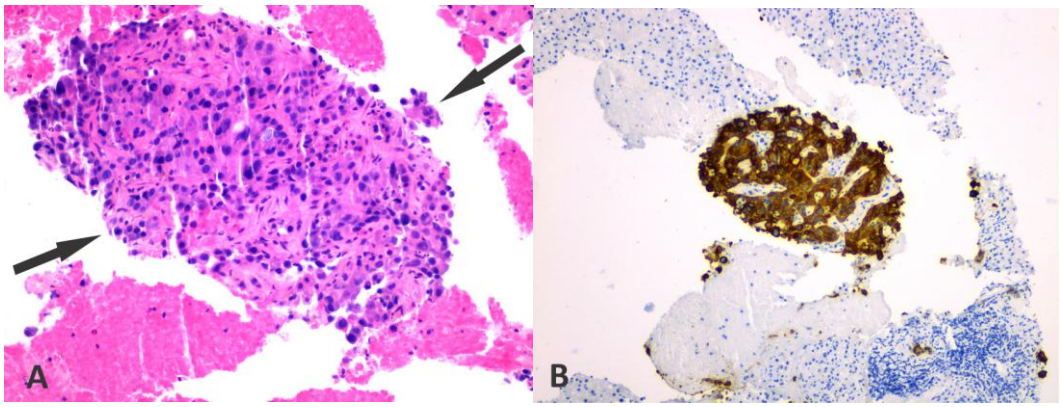


**Figure 2** The liver biopsy core showed groups of neoplastic glands (arrows) within liver parenchyma (A, H&E, 200x), consistent with an adenocarcinoma. These neoplastic glands stained positive for CK7 by immunohistochemistry (B, 100x).

The features were consistent with an adenocarcinoma. For further clarification, she had a CT guided core biopsy of the liver mass. It again revealed a poorly differentiated adenocarcinoma. Immunohistochemical stains showed strong positive staining for cytokeratin 7, negative for cytokeratin 20. The case was discussed at a multi-disciplinary tumor board. There was no clear consensus on whether the cancer originated in the common bile duct or the pancreatic head. It was decided to initiate palliative chemotherapy with Gemcitabine and a platinum agent.

The patient had a history of type II diabetes. In 2009, after having insufficient glucose control with metformin, she was started on exanetide. She took exanetide continuously from 2009-2014. She reported being concerned about news media reports about a purported link between pancreatic cancer and exanetide. The patient and her husband brought up this concern at not most of our visits.

After three cycles of gemcitabine/carboplatin, CT imaging revealed progression of her metastatic lesions in the liver. Her performance status had continued to decline, with progressive weakness and fatigue. She became dependent on others for her activities of daily living. After a family meeting, it was decided to transition to hospice care. She died approximately five months after her diagnosis.

# Conclusions

Exenatide, and other drugs that mimic or promote the activity of incretin, help diabetic patients with glucose control, and decrease the risk of cardiovascular morbidity. Given their benefits, discussing the issue of possible long term side effects should be done with extreme care, in an effort to avoid dissuading appropriate patients from pursuing these therapies. The current available literature does not provide sufficient data to conclude that there is a link between exenatide and pancreatic cancer. The majority of animal and human studies have not shown a significant correlation. Additionally, the FDA and EMA have extensively investigated the subject, and see no strong link based on the available data.

Nonetheless, there may be reason for further exploration, as stated in the joint commentary of these two agencies. As described by Yachida et al, the time lapse between the birth of a founder cell and the acquisition of metastatic ability is at least 5 years [29]. The speed at which PanIN lesions morph into pancreatic cancer is unknown [30]. Brat et al reported on three cases of documented progression from PanIN to pancreatic cancer, with the time lapsed between the two diagnoses being 17 months, nine years, and 10 years respectively [31]. Pancreatic cancer is typically diagnosed at a very advanced stage. Most of the studies reviewed above evaluated outcomes over a period of less than four years. Therefore, they provide information that may not be relevant to the question at hand. The most effective retrospective population studies may not be available for another decade. Given the high prevalence of type II diabetes and frequent use of GLP-1 based drugs, finding a toxicity signal, even if rare, is quite

important.

The patient and her family frequently expressed concern that their cancer was linked to the use of exanetide. They had seen advertisements for class-action lawsuits, and other literature on the purported link. Our visits often became oriented around this issue. This case highlights the importance of appropriate patient/physician communication. When lawyers or media personalities promote alarm for unproven findings, it can have unintended consequences, as patients have various means of obtaining an audience for their experience and opinions via social media and other modalities. On the other hand, it is not appropriate to completely dismiss concerns of this nature, and erode trust between patient and provider.

The progression from early intraepithelial neoplasia to pancreatic malignancy requires the accumulation of somatic mutations. The overlapping genetic findings in PanIN lesions and pancreatic cancer support the belief that PanIN is a precursor to malignancy. These mutations occur at different stages of progression along this continuum, with some typically occurring as an early event is neoplasia, and others occurring much later.

Genetic analyses have demonstrated correlations in types of mutations with the grade of dysplasia, giving clues to what stage of oncogenesis various mutations occur in. Activating point mutations in the KRAS2 gene and telomere shortening are typically seen early, and are often a feature of PanIN-1 lesions [30, 32, 33, 34]. There is a correlation in KRAS2 gene mutations and the grade of dysplasia [[35]]. The inactivation of p16/CDKNA appears to occur in PanIN-2 type lesions, suggesting that this may occur at an intermediate stage of carcinogenesis. TP53 appears to be a mutations typically associated with PanIN-3, and thus a later stage in oncogenesis [36, 37]. DPC4 mutations, similarly, appear to occur in the setting of more advanced dysplasia [36].

Whether or not GLP-1 agonists stimulate these transformations in the human pancreas, is an unanswered question. The relatively short evaluation periods of prior studies and the relative inaccessibility of pancreatic tissue in humans has hindered our ability to evaluate this question. In mice, GLP-1 agonists appear to have a stimulatory effect on pancreatic duct gland proliferation, and induce activation of proproliferative pathways. This may be enhanced in the setting of a KRAS mutation [24].

Areas of future study will include large prospective clinical trials, and retrospective reviews with a longer follow up time. Exploration of the accumulation of deleterious somatic mutations during or after treatment with GLP-1 agonists may be of interest as well. For the time being, there is no data that is persuasive enough to dissuade appropriate patients from this class of drugs, but we look forward to the availability of further information on this subject in the future.

# Consent

Written informed consent was obtained from the patient's next of kin for publication of this Case report and any accompanying images. A copy of the written consent is available for review upon request.

# Authors' contributions

TC wrote the majority of the manuscript. MA provided the image and caption for figure 1. JD provided editing and feedback. MK provided editing and contributed to the discussion portion. SR provided editing and contributed to the case report. All authors were involved in editing and final approval.

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