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PUBTEXTO

A Case of Intraductal Papillary Mucinous Neoplasm (IPMN) Analyzed by Curved Planar Reconstruction (CPR) With Treatment of Twymeeg and Equmet for Type 2 Diabetes (T2D)

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Abstract

The case is 74-year-old male with type 2 diabetes (T2D) for 11 years. In June 2022, he received abdominal CT scan, in which the atrophy of pancreas and the dilatation of main pancreatic duct was observed. As detail exams, Curved Planar Reconstruction (CPR) of CT, Magnetic Resonance Cholangiopancreatography (MRCP), and Endoscopic Ultrasonography (EUS) were performed. From these, Intraductal Papillary Mucinous Neoplasm (IPMN) with main pancreatic duct type was suggested. After the pancreatectomy in September 2022, his HbA1c value was elevated, but EquMet (vildagliptin and metformin) and Twymeeg (imeglimin) showed clinical effects for improvement of glucose variability for several months.

Keywords: Intraductal Papillary Mucinous Neoplasm (IPMN); Curved Planar Reconstruction (CPR); Twymeeg; Equmet; Endoscopic Ultrasonography (EUS)

Introduction

For the standard management of type 2 diabetes (T2D), "Standards of Care in Diabetes" was presented by American Diabetes Association (ADA) in Jan 2023 [1]. T2D is required to be controlled adequately from bio-psycho-social points of view [2]. It is one of non-communicable diseases (NCDs), and patient with T2D should maintain ordinary QOL as healthy people [3]. Several novel oral hypoglycemic agents (OHAs) are used for medical practice [4,5]. They include dipeptidyl peptidase-4 inhibitor (DPP-4i), sodium–glucose cotransporter 2 inhibitor (SGLT2i), glucagon-like-peptide 1 receptor agonist (GLP1-RA), and other effective agents. Latest novel agent is Twymeeg (imeglimin) which shows dual mechanism for T2D [6,7].

For standard treatment for T2D, metformin is for long the first-line OHA in medical practice [8]. As a similar molecule, imeglimin has been developed for novel and effective agent for T2D [9]. It can be applied to T2D patient for monotherapy and/or add-on therapy with other insulin and OHAs [10]. Further, it shows dual effects of reducing insulin resistance and increasing insulin secretion, in which administration twice a day (bid) would be meaningful [11]. Similarly, vildagliptin as DPP4-i is provided as bid, that contributes improved glucose profile and mean amplitude of glycemic excursions (MAGE) [12].

Authors and collaborators continued our diabetic research for years. We covered low carbohydrate diet (LCD), meal tolerance test (MTT), Carbo-70g loading test and various reports of OHAs [13,14]. Among them, some reports were found regarding Twymeeg and Vildagliptin and others [15-17]. We recently experienced a meaningful T2D case associated with complication of pancreatic neoplasm, which was intraductal papillary mucinous neoplasm (IPMN) [18]. For evaluating IPMN in detail, we have applied Curved Planar Reconstruction (CPR), in which our medical group have continued high resonance technology of CT and MRI so far. In this article, general case presentation and associated various perspectives will be described.

Case Presentation

The case is 74-year-old male who has been treated for type 2 diabetes (T2D) for 11 years. His diabetic control is rather stable. His HbA1c had been maintained under 7% level for long (Figure 1). In June 2021, he underwent abdominal CT scan for the evaluation of liver, gall bladder, pancreas, kidney and other visceral organs. As a result, he was pointed out to have the atrophy of pancreas and the dilatation of main pancreatic duct (Figure 2a). Biochemical exam showed unremarkable results. He was

recommended to take re-exam of abdominal CT 1 year later for careful follow-up.

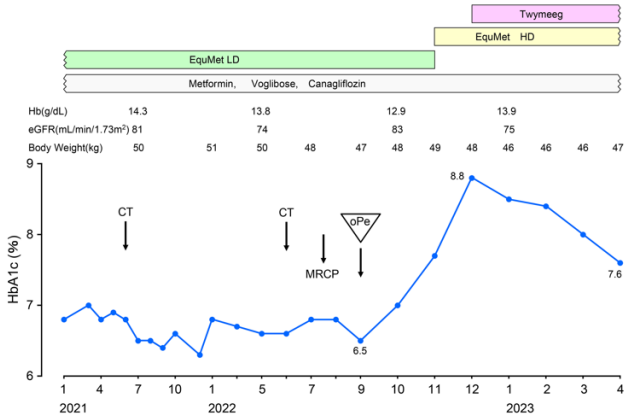

Figure 1: *Clinical progress with CT, MRCP, operation and treatment.*

Abdominal CT

One year later, he had abdominal CT scan in June 2022. The detail results of CT findings are in the following. 1) Pancreas; The parenchyma of the pancreas showed totally atrophy (Figure 2b). The main pancreatic duct is dilated as a whole, and is conspicuous at about 10 mm in diameter at the tail portion. Dilatation of branched pancreatic ducts or cystic structures are found here and there in the body and tail of the pancreas (Figure 3a). The fulfillment part cannot be pointed out. 2) Lung; The bulla was observed in the right lower lobe of the lung. There are no other obvious abnormal shadows in the lungs. 3) Mediastinum; No significant lymphadenopathy was observed in the mediastinum or hilum. No pleural effusion is seen. 4) Liver and kidney; The shape and size are within normal limits. Hepatic cysts and right renal cyst were found. The internal concentration of the liver showed rather heterogeneously decreased, and then fatty liver would be suggested. 5) Iliac artery: The right common iliac artery is calcified and mildly enlarged (Figure 3b). 6) Others; gallbladder, spleen, left kidney, and adrenal glands showed unremarkable findings. No obvious lymph node enlargement, including in the para-aortic region was found. No ascites was observed. The actual body of the pancreas is not straight but curved, and then it cannot be observed in one plane. Using the technique of Curved Planar Reconstruction (CPR), main duct of the pancreas was evaluated (Figure 4). It showed the dilatation of the main duct from head to the tail of the pancreas. Based on the above, Intraductal Papillary Mucinous Neoplasm (IPMN) with main pancreatic duct type has been suggested.

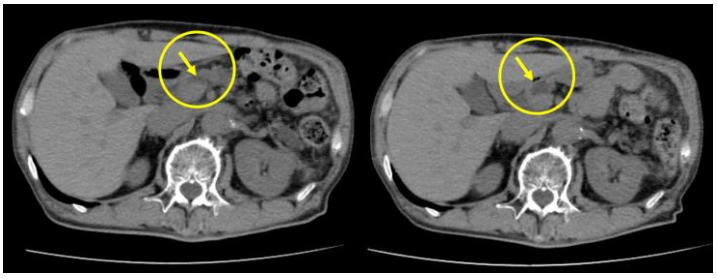

Figure 2: *Image of Intraductal Papillary Mucinous Neoplasm (IPMN)*

2a: abdominal CT in June 2021

2b: abdominal CT in June 2022.

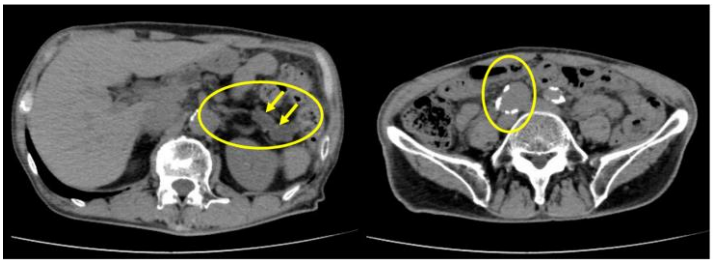

Figure 3: *Image of abdominal CT (June 2022)*
3a: dilated main duct of pancreas
3b: dilatation of right iliac artery.

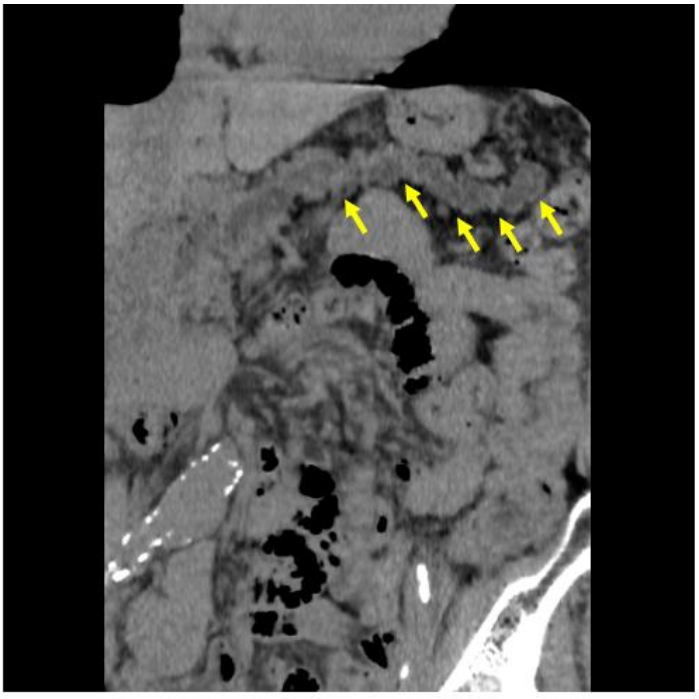

Figure 4: *Image of main duct of pancreas by Curved Planar Reconstruction (CPR).*

MRCP And EUS

For further evaluation, Magnetic Resonance Cholangiopancreatography (MRCP) was conducted in July 2022. As a result, pancreatic atrophy is generally observed. Dilatation of the main pancreatic duct is found, which is especially distinct in the tail portion. The tail showed multilocular cysts, beaded

situation and pancreatic duct has a maximum diameter of 14 mm (Figure 5). No apparent hyperintensity was observed in the diffuse image method. Biliopancreatic Endoscopic Ultrasonography (EUS) was performed. The main pancreatic duct extends more than 3 mm from the papilla, and the pancreatic head-to-body junction dilates to about 9 mm, while it showed about 5 mm for the pancreatic body with meanders. It expands gradually toward the tail of the pancreas, and dilatation of branched pancreatic ducts is observed around it. Formation of cysts is observed in the tail of the pancreas. Disruption of the main pancreatic duct is not found. In the main pancreatic duct, a structure is present which seemed to be mucus content. From these findings, it is probable the main pancreatic duct-type IPMN. Fatty filtration was observed in the pancreatic parenchyma, and the boundaries were unclear, but no obvious solid lesions were observed.

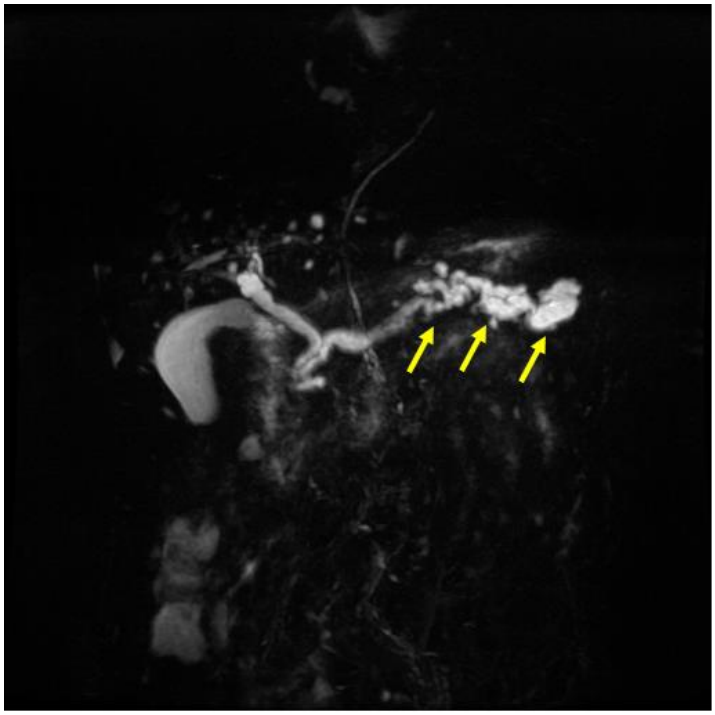

Figure 5: *Findings of Magnetic Resonance Cholangiopancreatography (MRCP)*

Dilatation of main pancreatic duct is found as 14mm.

Dilatation of branch-duct is also found.

Diagnosis And Treatment

From these findings, this case was diagnosed as probable main pancreatic duct-type IPMN. The value of CA 19-9 was 20 U/mL (0-37) in July 2022. At that time, no obvious mural nodules or malignant lesion was observed. Considering the risk of cancer development in the future, surgery was proposed and actually conducted in Sept 2022. At the time of surgery, a rapid tissue diagnosis was performed, and no malignant findings were observed at the margin of the resection site. Therefore, a partial pancreatic resection was performed instead of a total resection of the pancreas. The final diagnosis was the Intraductal papillary mucinous tumor of the pancreas. The operation was distal pancreatectomy and splenectomy. Final histological result was compatible finding with intraductal papillary mucinous neoplasia.

Post-Operative Progress

The operation was about two-thirds resection of the pancreas. After operation, the value of c-peptide index (CPI) in fasting morning was 0.7. Consequently, camostat mesylate (Foypan ^{R}) 300mg per day was continued for compensation of probable decreased pancreas function. The case did not show particular symptoms and signs at all. HbA1c was elevated to 7.7% in Nov 2022, and then EquMet LD was changed to EquMet HD. From Dec 2022, additional Twymeeg was begun for better glucose variability. After that, HbA1c was decreased from 8.8% to 7.6% for 4 months.

Discussion

The present case is a 74-year-old man with T2D who underwent surgery for intraductal papillary mucinous neoplasm (IPMN). HbA1c increased thereafter, but glycemic control was improved with administration of EquMet HD and Twymeeg. Several important perspectives are shown as i) mild exacerbation of diabetes after surgery, ii) Twymeeg, iii) diagnosis and management of IPMN, and iv) EUS. The discussion will be described in this order.

Firstly, this case had pancreatectomy for about two-thirds of the pancreas. After operation, post-prandial glucose was elevated, and c-peptide index (CPI) in fasting morning was 0.7. CPI in fasting early morning has been used as a useful index [19]. Good glycemic control has been reported to continue with diet therapy and OHA, when the CPI is 1.2 or higher. In contrast, it is necessary with insulin administration, when the CPI is less than 0.8. The calculation method is that CPI = blood CPR / blood glucose level × 100 [20]. This case showed impaired glucose variability from Sep-Dec 2022. It seemed to be incomplete recovery from the operation and/or insufficient function of pancreatic beta cell. After that, glucose variability was improved during Jan-Apr 2023, in which it was probably due to Twymeeg administration and/or recovered function of beta cell.

Secondly, he showed remarkable improvement of HbA1c after addition of Twymeeg in Dec 2022. A series of large studies of imeglimin were reported as TIMES 1,2, and 3 until now. The case has been provided Vildagliptin and metformin for years, which were DPP4-i and biguanides. From a series of TIMES researches, clinical effects of the add-on treatment have been shown. Thus, beneficial points of Twymeeg would be possible combination of OHAs. The efficacy of combined administration was reported. They include DPP4-i -0.92% and biguanides -0.67%, in which this case received add-on therapy of both agents. Furthermore, other efficacies were monotherapy of imeglimin -0.46%, α-GI -0.85%, SGLT2i -0.57%, sulfonyl urea -0.56%, and glinides -0.70% [21]. From these data, DPP-4i was the most effective, whereas the least effect was observed in GLP-1RA with mere -0.12% [22]. Both agents are known to include common pharmacological pathway.

However, the remarkable different may be from other function mechanism [23]. This function may suggest the involvement of endothelial route [24]. In the recent report, influence of imeglimin on glucose variability was shown by continuous glucose monitoring (CGM) [25]. Further development of research will be required concerning mitochondrial mechanism [26].

Thirdly, an international expert team presented 4 clinical questions (CQ) on IPMN in order to develop adequate management [27]. They used PubMed, Embase, Cochrane Library and others. Totally 1098 studies were analyzed, and 41 studies were reviewed leading to the recommendations. In conclusion, they propose an applicable definition of remnant portions of pancreas for guiding future prospective management. For the investigation of IPMN, 466 cases were analyzed who underwent pancreatectomy [28]. Among them, 258 (55%) showed malignant IPMN, and 208 (45%) showed benign histological results. For the detail of malignant IPMN (n=208), high-grade dysplasia was 158, and invasive carcinoma was 100. From the method of logistic regression analysis, three variables were found, which were cyst size, main pancreatic duct diameter and mural nodule size.

Concerning IPMN, dilatation of the main pancreatic duct (MPD) becomes a discussion for surgical indication. During 1994-2021, 3610 cases diagnosed as pancreatic cysts were analyzed [29]. Among them, IPMN were identified in 2829 cases. It included MPD ≥5 mm (n=282), which was examined risk of pancreatic carcinoma for short-term (≤6 months) and also long period. For analysis of 282 cases in short-term, 26% cases had pancreatic carcinoma by surgical and/or non-surgical evaluation. In the case of long period follow up (n=168), 14% was diagnosed as pancreatic carcinoma. For the analyses of cases with MPD ≥10 mm, the corresponding incidence was 16% and 33.3%, respectively. From these data, hazard ratios were 2.78 and 7.00 (vs <5mm) for the MPD 5-9.9mm and ≥10 mm, respectively.

Latest development for evaluating malignant conversion of IPMN is found [30]. Combined methods of probe electrospray ionization-mass spectrometry (PESI-MS) associated with machine learning may give a promising solution as to this clinical problem. For the novel method, 42 serum samples were analyzed using PESI-MS and divided into two categories, which were IPMN-low grade dysplasia (n = 17) group and advanced-IPMN (n = 25) group. Furthermore, 130 biomarkers were included for the evaluation. As a result, diagnostic accuracy was 88.1%, associated with AUC of receiver operating characteristics was 0.924. It took only 10 minutes for conducting this measure. Consequently, PESI-MS associated with machine learning would be clinically useful.

Fourthly, EUS has been applied for evaluating IPMN for diagnosing benign or malignant before the operation. In order to predict the IPMN pathology, the utility of EUS was investigated [31]. Patient with IPMN (n=115) was analyzed, in which ow-grade dysplasia (n=56), high-grade dysplasia (n=25) and invasive cancer (n=34). Some risk factors showed odd ratio for malignancy as follows: smoking history (OR 6.95), lymphadenopathy (OR 7.91), MPD > 7 mm (OR 4.75), and mural nodules > 5 mm (OR = 8.79). For recent measure for evaluate IPMC, contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) was evaluated [32]. It contribute d the diagnosis of malignant IPMN. Out of 5009 cases with IPMN, 115 cases received several exams including conventional EUS, contrast-enhanced computed tomography (CE-CT), CH-EUS, and surgical resection were enrolled. CH-EUS and conventional EUS had higher accuracy than CE-CT for detection of mural nodules, where the data are 92%, 83%, 72%, respectively. Similarly, diagnosis of malignancy for IPMN showed 75%, 73%, and 63%, respectively.

Certain limitation may exist as to the current report. Mutual relationships among T2D, IPMN, smoking, and other factors possibly contribute the development of the current situation. We cannot know whether the current IPMN will develop to malignancy or not in the future. However, operative management seemed to be adequate in the light large numbers of medical reports.

In summary, 74-year-old T2D patient developed IPMN with pancreatectomy. After operation, his glucose variability was improved by the administration of Twymeeg, which has dual clinical effects of increasing insulin secretion and reducing insulin resistance. It is expected that this article becomes one of the references for IPMN in the future research.

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