Answers to Reviewer

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

The manuscript has been under the process of language polishing.

**Conclusion:** Minor revision

**Former:** POPF is a complicated issue caused by increased biochemical activity, mechanical damage, and digestive reflux. Currently, it cannot be avoided when pancreatic stump manipulation and reflux into the pancreatic duct occur. However, by stopping the reflux, maintaining the pancreatic fluid flow, and allowing the anastomotic rupture to occur, we might be able to prevent POPF.

**After revision:** POPF is a complex condition that is caused by increased biochemical activity, mechanical damage, and digestive reflux. Currently, manipulation of the pancreatic stump and reflux into the pancreatic duct cannot be avoided. Based on these findings, stopping reflux and reducing inflammation in the pancreatic stump can decrease the occurrence of pancreatic fistulas. However, a more practical approach is to allow for the presence of inflammation and anastomotic dehiscence while controlling the proper flow of pancreatic juice, thereby breaking the logical relationship between anastomotic dehiscence and POPF.

**Specific Comments to Authors:** The manuscript entitled " Gradient Inflammation in the Pancreatic Stump after Pancreaticoduodenectomy: A Report of Two Cases" has been reviewed. This paper examines the causes of postoperative pancreatic fistula in cases of total pancreatectomy. It is an interesting paper. However, some modifications seem to be necessary.

(1) What stains are H and I in Figure 1?

***Former:*** (**H**): Weakening or disappearance of apoptosis in the pancreatic stump after PD. (**I**): Normal level of apoptosis in the pancreas.

***After revision:*** (**H**): Weakening or disappearance of apoptosis in the pancreatic stump after pancreaticoduodenectomy (TUNEL). (**I**): Normal level of apoptosis in control tissue of the pancreatic head before the POPF (TUNEL).

(2) How was the normal level of apoptosis defined?

Pancreatic head tissue was used as a control to define the normal level of inflammation and apoptosis.

(3) How was the ADM formed duct defined?

During ADM, acinar cells lose their normal shape and function and transform into ductal-like cells. Moreover, the ducts formed by ADM differed significantly in appearance from normal ducts and were characterized by duck-like cells and irregular lumens (Figure 1L). The original acinar cells were either pushed aside by the newly formed duct-like cells or incorporated into the newly formed ducts. Furthermore, it seems that the pressure in the lumen increased, resulting in the dilation of the regional ducts formed by the ADM (Figure 1M).

(4) L shows a similar histology when the pancreatic duct is sectioned along the long axis.

The ducts formed by ADM differed significantly in appearance from normal ducts and were characterized by duck-like cells and irregular lumens (Figure 1L). Additionally, we do not think the ADM-formed duct has the normal function as a pancreatic duct, as its lumen is characterized by regions of dilation and constriction. So the duct in the Figure L should be the ADM-formed duct. We have engaged in a thorough discussion with pathology experts and reached a consensus on the aforementioned conclusion. Therefore, we maintain our standpoint.

(5) All of Figure 2 and Figure 3B are difficult for the reader to understand. Please correct them.

For better understanding of Figure 2, we have incorporated two additional sections to elucidate the outcome. However, for a comprehensive understanding, readers are advised to acquire further knowledge about Principal Component Analysis (PCA) and unweighted pair group method with arithmetic mean (UPGMA) clustering tree from supplementary resources.

Principal Component Analysis (PCA) is a multivariate analysis that reduces

data dimensionality while preserving covariance. The most attractive property of PCA is that the distances between clusters reflect their genetic and geographical distances.

The distances between the samples demonstrated a much more clustered distribution in the PL than in the PZ through PCA.

For better understanding of Figure 3B, we have added four line to correlate Figure 3A and 3B. The inflammatory index was calculated using a histological scoring system for acute pancreatitis, including edema, inflammatory cell infiltration, and necrosis[1].

1. Moreno C, Nicaise C, Gustot T, Quertinmont E, Nagy N, Parmentier M, Louis H, Deviere J.Chemokine receptor ccr5 deficiency exacerbates cerulein-induced acute pancreatitis in mice. *Am J Physiol Gastrointest Liver Physiol* 2006, **291**(6):G1089-1099. [PMID: 16891300 DOI:10.1152/ajpgi.00571.2005]

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