Clinicopathological and immunological features of follicular pancreatitis—a distinct disease entity characterized by Th17 activation

Hironori Ryota¹, Mitsuaki Ishida², Sohei Satoi¹, Hiroaki Yanagimoto¹, Tomohisa Yamamoto¹, Hisashi Kosaka¹, Satoshi Hirooka¹, So Yamaki¹, Masaya Kotsuka¹, Yoichi Matsui¹, Tsukasa Ikeura³, Kazushige Uchida³, Makoto Takaoka³, Kazuichi Okazaki³, Koji Tsuta²

¹ Department of Surgery, Kansai Medical University, Osaka, Japan
² Department of Pathology and Laboratory Medicine, Kansai Medical University, Osaka, Japan
³ Department of Internal Medicine 3, Kansai Medical University, Osaka, Japan

Running title: Follicular Pancreatitis: Immune Profile

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/his.13802

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Correspondence to: Mitsuaki Ishida, Department of Pathology and Laboratory Medicine, Kansai Medical University, 2-5-1, Shinmachi, Hirakata-city, 573-1010 Osaka, Japan. E-mail: ishidamt@hirakata.kmu.ac.jp

Declaration of conflicts of interest: The authors have declared no conflicts of interest.

Abstract

Aim: Follicular pancreatitis is a recently recognized, distinct clinicopathological entity characterized by the presence of many intrapancreatic lymphoid follicles with reactive germinal centres. However, the clinicopathological and immunological features and causes have not yet been established. We assessed the clinicopathological and immunological profiles of patients with follicular pancreatitis who underwent surgery.

Methods and Results: This study included three patients with pancreatic masses (age range: 62-75 years; women:men: 1:2). A histopathological study of the resected pancreatic masses revealed abundant lymphoid follicles with reactive germinal centres in both periductal regions and diffusely within the parenchyma. No storiform fibrosis, obliterator phlebitis, or granulocytic epithelial lesions were observed. The immunohistochemical examination revealed an IgG4/IgG-positive plasma cell ratio <30% in all patients. Podoplanin (Th17 marker)-expressing lymphocytes were present in the lymphoid follicles of those with follicular pancreatitis, whereas these were absent in normal lymph nodes and in lymphoid follicles of those with IgG4-related autoimmune pancreatitis (AIP). An RNA digital counting assay clearly demonstrated that the expression counts of 20 genes, including dendritic cells and lymphoid follicles markers, and related cytokines were significantly higher in follicular pancreatitis than in IgG4-related AIP (p<0.01). The expressions of CCR6 and IL23A, which are genes related to Th17, were high.

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**Conclusions:** This study shows that follicular pancreatitis is a histopathologically and immunologically distinct disease entity of pancreatitis and is characterized by upregulated Th17 expression.

**Keywords:** Follicular pancreatitis, autoimmune pancreatitis, gene expression analysis, Th17 lymphocyte

**Introduction**

Several forms of chronic pancreatitis have been recognized as distinct clinicopathological entities, including autoimmune pancreatitis (AIP) and groove pancreatitis. AIP is subclassified into type 1, an IgG4-related disease, and type 2, which is characterized by the presence of granulocytic epithelial lesions\(^1\)-\(^3\). Recently, Zen et al. proposed a third form of chronic pancreatitis, namely follicular pancreatitis, which is characterized histopathologically by the presence of duct-centred, dense lymphoplasmacytic infiltration with many reactive lymphoid follicles bearing germinal centres\(^4\). This condition may be under-recognized and may have been previously reported as pancreatic pseudolymphoma or reactive lymphoid hyperplasia\(^5\)-\(^10\). To the best of our knowledge, only 13 patients have been reported on in the English literature\(^4\)-\(^11\), and only 2 patient series have been published\(^4\)-\(^11\). The immunological characteristics of IgG4-related AIP have been established. The activation of type 2 helper T cells (Th2) and regulatory T cells (Treg) in affected organs is characteristic of IgG4-related AIP. Tissue mRNA levels of Th2 cytokines, such as IL-4, IL-5, IL-10, and IL-13, are significantly higher, and many lymphocytes expressing IL-4 or IL.10 are present in the affected organs. Moreover, abundant infiltration of CD4\(^+\)/CD25\(^+\) Treg cells is also observed in IgG4-related AIP lesions, and a higher expression of FOXP3 mRNA is also noted\(^12\). However, the immunological characteristics of follicular pancreatitis have not been examined\(^4\)-\(^11\). Thus,
we studied the clinicopathological characteristics of three patients with follicular pancreatitis and assessed the gene expression profile of this disorder. Our aim was to determine the characteristic gene expression profile of follicular pancreatitis compared to that of IgG4-related AIP, and to determine whether follicular pancreatitis is a distinct clinicopathological entity of pancreatitis.

**Materials and Methods**

**Patients**

Three patients with pancreatic masses who underwent surgery at the Department of Surgery, Kansai Medical University (Osaka, Japan) between January 2006 and March 2017 and received diagnoses of pseudolymphoma, lymphoid hyperplasia, and follicular pancreatitis were enrolled in this study.

The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the institutional review board of our hospital (protocol no. 2017001, 1501-2).

**Immunohistochemistry and in situ hybridization**

Formalin-fixed and paraffin-embedded (FFPE) blocks of the resected specimens were cut into 4 μm-thick sections. Macrodissections of the lesions were performed using 18-G needles. Subsequently, the samples were deparaffinized and rehydrated. Immunohistochemical analyses were performed using an autostainer (Discovery XT System; Roche Diagnostics, USA, and Autostainer Link 48; Agilent Technology, Santa Clara, USA) according to the manufacturer’s instructions. The primary antibodies used in this study are shown in the Supplemental Table 1. *In situ* hybridizations for kappa and
lambda light chains were also performed using an autostainer (Discovery XT System; Roche Diagnostics, USA).

Lymph nodes of a patient with intraductal papillary mucinous adenoma and pancreatic tissues of patients with IgG4-related AIP were used as controls.

For podoplanin staining, complete circular staining of lymphocytes was considered to be a positive result. IgG4+ and IgG+ cells were counted using printed photographs of the same microscopic field under a ×40 objective lens in 10 high power fields. Immunohistochemical and in situ hybridization examinations were assessed independently by 2 pathologists who were blinded to the patients’ clinical features.

RNA extraction

For mRNA extraction, 5 μm-thick sections from the FFPE blocks were cut and NucleoSpin® total RNA FFPE kit (Macherey-Nagel, Germany), including on-column treatment with DNase, was used. A quantitative evaluation of RNA was performed using the Nanodrop 1000 spectrophotometer (Thermo Fisher Scientific, Wilmington, DE). RNA quality was evaluated based on a 260/280 nm ratio. We excluded samples in which the total amount of RNA was less than 50 ng/μL or the 260/280 ratio was less than 1.6.

Digital mRNA counts and analysis

We studied the expression of 770 immune-related genes (Supplemental Table 2) in three patients with follicular pancreatitis, two patients with IgG4-related AIP, two patients with chronic alcoholic pancreatitis, and one patient with a normal pancreas using the nCounter PanCancer Immune Profiling Panel (NanoString Technologies, Inc., Seattle, WA, USA). The nCounter assay was performed according to the manufacturer’s instructions. The
RNA was hybridized with the probe sets for 16 hours at 67°C, and the samples were then processed using an automated nCounter Sample Prep Station (NanoString Technologies, Inc.). Cartridges containing immobilized and aligned reporter complexes were subsequently imaged on an nCounter Digital Analyzer (NanoString Technologies, Inc.) that had been set at a data resolution of 555 fields of view. Reporter counts were collected and normalized using nSolver analysis software version 3.0 (NanoString Technologies, Inc.).

Results

Clinical characteristics

Table 1 summarizes the clinicopathological features of the three patients with follicular pancreatitis in this series (age range: 62-75 years; women:men - 1:2). The lesions were located in the tail of the pancreas in three patients and in the body in one patient (one patient had two lesions, one in the body and one in the tail). All patients were incidentally found to have pancreatic tumours and had no clinical symptoms. Pancreatic cancer was clinically diagnosed preoperatively in all patients, and distal pancreatectomies were performed. The serum IgG4 level was not elevated in patient 3 (30 mg/dL). The past medical histories of all patients were negative for autoimmune disorders.

Histopathological characteristics

Macroscopic features

All 3 patients had a yellowish tumorous lesion in the pancreatic body and/or tail. The boundaries were unclear, and the sizes of the lesions were approximately 20 to 30 mm in diameter. One patient had two lesions in the pancreatic parenchyma and the others each had one lesion.
Microscopic features

Many variable-sized lymphoid follicles with reactive germinal centres and intact mantle zones were diffusely distributed in the pancreatic parenchyma (Figure 1). Periductal lymphoid follicle formations were also noted in all patients (Figure 1). Infiltration of lymphocytes into the ductal epithelial cells was not observed, and there was no evidence of ductal epithelial cell injury. Moreover, granulocytic epithelial lesions were not observed in all patients. Mild plasma cell infiltrations were noted around the lymphoid follicles. Mild interlobular fibrosis and parenchymal atrophy were present, but storiform pattern fibrosis was not observed. Mild eosinophilic infiltration was seen in all three patients, however, neutrophilic infiltration was inconspicuous. Obliterative phlebitis was not identified in any of the patients.

The germinal centres were mainly composed of CD20-positive B-cells with scattered CD3-positive T-cells, had meshworks of CD21-positive follicular dendritic cells, and were positive for Bcl-6 and CD10 and negative for Bcl-2 (Figure 2). A few IgG4-positive plasma cells were observed in all patients, and the ratio of IgG4/IgG-positive plasma cells was less than 30% in all patients (Figure 2) (Table 1). Of note, podoplanin-positive lymphocytes were present in the germinal centres of the lymphoid follicles in all patients with follicular pancreatitis (Figure 3-a, b). These were rarely observed in the lymphoid follicles of patients with IgG4-related AIP or the lymph nodes of a patient with intraductal papillary mucinous adenoma, however, podoplanin-expressing follicular dendritic cells were present in these specimens.

In situ hybridization analyses demonstrated that kappa- and lambda-chain positive cells were evenly distributed, and monoclonality was not detected in any of the patient samples.
**RNA expression**

mRNA count data of 770 genes are shown in the Supplemental Table 2 and a cluster-classified gene heat map was prepared from the expression levels of the 770 genes (Figure 4). Follicular pancreatitis exhibited a different gene profile than IgG4-related AIP. The expression counts of 20 genes were significantly higher in patients with follicular pancreatitis compared to those with IgG4-related AIP ($p<0.01$) (Table 2). The expression levels of dendritic cells and lymphoid follicles markers and related cytokines were significantly higher in those with follicular pancreatitis. Furthermore, the expression levels of C-C chemokine receptor type 6 (CCR6), which is highly expressed in Th17 cells, and interleukin 23A (IL23A), which promotes the growth of Th17 cells, were significantly high.

**Discussion**

The clinicopathological characteristics and immunological mechanism of IgG4-related AIP have been established. However, those of follicular pancreatitis have not yet been clarified since it is a recently recognized entity and the number of patients is limited. This study clearly demonstrated the following: (1) RNA expression patterns in follicular pancreatitis are significantly different from those in IgG4-related AIP, with high expression levels of dendritic cells ($LAMP3$) and lymphoid follicle markers ($ICOS$ and $CR2$), related cytokines ($LTA$), and regulatory factors of Th17 ($CCR6$ and $IL23A$), and (2) podoplanin (Th17 marker)-expressing lymphocytes are present in the lymphoid follicles of patients with follicular pancreatitis.

Th17 represents a population of helper T-cells that was first reported for its involvement in experimental autoimmune encephalomyelitis in 2005$^{13}$. Since then, Th17 has been reported to contribute to the pathogenesis of several diseases including psoriasis$^{14}$,
rheumatoid arthritis, inflammatory bowel disease, and autoimmune thyroid disease. Moreover, Th17 plays an important role in the formation of normal lymphoid follicles. The naive T cells differentiate into Th1 or Th2 upon antigen presentation, and Th17 similarly differentiates. Co-stimulation of TGF-beta and IL-6 is essential for differentiation into Th17. After differentiation from naive T-cells, Th17 is proliferated by IL23A, which is secreted by dendritic cells. According to a report on the plasticity of Peyer’s patches, Th17 transforms into follicular helper T-cells and forms lymphoid follicles.

In this study, expression of Th17 and follicular helper T cell-related markers (CCR6, IL23A, ICOS, and LTA) was significantly higher in cases of follicular pancreatitis than they were in cases of IgG4-related AIP. CCR6 is expressed on Th17 and plays a role in Th17 migration. IL-23A is essential for maintaining the survival and proliferation of Th17 cells. Moreover, LTA is a chemokine that promotes the formation of lymphoid follicles. These results suggest that the development of follicular pancreatitis is highly associated with the activation of Th17. This may be a unique characteristic of this disease compared to IgG4-related AIP, which is characterized by activation of Th2 and Treg.

The possible cascade in the development of follicular pancreatitis is shown in Figure 5. Th17 cell proliferation is aided by IL-23A, which is produced by dendritic cells expressing LAMP3. Th17 then migrates to the pancreatic parenchyma. Subsequently, Th17 cells transform into follicular helper T-cells and then aggregate in lymphoid follicles.

Moreover, to evaluate the localization of Th17 in lesions of follicular pancreatitis, we examined the immunohistochemical staining for Th17. Podoplanin is specifically expressed on Th17 among the lymphocytes. In this study, podoplanin-expressing lymphocytes were observed in the germinal centres of the lymphoid follicles in all patients with follicular pancreatitis, but they were scanty in the lymphoid follicles of patients with IgG4-related AIP and the lymph nodes of a patient with intraductal
papillary mucinous adenoma. The presence of podoplanin-expressing lymphocytes may be a characteristic of follicular pancreatitis. It has been reported that Th17 may be involved in the pathogenesis of type 2 AIP, especially in cases leading to the formation of granulocytic epithelial lesions. However, a comprehensive immune-related gene expression profile was not analysed in this study\textsuperscript{24}. We performed a comprehensive analysis of the immune-related gene expression profile of follicular pancreatitis compared to that of IgG4-related AIP. The findings clearly demonstrated that dendritic cells and lymphoid follicle markers and regulatory factors of Th17 are significantly upregulated in cases of follicular pancreatitis. Although Th17 might be involved in the pathogenesis of both type 2 AIP and follicular pancreatitis, the significance and role of Th17 may be different in these two conditions. Thus, additional studies are needed to clarify the significance of Th17 in AIP.

The clinicopathological summaries of follicular pancreatitis in the previously reported 13 patients\textsuperscript{4-11} and the three patients in the present study are as follows: (1) this disease affects middle-aged to elderly patients (age range: 41-75 years; mean age: 62 years) with a predilection for male patients (men:women - 10:6), (2) most patients are asymptomatic (10 cases), with pancreatic tumours diagnosed incidentally, (3) there is no common location (lesions occurred in the pancreatic head in five patients, the body in two, and the tail in five, with dual lesions in the head and body, and body and tail). Of interest, diffuse dilatation of the pancreatic duct without a tumorous lesion was observed in two patients. Table 3 summarizes the clinicopathological characteristics of follicular pancreatitis in comparison with AIP. The histopathological characteristics include: (1) many reactive lymphoid follicles with germinal centres were present in the periductal regions and/or in a diffuse fashion throughout the parenchyma, (2) storiform fibrosis and obliteratorive phlebitis, characteristic findings of IgG4-related AIP, were rare or absent, and (3) IgG4/IgG-positive plasma cell ratio was not elevated (<30%). Based on the clinicopathological and immunological characteristics shown in the present study,
Follicular pancreatitis should be considered a clinicopathologically distinct disease entity and must be considered as a form of autoimmune pancreatitis.

Similar to this study, in most of the previous reports, pancreatic cancer or neuroendocrine tumours were suspected preoperatively\(^4\)-\(^11\). Therefore, surgical resection was performed in almost all reported patients. Of interest, one patient with follicular pancreatitis showed a 50% reduction in tumour size (on imaging) with steroid therapy\(^11\). Therefore, diagnostic and therapeutic strategies for follicular pancreatitis must be established to avoid unnecessary surgery, given the high complication rate associated with pancreaticoduodenectomy (~60%)\(^25\). In addition, clinical applications of Th17 inhibitors are gaining acceptance in Th17-related diseases\(^26\)-\(^28\), indicating their potential as therapeutic candidates for follicular pancreatitis.

In conclusion, to the best of our knowledge, this is the first report on the pathogenesis of follicular pancreatitis. Although this study is limited by the small number of patients, we have shown that the development of follicular pancreatitis is highly associated with the activation of Th17. Follicular pancreatitis should be considered as a clinicopathologically distinct disease entity and must be considered a form of autoimmune pancreatitis.

**Acknowledgments**

We thank all the patients, their families, and investigators who participated in the study. This study was partially funded by KONICA MINOLTA.

**Author contributions statement:**

HR, MI, and KT contributed to experimental design, pathological diagnosis, and manuscript preparation. HR performed molecular experiments. HR and MI performed immunostaining. SS, HY, TY, HK, SH, SY, MK, YM, TI, KU, MT, and KO contributed to patient data collection. All authors approved the final version of the manuscript.

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References


Figure legends

Figure 1. Histopathological features of follicular pancreatitis.

a) Case 1: Lymphoid follicles around main pancreatic duct (H&E × 40).

b) Case 2: Diffuse lymphoid follicle formation in the pancreatic parenchyma (H&E × 40).

c) Case 3: Diffuse lymphoid follicle formation in the pancreatic parenchyma (H&E × 40).

Figure 2. Immunohistochemical characteristics of follicular pancreatitis.

Germinal centres are negative for Bcl-2 (×100). CD21-positive follicular dendritic cells are present in the lymphoid follicles (×100). Only a few IgG4-positive plasma cells are observed (×100).

Figure 3. Immunostainings for podoplanin in lymphoid follicles.

(a) Podoplanin-positive lymphocytes are present in all cases of follicular pancreatitis.

Podoplanin expression is noted on the cell surface of the lymphocytes(arrows)(×200).

(b) Podoplanin is expressed only in the dendritic cells but not in the lymphocytes in the lymphoid follicles of the lymph node from intraductal papillary mucinous adenoma case (control) and IgG4-related autoimmune pancreatitis (×200).

Figure 4. Cluster classification and heatmap of gene expression level. Heatmap of the normalized data, scaled to give all genes equal variance, generated via unsupervised clustering. Red indicates high expression; green indicates low expression. This plot is meant to provide a high level exploratory view of the data. The enlarged view of the expression level, where characteristic changes are present in patients with follicular pancreatitis (right).

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Figure 5. The possible cascade of lymphoid follicles formation in follicular pancreatitis. Th17 is proliferated by IL-23A, which is produced by dendritic cells expressing LAMP3, and migrates to pancreatic parenchyma. Then, Th17 transforms to follicular helper T cells, followed by formation of lymphoid follicles.

DC: dendritic cell, Th: helper T cell, T: T cell area, B: B cell area, Tfh: follicular helper T cell, LAMP3: lysosomal associated membrane protein 3, CCR6: chemokine (C-C motif) receptor 6, ICOS: inducible T cell co-stimulator, LTA: lymphotoxin alpha
Table 1: Clinical and histopathological features of three cases of follicular pancreatitis

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Symptoms</th>
<th>Location</th>
<th>Size</th>
<th>EUS-FNA&lt;sup&gt;b&lt;/sup&gt; Findings</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>62/Male</td>
<td>Incidental</td>
<td>Tail</td>
<td>CECT: 29×25mm</td>
<td>Acinar cells and benign lymphocytes</td>
<td>Lymphoid follicles with Bcl-2 negative germinal centers in parenchyma</td>
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<td>Case 2</td>
<td>63/Male</td>
<td>Incidental</td>
<td>Body and tail</td>
<td>CECT&lt;sup&gt;a&lt;/sup&gt;: 20×18mm</td>
<td>Not done (cytology using ENPD&lt;sup&gt;c&lt;/sup&gt; juice was benign)</td>
<td>Lymphoid follicles with Bcl-2 negative germinal centers in parenchyma</td>
</tr>
<tr>
<td>Case 3</td>
<td>75/Female</td>
<td>Incidental</td>
<td>Tail</td>
<td>CECT&lt;sup&gt;a&lt;/sup&gt;: 25×21mm</td>
<td>Not done</td>
<td>Lymphoid follicles with Bcl-2 negative germinal centers in parenchyma</td>
</tr>
</tbody>
</table>

-<sup>a</sup> Contrast-enhanced computed tomography
-<sup>b</sup> EUS guided fine needle aspiration
-<sup>c</sup> Endoscopic nasobiliary drainage
-<sup>d</sup> Normal serum IgG4 level = 4.8-105 mg/dL

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Table 2 mRNA counts with significantly higher in follicular pancreatitis compared with IgG4-related autoimmune pancreatitis

<table>
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<tr>
<th>number</th>
<th>name</th>
<th>Log2 fold change</th>
<th>Std error</th>
<th>Lower confidence limit</th>
<th>Upper confidence limit</th>
<th>p value</th>
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<td>0.995</td>
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<tr>
<td>3</td>
<td>ICOS</td>
<td>1.41</td>
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<td>6</td>
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<td>0.459</td>
<td>1.22</td>
<td>3.01</td>
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Table 3: Comparison of pathological and clinical features in follicular pancreatitis and autoimmune pancreatitis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Follicular pancreatitis</th>
<th>Autoimmune pancreatitis</th>
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<td>Lymphoid follicles with germinal centers</td>
<td>Mainly periductal and diffuse throughout the parenchyma</td>
<td>Rarely (type 1)</td>
</tr>
<tr>
<td>Presence of Th17 cells</td>
<td>Mainly in germinal centers</td>
<td>Absent</td>
</tr>
<tr>
<td>Storiform fibrosis</td>
<td>Absent</td>
<td>Present (type 1)</td>
</tr>
<tr>
<td>Obliterative phlebitis</td>
<td>Absent</td>
<td>Present (type 1)</td>
</tr>
<tr>
<td>Significant difference of IgG4/IgG ratio</td>
<td>Absent</td>
<td>Present (type 1)</td>
</tr>
<tr>
<td>Response to steroids</td>
<td>Potential&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Good</td>
</tr>
</tbody>
</table>

<sup>a</sup>: the presence of IgG4 to IgG ratio of >40%

<sup>b</sup>: there was partial response<sup>8</sup>
Figure 1-a, b, c H&E × 40 (three follicular pancreatitis)
Figure 2. Immunostaining of Bcl-2, CD21 and IgG4 (× 100)
Figure 3-a. Immunostainings for podoplanin in lymphoid follicles (× 200)

Figure 3-b. Immunostainings for podoplanin in lymphoid follicles (× 200)
Figure 4. Cluster classification and heatmap of 770 gene expression level
Figure 5. The cascade of lymphoid follicles formation in follicular pancreatitis.