IgG4-related sclerosing cholangitis and type I autoimmune pancreatitis

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SUMMARY

Type 1 autoimmune pancreatitis (AIP) is a prototype of IgG4-related disease (IgG4-RD) and IgG4-related sclerosing cholangitis (IgG4-SC) is the biliary manifestation of IgG4-RD. Recently, IgG4-RD is well-recognized as a systemic disease affecting most organs and the diagnosis criteria in each organ has been established or is currently being researched. Both extrahepatic bile ducts and pancreatic ducts of the ventral pancreas embryologically originate from the common duct in the 4th fetal week. In addition to the similarities in their histogenesis and histology, similarities in AIP and IgG4-SC are also recognized such as prominent IgG4-positive cells, storiform-type fibrosis, and obliterative phlebitis in their affected portions. Although the diagnosis of IgG4-RD is relatively easy in surgical specimens, the tiny mucosal surface specimens obtained by biopsy procedure do not contain enough material to reach a definitive diagnosis. Moreover, the presence of IgG4-positive cells in tissue and increased serum IgG4 levels are often found in patients with biliary and pancreatic cancers. The diagnosis of IgG4-RD in the pancreatiobiliary system, especially in biopsy specimens, is clinicopathologically necessary to consider every possibility.

INTRODUCTION

Although patients with IgG4-related disease (IgG4-RD) or its similar diseases, including autoimmune pancreatitis (AIP), have been retrospectively reported as other disease names in several organs, such as Mikulicz disease and Sjögren's syndrome with IgG4 hypergammaglobulinemia, the characteristic of increased serum IgG4 levels as a unique clinicopathological entity in one type of AIP (type 1 AIP) has been reported by Hamano et al from Shinshu University in 2001 (1). IgG4 is the most minor immunoglobulin subtype of IgG (3–6% of all circulating IgG in adults) and lack a complement activity (1). The physiological and pathological significance of IgG4 remains unknown in both healthy and diseased individuals including IgG4-RD. Since the presence and etiopathogenesis of IgG4-RD have attracted widespread attention, almost all organs have been revealed to be affected in IgG4-RD (2). Type 1 AIP is the prototype of IgG4-RD and IgG4-related

sclerosing cholangitis (IgG4-SC) is a biliary manifestation of IgG4-RD. In this chapter, the histopathogenesis of type 1 AIP and IgG4-SC, and their similarities are introduced from several histopathological perspectives.

IgG4-RD

In present medical practice, IgG4-RD is always raised as a differential diagnosis in the diagnosis of tumorous or stenotic lesions in most organs (2, 3). Differing from the pancreatiobiliary system, gastrointestinal tracts are not typically affected in IgG4-RD and manifestation in this area is limited to several case reports (4). Regardless of the organ involved in IgG4-RD, elevated serum IgG4 values, marked IgG4-positive plasmacytic cell infiltration in affected organs, and marked efficacy of steroid therapy are common characteristics, in addition to organ-specific histological findings (1, 5, 6). A comprehensive diagnostic criterion (2) has been proposed, which can be applied to any affected organs, and organ-specific criteria systems have also been proposed in some organs including the pancreas and biliary tracts (7, 8). Comprehensive criteria (2) consist of increased IgG4 serum levels (>135 mg/dl) and prominent IgG4-positive cells (>40% of IgG-positive plasma cells being IgG4-positive and >10 cells/hpf) in biopsy specimens. In addition to these common features, as mentioned below, IgG4-related AIP (type 1 AIP) and IgG4-SC are histologically characterized by the unique pathologies of uncontrolled progressive fibrosis, inducing sclerosis, and storiform-pattern fibrosis, but several organs such as lymph nodes lack such fibrosis in IgG4-RD. Although the etiopathogenesis of IgG4-RD is still unknown, allergic or autoimmune mechanisms against extrinsic or intrinsic (auto-) antigens are speculated, because of the increased number of eosinophils, the presence of autoantibodies, and the effectiveness of immunosuppressive treatments (9, 10).

Type 1 AIP

The term AIP was first proposed by Yoshida et al. in 1995 (11). At present, broad AIP consists of two different etiopathogenesis, type 1 and type 2. Type 1 AIP is the prototype of IgG4-RD and originally reported as a lymphoplasmacytic sclerosing pancreatitis (LPSP) from the pathological concept in 1991 (12). In contrast, type 2 AIP is not associated with IgG4 and is characterized by the infiltration of neutrophils in epithelial layers of pancreatic ducts. Type 2 AIP is also known as idiopathic duct-centric chronic pancreatitis (IDCP) (13) or autoimmune pancreatitis with granulocytic epithelial lesion (GEL) (14). Among cases AIP in Japan, type 1 is common and type 2 is very rare.

In addition to clinical behaviors, such as increased IgG4 levels and a good response to steroid treatments, the histopathology of type 1 AIP is characterized by the presence of marked lymphoplasmacytic infiltration including IgG4-positive cells (mostly IgG4-positive plasmablasts), and fibrosis (Fig. 1A, D). In addition to these chronic inflammatory cells, several eosinophils and lymph follicle formations are also occasionally found. Lining epithelial cells are well-preserved (Fig. 1A) and erosive change with neutrophil infiltration is scarce. These inflammatory findings are predominantly found around pancreatic ducts. Pancreatic duct glands have recently been identified as a distinct ductal component of the pancreas and are located within the pancreatic duct wall (15, 16). There are no reports indicating that pancreatic duct glands are preferably affected in type 1 AIP, but pancreatic duct glands as well as pancreatic exocrine acinus is concurrently involved in inflammation. Although disease progression destroys the pancreatic exocrine acinus, the lobular architecture is relatively preserved (Fig. 1E). In particular, the fibrosis pattern in type 1 AIP is a characteristic sclerosing type called as a storiform or swirling fibrosis, which shows irregularly whorled patterns (Fig. 1E). Moreover, the intermingled fibrosis of many collagen and inflammatory cells are pathognomonic for this type fibrosis, differing from general scar-like secondary fibrosis. These fibrous and inflammatory changes cause thickening of the wall of the pancreatic duct and expanded into the acinus and also peripancreatic adipose tissue with the development of the disease state (Fig. 1E).

In peripheral pancreatic parenchyma and peripancreatic fatty areas, in addition to the storiform fibrosis, other pathognomonic findings, such as obliterative phlebitis in small venules and the concentration of IgG4-positive cells around nerve bundles, are often found (Fig. 1B, F). Therefore, the border between pancreatic parenchyma and peripancreatic fatty tissue is unclear in the development of interface inflammation and fibrosis (Fig. 1E). Because the comprehensive diagnostic criterion mentioned above is not sufficiently sensitive for the diagnosis of type 1 AIP, pancreas-specific diagnostic criteria have increased the sensitivity of diagnosis for type 1 AIP (8, 17). A marked IgG4-positive cell infiltration does not constitute adequate pathological evidence for the diagnosis of IgG4-RD. Care must be taken not to be overly influenced by diagnostic criteria that overemphasize IgG4-positive cell infiltration in affected organs.

IgG4-SC

IgG4-SC is a biliary manifestation of systemic IgG4-RD, which is diffusely or focally affected in the extrahepatic biliary tree consisting of the large bile ducts of hepatic hilus, common

bile ducts, and the gallbladder. IgG4-SC is preferably found in older males (male:female = 4:1; mean: 67 years; mostly 50 years or older) (18, 19). IgG4-SC is diagnosed in 13%–19.5% of patients with IgG4-RD. Serum IgG4 levels are elevated in 89.5% patients with IgG4-SC without AIP (9, 19, 20), indicating that only lesion of IgG4-SC could reflect the increased serum IgG4. IgG4-SC is accompanied by type 1 AIP in approximately 90% of patients (19, 21). On the other hand, approximately 80% of AIP patients have complications with the stenosis of the intrapancreatic bile duct (distal common bile duct) (22), but it is controversial whether this involvement of the intrapancreatic bile duct in AIP patients is associated specifically with IgG4-SC or not. Histopathologically, the morphology of IgG4-SC greatly resembles that of AIP and both share the same pathological characteristics as IgG4-RD. Primary sclerosing cholangitis (PSC) and cholangiocarcinoma are clinicopathologically important and require differentiation from IgG4-SC, because each of them requires an exact diagnosis for appropriate treatments. IgG4-SC complicating type 1 AIP can be differentiated using the same diagnostic criteria used for AIP (8). However, IgG4-SC without any lesions in the other affected organs, including the pancreas, is often hard to diagnose prior to commencement of treatment, and its differentiation from disease conditions including PSC and cholangiocarcinoma is especially important. Differing from PSC pathologically, the inflammation in IgG4-SC is prominently found in the peribiliary glands existing in the middle layer of the bile duct wall, rather than in the mucosal layer of the bile ducts (Fig. 1B, C). Therefore, biliary epithelial cells lining the bile ducts are usually well-preserved, and erosive change and neutrophil infiltration are scarce in the affected bile ducts (Fig. 1B). However, IgG4-SC cases with atypical features, such as those lacking increased serum IgG4 levels or with premalignant lesions, have been reported (23-25). Moreover, IgG4 reaction is often seen in several cancers including cholangiocarcinoma and pancreatic cancers (26, 27). Therefore, IgG4-positive cell infiltration is not a specific pathological finding in IgG4-RD. When making a pathological diagnosis, specific attention must be paid to this point. Recently, in clarifying the clinicopathological features and the pathogenesis of IgG4-RD and similar diseases, the diagnostic criteria of IgG4-SC has gradually being distinguished. At present, a diagnostic criteria for IgG4-SC has been proposed in Japan (7). Characteristic and diagnostically-useful histological findings of bile duct specimens include: 1. IgG4-positive plasmacytic cell infiltration (≥10/hpf and IgG4/IgG positive cell ratio ≥40%), 2. marked lymphoplasmacytic cell infiltration and fibrosis without neutrophil infiltration, 3. obliterative phlebitis or swirling fibrosis, and 4. storiform fibrosis. However, it is generally difficult to identify such histological features in small biopsy specimens obtained from the surface of bile

ducts. Each individual case should be diagnosed clinicopathologically based on its own individual features.

Similarity of pancreatiobiliary lesions in IgG4-RD

Embryologically, biliary tracts and the pancreas develop from the endoderm foregut from the 4th fetal week. In adults, extrahepatic bile ducts and pancreatic ducts are morph-phenotypically similar; that is, both are covered by a single layer of columnar cells with mucus production and the same keratin patterns, and both are accompanied by periductal glands such as peribiliary glands and pancreatic duct glands (15, 16). In addition to these embryological and histological similarities, some pancreatic and biliary diseases also share unique pathological features. For example, extrahepatic cholangiocarcinoma, pancreatic ductal adenocarcinoma, papillary neoplasia (intraductal papillary-mucinous neoplasm [IPMN] of pancreatic duct and intraductal papillary neoplasm of the bile duct [IPNB]), precancerous lesions (biliary intraepithelial neoplasia [BilIN], and pancreatic intraepithelial neoplasia [PanIN]) share many clinicopathological features (28). In addition to the associations with their carcinomas and carcinogenesis, the histopathology of bile duct lesions in IgG4-SC in some respects resembles those of the pancreatic duct in type 1 AIP and the same patients synchronously or asynchronously are affected with them. In addition to the common histological features in type 1 AIP and IgG4-SC, the following have also been suggested; 1. inflammation mostly affects the wall of the biliary and pancreatic ducts involving peribiliary glands and pancreatic duct glands; 2. lining epithelium in both ducts is relatively well-preserved, though their mucosa surfaces are inflamed accompanying IgG4-positive cells; 3. chronic sclerosing inflammation consisting of marked lymphoplasmacytic cells and fibrosis and inducing luminal stenosis; 4. storiform pattern fibrosis; 5. these inflammation and fibrosis extend into the adipose tissue around the pancreas and hepatic hilus; 6. immunohistochemistry highlights numerous IgG4-positive plasmablastic cells; 7. obliterative phlebitis and perineural infiltration of IgG4-positive cells in tissues; 8. tumor-like lesions, also referred to as mass-forming pancreatitis and inflammatory pseudotumor, are sometime complicated (Fig. 1H). Moreover, similar mechanisms are clarified. Th2 cells producing Th2 cytokines, such as IL4 and Foxp3+ regulatory T cells (Treg cells) producing interleukin 10 (IL10), are associated with the pathogenesis of AIP and also IgG4-SC (29). In particular, IL10 is a regulatory cytokine mainly produced by Treg cells, and Th2 cells induce the differentiation of IgG4-positive plasma cells or favor B cell switching to IgG4 in the presence of IL-4 (30, 31). Therefore, IgG4-SC and AIP form a disease spectrum in the pancreatico-biliary system against a background of the common pathophysiological features in bile ducts and the pancreas (28).

This concept could be applied in extrahepatic bile ducts, but not intrahepatic bile ducts. Intrahepatic and extrahepatic bile ducts share the same keratin patterns and drainage functions of bile, but differ from the histogenesis, mucus production, and accompanying periductal glands. As mentioned above, extrahepatic bile ducts, including the large bile duct in hepatic hilus and the gallbladder, and pancreatic ducts are developed from the foregut in the same fetal week. Intrahepatic bile ducts in the peripheral liver are derived from the ductal plate, which is thought to contain hepatic progenitor cells, and embryologically differ from extrahepatic bile ducts. The anatomical distribution of IgG4-SC is limited in extrahepatic bile ducts, reflecting the similarity in the pathogenesis of type 1 AIP. In fact, IgG4-positive cells are found in the peripheral small portal tracts, which are contained in the liver biopsies taken from patients with IgG4-RD (32). However, the presence of IgG4-posiive cells in small portal tracts is not the lesion affecting peripheral small bile ducts, which is speculated to be just the extended inflammation along the intrahepatic biliary tree from extrahepatic bile ducts in IgG4-SC. It is unknown why intrahepatic bile ducts are not directly affected in IgG4-RD as they are in IgG4-SC, but it suggests that the diseases and pathogenesis found in extrahepatic bile ducts is similar to those in pancreatic ducts, and that intrahepatic bile ducts do not apply to the "biliary diseases with pancreatic counterparts" (28).

IgG4 reaction in pancreatiobiliary carcinoma

Elevated serum IgG4 levels are not always helpful for achieving a differential diagnosis (1, 33). The elevation of serum IgG4 levels is important in the diagnosis of IgG4-RD, but is not necessarily specific to IgG4-RD, because this increase is found in patients with PSC, cholangiocarcinoma, pancatic cancers, and several inflammatory diseases of other organs, such as atopic dermatitis, pemphigus, asthma, and even a non-selected cohort of patients (approximately 7%), and approximately 10% patients of IgG-SC or AIP lack increased serum IgG4 levels (9, 22, 26, 34). Moreover, several cases of pancreatic cancer and cholangiocarcinoma are accompanied by IgG4 reaction and/or elevated serum IgG4 levels (27, 33, 35, 36) and also a few cases of pancreatic cancer or cholangiocarcinoma arising from IgG4-SC or type 1 AIP, respectively, have been reported (37, 38), suggesting an association between cancer-related immunity and IgG4 reaction. As mentioned above, Treg cells and regulatory cytokine IL10 are associated with the pathogenesis of AIP and IgG4-SC (29). Treg cells and IL10 are also involved in carcinogenesis of pancreatic duct carcinoma and cholangiocarcinoma, because this regulatory cytokine network reflects evasion from immune surveillance in carcinogenesis (26). An IgG4 reaction consisting of abundant IgG4-positive cells in tissue may simply be the result of an immunoreaction within a Th2 and regulatory cytokine milieu

(26, 29, 30). Therefore, an IgG4 reaction is speculated to nonspecifically occur in several inflammatory and cancerous lesions, and the presence of IgG4-positive cells is not a histological hallmark of IgG4-RD. To diagnose IgG4-SC and AIP, particularly to deny the malignancy in stenotic portions, biopsy and cytological examination are necessary to exclude malignancies and establish a diagnosis. Therefore, differentiating IgG4-SC or AIP cases without other organ involvement of IgG4-RD from PSC, cholangiocarcinoma, and pancreatic cancers is challenging (39-41). Moreover, carcinogenesis in IgG4-RD has been noted (42), and there have also been a few reported cases of IgG4-SC accompanied by cholangiocarcinoma or BilIN lesions (23, 37, 38, 43-46). Our previous survey demonstrated that the IgG4 reaction in biliary tract cancers occurs at various degrees in most cholangiocarcinoma cases located in the extrahepatic biliary tree (Fig. 2), but very rarely in cholangiocarcinoma of the liver (intrahepatic cholangiocarcinoma). It is unknown why intrahepatic cholangiocarcinoma accompanies scarce IgG4 reaction, but one interesting possibility is raised that this IgG4 reaction is limited by the embryological and anatomical similarities between extrahepatic bile ducts and pancreatic ducts (26, 28, 34, 47).

Concluding remarks

Increased IgG4 levels in serum and organs are unique and valuable features of IgG4-RD. Extrahepatic bile duct and the pancreas are also involved in this disease and their manifestations are recognized from the concept of this book, "Biliary diseases with pancreatic counterparts". The pathological significance of IgG4 reaction found in other contexts as well as IgG4-RD need to be determined by future investigation.

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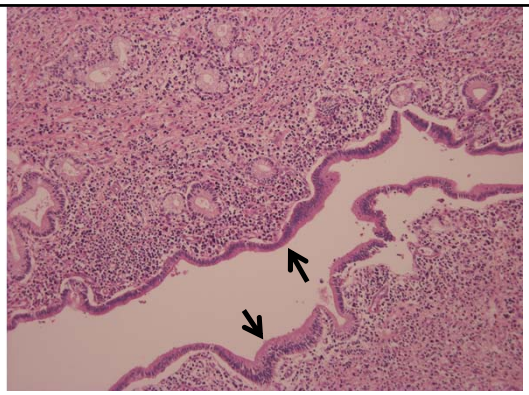
Figure legends

Fig. 1 Representative histological features in AIP and IgG4-SC. A: Pancreatic duct. Inflammation and sclerosing fibrosis are found in the periductal area in AIP. B: Lower common bile duct (intrapancreastic bile duct). Inflammation extends from the ductal wall into the periductal area, in which perineural inflammation is found (arrowhead). Lining epithelia is preserved (arrows). C: Upper common bile duct. Inflammation concentrated around the peribiliary glands (arrows). D: Inflammation consists of plasmablasts, plasma cells, and lymphocytes. E: Interface area of the pancreas (left below) and peripancreatic fatty tissue (upper right). Storiform pattern-severe sclerosing fibrosis (*) is found intermingling with inflammation. Acinus is destroyed and slightly atrophic with fibrosis, but lobular architecture is remaining (left below). F: Elastica van Gieson staining highlights obliterative phlebitis (arrow). G: IgG4 immunohistochemistry reveals abundant positive plasma cells or plasmablasts. H: Type 1 AIP forming a mass-like nodular formation (mass-forming pancreatitis).

Fig. 2 Cholangiocarcinoma with abundant IgG4-positive cells (common bile duct cancer). A: Ordinary adenocarcinoma is found with marked inflammation. B: IgG4 immunohistochemistry highlights abundant positive cells within the carcinoma. Scale is 5 mm.



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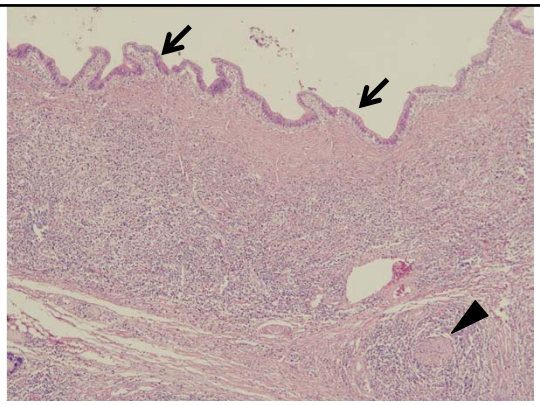

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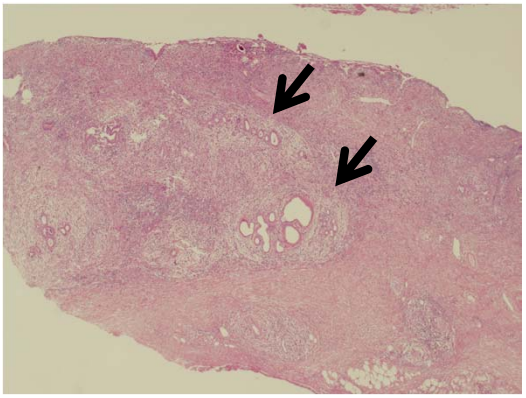

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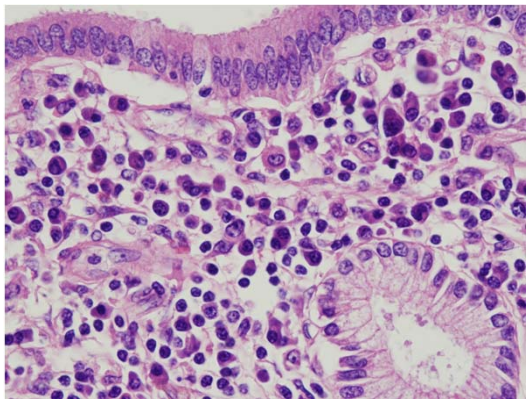

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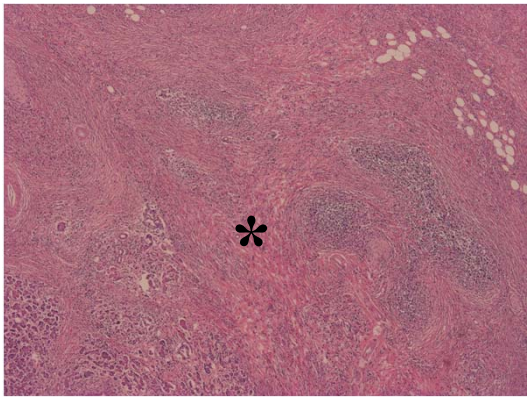

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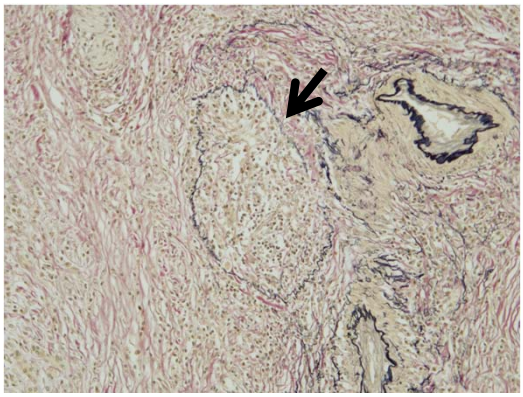

Fig.1F

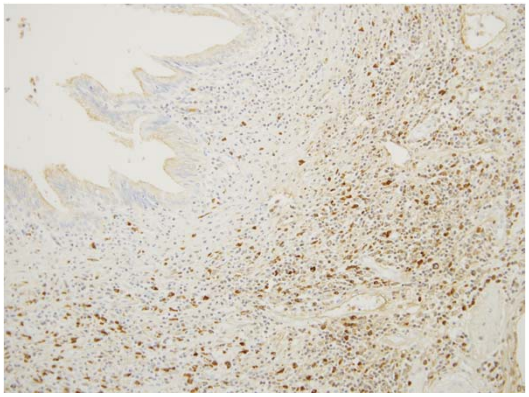

Fig.1G

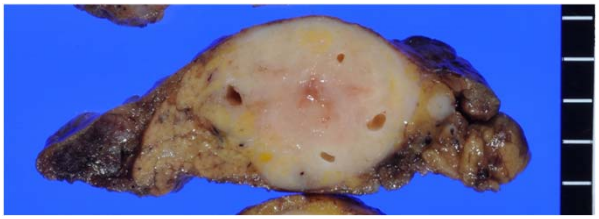

Fig.1H

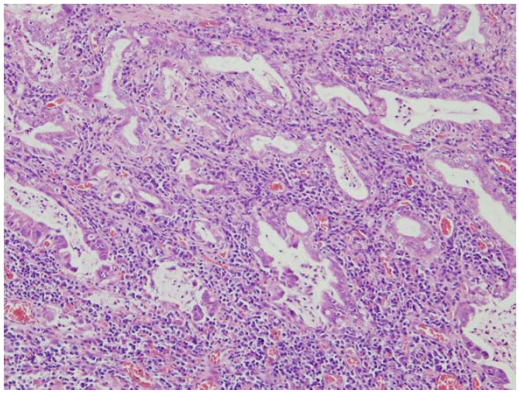

Fig.2A

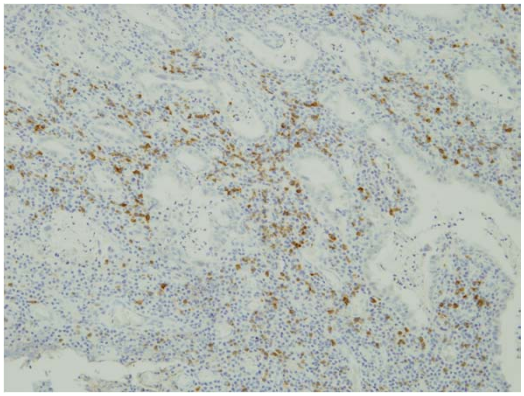

Fig.2B