Autoimmune pancreatitis should be differentiated from pancreatic and bile duct cancers because they often have similar clinical features and images. Accurate and practical diagnostic algorithm for AIP is important to avoid unnecessary surgery and delayed treatment. International Consensus Diagnostic Criteria for AIP suggested that diagnostic algorithms and the practical patterns considerably vary worldwide. Patients with clinically suspected AIP can be categorized into patients with typical features of AIP and patients with indeterminate features based on CT findings. Serology and other organ involvement can be used as collateral evidence of AIP. If a patient presents with diffuse pancreatic enlargement but is lack of collateral evidence, pancreatogram could be useful. If a patient has obstructive jaundice, biliary drainage and endobiliary biopsy are recommended. Duodenal papillary biopsy for IgG4 immunostain can be used during ERCP. In case of atypical imaging findings, EUS-guided FNA/biopsy is recommended to exclude pancreatic cancer and to obtain the suggestive findings of AIP. If type 2 is clinically suspected, EUS-guided core biopsy is required for the definite diagnosis. Short-term steroid trial can be performed to confirm the diagnosis of AIP when pancreatobiliary cancer workup shows negative results. However, clinical practice in diagnosing AIP varies depending on the local expertise, facilities, cost, prevalence of AIP and its subtypes.

Keywords: Autoimmune pancreatitis, International Consensus Diagnostic Criteria, Algorithm, IgG4

INTRODUCTION

Autoimmune pancreatitis (AIP) is a rare systemic fibro-inflammatory disease which can affect not only the pancreas but also a variety of organs such as the bile duct, salivary glands, kidney, prostate, lung, retroperitoneum and lymph nodes. This inflammatory process dramatically responds to steroid therapy. AIP should be differentiated from pancreatic and bile duct cancer because they often have similar clinical features and imaging findings such as pancreatic enlargement, mass formation and obstructive jaundice. Therefore, accurate and practical diagnostic algo-
algorithm for AIP is important to avoid unnecessary surgery for AIP and delayed operation for pancreatobiliary malignancies. In 2011, International Consensus Diagnostic Criteria (ICDC) for AIP was introduced. The concepts of typical type, indeterminate/atypical type and 5 cardinal features (radiologic images, serology, other organ involvement, histology and response to steroid) are generally agreed. Although ICDC suggested a diagnostic algorithm for AIP, clinical practice still considerably varies worldwide. In particular, there is a discrepancy in the use of endoscopy for the diagnosis of AIP between Eastern and Western countries. Korean and Japanese doctors still use endoscopic retrograde cholangiopancreatography (ERCP) for the differentiation of AIP from pancreatic cancer (PC). However, Western doctors prefer magnetic resonance cholangiopancreatography (MRCP) to ERCP and frequently perform endoscopic ultrasonography (EUS)-guided core biopsy not only to diagnose AIP but also to differentiate two types of AIP. The difference in practice also depends on the fact whether pancreatologists themselves are endoscopists or not, facilities, cost of endoscopy, and prevalence of type 2 AIP.

**DIAGNOSTIC METHODS AND ALGORITHM**

Because symptoms and laboratory findings are nonspecific and similar between AIP and pancreatobiliary malignancies, cross-sectional images are first used for the differential diagnosis. Dynamic computed tomography (CT) provides many information including enhancement patterns, peripancreatic low density rim, ductal dilatation, surrounding lymph nodes and organs. CT features can be classified into typical of AIP, indeterminate features and typical of PC. There are many studies on the typical CT imaging features of AIP and PC. Therefore, most diagnostic algorithms start from CT-based stratification. Highly suggestive findings for AIP are diffuse enlargement with delayed homogenous enhancement, capsule-like rim and lack of significant dilatation of upstream pancreatic duct. Highly suggestive findings for PC are non-enhanced mass with prominent dilatation of upstream pancreatic duct and the parenchymal atrophy. Magnetic resonance imaging (MRI) is also helpful to differentiate AIP from PC. However, imaging alone is not perfect to distinguish AIP from PC.

In the following step for the diagnosis of AIP, ICDC recommended to check serology and the presence of other organ involvement (OOI). In serology, total serum immunoglobulin G (IgG), IgG4 and autoantibodies have been used for the diagnosis of AIP. If total serum IgG is included in diagnostic criteria, the sensitivity increases but specificity can be sacrificed. ICDC included only IgG4 as a serologic marker of AIP to exclude the false positivity in pancreatic cancer and other diseases. Serum IgG4 (≥135 mg/dL) is the most sensitive (52-80%) and specific (93-99%) serologic marker for the diagnosis of AIP. Serum IgG4 may be mildly elevated in 5-10% of pancreatic cancer. Serum IgG level (≥1,800 mg/dL) is less sensitive (43-70%) and less specific (88-93%). ICDC divided the serologic criterion into level 1 and level 2; level 1 if serum IgG4 level is higher than two times the upper limit of normal and level 2 if it is lower than two times the upper limit of normal. When the cut-off value of serum IgG4 is raised to two times the upper limit of normal, the specificity improves to 97-100% but the sensitivity decreases to 34-50%. Level 1 of serum IgG4 is not necessarily sufficient to exclude pancreatic cancer.

A variety of extrapancreatic lesions have been noted in patients with AIP including bile duct, lachrymal and salivary glands, retroperitoneum, thyroid, kidney and prostate. The presence of extrapancreatic involvement could be used for the collateral evidence of AIP. ICDC stratified the level of OOI. Sclerosing cholangitis, retroperitoneal fibrosis or
strong histologic evidence of other organs are included in level 1 criterion. Salivary/lacrimal glands and renal involvement are included in level 2. However, it is unclear why Mikulicz’s disease and renal involvement are classified as level 2 OOI. Mediastinal or hilar lymphadenopathies and intrapancreatic bile duct strictures are not specific to AIP. ICDC also recommended ampullary biopsy as collateral evidence if there is insufficient evidence of OOI and serology. Ampullary biopsy with IgG4 immunostain (more than 10 IgG4-positive cells per high power field) has a sensitivity of 52% to 89% and specificity of 89% to 100%. It is a simple and safe adjunctive method to get collateral evidences of AIP. However, ampullary biopsy can be performed at the same time during ERCP. Pancreatogram is important to differentiate AIP from pancreatic cancer. Four ERP features are highly specific to AIP: long (>1/3 of the length of main pancreatic duct) narrow stricture, a lack of upstream dilatation from the stricture (<5 mm), multiple strictures, side branches arising from the stricture site. Highly suggestive findings for PC are cut-off of pancreatic duct or prominent dilatation of upstream pancreatic duct. ERCP also provides endobiliary biopsy and biliary drainage in patients with obstructive jaundice. ERCP is helpful to diagnose AIP with atypical CT findings but has little added benefits in patients with typical CT findings. Western endoscopists generally avoid ERCP to diagnose AIP due to the fear of post-ERCP pancreatitis. However, post-ERCP pancreatitis is rare and mild in patients with AIP because AIP is a kind of chronic pancreatitis in which post-ERCP pancreatitis develops less frequently due to fibrosis and decreased enzymatic activity. That Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive alternative method to evaluate pancreatic ducts. It can be used to support the diagnosis of AIP. However, it could not reveal the narrowed portion of the main pancreatic duct and sometimes inadequate to differentiate mass-forming AIP from PC. MRCP cannot entirely replace ERCP. Accuracy of MRCP in depicting the main pancreatic duct morphology of AIP is moderate (65-69%). Multiple narrowing or skipped pancreatic duct and absence of upstream ductal dilatation suggest AIP. Therefore, MRCP may be useful in patients with diffuse pancreatic enlargement without other collateral evidence and jaundice. MRCP is also useful to evaluate treatment response in AIP.

Positron emission tomography shows increased uptake of fluorodeoxyglucose in both AIP and PC. The pattern of fluorodeoxyglucose uptake in PC is nodular, homogenous and solitary whereas the uptake in AIP is longitudinal, heterogeneous and multiple in the pancreas and extrapancreatic sites including salivary glands, bile duct, retroperitoneum and kidney. However, routine use of positron emission tomography is not recommended because of the high cost and high dose of radiation exposure.

In some case of AIP, the diagnosis can be only made by resected tissue or biopsy specimen. According to ICDC, AIP is classified into 2 subtypes: type 1 is related with IgG4 (lymphoplasmacytic sclerosing pancreatitis, LPSP) and type 2 is related with granulocytic epithelial lesion (idiopathic duct centric pancreatitis, IDCP). These two types were identified by pathologic studies of resected pancreases misdiagnosed with pancreatic cancer. While IDCP patients account for at least one-third of all AIP patients in Europe and the USA, they are still rare in Korea and Japan. Because patients with type 2 AIP are unlikely to have OOI and do not have serologic markers, type 2 can be definitely diagnosed only by histologic examination. Normal s-IgG4 level and absence of OOI do not necessarily mean type 2 AIP. Indeed, type 1 AIP with normal serum IgG4 and absence of OOI is more probable than type 2 AIP in Korea. Histologic diagnosis could be achieved by endoscopic ultrasound (EUS)-guided core biopsy but it is technically difficult, especially in pancreatic head lesion. In addition, sampling error may occur as the pancreas is not uniformly involved.
Therefore, it is challenging to make a definite diagnosis of AIP and perform typing with small biopsy specimen. For this reason, correlation with other clinical and radiologic features is necessary.25,26 Also, some features of type 1 could be seen in type 2 AIP and GEL could be seen in 27% of type 1 AIP. Instead, EUS-guided fine needle aspiration may show suggestive findings of AIP such as lymphoplasmacytic infiltration and many IgG4-positive plasma cells or inconclusive results. Because some features of LPSP and IDCP can be also seen in pancreatic cancer, we have to be careful. Nevertheless, EUS-FNA has an important role for the exclusion of PC in atypical cases because it provides a sensitivity of 80-90% and specificity of 95-100% for the diagnosis of PC.12 Recently, fine needle aspiration biopsy is available and easier to be performed than trucut core biopsy at pancreatic head lesion.27 We also need to keep in mind that PC is about 100 times more prevalence than AIP. Therefore, EUS-guided FNA/biopsy is recommended in all patients with focal mass-forming pancreatitis to exclude malignancy.

In patients with appropriate collateral evidence of AIP, steroid trial can be used to assist in making the diagnosis when it is used appropriately. Steroid trial should not be abused and must be performed only when workup results for pancreatobiliary malignancies are negative. Objective improvement of the pancreatic parenchymal and ductal images should be evident within 2 to 4 weeks. Improvement of symptoms, laboratory findings, tumor markers

![Fig. 1. Algorithm for the diagnosis of autoimmune pancreatitis (AIP) in Korea. OOI; other organ involvement, LPSP; lymphoplasmacytic sclerosing pancreatitis, IDCP; idiopathic duct-centric pancreatitis, MPD; main pancreatic duct.](image-url)
and serum IgG4 level should not be used to assess response to steroids.

CONCLUSIONS

Diagnostic algorithm for AIP can be different according to countries, institutions and physicians. Figure 1 is my suggestion of practical algorithm for Korean population. Patients with clinically suspected AIP can be first categorized into patients with typical features of AIP, patients with indeterminate CT features and patients with typical features of PC based on the CT findings. Then, serology and other organ involvement can be used as collateral evidence of AIP. If a patient has diffusely enlarged pancreas but lacks of collateral evidence, pancreatogram by ERCP or MRCP can be performed. If a patient has obstructive jaundice, biliary drainage and endobiliary biopsy are recommended. Duodenal papillary biopsy for IgG4 immunostain can be used at the same time during ERCP. If a patient shows atypical imaging, EUS-guided FNA/biopsy is recommended to exclude pancreatic cancer and could obtain the suggestive findings of AIP. If type 2 AIP is clinically suspected, EUS-guided core biopsy is required for the definite diagnosis. Short-term steroid trial can be performed to confirm the diagnosis of AIP when workup results for pancreaticobiliary cancer are negative.

REFERENCES


