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Original Article

Immunoglobulin G4-related diseases: Autoimmune pancreatitis and cholangitis

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Abstract

Objective: Autoimmune pancreatitis (AIP) and cholangitis are chronic inflammatory diseases characterized by the infiltration of lymphoplasmocytic cells into the pancreas and biliary tract and fibrosis. This is often accompanied by increased serum immunoglobulin G4 (IgG4) levels. An early and accurate diagnosis is extremely important because they display similar features to other malignant diseases of the pancreas and biliary tract and primary sclerosing cholangitis. In this study, we aimed to convey our clinic's experiences on this topic.

Methods: The patients who were diagnosed with IgG4 (+)/(-) AIP and IgG4 (+) sclerosing cholangitis by excluding other causes with clinical, radiological, serological, and pathological examinations and treatment response between July 2014 and June 2020 were included in the study. The data of the patients were analyzed retrospectively.

Results: A total of 12 patients, 8 men and 4 women, were included in the study. The mean age of the patients was 39.4 (13-66) years. Abdominal pain of varying degrees was the main reason for admission in all patients. The time of diagnosis and follow-up was 19.2 (2-66) months on average. The average number of attacks during the follow-up was 2.9 (2-8) times. The average IgG4 level of the patients was calculated as 250.1 (133-409) mg/dL. All the patients were given 24-48 mg methylprednisolone at reduced doses for 6-8 weeks.

Conclusion: High serum IgG4 levels are the key indicators for diagnosis, and an early and accurate differential diagnosis is extremely important for malignant diseases of the pancreas and biliary tract. A good response to steroids is an important criterion for diagnosis as well as treatment.

Keywords: Autoimmune diseases, immunoglobulins, cholangitis, pancreatitis

Introduction

Autoimmune pancreatitis (AIP) and cholangitis are chronic inflammatory diseases characterized by the infiltration of the pancreas and biliary tract with lymphoplasmocytic cells and fibrosis (1, 2). Increased serum immunoglobulin G4 (IgG4) levels are frequently seen in both diseases and are very important for diagnosis (3, 4). These diseases, which can affect other organ systems, are classified as IgG4-related diseases (IgG4-RD) (1, 2, 5).

Generally, AIPs are classified as type 1 and type 2. In type 1 AIP, serum IgG4 elevation and IgG4 (+) plasma cell infiltration into the pancreas are observed. Although type 2 AIP has similar clinical and laboratory features as type 1, IgG4 is negative (6). IgG4-associated cholangiopathy has been known by different names; however, the definition of IgG4-associated sclerosing cholangitis (IgG4-SC) recommended by the European liver research association has been widely accepted (7). IgG4-SC is characterized by increased serum IgG4 level, fibrosis in the bile duct wall, and obliterative phlebitis is the biliary form of IgG4-RD (2, 8). The diagnosis of both AIP and IgG4-SC is based on a combination of radiological, serological, and histopathological examinations and response to steroid therapy (5, 8, 9).

IgG4-RD show characteristics similar to those of pancreatic and biliary tract malignant diseases and primary sclerosing cholangitis (PSC) on clinical, laboratory, and imaging observations (5, 8). Therefore, accurate and early differential diagnosis is extremely important to avoid unnecessary major surgeries and oncological treatments. In this study, our goal was to convey our clinic's experiences on this topic.

Methods

The patients who were diagnosed with IgG4 (+)/(-) AIP and IgG4-SC by excluding other causes with clinical, radiological, serological, and pathological examinations and treatment response in our clinic between

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July 2014 and June 2020 were included in the study. The demographic features, laboratory values, radiological and endoscopic imaging findings, and treatment methods and responses of these patients were retrospectively analyzed. Laboratory reference range for IgG4 was 0-125 mg/dL, and cases of patients with more than 125 mg/dL were accepted as positive. In addition, 3 patients whose IgG4 levels were in the normal range, whose malignancy could not be demonstrated by imaging methods or histopathology, and who had a complete response to steroid treatment were accepted as IgG4 (-) AIP and included in the study. The patients who had alcohol and toxic drug or herbal agent consumption anamnesis, were excluded from the study. Moreover, the patients who were diagnosed with pancreatic and biliary tract cancers, sphincter oddi spasm, gallbladder or biliary tract stones detected by endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), ultrasonography (USG), computed tomography (CT), and histopathological examination were not included in the study.

The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all the patients, and ethical approval was given by the local Ethics Committee of SANKO University (Approval Date: August 13, 2020; Approval Number: 2020/14-01).

Statistical analysis

The mean value calculations were performed using the Excel software (Microsoft; Redmond, Washington, USA).

Main Points

- High serum immunoglobulin G4 (IgG4) levels are the key indicators for diagnosis of autoimmune pancreatitis and cholangitis.
- Although it is generally an advanced age disease, it can also be seen in very young patients. It is more common in men, and recurrence is common after treatment.
- Early and accurate differential diagnosis of IgG4-related disease is immensely important to differentiate it from other malignant diseases of the pancreas and biliary tract.
- It should be noted that serum IgG4 levels may not be high in all patients.
- High response to steroids is an important criterion for diagnosis as well as treatment.

Results

A total of 12 patients, including 8 men and 4 women, were included in the study. The mean age of the patients was 39.4 (13-66) years. Abdominal pain at different levels was the main reason for admission in all the patients. Other clinical complaints were itching, jaundice, and weakness. Moreover, 1 patient had a history of previous cholecystectomy, cesarean, and gastric surgeries. The time of diagnosis and follow-up was 19.2 (2-66) months on average. The average number of attacks during the follow-up period was 2.9 (2-8). The average IgG4 level of the patients was calculated as 250.1 (133-409) mg/dL. All patients were radiologically examined using USG, CT, and MRCP. ERCP was performed in 6 patients, and endoscopic ultrasonography (EUS) was performed in 5 patients. Histopathological evaluation was performed, accompanied by EUS in only 1 patient. On laboratory and medical imaging, 2 patients had cholangitis, 5 had pancreatitis, and the other 5 had both cholangitis and pancreatitis. Methylprednisolone (Prednol; Mustafa Nevzat İlaç San., İstanbul, Turkey) was given to all the patients at a dose of 24-48 mg. Doses were gradually reduced and discontinued after 6-8 weeks. The steroid was restarted in patients with recurrence. Various doses of ursodeoxycholic acid (Ursofalk; Ali Raif İlaç San., İstanbul, Turkey) for 7 patients and azathiopurine (Imuran; Aspen, İstanbul, Turkey) for 1 patient were added to the steroid therapy. No drug-related side effects were observed in any of the patients.

Discussion

Data related to the prevalence of AIP and IgG4-SC, which are rare diseases, are limited. In a study conducted in Japan, the prevalence was reported as 2.2 per 100,000 (4, 7, 10). In another study, 21 of 451 patients with chronic pancreatitis were diagnosed with AIP (11). Although both are advanced age diseases, the patients diagnosed in the first decade have also been reported (12). In IgG4-RD, which has different guidelines and classifications for its diagnosis, there is distinct male sex superiority, varying 2-8 times in many publications (7, 10, 12). In our study, the average age was lower than that mentioned in the literature, and 2 of our patients diagnosed with IgG4 (+) AIP who had a complete response with steroid therapy were 13 and 15 years old. The limited number of patients and the fact that 2 patients were under 20 years might explain the low average age. Similar to the literature, there was male sex superiority in our study.

Clinical findings vary depending on the type, location, and severity of the disease. Abdominal pain, jaundice, itching, weight loss, and loss of appetite can be seen in the epigastric region (7, 13). In our study, epigastric pain was prominent in the AIP group, but jaundice and itching were more prominent in the IgG4-SC groups. Jaundice develops slowly in PSC, which is an important disease in the differential diagnosis, but develops faster in IgG4-RD (2, 13).

Laboratory findings of these diseases vary. Depending on the level of the pancreatic and biliary segment affected in both IgG4-RD, there may be elevations in amylase, lipase, and cholestasis enzymes at different levels. However, none of these are specific. The most valuable laboratory parameter is IgG4 positivity. Although IgG4 is not positive in all patients, the higher is its value, the higher is the sensitivity and specificity in diagnosis and differential diagnosis (2, 14, 15). In our study, although IgG4 was positive in all the patients in the cholangitis group, it was negative in 3 patients in the AIP group, and the diagnosis was established by imaging, pathological examination, and response to steroid therapy.

Radiologic imaging methods are very important in the diagnosis, differential diagnosis, and follow-up of IgG4-RD. Extrahepatic biliary stenosis and stones can be demonstrated by USG, and swollen sausage-like pancreas can be seen in AIP (2, 7, 16). Unlike pancreatic cancer, which is the most important disease in the differential diagnosis, delayed involvement owing to lymphoplasmocytic infiltration and fibrosis is seen on CT and MRI in IgG4-RD (17). Heterogeneous and irregular wall structure is observed in cholangiocarcinoma, whereas long involvement and homogeneous and regular wall structure are observed in IgG4-SC. Beads, multiple stenoses, and dilatations are observed on ERCP in PSC, which is the other disease in the differential diagnosis, and the prestenotic dilatations and often stenosis in the distal common bile duct are observed in IgG4-SC (7, 13, 14, 18). In our study, all the radiologic methods were used for the diagnosis and differential diagnosis, and an examination was carried out by ERCP and EUS for some patients. Extrahepatic and distal common bile duct stenosis was detected in all the patients with cholangitis.

Although there are different alternatives in treatment, steroids are the primary and most effective option (2, 7, 8, 13, 14, 19). There is no definite consensus between the Japanese and Western guidelines on treatment duration and medication dosage (2, 5-7, 10, 13, 19). Azathiopurine and rituximab can be used in patients with steroid side effects, relapse, or resistance (20, 21). Rapid remission was achieved with steroid therapy in all the patients in our study.

Azathiopurine was added to the treatment for 1 patient who had stenosis in the distal common biliary duct and had frequent recurrence. Recurrence is an important problem in both the diseases, and different rates of recurrence have been reported (2, 8, 19, 21, 22). In our study, multiple recurrences were observed during the follow-up period because of both disease characteristics and treatment noncompliance.

Ethics Committee Approval: Ethics committee approval was received for this study from the local Ethics Committee of SANKO University (Approval Date: August 13, 2020; Approval Number: 2020/14-01).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

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