Autoimmune Pancreatitis Accompanied by Eosinophilic Cholecystitis Diagnosed After Surgery: Report of a Case with Histopathological, Radiological, and Clinical Approach

Cerrahiden Sonra Tanı Alan Eozinofilik Kolesistitin Eşlik Ettiği Otoimmün Pankreatit: Histopatolojik, Radyolojik ve Klinik Yaklaşımla Olgu Sunumu

Güldal YILMAZ,[a]
Berna SAVAŞ,[a]
Çetin ATASOY,[b]
Kaan KARAYALÇIN,[c]
Esra ERDEN[a]

Departments of
[a]Pathology,
[b]Radiology,
[c]Surgery,
Ankara University Faculty of Medicine, Ankara

Geliş Tarihi/*Received:* 20.02.2011
Kabul Tarihi/*Accepted:* 23.12.2011

Yazışma Adresi/*Correspondence:*
Güldal YILMAZ
Ankara University Faculty of Medicine, Department of Pathology, Ankara, TÜRKİYE/TURKEY
drguldal@yahoo.com

ABSTRACT Autoimmune pancreatitis (AIP) is a special type of chronic pancreatitis that has increasingly been recognized in recent years. We reported a case of AIP which involved mainly the head of the pancreas and the common bile duct, presenting with the features of an accompanying eosinophilic cholecystitis. A 39-year-old woman presented with jaundice, weight loss, and abdominal pain. Radiological examination, together with clinical findings proposed the diagnosis of pancreatic carcinoma. The patient underwent pancreaticoduodenectomy and gross examination of the specimen revealed a firm, mass-like enlargement at the head of the pancreas. Histological findings were characterized by diffuse lymphoplasmacytic infiltration with marked interstitial fibrosis and focal acinar atrophy, obliterative phlebitis of the pancreatic veins, and perineural inflammatory infiltration. Inflammatory component involving the gallbladder was mainly composed of eosinophilic leucocytes. Unfortunately, soon after the operation, the patient started to bleed at the site of gastroenterostomy. Twenty days later, pulmonary thromboemboli developed and the patient died. AIP, which can readily be mistaken for pancreatic carcinoma, may be treated with systemic steroids, if recognized preoperatively. Pathological examination is critical in the evaluation of such cases.

Key Words: Pancreatitis, chronic; autoimmune diseases; cholecystitis; surgical procedures, operative

ÖZET Otoimmün pankreatit (OİP) son yıllarda giderek daha sık tanımlanan özel bir kronik pankreatit tipidir. Bu yazıda, pankreas başında ve ana safra kanalınında tutulum oluşturan bir OİP olgusu ve buna eşlik eden eozinofilik kolesistit tablosu sunulmuştur. Otuz dokuz yaşında kadın hasta sarılık, kilo kaybı ve karın ağrısı nedeniyle başvurdu. Klinik bulgularla birlikte radyolojik muayene pankreas kanseri tanısını düşündürdü. Pankreatikoduodenektomi yapıldı ve örneğin makroskobik incelemesinde pankreas başında sert, kitle benzeri genişleme saptandı. Histolojik bulgular belirgin interstisyel fibrozis ve fokal asiner atrofi, pankreatik venlerin oblitere filebiti ve perinöral inflamatuvar infiltrasyon ile birlikte difüz lenfoplazmositik infiltrasyonla karakterize idi. Safra kesesini tutan inflamatuvar komponent başlıca eozinofil lökositlerden oluşmaktaydı. Ancak, operasyondan kısa bir süre sonra gastroenterostomi bölgesinden kanama meydana geldi. Yirmi gün sonra hastada pulmoner tromboemboli gelişti ve hasta kaybedildi. Pankreas kanseri ile karışabilen OİP, preoperatif dönemde tanımlanması durumunda sistemik steroitlerle tedavi edilebilir. Böyle olguların değerlendirilmesinde patolojik inceleme kritiktir.

Anahtar Kelimeler: Pankreatit, kronik; otoimmün hastalıklar; kolesistit; cerrahi işlemler, operasyon.

Turkiye Klinikleri J Med Sci 2012;32(5):1471-6

Autoimmune pancreatitis (AIP) is a recently proposed chronic fibroinflammatory condition primarily affecting the pancreas.[1,2] AIP is divided into two major groups: (i) lymphoplasmacytic sclerosing

doi: 10.5336/medsci.2010-16865

pancreatitis, and (ii) idiopathic duct-centric pancreatitis. It is characterized by diffuse or focal swelling of the pancreas, irregular narrowing of the main pancreatic duct, hypergammaglobulinemia, and on occasion, the presence of autoantibodies and associated autoimmune diseases together with responsiveness to corticosteroid therapy.[3] The focal swelling of the pancreas may give rise to high suspicion of pancreatic cancer. In this report, detailed histopathology of AIP-that shows the features of lymphoplasmacytic sclerosing pancreatitis-with associated gallbladder findings was presented and the diagnostic pitfalls, findings suggesting AIP, and relationship of this relatively new condition with surgery were discussed.

CASE REPORT

A 39-year-old woman presented to the hospital with epigastric pain, fever, weakness, jaundice with passage of dark urine, and pruritis. She had lost seven kilograms in one month. She reportd using oral antibiotic drugs, which did not relieve her symptoms. The patient had an unremarkable medical history except for suffering from goiter for ten years and reported no alcohol consumption. On physical examination, the thyroid gland was diffusely enlarged and was easily palpable. The skin and sclera were icteric. Although the abdomen was tender, there was no palpable mass. On admission, her serum total bilirubin level was 10.93 mg/dL [Normal level (N): 0.3-1.2], glucose 127 mg/dL (N:74-106), aspartate transaminase 77 UI/L (N: 0-31), alanin transaminase 91 UI/L (N: 0-34), lactate dehydrogenase 304 UI/L (N: <248), alkaline phosphatase 358 UI/L (N: 30-120), gastrin 127.5 pg/mL (N: 25-111), erythrocyte sedimentation rate 43 mm/hour (N: 0-20), C-reactive protein 4.85 mg/L (N: 0-3), and urinary bilirubin level was 6 mg/dL (N:<1), which were all higher than the normal levels. Antithyroglobulin level was 14.72 IU/mL (N: 10-115), anti-TPO 9.63 IU/mL (N:5-34), free fragments of T3 and T4 were 19.43 (N: 10-22) and 4.41 (N: 3-6.5) pmol/L, respectively, which were considered normal. Thyroid stimulating hormone level was 0.056 mIU/mL (N: 0.3-4.5), which was lower than normal limits. Blood counts including haemoglobin, mean erythrocyte volume, and mean erythrocyte haemoglobin levels were slightly lower than normal. In addition, some other tests related to immunity were carried out in which serum C_3 level was 2.830 g/L (N: 0.9-2), C_4 0.413 g/L (N: 0.2-0.6), alpha-2 globulin 13.4% (N: 7.1-11.8), and beta-2 globulin 7.4% (N: 3.1-6.7). All other tests including antinuclear antibody, antidouble stranded DNA, antimitochondrial antibody, antismooth muscle antibody, antineutrophil cytoplasmic antibody, antibodies against specific liver antigens, and antibodies against nuclear antigens were negative. The levels of tumour markers were within normal limits: CA19.9 level 34.64 U/mL (N: 0-39), CA15.3 12.74 U/mL (N: 0-25), CA125 15.71 U/mL (N: 0-35), alpha fetoprotein 4.64 ng/mL (N: 0-13.6) and CA72.4 2.7 U/mL (N:0-4). Endoscopic retrograde cholangiopancreatographic examination (ERCP) showed concentric narrowing of distal (intrapancreatic) part of the common bile duct (2.2 cm in lenght), while proximal was seen to be dilated. Intrahepatic bile ducts were partially dilated and they showed wall irregularities, raising the suspicion of pancreatic carcinoma, cholangiocarcinoma, and primary sclerosing cholangitis. In AIP, the narrowed bile duct segment is longer, in contrast with short narrowed segment of the primary sclerosing cholangitis. Moreover, in cholangiocarcinoma or pancreatic adenocarcinoma, the lenght of the narrowed segment depends on tumoral infiltration. With minimal sphincterotomia, a stent was inserted into the proximal portion of the narrowed area. The pancreatic lesion could only be detected by dynamic contrast-enhanced computed tomographic (CT) scanning, which revealed a subtle 3x2 cm diameter hypodense solid mass confined to the pancreatic head (Figure 1). There was no liver metastasis or retroperitoneal lymphadenopathy. On the basis of these clinical, laboratory, and radiological data mentioned above, the patient underwent pancreaticoduodenectomy (Whipple operation) with cholecystectomy because of high suspicion of malignancy in the pancreatic head, although during the operation, frozen section did not confirm the malignancy. On gross examination, the pancreas was quite hard on palpation. The cut surface of the

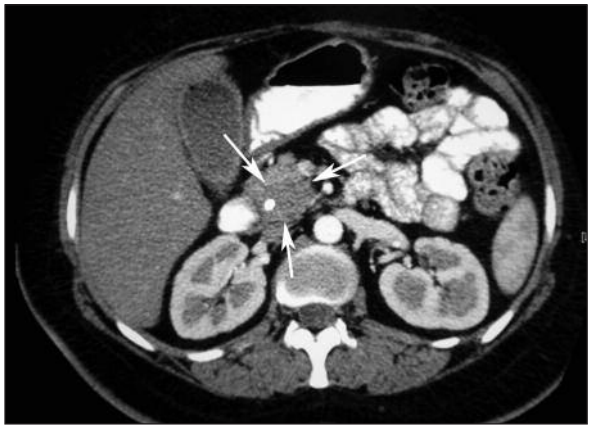

FIGURE 1: Arterial phase pancreatic computed tomography shows a 3 cm diameter hypodense mass in the pancreatic head (arrows), with subtle attenuation difference and loss of normal pancreatic texture. Also note the biliary stent in the common bile duct.

pancreas showed a grey-white, firm, mass-like appearance of 3 cm in diameter with indistinct borders and slight remnant of lobular architecture, which replaced particularly the head of the pancreas and the neighboring soft tissue. On histopathological examination, a dense lymphoplasmacytic infiltrate of the pancreatic parenchyme with secondary extensive fibrosis was seen (Figure 2). There was a collar of inflammation around interlobular ducts, predominantly composed of lymphocytes, sometimes forming germinal centers and to a lesser extent loss of acinar parenchyme. Eosinophil leucocytes were also noted among the inflammatory infiltrate. Periphlebitis and obliterative phlebitis (Figure 3) were seen and were highlighted by elastic stain. Several involved pancreatic veins were obscured by inflammation and their presence was identified by locating their companion arteries. This was accompanied by perineural inflammation. The gallbladder was characterized by diffuse inflammatory infiltrate, which was mainly confined to the lamina propria with areas of dense transmural infiltration typically composed of a mixture of lymphocytes, plasma cells, and more remarkably of eosinophil leukocytes (Figure 4). The day after the operation, urgent laparatomy was performed for bleeding at the site of gastroenterostomy. Twenty days after this manipulation, she developed pulmonary thromboemboli. Despite all necessary treatment, she died three weeks after the operation.

DISCUSSION

AIP, a relatively newly described and a special type of chronic pancreatitis, has increasingly been recognized in recent years. Idiopathic chronic pancreatitis with marked inflammatory infiltration was first described in 1961 by Sarles et al.[4] In 1995, Yoshida et al. proposed the term "autoimmune pancreatitis" as an evidence of autoimmune basis for chronic pancreatitis.[5] Clinically, AIP is a heterogeneous disease that may present with the symptoms of chronic pancreatitis but with relatively lesser abdominal pain, weight loss, jaundice, and a mass lesion particularly at the head of the

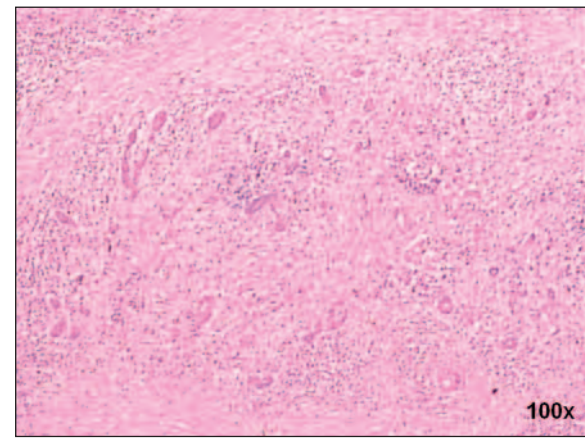

FIGURE 2: Dense lymphoplasmacytic infiltrate of the pancreatic parenchyma with secondary extensive fibrosis (HE, x100).
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

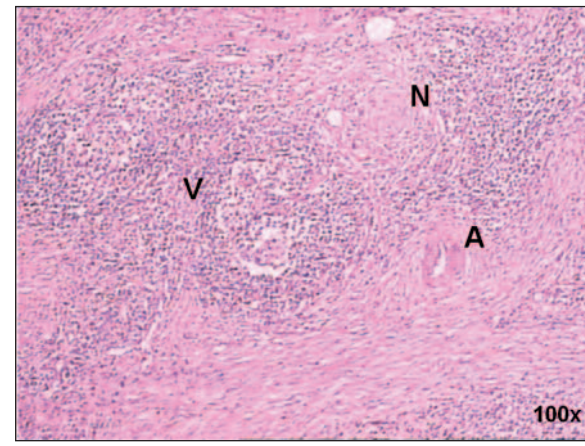

FIGURE 3: Periphlebitis and obliterative phlebitis with neural structures showing perineural inflammation (HE, x200).
A: Artery; V: Vein; N: Nerve.
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

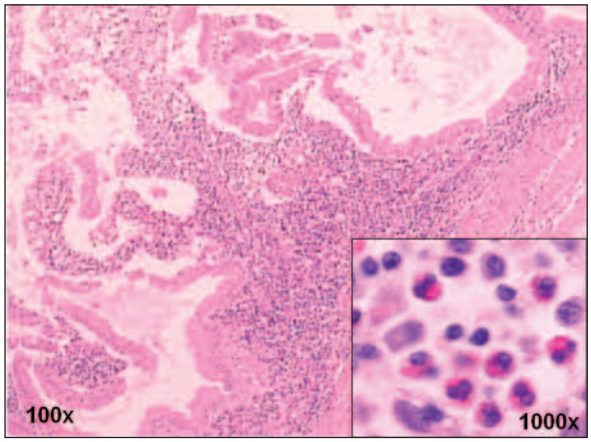

FIGURE 4: Gallbladder with diffuse inflammatory infiltrate typically composed of a mixture of lymphocytes, plasma cells and more remarkably the eosinophilic leucocytes. Mainly confined to the lamina propria, showing dense transmural infiltration. (HE, x100, INSET, x1000).
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

pancreas, which simulates malignancy.[1,2,6,7] On occasional cases, the most common acute symptom of AIP is obstructive jaundice. But, during the postacute phase of AIP, extrapancreatic symptoms might be leading and there might be a persistent mass or athrophic changes. Moreover, in some cases, there might be no radiologic sign in the pancreas, at all.

Cheri et al. suggested diagnostic criteria concerning the Mayo Clinic experience depending on pancreatic histology, typical serology and imaging, and response to steroids.[6] Surgical series about AIP have reported a male predominance in the late adulthood.[6,8]

Ultrasonographic examination may reveal diffuse hypoechoic swelling of the pancreas.[2] Focal main pancreatic duct stenosis with a degree of dilation in the rest can be visualized with ERCP and stenosis of the lower common bile duct with dilation of the upper part can be demonstrated on cholangiography.[2] Characteristic CT features include diffuse enlargement of the pancreas, effacement of pancreatic parenchymal margins, and absence of a discrete mass. Typical two imaging features in AIP patients mentioned as diagnostic meeting criteria of the Mayo Clinic are (1) CT or magnetic resonance imaging scan showing diffusely enlarged pancreas with delayed and "rim" enhancement and (2) pancreatogram showing diffusely irregular pancreatic duct.[6] On the other hand, according to the criteria of Japanese Pancreas Society typical imaging, which is diffuse enlargement of the pancreas along with diffuse (>33%) main pancreatic duct narrowing with an irregular wall, is claimed as mandatory criteria plus at least one of the others (i,e. serology and histopathology) mentioned among the supportive criteria.[9]

In young adults, pancreatic carcinoma is rare, unless there is a hereditery condition of chronic pancreatitis. It is not always possible to get optimal results and enough diagnostic material via core biopsy, sampling the mass with the help of endosonographic ultrasonography (EUS) is a better way.[10] EUS, a relatively new and trendy procedure, has a rate of accuracy for about 50% in the diagnosis of AIP and it enables tissue sampling or fine needle aspiration with minimal risk of complication during the procedure, although not enough data has been collected yet.[10]

In some patients, the levels of serum gammaglobulins, particularly the IgG4 subtype may elevate.[11] IgG4 positive plasma cells were also demonstrated in the pancreatic inflammatory infiltrate of patients with AIP.[3,5] In contrast, some cases of AIP do not bear elevated levels of serum gammaglobulin, as it happened in our case, but the diagnosis of AIP can be made if the characteristic lymphoplasmacytic infiltrate has >10 IgG4-positive/HPF.[6] In more than half of AIP patients, anticarbonic anhydrase II and anti-lactoferrin levels may be elevated.[12] An autoimmune pathogenesis has been proposed because the condition is occasionally associated with autoantibodies or other autoimmune-associated diseases.[6] Zamboni et al. have reported Sjögren's syndrome being the most frequent autoimmune disease in patients with AIP.[8] In some autoimmune diseases, such as Sjögren's syndrome, the pancreas and the bile tract may also be involved as a part of the main disease.[13] Recent studies suggest that breast and stomach might be affected by this disease.[14,15] In our patient, there was a pathology of the thyroid gland, which is not mentioned in the literature as a target of common organ involvement. In contrast to alcoholic pancreatitis, which is the most frequent type of chronic pancre-

atitis in Western countries, it is not typical in AIP to possess calculi, pseudocysts, focal autodigestive necrosis, and duct dilation with mucoprotein plugs. According to the meeting criteria of the Mayo Clinic, there are two histopathological criteria, which are referred to diagnostic pancreatic histology of AIP. The first is a tissue specimen showing the full spectrum of changes of lenfoplasmacytic sclerosing pancreatitis (i.e. periductal lymphoplasmacytic infiltrate with obstructive phlebitis and storiform fibrosis). The second is ≥10 IgG4-positive cells/HPF on immunostain of pancreatic lymphoplasmacytic infiltrate.[6] AIP may involve the vessels, mostly the veins, forming obliterative vasculitis and phlebitis.[2,16] Histopathological features such as phlebitis and obliterative vasculitis were invariably present in our case, which were particularly helpful in establishing the diagnosis of AIP. Perineural inflammation is noted as a nonspecific feature. Response to steroids is also mentioned as a diagnostic indicator in the meeting criteria of Mayo Clinic.

Among the histopathologic features of AIP, a conspicuous eosinophilic component is reported.[16,17] In our case, there was a dense mucosal and submucosal eosinophilic cellular infiltration in the gallbladder. Eosinophilic cholecystitis (EC) is a rare entity and the diagnosis is based on the presence of >90% eosinophilic infiltration within the gallbladder. Peripheral eosinophilia was not observed. EC was originally described in 1949 and the entities that were reported to be associated to EC include eosinophilic cholangitis, hypereosinophilic syndromes, and parasitic infections.[18] Eosinophylic infiltration, as well as plasmacytic infiltration, might be associated with the immunologic reactions caused by the disease, but in the English literature there is no other autoimmune pancreatitis or any other autoimmune disease that is associated with EC, so our case of AIP accompanied by EC seems to be the first case. Further evaluation and accumulation of similar data are needed concerning this subject to find out the relationship with autoimmunity.

In this case, the leading clinical symptoms were epigastric pain, jaundice, dark urine, pruritis, and abrupt weight lost. Although it is well known that the level of IgG4 is significantly high, i.e. 70%, in AIP, detection of IgG4 level could not be available in the course. Although the patient indicated she has had goiter for ten years, she did not undergo an operation and had no specific diagnosis concerning the thyroid. As the clinical symptoms were unbearable for the patient, indicating an almost complete obstruction of the bile duct system and with the radiological evidence of a large and infiltrative mass, the Whipple operation was done. Patients may undergo pancreaticoduodenectomy either on strong suspicion of malignancy or for relief of symptoms and for a subjectively improved quality of life.[2,7] Studies reported that 423 cases of chronic pancreatitis underwent surgery with a presumptive diagnosis of malignancy with 91 cases later diagnosed with AIP.[7,8] Because there are similarities in the presentation of the AIP and pancreatic adenocarcinoma, it is not surprising that the preoperative diagnosis in AIP is most commonly pancreatic cancer. Whipple resection has also been reported to be a common operative procedure in patients with chronic pancreatitis who have symptoms that are intractable with medical therapy.

AIP mimics pancreatic adenocarcinoma with its clinical presentation, though CT findings may suggest a diagnosis of AIP. Nevertheless, it is difficult to differentiate AIP from pancreatic neoplasia. When recognized preoperatively, AIP could be treated with systemic steroids, often with resolution of symptoms, and surgical treatment may be required in only a minority of cases.[3,5,11] However, the therapy with steroid drugs requires a tissue diagnosis based on a pancreatic biopsy. Yet the information available about the value of this method for establishing the diagnosis of AIP is scarce. In conclusion, AIP has unique histologic features that may be used to differentiate it from other forms of chronic pancreatitis. Problems of sampling error and small sample size are always the limitations of pancreatic biopsies. Although tissue sampling will maintain its significance or become a more common procedure, the purpose of biopsy in AIP is still primarily to exclude malignancy, but then to mention the possible diagnosis of AIP. The increasing procedures of biopsy and fine needle aspiration

(FNA) via EUS and routine usage of immunostaining for IgG4, even with the help of FNA-derived cell blocks, will obviously make the diagnosis of AIP more clear and accurate in the near future.

As AIP is a distinctive type of chronic pancreatitis that shows reversible improvement with oral steroid therapy, the suspicion of AIP will help clinicians in recognizing this disease, so that unnecessary surgical procedures will not be attempted. Since most diagnoses still can be made on pancreticoduodenectomy specimens, it is advisable for a pathologist to obtain additional clinical and laboratory information when fibrosis, dense lymphoplasmacytic infiltration, and obliterative phlebitis are seen in a biopsy specimen in order to exclude or establish the diagnosis of AIP.

REFERENCES

1. Kamisawa T, Egawa N, Nakajima H, Tsuruta K, Okamoto A, Kamata N. Clinical difficulties in the differentiation of autoimmune pancreatitis and pancreatic carcinoma. Am J Gastroenterol 2003;98(12):2694-9.
2. Notohara K, Burgart LJ, Yadav D, Chari S, Smyrk TC. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. Am J Surg Pathol 2003;27(8):1119-27.
3. Ito T, Nakano I, Koyanagi S, Miyahara T, Migita Y, Ogoshi K, et al. Autoimmune pancreatitis as a new clinical entity. Three cases of autoimmune pancreatitis with effective steroid therapy. Dig Dis Sci 1997;42(7):1458-68.
4. Sarles H, Sarles JC, Muratore R, Guien C. Chronic inflammatory sclerosis of the pancreas--an autonomous pancreatic disease? Am J Dig Dis 1961;6:688-98.
5. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci 1995;40(7):1561-8.
6. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol 2006;4(8): 1010-6; quiz 934.
7. Abraham SC, Wilentz RE, Yeo CJ, Sohn TA, Cameron JL, Boitnott JK, et al. Pancreaticoduodenectomy (Whipple resections) in patients without malignancy: are they all 'chronic pancreatitis'? Am J Surg Pathol 2003;27(1): 110-20.
8. Zamboni G, Lüttges J, Capelli P, Frulloni L, Cavallini G, Pederzoli P, et al. Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. Virchows Arch 2004;445(6):552-63.
9. Pearson RK, Longnecker DS, Chari ST, Smyrk TC, Okazaki K, Frulloni L, et al. Controversies in clinical pancreatology: autoimmune pancreatitis: does it exist? Pancreas 2003;27(1):1-13.
10. Levy MJ, Wiersema MJ, Chari ST. Chronic pancreatitis: focal pancreatitis or cancer? Is there a role for FNA/biopsy? Autoimmune pancreatitis. Endoscopy 2006;38(Suppl 1): S30-5.
11. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001;344(10):732-8.
12. Rerknimitr R. Asian chronic pancreatitis: the common and the unique. J Gastroenterol Hepatol 2011;26(Suppl 2):6-11.
13. Akarca US, Günşar F. [Liver, pancreas and biliary involvement in Sjogren's syndrome]. Turkiye Klinikleri J Immunol Rheumatol-Special Topics 2008;1(1):55-9.
14. Zen Y, Kasahara Y, Horita K, Miyayama S, Miura S, Kitagawa S, et al. Inflammatory pseudotumor of the breast in a patient with a high serum IgG4 level: histologic similarity to sclerosing pancreatitis. Am J Surg Pathol 2005; 29(2):275-8.
15. Shinji A, Sano K, Hamano H, Unno H, Fukushima M, Nakamura N, et al. Autoimmune pancreatitis is closely associated with gastric ulcer presenting with abundant IgG4-bearing plasma cell infiltration. Gastrointest Endosc 2004;59(4):506-11.
16. Klöppel G, Lüttges J, Löhr M, Zamboni G, Longnecker D. Autoimmune pancreatitis: pathological, clinical, and immunological features. Pancreas 2003;27(1):14-9.
17. Abraham SC, Leach S, Yeo CJ, Cameron JL, Murakata LA, Boitnott JK, et al. Eosinophilic pancreatitis and increased eosinophils in the pancreas. Am J Surg Pathol 2003;27(3):334-42.
18. Albot G, Poilleux, Olivier C, Libaude H, Cascarigny P. Les cholecystites a eosinophils. (Eosinophilic cholecystitis). Presse Med 1949;57(39):558-9.