Pancreatic involvement in pediatric inflammatory bowel diseases

Sabrina Cardile, Antonino Randazzo, Simona Valenti, Claudio Romano
Messina, Italy

Background: **Inflammatory bowel diseases (IBDs) are a group of chronic diseases affecting the gastrointestinal tract, with a disabling course. The incidence of IBDs is increasing in different geographical areas, indicating its emergence as a global disease, especially in children. Many patients with IBDs develop extraintestinal manifestations (EIMs) during follow-up, as IBDs have a potential risk of systemic involvement..**

Data sources: **A systematic review of the literature was made to analyze latest studies on pancreatic involvement in children with IBD including our experience in assessing possible implications and its future application.**

Results: **The involvement of the hepatobiliary system is considered a rare EIM of children with IBD, with an incidence much higher than that in the general population. Isolated pancreatic hyperenzymemia, which occurs in the absence of typical symptoms and/or characteristic imaging findings, may be found in many patients with IBD. The frequent causes of pancreatitis are drugs, bilio-pancreatic disorders, immunologic disturbances and pancreatic auto-antibodies, although in some cases idiopathic forms have been described.**

Conclusions: **It is important to establish a correct diagnostic approach based on etiology and to assess the most appropriate therapeutic strategy, thus avoiding complications and improving the quality of life of children with IBD.**

World J Pediatr 2015;11(3):207-211

Key words: **Crohn's disease;**
extraintestinal manifestations;
inflammatory bowel diseases;
pancreatitis;
ulcerative colitis

Review article

Introduction

Inflammatory bowel diseases (IBDs) are chronic relapsing inflammatory conditions of the intestinal tract, most commonly represented by Crohn's disease (CD) and ulcerative colitis (UC). IBDs have the potential risk of involving organs other than the intestinal tract, and systems (joints, skin, bones, liver, eyes, and pancreas), and can affect morbidity and mortality of IBD patients. They are defined as extraintestinal manifestations (EIMs) and may have a mild and transient or debilitating course. Some EIMs are closely related to inflammation or autoimmune phenomena, while others are the result of nutritional or metabolic disorders.[1] In children, the incidence of EIMs seems to vary between 21% and 47%. Dotson et al[2] reported an incidence of EIMs of approximately 28% in children with IBD (1009 patients <16 years), and follow-up studies revealed that 29% of children with IBD developed an EIM in a period of 15 years.[3] Unlike patients with UC, risk factors predisposing the onset of EIMs were identified in patients with CD, such as colonic disease and/or family history of IBD.[4] The most common EIMs are related to the joints (arthritis axial and/or peripheral), skin (erythema nodosum and pyoderma gangrenosum), eyes (episcleritis and uveitis), mouth (aphthous stomatitis), and hepatobiliary system.[5] Some of which involve the skin, eyes and joints can be correlated with the activity of bowel diseases; generally, diseases involving the hepatobiliary system and lungs have an independent course. Hepatobiliary system involvement (the liver, pancreas, biliary-pancreatic ducts) can be closely related to the pathogenesis of IBD or, in some cases, to adverse effects secondary to the use of drugs such as mesalazine, immunosuppressants and biological agents.[6] Diagnosis of hepato-biliary disorders follows the standard investigatory pathways, including liver function tests, serology tests to identify specific causes of autoimmune and infectious diseases, and imaging techniques.[7]

Author Affiliations: Department of Pediatrics, IBD Unit, University of Messina Via Consolare Valeria, Messina 98125, Italy (Cardile S, Randazzo A, Valenti S, Romano C)

Corresponding Author: Claudio Romano, Pediatrics Department, IBD Unit, University of Messina, Via Consolare Valeria, Messina 98125, Italy (Tel: 390902212918, 390902212919; Fax: 390902213788; Email: romanoc@unime.it)

doi: 10.1007/s12519-015-0029-z

Idiopathic pancreatitis in IBD

Pancreatic involvement in children is considered a rare form of EIM (0.7%-1.6%), although the incidence of pancreatitis is higher in patients with IBD than in the general population. Le Large-Guiheneuf et al[9] have reported a higher incidence in females than in males in children with IBD (P=0.04), with a greater occurrence of symptomatic pancreatitis in those with active and severe diseases (P=0.006). The diagnosis of acute pancreatitis (AP) in children is based on the presence of at least 2 of the following 3 criteria: 1) typical abdominal pain; 2) serum amylase and/or lipase at least 3 times the upper limit of normal value, and 3) imaging findings of the pancreas compatible with AP. Acute recurrent pancreatitis, however, is defined as the presence of at least two distinct episodes of AP with complete resolution of pain or complete normalization of pancreatic enzymes (amylase and lipase) in the inter-critical periods. Finally, chronic pancreatitis (CP) instead requires at least 1 of the 3 following criteria for diagnosis: 1) abdominal pain of pancreatic origin in the context of imaging compatible with chronic pancreatic damage; 2) exocrine pancreatic insufficiency with imaging abnormalities suggestive of CP; 3) endocrine pancreatic insufficiency with imaging abnormalities compatible with CP.[8] The majority of cases are clinically silent or do not present characteristic symptoms, and the detection of benign pancreatic hyperenzymemia is significantly superior to that of pancreatitis.[9] In a Polish study, benign hyperamylasemia was observed more often (27.3% of children with CD, 12.7% with UC) than acute pancreatitis (4.5% of children with CD, 5.1% with UC).[10] Patients with IBD also have an elevated risk for developing CP and/or pancreatic insufficiency, even if the etiology of pancreatic duct changes and/or exocrine insufficiency remains unclear.[11] These patients also have a high incidence of development of autoimmune pancreatitis (AIP) with approximately 30% of reported AIP IBD-associated patients. Moreover, IBD seems to be related to both forms of AIP, more so with type 2.[12] In most patients, although pancreatic involvement often presents a mild-moderate recurrent course, it may have a high morbidity or mortality. A multifactorial pathogenesis is recognized, but in some patients idiopathic forms may occur before the onset of IBD.[13] In children, idiopathic chronic pancreatitis occur ten months before the diagnosis of CD with a severe phenotype.[14] Clinical and biological surveys have shown that 20%-30% of patients with pancreatitis remain unknown or idiopathic (Table 1).[15]

Table 1. Principal factors influencing the incidence of pancreatitis in IBD

Drugs
Immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine), 3%-15%
Salycilates (sulfasalazine and 5-aminosalicylic acid), uncommon
Antibiotics (metronidazole), rare
Corticosteroids (prednisone, budesonide), few cases reported
Bilio-pancreatic disorders
Immunologic disturbances (pancreatic autoantibodies)
Idiopathic forms

A multifactorial pathogenesis is recognized in pediatric patients with IBD who develop pancreatitis, even if drug use, duodenal localization of CD, hepatobiliary complications, or immunologic disturbances seem to be the most common causes in pediatric populations. Other rare causes appear to be postendoscopic complications of retrograde cholangiopancreatography and postoperative complications. In adult patients with IBD, however, gallstones, and significant alcohol intake represent the most common cause of pancreatitis. Despite this, idiopathic forms that may occur before the onset of IBD (20%-30%) have been described in some cases. IBD: inflammatory bowel disease; CD: Crohn's disease.

Pancreatitis and drugs

Drugs can cause AP with varied incidences. They can induce pancreatic insult with mechanisms which have been defined probable or questionable, as a direct cause-effect relationship is not always recognized. Among the mechanisms that have been proposed forms because of direct toxicity, hypersensitivity or secondary hyperlipidemia and hypercalcemia can be recognized although they have not been clearly identified. In children with drug-associated AP, admitted to hospitals, approximately 11% have CD and 9% have UC as a comorbidity.[16] Molecules involved in determining pancreatic damage include immunomodulators, aminosalicylates, corticosteroids, and antibiotics. Azathioprine (AZA) is considered a drug with the highest risk for pancreatitis, usually 3 weeks after therapy.[17] In a recent study, the cumulative incidence of thiopurine-induced acute pancreatitis was not different between CD and UC patients (2.6% *vs*. 3.7%), and occurred within 30 days after therapy, with a higher risk in females.[18] The European Crohn's and Colitis Organization and European Society for Pediatric Gastroenterology, Hepatology and Nutrition Consensus Guidelines suggest, in this case, to discontinue thiopurines in UC children with clinically significant pancreatitis.[19] However, successful introduction of a second thiopurine, subsequent to documented thiopurine-inducted pancreatitis in 4 children with CD, has been reported in a small series of children.[20] Monitoring of AZA/6-mercaptopurine (MP) metabolite levels may be useful to guide and optimize the dose of AZA/6-MP therapy in a cohort of children with IBD, avoiding adverse effects and minimizing the risk of drug toxicity.[21] Drug-induced pancreatitis usually occurs in the first weeks of exposure and presents in mild form with normalization after discontinuation of therapy.[22]

Biliopancreatic disorders and pancreatitis

Formation of cholesterol or pigment gallstones are reported in 15%-35% of patients with CD, with an incidence significantly higher than that in the general population. Cholesterol gallstones are due to abnormal composition of bile formation associated with motility disorders of the gallbladder, infections, and interruption of the enterohepatic circulation of bile acids.[23] Obstruction of the papilla or duodenal reflux is also potentially involved as the cause of pancreatitis in the course of IBD. Duodenal localization in CD may be related to increased risk of pancreatitis or pancreatic compression interrupter due to flow obstruction, reflux of duodenal contents into the pancreatic ducts caused by an inflamed sphincter or for the presence of duodenal-pancreatic duct fistulae.[24] Other forms of secondary pancreatitis may also be associated with primary sclerosing cholangitis (PSC). PSC is a chronic inflammatory disease of the intrahepatic and extrahepatic system characterized by fibrosis which causes cholestasis, biliary cirrhosis and liver failure, with occasional involvement of the pancreatic ducts (0%-77%) and development of pancreatitis.[25] IBD is associated with PSC in more than 80% of patients, and thus the guidelines recommend total colonoscopy with biopsies in patients in whom the diagnosis of PSC has been established without known IBD.[26]

Autoimmune pancreatitis

In patients with IBD, dysregulation of immune function which determines the formation of autoantibodies is recognizable. In patients with IBD, AIP has been described with a risk of 12-15 times greater than the general population. In these patients, high levels of serum immunoglobulin G4 with associated phenotype of disease (pancolitis) have been demonstrated.[27] Clinical manifestations may include obstructive jaundice, abdominal pain, onset of diabetes mellitus and steatorrhea. Important diagnostic support includes imaging techniques such as magnetic resonance imaging or computed tomography of the pancreas: classification based on the histology, imaging & serology, response to steroids criteria, developed in 2006 by Chari et al at the Mayo Clinic, may be used with inclusion of the most significant variables such as histology, imaging, serology, other organ involvement and response to therapy.[28] In some trials in children and adults, autoantibodies against exocrine pancreas and recombinant pancreas antigen were isolated.[29]

Personal casistic

In this study, the personal casistic was revised. We retrospectively reviewed children with IBD and their pancreatic involvement (acute, chronic and recurrent pancreatitis), at our Pediatric IBD Unit. The data were collected from 107 children (age: 3-18 years), among them 70 patients with UC and 37 patients with CD from January 2001 to September 2014. Demographic and clinical data, IBD type, disease extension activity, laboratory data, IBD therapy, imaging findings and therapeutic interventions were evaluated (Table 2). IBD was diagnosed according to endoscopic and histological findings, while pancreatitis was diagnosed according to the established international criteria. In these patients, there was no family history of pancreatitis or biliary tract disease. History was negative for abdominal trauma and/or alcohol intake. Nine patients (8.4%, 8 patients with UC; 1 patient with CD) showed pancreatic involvement during follow-up. The mean age of patients with IBD at diagnosis was 12.11±3.49 years, and that of those with pancreatitis 13.23±3.49 years. One patient showed pancreatitis at diagnosis of IBD, and in others, time to onset of pancreatitis compared with IBD was 1.12±1.43 years. Five patients had pancreatitis after

Table 2. Clinical characteristics of pediatric casistic

Patients	Sex	Disease (CD/UC)	Age of IBD diagnosis (y)	Age of pancreatic involvement diagnosis (y)	Causes	Symptoms	Course of pancreatitis
Patient 1	M	UC	10.50	11.00	Mutation in *CFTR* gene (IVS-8 polyT 5T/5T 12TG/12TG)	Vomiting/nausea/abdominal pain	Recurrent
Patient 2	M	CD	11.08	11.66	After AZA start	Nausea/vomiting	Acute
Patient 3	F	UC	14.25	14.41	After AZA start	Fever/abdominal pain/vomiting	Acute
Patient 4	M	UC	11.41	15.75	After AZA start	Abdominal pain/nausea	Acute
Patient 5	F	UC	15.33	15.33	During relapse of disease	Vomiting/abdominal pain	Recurrent
Patient 6	F	UC	3.66	4.58	After AZA start	Fever/abdominal pain/vomiting	Acute
Patient 7	F	UC	15.75	16.00	Durante relapse	Vomiting/abdominal pain	Recurrent
Patient 8	M	UC	12.50	15.58	Idiopathic	Vomiting/nausea/abdominal pain	Recurrent
Patient 9	F	UC	14.58	14.83	After AZA start	Fever/acute abdominal pain	Acute

M: male; F: female; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; *CFTR*: cystic fibrosis transmembrane regulator; AZA: azathioprine.

treatment with AZA, with normal pancreatic enzymes after discontinuation of the treatment. In two patients, the course of intestinal disease was correlated with pancreatic involvement. In clinical symptoms, epigastric pain (88%) was frequently seen, followed by nausea/vomiting (77%). Most of the patients presented a benign course, with resolution of symptoms and normalization of pancreatic enzymes within 3-6 months. Serological investigations combined with imaging techniques excluded hepato-biliary diseases or primitive abnormalities of the pancreatic ducts. Radiological investigations did not show any pancreatic changes; but edema and other changes of eco-pancreatic structure were the most frequent radiological findings. In patients whose causes had not been identified, a molecular analysis of the cystic fibrosis transmembrane regulator (*CFTR*) gene, serine protease inhibitor Kazal-type 1 and protease serine 1 was also performed. One patient in the analysis of the *CFTR* gene sequencing showed the presence of the IVS-8 polyT 5T/5T 12TG/12TG (homozygous) polymorphism. This patient wtih UC showed a severe form of idiopathic acute pancreatitis with frequent relapse and was hospitalized during acute episodes (recurrent pancreatitis) with normalization of pancreatic enzymes.

Discussion

Pancreatic involvement, although a rare form of EIMs in IBD with varied incidences, can occur more often in children than in the general population. No epidemiological data on children are available, despite drug-related pancreatitis is considered the most common condition. An appropriate diagnostic approach is essential to limit the risk of complications and hospitalization. The level of serum pancreatic enzymes in the absence of pancreatic disease defined as "benign pancreatic hyperenzymemia" is elevated frequently in the IBD population, and proper diagnosis of this condition is of vital importance. In adult patients with IBD, however, gallstones and alcohol intake are the most common causes of pancreatitis. The certain pathogenic mechanisms underlying pancreatic damage remain obscure. The role of autoantibodies against the exocrine pancreas, causing direct pancreatic damage with enzyme leakage into the bloodstream, and the histological proof of a granulomatous inflammation of the pancreas has been proposed.[30] Another possible explanation may be linked to abnormal reabsorption of pancreatic amylase/lipase from the gut lumen to the bloodstream because of the increased permeability of the inflamed mucosa. Furthermore, the elevated level of pancreatic enzymes observed in IBD patients may be associated with extrapancreatic lipase/amylase activity in the small bowel and colon; lipase and amylase may be absorbed excessively into the blood in the case of increased inflammatory activity T.[31] A flow-chart approach for suspected pancreatitis in IBD patients is shown in Fig.[32]

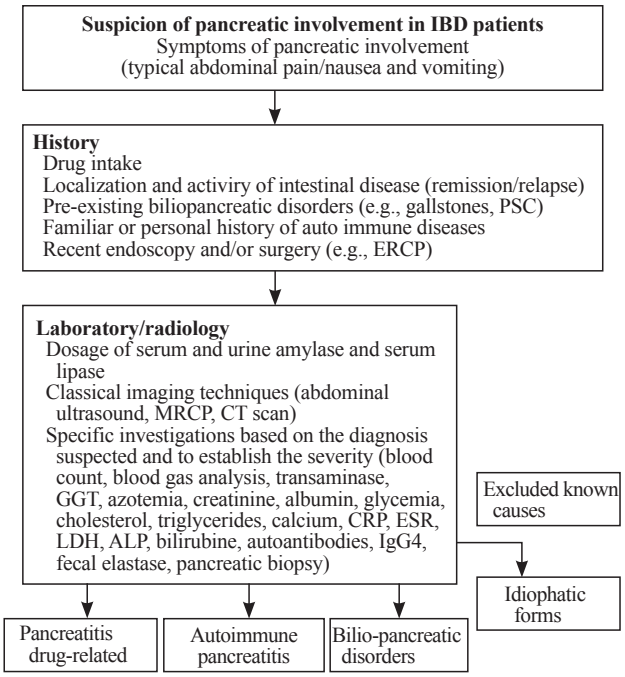

Fig. Diagnostic flow-chart approach for suspected pancreatitis in IBD pediatric patients. Pancreatic involvement is an important complication, although rare, in patients with IBD, and prompt diagnosis and careful monitoring over time is needed. For this reason it is essential to recognize a correct diagnostic approach to search for known causes: especially, family history, drugs taken by the patient, localization and activity of intestinal disease (remission/relapse), pre-existing biliopancreatic disorders (gallstones, PSC) and recent endoscopy and/or surgery (e.g., ERCP). In patients with suspected pancreatic involvement, the dosage of serum and urine amylase and serum lipase associated with classical imaging techniques (abdominal ultrasound, CT scan, MRCP) and specific investigations based on the diagnosis suspected and to establish the severity can facilitate the diagnosis and establish a correct therapeutic approach. IBD: inflammatory bowel disease; CT: computed tomography; IgG4: immunoglobulin G4; PSC: primary sclerosing cholangitis; ERCP: endoscopic retrograde cholagiography-pancreaticography; MRCP: magnetic resonance cholangiography; GGT: gamma-glutamyl transferase; CRP: C reactive protein; ESR: eritro sedimation rate; LDH: lactate dehydrogenase; ALP: alkaline phospatase.

Conclusions

Pancreatic involvement as an important EIM also seen in children with IBD needs prompt diagnosis and careful monitoring over time. Benign pancreatic hyperenzymemia and drug-related pancreatitis are quite common clinical conditions in children. The symptoms of AP often mimic a relapse of intestinal disease, and pancreatic involvement should be considered when bowel symptoms are nonspecific. Medical history, clinical symptoms, laboratory results and radiological findings are helpful to identify the etiology of pancreatitis.

Funding: None.
Ethical approval: Not necessary.
Competing interest: The authors declare that they have no conflicts of interest relevant to this review.
Contributors: Romano C and Cardile S have contributed equally to the writing of the manuscript.

References

1 Veloso FT. Extraintestinal manifestations of inflammatory bowel disease: do they influence treatment and outcome? World J Gastroenterol 2011;17:2702-2707.
2 Dotson JL, Hyams JS, Markowitz J, LeLeiko NS, Mack DR, Evans JS, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. J Pediatr Gastroenterol Nutr 2010;51:140-145.
3 Jose FA, Garnett EA, Vittinghoff E, Ferry GD, Winter HS, Baldassano RN, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2009;15:63-68.
4 Vavricka SR, Brun L, Ballabeni P, Pittet V, Prinz Vavricka BM, Zeitz J, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol 2011;106:110-119.
5 Su CG, Judge TA, Lichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. Gastroenterol Clin North Am 2002;31:307-327.
6 Navaneethan U, Shen B. Hepatopancreatobiliary manifestations and complications associated with inflammatory bowel disease. Inflamm Bowel Dis 2010;16:1598-1619.
7 Van Assche G, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. J Crohns Colitis 2013;7:1-33.
8 Morinville VD, Husain SZ, Bai H, Barth B, Alhosh R, Durie PR, et al. Definitions of pediatric pancreatitis and survey of present clinical practices. J Pediatr Gastroenterol Nutr 2012;55:261-265.
9 Le Large-Guiheneuf C, Hugot JP, Faure C, Munck A, Mougenot JF, Navarro J, et al. Pancreatic involvement in inflammatory bowel diseases in children. Arch Pediatr 2002;9:469-477. [In French]
10 Stawarski A, Iwańczak F. Incidence of acute pancreatitis in children with inflammatory bowel disease. Pol Merkur Lekarski 2004;17:33-36. [In Polish]
11 Herrlinger KR, Stange EF. The pancreas and inflammatory bowel diseases. Int J Pancreatol 2000;27:171-179.
12 Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011;40:352-358.
13 Broide E, Dotan I, Weiss B, Wilschanski M, Yerushalmi B, Klar A, et al. Idiopathic pancreatitis preceding the diagnosis of inflammatory bowel disease is more frequent in pediatric patients. J Pediatr Gastroenterol Nutr 2011;52:714-717.
14 Knafelz D, Panetta F, Monti L, Bracci F, Papadatou B, Torre G, et al. Chronic pancreatitis as presentation of Crohn's disease in a child. World J Gastroenterol 2013;19:5204-5206.
15 Frossard JL, Felley C, Michetti P. Recurrent acute pancreatitis and therapy for ulcerative colitis. Case Rep Gastroenterol 2010;4:304-306.
16 Bai HX, Ma MH, Orabi AI, Park A, Latif SU, Bhandari V, et al. Novel characterization of drug-associated pancreatitis in children. J Pediatr Gastroenterol Nutr 2011;53:423-428.
17 Keljo DJ, Sugerman KS. Pancreatitis in patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1997;25:108-112.
18 van Geenen EJ, de Boer NK, Stassen P, Linskens RK, Bruno MJ, Mulder CJ, et al. Azathioprine or mercaptopurine-induced acute pancreatitis is not a disease-specific phenomenon. Aliment Pharmacol Ther 2010;31:1322-1329.
19 Turner D, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr 2012;55:340-361.
20 Ledder OD, Lemberg DA, Ooi CY, Day AS. Are thiopurines always contraindicated after thiopurine-induced pancreatitis in inflammatory bowel disease? J Pediatr Gastroenterol Nutr 2013;57:583-586.
21 Ooi CY, Bohane TD, Lee D, Naidoo D, Day AS. Thiopurine metabolite monitoring in paediatric inflammatory bowel disease. Aliment Pharmacol Ther 2007;25:941-947.
22 Bermejo F, Lopez-Sanroman A, Taxonera C, Gisbert JP, Pérez-Calle JL, Vera I, et al. Acute pancreatitis in inflammatory bowel disease, with special reference to azathioprine-induced pancreatitis. Aliment Pharmacol Ther 2008;28:623-628.
23 Pitchumoni CS, Rubin A, Das K. Pancreatitis in inflammatory bowel diseases. J Clin Gastroenterol 2010;44:246-253.
24 Evans JS, George DE, Barwick KW, Lafer DJ. Crohn's disease presenting as chronic pancreatitis with biliary tract obstruction. J Pediatr Gastroenterol Nutr 1996;22:384-388.
25 Heikius B, Niemelä S, Lehtola J, Karttunen T, Lähde S. Hepatobiliary and coexisting pancreatic duct abnormalities in patients with inflammatory bowel disease. Scand J Gastroenterol 1997;32:153-161.
26 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51:237-267.
27 Ravi K, Chari ST, Vege SS, Sandborn WJ, Smyrk TC, Loftus EV Jr. Inflammatory bowel disease in the setting of autoimmune pancreatitis. Inflamm Bowel Dis 2009;15:1326-1330.
28 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;4:1010-1016.
29 Kovacs M, Lakatos PL, Papp M, Jacobsen S, Nemes E, Polgar M, et al. Pancreatic autoantibodies and autoantibodies against goblet cells in pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2012;55:429-435.
30 Smyk DS, Rigopoulou EI, Koutsoumpas AL, Kriese S, Burroughs AK, Bogdanos DP. Autoantibodies in autoimmune pancreatitis. Int J Rheumatol 2012;2012:940831.
31 Heikius B, Niemelä S, Lehtola J, Karttunen TJ. Elevated pancreatic enzymes in inflammatory bowel disease are associated with extensive disease. Am J Gastroenterol 1999;94:1062-1069.
32 Triantafillidis JK, Merikas E, Malagarinos G, Panteris V, Peros G. Acute idiopathic pancreatitis preceding diagnosis of Crohn's Disease. Description of three cases. Rev Med Chir Soc Med Nat Iasi 2009;113:97-102.

Received August 21, 2014
Accepted after revision November 18, 2014