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Chronic pancreatitis complicating Crohn's disease

Crohn hastalığında kronik pankreatit komplikasyonu

Murat PALABIYIKOĞLU MD, Hülya ÇETİNKAYA MD, Kadir BAHAR MD,
Ali GÖREN MD, Rafet KOÇ MD, Ali ÖZDEN MD

Departments of Internal Medicine and Gastroenterology, School of Medicine, Ankara University, Ankara

ÖZET: *Bu olgu sunusunda, yaklaşık 20 yıllık Crohn hastalığı bulunan bir hasta tanıtılmaktadır. Anamnezinde safra kesesi veya safra yolu taşı, alkolizm, ailevi pankreatit, primer sklerozan kolanjit, hipertrigliseridemi, abdominal travma, hiperkalsemi ve parenteral nutrisyon gibi bir özellik bulunmayan hasta uzun yıllar boyunca salisil-azosulfapridin ve steroid kullanmış ve daha sonra 5-ASA almağa başlamış. Değişik türde karın ağrısı yakınması nedeniyle yatırıldığında pankreasta yaygın kalsifikasyonlar gözlendi ve duodenum normal bulundu. Azathioprin'in de eklendiği bir tedavi programı sonrası benzer yakınmalarla yeniden hospitalize edilen olguda pankreasta 4-5 adet psödokist, kanal içi taşlar ve yüksek amilaz-lipaz değerleri izlendi. Pankreatik sfinkterotomi yapılan ve intraduktal stent yerleştirilen hastada yeniden 5-ASA başlandıktan sonra nüks gözlenmedi. Literatürde Crohn ve kronik pankreatit ilişkisi hakkındaki birikim azdır. Bu olgu ile elde edilen bilgiler, mekanizması henüz açık olmamakla ve tartışmalar devam etmekle birlikte, Crohn hastalığı ve pankreas arasında primer yerleşim veya ekstraintestinal bir gösterge şeklinde açıklanabilecek ilişkiyi destekler niteliktedir.*

Anahtar Kelimeler: **Kronik pankreatit, Crohn hastalığı**

SUMMARY: *An example of chronic pancreatitis developing in a patient with 20-year-duration of Crohn's ileocolitis is reported. The patient denied any history of gallbladder disease, alcoholism, familial pancreatitis, sclerosing cholangitis, hypertriglyseridemia, abdominal trauma, hypercalcemia and parenteral nutrition. He was under salicylazosulphapyridin and corticosteroid treatment for many years and was under 5-ASA and corticosteroid when first seen. Because of a different epigastric pain, he was hospitalized and diffuse calcifications in pancreas were shown by ultrasonography. On upper GI endoscopy, the duodenum was normal. Inraductal stones and pseudocysts as well as high amylase and lipase values were detected after additional azathioprine therapy. He was treated by sphincterotomy and intraductal stent placement. Rechallenge with 5-ASA did not induce recurrent pancreatitis. This case report supports the association, between Crohn's disease and chronic pancreatitis either in terms of a primary site or as an extraintestinal manifestation of Crohn's disease.*

Key Words: **Chronic pancreatitis, Crohn's disease**

A 45-year-old male patient suffering from right lower quadrant pain and diarrhoea since 1976, was first diagnosed with Crohn's disease (CD) in 1978. He was regularly followed up on a 6-monthly-basis programme until 1981 and was given salicylazosulphapyridin (SAS) and corticosteroid (CS) intermittantly. Later on, he left himself out of the control schedule and used SAS irregularly during acute attacks taking place once or twice every month with 2-3 stools/day. In mid-1995, abdominal pain became more severe and he was started 5-ASA, but stopped later on because of poor tolerance.

In November 1995, he suffered from a different epigastric pain radiating to lomber and dorsal areas, sometimes leading to acute episodes with nausea and vomiting between November 1995 and January 1996. In January, he was admitted to Gastroenterology Section of İbn-i Sina Hospital with these symptoms. Physical examination was normal apart from slight epigastric tenderness. Raised levels of leucocyte (10900/mm3) and C-reactive protein (CRP) (22.80mg/L) (N: 0-5 mg/L) indicated acute inflammation. All other routine laboratory tests, immunoglobulins, urinanalysis and ECG were in normal range. Mild antral gastritis and Helicobacter pylori were detected on gastroduodenoscopy and eradication treatment for H. pylori was started. Ultrasonography demonstrated wall thickening in ascending and transverse colon with small-sized calcifications in pancreas. Abdominal tomography supported ultrasonographic findings (Fig. 1,2,3). Colonoscopy showed longitudinal and/or star-like, aftous ulcerations beginning from the 60th cm and spread into the transverse and ascending colon leading to

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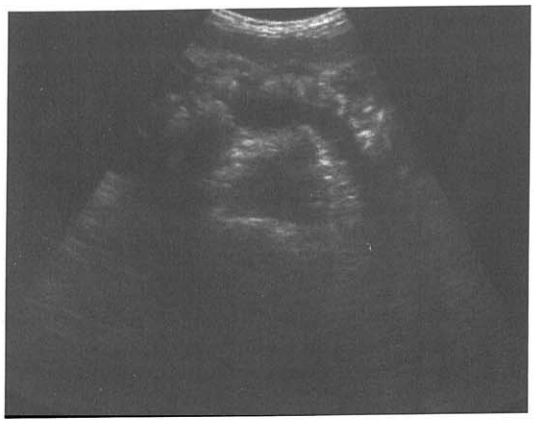


Figure 1. *Ultrasonographic picture of pancreas showing calcifications in pancreas*

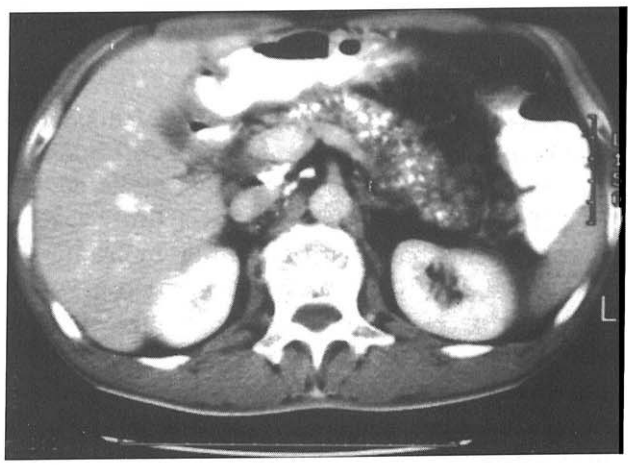
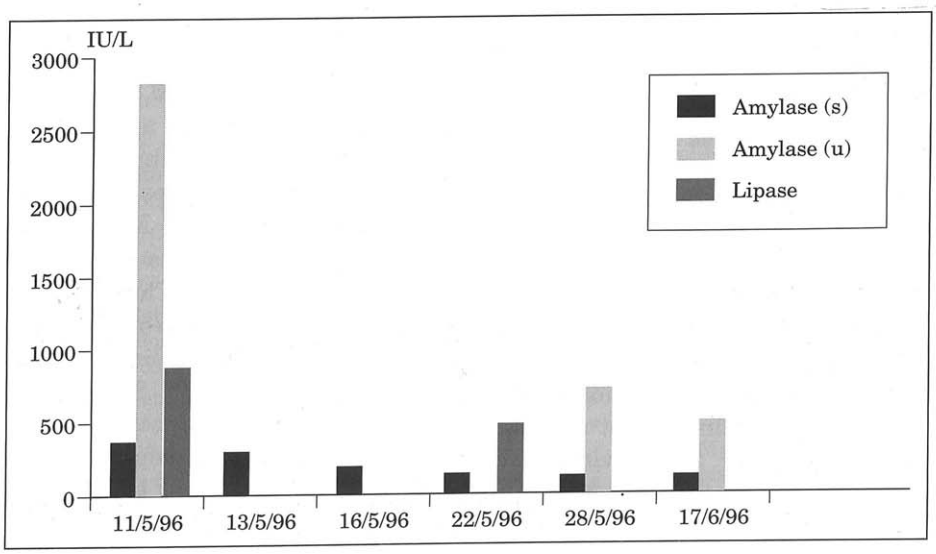


Figure 2. *CT appearence of pancreatic calcifications*

narrowing in two regions. Biopsies were carried out and the results were in harmony with CD. Small intestine and duodenum were not affected. Profilactic treatment with ofloxacin and metronidazole were started for possible infections and amebiasis. Afterwards, 40 mg CS, 1.5 gr 5-ASA and folic acid were administered with tapering the steroid dose 5 mg every 5 days. While taking 20 mg CS, 5-ASA enema was added. When CS dose was reduced to 5mg every other day, azathioprine (50mg/day) was administered. As clinical improvement was observed, he was discharged with the same treatment to be controlled after 2 months.

With the absence of diarrhoea and right lower quadrant pain, but suffering from epigastric pain radiating to the back, the patient was re-hospitalized in May 1996. At that time, he was under CS (5mg every other day) +5-ASA (1,5 gr/day) treatment and physical examination revealed right upper quadrant tenderness. The patient denied any history of gallbladder disease, alcoholism, familial pancreatitis, sclerosing cholangitis, hpertrigly ceridemia, abdominal trauma, hypercalcemia and parenteral nutrition. High levels of leucocyte (9800/mm3), sedimentation (38mm/h) and CRP(70 mg/L) (N: 0-5 mg/L) was detected. Serum amylase was 316 IU/L (N: 25-125 IU/L), urine amylase was 2790 IU/L (N: 75-150 IU/L) and lipase was 908 U/L (N: 0-200 U/L) (Graph. 1). All other laboratory values and ECG were within normal range. In addition to 5-ASA (1,5 gr/day), cephalosporin and somatostatin (IV) were started and CS was stopped. Abdominal tomography and MRI of pancreas demonstrated 4-5 pseudocysts in the head of the pancreas with numerous calcifications in the whole organ, enlarged mesenteric lymph nodes and intestinal wall thickening in terminal ileum (Fig. 4,5). At the end of a 10-day tre-



Graph 1. *Serum, urine amylase and lipase values during hospitalization*

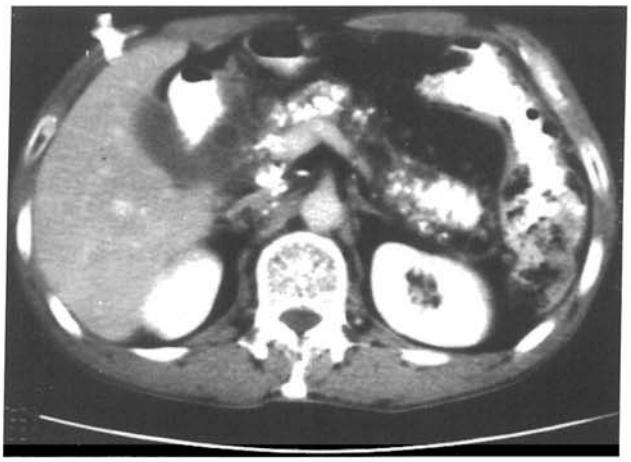


Figure 4. *Mesenteric lymph node enlargement on CT*

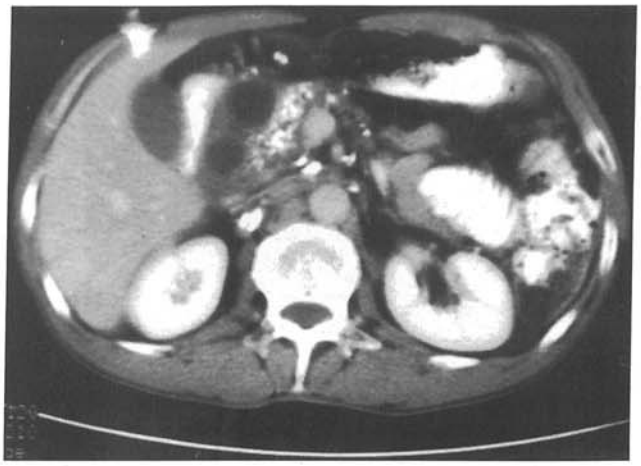


Figure 5. *CT appearance of wall thickening in terminal ileum*

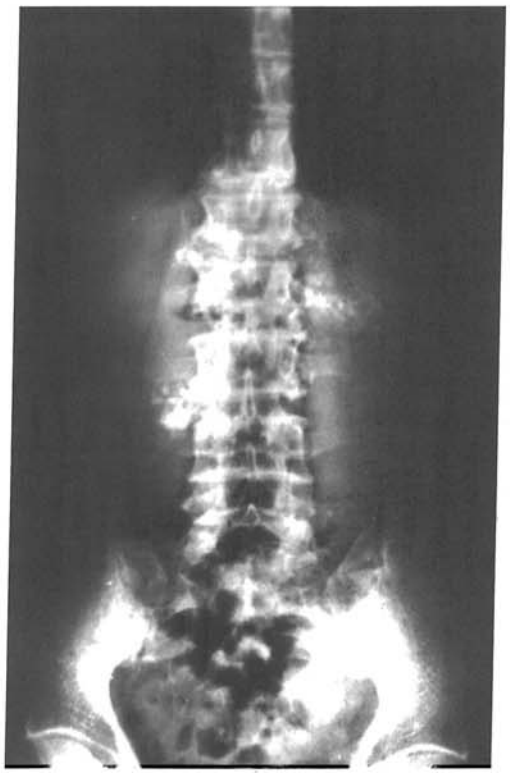


Figure 3. *Mid abdominal calcifications on plain abdominal film.*

atment, amylase and lipase values decreased to normal range. ERCP showed stones both in the parenchyma and the main duct. After pancreatic sphincterotomy, most of the stones were either extracted or became fragmented. A stent was placed to the main duct and was taken out after sufficent decompression. Patient showed a good clinical improvement and was discharged under 5-ASA (1,5 gr/day), omeprazole (20 mg/day) and folic acid therapy until his next control.

DISCUSSION

This case is one of CD not involving the duodenum and being associated with pancreatitis. Pancreatitis has rarely been reported to be associated with CD. If the literature is reviewed, mainly case reports on acute pancreatitis of different origins can be seen (1-11). Reports also concerning asymptomatic rising of the pancreatic enzymes, exocrine pancreas function and autoantibodies against exocrine pancreas can be found (12-15). Seyrig et al (16) reported cases of pancreatitis in CD with intact duodenum, also without drug therapy such as azathioprine which has been thought to be related to pancreatitis (17). Our patient had used SAS that is associated with pancreatitis, for a long time before changing it to 5-ASA.

The first reports of drug-induced pancreatitis with CD concern SAS (4,18). The toxic effect of SAS was linked to the sulfonamide part of the double molecule. However, there are cumulating number of articles about acute pancreatitis which occurs with monosubstance 5-ASA (6,8,10,11). It is reported that both oral and rectal applications of mesalazine and olsalazine can bring about pancreatitis. As either first or re-exposures to the drug may be the cause, Tromm and May presumes that these findings result from a dose independent side-effect of the drug (1). They also report that azathioprine and its active metabolite, 6-mercaptopurine, which are second-line medications, can induce acute pancreatitis. Sturdevant et al informed that 4.4% of Crohn patients receiving azathioprine and Haber et al reported that 3.25% of patients with inflammatory bowel disease under 6-mercaptopurine developed acute

pancreatitis (7). In addition to these drugs, there is still controversy whether CS or metronidazole can induce acute pancreatitis.

On the other hand, there are only a few reports in literature concerning chronic pancreatitis and CD. There was no evidence of a known etiological factor for chronic pancreatitis in our patient. No gallbladder stone, sludge, sclerosing cholangitis or duodenal pathology was detected. SAS and 5-ASA are the first factors attracting attention in the etiology. He had used SAS and CS for many years and when changing SAS to 5-ASA, he couldn't tolerate it well and had to stop the therapy. The different type of radiating epigastric pain described also shows coincidence with 5-ASA administration. However, despite continuation of 5-ASA + CS treatment, no biochemical and clinical evidence of pancreatitis was observed afterwards. Another point of attention is that after azathioprine therapy (50 mg/day) for 2 weeks, the drug was discontinued because of an acute flare of chronic pancreatitis. The enzymes returned to normal values after azathioprine therapy was discontinued.

Nevertheless, the results of recent reports suggest that unexplained pancreatitis associated with CD might be an extraintestinal manifestation of the latter (19,20), and such an association, being debated at the moment, is still controversial. A pathophysiologic mechanism associating inflammatory bowel disease with pancreatitis is unknown. Matsumoto et al stated that because of the high frequency of gallstones, undetected gallstones or sludge may be related to the pathogenesis (19,21). Ball et al documented mild to moderate pancreatic fibrosis at autopsy in 387 patients with CD and the inflammatory process was chronic pancreatitis with interlobular fibrosis (22). Stocker et al and Seibold et al found autoantibodies against exocrine pancreatic tissue in 39% and 31% of patients with CD, respectively (14,15). As they can be seen in only 4% of patients with ulcerative colitis and not in other infectious diseases, they seem to be highly specific for CD. Montefusco et al showed an association between sclerosing cholangitis and pancreatitis explaining it to be immunologically mediated and part of a syndrome complex (23). Because sclerosing cholangitis is associated with CD, perhaps the pancreas is involved as well, thus giving a "sclerosing cholangitis" of the pancreas. It is not known whether pancreas can be the site of primary CD. Granulomatous lesions of the pancreas have been reported in sarcoidosis and tuberculosis but pancreatitis is virtually unknown in these patients.

In conclusion, the occurrence of pancreatitis in patients with CD needs the exclusion of other aetiologic factors (e.g. bile stones, alcohol, etc.), analysis of treatment (salicylates, azathioprine) and histologic analysis of the upper gastrointestinal tract (duodenal CD, sclerosing cholangitis) to be certain that the pathology is truly related to the primary disease. The clinician must consider pancreatitis when caring for the patient with Crohn's disease with abdominal pain, especially in patients with a long history. Further studies concerning the incidence of acute and chronic pancreatitis in CD are needed to highlight various questions.

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