LETTERS TO THE EDITOR
EDİTÖRE MEKTUPLAR
Infliximab treatment of massive upper gastrointestinal bleeding in gastroduodenal Crohn's disease

Gastroduodenal Crohn hastalığına bağlı masif üst gastrointestinal sistem kanamasında infliximab tedavisi

To the Editor

Severe bleeding is a rare finding in inflammatory bowel disease, with most series quoting a 2% to 3% incidence (1). When Crohn's disease (CD) is considered to be responsible for acute massive gastrointestinal bleeding (GIB), the main bleeding sites are small bowel, ileo-colon, and colon (2). However, gastric CD may be the massive bleeding site (3). Infliximab, with its rapid mucosal healing effect, was found effective in the management of lower GIB caused by ileo-colonic ulcers in CD (4). However, there is no report in the literature regarding the efficacy of infliximab therapy in the management of upper GIB complicating gastroduodenal CD.

A 23-year-old woman was hospitalized at another hospital for evaluation of diarrhea and abdominal pain and was diagnosed with CD in January 2005. Upper gastrointestinal endoscopy was normal at that time. She had been given steroid and azathioprine. She had irregular polyclinic follow-up due to non-adherence to the treatment. She quit azathioprine of her own accord due to social and psychiatric problems in November 2006. Two months after cessation of azathioprine, she presented in January 2007 with hematemesis and massive melena with hemorrhagic shock. The patient had no diarrhea, abdominal pain, or other CD activity-related symptoms before GIB. As the patient's admission hemoglobin and hematocrit levels were 5.4 g/dl and 16%, respectively, the patient was managed with 6 units of packed red blood cells. Inflammatory signs (C-reactive protein, 10 mg/dl; sedimentation rate, 65 mm/h) were positive. Endoscopy revealed erosive antral gastritis and diffuse erosions and multiple linear ulcers in the bulbus (Figure 1a). Endoscopic hemostasis with 10 ml adrenalin was accomplished. Multiple biopsies were taken from the ulcers and erosions in the antrum and duodenum. Intravenous proton pump inhibitor (PPI) (omeprazole) at a dose of 200 mg/day was given to the patient for three days. Infliximab therapy at an infusion dose of 5 mg/kg was established along with PPI therapy on the basis of a possibility of gastroduodenal CD. Biopsy findings were consistent with gastroduodenal CD. PPI was stopped on the third day of the patient's admission in order to evaluate the effectiveness of infliximab for the healing of ulcers and erosions. Afterwards, the patient was commenced on the azathioprine treatment. The colonoscopy revealed multiple ulcers in the ileum and ascending colon. The hospital course of the patient was uneventful. Infliximab infusion at a dose of 5 mg/kg was repeated two and six weeks after the initial infusion. There was almost complete mucosal healing at follow-up endoscopy in March 2007 (Figure 1b). The patient had no recurrent bleeding in the five-month follow-up. Moreover, colonoscopy also showed excellent healing of ulcers localized in the ileo-colonic region.

As infliximab therapy in lower GIB was found effective against recurrence of bleeding, we assumed that infliximab not only induced rapid mucosal healing, but also prevented massive recurrent bleeding (4), which would necessitate a surgical resection. Any delay in complications and invasive

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Manuscript received: 25.07.2007 **Accepted:** 21.02.2008

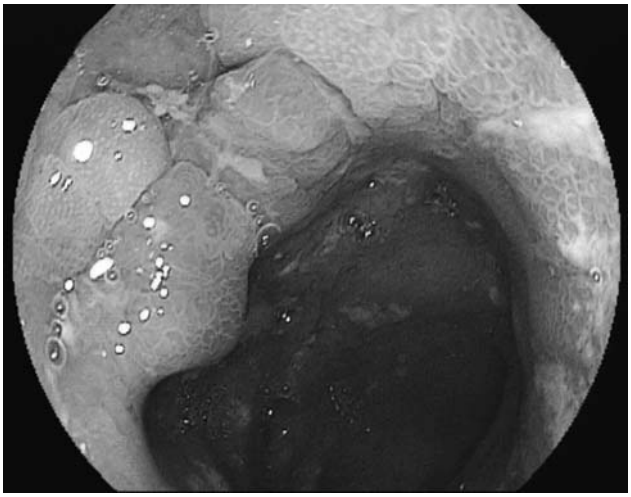

Figure 1a. Upper gastrointestinal endoscopy showing diffuse erosions and multiple linear ulcers in the bulbus.

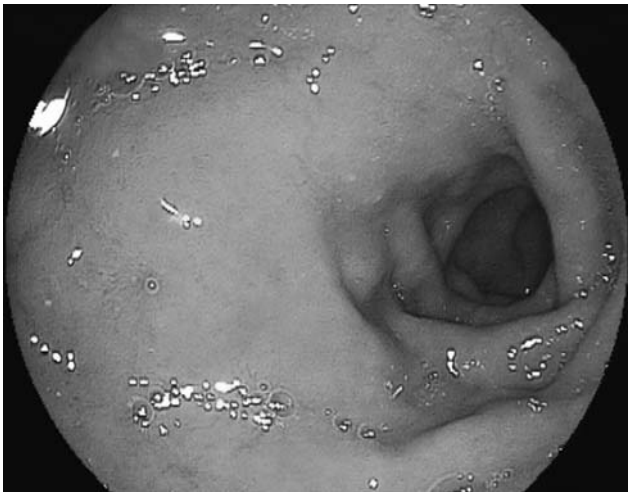

Figure 1b. Control upper gastrointestinal endoscopy showing a nearly complete healing of the erosions and ulcers in the bulbus.

management that can be achieved with medical therapies under appropriate conditions should be accepted as a success in CD, a disease for which the hourglass (natural course) cannot be upturned.

In conclusion, gastroduodenal CD can cause life-threatening bleeding in patients with CD. Non-invasive management such as endoscopic and/or medical approach should be the first- line therapy in the treatment of patients with massive upper GIB caused by CD. Infliximab therapy, with its rapid mucosal healing effect, may be offered as an initial medical treatment to patients with upper GIB complicating CD.

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Prevalence of appendectomy and tonsillectomy in patients with inflammatory bowel disease: a case-control study

İnflamatuvar barsak hastalarımızda appendektomi ve tonsillektomi sıklığı: Olgu-kontrollü bir çalışma

To the Editor,

An important clinical observation has been the decreased prevalence of appendectomy among patients with ulcerative colitis (UC). We performed a case-control study comparing the prevalence of appendectomy and tonsillectomy prior to disease onset in patients with inflammatory bowel disease (IBD) and healthy controls (HC). There were 176 patients with UC, 97 patients with Crohn's disease (CD) and 235 HC, consisting of patients of our orthopedic clinic. There were no significant differences between groups regarding age and gender. Demographic characteristics of IBD patients including age, age at disease onset, sex, duration and extent of disease, family history, smoking status, history of appendectomy and tonsillectomy, and age at appendectomy or tonsillectomy were recorded. The contribution of each factor to the development of IBD was assessed by means of backwards, stepwise logistic regression analysis.

The appendectomy rates were 4% - 7.2% - 9.4% and the tonsillectomy rates were 4.5% - 2.1% - 6% in patients with UC, CD, and HC, respectively. The active smoker rates were 19% - 61% - 48% and former smoker rates were 28% - 2.1% - 9% in patients with UC, CD, and HC, respectively. The age- and sex-adjusted logistic regression analysis identified two parameters, namely presence of appendectomy and smoking, as protective factors against the development of UC (Table 1). However, when further analyzed, this overall effect was only observed if the appendectomy was performed before 20 years of age [Odds ratio (OR) 0.26; 95% confidence interval (CI) 0.09–0.76; p=0.013]. In CD patients, prior appendectomy and tonsillectomy had no influence on disease development but smoking proved to be an important environmental factor (Table 1).

The first reports showing that patients with UC were less likely to have been subjected to appendectomy were published as early as the 1980s (1, 2). The biological explanation for this association was unclear and there were two hypotheses: whether factors predisposing to appendicitis might protect against UC or whether removal of appendix could alter the mucosal immune response making the development of UC less likely. Like in our study, the large cohort study of Andersson et al. (3) was able to prove that only removal of an infla-

Table 1. Results of backward-stepwise logistic regression analysis disclosing significant factors influencing the development of ulcerative colitis and Crohn's disease

Variable	B	Standard error	df	p	Exp (B)	95% CI Lower	Upper
Ulcerative Colitis							
Smoker			2	< 0.001			
Active	0.88	0.205	1	< 0.001	2.42	1.63	3.60
Former	- 1.02	0.172	1	< 0.001	0.36	0.26	0.50
Appendectomy	- 0.57	0.243	1	=0.019	0.56	0.35	0.91
Crohn's disease							
Smoker			2	=0.026			
Active	-1.24		1	=0.017	0.29	0.10	0.80
Former	0.77		1	=0.007	2.16	1.23	3.78
Family history	0.73		1	=0.018	2.07	1.13	3.81

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Manuscript received: 20.08.2007 **Accepted:** 17.04.2008

med appendix before 20 years of age was protective against the development of UC, and this was explained by the suggestion that appendicitis and UC were related to different pathways.

We did not find any significant association between CD and appendectomy, but in the study of Frisch et al. (4), the relative risk of CD development was higher than expected after appendectomy and notably in the first year after the procedure. However, since this effect did not remain significant five years after the operation, the authors concluded that the excess of CD shortly after appendectomy most likely could reflect differential diagnostic problems in patients newly presenting with abdominal pain. Regarding tonsillectomy, we could not find any significant associations between this and either disease, as in many other studies.

Our data about smoking habits is in agreement with the current literature (5, 6). In our study, smoking had a protective role against UC whereas it proved to be a risk factor for developing CD.

In conclusion, this case-control study from Turkey adds to the growing body of evidence that appendectomy, when performed in childhood or adolescence, is a protective factor against the subsequent development of UC. Smoking seems to be a protective factor against UC whereas it promotes the development of CD.

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A transverse colonic mass secondary to Actinomyces infection mimicking cancer

Kanseri taklit eden Aktinomikoz enfeksiyonuna sekonder bir transvers kolon kitlesi olgusu

To the Editor,

Actinomycosis is a rare disease that is caused by an anaerobic bacterium *Actinomyces israeli.* It is a gram(+) bacterium found in the normal body flora and tends to cause infection in injured and relati-

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Manuscript received: 20.09.2007 **Accepted:** 10.01.2008

vely microaerophilic tissues. Its virulence is low. Primary colonic infection is rare. The most frequently infected organs are the appendix and cecum (1).

Abdominal actinomyces could mimic diverticulitis, inflammatory bowel disease and malignant tumors, and it is generally diagnosed after operation (1, 2). Here, we report the first case of a patient with transverse colonic mass secondary to actinomyces infection mimicking cancer.

A 45-year-old female patient was sent from the provinces to our emergency service because of an increasing abdominal pain that began six months before. Her complaints during the six-month period were no appetite, weakness, 5 kg weight loss, and occasional constipation. She was also currently experiencing vomiting. Her physical examination revealed paleness and fever of 37.2°C. Her blood pressure was 110/70 mmHg, heart rate 66 beats/m (regular), and breath rate 13/m (regular). There was a widespread sensitivity on her abdomen. A mobile, nearly 6x7 cm mass was palpated between the umbilicus and left lower quadrant. Laboratory results were as follows: Hb: 10.3 g/dl, leukocyte: 13000/mm^3, platelet: 386000/mm^3, urea: 13 mg/dl, creatinine: 0.6 mg/dl, AST: 19 U/L, ALT: 22 U/L, and K: 3.8 mg/dl. Abdominal computed tomography demonstrated a 10x8x8 cm mass with soft tissue density in the left lower quadrant, invading the abdominal wall and mesentery. Attempted colonoscopy was unsuccessful because of patient intolerance.

A 7x8x8 cm mass was seen during operation, originating from the middle part of the transverse colon and invading the abdominal wall and sigmoid colon. Since there was a suppurative leak from the mass in the dissection, a sample was taken for microbiologic examination. After the adhesions were separated, a 5 cm infected colonic segment was resected. In microscopic pathologic evaluation, chronic inflammation in the pericolonic fat tissue and sulfur granules were seen (Figure 1).

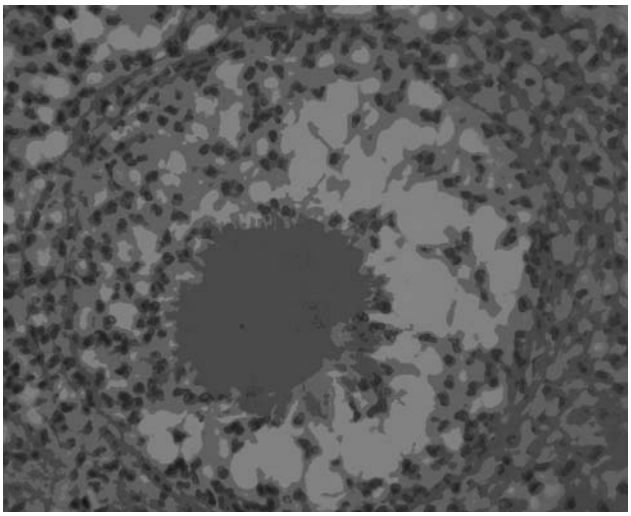

Figure 1. Actinomycotic abscess in the serosal layer of the colon. A colony of sulfur granules appearing as a dark blue mass with radiating filaments (hematoxylin and eosin x400).

In conclusion, abdominal actinomycosis incidence is increasing. Especially in female patients, actinomycosis should be considered in the presence of inflamed and tumoral masses in the abdomen in view of the reported association of intrauterine device and *A. israeli* (3). In general, the diagnosis is difficult; in this regard, demonstration of the sulfur granules by pathologic evaluation of the specimen is helpful.

The conventional therapy for actinomycosis is penicillin (4-6). The most effective treatment is the combination of surgery and antibiotherapy.

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Elevations of serum aminotransferase in muscular dystrophy

Musküler distrofide serum aminotransferaz yüksekliği

To the Editor,

Serum aminotransferase elevations are encountered frequently in childhood and require long-term follow-up. They may be due to hepatic or non-hepatic causes. Many diseases such as infectious, systemic and metabolic diseases cause aminotransferase elevations aside from primary childhood hepatic diseases (1, 2). Muscular dystrophy (MD) may cause aminotransferase elevation due to enzyme passage from the damaged muscle membrane, without affecting the liver, and should be included in the differential diagnosis of long-term transaminase elevations (3, 4).

We wanted to emphasize, in view of the two cases presented herein, that muscle disease should be kept in mind for cases in whom aminotransferase elevation cannot be explained and that serum creatine kinase (CK) levels should also be determined.

CASE 1

A six-year-old patient with Duchenne muscular dystrophy (DMD) was being prepared for a tonsillectomy when the liver function test results were found to be elevated, with an aspartate aminotransferase (AST) value of 139 U/L and alanine aminotransferase (ALT) of 150 U/L. No liver problems were found and the aminotransferase elevation was thought to be secondary to the MD.

CASE 2

A four-year-old patient was being prepared for phimosis surgery when the liver function test results were found to be elevated and a pediatric consultation was obtained. Liver function test results had been elevated two years ago and no reason had been found at that time. Physical examination revealed no new pathology besides gastrocnemius pseudohypertrophy. Laboratory tests revealed an AST level of 128 U/L and ALT of 115 U/L, while the results of other liver tests were normal. The CK level, measured because of its association with muscle disease, was found to be 9004 U/L, and the muscle biopsy results were consistent with MD. The long-term serum aminotransferase elevation, absence of liver disease and presence of pseudohypertrophy were indicative of muscle disease in this case.

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Manuscript received: 25.07.2007 **Accepted:** 09.08.2007

Pleural effusion: Always innocent?

Plevral Efüzyon: Daima masum mudur?

To the Editor,

A five-year-old boy had admitted to hospital with a three-month history of chest pain referred to the left shoulder, abdominal pain and dyspnea. He had been diagnosed with pneumonia, pleural effusion and pancreatitis; intravenous fluids and systemic antibiotics were given. A month later he had complaints of dyspnea and abdominal pain. Examination was normal except for absence of breath sounds on left hemithorax and mild epigastric tenderness. Chest radiography and thorax ultrasonography (USG) revealed massive left pleural effusion. Abdominal USG and computerized tomography (CT) showed a pseudocyst measuring 29x24 mm localized at the pancreatic head. Amylase, lipase and albumin concentrations of pleural fluid were 1700 IU/L, 1662 IU/L, and 3.1 g/dl, respectively. The hematologic and biochemical tests were within normal range except for high plasma amylase: 214 IU/L (normal: 25-125 IU/L), lipase: 99 IU/L (normal: 8-80 IU/L) and lactate dehydrogenase: 7431 IU/L (normal: 108-190 IU/L) levels. Urine amylase and amylase clearance were 2087 IU/L and 5.5, respectively. Although the fistula tract was not visualized on magnetic resonance cholangiopancreatography (MRCP) (Figure 1) or thoracoabdominal magnetic resonance imaging (MRI), we considered the diagnosis as pancreaticpleural fistula (PPF) because of high chest drainage volumes of amylase-rich fluid. A second abdominal USG was performed upon an increase in the patient's abdominal pain. It showed irregular pancreatic duct and an increase in the diameter of the pseudocyst. Diagnostic and therapeutic endoscopic retrograde cholangiopancreatography (ERCP) and papillotomy were performed.

Patients with chronic pancreatitis and pleural effusions due to PPF mostly have complaints related to the respiratory system. In some cases, pleural effusion can be the first and only symptom of pancreatitis; thus, abdominal symptoms are not always obligatory (4). Therefore, the diagnosis of pancreatitis requires a high index of suspicion. ERCP, MRCP and CT can demonstrate the fistula. However, the diagnostic accuracy rates of ERCP and CT are variable, ranging from 0-100% (5,6), with an average of 42 to 59% (3). We had to perform MRCP, CT, thoracoabdominal MRI and ERCP to confirm the presence of PPF. Imaging techniques failed to demonstrate the fistula, but according to the mentioned diagnostic accuracy rates, it may not be possible to show fistulas in every patient. A reduction of cyst size was observed by USG after papillotomy, and no other intervention was required during the follow-up. ERCP findings may help in performing specific interventions such as endoscopic insertion of pancreatic duct stent, distal pancreatectomy or pancreaticojejunostomy. In summary, pancreatitis and PPF are rare causes of pleural effusion in children. Presen-

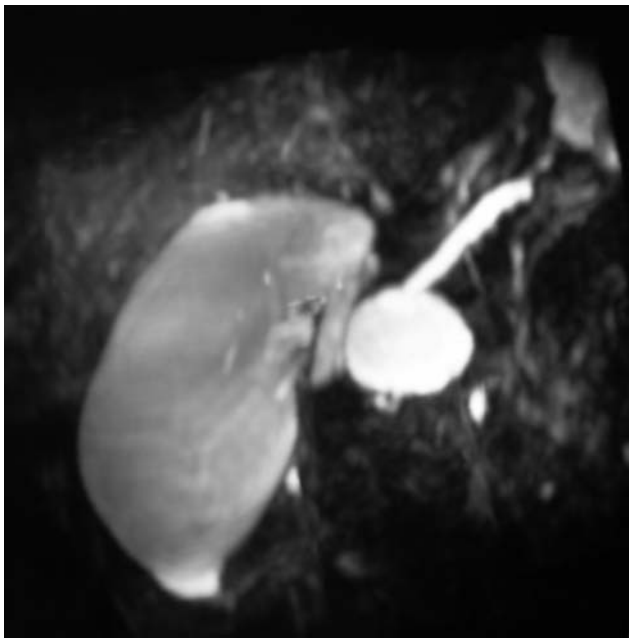

Figure 1. Magnetic resonance cholangiopancreatography imaging of the pseudocyst.

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ting symptoms are often respiratory in nature and diagnosis requires a high index of suspicion. Once the diagnosis is considered, pleural fluid amylase level should be assayed. Radiologic studies help to clarify the evidence of PPF but may be insufficient in some cases.

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A case report of highly suspected ciprofloxacin-induced hepatotoxicity

Muhtemel siprofloksasine bağlı bir hepatotoksisite olgusu

To the Editor,

We report a case of a 39-year-old female presenting to a community-based hospital in Winnipeg (Canada) with a six-day history of nausea, vomiting, anorexia, and epigastric pain. One day prior to presentation, she was noted to be jaundiced.

Two months prior to admission, she was seen at a peripheral hospital for bilateral lower quadrant abdominal pain, and was found to have a diverticular abscess. She was treated with a 14-day course of oral ciprofloxacin at a dose of 500 mg bid and oral metronidazole at a dose of 500 mg tid. A follow-up computed tomography scan approximately one month later showed almost complete resolution of the fluid collection.

The patient admitted to only occasional ethanol use and denied sexual promiscuity and intravenous drug abuse. She did not have any tattoos and had never received any blood products. There was no recent travel history, and, in fact, the patient had not been outside of North America. She was married with two children. No significant family history was revealed.

On physical examination, she was comfortable and alert. Specifically, there was prominent scleral icterus and jaundice. Her liver was tender and palpable at the costal margin, with a span of 11 cm in the mid-clavicular line. She had palmar erythema but no other stigmata of liver disease.

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Manuscript received: 25.06.2007 **Accepted:** 21.02.2008

Laboratory investigations revealed a leukocyte count of $4.4x10^9$/L with no eosinophilia. The remainder of the complete blood count, electrolytes, and renal function tests were within the normal range. The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 1406 U/L and 2009 U/L, respectively (normal <35 U/L). The alkaline phosphatase was 160 U/L (normal <118 U/L) and GGT was 230 U/L (normal <55 U/L). The total and direct bilirubin levels were 278 umol/L and 184 umol/L, respectively (normals <18 and <8 umol/L). The INR was 1.59 (normal <1.2) and albumin 33 g/L (normal 30-50 g/L). Viral serologies for hepatitis A, B, and C were negative. Anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-mitochondrial antibody (AMA) and ceruloplasmin levels were also negative. The chest and abdominal X-rays were unremarkable. Abdominal ultrasonography revealed a normal liver, no gall stones, and no dilatation of the biliary tree. There was mild splenomegaly and evidence of renal sinus lipomatosis. Computed tomography of the abdomen with infusion showed minimal edema around the portal triads with some prominence of the adjacent lymph nodes, possibly consistent with hepatitis.

Based on published guidelines suggesting that idiosyncratic drug reaction of sufficient severity to cause jaundice be treated with an empiric course of corticosteroids, the patient was started initially on prednisone at a dose of 60 mg/day, and transferred to the Health Sciences Center (a tertiary care center in Winnipeg, Canada) for further evaluation and management. Subsequently, a transjugular biopsy of the liver was performed. The histological specimen is shown in Figure 1.

The biopsy revealed infiltration of portal tracts by a mixed inflammatory infiltrate with prominent eosinophils. The infiltrate extended into adjacent lobules. Hepatocytes were markedly swollen with areas of individual cell necrosis in the mid and peri-central zones. There was no granuloma and no established fibrosis to suggest chronicity.

The patient was tapered off prednisone over a three-month period with gradual normalization of the AST and ALT levels and of liver function tests over the same time period.

Ciprofloxacin is a widely used antimicrobial agent, with more than 800 million patients worldwide having received treatment (2). Its potential hepatotoxicity has been noted previously in case reports, and is thought to be idiosyncratic in nature (3-7). The patient's presentation and histologic findings were felt to be most consistent with drug-induced hepatitis. Although the patient received metronidazole (8, 9) in the few reported cases of metronidazole-induced liver injury, the liver enzyme pattern tended to be more cholestatic in nature and the injuries were noted to be dose-dependent. In the present case, the serum alkaline phosphatase level was only minimally elevated and the dose prescribed was not excessive. Thus, ciprofloxacin rather than metronidazole was considered the more likely etiologic agent.

In the recent report published by Zimpfer et al. (3), it was suggested that the diagnosis of ciprofloxacin-induced hepatic injury should be entertained if three clinical criteria are met: (1) history of drug use (1-21 days), (2) liver biopsy illustrating hepatocellular necrosis and/or cholestasis with a mixed inflammatory infiltrate containing eosinophils, and (3) effective exclusion of other more common causes of hepatitis (viral, alcohol, autoimmune etc.). In this case, the biopsy with its eosinophilic infiltration was consistent, and other causes of hepatitis were effectively ruled out. Interestingly, our case report is novel in that it took significantly longer than in previous case reports for symptomatology to develop. The reason for this delay is unclear at present.

In conclusion, although ciprofloxacin is generally considered a well-tolerated and safe medication, clinical practitioners should be aware of its potential for hepatotoxicity.

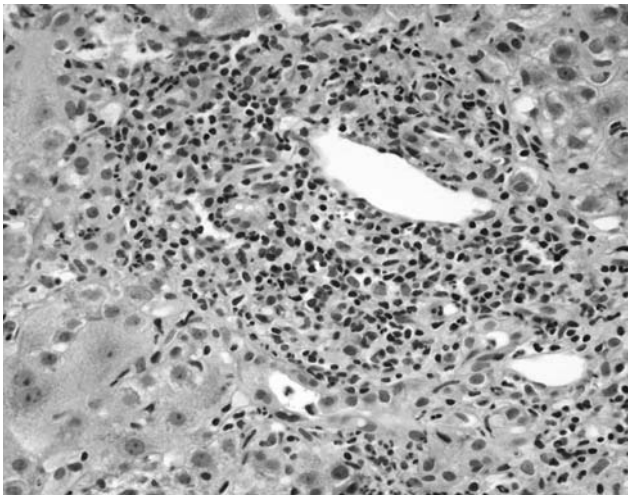

Figure 1. The liver biopsy shows extensive infiltration of the portal tracts by a mixed inflammatory infiltrate including prominent eosinophils (hematoxylin-eosin, original magnification x 400).

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