Virchows Arch (2000) 437:656–661
DOI 10.1007/s004280000294

ORIGINAL ARTICLE

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Phlegmonous colitis: a specific and severe complication of chronic hepatic disease

Received: 24 March 2000 / Accepted: 7 July 2000 / Published online: 21 October 2000

Abstract Phlegmonous colitis (PC) is an acute infectious entity caused by bacteria. In this study, we reviewed 8822 autopsy cases and found 13 cases of PC (0.15%). PC affected 2.43% of patients with hepatic cirrhosis or subacute liver atrophy, both of which were considered to be due to hepatitis viral infection. Before autopsy, none of the cases studied was suspected to involve PC, irrespective of the immediate cause of patient death. Thirteen autopsy cases showed some or all of the following pathohistologic characteristics: (1) involvement of the cecum (9 cases, 76.9%), (2) phlegmonous inflammatory changes and edema in the submucosa (100%), (3) bacterial infection (100%), (4) no microscopically detectable mucosal injuries (12 cases, 92.3%), and (5) acute serositis (peritonitis) (2 cases, 15.4%). These results suggest that PC is an unrecognized, but fatal complication of patients with some hepatic diseases and that PC has pathohistologic characteristics in common with previously reported spontaneous bacterial peritonitis in animal models. PC probably arises due to spontaneous infection in patients with hepatic cirrhosis.

Keywords Phlegmonous colitis · Hepatic cirrhosis · Bacterial infection · Autopsy

Introduction

Phlegmonous colitis (PC) is an acute infectious entity caused by bacterial infection [13, 18, 21]. Early studies of phlegmonous inflammation of the gastrointestinal tract have demonstrated that a lesion develops at various sites in patients without an underlying disease [2, 3, 25]. Local bacterial infection secondary to mucosal injury (due to fish bones, feces, and parasite infection) or sepsis is suspected to be an etiology of these diseases [2, 3, 25]. Cases in patients with hepatic disease (epidemic hepatitis and alcoholic hepatic cirrhosis) have been reported as phlegmonous enterocolitis. Causative agents have been considered to be enteric gram-negative bacilli, particularly *Escherichia coli* (*E. coli*). Because no or only mild mucosal injuries are generally detectable microscopically, the pathogenesis of phlegmonous enterocolitis in these cases has been attributed to alcoholic mucosal injury [21], a prominent submucosal edema [13], or presumed mucosal injury so small as to be undetectable microscopically [11]. Since 1978, however, with the exception of an experimental paper [8] and a case report [19], no studies have focused on PC. Therefore, the incidence, clinical significance, and histologic characteristics of phlegmonous enterocolitis and whether the condition is a primary or secondary infectious disease, remain unclear. The possible mechanism of bacterial infection into the intestinal wall is also poorly understood.

In the present study, we reviewed 8822 autopsy cases and selected 13 cases of PC for further analysis. We analyzed the clinical specificities of the patients and the histologic characteristics of PC. The results demonstrate for first the time that PC is an unrecognized, but fatal complication in patients with chronic hepatic disease, particularly in those with hepatic cirrhosis, and that the condition probably arises due to spontaneous infection in patients with hepatic cirrhosis.

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Material and methods

Materials

We searched the autopsy files of the Department of Pathology of the School of Medicine, Keio University (1961–1984) and the Department of Pathology of the Saga Medical School (1985–1998). First, we selected all cases with an autopsy diagnosis of inflammatory lesion, including circulatory disturbance-related lesions, ulcerative lesions, and various types of colitis in the large intestine. Of these selected cases, all available hematoxylin and eosin-stained slides were reviewed to verify the diagnosis of PC and other types of inflammatory lesion. The criteria for histologic diagnosis of phlegmonous enterocolitis included an acute suppurative pro-

cess and, in many cases, bacterial infection involving the submucosa and/or the intact mucosa [2, 13, 18, 21].

Clinical records

Clinical data was obtained from clinical records. Age, sex, underlying diseases, infection, sepsis, thrombosis, shock, heart disease, abdominal pain, peritonitis, peripheral blood count, and serum bilirubin level were examined. With respect to the peripheral blood counts and bilirubin levels, the data obtained on the date closest to the date of death were used.

Pathologic studies

Pathological examination of lesions in the intestinal tract was carried out macroscopically and histologically. For macroscopic examination, slides of macroscopic images and the findings described in autopsy records were used. For histologic examination, new histologic slides were prepared from preserved tissue blocks, and slides that had been previously prepared were also analyzed. Periodic acid Schiff (PAS)-stained and gram-stained tissue sections were prepared to investigate the presence of bacterial infection. Autopsy records and stained tissue specimens were investigated to detect infection, sepsis, thrombosis, and infarction in systemic organs. Tissue degeneration and destruction in the mucosa that were not accompanied by biological reactions, such as inflammatory cell infiltration and fibrinous exudate, were regarded as postmortem changes. Bacterial proliferation on the mucosal surface was also regarded as a postmortem change if it was confined to the surface of the mucosa without biological reactions.

Statistical analysis

Submucosal bacterial infection was graded as follows: mild (intracellular discrete granules and/or small number of bacteria) and moderate to severe (a moderate or large number of bacteria). Submucosal neutrophilic infiltration was graded as follows: mild (distinct infiltration at low magnification) and moderate to severe (abscess formation). Weights were graded as follows: <2 mm or ≥2 mm for submucosal edema, <2000 ml or ≥2000 ml for ascites, and <250 g or ≥250 g for splenic weight. Submucosal bacterial infection and other parameters were analyzed with a Student's *t*-test for continuous variables and 2×2 tables were analyzed with Fisher's exact-probability test for categorical variables. P values <0.05 were considered statistically significant.

Results

Clinical findings

Table 1 shows the clinical features for 13 cases of PC. Patients ranged in age from 35 to 70 years (mean: 55.4 years) at the time of death. The male-female ratio was 12:1. All 13 cases were clinically diagnosed as hepatic diseases due to hepatitis virus infection; the hepatic disease was hepatic cirrhosis in 11 cases (84.6%; hepatic cancer was also present in six of these cases) and acute exacerbation of chronic hepatitis in two cases (15.4%). Nine cases (69.2%) were serologically diagnosed as hepatitis viral infection, and the remaining four cases, which were not serologically tested for hepatitis virus, did not involve a patient history of alcohol consumption, drug administration, or heart failure. Five patients (38.5%) had suffered fever, but abdominal symptoms were rare in any of these patients. Acute peritonitis (with turbid ascites) was clinically diagnosed in two patients (15.4%) before death. Bacterial culture was performed before death in only one patient, and *E.* coli was isolated from the ascitic fluid and peripheral blood. The white blood-cell count in the peripheral blood ranged from 1000 to 33 200/mm^3 (mean: 10 615/mm^3). Two cases (cases 10 and 11) involved peripheral white blood-cell counts of 30 000/mm^3 or more, but bacteremia was not detected in the arterial blood collected immediately before death in either of these patients.

General autopsy findings

Histologic results of the autopsied liver tissue showed hepatic cirrhosis or subacute liver atrophy (Table1). These hepatic lesions were non-alcoholic, and the histologic features suggested hepatitis viral infection. The ascites ranged from 20 to 6100 ml (mean: 2267 ml), and the splenic weight ranged from 80 to 400 g (mean: 245 g). Bacterial culture of the ascitic fluid was performed in only one case (case 12) at the time of autopsy, and *E.* coli was isolated. No autopsy results showed any infectious lesions other than PC. Although PC was judged to be the immediate cause of death in most patients, it was not detected before autopsy in any of them.

Incidence of PC

PC affected 0.15% of all 8822 autopsies studied and 2.43% of patients with hepatic cirrhosis or subacute liver atrophy, both of which were considered due to hepatitis viral infection. The male-female ratio among the autopsy cases with hepatic lesions was 8:1, and the above-mentioned PC male-female ratio appeared to be attributable to this general male-female ratio.

Macroscopic findings of PC

Phlegmonous inflammation in the gastrointestinal tract was only localized in the large intestine in all cases, and it predominantly involved the cecum in nine cases (76.9%). In three cases (23%), the lesions were extensive and involved the rectum. Macroscopically, typical lesions showed a large, undulating elevation covered with mucosa (Fig. 1). In the cut section of most lesions, varying degrees of submucosal edema were seen. Multiple focal or diffuse changes in color to a yellowish white (due to PC) were noted in the submucosa in some cases. Mild or moderate hemorrhage was also found in some lesions (Fig. 1).

Microscopic findings of PC

The histologic characteristics of PC included varying degrees of edema, neutrophils, macrophages, and bacterial infection in the submucosa. The proportions of these elements varied from case to case. In cases in which phlegmonous inflammation was severe, numerous or diffuse

Table 1 Clinical data and autopsy findings in patients with phlegmonous colitis. *F* Female, *M* male, *LC* liver cirrhosis, *AE in CH* acute exacerbation in chronic hepatitis, *B* hepatitis virus B, *NANB* hepatitis virus non-A and non-B, *C* hepatitis virus C, *SLA* subacute liver atrophy, *HCC* hepatocellular carcinoma, *HCC/CCC* mixed HCC and cholangiocellular carcinoma, *WBC*white blood cell count in the peripheral blood, *TB* total bilirubin in the peripheral blood, *Ce* cecum, *A* ascending colon, *D* discending colon, *R* rectum. (ex. *Ce-R* cecum to rectum), *SBI* submucosal bacterial infection, *mild* as intracytoplasmic discrete granules and/or small number of free bacteria, *moderate* as a moderate number of free bacteria, *severe* as numerous free bacteria, *SE* submucosal edema as thickness at the bottom of mucosal folds, *SNI* submucosal neutrophilic infiltration, # abdominal pain, ## acute peritonitis diagnosed by punctation with turbid ascites

Clinical data							Autopsy findings						
Case no.	Age (years)	Gender	Clinical diagnosis of	Abdominal symptoms[a]	WBC[a] (mm^3)	TB[a] (mg/dL)	Histology of the liver	Ascites (mL)	Spleen (g)	Phlegmonous colitis			
										Location	SBI	SE (mm)	SNI
1	62	M	LC		3100 [–20]	9.1 [–20]	LC	2100	190	Ce	moderate	4.0	mild
2	47	M	LC		5000 [–3]	8.3 [–1]	LC	3600	340	Ce-A	mild	2	moderate
3	49	M	LC	##[–2]	8200 [–2]	45.5 [–10]	LC	800	205	Ce-A	mild	4	severe
4	57	M	LC	#[–1]	4000 [–0]	4.6 [0]	LC	480	200	Ce	mild	1	mild
5	35	M	AE in CH(B)		6000 [–0]	43.1 [0]	SLA	4000	110	D-R	mild	1.5	moderate
6	64	M	LC(NANB), hepatoma	##[–1]	13100 [–3]	7.2 [–3]	LC, HCC	450		Ce-R	severe	1.5	moderate
7	65	M	LC(NANB), hepatoma		11800 [–1]	7.9 [–1]	LC, HCC	2520	110	Ce-R	moderate	0,5	moderate
8	56	F	LC(B), hepatoma		9100 [–1]	7.5 [–1]	LC, HCC	6100	320	Ce-A	mild	4.1	severe
9	58	M	LC(B)		7800 [0]	12.1 [0]	LC	20	330	R	moderate	4.5	severe
10	59	M	LC(NANB), hepatoma		33200 [0]	31.9 [0]	LC, HCC	1500	200	Ce-A	mild	2	mild
11	43	M	LC(B), hepatoma		33100 [–1]	42.5 [3]	LC, HCC/CCC	4000	400	Ce-R	mild	3.5	severe
12	40	M	AE in CH(B)		2600 [–1]	19.0 [1]	SLA	2700	140	A	mild	3	severe
13	70	M	LC(C), hepatoma		1000 [0]	1.6 [-0]	LC, HCC	1200	390	Ce-A	severe	7,5	mild

[a] Before death; day 0 indicates the day of patient's death

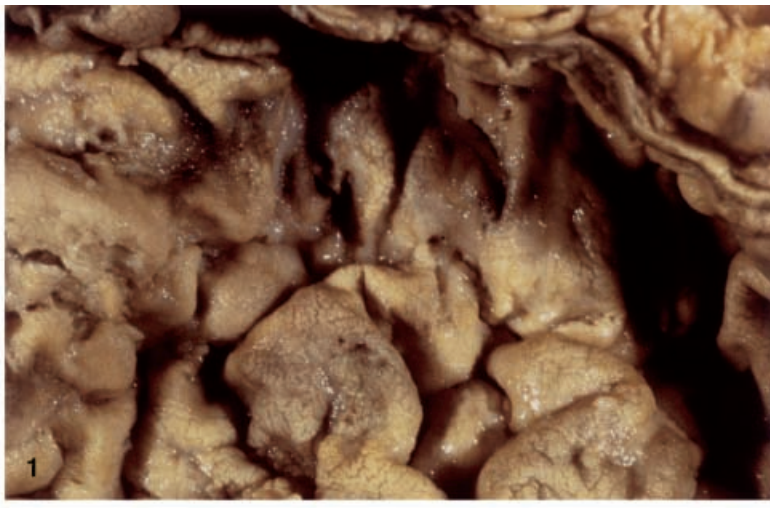

Fig. 1 Typical macroscopic findings of phlegmonous colitis (PC) after formalin-fixed specimens (case 11). Large, undulating elevations, mostly covered with normal mucosa, were observed in the cecum. Notable necrosis, ulcer, and pseudomembrane were not observed

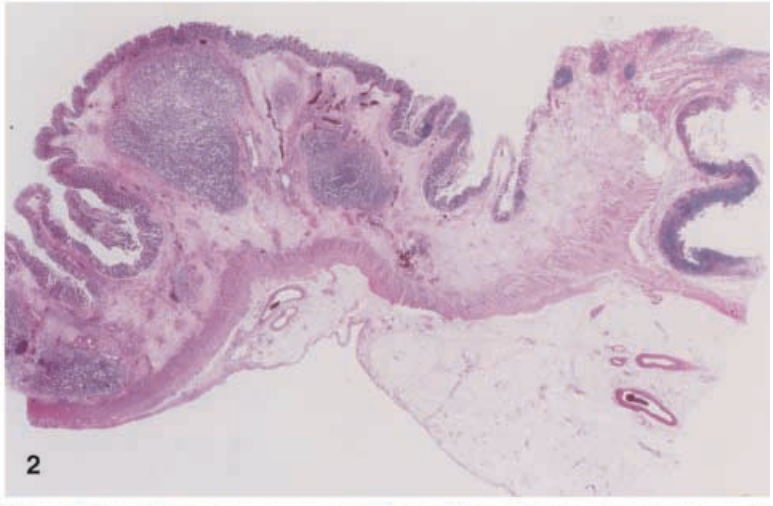

Fig. 2 Histologic findings of phlegmonous colitis (PC) (case 11): phlegmonous inflammation with several abscesses is seen against the background of edema in the submucosal tissues of the cecum (*left*) (*right* ileocecal valve and ileum). Hematoxylin and eosin stained, ×16

Fig. 3 Infiltration of neutrophils and histiocytes and bacterial infection consisting of bacilli were noted at the site of phlegmonous inflammation. Phagocytosis by histiocytes and neutrophils was observed. Hematoxylin and eosin stained, ×1000

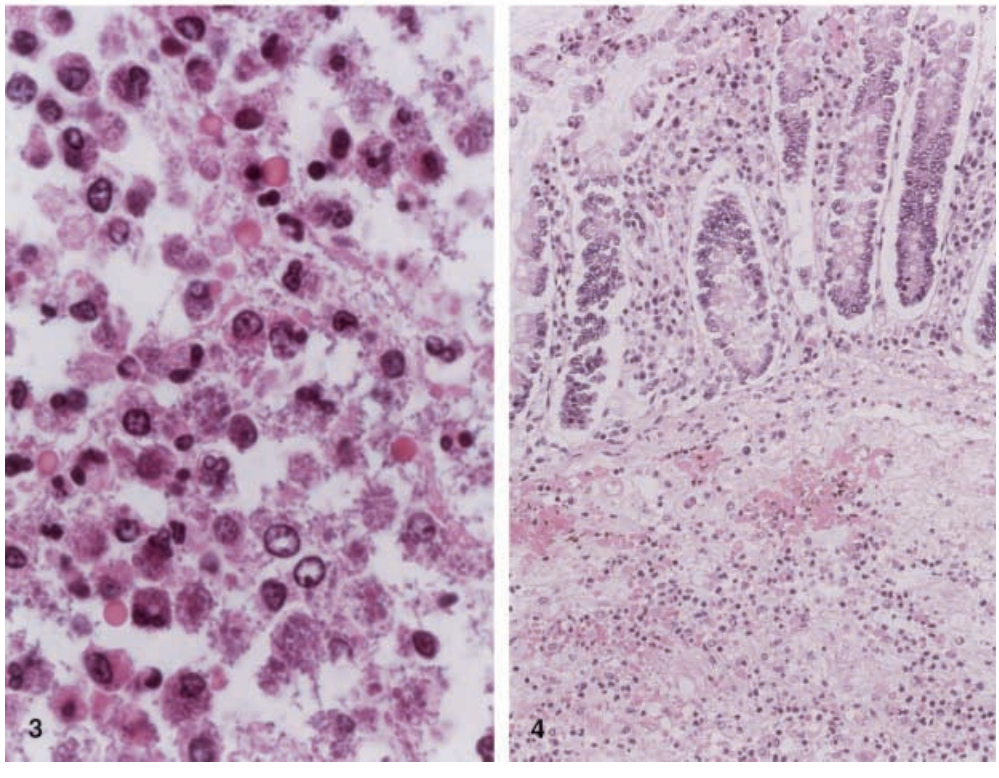

Fig. 4 Infiltration of numerous neutrophils, including histiocytes was noted in the submucosa without notable microscopic injury or neutrophilic infiltration (case 7). Mucosal epithelial changes are regarded to be postmortem changes. Hematoxylin and eosin stained, ×200

abscesses had formed in the submucosa (Fig. 2), and inflammation was found to reach the muscular layer proper and the adventitial or subserosal fat tissue. In one case, granulation-like vascularization and lymphocyte infiltration surrounded the abscess. Suppurative or fibrinous peritonitis was observed in three cases (23%) (cases 3, 4, and 6). Growth of gram-negative bacilli, free or phagocytosed by macrophages or neutrophils, was seen within the inflammatory region in the submucosa in eight cases (62%) (Fig. 3). In the remaining five cases (38%), bacterial infection was observed as intracellular discrete granules [8] stained with PAS in macrophages. These granules were considered digested organisms. In one case (case 6), severe bacterial growth had reached the muscular layer proper. Small amounts of gram-positive cocci were also noted in several cases. In most cases, mild or moderate vasodilatation or fresh hemorrhage was seen in the region of phlegmonous inflammation. No cases showed microscopic injury of the mucosa (Fig. 4), with the exception of case 9, which showed severe PC with hemorrhage and apparent secondary mucosal erosion. Though fresh fibrin thrombi due to disseminated intravascular coagulation was seen in the capillaries in the mucosa in one case (case 13), ischemic colitis [28] was not noted. When the relation between submucosal bacterial infection and submucosal edema or submucosal neutrophilic infiltration was examined, no association was found ($P<0.59$ and $P<0.14$, respectively). No direct relation was noted between submucosal bacterial infection and ascites or splenic weight ($P<0.41$ and $P<0.58$, respectively). There was no direct relation between submucosal bacterial infection and total bilirubin or white blood-cell count in the peripheral blood ($P<0.18$ and $P<0.59$, respectively).

Mucosal bacterial infection, microscopic injuries, and secondary phlegmonous inflammation in inflammatory lesions other than PC

To confirm the histologic specificity of PC, we investigated all other autopsy cases that showed inflammatory lesions in the large intestine (n=165, 1961–1984), including the cases of circulatory-disturbance-related lesions (n=89; mesenteric arterial thrombosis and nonocclusive lesions [1, 14, 15, 16, 27]), ulcerative lesions (n=46), pseudomembranous colitis (n=10), neutropenic colitis (n=18) [6], inflammatory bowel disease (n=2; classified as ulcerative colitis, Crohn's disease), and amyloidosis (n=1). Bacterial and/or fungal infection was noted in the mucosa in some cases and was accompanied by distinct neutrophilic infiltration and/or mucosal injuries. Phlegmonous inflammation or gangrene secondary to the mucosal injuries was observed in some cases, particularly in those with neutropenic colitis or a severe form of circulatory-disturbance-related lesions (ischemic gangrene). Thus, submucosal bacterial infection without microscopically detectable injuries of the mucosa was proven to be specific to PC.

Inflammatory lesions other than PC in autopsied cases of hepatic cirrhosis or subacute liver atrophy

When the autopsy diagnosis was hepatic cirrhosis or subacute liver atrophy (n=535), the only lesions of the large intestine other than PC were ulcers in two cases.

Discussion

Early studies showed that phlegmonous enterocolitis is closely associated with chronic hepatic disease and that it is typically diagnosed at autopsy [13, 18, 21]. Lucke and coworkers [13] observed PC in 15 autopsies of military subjects with epidemic hepatitis. In the present study, we reviewed 8822 autopsy cases from two hospitals in Japan over the past three decades and demonstrated that 2.43% of the cases of hepatic cirrhosis or subacute liver atrophy, conditions usually considered associated with hepatitis viral infection, showed a fatal complication of PC. Furthermore, the present report is the first to analyze the incidence of PC in a large series. This incidence was very low. Because PC was not detected in any of these patients before death, it would appear that PC can go unrecognized by clinicians and, thus, these findings are of immediate clinical importance in the management of patients with these hepatic diseases.

PC has been considered to be induced by bacterial infection, especially *E. coli* [2, 3, 13, 18, 21, 25]. However, the mechanism by which bacteria enter the submucosa is poorly understood. In general, the histologic characteristics of acute bacterial colitis have been described as the presence of neutrophilic infiltration, ischemic change, and epithelial change in the mucosa [6, 11, 17]. However, these changes were not found in either previous cases [13, 18] or in those studied here. Some investigators have suggested that the mucosa in PC is not actually intact and that it has injuries too small to be detected microscopically [11, 13]. In all 13 cases of the present series, however, the mucosa did not show a predisposition to develop any of the types of microscopic mucosal injuries that were observed in all other inflammatory lesions over the same period. In addition, no sepsis or causative infections in other organs were noted in any of the 13 cases. Submucosal bacterial growth in the cases reviewed here may be, at least in part, a postmortem artifact that is different in each case. However, submucosal infection in our present cases was considered to be actually present because an infection selectively limited only to the submucosa was not found in other lesions than PC. Indeed, bacteria are mostly not detectable with histologic analysis, which is rather insensitive since it requires approximately 10^6 organisms/g tissue [8]. This insensitivity and a postmortem artifact may explain why a submucosal infection did not correlate with parameters such as submucosal edema, ascites, or splenic weight. Consequently, or findings imply that, even if PC is due to bacterial infection, PC differs from other types of common infectious colitis and is specific to the large intestine in patients with hepatic cirrhosis or subacute liver atrophy.

Patients with hepatic cirrhosis are known to be susceptible to bacterial infection [4, 29, 30]. Many such cases consist of spontaneous infections, such as spontaneous bacterial peritonitis (SBP) or bacteremia, without any microscopically detectable mucosal injury [5, 7, 10, 20]. Enteric gram-negative bacilli, particularly *E. coli*, are the main causative agents of these infections [5, 7, 8, 12, 20, 23]. Therefore, bacterial translocation from the intestinal lumen to the peritoneal cavity is considered to be the pathogenesis of SBP in humans [5, 7, 8, 12, 23]. Though the exact mechanism of bacterial translocation remains unclear, it has recently been reported that neutrophilic chemotaxis [9], opsonic activity [22], and bactericidal activity [26] are altered in individuals with chronic hepatic disease. In addition, *E. coli* with the K1 capsular serotype is associated with increased resistance to complement activation, poor opsonization, and phagocytosis [24]. Interestingly, we found histologic similarity between PC cases in the present study and acute inflammation in the cecal wall in certain cases of SBP in experimentally induced hepatic cirrhosis of rats [8]. We therefore hypothesize that, like SBP, PC may be a spontaneous infection in patients with hepatic cirrhosis. Further, our data suggest that the absence of neutrophilic infiltration into the mucosa may be related to bacteria passing through the mucosa without leaving microscopically detectable injuries. However, there is a limit to which these matters can be clarified with autopsy findings. Experimental studies with animal models will also be needed to clarify the relation between the absence of neutrophilic chemotaxis in the mucosa and bacterial translocation. Such studies may also be helpful for elucidating the pathogenesis of other spontaneous infections in which bacterial translocation is assumed to be the etiology.

In conclusion, in this study, we reviewed 8822 autopsy cases and found 13 cases of PC (0.15%). PC affected 2.43% of patients with hepatic cirrhosis or subacute liver atrophy, both of which were considered to be due to hepatitis viral infection, and was an unrecognized, but fatal complication of patients with these hepatic diseases. The fact that, despite microscopically detectable mucosal injuries, submucosal phlegmonous inflammation accompanies gram-negative bacilli suggests that PC is probably a spontaneous infection in patients with hepatic diseases.

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