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Abnormal bile duct epithelium accompanying septicaemia

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Summary. A 56-year-old female without previous hepatobiliary disease developed a severe obstructive cholestasis following *E. coli* urinary tract infection with septicaemia. Liver biopsy showed cholangiolitis and a unique abnormality of almost all the interlobular bile ducts; the epithelium was irregular with polymorphic, angular, and hyperchromatic or pyknotic nuclei. Some ducts were ectatic, others narrowed due to protrusion of proliferating epithelium. In some areas the ducts were blurred or completely destroyed. Cholangitis or granulomas were, however, not present.

Abnormal interlobular bile ducts have to our knowledge not previously been described in septicaemia. The lesion is morphologically distinguishable from other types of abnormal bile ducts. It is considered to be caused by endotoxaemia and seems to be reversible. The cholestasis may be due to endotoxic alteration of biliary secretion, bacterially induced inspissation of bile, and/or mechanical obstruction due to the bile duct lesions.

Key words: Abnormal bile ducts – Septicaemia – Cholestasis

The aim of the present paper is to describe a new type of abnormal bile duct epithelium observed in a case of severe cholestatic liver lesion probably caused by septicaemia. Abnormal bile ducts have formerly been described in a variety of liver diseases such as hepatitis, primary biliary cirrhosis, and drug lesions (International group 1983; Poulsen and Christoffersen 1979). To our knowledge abnormal bile ducts have never been demonstrated in septicaemia in the absence of cholangitis.

Jaundice accompanying bacterial infections outside the liver and the biliary tract is a well-known phenomenon (Zimmerman et al. 1979). Mor-

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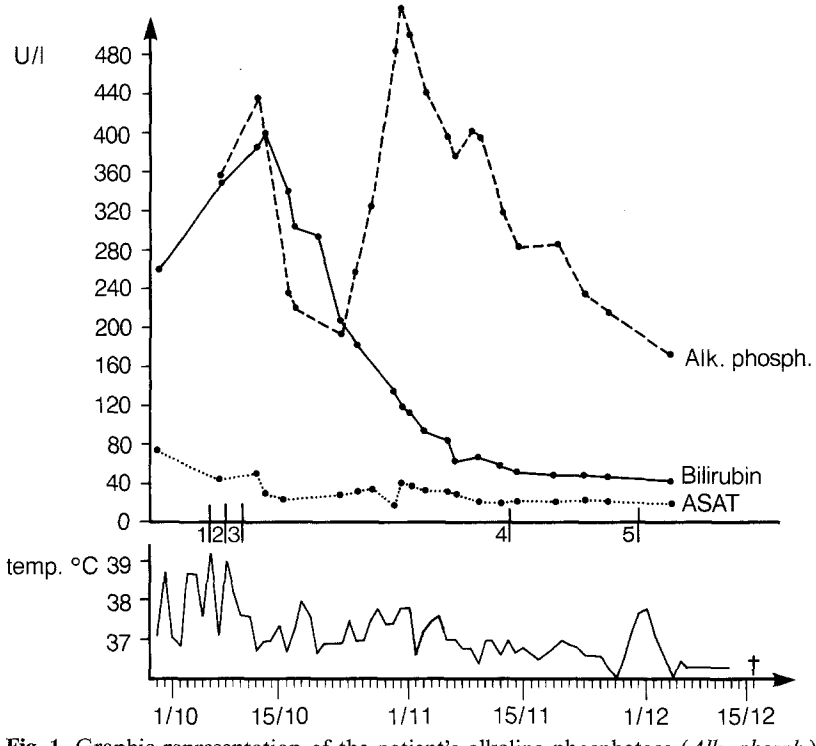


Fig. 1. Graphic representation of the patient's alkaline phosphatase (*Alk. phosph.*), bilirubin, aspartate aminotransferase (*ASAT*), and temperature (*temp.*) levels during the admission. Some major events are marked by numbered vertical lines: *1.* Blood culture: *E. coli*, *2.* Blood culture: *K. pneumoniae*, *3.* Laparotomy, first liver biopsy, *4.* ERCP, second liver biopsy, *5.* Blood culture: *K. pneumoniae* and *S. aureus*. Dates are indicated on the abscissa

phologically the liver lesions are usually limited to slight non-specific changes in parenchyma and portal tracts. A few cases have presented as acute cholangitis (Ishak and Rogers 1981) or bile ductular cholestasis (Lefkowitch 1982) but without the bile duct lesions to be described.

Case report

The patient was a 56-year-old female admitted after two weeks of generalized malaise, vomiting, and increasing tiredness. No previous history of hepato-biliary, cardiac or urinary tract disease was obtained. During 3 years she had been treated with chlorothiazide for slight hypertension.

The clinical examination revealed dehydration and jaundice. The temperature was normal and there were no other symptoms or signs of infection. Blood pressure was 110/50 mm Hg. Laboratory data (normal ranges in brackets): Haemoglobin 11.0 mmol/l (7–10), leukocyte count 17.7×10^9/l ($3–9 \times 10^9$), bilirubin 259 U/l (5–17), alkaline phosphatase 359 U/l (30–90), aspartate aminotransferase (ASAT) 74 U/l (10–25). The day after admission there was an increase in temperature to 38.7° C lasting for one day. Figure 1 is a graphic representation of the patient's temperature, bilirubin, ASAT, and alkaline phosphatase levels during the admission.

Four days after the admission, the patient became febrile again. Urine microscopy showed many neutrophils, few erythrocytes, and many bacteria. Urine culture as well as blood culture

yielded growth of *Escherichia coli*. No other focus of infection was revealed. Antibiotic treatment with ampicillin was started.

Five days later, the temperature increased with chills. Blood culture now yielded *Klebsiella pneumoniae*. Ampicillin was supplemented with gentamicin. The temperature decreased during the following days. At the same time the patient slowly deteriorated and developed coma, from which she never recovered.

Because of increasing values of alkaline phosphatase and bilirubin an obstruction of the large bile ducts was suspected and an explorative laparotomy was undertaken on the 12th day after admission.

The liver was found to be slightly enlarged, firm, greenish, without focal changes. The gall-bladder, biliary tract, and pancreas were normal. A peroperative cholangiography showed no abnormalities. A peroperative Menghini liver biopsy was performed (1st biopsy, see below).

In the following postoperative weeks the bilirubin fell slowly without reaching normal values (see Fig. 1). A second rise in alkaline phosphatase was registered two weeks after the operation with a peak value of 525 U/l. The transferase quickly decreased to just above the normal level. The temperature normalized in relation to the antibiotic treatment but later there were several subfebrile attacks.

Six weeks after admission an endoscopic retrograde cholangio-pancreaticography (ERCP) was done, showing no abnormalities. At the same time a percutaneous Menghini liver biopsy was performed (2nd biopsy, see below).

Eight weeks after the admission a new rise in temperature was registered. Blood culture revealed *Klebsiella pneumoniae* and *Staphylococcus aureus*. The patient was treated with ampicillin and gentamicin but developed oliguria and pulmonary oedema and died 79 days after the admission.

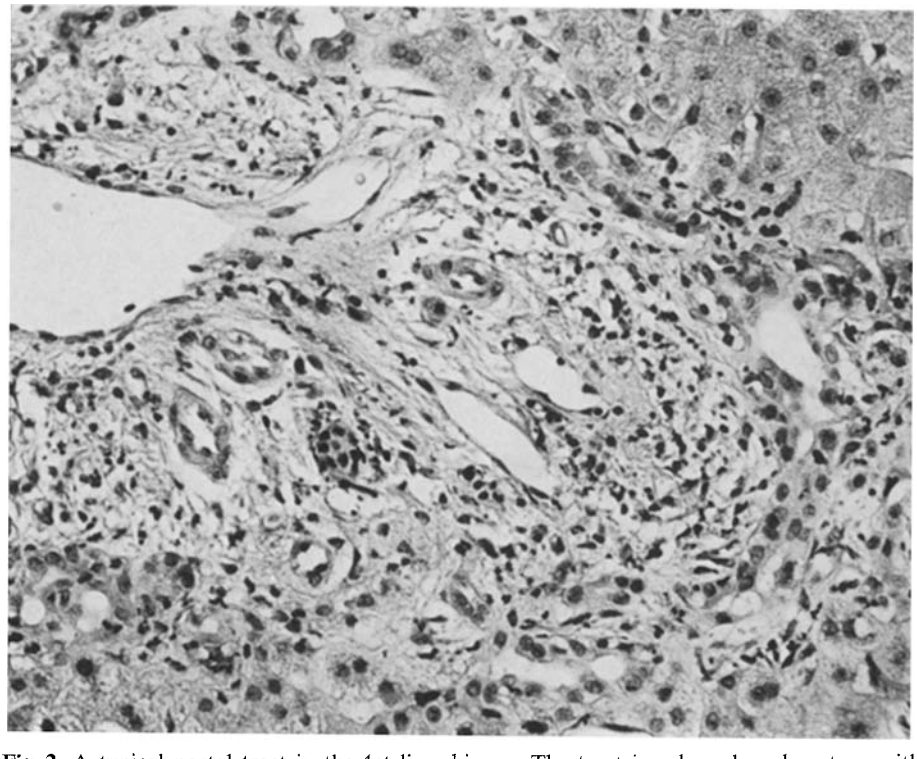


Fig. 2. A typical portal tract in the 1st liver biopsy. The tract is enlarged, oedematous with severe marginal bile duct proliferation and dilatation with many neutrophils. The original bile duct in the centre appears shrunken with pyknotic nuclei

Pathological findings

First liver biopsy

The biopsy was 5 cm long. The architecture was preserved. The parenchyma showed severe centrilobular cholestasis with feathery degeneration and a few bile infarcts. There were no histological signs of hepatitis, no abscesses and no iron deposits. All portal tracts (see Fig. 2) were enlarged due to inflammation with pronounced oedema, which occurred mainly in the periphery. This was accompanied by a heavy proliferation of the marginal bile ducts, which were distended, lined with an irregular, often granulocyte infiltrated epithelium. A few had luminal bile plugs. In the central area of the portal tracts a modest, diffuse infiltrate of lymphocytes, plasma cells, histiocytes (with ceroid), and a few neutrophils and eosinophils were present. A gram stain revealed no bacteria.

Almost all the original (interlobular) small and medium sized bile ducts were abnormal. The biopsy did not include large ducts. Figure 3 shows selected step sections of a typical bile duct. The epithelial cells are of varying size and shape often with polymorphic, angular, and hyperchromatic or pyknotic nuclei. In sections a and b the duct structure is fairly normal. Subsequently, the epithelium becomes increasingly irregular (sections c–f) with protrusion of cells into the lumens (g–j). The lumen disappears and the duct shrinks (k–l). Finally, it returns to near normal (m). There are no inflammatory cells around or in the duct. This series represents a duct length of 150 μm.

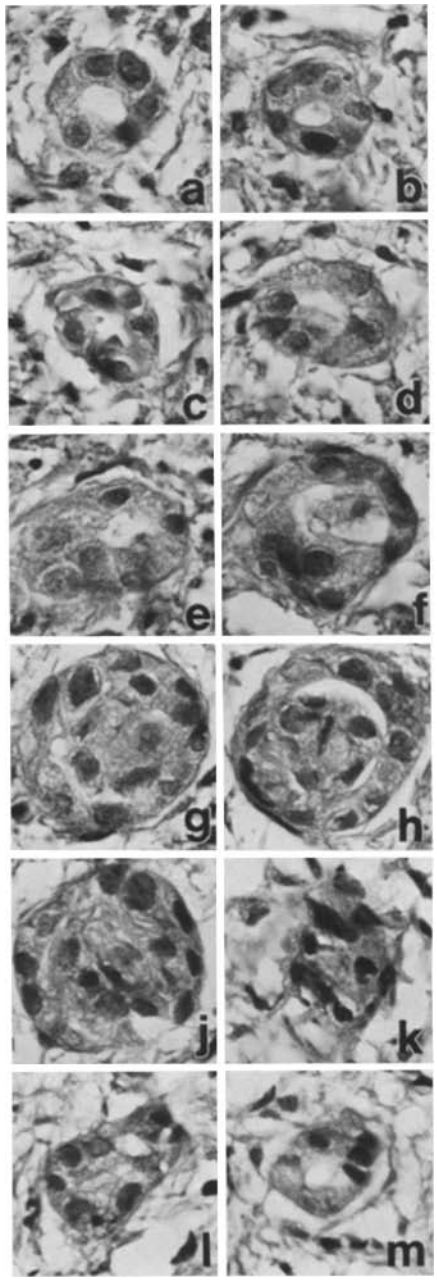
Figure 4 shows selected step sections from another bile duct. The epithelial cells reveal the same changes as described above, but in addition the cytoplasm of some cells is vacuolated. The duct lumen becomes increasingly distended (sections b–e) with a content of a few necrotic cells. The lining epithelium is flattened. Abruptly, the lumen disappears (f) and the duct structure becomes increasingly blurred (g–l), whereafter it returns to near normal (m). The duct is surrounded by a scanty inflammatory infiltrate consisting of mononuclear cells plus one or two neutrophils but there is no infiltration of the duct. This series represents a duct length of 90 μm.

Second liver biopsy

The second biopsy was 3.2 cm long with preserved architecture. There was a moderate periportal fibrosis with minimal inflammation. There were many dilated (marginal) bile ducts containing bile plugs and lined with an atrophic epithelium. The original bile ducts could be demonstrated in most portal tracts. They were all lined with a normal epithelium. In the parenchyma, many bile thrombi were seen centrilobularly.

Autopsy

The liver was slightly enlarged, smooth, reddish brown with a faint greyish green hue and slightly increased consistency. There were no focal changes.



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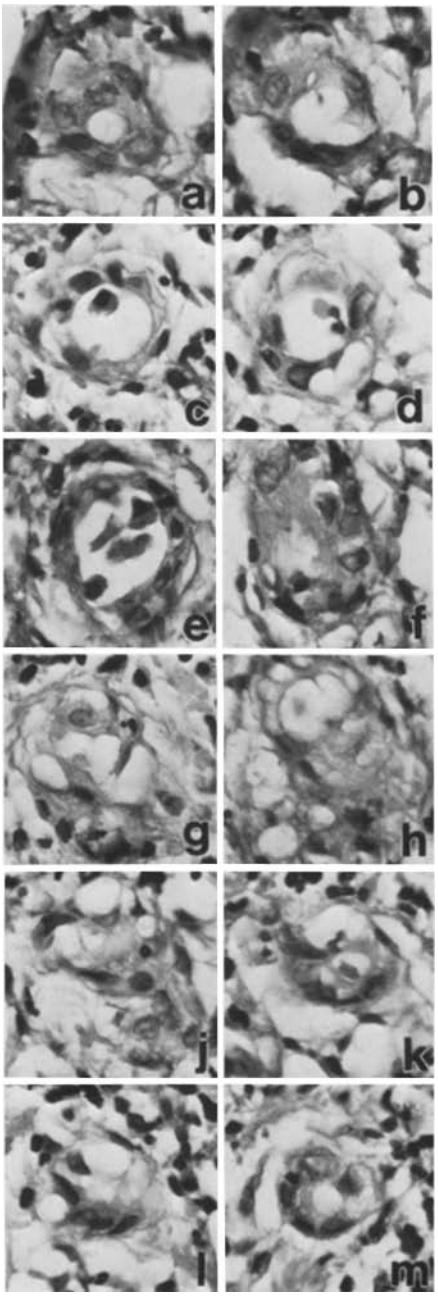

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Fig. 3a–m. Selected step sections from first liver biopsy illustrating the changes in an abnormal bile duct. For details see text. Section depth in μm: **a** 0, **b** 15, **c** 30, **d** 50, **e** 65, **f** 80, **g** 90, **h** 100, **j** 115, **k** 125, **l** 140, **m** 150

Fig. 4a–m. Selected step sections from first liver biopsy illustrating the changes in another abnormal bile duct. For details see text. Section depth in μm: **a** 0, **b** 5, **c** 15, **d** 25, **e** 45, **f** 55, **g** 60, **h** 65, **j** 70, **k** 75, **l** 80, **m** 90

Histologically, the liver showed the same changes as the second liver biopsy. Likewise, no abnormal bile ducts were found in this specimen. The larger intrahepatic and the extrahepatic bile ducts as well as the gall bladder were filled with inspissated bile but there was no dilatation. Histological examination of the common bile duct revealed no changes.

The papilla of Vater, pancreas and portal vein were normal. The heart was moderately hypertrophic. Three crisp, greyish red vegetations, 3–6 mm in diameter, occurred on the mitral valves. Histologically, there was ulceration of the valves. The vegetation consisted of fibrin with granulocytes and calcifications but no bacteria were demonstrated. The kidneys and the lower urinary tract revealed no abnormalities. Finally, the autopsy showed infarction of the parietal and occipital lobes of the right cerebral hemisphere and confluent bronchopneumonia.

Discussion

The following diseases are known to affect the intrahepatic bile duct epithelium in adults (International group 1983; Poulsen and Christoffersen 1979): acute and chronic viral hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, suppurative cholangitis, parasitic infestation, drug reactions and toxic damage, sarcoidosis, graft-versus-host disease, liver transplant rejection, and lymphoma.

The abnormal bile duct epithelium found in this case had features in common with the "hepatitis type" abnormal epithelium: vacuolization, stratification, and blurring. But in some respects it had also features of the "primary biliary cirrhosis type": crowding of cells, pyknotic nuclei, and necrotic cells in the lumen. However, the present lesion differed from the above mentioned changes in several important aspects: the lesion was much more wide-spread involving most of the original bile ducts; the duct diameter was often decreased, and the lumen was stenosed or obliterated due to either epithelial protrusion or duct shrinkage. There were only scanty inflammatory infiltrates around the ducts, and granulomas or inflammatory infiltration of the epithelium were never present.

Chlorothiazide, which was the only drug the patient had received before the admission, is an exceptionally rare cause of cholestasis (Huseby 1964). Affection of the intrahepatic bile ducts has not been described. Though chlorothiazide as a cause of the bile duct lesion can not be totally excluded, we find this unlikely, as the patient took the drug for years without side effects, and the liver disease developed rapidly in close conjunction with septicaemia.

Unfortunately, examinations for autoimmune diseases, such as primary biliary cirrhosis, were not performed but neither the clinical course nor the histological findings suggest an immunological disorder.

Jaundice complicating bacterial infections has often been reported in infants and occasionally in adults. A survey by Zimmerman et al. (1979) showed that gramnegative bacteria and especially *E. coli* were most often involved. *K. pneumoniae* had only been found in a single case. The most frequent site of gram-negative bacillary infection was the urinary tract.

Many of the cases were complicated by septicaemia. In most instances the serum bilirubin and alkaline phosphatase were only moderately elevated. However, there have been a few reports of a marked elevation of the alkaline phosphatase (Chu et al. 1980; Fang et al. 1980). The histological changes have usually been sparse and non-specific with focal necroses and cholestasis in the parenchyma and slight portal tract inflammation (Zimmerman et al. 1979).

Lefkowitch (1982) has published three cases of bile ductular cholestasis ("cholangiolitis lenta") related to sepsis in the course of gram-negative infections. The histological changes of the portal tracts were comparable to those described in this paper, but the interlobular ducts were specified as normal.

Ishak and Rogers (1981) described eight cases of severe acute cholangitis in young patients with signs of infections outside the liver and biliary tract; six patients presented clinically as the toxic shock syndrome. Histologically these cases showed acute suppurtative cholangitis, which was not present in our case.

The pathogenesis of cholestasis in septicaemia is only partly understood. Utili et al. (1977) have shown experimentally that *E. coli* inhibits the excretion of the bile salt independent fraction of the bile. The altered composition may impair the bile flow resulting in cholestasis. Furthermore, many bacteria, and especially *E. coli*, produce β-glucuronidase which in the bile acts through dissolution of the bilirubin glucuronide conjugate (Maki 1966; Matsushiro 1965). The free bilirubin subsequently combines with calcium and precipitates. These mechanisms are thought to be part of the pathogenesis of recurrent pyogenic cholangitis which usually presents with intrahepatic pigment stones and bile sludge (Chou and Chan 1960; Ong 1962). Finally, dehydration complicating an infection may possibly promote inspissation through reabsorption of water from the ductal bile.

The pathogenesis of abnormal bile duct epithelium in viral and other diseases is unknown. In septicaemia it may possibly be considered as an analogue to the degenerative liver cell changes in experimental endotoxic shock (Nordstoga and Aasen 1979). We propose that endotoxaemia due to the urinary tract infection with *E. coli* is the major cause of the lesions described, possibly in association with *K. pneumoniae*. The second increase in alkaline phosphatase one month after the admission is unexplained but may be ascribed to the bile duct lesion.

The fact that the interlobular bile ducts were normal in the second biopsy, performed when the liver affection was biochemically regressing, suggests that the bile duct lesions are reversible.

In conclusion we found a unique liver lesion presenting biochemically as obstructive cholestasis but without impairment of the larger bile ducts. The conspicuous plugging of the proliferating marginal bile ducts (which is rarely seen in large duct obstruction) may be related to the old entity "cholangiolitis lenta" (Lefkowitch 1982), seen in cases of septicaemia. The abnormal epithelium of the interlobular bile ducts accompanying septicaemia seems to be a new entity.

The cholestasis may be caused by one or probably more of the following

factors: 1) altered bile composition due to endotoxic damage of the secretory mechanisms, 2) inspissated bile due to the *E. coli* infection, and 3) mechanical obstruction due to obliteration of the abnormal interlobular bile ducts.

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