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Morphological Changes Around the Portal Complex and Hepatic Vein During Experimental Cholangitis

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ABSTRACT

Background: Cholangitis, or acute inflammation of the bile ducts, is associated with infection in the bile ducts during severe obstruction. Cholangitis is considered a clinical condition that requires urgent treatment. Despite a wide range of surgical methods, the search for the most effective method to treat cholangitis efficiently continues today. Against this background, studies on the portal triad structures are undoubtedly relevant.

Objectives: This study aims to study the morphological changes of the biliary vascular structures of the portal triad and the hepatic veins during experimental cholangitis.

Methods: Twenty-five rat models were used for experimental cholangitis. Morphological changes of the portal triad structures and hepatic veins were studied by histological (hematoxylin and eosin staining), immunohistochemical (Pan Cytokeratin AE1/AE3 staining), and histochemical (Masson's Trichrome staining) methods.

Results: There are infiltration areas around the portal triad; the bile ducts are dilated, infiltrative changes are observed on the atrophied walls, and sharp sinusoidal dilatation, edema, and hemorrhage are revealed. Microthrombi and inflammatory processes with lymphocytes and neutrophils are detected in the central vein. Bacterial colonies are present in the bile ducts.

Conclusions: During cholangitis, pathological processes in the liver develop very quickly. The bile is infected; due to many bacteria and a high concentration of endotoxins, inflammatory reactions develop in the sinusoids. Severe venous outflow impairment takes place.

Keywords: Bile duct; cholangitis; hepatic vein; portal complex; portal triad.

BACKGROUND

The development of infection in the liver during biliary obstruction has a high morbidity and mortality rate, which has become the subject of research by many scientists.[1-5]

Studies have confirmed that due to developed cholestasis and infection in the liver, the patients suffering from cholangitis have a more severe course of the disease than those infected by the same bacteria in other locations.[6-10]

There are different ways for bacteria to enter the liver from the gastrointestinal tract. Such a penetration zone may be the portal vein or the lymphatic system. Obstruction of the bile ducts contributes to the development of cholangitis, and ultimately, the entire liver is involved in the inflammatory process.[2,6,8,11,12] In the previous century, according to scientists (1959), three factors were necessary to develop cholangitis: (i) Bile flow interruption; (ii) Bile colonization by bacteria or fungi; (iii) Increased internal pressure in the bile ducts. The presence of bacteria during cholangitis is a result of increased pressure in the bile duct, which contributes to the outflow of bacteria into the bloodstream and lymphatic system.[13]

Although during acute cholangitis, antibiotic therapy can improve the patient's clinical condition in 80% of the patients, sepsis develops in 20% of the patients, and urgent biliary decompression is required.[14,15]

Studies have not firmly established the duration of antibiotic therapy for treating cholangitis. However, general guidelines consider continuing antibiotic therapy until the complete removal of biliary obstruction and improvement or normalization of biochemical tests for liver function.[16,17]

The authors' group modeled cholangitis in Wistar rats by introducing E. coli culture into the common bile duct and established the relationship between mechanical jaundice, acute cholangitis, and biliary sepsis.[18,19] The group of authors has determined that the ligation of the common bile duct and simultaneous infestation of the bile leads to malignant cholangitis on the seventh day when focal damage of the mucous membrane of the ducts begins.[20]

Since the data on the morphological changes of the structures of the portal triad and the hepatic veins in the latest searched literature are scarce, this study aimed to study the morphological changes of the biliary and vascular structures and the hepatic veins at different times from the occlusion of the bile duct during experimental cholangitis.

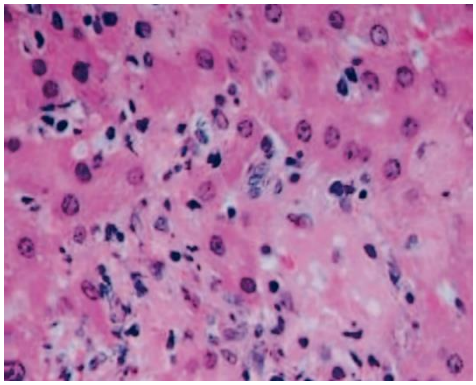
METHODS

The Cholangitis model was developed in white Wistar rats weighing 200-250g. After laparotomy, the common bile duct was ligated distally. A microbial suspension of hemolytic E. Coli strain N195 (1.105CFU) (colony-forming unit) at 1 ml/kg body weight was injected into the common bile duct just above the ligature. Rats were removed from the experiment on the 3rd, 6th, and 12th day after administration of the microbial suspension under deep ether anesthesia. Liver tissue was studied with hematoxylin and eosin staining; monoclonal antibodies AE1/AE3 were used to reveal bile duct epithelial cells; for differentiation of liver connective tissue, Masson's method was used, according to the instructions.

RESULTS

On the third day after ligation of the common bile duct, slightly enlarged bile ducts were observed during the investigation of the abdominal cavity after laparotomy. In preparations stained with hematoxylin and eosin, the bile ducts were dilated, the ductular reaction was detected, the walls of the ducts were slightly thickened, and minor infiltration changes were observed in the portal tract (Fig.1).

FIGURE 1. Experimental cholangitis on the 3th day after surgery. H&E stain, 10X40

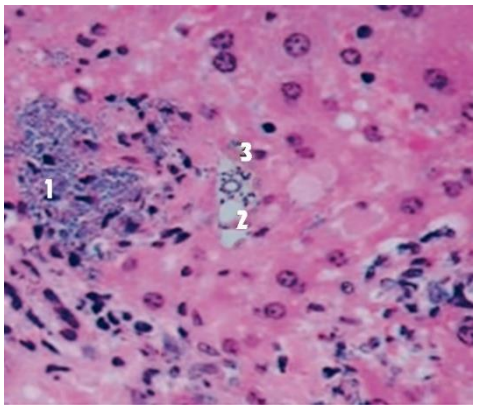


Explanations: Inflamation changes and bacterial colonization in rat's liver.

On the sixth day after the ligation of the common bile duct, a post-laparotomy investigation showed a greatly distended bile duct proximal to the ligated duct; the liver was hardened and hemorrhagic; bacterial colonies were expressed in the portal triad and periportal zone at the microscopic level; sinusoidal dilatation, erythrocyte swelling, and necrosis were observed (Fig.2).

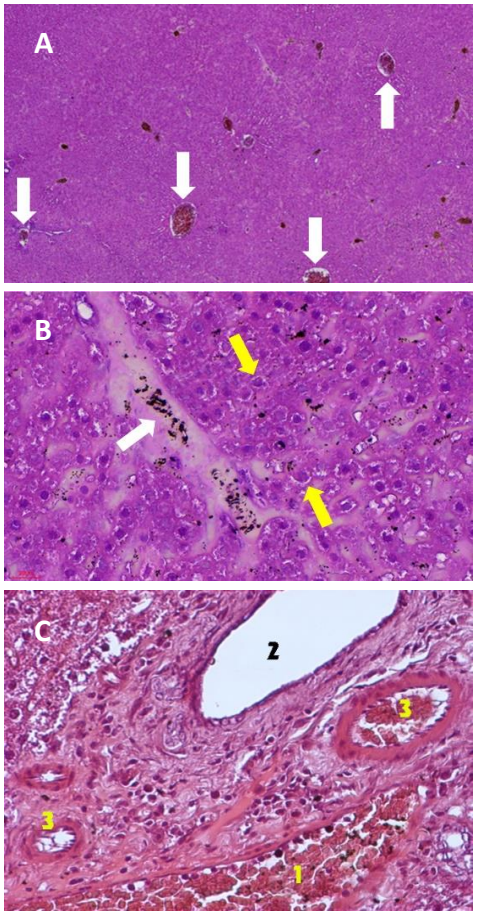
On the 12th day, there are infiltrated areas around the portal complex; bile ducts are dilated, infiltration in the atrophied walls, significant sinusoidal dilatation, edema and hemorrhage, spread of inflammatory infiltrate from the portal tract inside, and sinusoidal bacterial growth in the liver was observed. Central vein microthrombi and inflammatory process with lymphocytes and neutrophils were expressed. There were severe impairments of venous outflow, which was doubled because of the infection, bile stasis, and ischemic damage (Fig.3)

FIGURE 2. Experimental cholangitis on the 6th day. H&E stain, 10X30 Zeiss AxionKop$_2$



Explanations: 1. Bacterial colonization in portal triad, which spread in periportal area; 2. A new formed bile duct; 3. Central vein, with a new formed bile duct with bacterial colonization.

FIGURE 3. Experimental cholangitis on the 12th day after surgery. Rat liver. H&E, 10X5.



Explanations: A. B Thrombosis of the portal tract and hepatic veins marked with an arrows; B. The subsegmental vein with bacterial colonies (white arrow). The perinuclear edema and coagulation of plasma in the vein and adjacent sinusoidal part (yellow arrows). C. Portal vein (1), periductular fibrosis (2), and arteries (3).

DISCUSSION

Experimental studies have established that biliary obstruction combined with bacterial liver infection results in

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morbidity and mortality, confirmed by the experiments; biliary obstruction itself hurts the clearance of liver infection, even if the bacteria is introduced into the liver by a non-biliary route.[21-25] On the third day after ligation of the common bile duct, the bile ducts were dilated, the ductular reaction was expressed, the duct walls were slightly thickened, and infiltrative changes were observed in the portal tract.

On day 6, after common bile duct ligation, the liver was indurated and hemorrhagic. At the microscopic level, inflammatory changes were observed in the portal complex and the periportal zone and bacterial colonies were expressed; sinusoidal dilatation, swelling of sinusoidal dilatation, erythrocytic edema, and necrosis were observed.

Infiltration areas around the portal complex appeared on the 12th day of common bile duct ligation. Inflammatory infiltrate spread from the portal tract inward due to the destruction of hepatocytes in the lobule; micro thrombi of the central vein were also expressed. A severe congestive impairment of venous outflow aggravated by infection, bile stasis, and ischemic damage was present. Cholangitis at this stage, during the mentioned period, showed parameters consistent with a 95% lethal outcome.

An essential factor in the pathogenesis of cholangitis was increased pressure in the ducts. Cholangiovenous shunt developed along with the increased pressure. Bacteria entered the sinusoids of the liver from the bile ducts via the space of Disse.

CONCLUSIONS

Pathological processes in the liver during cholangitis develop very quickly. The bile is completely infected. Due to the large number of bacteria, an inflammatory reaction develops in the sinusoids. Microthrombi appear in the central vein. There is a severe congestive impairment of venous outflow. The presence of bacteria in the duct's lumen prevents bile duct proliferation. Finally, epithelic cells in the lumen of the ducts start shedding, and necrosis develops.

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