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CLINICAL AND MORPHOLOGICAL INTERRELATIONS OF EXTRAHEPATIC BILE DUCTS IN COMPLICATED CHOLELITHIASIS

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Relevance. Gallstone disease (GSD) has remained one of the most common causes of surgical hospitalizations in recent decades. Its prevalence in industrialized countries reaches 15-20% of the adult population, with the incidence increasing two- to three-fold in individuals over 60 years of age. Complicated forms of GSD account for over 40% of hospitalizations for gastrointestinal diseases, and the number of biliary tract surgeries performed annually worldwide is estimated at over 2.5 million (1, 3, 5).

In clinical practice, bile duct injuries are detected in 0.3-1.4% of surgeries for gallstone disease. However, in inflammatory-infiltrative forms, Mirizzi syndrome, and recurrent or repeated interventions, this figure rises to 3-5%. Despite their low incidence, these complications account for up to 20% of postoperative mortality and up to 60% of cases of permanent disability (2, 4).

The introduction of laparoscopic technologies has radically changed approaches to the surgical treatment of gallstone disease, but has also brought new technical complications. Due to infiltration, cicatricial changes, and

Mirizzi syndrome, bile duct injuries during laparoscopic cholecystectomy occur 3-5 times more frequently than during traditional surgeries. Moreover, even minimal ischemic injury to the common bile duct (CBD) wall can lead to late stricture, requiring complex reconstructive intervention.

The aim of the study: to develop methods for determining the clinical and morphological relationships of damage to the extrahepatic bile ducts in complicated cholelithiasis.

Materials and Methods. The clinical material consisted of 127 patients with complicated forms of cholelithiasis, accompanied by lesions of the extrahepatic bile duct of varying severity, who were treated and examined at the Republican Scientific Center for Emergency Medical Care of the Ministry of Health of the Republic of Uzbekistan and at the Department of Faculty and Hospital Surgery of the Bukhara State Medical Institute named after Abu Ali Ibn Sina in the period from 2020 to 2025. All patients were divided into two chronological groups according to the conditions of the study: the control group, including 62 (48.8%) patients treated in 2020-2022 using traditional laparoscopic surgery methods, and the main group, consisting of 65 (51.2%) patients operated on in 2023-2025 using developed technologies for diagnosis, prognosis, and surgical treatment of lesions of the extrahepatic bile duct.

Results and discussion. The microscopic structure of the bile duct wall in complicated gallstone disease without signs of cholangitis was characterized by the preservation of typical architecture and layering, reflecting the physiological ordering of tissue elements. The epithelial covering consisted of a single-row columnar epithelium with clearly defined basal borders and a uniform distribution of nuclei, localized primarily in the basal one-third of the cytoplasm. The epithelial cells were moderately elongated, with round-oval nuclei containing finely dispersed chromatin and 1-2 small nucleoli. The cytoplasm was moderately oxyphilic and clearly separated from the underlying

basement membrane, indicating its morphological integrity. The duct lumen was lined with a smooth, continuous epithelial lamina, without areas of destruction, desquamation, or proliferation, confirming the absence of an active inflammatory process. The structure of the connective tissue matrix appears uniform, without signs of edema or coarse fibrous condensation zones. Individual thin-walled vessels of the microcirculatory bed (capillaries, postcapillary venules) are clearly visible; their endothelium is lined with flat cells with smooth contours; the vascular lumens are free, without signs of stasis or thrombus formation. The perivascular space is clear, delimited by ordered connective tissue fibers, indicating preserved trophic support of the epithelium.

The adventitia is thickened, and the boundaries between it and the surrounding tissue are blurred due to infiltration and perivascular edema. Dilated vessels are visible within it, engorged with blood cells and accumulations of formed elements. Their walls are uneven, with local signs of endothelial destruction. Zones of loose infiltrate are observed around the vessels, containing lymphocytes, isolated eosinophils, and macrophages.

Against the background of intense staining, areas where α-SMA-positive fibers are interrupted by zones of lysis and destruction, corresponding to foci of destruction of the basement membrane and interstitial matrix, are clearly visible. In these areas, foci of cellular debris and small clusters of inflammatory elements persist. In places, dilated lymphatic clefts are visible, delimited by thin α-SMA-positive walls, reflecting tissue drainage remodeling.

Overall, the morphological pattern of intense α-SMA expression reflects a state of active inflammatory remodeling, with predominant processes of fibroplastic activation and remodeling of vascular-stromal structures. The presence of multiple α-SMA-positive myofibroblasts throughout the wall thickness, thickening of the periductal zone, and foci of basement membrane destruction demonstrate the morphological basis for the formation of fibrotic

changes. This α-SMA expression is considered a morphological marker of an active myofibroblastic reaction and an early stage of fibrosis in cholangitis caused by complicated gallstone disease.

An immunohistochemical study of the periductal vasculature of the CBD wall in patients with cholangitis complicating cholelithiasis reveals pronounced signs of endothelial disorganization and microcirculatory disturbances. Normally, CD31 expression uniformly outlines the contours of capillaries and small vessels, forming a continuous network of brown-stained endothelial sheets. However, in this specimen, a sharp decrease in CD31 staining intensity is observed, accompanied by areas of focal disappearance of the endothelial layer. The endothelium is partially fragmented, and in places, it completely loses its continuity, manifested by intermittent or dotted staining lines along the vessel walls. This mosaic pattern indicates damage to endothelial cells and disruption of their intercellular contacts under the influence of inflammatory and toxic factors and biliary hypertension.

The perivascular spaces are dilated and contain an amorphous, weakly eosinophilic exudate, with signs of serous edema visible between the connective tissue fibers. In these areas, the CD31 reaction is virtually absent, indicating the loss of vascular structures due to inflammatory damage. At the periphery of the infiltrates, isolated residual vascular fragments with preserved staining are observed, surrounded by accumulations of lymphocytes and macrophages, reflecting compensatory processes of angiogenesis and restoration of the microvascular bed.

Along with endothelial destruction, a compensatory response is observed in the form of localized areas of vascular neoplasm, confirmed by the appearance of small, irregularly shaped CD31-positive loops. These areas of angiogenesis are predominantly found at the periphery of inflammatory foci and are characterized by uneven thickness of the endothelial layers. In these

areas, capillaries have a tortuous course, their lumens are narrowed or collapsed, and endothelial cells are swollen and randomly distributed. Although these structures are less intensely stained, their presence reflects an attempt to restore microcirculation in the face of chronic inflammation.

In summary, decreased CD31 staining intensity, discontinuous vessel contours, widened intercapillary spaces, and signs of perivascular edema represent morphological manifestations of endothelial dysfunction and microcirculatory impairment in cholangitis. Focal endothelial destruction, reduction of the capillary network, and fibroblast activation reflect the transition of the inflammatory process from the stage of active exudative damage to the tissue remodeling phase. This combination of features is a morphological marker of chronic ischemic damage to the periductal stroma and serves as the basis for the subsequent development of fibrosis, which is detected by Masson staining and confirmed in subsequent preparations.

The histological image presented in the preparation demonstrates pronounced structural changes in the connective tissue framework of the gallbladder wall in cholangitis, which complicates the course of gallstone disease. Masson staining clearly reveals intense deposition of collagen fibers, stained in various shades of blue. Collagen types I and III are detected predominantly in the submucosal and periductal layers, where they form coarse, dense fields with uneven staining density and significant disorganization of spatial orientation. The architecture of the tissue is lost, the fibers lose their order and form areas with radially diverging and intersecting bundles, which gives the structure a chaotic, scarred appearance.

Comprehensive immunohistochemical analysis confirmed that the progression of the inflammatory-obstructive process in complicated gallstone disease is accompanied by systemic remodeling of the cellular and extracellular structures of the bile duct wall. Increased α-SMA expression reflects

myofibroblast activation and the development of a fibroplastic reaction, decreased CD31 staining indicates endothelial destruction and microvascular reduction, and Masson staining demonstrates a consistent increase in collagen fiber density and maturity with the formation of coarse fibrous fields. Taken together, these features indicate a gradual transformation of the duct wall from moderate adaptive changes to chronic fibrotic remodeling. The data obtained allowed us to identify morphological phenotypes that differ in the severity of myofibroblast activation, vascular-stromal abnormalities, and the degree of collagen formation, which served as the basis for analyzing their correlation with clinical and intraoperative parameters.

CONCLUSIONS:

1. The morphological and immunohistochemical study not only established patterns of tissue remodeling in the extrahepatic bile duct wall in complicated cholelithiasis but also, for the first time, comprehensively linked microstructural changes with clinical and surgical manifestations. The data obtained convincingly demonstrated that the combination of endothelial dysfunction, myofibroblast activation, and collagen remodeling forms a stable morphogenetic continuum that determines the transition from compensated forms of the disease to inflammatory-fibrous ones.

2. The obtained results form a solid foundation for the next stage of research, namely, the development of a prognostic scale for morphological verification, designed to determine the risk of complications and justify the choice of surgical approach. The identified patterns also necessitate the development of new surgical techniques tailored to the morphological phenotype of the lesion and the construction of a comprehensive surgical treatment algorithm that would include objective tissue criteria, immunohistochemical indicators, and intraoperative parameters.

3. The morphological and immunohistochemical characteristics of the gallbladder wall are key to predicting outcomes and developing personalized surgical solutions.

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