

Features of Extrahepatic Bile Ducts in Complicated Cholelithiasis

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Abstract Gallstone disease (GSD) is a major cause of surgical morbidity, and its complicated forms involving the extrahepatic bile ducts remain a serious clinical problem. These lesions are associated with a high risk of cholangitis, biliary strictures, liver dysfunction, and septic complications, while timely diagnosis and adequate surgical management remain challenging. Aim. To evaluate the clinical and morphological features of extrahepatic bile duct lesions in complicated cholelithiasis. Methods. A total of 127 patients with complicated gallstone disease treated between 2020 and 2025 were analyzed. Clinical, instrumental, morphological, and immunohistochemical assessments were performed, including α -SMA, CD31, and Masson staining. Results. In patients without cholangitis, the bile duct wall preserved its normal structure. In contrast, cholangitis was associated with marked inflammatory-destructive changes, activation of myofibroblasts (α -SMA overexpression), endothelial dysfunction (reduced CD31), and progressive collagen deposition, indicating fibrotic remodeling of the duct wall. Conclusion. Extrahepatic bile duct lesions in complicated gallstone disease are characterized by a consistent transition from inflammatory injury to chronic fibrotic remodeling. Morphological and immunohistochemical markers provide an objective basis for prognostic assessment and for optimizing surgical tactics.

Keywords Gallstone disease, Extrahepatic duct lesions, Complications, Morphology

1. Introduction

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].

A special place among complications is occupied by lesions of the extrahepatic bile ducts (EHD), which include inflammatory and destructive changes, strictures, and iatrogenic injuries. These lesions represent one of the most challenging problems in modern biliary surgery, as they are accompanied by a high risk of biliary hypertension, cholangitis, liver failure, and septic complications.

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 [2,4,6].

The clinical severity of this pathology is determined by a combination of two factors: the difficulty of timely diagnosis and the high probability of fatal consequences with delayed correction. In the early stages, damage or cicatricial-inflammatory stenosis of the duct may manifest only as prolonged cholestatic jaundice or symptoms of chronic cholangitis. According to P. Vincenzi et al., as well as J.G.A. In 40% of cases, diagnosis is made only 2-4 weeks after surgery, when biliary fistulas or purulent-inflammatory complications develop. The lack of visual control during laparoscopic procedures, the variability of duct anatomy, and the deformation of landmarks in the area of the triangle of Callot contribute to misdiagnosis and injury to the main bile ducts [7,9].

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 [8,10].

Thus, despite significant advances in laparoscopic and reconstructive surgery, biliary tract lesions associated with complicated gallstone disease remain one of the most

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challenging categories of hepatobiliary pathology. High variability in anatomy, the frequency of diagnostic errors preoperatively and intraoperatively, and the lack of a unified algorithm for tactical decisions lead to persistent biliary complications and the development of secondary strictures. Insufficient standardization of reconstructive interventions and the limited reproducibility of existing techniques result in a significant number of unsatisfactory results. All of this necessitates the development of a pathogenetically and technologically sound surgical treatment system integrating modern imaging techniques, lesion severity prediction, minimally invasive procedures, and reconstructive technologies aimed at restoring biliary tract patency and preventing recurrent complications.

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.

2. 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.

The inclusion criteria for patients in the study were: age over 18 years; The presence of a complicated form of cholelithiasis (acute or chronic cholecystitis, choledocholithiasis, cholangitis, cicatricial and inflammatory changes in the wall of the extrahepatic bile duct); the presence of signs of damage to the extrahepatic bile duct (dilation, narrowing, strictures, deformation or signs of biliary hypertension) confirmed by instrumental methods (ultrasound, MRCP, ERCP); the presence of indications for surgical treatment with the possibility of performing laparoscopic intervention; the absence of signs of mechanical jaundice of tumor origin or other diseases requiring an oncological approach; stable general condition of the patient, allowing surgery to be performed under general anesthesia; obtaining written informed consent to participate in the study, the use of clinical and laboratory data and morphological analysis of the biological material.

The exclusion criteria from the study were: the presence of mechanical jaundice of tumor genesis (pancreatic head cancer, cholangiocarcinoma, metastatic lesions of the hepatoduodenal zone); post-traumatic and postoperative

strictures of the bile duct formed after reconstructive interventions; severe somatic diseases that limit the possibility of performing anesthesia or laparoscopic surgery (decompensated forms of cardiovascular, respiratory or renal failure); acute inflammatory processes of other localizations requiring urgent treatment and creating a risk of generalized infection; identified systemic diseases of connective tissue and autoimmune cholangiopathy that can distort the morphological and clinical picture; the presence of pregnancy, severe coagulopathy or bleeding of unknown genesis; patient refusal to participate in the study or the inability to obtain informed consent. An analysis of the complication profile in patients included in the study revealed that in all cases, complicated gallstone disease developed against a background of calculous cholecystitis involving the bile duct to varying degrees. Choledocholithiasis remained the most common complication, diagnosed in 72 patients (56.7%), of whom almost half (43.3%) had clinical signs of acute or recurrent cholangitis. This ratio reflects a typical clinical picture, in which the prolonged presence of stones in the bile duct is accompanied by biliary hypertension and bacterial contamination, leading to the development of inflammatory and destructive changes. Moreover, the incidence of acute cholangitis in both groups was comparable, ruling out the influence of infectious factors on subsequent evaluation of treatment outcomes.

Mirizzi syndrome, diagnosed in a total of 25 patients (19.6%), occupied a prominent place in the complication profile. The distribution by type revealed a consistent relationship between the severity of local changes and the chronological period of treatment. While types I and II, characterized by extraductal compression by a cystic calculus or partial erosion of the CBD wall, were predominant in the control group, types III and IV, characterized by the formation of fistulas and cicatricial inflammatory infiltrates in the area of the CBD, were more common in the study group. This pattern suggests that more complex morphological forms of the disease have been included in the study in recent years, increasing the objectivity of subsequent evaluations of the effectiveness of the proposed surgical techniques.

Cicatricial-inflammatory strictures of the CBD were diagnosed in 17 patients (13.4%), and in some cases they were associated with residual stones or post-inflammatory dilation. Such combined forms occurred in 15 patients (11.8%) and were more common in the study group, highlighting the multifocal nature of the lesion and the complexity of intraoperative orientation during laparoscopic intervention.

The study of morphological and immunohistochemical changes in the CBD wall in patients with complicated cholelithiasis is key to understanding the pathogenesis of inflammatory-obstructive processes and developing surgical approaches that minimize the risk of strictures and reconstruction failure. While the previous chapter focused on the clinical, laboratory, and intraoperative features of the disease, as well as the outcomes of surgical treatments, this

section aims to identify tissue patterns underlying structural and functional abnormalities of the CBD wall. Morphological examination allows for an objective assessment of the integrity of the epithelium, submucosa, and periductal zones, the severity of inflammatory infiltration, and the nature of connective tissue remodeling. This can be particularly important in complicated gallstone disease, where prolonged biliary hypertension and bacterial contamination lead to the development of cholangitis, the formation of periductal fibrous areas, and decreased duct wall elasticity. In such circumstances, histological assessment becomes the most reliable method for determining the boundary between reversible and irreversible changes, which has direct practical implications for the selection of intervention and drainage tactics.

A comprehensive morpho-immunohistochemical study makes it possible to trace the evolution of the pathological process, specifically from structures that retain an ordered architecture in compensated forms of cholelithiasis to pronounced inflammatory-destructive and fibrosing changes in cholangitis. This comparison allows us to consider the tissue remodeling of the gallbladder not as an isolated phenomenon, but as a consistent morphogenetic chain reflecting the transition of compensatory mechanisms to a stage of chronic remodeling.

3. 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 subepithelial layer is composed of loose fibrous connective tissue, predominantly collagen and fine elastic fibers, oriented primarily parallel to the longitudinal axis of the duct. Between the fibers are isolated spindle-shaped fibroblasts with narrow basophilic nuclei, the cytoplasm of which is weakly stained and barely distinguishable against the interstitial matrix. 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 microscopic structure of the duct wall in patients with cholangitis associated with complicated cholelithiasis demonstrates pronounced signs of inflammatory-destructive and compensatory-proliferative changes. Compared to the morphological picture in uncomplicated cases, this specimen shows thickening of the duct wall, disruption of the layer order, and an uneven epithelial contour. The epithelial lining loses its clear boundaries in places, with foci of proliferation and loosening observed, and in some areas, partial desquamation of cells into the lumen, creating the impression of an uneven epithelial layer. The cytoplasm of the epithelial cells is moderately eosinophilic, and the nuclei are enlarged and rounded, with a prominent nucleolus, reflecting their hyperfunctional state. Some cells show signs of cytoplasmic vacuolization and nuclear pyknosis, indicating the initial manifestations of dystrophy. The muscular layer of the ductal wall undergoes significant changes during inflammation, with smooth muscle cells partially disorganized, their bundles losing their clear orientation, and the boundaries between fibers blurred. In areas of contact with periductal infiltration, partial destruction of muscle fibers is observed, accompanied by their fragmentation and cytoplasmic granulation. Increased interstitial space and accumulation of inflammatory elements are observed between the cells, giving the muscular layer a loose, disordered appearance.

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.

The overall microscopic picture is defined as a combination of the inflammatory and reparative phases of the tissue process. Thickening of the duct wall and increased cellularity reflect the morphological equivalent of an active inflammatory response against a background of increased biliary pressure. In some areas, signs of exudation and infiltration predominate, while in others, initial manifestations of an organized and fibroplastic response are observed. Periductal edema, a pronounced vascular reaction, and the presence of fibrotic foci indicate impaired barrier function of the wall and involvement of the microcirculatory system in the pathological process. The combination of productive inflammation with epithelial degeneration and muscle discomposition creates the morphological basis for the formation of cicatricial changes and strictures characteristic of chronic cholangitis.

Thus, a morphological examination of the bile duct wall in complicated gallstone disease revealed consistent structural changes reflecting the transition from a compensated state without signs of inflammation to the stage of active cholangitis with pronounced signs of tissue disorganization. In patients without cholangitis, the ordered architecture of

the epithelium and submucosa was preserved, the stromal structure remained balanced, and the vascular pattern was clear and uniform. As cholangitis developed, wall thickening, epithelial loosening and deformation, lymphocytic-plasmacytic infiltration, periductal edema, and foci of fibroplastic activity were observed, indicating the development of chronic inflammatory remodeling. The obtained results confirmed the morphogenetic relationship between the degree of inflammatory activity and the severity of structural abnormalities, which served as a morphological basis for subsequent immunohistochemical analysis and the determination of prognostic phenotypes of cholangitis lesions.

The immunohistochemical pattern of α -SMA expression in the CBD wall in patients with cholangitis secondary to complicated cholelithiasis is characterized by a markedly increased reaction and profound morphofunctional changes in the periductal zone. Unlike control cases without cholangitis, where α -SMA-positive elements were limited to a thin periductal band, in inflammatory cases, staining extends throughout the entire submucosal and partially muscular layers. The reaction has an intense brown hue, uniformly covering the periductal tissue and creating a dense field of stained elements, indicating a significant increase in smooth muscle actin expression.

The muscularis propria of the duct loses its previous order: the boundaries between the circular bundles are blurred, the fiber orientation is disrupted, and α -SMA-positive structures penetrate into the deep sections of the adventitia, indicating involvement of the entire wall thickness in the inflammatory process and the gradual replacement of smooth muscle cells by activated myofibroblasts. This phenomenon is considered a morphological correlate of wall remodeling with the transition of the inflammatory process to the organization and scarring stage.

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.

A characteristic feature of the microscopic specimen is the uneven expression of CD31 between different areas of the visual field. Near foci of cellular infiltration, the staining intensity decreases until it completely disappears. In areas of relative tissue preservation, the staining becomes faint and diffuse, with the endothelium retaining only isolated areas of linear reaction. Some vessels exhibit lumen deformation and uneven wall thickness, due to edema and perivascular compression. The capillary network density is significantly reduced, its structure becomes loose and disordered, with disrupted mutual arrangement of arterioles and venules.

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.

Thus, we have identified the morphological basis of chronic fibrotic remodeling of the bile duct wall in cholangitis developing against the background of complicated gallstone disease. The combination of pronounced collagen formation, fiber disorganization, vascular compression, and reduction of cellular elements forms a mature type of sclerosing fibrosis, which serves as a morphological equivalent of the transition of the inflammatory process to the stage of scarring and remodeling of the bile duct wall.

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.

4. 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. A unified morphofunctional basis was identified that explains not only the morphological variability of lesions but also the clinical features of the disease course, the complexity of the surgical approach, and the structure of complications.
3. 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.
4. The morphological and immunohistochemical characteristics of the gallbladder wall are key to predicting outcomes and developing personalized surgical solutions.

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