

## **ANALYSIS OF PATHOMORPHOLOGICAL CHANGES IN CHRONIC FIBROSIS CHOLECYSTITIS**

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**Resume:** In this article, the causes that lead to cancer in many patients under the influence of gallbladder cancer, using biopsy material of chronic fibrous cholecystitis, as well as the results of immunohistochemical studies using 4 markers, namely markers Ki-67, Bcl-2, R53 and CyclinD1, their varying degrees of expression. the results of analyses determining the degree of transition are presented

**Keywords:** immunogistochemical, cholecystitis, pathomorphology, marker.

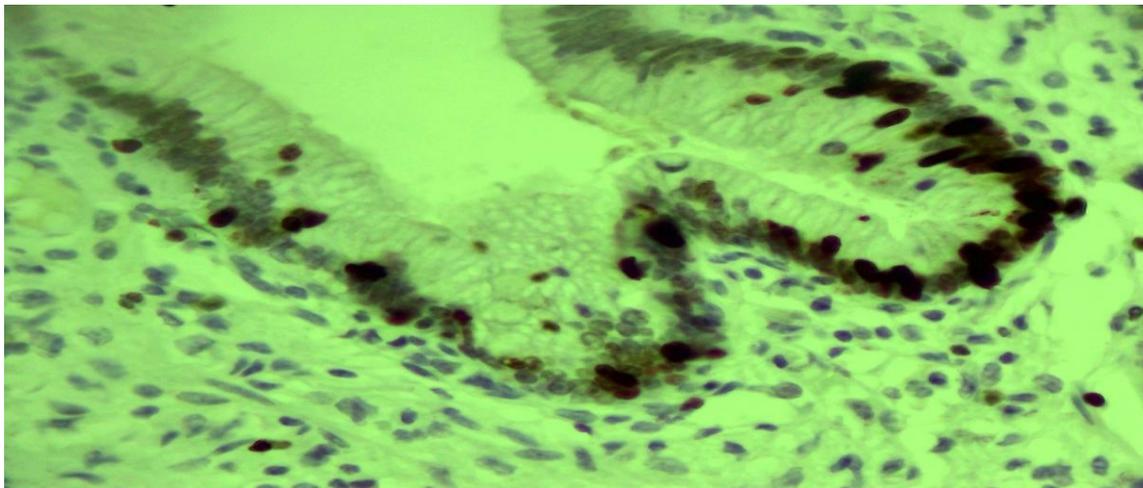
**Abstract:** Diseases of the biliary system account for more than 25% (up to 50%) of patients with pathology in the digestive system. In about 5-10% of cases, gallbladder pathology is noted in patients treated in general treatment hospitals. Chronic cholecystitis takes the main place among bile duct diseases. According to surgeons, gallstone disease occurs in 60-80% of patients with cholecystitis. In almost 100% of cases, dyskinesia occurs in the gallbladder and sphincter apparatus in patients with diseases of the gastrointestinal tract. Gallstone disease is one of the common diseases. In the United States, this disease occurs in about 15,000,000 cases. Gallstone disease is observed in 1/3 of women and 1/4 of men over 50 years of age in Europe and the United States. There is a clear correlation between the prevalence of the disease and gender. Until now, there are uncertainties about the prevalence of the disease, with 5% of the population in Ireland and 38% in Sweden suffering from gallstone disease.

However, there have been no studies aimed at studying the morphogenesis and morphological characteristics of the precancerous state of the gallbladder. For this reason, it is necessary to carry out these scientific studies.

**The purpose of the work** is to study the relationship between the expression of Ki-67, Bcl-2, r53 and CyclinD1 markers and the analyzes that determine the degree of progression of the disease to the tumor process using the biopsy material of chronic fibrosing cholecystitis.

**Materials and methods:** 1,247 chronic cholecystitis patients who were monitored in 2016-2020 at the Department of Adult Pathology and Biopsy Diagnostics of the Republican Center for Pathological Anatomy were included in the study, and 69 of them had pre-tumor dysregenerative changes and various forms of immunohistochemical examination of 4 markers, i.e. Ki-67, Bcl -2, r53 and CyclinD1 markers were investigated.

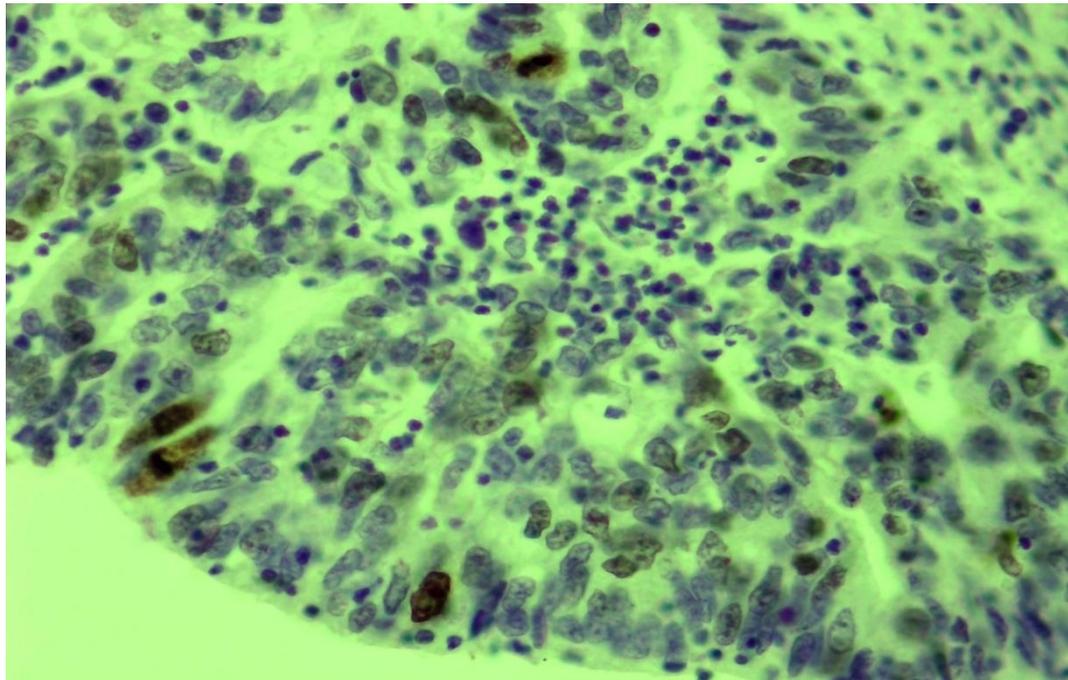
**Discussion of the obtained results:** in 26 out of 310 cases of chronic cholecystitis with adenomyomatosis and polyposis hyperplasia, 8.4% of them were found to have advanced metaplasia and dysplasia processes with disregenerative changes as a result of histological examination. The results of immunohistochemical examination also showed that in this type of chronic cholecystitis, immunohistochemical markers confirming the pro-tumor process, namely Ki-67, Bcl-2, R53 and CyclinD1, were more strongly expressed than in other groups of chronic cholecystitis. The protein Ki-67, which is located in the cell nucleus and activates its proliferation, is observed to be strongly expressed (67.5%) in almost all cells of the deep crypts of the hyperplastic mucous membranes of the papillae in the form of polyposis (Fig. 1).



**Figure 1.** Ki-67 was strongly expressed in the epithelial cells of the crypts of the mucous membrane. The material is stained by immunohistochemical method: 10x40.

This type of change confirms that the lining epithelium of the gall bladder is hyperplastic and polyps are formed. In the form of adenomatosis, it is observed that

the epithelium of hyperplastic glandular structures has become multiline type, and Ki-67 protein is expressed at a positive level in the nucleus of most of them (Fig. 2).



**Figure 2.** Ki-67 protein is positively expressed in the nucleus of glandular epithelial cells. The material was immunohistochemically stained at X: 10x40.

It is known that when strong disregenerative changes develop in the tissue, Bcl-2, an intracellular protein that blocks the process of apoptosis, begins to be strongly expressed in the cells. This apoptosis-blocking immunohistochemical marker is confirmed to be strongly expressed mainly in actively proliferating cells in the crypts of the mucosal papilla (Fig. 3). Histologically, it is observed that hyperplastic gland structures due to adenomyomatosis are of different sizes and shapes. In almost all of these glandular structures, the Bcl-2 protein is strongly expressed (56.4%) in the epithelium of emerging cells as well (Fig. 4).

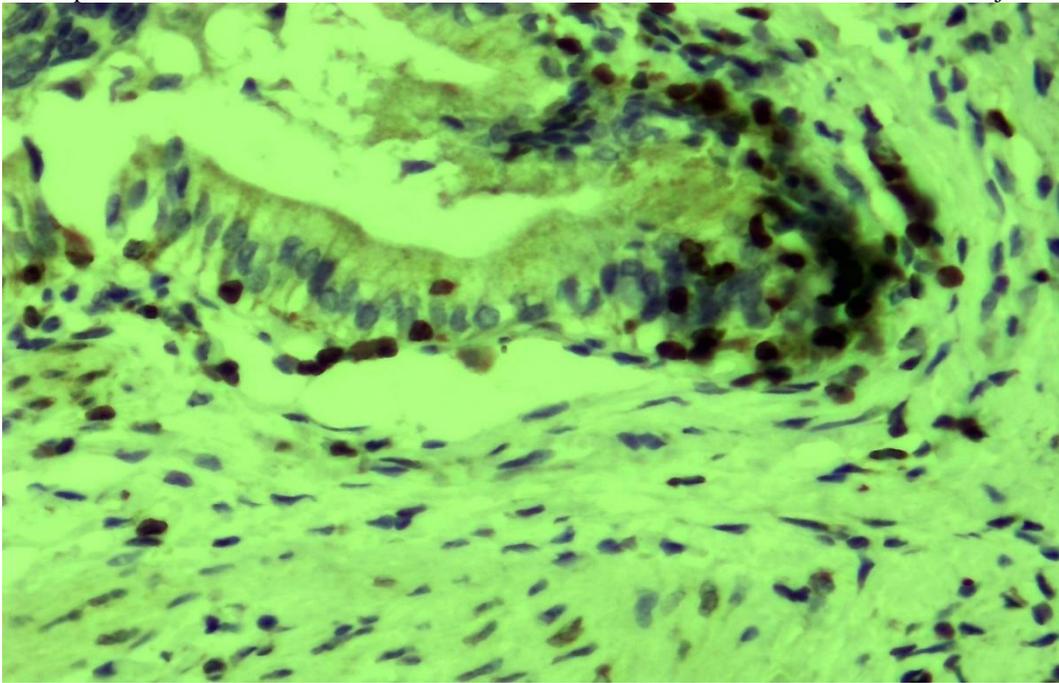


Figure 3. Bcl-2 is strongly expressed in actively proliferating cells in the crypts of the mucous membrane. The material was immunohistochemically stained at X: 10x40.

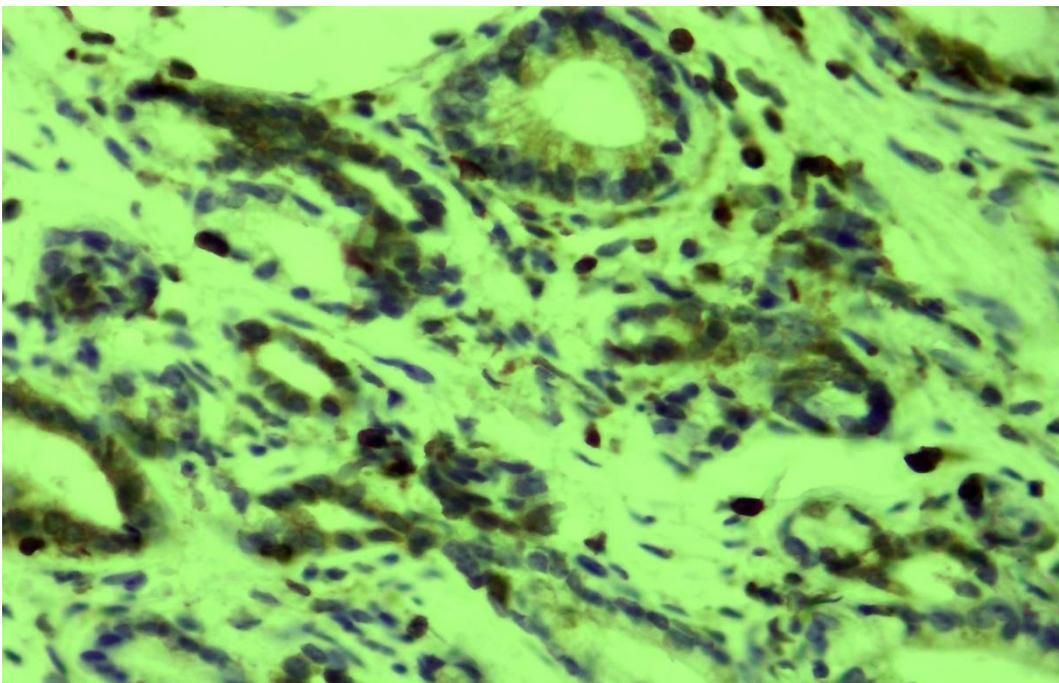


Figure 4. Bcl-2 protein is strongly expressed in almost all glandular structures, including the epithelium of nascent cells. The material was immunohistochemically stained at X: 10x40.

The R53 gene suppressor is activated in several chronic precancerous diseases. The concentration of r53 protein increases in rapidly proliferating cells.

Based on this, in chronic cholecystitis with adenomyomatosis and polyposis, since the epithelium covering the polypous tumors has a strong proliferative activity, the cells lining the deep crypts of the suckers have proliferated and turned into a multi-line epithelium, and it is observed that this gene is significantly (32.6%) expressed in their nuclei (Fig. 5). It is determined that the stroma of polypous tumors consists of dense cellular inflammatory connective tissue.

In this type of chronic cholecystitis, glandular structures with adenomyomatous hyperplasia are densely surrounded by multicellular connective tissue stroma. There is no basement membrane between the glandular structures and the stroma. Epithelium of glandular structures has in some places become multi-rowed epithelium, their cytoplasm is expanded, nuclei are located in the basal part. It is determined that the R53 gene suppressor is expressed at different levels in the nuclei of glandular epithelium. It is observed that the expression of this gene is stronger in areas that have become multi-line epithelium.

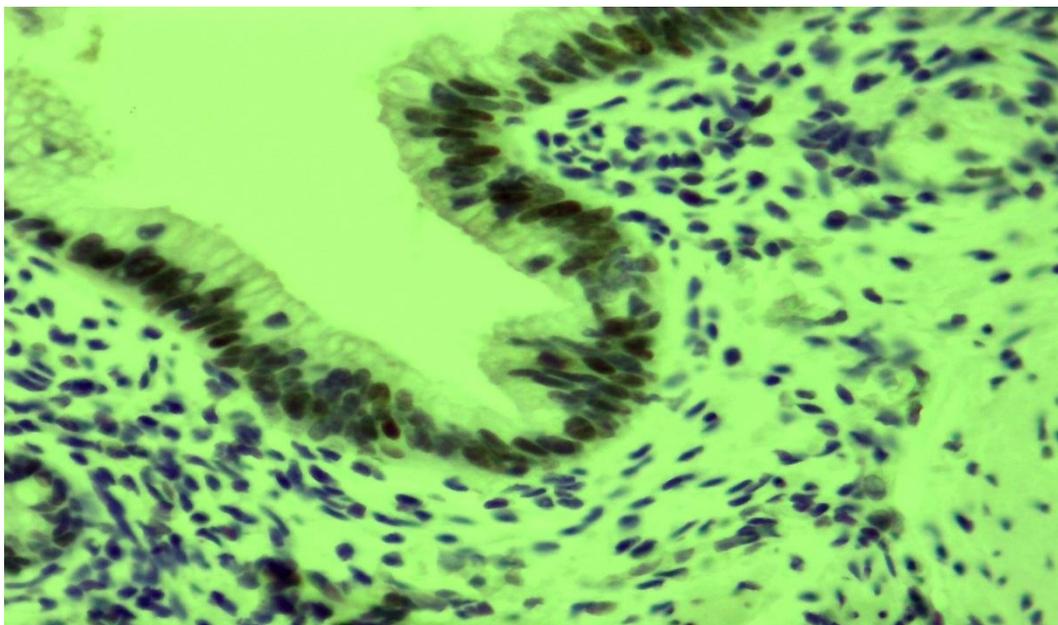


Figure 5. The R53 gene is significantly expressed in the nuclei of the lining epithelium of the teat crypts. The material was immunohistochemically stained at X: 10x40.

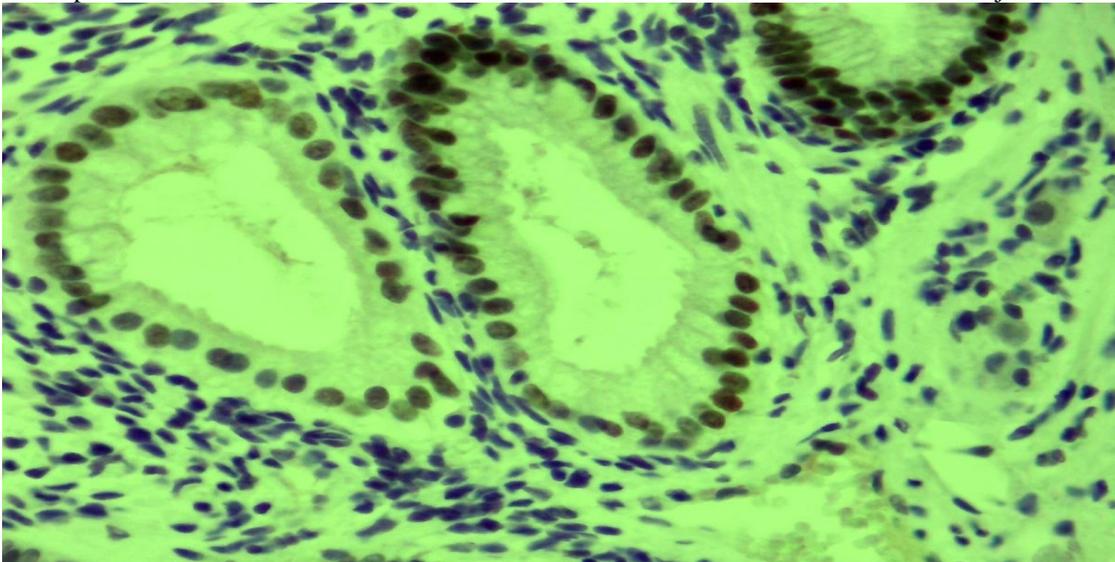


Figure 6. The R53 gene suppressor is differentially expressed in the nuclei of glandular epithelium. The material was immunohistochemically stained at X: 10x40.

Our next immunohistochemical examination will be devoted to Cyclin D1 marker, a protein belonging to the cyclin family in cells, which ensures the transition of the G1/S-phase to the next phases of the cell division cycle. Cyclin D1 protein is overexpressed when cells proliferate and become tumors. In our material, this protein is well expressed in the nuclei of epithelial cells lining the nipples and crypts of polypous structures (see Fig. 7).

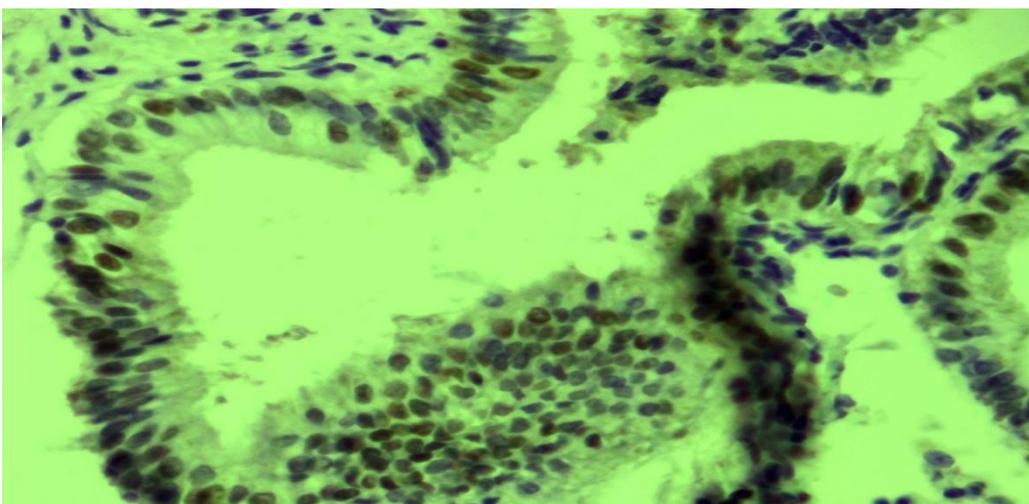


Figure 7. Polypous structures are well expressed in the nuclei of epithelial cells covering the nipples and crypts. The material was immunohistochemically stained at X: 10x40.

It is especially well defined in the areas of the epithelium of the nipples, which have become multi-line epithelium. Adenomyomatous glandular structures actually produced cells of various sizes, among which the absence of stromal structures confirms true adenomatous hyperplasia. In this case, the glandular epithelium is irregularly located, and in some areas it has metaplasia into multi-rowed epithelium. Cyclin D1 protein is expressed at different levels in the nuclei of the gland epithelium (Fig. 8).

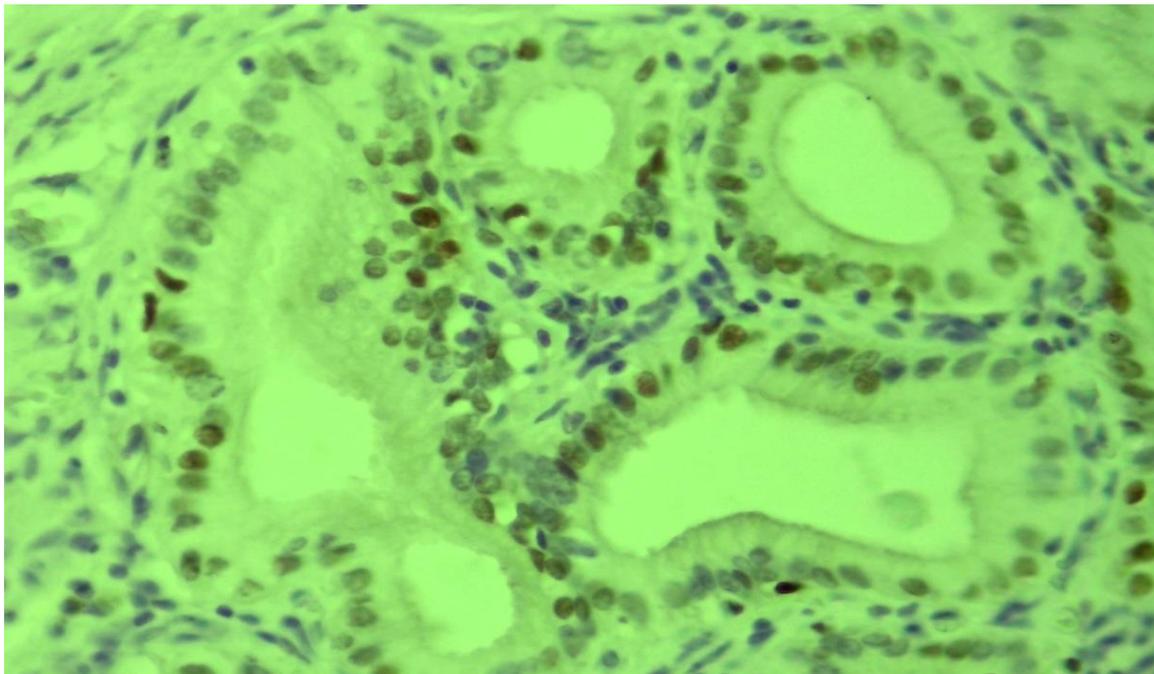


Figure 8. Cyclin D1 protein is expressed to varying degrees in the nuclei of glandular epithelium. The material was immunohistochemically stained at X: 10x40.

**Conclusion:** Cyclin D1 protein is observed to be well expressed in the nuclei of epithelial cells lining the papillae and crypts of polypous structures. It is especially well defined in the areas of the epithelium of the nipples, which have become multi-line epithelium. Adenomyomatous glandular structures actually produced cells of various sizes, among which the absence of stromal structures confirms true adenomatous hyperplasia. In this case, the glandular epithelium is irregularly located, and in some areas it has metaplasia into multi-rowed epithelium. Cyclin D1 protein is expressed at different levels in the nuclei of glandular epithelium.