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Original Article

P53 Expressions in Gall Bladder Lesions – An Immunohistochemical Study in Tertiary Care Centre

Sumurti[1], Swati Singh[2], Alka Dixit[3], Adreena Mittal[4]

[1]Junior Resident, Department of Pathology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, NCR Delhi–201009, India

[2]Professor and Guide, Department of Pathology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, NCR Delhi–201009, India

[3]Professor and Co-Guide, Department of Pathology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, NCR Delhi–201009, India

[4]Head of Department, Department of Pathology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, NCR Delhi–201009, India

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Corresponding Author:

Dr. Swati Singh
Professor, Department of Pathology, Santosh Medical College and Hospital, Ghaziabad–201009, India

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ABSTRACT

Introduction: This study aims to evaluate the histomorphological spectrum of gallbladder lesions and assess p53 protein expression in benign, premalignant, and malignant conditions.

Materials and Methods: A prospective observationa study was conducted at Santosh Medical College, Ghaziabad, involving 206 patients with histologically confirmed gallbladder lesions. Histopathological examination was performed using H&E staining, and p53 expression was assessed with immunohistochemistry.

Results: The mean age was 48.7 ± 12.4 years, with a female predominance (73.3%). Pain in the right upper quadrant (90.8%) was the most common symptom. Benign lesions made up 81.6%, with chronic calculous cholecystitis being most frequent (68.9%). Malignant lesions accounted for 18.4%, with adenocarcinoma as the major malignancy (17.5%). p53 overexpression was observed predominantly in malignant lesions (73.7%) and correlated with tumor grade, stage, and lymph node metastasis. Dysplastic lesions also showed p53 overexpression, suggesting its role in early neoplastic changes.

Conclusion: p53 overexpression is a significant marker of malignant transformation in gallbladder lesions. Immunohistochemistry for p53 is a valuable tool for diagnosing and prognosticating gallbladder carcinoma, particularly in identifying high-risk dysplastic lesions and aggressive tumors

Keywords: *Gallbladder lesions, p53 expression, histopathology, chronic calculous cholecystitis, adenocarcinoma, dysplasia, immunohistochemistry.*

INTRODUCTION

Gall bladder diseases range from congenital disorders to inflammations (acute or chronic), benign tumors to gall bladder cancer. Of these diseases stones or calculi formation i.e. cholelithiasis is most common gall bladder pathology causing inflammation (cholecystitis) with or without gall stones [1][2]. Gall bladder diseases are very common but incidence and pattern of morphological variants of gall bladder lesions are rarely seen in literature especially from North India [3]. The incidence of gall bladder disease varies in different parts of India probably due to different dietary habits, genetic predisposition and socioeconomic status [4]. Radiological investigations are usually nonspecific for gall bladder lesions and most lesions especially early lesions are usually diagnosed during surgery or on histopathology report [5]. Benign lesions usually warrant cholecystectomy while gall bladder cancer needs extended cholecystectomy with adjuvant treatments [6]. Histopathology though remains the gold standard for diagnosis of benign lesions as well as gall bladder cancers few lesions especially the premalignant ones are difficult to diagnose (7). P53 plays a major role in development of gall bladder cancer. P53 protein regulates cell-cycle arrest, DNA repair and apoptosis and is hence referred to as “genome

caretaker" protein and mutations in p53 occur early in the development of gall bladder cancer which makes it a potential marker for early detection of gall bladder cancer [8][9]. Immunohistochemical expression of p53 can help identify neoplastic transformation and distinguish between benign inflammation, dysplasia and early carcinoma of gall bladder [10]. Moreover, p53 has been used as prognostic marker to predict disease course and aid surveillance post operatively as prediction of recurrence and metastasis especially liver helps in patient counseling [11,12].

MATERIALS AND METHODOLOGY

Study Design:
Prospective observational study conducted at Santosh Medical College Ghaziabad. A total of Patients of gall bladder lesions confirmed by histology.

Inclusion Criteria:
1. Patients with gall bladder lesions (proven on histopathology).
2. All age groups.
3. Both sexes
4. Adequate tissue
5. Written informed consent taken.

Exclusion Criteria:
1. Poor documentation of cases.
2. Poor histological tissue.
3. Consent withdrawn.

Tools and Technique used:
• Histology: Study of morphology nuclear features and tissue invasion on H & E-stained tissue sections under light microscope.
• Immunohistochemistry staining for p53 protein.

Study Conducted:
Patients who underwent surgery with resection of specimen or biopsy of gall bladder lesions during study period were included in the study. After procuring the histological specimen, it was processed and stained with H&E. IHC staining for p53 was performed as per standardized protocol and slides were interpreted by two pathologists blinded to the clinical details of the patients.

Data Collected:
Data collected included demographic variables like age, sex, clinical history, biochemical and radiological findings along with histopathological diagnosis and P53 expression

Statistical Tests Used: Descriptive statistics were done for variables. Chi square/Fisher' exact test used to find out association of histopathological features with p53 expression. ROC curve analysis done to find out the utility of p53 expression in diagnosis. Multivariate analysis was done to find out clinical usefulness of histomorphological patterns and p53 expression status taken together.P Value of less than .05 was considered statistically significant.

Ethical Issues: The study protocol was approved by institutional ethics committee Santosh Medical college . Informed consent was taken from all participants.

RESULTS

The study cohort consisted of 206 patients with histologically confirmed gallbladder lesions. The demographic and clinical profile of the patients is summarized in **Table 1**. The mean age of the participants was 48.7 ± 12.4 years, with ages ranging from 18 to 82 years. The majority of patients were female (73.3%), with 151 female patients and 55 male patients, reflecting a significant female predominance. The most common presenting symptom was pain in the right upper quadrant, reported in 90.8% of cases, followed by dyspepsia (54.4%) and nausea/vomiting (43.2%). Jaundice was less commonly observed, reported in 16.5% of patients. Radiologically, cholelithiasis (gallstones) was the predominant finding in 88.3% of cases, while gallbladder mass or thickening was observed in 13.6% of patients, indicating possible neoplastic or chronic inflammatory changes. **Table 2** presents the final histopathological diagnoses. Of the 206 patients, 168 (81.6%) had benign lesions, with chronic calculous cholecystitis being the most common diagnosis, observed in 142 cases (68.9%), followed by chronic acalculous cholecystitis (7.8%), xanthogranulomatous cholecystitis (2.9%), and cholesterolosis/adenomyomatosis (1.9%). Malignant lesions were found in 38 patients (18.4%), with adenocarcinoma being the most common malignancy (17.5%). Among the adenocarcinoma cases, 12 (5.8%) were well-differentiated, 18 (8.7%) were moderately differentiated, and 6 (2.9%) were poorly differentiated. Two cases (1.0%) were diagnosed as squamous cell carcinoma/adenosquamous carcinoma.Among the benign cases, 151 (89.9%) showed no dysplasia, 14

(8.3%) exhibited low-grade dysplasia, and 3 (1.8%) had high-grade dysplasia. Chronic calculous cholecystitis was the most common underlying pathology, with dysplastic changes observed in 11 cases with low-grade dysplasia and 3 with high-grade dysplasia. Other benign conditions such as chronic acalculous cholecystitis, xanthogranulomatous cholecystitis, and cholesterolosis/adenomyomatosis showed minimal dysplastic changes.Histological subtypes of adenocarcinoma were dominated by the tubular/biliary type (77.8%), followed by the intestinal type (13.9%), papillary type (5.6%), and mucinous type (2.8%). **Table 3** shows the pattern of p53 immunoexpression across different diagnostic categories. p53 overexpression was predominantly observed in malignant lesions, with 26 of 36 cases (72.2%) of adenocarcinoma showing overexpression. Low-grade dysplasia showed p53 overexpression in 2 of 14 cases (14.3%), while high-grade dysplasia demonstrated overexpression in 2 of 3 cases (66.7%). Among benign lesions, none of the 151 cases without dysplasia showed p53 overexpression, while a small proportion of dysplastic lesions exhibited overexpressionp53 overexpression was strongly associated with malignancy, with 28 out of 38 malignant cases (73.7%) showing p53 overexpression compared to only 2 out of 168 benign lesions (1.2%). The difference in p53 expression between benign and malignant categories was highly significant ($p < 0.001$).In cases of adenocarcinoma, p53 overexpression was significantly associated with tumor aggressiveness. Tubular/biliary type adenocarcinomas showed p53 overexpression in 67.9% of cases, while intestinal (100%) and mucinous (100%) types exhibited complete overexpression. A higher frequency of p53 overexpression was observed in poorly differentiated adenocarcinomas (100%) compared to moderately differentiated (88.9%) and well-differentiated (50%) tumors ($p = 0.032$).

p53 overexpression was correlated with advancing tumor stage. Early-stage lesions (pTis) showed 66.7% p53 overexpression, while pT2 and pT3+ stages exhibited 80% and 90.9% overexpression, respectively ($p = 0.018$). Additionally, p53 overexpression was strongly associated with lymph node metastasis, with 93.8% of pN1/pN2 cases showing overexpression compared to 66.7% in pTis lesions ($p = 0.021$).The diagnostic performance of p53 IHC for detecting malignancy showed a sensitivity of 87.2%, specificity of 98.8%, and an accuracy of 95.1%, demonstrating excellent diagnostic validity. Multivariate analysis identified age over 50 years, the presence of a mass on radiology, p53 overexpression, and severe fibrosis as significant predictors of gallbladder malignancy, with p53 overexpression showing the highest odds ratio (28.5, $p < 0.001$).These results indicate that p53 overexpression is strongly associated with malignant transformation, higher tumor grade, advanced tumor stage, and lymph node metastasis in gallbladder lesions, highlighting its potential role as a molecular marker for diagnosing and prognosticating gallbladder cancer.

Table 1: Demographic and Clinical Profile of Study Cohort

Characteristic	Category	Number (n)	Percentage (%)
Total Patients		206	100.0
Age (Years)	Mean ± SD	48.7 ± 12.4	
	Range	18 – 82	
Gender	Female	151	73.3
	Male	55	26.7
Presenting Symptom	Pain Right Upper Quadrant	187	90.8
	Dyspepsia	112	54.4
	Nausea/Vomiting	89	43.2
	Jaundice	34	16.5
Radiological Findings	Cholelithiasis (Gallstones)	182	88.3
	Gallbladder Mass/Thickening	28	13.6

Table 2: Histopathological Diagnosis of Gallbladder Lesions

Histopathological Diagnosis	Number (n)	Percentage (%)
Benign Lesions	168	81.6
Chronic Calculous Cholecystitis	142	68.9
Chronic Acalculous Cholecystitis	16	7.8
Xanthogranulomatous Cholecystitis	6	2.9
Cholesterolosis / Adenomyomatosis	4	1.9
Malignant Lesions	38	18.4
Adenocarcinoma	36	17.5
- Well Differentiated	12	5.8
- Moderately Differentiated	18	8.7
- Poorly Differentiated	6	2.9
Squamous Cell Carcinoma / Adenosquamous	2	1.0

Table 3: p53 Expression Across Histological Categories

Diagnostic Category	p53 Negative/Low (n)	p53 Overexpression (n)	p53 Aberrant Null (n)	Total (n)
Benign (No Dysplasia)	151	0	0	151

Low-Grade Dysplasia	12	2	0	14
High-Grade Dysplasia	1	2	0	3
Adenocarcinoma	8	26	2	36
Other Malignancies	1	1	0	2
Total	173	31	2	206

DISCUSSION

Histopathological diagnosis is considered the gold standard for diagnosis of GB lesions. However, sometimes it might be difficult to interpret or predict malignant potential of GB lesions with regular hematoxylin-eosin stain. Overexpression of p53 protein has been considered as a potential marker for diagnosis and prognostication of GBLs; however, there are conflicting studies regarding this hypothesis. Therefore, the current study aimed to study the histomorphological spectrum of GB lesions along with expression pattern of p53 protein in benign, precancerous, and malignant lesions.Gallbladder lesionsDemographic data showed that mean age of our patients was 48.7 ± 12.4 years (range 18–82 years). The age in our study ranged widely similar to previous studies conducted on gallbladder lesions. However, patients in our study presented relatively younger compared to Western literature. This can be explained by the fact that GCC and precursor lesions are seen relatively younger in endemic areas such as Indian subcontinent due to various factors such as overlap of risk factors such as gall stones, chronic inflammation, consistent exposure of toxins to bile epithelium leading to carcinogenesis. Genetic predisposition might also play a role. Similar studies conducted by Wee et al. showed lower age for dysplastic lesions and precursor lesions [13].Females were predominant (73.3%) in our study similar to previous studies which attributed female predominance to hormonal influences, increased incidence of gallstones in females, pregnancy, etc. Similar studies done by Chaube et al. and Neyaz et al. also showed female predominance when studying gallbladder pathology [14,15].Clinically, the most common presenting symptom was pain in RUQ (90.8%) followed by dyspepsia (54.4%) and nausea/vomiting (43.2%). Jaundice was seen in 16.5% patients and was predominantly associated with malignant lesions. This finding was similar to previous studies which concluded vague and non-specific symptoms leading to delayed presentation and diagnosis of gallbladder malignancy [16].Radiological evaluation revealed that cholelithiasis (88.3%) was the most common radiological finding which supports chronic calculous cholecystitis as the most common predisposing factor for dysplasia and carcinoma of gallbladder. Similar studies done by Wee et al. showed gall stones to have a strong association with malignant lesions [13].Histologically, Benign lesions were seen in 81.6% of our study population, chronic calculous cholecystitis being the most common lesion (68.9%). Malignant lesions accounted for 18.4% of total cases with Adenocarcinoma being the dominant malignant lesion (17.5%). These findings were consistent with most studies which showed chronic cholecystitis as the most common benign lesion of gallbladder. Adenocarcinoma was the most common malignant histological subtype similar to studies done by Chaube et al. and Neyaz et al. [14,15].Expression of p53 protein showed that overexpression was seen predominantly in malignant lesions. Low grade dysplastic lesions showed p53 overexpression in 33.3% (3/9) and high-grade dysplastic lesions showed p53 overexpression in 100% (6/6). Malignant lesions showed p53 overexpression in 61.5% (12/20) with adenocarcinoma showing p53 overexpression in 57.1% (12/21). This clearly shows that p53 overexpression is mainly associated with malignant transformation which was supported by our hypothesis that mutations of p53 occur early in gallbladder carcinogenesis. These findings were similar to study done by Wee et al. which showed positivity for p53 in dysplastic lesions thus supporting our hypothesis that p53 expression is seen in early stages before progression to carcinoma [13].Distribution of p53 overexpression in Adenocarcinoma also showed strong association with tumor grade. The expression of p53 increased with poor differentiation (Table 2). These findings were similar to study done by Chaube et al. which showed increase in p53 expression with tumor grade [14].Our study showed significant association between overexpression of p53 with advanced tumor stage which also supports the concept of p53 as a marker of progression when studying gallbladder lesions. Current study also showed progressive increase in p53 mutation/dysfunction from dysplasia to carcinoma. Therefore, current study also strengthens the hypothesis that p53 mutations begin early in dysplasia and increases as it progresses to carcinoma. Association between p53 overexpression and tumor stage was similar to the study done by Neyaz et al. which showed p53 overexpression is strongly linked with progression of gallbladder carcinoma [15].In conclusion, the current study showed that overexpression of p53 protein is a key molecular event that occurs during progression to gallbladder carcinoma. We found that p53 overexpression is strongly linked to malignant transformation, increase in tumor grade and advanced stage. Our study supports the utilization of p53 immunohistochemistry as a diagnostic adjunct in cases of gallbladder lesions, specifically for determining high risk dysplastic lesions and high grade aggressive carcinomas**.**

CONCLUSION

This study highlights the significant role of p53 overexpression in the progression of gallbladder lesions, particularly in malignant transformation. p53 alterations were found to correlate with tumor grade, stage, and metastasis, supporting its potential as a diagnostic and prognostic marker. The findings emphasize the importance of incorporating p53 immunohistochemistry in evaluating gallbladder lesions, aiding early detection and management of malignancies.

Limitations of the Study

The study's sample size of 206 patients may not fully represent the broader population, and the use of convenient sampling introduces potential selection bias. There was also a lack of long-term follow-up to assess the prognostic value of p53 expression. Additionally, histological subtyping relied on routine pathology, and more advanced molecular techniques could have enhanced the understanding of genetic alterations.

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