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Original Article

Histopathological Study and Expression of Beta-Catenin in Congenital Choledochal Cyst in a Tertiary Care Pediatric Referral Center in South India

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: Choledochal cysts are congenital anomalies that occur as localized cystic or fusiform dilatations of the biliary tree. Reflux and stasis of pancreatic enzymes in the biliary duct may relate to the development of intestinal metaplasia which might be an important factor related to the carcinogenesis of choledochal cyst, thus the expression of beta-catenin in the metaplastic epithelium might be associated with malignant transformation of choledochal cyst epithelium.
Methods: This study was conducted at a tertiary care pediatric center between October 2014 and March 2017. Forty patients were evaluated for epithelial lining, mural ulceration, fibrosis, inflammation, and metaplasia.
Results: Out of 40, 12 cases (30.0%) were the infantile age group and 28 cases (70.0%) were in the classic pediatric group. Ulceration was classified as grade 0 (14 cases, 35.0%), grade 1 (17 cases, 42.5%), or grade 2 (nine cases, 22.5%). Inflammation was classified as grade 0 (2 cases, 5.0%), grade 1 (26 cases, 65.0%), or grade 2 (12 cases, 30.0%). Fibrosis was classified as grade 0 (five cases, 12.5%), grade 1 (11 cases, 27.5%), grade 2 (17 cases, 42.5%), or grade 3 (seven cases, 17.5%). Metaplasia was noted in five (12.5%) out of 40 cases. All choledochal cysts with metaplasia showed beta-catenin nuclear positivity on immunohistochemistry and were followed up.
Conclusion: This study emphasizes the importance of detailed histopathological examination and documentation of metaplastic changes. Metaplasia was associated with beta-catenin nuclear positivity. These findings suggest a potential role for beta-catenin as a marker of metaplastic changes in choledochal cysts.

Keywords: Beta-catenin; Choledochal cyst; Metaplasia; Immunohistochemistry

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INTRODUCTION

Choledochal cysts are rare congenital dilatations of the extrahepatic biliary tract first described by Vater [1] in 1723. These cysts are typically observed during infancy and childhood. Patients under the age of 10 have a risk of 0.7% for developing biliary duct cancer, and this risk increases to 14.3% for those over 20 [2,3]. Studies suggest that metaplastic changes in the cyst wall epithelium are secondary to reflux and stasis of pancreatic enzymes, which may be a predisposing factor for malignancy [4-7]. The expression of beta-catenin in the metaplastic epithelium may be associated with malignant transformation of choledochal cyst epithelium [8,9]. This study aims to examine the clinical profile and histomorphology of choledochal cysts in pediatric patients and to analyze the immunoexpression of beta-catenin in the lining epithelium of a choledochal cyst.

MATERIALS AND METHODS

Data collection

This study was conducted at the Department of Pathology of a tertiary care pediatric center in South India from October 2014 to March 2017. Forty cases were examined in this study. All cases of choledochal cysts identified clinically and radiologically were included, and clinical data was obtained from hospital records. Patients with type V choledochal cysts and children aged >12 years were excluded. All patients underwent preoperative abdominal ultrasonography. Contrast-enhanced computed tomography of the abdomen and magnetic resonance cholangiopancretography were performed whenever necessary to confirm the diagnosis and classify the cyst into subtypes. All patients underwent cyst excision via Roux-en-Y hepaticojejunostomy.

Methodology

Resected specimens were sent to the pathology department. Gross examination of the specimens was performed, and representative sections (2–3 per case) were obtained. Specimens were fixed in 10% buffered formalin and processed using an automatic tissue processor. Routine paraffin embedding was performed, and 4 microns sections were stained with hematoxylin and eosin (H&E) and the tissue sections were examined microscopically. All slides were evaluated for the following histological features: simple columnar epithelium, proliferative changes within the epithelium, mural ulceration, mural fibrosis, inflammation, and metaplasia. The cases were graded according to the system proposed by Sharma et al. [10]. They were further graded based on the epithelial lining and mural score (ELMS), as described by Turowski et al. [11]. Representative paraffin blocks were subjected to immunohistochemistry (IHC) for beta-catenin using standard Dako staining protocol. Positive and negative controls were included. Positive staining was observed in cases with metaplasia (ELMS score 3), which expressed beta-catenin nuclear positivity, while those without metaplasia showed no nuclear positivity.

RESULTS

The age of patients ranged from 45 to 12 years. Of the 40 cases studied, 12 cases (30.0%) were infantile age group (≤1 year) and 28 cases (70.0%) were classic pediatric group (1–12 years). Most of the cases were observed in the age group of 1 to 4 years (27.5%). Sixteen (40.0%)

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were male and 24 (60.0%) were female. The male:female ratio was 1:1.5. Most common clinical presentations were abdominal pain (28 patients, 70.0%), jaundice (23 patients, 57.5%), abdominal lump (12 cases, 30.0%), and vomiting (eight cases, 20.0%). The classic triad of abdominal pain, lump, and jaundice was observed in 18 patients (45.0%). In the present study, most cases belonged to type I cysts (n=26, 65.0%), followed by type II (n=8, 20.0%), type III (n=2, 5.0%), and type IV (n=4, 10.0%) (**Table 1**).

Histopathological grading of choledochal cyst

Histopathological grading of the choledochal cysts was performed in all 40 patients using the grading system proposed by Sharma et al. [10]. Choledochal cysts with ulceration were classified as grade 0 (14 patients, 35.0%), grade 1 (17 patients, 42.5%), and grade 2 (9 cases, 22.5%), as shown in **Fig. 1**. Inflammation was assessed as grade 0 (2 cases, 5.0%), grade 1 (26 cases, 65.0%), grade 2 (12 cases, 30.0%), and fibrosis as grade 0 (five cases, 12.5%), grade 1 (11 cases, 27.5%), grade 2 (17 cases, 42.5%), grade 3 (seven cases, 17.5%). Metaplasia was noted in five (12.5%) out of 40 cases (**Fig. 2**). **Tables 2** and **3** present the number of cases for each grade and each parameter, offering a comprehensive overview of the distribution patterns. This information allowed a detailed analysis of the occurrence and severity of these factors in specific age cohorts. Based on histological examination, they were graded as per the ELMS studies performed by Turowski et al. [11], based on the quality of the epithelium and subjacent elements (**Table 4** and **Fig. 3**).

Table 1. Sex distribution, type of cyst, and clinical features

Age distribution	<1 yr (n=12)	1–4 yr (n=11)	4–8 yr (n=8)	8–12 yr (n=9)
Sex				
Male	4	7	3	2
Female	8	4	5	7
Type of cyst				
Type 1	11	6	5	4
Type II	-	3	2	3
Type III	-	1	-	1
Type IV	1	1	1	1
Clinical features				
Abdominal pain	4	10	10	4
Jaundice	11	5	4	3
Abdominal lump	-	-	9	3
Vomiting	5	2	1	-
Classical triad	-	2	10	6

Values are presented as number only.
-: not available.

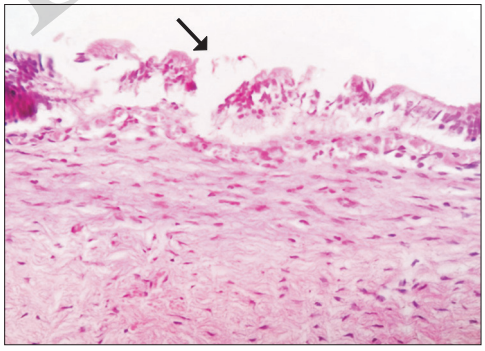

Fig. 1. Choledochal cyst wall epithelium showing focal ulceration (indicated by black arrow; 400× magnification, hematoxylin and eosin staining).

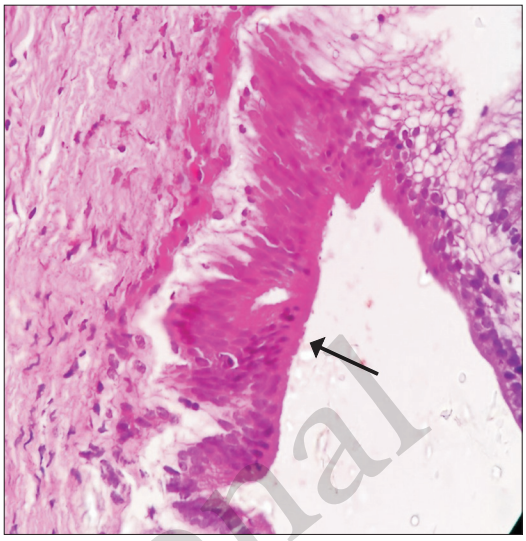

Fig. 2. Choledochal cyst wall epithelium showing hyperplasia with anisokaryosis and mucinous metaplasia (black arrow; 400× magnification, hematoxylin and eosin staining).

Table 2. Histological findings with age wise distribution

Age group	Ulceration			Inflammation			Mural fibrosis				Metaplasia	
	Grd 1	Grd 2	Grd 3	Grd 0	Grd 1	Grd 2	Grd 0	Grd 1	Grd 2	Grd 3	Prst	Ab
<1 yr	10	2	-	2	8	2	5	7	-	-	-	12
1–4 yr	8	2	1	9	1	1	5	3	3	-	-	11
4–8 yr	2	4	2	1	3	4	-	1	1	6	1	7
8–12 yr	-	2	7	-	1	8	-	-	1	7	4	5

Grd: grade, Prst: present, Ab: absent, –: not available.

Table 3. Histologic findings

Histology	Categories	Total number of cases (n=40)
Ulceration		
Grade 1	No ulceration	14 (35.0)
Grade 2	Focal ulceration	17 (42.5)
Grade 3	Diffuse ulceration	9 (22.5)
Inflammation		
Grade 0	No inflammation	2 (5.0)
Grade 1	Focal or mild inflammation	26 (65.0)
Grade 2	Diffuse or chronic inflammation	12 (30.0)
Mural fibrosis		
Grade 0	No fibrosis	6 (15.0)
Grade 1	Minimal fibrosis	11 (27.5)
Grade 2	Focal or moderate fibrosis	17 (42.5)
Grade 3	Diffuse or severe fibrosis	7 (17.5)
Metaplasia	Present	5 (12.5)
	Absent	35 (87.5)

Values are presented as number (%).

Out of the 40 cases studied, the majority showed an ELMS score 1 (8 cases) and 2 (22 cases). Five cases were identified with ELMS score 3, featuring metaplastic changes, and ELMS score 0 was found in five cases. None of the patients in the present study had ELMS score 4 (severe). We subjected all cases of the choledochal cyst to IHC with beta-catenin. Cases with metaplasia (ELMS score 3) expressed beta-catenin nuclear positivity (**Fig. 4A**), while those without metaplasia showed no nuclear positivity (**Fig. 4B**). All the cases with metaplasia and beta-catenin positivity are currently under follow-up.

Table 4. Epithelial lining/mural score

ELMS score	Changes	Quality of epithelium/wall	Total number of cases
0	None (normal)	No hyperplasia, columnar epithelium, no fibrosis	5 (12.5)
1	Minimal	Focal hyperplasia, chronic inflammation, no fibrosis	8 (20.0)
2	Mild	Diffuse hyperplasia, anisokaryosis, chronic inflammation, mild fibrosis	22 (55.0)
3	Moderate	Diffuse hyperplasia with focal anisocytosis, anisokaryosis, mucinous metaplasia, granulation tissue, moderate fibrosis	5 (12.5)
4	Severe	Biliary necrosis, biliary impregnation	0 (0.0)

Values are presented as number (%).
ELMS: epithelial lining/mural score.

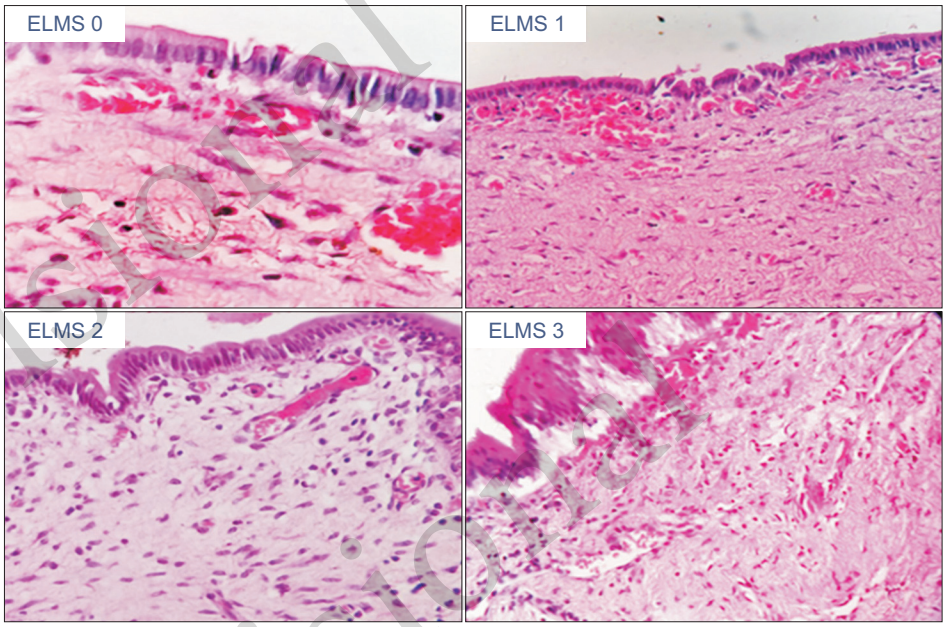

Fig. 3. Choledochal cyst wall epithelium characterized by different ELMS grading (400× magnification, hematoxylin and eosin staining). (ELMS 0) No hyperplasia, tall columnar epithelium and no fibrosis. (ELMS 1) Focal ulceration and chronic inflammation. (ELMS 2) Chronic inflammation and mild fibrosis. (ELMS 3) Diffuse hyperplasia with mucinous metaplasia and granulation tissue. ELMS: epithelial lining/mural score.

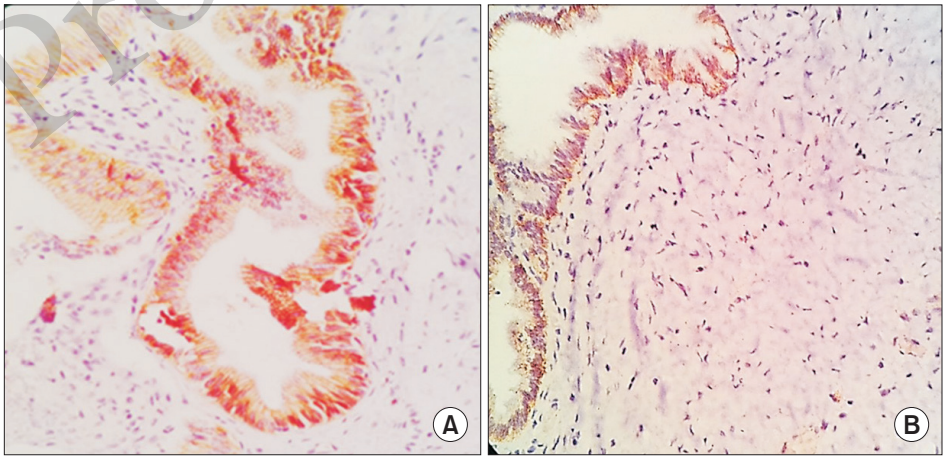

Fig. 4. At 400× magnification: (A) Positive immunostaining for β-catenin in metaplastic epithelium; (B) Negative immunostaining for β-catenin in normal epithelium.

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DISCUSSION

Choledochal cysts are rare congenital anomalies defined as abnormal, disproportionate, and cystic dilatations of the intra- and extrahepatic biliary tree [12]. Incidence of choledochal cysts is approximately one in 100,000-150,000 live births in the Western population. However, it has been reported to be as high as one in 13,500 live births in the United States and one in 15,000 live births in Australia [13]. Choledochal cysts are more common in Asia, with two-thirds of the cases occurring in Japan [14]. Incidence in India is not available, except for one large series of 79 cases from West Bengal, India [15].

Choledochal cysts can present at any age, but are most common during childhood. Approximately 25% of choledochal cysts are diagnosed antenatally or within the first year of life, 60% during the first decade of life, and about 20% remain undiagnosed into adulthood [16]. There is also an unexplained male-to-female ratio, commonly reported as 1:4 or 1:3 [17]. The youngest patient in our study was a 45-day-old male. We observed that the diagnosis of choledochal cysts were more frequently in children over 1 year of age, showing a female preponderance. The majority of these cases were identified as type 1 cysts.

The classic triad of clinical symptoms was first described by Alonso-Lej et al. [2] that includes right hypochondriac pain, palpable abdominal mass, and jaundice [18]. In a study conducted by Arah et al. [19], the most common presenting symptom was abdominal pain (77–80%), followed by vomiting (60%) and jaundice (35%). In a study by Chatura et al. [20], all children presented with fever and jaundice, whereas abdomen pain and vomiting were observed in 18.75% of cases, and palpable mass in the right upper quadrant was noted in 12.5% of cases. In our study, patients presented most commonly with abdominal pain (28 cases, 70.0%) followed by jaundice (23 cases, 57.5%), abdominal lump (12 cases, 30.0%), and vomiting (8 cases, 20.0%), consistent with previous literature [20-22]. The classical triad of pain, lump, and jaundice was observed in 18 patients.

Excision with reconstruction is the treatment of choice for most choledochal cysts. Foo et al. [22] evaluated clinical outcome and optimal timing of definitive treatment of patients with choledochal cysts diagnosed prenatally or after birth. Based on the analysis of 45 patients, they concluded that prenatal diagnosis of CC resulted in earlier definitive surgery. More adverse complications were observed in the patients who underwent surgery at an older age [21]. In the present study, most patients who underwent cyst excision with Roux-en-Y hepaticojejunostomy were <4 years of age.

The characteristic sequence that appears in choledochal cysts is an initial generalized reactive hyperplasia, followed by islands of abnormal mucosa within a denuded, chronically inflamed, and fibrotic wall [23]. In most cases, histological sections revealed a thick-walled structure composed of dense connective tissue with interspersed smooth muscle, frequently without an epithelial lining and usually with little to no inflammation. Mucosal hyperplasia and papillomatosis of the biliary tree have been reported in patients with choledochal cysts.

Necrosis and squamous metaplasia, with subepithelial inflammatory infiltration and fibrosis appearing later, progress to dysplasia and invasive malignancy, phenomenon predominantly observed in adults [24].

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According to Ozolina et al. [25], the younger the patient, the poorer the development of the muscle layer. As age increased, more fibrous tissue was observed. However, granulation was better developed in older patients, along with the extent of inflammatory cell infiltration. The authors also postulated that bile from patients with congenital choledochal cyst can promote the proliferation of epitheliocytes and human cholangiocarcinoma cells [25]. Sharma et al. [10] examined the cyst wall lining with similar parameters, such as ulceration, inflammation, fibrosis, and metaplasia, which are directly correlated with intra-choledochal cystic pressure. In the present study, the infantile age group (<1 year) showed a simple cuboidal epithelium with minimal fibrosis and mild inflammation, whereas the pediatric age group (>1 year) showed focal mucosal ulceration, moderate to diffuse inflammation, and moderate to severe fibrosis. These findings are comparable to those of Sharma et al. [10] and Ozolina et al. [25].

Metaplasia was observed in five patients aged 7 to 9 years. Thus, the risk of metaplasia increases with age. It is possible that activated enzymes cause epithelial cellular damage, manifested as metaplasia, dysplasia, and biliary tract carcinoma [26], after many years of exposure. Katabi et al. [21] (n=36, age range 11–67 years) found metaplasia in 38.9% of the cases (14/36).

Turowski et al. [11] attempted to classify histopathological changes in the cyst wall based on the criteria they specified, referred to as ELMS. This scoring system consists of hyperplasia, inflammation, fibrosis, and epithelial lining. Out of total 73 cases, they revealed ELMS score 1 (n=26 patients, 35.6%), ELMS score 2 (n=27, 37.0%), ELMS score 3 (n=13, 17.8%), and ELMS score 4 (n=7, 9.6%) [11]. In our study, eight cases (20.0%) showed ELMS score 1 (minimal), 22 (55.0%) showed ELMS score 2 (mild), five (12.5%) showed ELMS score 3 (moderate) with metaplastic changes, and five (12.5%) showed ELMS score 0 (normal). None of the patients in our study had ELMS score 4 (severe). Ulceration and inflammation represent acute insult, whereas fibrosis and metaplasia represent chronic sequelae of the cyst wall.

Beta-catenin is an intracellular protein that is an integral component of the cadherin-mediated cell-cell adhesion and a downstream transcriptional activator in a Wnt signal transduction pathway [5]. The signaling activity of beta-catenin is mediated through its interaction with the Tcf/Lef-12 family of transcription factors and subsequent activation of target genes [27]. Activating mutations in exon 3 of the beta-catenin gene, at the phosphorylation sites for ubiquitination and degradation of beta-catenin, appear to be a crucial step in the progression of a variety of cancers. In a study by Chen et al. [28], upregulation of Wnt2 might initiate the canonical Wnt signaling pathway, enhance c-Myc production, and potentially lead to tumorigenesis.

Nakanuma et al. [29] found that the nuclear accumulation of beta-catenin correlates with more malignant behavior and activation of target genes, including cyclin D1 and c-Myc, in biliary tract tumors such as intraductal papillary neoplasm of the bile duct and in cholangiocarcinoma. According to Huang et al. [9] who studied beta catenin and c-Myc expression in choledochal cyst in different groups, they found that the expression of beta-catenin in adult and children groups were higher than that in term newborn group. Therefore, it is postulated that beta-catenin and c-Myc might be associated with malignant transformation of choledochal cyst epithelium [9].

Limitations of the study

The main limitations of the study include restricted geographical localization i.e conducted in a single tertiary care pediatric center in South India hence the findings may not be representative of the broader population and lack of long-term follow-up.

In conclusion, the choledochal cysts are benign with a potential risk of malignant transformation. Therefore, a detailed assessment of ulceration, inflammation, mural fibrosis, and metaplasia should be performed. Metaplasia was associated with beta-catenin nuclear positivity. These findings suggest a potential role for beta-catenin as a marker of metaplastic changes in choledochal cysts. Further research is warranted to better understand the clinical significance of beta-catenin expression and its association with malignant transformation of choledochal cysts. Prospective studies with long-term follow-up are needed to evaluate the utility of beta-catenin as a prognostic marker and its potential role in guiding management decisions in patients with choledochal cysts.

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