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Primary Squamous Cell Carcinoma of the Gallbladder: A Case Report

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Case Report

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Abstract

Background: Gallbladder carcinoma has a hidden onset and most cases are already in the advanced stage when diagnosed with a poor prognosis. The common type is adenocarcinoma, and primary gallbladder squamous cell carcinoma is the rarest histological type in Gallbladder carcinoma.

Case presentation: A 56-year-old male was admitted to the hospital due to upper abdominal pain for 2 months without an obvious cause. The pain was more pronounced in the right upper abdomen, presenting as intermittent colicky pain, accompanied by radiating pain to the lower back. The microscopic examination demonstrated that Squamous metaplasia and dysplasia of the gallbladder epithelium were observed .The tumor consisted of well-differentiated squamous cell carcinoma tissue, which exhibited infiltrative growth into the subserosal fibrous and surrounding adipose tissue. Immunohistochemical staining showed the malignant cells were positive for P40, CK, CK5/6, CK19 and Ki-67 (index 60%) , weakly positive for CK7 and CEA. Pathological diagnosis indicated that well-differentiated squamous cell carcinoma of the gallbladder with infiltrative growth.

Conclusion: This report describes an unusual case of squamous cell carcinoma of the gallbladder to enhance the clinical comprehension of this uncommon disease.

Introduction

Gallbladder carcinoma is an aggressive biliary malignancy with poor prognosis. It originates from mucosal squamous metaplasia induced by chronic inflammation and persistent gallstone irritation. Unlike conventional gallbladder adenocarcinoma, GBSCC possesses unique histopathological and immunohistochemical features and more aggressive biological properties.

GBSCC's low incidence results in limited clinical research, with current evidence mainly from sporadic case reports and small retrospective studies. Poor clinical recognition commonly causes diagnostic delay or misdiagnosis. Patients present with non-specific symptoms such as right upper abdominal pain, fever and distension, which resemble acute cholecystitis, gallstone disease and advanced gallbladder adenocarcinoma. Different from adenocarcinoma, GBSCC rarely elevates serum CA19-9 and CEA levels, increasing the difficulty of early differentiation. Common imaging modalities including ultrasound, contrast-enhanced CT and MRI show no pathognomonic signs, and most patients present with invasive masses complicated by hepatic invasion, perineural infiltration and lymph node metastasis at first diagnosis. Histopathological and immunohistochemical examinations remain the gold standard for definite GBSCC diagnosis.

The 5th WHO Tumor Classification defines primary GBSCC as an independent gallbladder epithelial tumor. GBSCC shows obvious biological heterogeneity: most cases manifest aggressive local invasion, high recurrence risk and distant metastasis with poorer prognosis than adenocarcinoma, while few progress indolently. No unified specialized therapeutic guidelines are available due to insufficient clinical data. Current treatment adopts a multidisciplinary model covering radical resection, adjuvant

chemoradiotherapy and palliative systemic therapy. By reporting a confirmed GBSCC case and reviewing updated literature, this study summarizes its clinicopathological features, diagnostic criteria and therapeutic progress, aiming to elevate clinical cognition and optimize individualized treatment strategies.

Epidemiology

Gallbladder carcinoma (GBC) is the most common malignancy of the biliary system, characterized by high malignancy and poor prognosis. Adenocarcinoma is the predominant histological type, accounting for approximately 97% of cases .GBSCC is extremely rare, comprising only 1.1%–3.7% of all GBC cases. It is more frequently observed in females, with a male-to-female ratio of 1:2.5. The average age of onset is 62.9 years, with no significant gender difference reported.

Patient Information

Age: 56 years

Sex: Male

Primary concerns: Abdominal pain for 2 months without an obvious cause. The pain was more pronounced in the right upper abdomen, presenting as intermittent colicky pain, accompanied by radiating pain to the lower back, but without nausea, vomiting or other symptoms

Medical history: No significant past medical history

Family history: No family history of gallbladder carcinoma

Psychosocial history: Not reported

Relevant past interventions: None

Clinical Findings

Vital signs: Stable

Physical examination:The abdomen was flat, with no visible gastrointestinal peristalsis or peristaltic waves. Jaundice was observed on the skin and mucous membranes. Tenderness was detected in the right upper abdomen, but there was no significant rebound tenderness or muscle tension. The liver and spleen were not palpable below the rib margin, nor were any masses detected. Murphy's sign was negative, shifting dullness was negative, and bowel sounds were normal

Other findings: No fever, no low back pain, no significant weight loss

Timeline

Date (2021) Event

July:Admission with upper abdominal pain for 2 months without an obvious cause

July :Pathological examination and immunohistochemistry

July:Diagnosis confirmed: Primary squamous cell carcinoma of the gallbladder

Diagnostic Assessment

Diagnostic methods:

Laboratory: AST: 498 U/L(markedly elevated) ;ALT: 703 U/L(markedly elevated);ALP: 300 U/L(elevated);Total protein:81g/L(within normal range);Albumin: 49 g/L(within normal range);Total bilirubin: 44.3 μmol/L(elevated above ULN);Direct bilirubin: 24.1 μmol/L (markedly elevated above ULN)

Imaging

MRCP scan showed a nodule was found at the gallbladder fundus, with abnormal signals in the gallbladder fossa, possibly indicating an abscess, along with biliary tract inflammation and multiple nodules in the abdominal cavity.

Enhanced CT scan showed a increased gallbladder tension, thickened and irregular gallbladder wall with local diverticulum-like protrusions. Uneven arterial-phase enhancement in the gallbladder fossa region of the liver, mild dilation of intrahepatic and extrahepatic bile ducts, and thickening of the extrahepatic bile duct wall with delayed enhancement.

Surgical findings

Laparoscopic gallbladder carcinoma resection was performed. During surgery, extensive adhesions were observed around the gallbladder, with a 5.0cm×5.0cm proliferative mass that was indistinctly demarcated from the gallbladder. The gallbladder wall was slightly thickened and hardened, containing a large amount of purulent bile.

Rapid frozen section pathological examination confirmed the diagnosis as squamous cell carcinoma.

Pathological findings:

Gross: The gallbladder measured 7cm×4cm×2.5cm. The mucosa was detached, and a gray-white to gray-brown tumor measuring 4cm×2.5cm×1.5cm was observed beneath the serosa. The tumor was hard in texture and had unclear boundaries.

Light microscopy: Partial detachment of the gallbladder mucosa was noted.The microscopic examination demonstrated that Squamous metaplasia and dysplasia of the gallbladder epithelium were observed (Fig. 1A) .The tumor consisted of well-differentiated squamous cell carcinoma tissue (Fig. 1B), which exhibited infiltrative growth into the subserosal fibrous and surrounding adipose tissue. Tumor thrombi were present in blood vessels. No tumor cells were detected at the cystic duct or gallbladder fundus margins.

Immunohistochemistry: p40(diffuse strong nuclear positivity), CK(diffuse strong cytoplasmic positivity), CK5/6(diffuse strong cytoplasmic positivity), CK19 (diffuse strong cytoplasmic positivity), CK7(negative), CEA(negative); Ki-67 proliferation index approximately 60%(Fig. 2A-D).

Diagnostic challenges: Non-specific symptoms, resemble acute cholecystitis or gallstone disease, often leading to delayed diagnosis and treatment

Diagnosis: Well-differentiated squamous cell carcinoma of the gallbladder with infiltrative growth

Differential diagnoses considered:

Conventional gallbladder adenocarcinoma (CEA positive, CK20 positive, CK8/18 positive, p40 negative, CK5/6 negative, p63 negative)

High-grade squamous intraepithelial neoplasia of the gallbladder (no lamina propria / invasion of the gallbladder wall, the lesion is limited to the mucosal layer and the basement membrane is intact)

Acute cholecystitis (persistent severe right upper quadrant pain induced by greasy diet, fever, positive Murphy's sign)

Cholecystolithiasis (mobile hyperechoic lesions with acoustic shadow within the gallbladder on ultrasound)

Prognostic characteristics: High Ki-67 (60%), local invasion (invasion of the gallbladder wall) — suggests aggressive biological behavior

Therapeutic Intervention

Type of intervention: No therapeutic intervention was administered in this case report as the focus was on diagnosis. The patient was referred for multidisciplinary discussion.

Follow-up and Outcomes

Clinician- and patient-assessed outcomes: Not reported in this case

Important follow-up diagnostic results: Not reported

Intervention adherence and tolerability: Not applicable

Adverse and unanticipated events: None reported

Diagnosis

(Gallbladder biopsy tissue) Well-differentiated squamous cell carcinoma with infiltrative growth.

- A. Squamous metaplasia of the gallbladder mucosa (HE, × 200).
- B. Infiltrative growth of well-differentiated squamous cell carcinoma in the gallbladder (HE, × 200).

- A. Well-differentiated squamous cell carcinoma of the gallbladder, positive for p40 (IHC, × 200).
- B. Upregulation of CK5/6 in Squamous cell carcinoma (IHC, × 200).
- C.Well-differentiated squamous cell carcinoma of the gallbladder, positive for CK19 (IHC, × 200).
- D. High proliferation index indicated by Ki-67 staining in tumor cells compared with normal squamous epithelium(approximately 60%) (IHC, × 200).

Discussion

The pathogenesis of GBSCC remains unclear, with two main hypotheses proposed: gallstones and parasitic infections. The former is considered the most critical risk factor for GBC, with reports indicating that 95% of GBC cases are associated with gallstones. Some scholars found gallstones in 81% of cases, though no gallstones were observed in this particular case.The histological origin of GBSCC is still uncertain. Some studies suggest that GBSCC originates from squamous metaplasia of multipotent basal cells in the gallbladder mucosa. Some scholars observed transformation between squamous epithelial cells in GBSCC, linking squamous metaplasia with atypical hyperplasia, squamous cell carcinoma in situ, and invasive carcinoma. In this case, microscopic examination revealed squamous metaplasia, atypical hyperplasia, and squamous cell carcinoma of the gallbladder mucosa, supporting the hypothesis that GBSCC is related to gallbladder mucosal squamous metaplasia. Other research suggests that adenocarcinoma develops first, undergoes squamous metaplasia, gradually transforms into adenosquamous carcinoma, and ultimately becomes pure squamous cell carcinoma.

Histopathological Features: GBSCC is classified into two types: (1) Keratinizing type: Well-differentiated squamous cells are arranged in nests or trabecular structures. The presence of at least one keratin pearl confirms the diagnosis of keratinizing carcinoma. Tumor cells exhibit eosinophilic cytoplasm, intercellular bridges, and the diagnosis is relatively straightforward. (2) Non-keratinizing type: Characterized by individual keratinized cells rather than keratin pearls within squamous epithelial nests. Cell boundaries are unclear, and nuclei appear round or oval with coarse, fragmented chromatin. Extensive mitotic activity is observed.

Immunophenotypic Characteristics: Immunohistochemistry is crucial for diagnosis and differential diagnosis. Some SCC cells form solid or sheet-like structures with clear cytoplasm.

Immunohistochemical markers such as CK(AE1/AE3), CK5/6, p63, and p40 are positive, aiding in the diagnosis of poorly differentiated squamous cell carcinoma. The absence of CK8/18, CK20, and CEA helps exclude invasive adenocarcinoma components. The Ki-67 proliferation index (60%) is highly variable, and a high index may indicate more aggressive biological behavior.

Differential Diagnosis: The main differential diagnoses include: (1) Conventional gallbladder adenocarcinom, high-to-mid-grade tubular adenocarcinoma is the most common type.shows positive immunoreactivity for CEA, CK20 and CK8/18, whereas p40, CK5/6 and p63 are negative. (2) High-grade squamous intraepithelial neoplasia of the gallbladder, no lamina propria / invasion of the gallbladder wall, the lesion is limited to the mucosal layer and the basement membrane is intact. (3) Acute cholecystitis, caused by intake of greasy food or overeating, presenting with persistent right-upper-quadrant abdominal pain with paroxysmal exacerbation. Pain may radiate to the right shoulder and back, accompanied by fever.(4)Cholecystolithiasis, Abdominal ultrasound is the first-choice examination. Ultrasonography shows strong-echo masses within the gallbladder lumen with posterior acoustic shadowing, which move with change of body position. Gallbladder wall may be normal or mildly thickened.

Clinical manifestation :The clinical presentation of GBSCC is generally non-specific. The most common symptom is right upper abdominal pain (81.2%), followed by:Fever (25.7%),Tenderness (24.8%),Abdominal mass (22.8%) and Jaundice (17.8%) [1].The abdominal pain may be persistent or intermittent, dull, or colicky, sometimes radiating to the right shoulder or back. These symptoms are non-specific and resemble acute cholecystitis or gallstone disease, often leading to delayed diagnosis and treatment.

Surveillance: Most patients present at mid-to-late stages, with a low overall survival rate. Due to the lack of specific symptoms and signs, clinical diagnosis primarily relies on ultrasound, CT and MRI imaging [2]. CT and MRI are particularly useful for diagnosing the disease, assessing tumor progression, detecting cancer metastasis, and preoperative surgical planning. However, GBSCC lacks distinctive imaging characteristics, making diagnosis challenging.

Treatment Modalities: The treatment of GBSCC is similar to that of other GBC, with surgery being the only effective treatment. Radical or extended radical surgery includes: Extrahepatic bile duct resection, Partial hepatectomy, Pancreaticoduodenectomy, Right hemihepatectomy or right trisegmentectomy. In some cases, hepatic-pancreaticoduodenectomy may be performed [3]. According to the literature, radical cholecystectomy with negative surgical margins along with systemic chemotherapy and/or radiotherapy appears to be the best treatment strategy [4].

Recently, Li et al. [5] used systemic inflammatory markers to predict the prognosis of a case of advanced GBSCC. The study indicated that systemic inflammatory biomarkers, such as: Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio ,Lymphocyte-to-monocyte ratio and Jaundice may have potential prognostic value in advanced GBC. He et al. [6]report the case of gallbladder SCC with diffuse β-hCG

expression and markedly elevated serum β-hCG levels. Diffuse β-hCG expression may reflect a dedifferentiated and aggressive tumor phenotype associated with early metastasis and poor prognosis. However, these are single case reports, and further studies with larger sample sizes are needed for confirmation.

Clinical Management and Prognosis: GBSCC accounts for 1%- % of all gallbladder malignancies, strongly associated with cholelithiasis. It demonstrates aggressive biological behaviour and is frequently diagnosed at advanced stages. R0 radical resection, including cholecystectomy, wedge resection of liver bed and regional lymphadenectomy, is the only curative option. Extended resection with en-bloc adjacent organ resection is performed for locally invasive disease. Most patients present unresectable at initial diagnosis. Peri-operative chemotherapy (gemcitabine-platinum-based regimens) and chemoradiation are applied in multidisciplinary settings; immune-checkpoint inhibitors and NGS-guided targeted therapy are reserved for advanced-stage disease. Prognosis is poorer than gallbladder adenocarcinoma even after R0 resection. Median overall survival is approximately 9 months for the whole cohort; median survival after R0 resection reaches roughly 13 months. Positive surgical margin, advanced TNM stage, lymph-node metastasis and perineural invasion predict dismal outcomes. Therefore, a multidisciplinary team approach is crucial for optimal management.

Suggested Treatment Approach Based on Literature Review:

Due to the rarity of this entity, no standardized treatment protocol exists. Based on available literature and multidisciplinary team collaboration model, the following approaches have been employed:

Radiotherapy:

R1 resection: 45-50.4 Gy, boost to 54–60 Gy for positive margin.- High-risk R0 resection: 45-50.4 Gy.

Definitive chemoradiation for unresectable local disease: 50.4–60 Gy (1.8-2.0 Gy/fraction).

Palliative radiotherapy: 30–40 Gy for locoregional symptom control; 20–30 Gy for bone-metastasis pain relief.

Chemotherapy:

GC regimen (first-line)Gemcitabine 1000 mg/m² iv d1, d8 + Cisplatin 25–30 mg/m² iv d1-d3, q21-day cycle.

GEMOXGemcitabine 1000 mg/m² iv d1,d8 + Oxaliplatin 100 mg/m² iv d1, q21d.

CAPOXOxaliplatin 130 mg/m² iv d1 + Capecitabine 1000 mg/m² po bid d1-14, q21d.

Concurrent chemoradiation (radiosensitizer)Capecitabine 825 mg/m² po bid on radiotherapy days only.

Targeted therapy: No specific targeted regimen exists for gallbladder squamous-cell carcinoma.Targeted agents are applied only for patients with actionable molecular alterations identified by NGS.

HER2 amplification/overexpression: Trastuzumab-deruxtecan: 5.4 mg/kg iv q3w.

NTRK fusion :Larotrectinib: 100 mg po bid.

BRAF V600E : Dabrafenib 150 mg po bid + trametinib 2 mg po qd.

RET fusion: Selpercatinib 160 mg po bid.

FGFR2 fusion: Pemigatinib 13.5 mg po qd (2-week-on /1-week-off); Futibatinib 20 mg po qd.

Limitations

This study has several limitations. First, comprehensive genomic profiling (CGP/NGS/FISH) is not routinely performed in our institution; therefore, molecular testing for NTRK fusion, BRAF V600E, RET fusion and FGFR2 fusion was not carried out. Second, as this is a retrospective case report focusing on diagnosis, long-term follow-up and MDT treatment outcomes are not available.

Conclusion

Primary gallbladder squamous cell carcinoma is a rare biliary malignancy with unique clinicopathological characteristics. Clinicians should closely monitor patients with gallbladder space-occupying lesions combined with severe inflammation.Definitive diagnosis depends on typical squamous cell morphological alterations and specific immunohistochemical results, characterized by positive squamous markers and negative glandular epithelial markers. This tumor presents strong local invasiveness and metastatic capacity, requiring standardized and individualized treatment regimens. Radical surgical resection serves as the core treatment, supplemented by postoperative chemotherapy, radiotherapy, targeted therapy and immunotherapy, with multidisciplinary collaboration throughout the treatment process. In-depth recognition of this disease facilitates early detection, precise diagnosis and rational treatment, and ultimately improves patients' overall survival. Further large-sample clinical trials and molecular biological researches are essential to clarify its pathogenesis and optimize standardized therapeutic strategies.

Declarations

Ethical approval

This study was approved by the Ethics Committee of the Affiliated Hospital of Yanbian University (Approval No.: 20260061), Yanji, Jilin Province, China, in accordance with the ethical guidelines of the Declaration of Helsinki (1975 and its later amendments).

Consent to participate

Informed consent was obtained from the patient for participation in this study.

Consent to publish

Informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Jia Jiao performed the original draft writing, investigation and data curation; Jingshu Cui was responsible for writing-review&editing; Jun Jin contributed to writing-review&editing and supervision; Haiyue Chen took charge of writing-review & editing, validation, supervision and methodology.

Data Availability

All data generated or analysed during this study are included in this published article.

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Figures

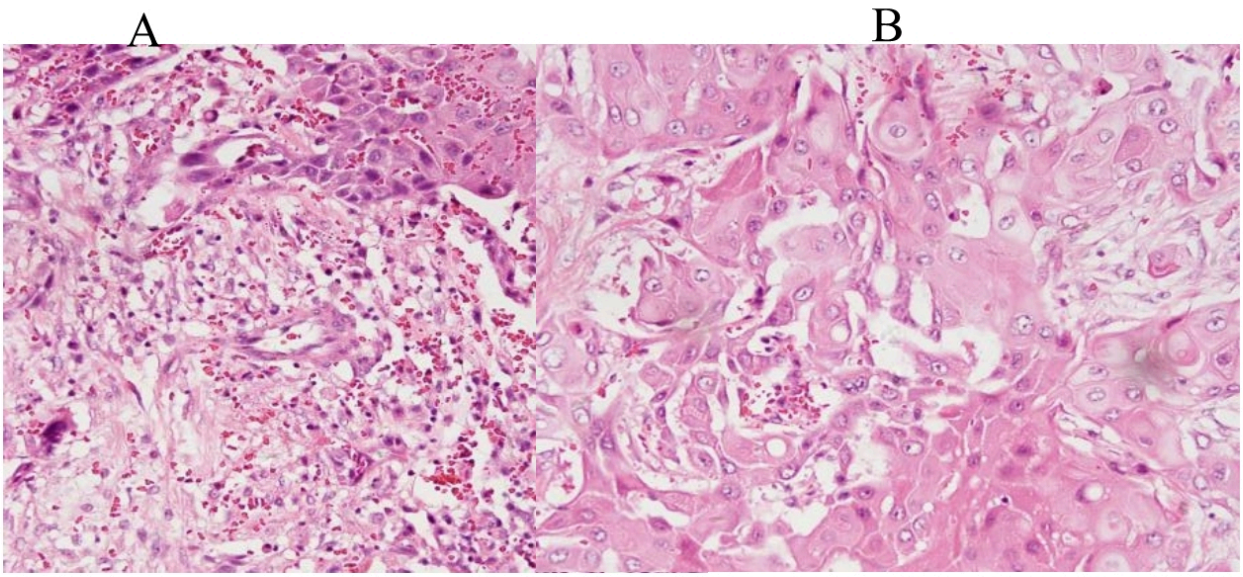


Figure 1

A. Squamous metaplasia of the gallbladder mucosa (HE, × 200).

B. Infiltrative growth of well-differentiated squamous cell carcinoma in the gallbladder (HE, × 200).

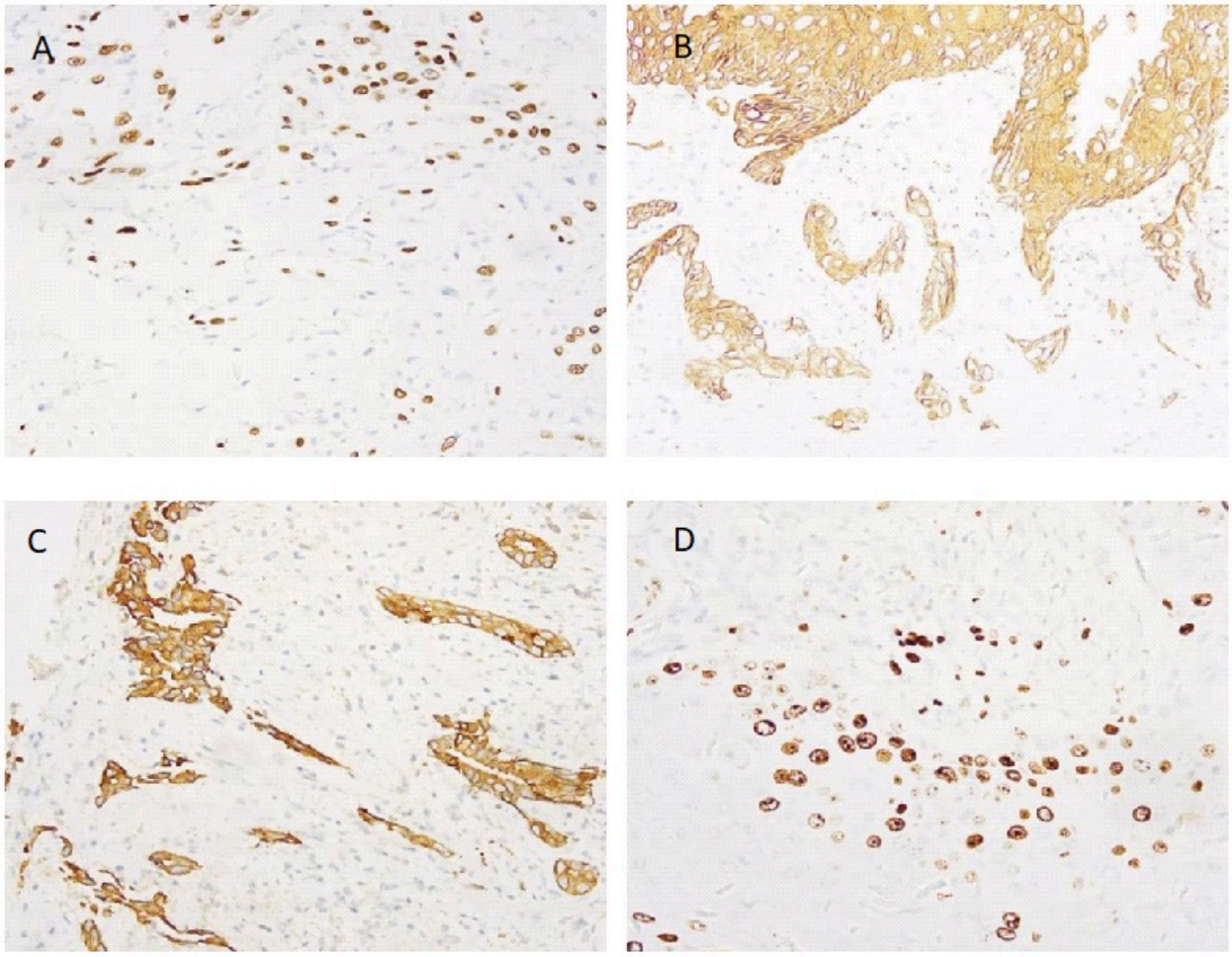


Figure 2

A. Well-differentiated squamous cell carcinoma of the gallbladder, positive for p40 (IHC, × 200).

B. Upregulation of CK5/6 in Squamous cell carcinoma (IHC, × 200).

C.Well-differentiated squamous cell carcinoma of the gallbladder, positive for CK19 (IHC, × 200).

D. High proliferation index indicated by Ki-67 staining in tumor cells compared with normal squamous epithelium(approximately 60%) (IHC, × 200).