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Original Article

Clinicopathological characterization of gall bladder neuroendocrine neoplasm. A case series.

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Abstract

Background
Gallbladder neuroendocrine neoplasms (GB-NENs) are rare, aggressive tumors with limited data on their clinicopathological characteristics. This study aims to evaluate the clinical presentation, radiological features, histopathology, and immunohistochemical (IHC) profile of GB-NENs to enhance diagnostic and therapeutic strategies.

Methods
A retrospective case series of 15 patients diagnosed with GB-NENs at Homi Bhabha Cancer Hospital and Research Centre over one year was analyzed. Clinical symptoms, radiological findings, tumor markers, histopathology, and IHC markers were reviewed.

Results
Most patients were female (80%), with a mean age of 56.7 years. Abdominal pain (100%) was the most common symptom, while hepatic invasion (53.3%) was frequently observed on imaging. Histopathology revealed small cell neuroendocrine carcinoma (66.6%), neuroendocrine tumor grade 3 (20%), and mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) (13.3%). IHC positivity for PanCK, INSM1, and chromogranin confirmed neuroendocrine differentiation.

Conclusion
GB-NENs exhibit aggressive behavior with poor prognosis, emphasizing the need for early diagnosis and standardized treatment approaches. Further studies focusing on molecular profiling and targeted therapies are essential for improving patient outcomes.

Recommendation
Given the rarity and diagnostic complexity of GB-NENs, clinicians should maintain a high index of suspicion in gallbladder masses with atypical imaging or histological features. Routine inclusion of neuroendocrine markers such as INSM1 and chromogranin in gallbladder biopsy evaluations can improve diagnostic accuracy. Multicenter collaborations, molecular characterization, and standardized therapeutic protocols are strongly recommended to enhance patient outcomes and guide future clinical practice.

Keywords: *Gallbladder, Neuroendocrine neoplasm, Small cell carcinoma, Immunohistochemistry*
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Introduction

Neuroendocrine neoplasms (NENs) of the gallbladder are exceedingly rare, constituting a small fraction of all gallbladder cancers [1]. Unlike the more common adenocarcinomas of the gallbladder, neuroendocrine neoplasms present unique challenges in diagnosis and management due to their indolent presentation and

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aggressive behavior. Despite their rarity, the incidence of gallbladder NENs appears to be increasing, perhaps due to improved diagnostic techniques and greater clinical awareness [2,3].

The gallbladder is an uncommon site for neuroendocrine tumors, which more frequently occur in the gastrointestinal tract and pancreas. Gallbladder NENs are often diagnosed incidentally during histopathological examination of biopsies or cholecystectomy specimens for presumed benign conditions or gallbladder adenocarcinoma [4]. The clinicopathological features of gallbladder NENs can vary significantly, which affects treatment strategies and prognostic outcomes. This variability underscores the importance of accumulating and analyzing more case-specific data to better understand and manage this rare entity [5,6].

Despite the rarity, the incidence of gallbladder neuroendocrine neoplasms (NENs) seems to be on the rise, potentially attributed to advancements in diagnostic technologies. Neuroendocrine neoplasms of the gallbladder make up only 0.5% of all neuroendocrine neoplasms and 2.1% of all gallbladder tumors.

However, in my study, I discovered 15 cases of NENs out of 248 over a period of one year, which represents approximately 6%. Gallbladder NENs are frequently identified incidentally during the histopathological examination of biopsies or cholecystectomy specimens that were initially taken for presumed benign conditions or gallbladder adenocarcinoma.

This case series aims to provide a detailed clinicopathological characterization of gallbladder neuroendocrine neoplasms, documenting aspects such as demographic details, clinical presentation, histopathological features, treatment modalities, and patient outcomes. Through this series, we intend to contribute to the limited but growing body of literature on gallbladder NENs, facilitating better diagnostic precision and treatment planning for these challenging tumors.

Methodology

Study design and setting

This study is a retrospective case series conducted at Homi Bhabha Cancer Hospital and Research Centre (HBCHRC), Muzaffarpur, Bihar, India, from January 2024 to January 2025. HBCHRC is a tertiary-level oncology center functioning under the Tata Memorial Centre (TMC), Department of Atomic Energy, Government of India. It serves as a regional referral hub for comprehensive cancer care, catering to patients from North and East Bihar, Jharkhand, and parts of Uttar Pradesh. The center provides specialized services in surgical oncology, medical oncology, radiotherapy, pathology, radiodiagnosis, and palliative care, with an attached research unit supporting clinical and translational studies.

The study was conducted in accordance with institutional ethical guidelines. Ethical approval was obtained from the Institutional Ethics Committee of HBCHRC. Informed consent was obtained from all patients or their legal representatives wherever applicable.

Study population

A total of 15 patients out of 248 total cases diagnosed with gallbladder neuroendocrine neoplasm (GB-NEN) were included in the study. The inclusion and exclusion criteria were as follows:

Inclusion criteria

- Histopathologically confirmed cases of gallbladder neuroendocrine neoplasm.
- Patients who underwent cholecystectomy, biopsy, or other surgical interventions with histological and immunohistochemical confirmation of neuroendocrine neoplasm.
- Availability of complete clinical, radiological, and histopathological data.

Exclusion criteria

- Patients with incomplete medical records.
- Cases where definitive histopathological classification was not possible.
- Patients diagnosed with other histological variants with predominant non-neuroendocrine features.

Data collection

Data were collected retrospectively from hospital records, including clinical, radiological, histopathological, and follow-up details. The following parameters were recorded for each patient:

Demographic Data: Age, gender, clinical symptoms at presentation.

Clinical Features: Presence of gallbladder-related symptoms (e.g., right upper quadrant pain, jaundice, nausea, weight loss).

Radiological Findings: Ultrasound, CT scan, or MRI findings indicative of gallbladder mass or incidental lesions.

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Histopathological analysis

Tumor size, location, and gross morphology.
Microscopic evaluation, including tumor architecture, cellular morphology, mitotic index, necrosis, and invasion pattern.
Immunohistochemistry (IHC) Markers: Chromogranin A, Synaptophysin, Ki-67 index, CD56, and additional markers for neuroendocrine differentiation.

Staging and grading

Tumor classification based on the WHO 2019 classification for neuroendocrine neoplasms and the AJCC TNM staging system.
Differentiation into neuroendocrine tumor (NET), neuroendocrine carcinoma (NEC), or mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN).

Treatment modalities

Type of intervention (cholecystectomy, chemotherapy, radiotherapy, or palliative care).

Follow-up and outcomes

Recurrence, metastasis, and survival status at last follow-up.

Statistical analysis

Descriptive statistics were used to analyze the data. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables were presented as frequencies and percentages. Kaplan-Meier survival analysis was used to estimate survival rates where applicable. Data analysis was performed using [statistical software, e.g., SPSS, R, or Excel].

Case report

Case 1

Demographic header

A 61-year-old Indian female with no known comorbidities or chronic liver disease, a non-smoker, non-alcoholic, presented with abdominal pain for 2 months.

Timeline

Symptom onset: November 2023
Presentation: January 2024 at HBCHRC Muzaffarpur
Imaging: CT TAP (Jan 2024) revealed a 1.5 × 1.2 cm lesion in the gallbladder; CECT showed a 10.2 × 8.7 cm heterogeneously enhancing mass with invasion into hepatic segments IV and V.
Biopsy: Core biopsy performed in January 2024.
Treatment initiation: February 2024 — commenced on cisplatin + etoposide.
Last follow-up: July 2024 — partial response observed.

Clinical findings & diagnosis

Histopathology revealed hepatic parenchyma infiltrated by a tumor showing features of small cell neuroendocrine carcinoma with lymphoid infiltration and high mitotic activity (15/10 HPF).
IHC: Positive for CD56 and CK7 (cytoplasmic granular positivity), negative for CK20 and CDX2. Ki-67 index 90%.

Final diagnosis

Small cell neuroendocrine carcinoma with liver infiltration.

Management & interventions

No surgical resection was performed due to local hepatic invasion. The patient received 6 cycles of cisplatin (75 mg/m²) + etoposide (100 mg/m² days 1–3) every 21 days.

Outcome

Partial radiological response with reduction in hepatic lesion size. No treatment-related adverse events were recorded up to the last follow-up (July 2024).

Lessons learned

High Ki-67 and INSM1 positivity confirm aggressive behavior; early suspicion and combined chemo-regimens may improve outcomes in unresectable GB-NENs.

Case 2

Demographic header

A 77-year-old Indian female, hypertensive on amlodipine, a non-smoker, presented with dull right upper quadrant abdominal pain for 1 month.

Timeline

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Symptom onset: February 2024
Presentation: March 2024 at HBCHRC
Imaging: CECT (March 2024) showed hepatomegaly with fatty liver infiltration.
Biopsy: Core biopsy in March 2024.
Treatment initiation: April 2024 — cisplatin + etoposide started.
Outcome: Died in June 2024.

Clinical findings & diagnosis

Histology revealed infiltration by nests and sheets of small round cells with hyperchromatic nuclei and scant cytoplasm. Brisk mitotic activity noted.
IHC: Positive for PanCK and Synaptophysin, focal CK7 positivity, negative for LCA (CD45).

Final diagnosis

Small cell neuroendocrine carcinoma of the gallbladder.

Management & interventions

Due to inoperability, systemic chemotherapy with cisplatin + etoposide was initiated. No surgical or radiotherapeutic intervention was possible.

Outcome

Despite initial therapy, the patient's condition deteriorated, and she succumbed to progressive disease in June 2024. No major treatment-related adverse events recorded.

Lessons Learned

Older patients with poor baseline status and advanced hepatic infiltration have limited tolerance and poor outcomes despite systemic chemotherapy.

Case 3

Demographic header

A 45-year-old Indian female with no significant comorbidities, a non-smoker, non-alcoholic, presented with right upper quadrant pain for one week.

Timeline

Symptom onset: March 2024
Presentation: March 2024
Imaging: CECT showed a soft tissue lesion in the gallbladder fossa with local invasion into hepatic segments IV & V.
Biopsy: March 2024
Treatment initiation: April 2024
Last follow-up: August 2024

Clinical Findings & diagnosis

Histopathology revealed fibrocollagenous tissue infiltrated by tumor cells arranged in nests and sheets with a high N/C ratio, irregular nuclear membrane, and mitoses (18–20/10 HPF). Areas of necrosis are present.
IHC: PanCK+, CK7 (focal)+, Chromogranin+, CK20–, INSM1–.

Final diagnosis

Gallbladder neuroendocrine tumor grade 3 (NET G3).

Management & interventions

Due to locally advanced disease, the patient received Carboplatin + Etoposide (6 cycles). Surgery was deferred due to hepatic invasion.

Outcome

Good partial response at 4-month follow-up. No chemotherapy-related complications reported.

Lessons Learned

Chromogranin and CK7 positivity aid differentiation of NET from adenocarcinoma; Carboplatin–Etoposide is effective in high-grade NET G3.

Case 4

Demographic header

A 69-year-old Indian female, hypertensive on medication, presented with abdominal pain for three months.

Timeline

Symptom onset: November 2023
Presentation: February 2024
Imaging: CECT showed a well-defined lesion in the gallbladder fossa without hepatic invasion.
Biopsy: February 2024
Treatment initiation: March 2024
Follow-up: August 2024

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Clinical findings & diagnosis

Tumor arranged in nests and sheets with a high N/C ratio and brisk mitosis (22/10 HPF).
IHC: PanCK (patchy)+, CK7 (focal)+, INSM1 (scattered)+, Chromogranin–.
Final Diagnosis: Neuroendocrine tumor grade 3.

Management & Interventions

Received 6 cycles of Carboplatin + Etoposide.

Outcome

Clinically stable with partial regression on follow-up imaging. No adverse effects noted.

Lessons Learned

INSM1 expression, even if focal, supports neuroendocrine differentiation in morphologically ambiguous tumors.

Case 5

Demographic header

A 69-year-old Indian female, with no known comorbidities, presented with abdominal pain and appetite loss.

Timeline

Symptom onset: February 2024
Imaging: USG showed a distended GB with sludge; CECT revealed a large polypoidal lesion in the GB neck.
Biopsy: February 2024
Treatment: March 2024
Follow-up: July 2024

Clinical findings & diagnosis

Small cell neuroendocrine carcinoma with necrosis.
IHC: INSM1+, Chromogranin+, Ki-67 70%.
Final Diagnosis: Small cell neuroendocrine carcinoma.

Management & interventions

Received Cisplatin + Etoposide (6 cycles).

Outcome

Marked symptomatic improvement and tumor regression after therapy.
Lessons Learned:
INSM1 and high Ki-67 confirm high-grade NEC; early systemic therapy offers a good short-term response.

Case 6

Demographic header

A 54-year-old Indian female with no chronic illness presented with abdominal pain for 3 months.

Timeline

Symptom onset: November 2023
Imaging: CECT showed thickening of the GB fundus with loss of fat plane with liver segment V.
Biopsy: December 2023
Treatment: January 2024
Follow-up: July 2024

Clinical findings & diagnosis

Fibrocollagenous tissue infiltrated by nests of tumor cells with mild pleomorphism, and necrosis is present.
IHC: INSM1 (focal)+, PanCK (weak)+, CK7–, p53 heterogeneous.

Final diagnosis

Neuroendocrine tumor grade 3.

Management & interventions

Received Cisplatin + Etoposide (6 cycles).

Outcome

Partial response. No significant toxicity noted.

Lessons learned

Heterogeneous p53 staining and INSM1 positivity support a high-grade NEC phenotype.

Case 7

Demographic header

A 43-year-old Indian female, a non-smoker, presented with abdominal pain, jaundice, and appetite loss.

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Timeline

Symptom onset: December 2023
Imaging: CECT showed a hypodense lesion in the GB body and neck invading liver segments IV and V.
Biopsy: January 2024
Treatment: February 2024
Follow-up: August 2024

Clinical findings & diagnosis

Tumor cells arranged in sheets and nests, mitosis 23/10 HPF, no necrosis.
IHC: INSM1+, CK7 (focal)+, CK20–.

Final diagnosis

Neuroendocrine tumor grade 3.

Management & interventions

Chemotherapy with Cisplatin + Etoposide (6 cycles).

Outcome

Significant symptomatic improvement; bilirubin normalized.

Lessons learned

In jaundiced patients, early systemic therapy before biliary decompression may yield rapid relief.

Case 8

Demographic header

A 72-year-old Indian male, a non-smoker, presented with abdominal pain and vomiting for one week.

Timeline

Symptom onset: February 2024
Imaging: CECT showed a lesion in the GB fossa with hepatic invasion; USG revealed CBD infiltration.
Biopsy: February 2024
Treatment: March 2024
Outcome: June 2024

Clinical findings & diagnosis

Histopathology showed small cell NEC; necrosis present.
IHC: INSM1+, PanCK (focal)+.

Final diagnosis

Small cell neuroendocrine carcinoma.

Management & interventions

Received Cisplatin + Etoposide for 3 cycles.

Outcome

The disease progressed rapidly; the patient died in June 2024. No major chemo-related adverse events.

Lessons learned

Hepatic and CBD involvement portend a poor prognosis despite chemotherapy.

Case 9

Demographic header

A 67-year-old Indian male, a non-smoker, presented with abdominal pain for 10 days.

Timeline

Imaging: CECT revealed a soft tissue lesion in the GB fundus with hepatic invasion.
Biopsy: March 2024
Treatment: April 2024
Follow-up: August 2024

Clinical findings & diagnosis

Histopathology: small cell NEC with 28 mitoses/10 HPF.
IHC: INSM1 (diffuse)+, Chromogranin+.

Final diagnosis

Small cell neuroendocrine carcinoma.

Management & interventions

Received Cisplatin + Etoposide (6 cycles).

Outcome

Partial response with improved liver function tests.

Lessons learned

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Diffuse INSM1 staining supports definitive neuroendocrine diagnosis even with limited biopsy tissue.

Case 10

Demographic header

A 45-year-old Indian female, a non-smoker, presented with chronic abdominal pain.

Timeline

Imaging: CT revealed an ill-defined lesion (7.2 × 6.2 cm) with liver invasion.
Biopsy: February 2024
Treatment: March 2024
Follow-up: August 2024

Clinical findings & diagnosis

Histopathology: small to medium cells, necrosis, high mitotic rate.
IHC: PanCK+, INSM1+, Chromogranin+.

Final diagnosis

Small cell neuroendocrine carcinoma.

Management & interventions

Received Cisplatin + Etoposide (6 cycles).

Outcome

Good partial response at 5 months. No treatment-related complications.

Lessons learned

Calcified lesions may still represent NEC; histopathology remains definitive.

Case 11

Demographic header

A 68-year-old Indian female, a non-smoker, presented with abdominal pain.

Timeline

Imaging: CECT revealed a lesion in the anterior GB wall with hepatic invasion.
Biopsy: January 2024
Treatment: February 2024
Outcome: June 2024

Clinical findings & diagnosis

Histopathology: small cell NEC with necrosis.
IHC: PanCK+, INSM1 (focal)+, Chromogranin+.

Final diagnosis

Small cell neuroendocrine carcinoma.

Management & interventions

Received 3 cycles of Cisplatin + Etoposide; further therapy was stopped due to deterioration.

Outcome

Died in June 2024 from progressive disease.

Lessons learned

Early hepatic involvement remains the strongest negative prognostic factor.

Case 12

Demographic header

A 50-year-old Indian female, a non-smoker, presented with abdominal pain.

Timeline

Imaging: CECT showed a 3.5 × 2 × 2 cm fundus-body lesion.
Surgery: Simple cholecystectomy performed in February 2024.
Biopsy: February 2024
Outcome: June 2024

Clinical findings & diagnosis

Histopathology: transmural infiltration by small round tumor cells; necrosis and squamous differentiation noted.
IHC: PanCK (focal)+, Synaptophysin (focal)+, INSM1 (focal)+, Chromogranin+, CK7–, P40–, P63–.

Final diagnosis

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Small cell neuroendocrine carcinoma.

Management & interventions

Post-surgery Cisplatin + Etoposide initiated.

Outcome

Died in June 2024 due to progression.

Lessons learned

Even small resected tumors can behave aggressively—necessitating adjuvant chemotherapy.

Case 13

Demographic header

A 48-year-old Indian male, a non-smoker, presented with abdominal pain and jaundice.

Timeline

Imaging: CECT revealed a GB mass infiltrating hepatic parenchyma.
Biopsy: March 2024
Treatment: April 2024
Follow-up: August 2024

Clinical findings & diagnosis

Tumor with mixed adenocarcinoma and neuroendocrine components.
IHC: Adenocarcinoma (PanCK+, CK7+); Neuroendocrine (INSM1+, Chromogranin+).

Final diagnosis

Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN).

Management & interventions

Received Carboplatin + Etoposide (6 cycles).

Outcome

Partial regression, stable at last follow-up.
Lessons Learned:

MiNENs require dual-pathway therapy; neuroendocrine-targeted chemo offers better disease control.

Case 14

Demographic header

A 45-year-old Indian male, a non-smoker, presented with abdominal pain for six weeks.

Timeline

Imaging: CECT showed a 4.3 × 2.9 cm fundal lesion invading the liver; USG showed cholelithiasis.
Biopsy: March 2024
Treatment: April 2024
Follow-up: August 2024

Clinical findings & diagnosis

The tumor showed both neuroendocrine and adenocarcinoma features.
IHC: PanCK+, INSM1+, Chromogranin+, Ki-67 50%.

Final diagnosis

Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN).

Management & interventions

Received Cisplatin + Etoposide for 6 cycles.

Outcome

Clinically stable; good symptomatic improvement.

Lessons learned

Mixed histology requires careful sampling; Ki-67 is critical for guiding therapy intensity.

Case 15

Demographic header

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A 44-year-old Indian male, a non-smoker, presented with abdominal pain for one month.

Timeline

Imaging: CECT revealed a nodular lesion in the posterior GB wall; no hepatic invasion.
Biopsy: February 2024
Treatment: March 2024
Follow-up: August 2024

Clinical findings & diagnosis

Histology revealed small cell NEC with crushing artifacts and a high mitotic index.
IHC: PanCK+, INSM1+, Chromogranin+.

Final diagnosis

Small cell neuroendocrine carcinoma.

Management & interventions

Received Cisplatin + Etoposide (6 cycles).

Outcome

Partial response with improved clinical condition. No adverse events.

Lessons learned

Localized small-cell NEC responds favorably to systemic chemotherapy; early intervention is key.

Table 1a): Summary of all cases, including demographics, clinical features, radiology, histopathology, immunohistochemistry, and final diagnosis

Case No.	Age (years)	Gender	Symptoms	Tumor Markers	Radiological Findings	Histopathology	IHC Markers	Final Diagnosis	Treatment	Follow up
1	61	Female	Pain abdomen (2 months)	AFP=0.95, CA19.9=11.18, CEA=3.86	CT TAP: 1.5x1.2 cm lesion; CECT: 10.2x8.7 cm mass, liver invasion	Small cell NEC, liver infiltration	CD56+, CK7+, CK20-, CDX2-, Ki67 90%	Small Cell Neuroendocrine Carcinoma with Liver Infiltration	Chol, cisplatin, Etoposide	Responding
2	77	Female	Abdominal pain (1 month)	NA	CECT: Hepatomegaly with fatty infiltration	Small cell NEC	PanCK+, Synaptophysin+, CK7 (focal)+, LCA (CD45)-	Small Cell Neuroendocrine Carcinoma	Cisplatin Etoposide	Died
3	45	Female	Pain abdomen (1 week)	AFP<1.3, CEA=50.92, CA125=37.5, CA19.9=56.14	CECT: Soft tissue lesion in GB fossa, liver invasion; USG: Infiltrating GB mass	GB NET G3	PanCK+, CK7 (focal)+, Chromogranin+, CK20-, INSM1-	Neuroendocrine Tumor Grade 3	Carboplatin Etoposide	Responding

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4	69	Female	Pain abdomen (3 months)	AFP=3.3, CEA=0.26, CA125=4.1, CA19.9=27.32	CECT: Well-defined lesion, no liver invasion	GB NET G3	PanCK (patchy & weak) +, CK7 (focal)+, INSM1 (scattered)+, Chromogranin -	Neuroendocrine Tumor Grade 3	Carboplatin Etoposide	Responding
5	69	Female	Pain abdomen, loss of appetite	NA	USG: Distended GB with sludge; CECT: Large polypoidal lesion	Small cell NEC	INSM1+, Chromogranin +, Ki67 70%	Small Cell Neuroendocrine Carcinoma	Cisplatin Etoposide	Responding
6	54	Female	Pain abdomen (3 months)	CEA=7.56, CA19.9=WNL, CA125=271	CECT: GB fundus thickening, loss of fat with liver segment V	GB NET G3	INSM1 (focal)+, PanCK (perinuclear weak)+, CK7-, P53 (heterogeneous)	Neuroendocrine Tumor Grade 3	Cisplatin Etoposide	Responding
7	43	Female	Pain abdomen, jaundice, loss of appetite	Total Bilirubin=16.6	CECT & CT Abdomen: Hypodense lesion in the GB, liver invasion	GB NET G3	INSM1+, CK7 (focal)+, CK20-	Neuroendocrine Tumor Grade 3	Cisplatin Etoposide	Responding

Table 1b): Summary of all cases, including demographics, clinical features, radiology, histopathology, immunohistochemistry, and final diagnosis.

1	**72**	**Female**	**Pain abdomen, vomiting (1 week)**	**NA**	**CECT: Well-defined lesion with liver invasion; USG: Collapsed GB, CBD infiltration**	**Small Cell NEC**	**INSM1+, PanCK (focal)+**	**Small Cell Neuroendocrine Carcinoma**	**Cisplatin Etoposide**	**Died**
2	67	Female	Pain abdomen (10 days)	AFP=3.5, CEA=3.06, CA19.9=1.4	CECT: Soft tissue lesion in the GB fundus, liver invasion	Small Cell NEC	INSM1 (diffuse)+, Chromogranin +	Small Cell Neuroendocrine Carcinoma	Cisplatin Etoposide	Responding
3	45	Female	Pain abdomen (3	AFP=4.5, CEA=1.85, CA125=49.	CT: Ill-defined lesion with	Small Cell NEC	PanCK+, INSM1+, Chromogranin	Small Cell Neuroendocrine Carcinoma	Cisplatin Etoposide	Responding

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			months)	9, CA19.9=10.89	calcification, liver invasion		+			
4	68	Female	Pain abdomen	AFP=1.5, CEA=1.53, CA19.9=35.66	CECT: Soft tissue lesion in the GB anterior wall, liver invasion	Small Cell NEC	PanCK+, INSM1 (focal)+, Chromogranin +	Small Cell Neuroendocrine Carcinoma	Cisplatin Etoposide	Died
5	50	Female	Pain abdomen	AFP<1.3, CA125=7, CEA=2.65, CA19.9=12.32	CECT: 3.5x2x2 cm mass at fundus & body	Small Cell NEC	PanCK (focal)+, Synaptophysin (focal)+, INSM1 (focal)+, Chromogranin +, CK7-, P40-, P63-, NUT1-	Small Cell Neuroendocrine Carcinoma	Cisplatin Etoposide	Died
6	48	Male	Pain abdomen, jaundice	AFP<1.3, CEA=2.18, CA125=9.7, CA19.9=16.22	CECT: GB fossa mass lesion, hepatic infiltration	MiNEN	Adenocarcinoma: PanCK+, CK7+; Neuroendocrine: INSM1+, Chromogranin +	Mixed Neuroendocrine-Non Neuroendocrine Neoplasm (MiNEN)	Carboplatin Etoposide	Responding
7	45	Male	Pain abdomen (6 weeks)	AFP=1.7, CEA=1.27, CA125=30.6, CA19.9=35.7	CECT: Cholelithiasis, 4.3x2.9 cm lesion, liver invasion; USG: Chronic cholelithiasis, mass	MiNEN	PanCK+, INSM1+, Chromogranin +, CD45-, Ki67 50%	Mixed Neuroendocrine-Non Neuroendocrine Neoplasm (MiNEN)	Cisplatin Etoposide	Responding
8	44	Male	Pain abdomen (1 month)	AFP=1.8, CEA=2.32, CA19.9=8.69	CECT: Nodular lesion in the posterior GB wall, no hepatic invasion; USG: Hypoechoic mass	Small Cell NEC	PanCK+, INSM1+, Chromogranin +	Small Cell Neuroendocrine Carcinoma	Cisplatin Etoposide	Responding

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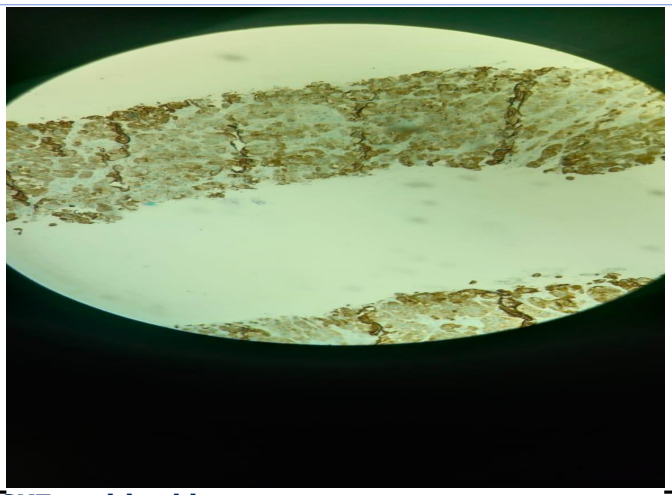
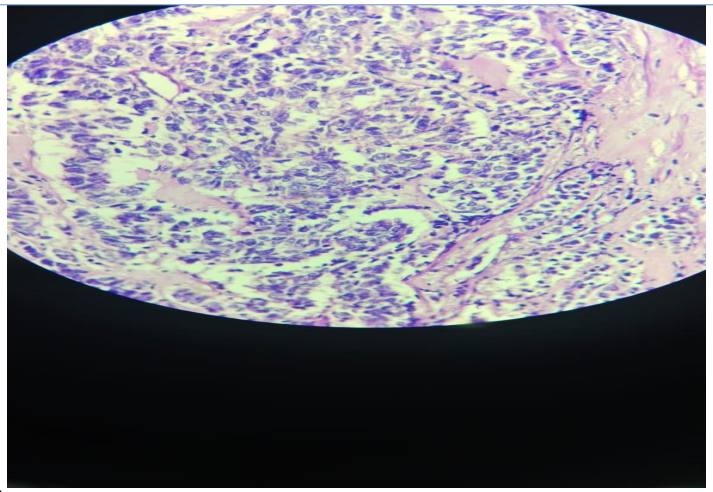


CK7 positive biopsy,



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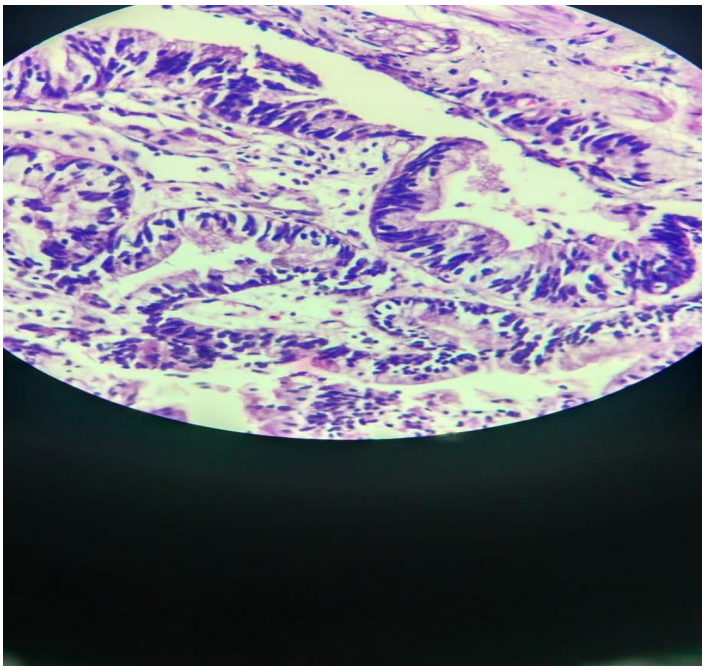

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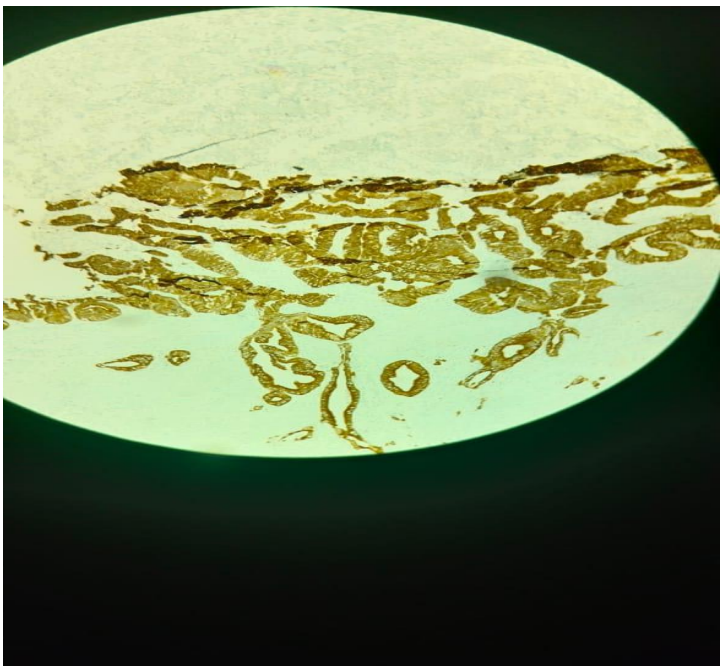

CK7 positive

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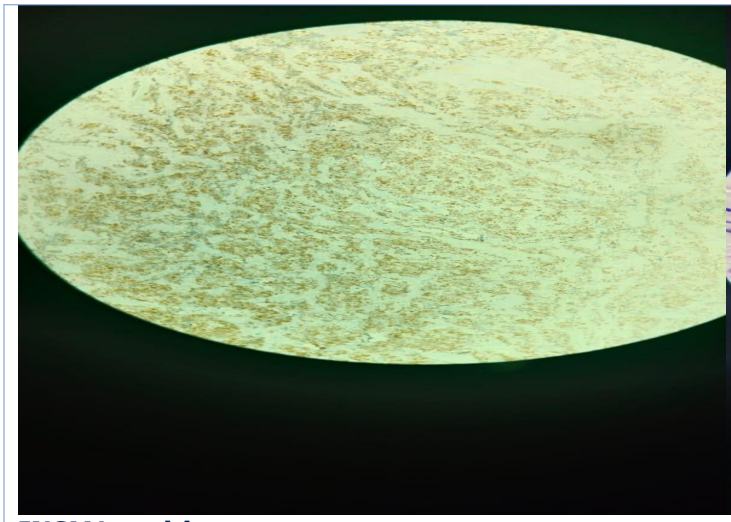
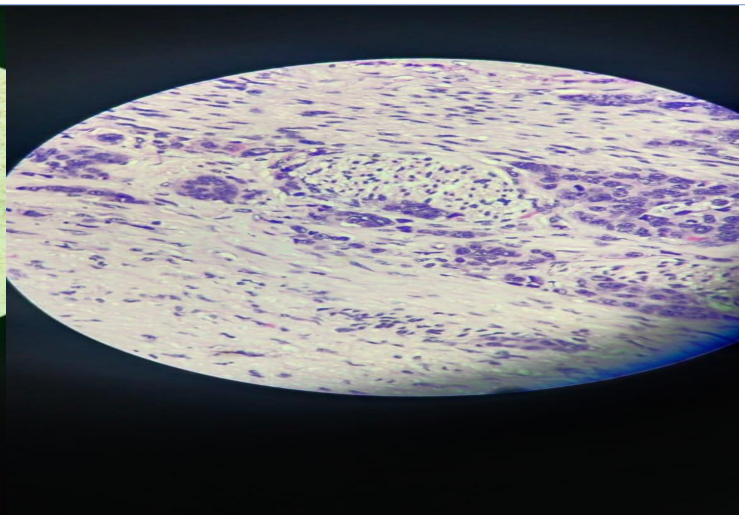
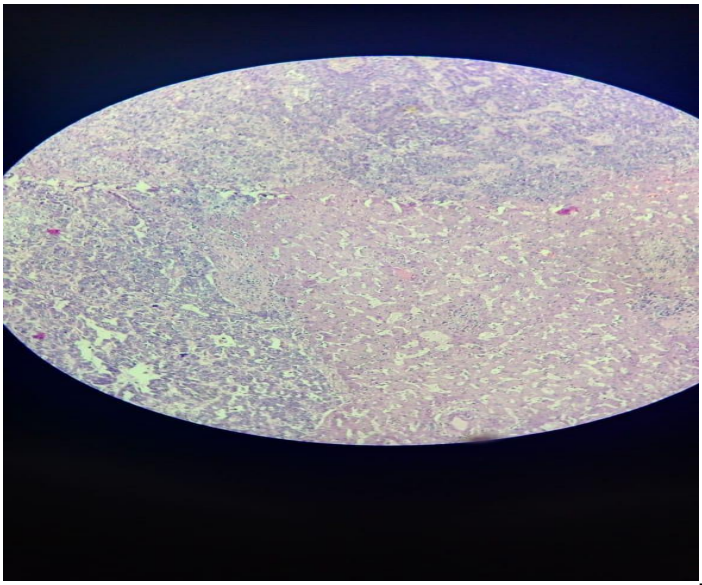


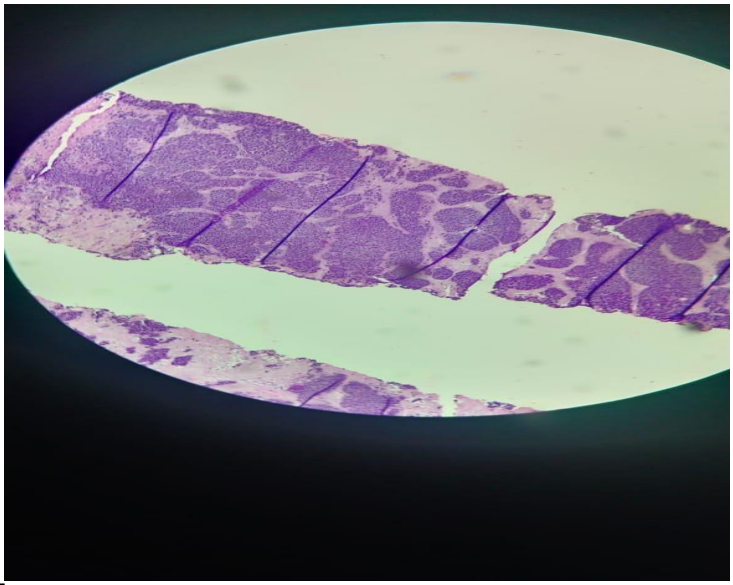
INSM1 positive



Perineurial invasion by NE cells in resection



Liver infiltration



NET biopsy

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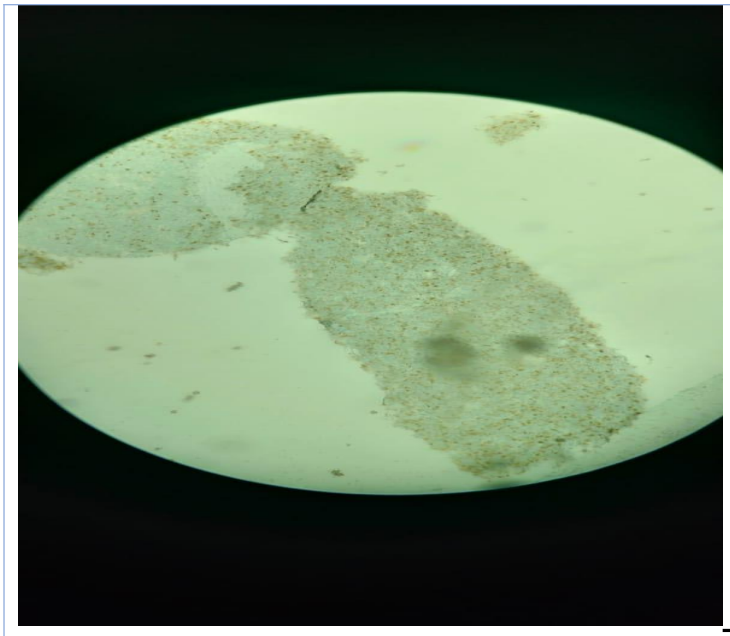
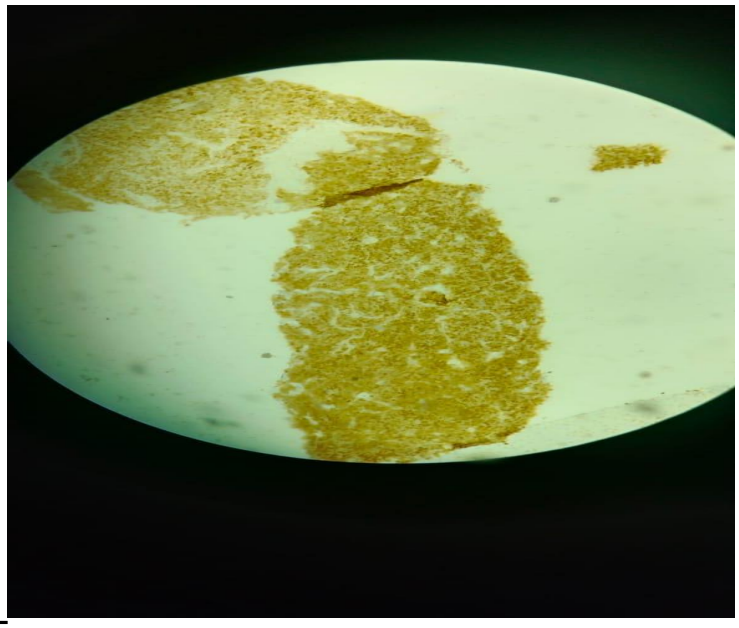
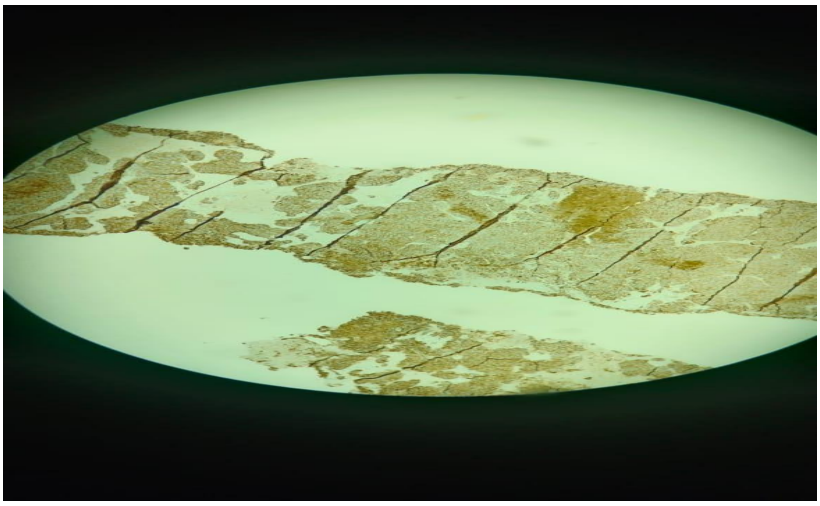




Ki 67 90% **INSM1 positive**



CK7 +

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Discussion

Gallbladder neuroendocrine neoplasms (GB-NENs) represent an uncommon subset of gallbladder malignancies, often associated with aggressive clinical behavior and diagnostic challenges. This case series of 15 patients provides valuable insight into their clinicopathological, radiological, and immunohistochemical characteristics, reflecting the regional disease profile and outcomes from a tertiary oncology center in India.

The majority of patients in this study were female (80%), with a mean age of 56.7 years, consistent with existing literature showing female predominance in gallbladder cancers. Abdominal pain was the most frequent symptom (100%), followed by jaundice and loss of appetite in a minority of cases. Radiologically, over half of the patients (53.3%) demonstrated hepatic invasion, highlighting the disease's aggressive nature at diagnosis.

The female predominance observed can be partly attributed to the higher prevalence of chronic cholelithiasis and hormonal factors that predispose women to gallbladder pathology. The frequent hepatic invasion observed in imaging likely reflects late clinical presentation and the thin anatomical interface between the gallbladder and liver parenchyma, facilitating tumor spread.

Histopathologically, small cell neuroendocrine carcinoma (SCNEC) was the most common subtype (66.6%), followed by neuroendocrine tumor grade 3 (NET G3) and mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN). This distribution is consistent with previous reports by Zhang et al. (2019) and Albores-Saavedra et al. (2004), who noted that SCNEC is the predominant and most aggressive form of GB-NENs.

Positive expression of PanCK, INSM1, and Chromogranin confirmed neuroendocrine differentiation. INSM1, a relatively novel marker, showed superior sensitivity for detecting poorly differentiated NECs compared to traditional markers. The high Ki-67 index (>50%) in most SCNEC cases corroborated the high proliferative and aggressive biological behavior of these tumors.

The study findings are in concordance with those of Moran et al. (2017) and Roy & Chetty (2016), who demonstrated similar clinicopathological behavior and poor survival outcomes in patients with small cell variants. Additionally, Igarashi et al. (2021) emphasized the prognostic significance of multimodal therapy combining surgical resection and systemic chemotherapy — an observation relevant to the management strategies in our patient cohort.

Cisplatin–Etoposide and Carboplatin–Etoposide regimens were used in all patients, yielding partial responses in several cases, particularly in those without distant metastasis. However, patients with hepatic or biliary invasion exhibited poorer outcomes. This supports the growing consensus that early diagnosis and multimodal management significantly influence survival.

GB-NENs can mimic adenocarcinoma both radiologically and morphologically. Therefore, IHC confirmation using INSM1, Chromogranin, and Synaptophysin is indispensable. High-grade NECs with necrosis and mitotic figures may be misdiagnosed as undifferentiated carcinoma if the neuroendocrine component is not suspected.

Despite partial responses to chemotherapy, the overall prognosis remains poor, particularly for SCNEC and MiNEN subtypes. The need for molecular characterization is crucial, as potential therapeutic targets (e.g., somatostatin receptor expression or Ki-67-driven targeted therapy) could improve management outcomes.

Generalizability

Although based on a single tertiary cancer center, the findings are relevant to populations in South and Southeast Asia, where gallbladder carcinoma is relatively common. The demographic trends, clinical presentation, and histopathological patterns observed here are likely generalizable to similar settings with high gallstone prevalence. However, variations in healthcare access and diagnostic infrastructure may influence disease detection and management in rural or resource-limited areas.

Conclusion

Gallbladder neuroendocrine neoplasms (GB-NENs) are rare but highly aggressive malignancies with diverse histopathological and immunohistochemical profiles. This case series highlights the predominance of small-cell neuroendocrine carcinoma (SCNEC) and high-grade neuroendocrine tumors (NET G3), often presenting with hepatic invasion and advanced disease at diagnosis. Also, the study shows a high incidence of gall bladder neuroendocrine neoplasms in our region within a period of one year.

Despite advancements in imaging and pathology, early detection remains challenging, and tumor markers lack specificity. Immunohistochemistry plays a crucial role in confirming diagnosis, with PanCK, INSM1, and chromogranin emerging as key markers. Given the poor prognosis and lack of standardized treatment protocols, future studies should focus on multicenter collaborations,

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molecular profiling, and targeted therapies to improve patient outcomes.

Limitations

- Small sample size — limited to 15 patients due to the rarity of GB-NENs.
- Single-center study, restricting external validity.
- Retrospective design, depending on medical record accuracy.
- Short follow-up period, preventing long-term survival analysis.
- Heterogeneity in treatment regimens, as some patients received different chemotherapy protocols based on clinical status.

Recommendations

Clinicians should suspect GB-NEN in gallbladder masses showing atypical morphology or rapid progression.
Routine inclusion of INSM1, Chromogranin, and Synaptophysin in IHC panels can enhance diagnostic precision.
Multicenter prospective studies with molecular profiling are needed to identify prognostic biomarkers and therapeutic targets.
Standardized treatment algorithms integrating surgery, systemic therapy, and immunotherapy should be developed.
Regional cancer registries should systematically document NEN cases to support epidemiological analysis.

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Conflict of interest

The authors declare no conflict of interest related to this publication.

List of abbreviations

GB Gallbladder
NEN Neuroendocrine Neoplasm
NEC Neuroendocrine Carcinoma
NET Neuroendocrine Tumor
MiNEN Mixed Neuroendocrine–Non-Neuroendocrine Neoplasm
IHC Immunohistochemistry
SCNEC Small Cell Neuroendocrine Carcinoma
CECT Contrast-Enhanced Computed Tomography
CT Computed Tomography
INSM1 Insulinoma-Associated Protein 1
CK Cytokeratin
AFP Alpha-Fetoprotein
CEA Carcinoembryonic Antigen
CA19.9 Carbohydrate Antigen 19.9
HBCHRC Homi Bhabha Cancer Hospital and Research Centre

Author biography

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

Aarushi Anupriya: Conceptualization, data collection, manuscript drafting

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Ravi Reshav: Literature review, data interpretation, and manuscript editing

Zikki Hasan Fatima: Histopathological evaluation, immunohistochemical analysis, supervision

Swarnim Kumar: Clinical data acquisition, patient management, and critical review of the manuscript

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