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RESEARCH ARTICLE
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CASE SERIES OF EXTRAPULMONARY SMALL CELL CARCINOMA IN A TERTIARY CARE CENTER OF ROHILKHAND REGION

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ABSTRACT

Background: Extra Pulmonary Small Cell Carcinoma (EPSCC) is a rare, aggressive malignancy that originates outside of the lungs, yet shares histopathological features with Small Cell Lung Carcinoma (SCLC). Extrapulmonary sites constitute 5.8% of all small cell carcinoma (SCC) cases. Unlike its pulmonary counterpart, which is more commonly recognized, EPSCC typically originates in other anatomical sites, including the gastrointestinal tract, genitourinary system, and skeletal muscular system.[1,2]

Objective: To describe the clinical presentation, histopathological characteristics, immunohisto chemical profiles of patients diagnosed with EPSCC in a tertiary care center in the Rohilkhand region over a two-year period.

Methods: A retrospective case series was conducted at the Department of Pathology, SRMS IMS, from March 2023 to February 2025. Eleven patients diagnosed with EPSCC were included. Clinical data, imaging findings, histopathological features, and immunohistochemical markers (Synaptophysin, CD56, Ki-67%) were reviewed. All patients had no evidence of a primary lung lesion.

Results: Of the 11 cases, 7 were male and 4 were female, with a median age of 60 years (range: 40–82). A history of smoking was noted in 8 patients. Primary tumor sites included the esophagus (3), urinary bladder (3), female genital tract (3), rectum (1), and oral cavity (1) Histologically, tumors demonstrated small, round to oval cells with hyperchromatic nuclei and scant cytoplasm. Immunohistochemistry confirmed neuroendocrine differentiation in all cases, with high Ki-67 proliferation indices (80–90%).

Conclusion: EPSCC is a highly aggressive tumor that can arise in various extrapulmonary locations, most commonly in the gastrointestinal and genitourinary tracts. Despite histopathological similarities to SCLC, the diagnosis of EPSCC requires thorough clinical, radiologic, and immunohistochemical evaluation to exclude pulmonary origin. Early diagnosis and staging are crucial for effective management. This study highlights the diverse presentation of EPSCC and emphasizes the need for increased awareness and further research to establish standardized treatment protocols.

INTRODUCTION

Extra Pulmonary Small Cell Carcinoma (EPSCC) is a rare, aggressive malignancy that originates outside of the lungs, yet shares histopathological features with Small Cell Lung Carcinoma (SCLC).[1] Extrapulmonary sites constitute 5.8% of all small cell carcinoma (SCC) cases. A better 3-year survival has been reported for patients with extrapulmonary small cell carcinoma (EPSCC) as compared to small cell lung cancer (19% vs 5%).[3]

Most of the cases of EPSCC arise in the gastrointestinal tract (68%), with esophagus being the most common site.[3] Head and neck SCC constitutes 11-21% of all extrapulmonary sites.[4,5,6] The largest series retrospectively reviewed a cancer database in Southeast England over 34 years and found 1600 cases of EPSCC, with gastrointestinal origin occurring most commonly (33%) followed by genitourinary (20%), head and neck (11%), and breast (10%)

This tumor typically demonstrates a high propensity for early metastasis, often to the liver, bones, and brain. The exact molecular mechanisms driving EPSCC are not fully understood, but like its pulmonary counterpart, it is associated with mutations in tumor suppressor genes such as p53 or RB1, leading to uncontrolled cellular proliferation and resistance to apoptosis. The presence of bone metastases in EPSCC patients is associated with a poor overall survival rate, as these lesions often cause severe complications such as pain, fractures, and spinal cord compression.[7]

Histologically, EPSCC is identical to pulmonary small cell carcinoma: round to oval small cells with hyperchromatic nuclei, inconspicuous nucleoli, and scant cytoplasm.[8] Given its pathologic similarity to pulmonary small cell carcinoma, it is important to ensure that newly diagnosed tumors are true primary sites of disease and not metastases from a pulmonary tumor.

Immunohistochemically, EPSCC shows both epithelial and primitive neuroendocrine differentiation, often staining positive for markers such as chromogranin A and synaptophysin. Given its rarity, epidemiologic data for EPSCC are limited.[8]

As we delve into each case, we will discuss the presenting symptoms and the histopathologic diagnosis and review the current literature pertaining to each condition, placing our findings in the context of existing knowledge and highlighting any novel aspects observed in our cases. By presenting these challenging diagnoses, we hope to contribute to the growing body of knowledge on rare extrapulmonary small cell carcinomas and provide valuable insights that may aid clinicians in navigating similar cases in their own practice.

MATERIAL AND METHODS

A retrospective case series was conducted at the Department of Pathology at SRMS IMS, over a period 2years from March 2023 to March, 2025. During the study period, a total of 11 patients were diagnosed with extrapulmonary small cell carcinoma. Among these cases, one was located in the oral cavity, four in the gastrointestinal tract (GIT), 3 in the urinary bladder, and 3 in the female genital tract (FGT).

By definition, patients were included if they had no parenchymal lung lesion found on chest CT scan, sputum cytology and/or bronchoscopic examination. The histological criteria for the diagnosis of EPSCC was similar to that of SCLC: round to oval small cells with hyperchromatic nuclei, stippled “salt & pepper” chromatin, inconspicuous nucleoli, and scant cytoplasm. Crushing artifacts and nuclear molding was noted in 5 cases. All cases expressed a neuroendocrine antigen such as synaptophysin or CD56 as a result of immunohistochemistry analysis. Ki67% index was found to be high in all the cases (80-90%).

Clinical data, histopathological features, and IHC profiles were retrieved from departmental archives. All patients provided informed consent. Parameters evaluated included age, gender, primary site of tumor, history of smoking, clinical features, radiological findings, histological findings and IHC.

RESULTS

A total of 11 patients with EPSCC were seen at the Department of Pathology, SRMS IMS, Barielly, for a period of 2 years since March,23- March,25. Their detailed clinical characteristics at presentation are outlined in **Table I**.

Of the 11 patients, 4 were female and 7 were male.

Their median age at diagnosis was 60years (ranging from age 40-82).

History of smoking was associated with 8 cases.

Of the anatomic sites of primary tumors, esophagus and urinary bladder were the most frequent sites (accounting for 27% each), followed by uterine cervix (18%). Remaining 27% accounted for one case each from tongue (9%), rectum (9%) and vagina (9%).

In this series of extrapulmonary small cell carcinoma (EPSCC) cases, the clinical features closely correlate with the primary site of the tumor. Lesions in the base of the tongue presented with a non-healing ulcer and pain. Esophageal tumors (mid and lower) commonly caused dysphagia and weight loss. Rectal involvement led to bleeding per rectum and abdominal pain. Urinary bladder tumors typically presented with hematuria, increased frequency, or pain during urination. Cervical and vaginal tumors were associated with abnormal vaginal bleeding and pelvic pain.

All cases were confirmed on histopathology- classic features of small cell carcinoma—small round to oval cells with hyperchromatic nuclei, stippled “salt & pepper” chromatin, inconspicuous nucleoli and scant cytoplasm. Areas of crushing artifact, nuclear molding, frequent mitotic figures and necrosis were also seen. This was supported with immunohistochemical (IHC) markers including Synaptophysin, CD56 and Ki67% labelling index (done to see tumor proliferation). All tumor cells showed diffuse cytoplasmic positivity for synaptophysin. Membranous positivity in tumor cells for CD56 was noted in all cases. Ki67% index was found to be high in all the cases (80-90%). (Fig: 1-4).

Table 1: Clinicopathological Profile of Patients with EPSCC

Case	Age (year)	Gender	Primary site	Clinical features	Smoking	Radiological findings	Histological findings
1.	40	Male	Base of Tongue	Non healing ulcer and pain.	Yes	N/A	Sheets and nest of small sized atypical cells. Hyperchromatic nuclei, stippled chromatin, inconspicous nucleoli. Crushing artifact. Nuclear moulding.
2.	70	Male	Lower esophagus	Dysphagia	No	Circumferential mural thickening causing luminal narrowing.	Sheets of mono-morphic tumor cells showing hyperchromatic nuclei, inconspicuous nucleoli, stippled chromatin and scant cytoplasm. Necrosis and mitotic figures
3.	57	Female	Mid esophagus	Dysphagia, weight loss	Yes	N/A	Sheets of round to spindled neoplastic cells with hyper-chromatic nuclei and scant cytoplasm. Mitosis and necrosis
4.	67	Male	Mid & Lower esophagus	Weight loss, dysphagia.	Yes	Esophageal enhancing circumferential mural thickening	Round to oval hyperchromatic tumor cells with scant cytoplasm and inconspicous nucleoli. Nuclear molding.
5.	82	Male	Rectum	Bleeding per rectum and pain in abdomen	Yes	Concentric enhancing wall thickening in rectum	Small to medium hyperchromatic cells with scant cytoplasm and inconspicous nucleoli. Crushing artifact, necrosis and mitosis

						extending up to anal verge	
6.	43	MALE	Urinary Bladder	Hematuria, increased frequency	Yes	Thickening of bladder wall with exophytic contour bulge in perivascular space	Small to medium hyperchromatic cells with inconspicous nucleoli, stippled chromatin. LVI seen
7.	50	MALE	Urinary Bladder	Hematuria, pain in micturation	Yes	Thickening of right lateral wall and trigone of bladder.	Medium sized hyperchromatic cells with scant cytoplasm and stippled chromatin. LVI seen. necrosis and mitosis. Nuclear moulding.
8.	68	Male	Urinary Bladder	Hematuria, pain in abdomen	Yes	N/A	Round to oval cells with hyper-chromatic nuclei, stippled chromatin, scant cytoplasm. Tumor invades muscularis propria
9.	69	Female	Cervix	Bleeding per vagina, lower abdominal pain.	No	N/A	Medium round to oval hyperchromatic cells, scant cytoplasm. Frequent mitosis.
10.	58	Female	Cervix	Bleeding per vagina	Yes	N/A	Sheets of hyperchromatic cells with scant cytoplasm. Nuclear molding and crushing artifact
11.	62	Female	Vagina	Bleeding per vagina	No	Well defined lobulated mildly enhancing mass lesion of soft tissue with intraluminal extension.	Small round cells with hyperchromatic nuclei, inconspicuous nucleoli, scant cytoplasm. Frequent mitosis and nuclear molding.

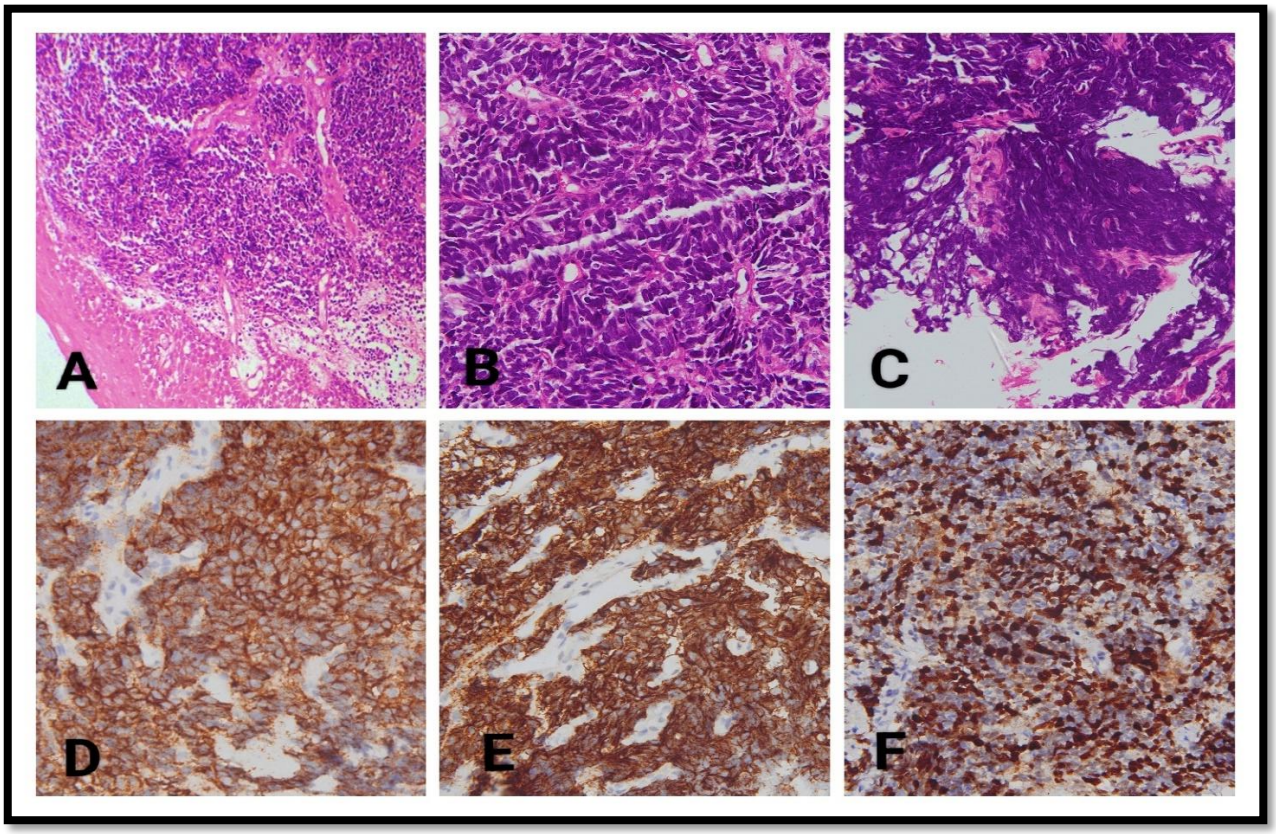

FIGURE 1: SMALL CELL CARCINOMA ESOPHAGUS
A) H&E(10x): Tissue lined by stratified squamous epithelium. Sub-epithelium is infiltrated by small round tumor cells arranged in sheets.
B) H&E(40x): Tumor cells showing hyperchromatic nuclei, stippled chromatin, inconspicuous nucleoli and scant cytoplasm. Frequent mitosis and nuclear molding seen.
C) H&E(40x): Crushing artifact
IMMUNOHISTOCHEMISTRY
D) CD56: Tumor cells showing diffuse membranous positivity
E) Synaptophysin: Diffuse cytoplasmic and membranous positivity
F) Ki67% index: 85-90%

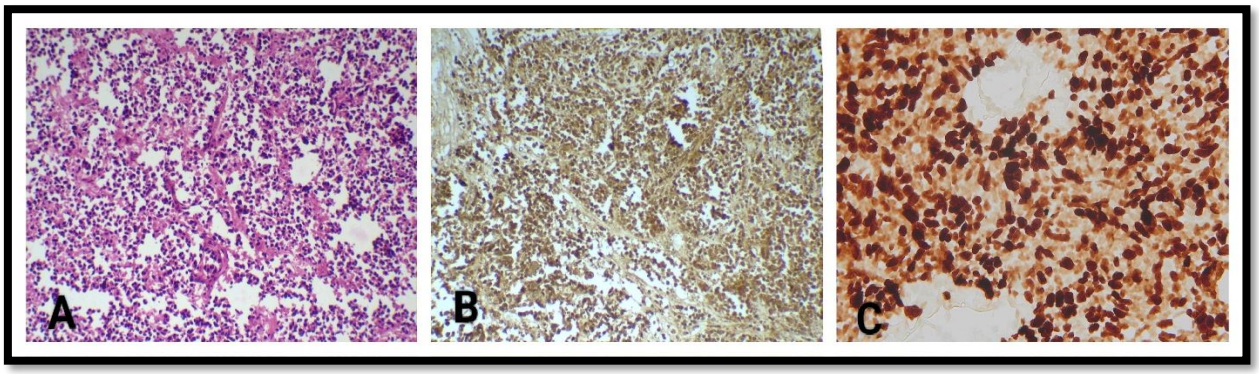

FIGURE 2: SMALL CELL CARCINOMA URINARY BLADDER
A) H&E: Small round tumor cells arranged in sheets
B) IHC: Tumor cells showing diffuse cytoplasmic positivity for Synaptophysin
C) Ki67%- 90%

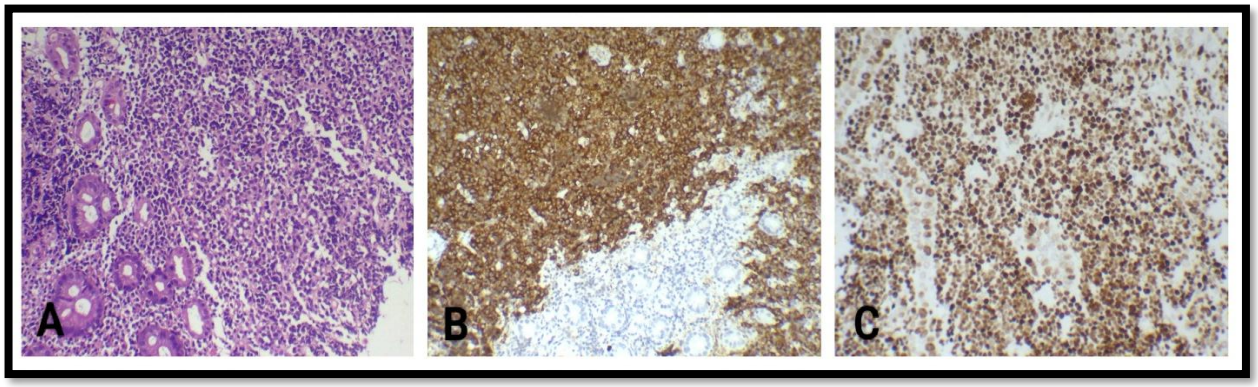

FIGURE 3: SMALL CELL CARCINOMA RECTUM
A) H&E: Small round tumor cells infiltrating the stroma adjacent to colonic glands
B) IHC: Tumor cells showing diffuse positivity for Synaptophysin
C) Ki67% index- 85-90%

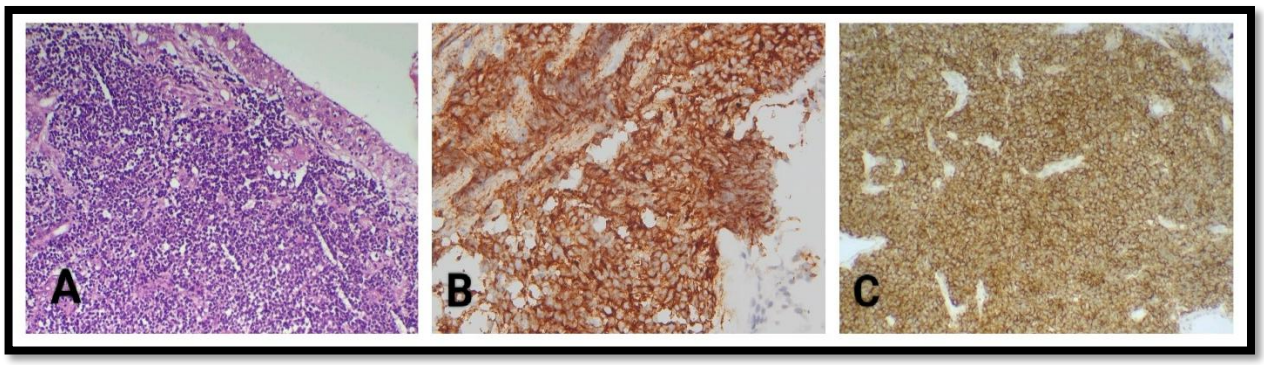

FIGURE 4: SMALL CELL CARCINOMA CERVIX
A) H&E: Tissue lined by Stratified squamous epithelium. Sub-epithelium infiltrated by small round tumor cells arranged in sheets.
B) IHC: Tumor cells showing diffuse cytoplasmic positivity for synaptophysin
C) IHC: Tumor cells showing diffuse membranous positivity for CD56.

DISCUSSION

Extrapulmonary small cell carcinoma (EPSCC) is an uncommon but highly aggressive neoplasm, sharing morphological and immunohistochemical characteristics with small cell lung carcinoma (SCLC), yet arising in non-pulmonary locations.[3] In our retrospective case series of 11 patients over a two-year period, EPSCC presented predominantly in the gastrointestinal tract and urinary bladder, consistent with previously published data that identify these as common extrapulmonary sites.[3,4,9]

Within the GI tract, in this study esophagus primary tumors are more frequent which co-relates with previous study.[10]

Male predominance observed in present study (63.6%). This co-relates with previous studies showing male predominance in cases of EPSCC. [4,11,12,13]

Across all anatomical sites, symptoms are primarily localized to the organ involved. Common features such as bleeding, pain, or functional obstruction (e.g., dysphagia, hematuria) reflect the aggressive nature of small cell carcinomas, characterized by rapid growth, early invasion, and neuroendocrine behavior. Recognizing these patterns is crucial for early detection and appropriate management of extrapulmonary small cell carcinoma.

Strong association with smoking was seen in present study (72.7%) which aligns with the epidemiologic profile documented in earlier studies.[14]

Histopathological examination in all cases revealed classic features of small cell carcinoma—small round to oval cells with hyperchromatic nuclei, stippled chromatin, scant cytoplasm, nuclear molding, crushing artifacts—alongside characteristic immunohistochemical positivity for neuroendocrine

markers such as synaptophysin and CD56. High Ki-67 proliferation indices (ranging from 80% to 90%) further underscore the aggressive biological behavior of these tumors.
Interestingly, the female genital tract accounted for nearly one-third of the cases, with involvement of the cervix and vagina. All the patients presented with vaginal bleeding. This distribution, while less commonly reported, highlights the necessity of considering EPSCC in differential diagnoses of small round blue cell tumors in gynecologic pathology.
This study contributes to the limited Indian literature on EPSCC and underscores the need for a high index of suspicion, especially in atypical tumor sites. Furthermore, the inclusion of immunohistochemistry as a routine diagnostic tool proved indispensable in confirming the diagnosis and guiding treatment planning.
Due to the rarity and heterogeneous presentation of EPSCC, further multi-institutional studies are required to establish evidence-based guidelines for diagnosis, staging, and treatment. Raising clinical awareness and expanding pathological reporting will be key to improving outcomes in patients with this challenging diagnosis.

CONCLUSION

Extrapulmonary small cell carcinoma represents a rare, aggressive malignancy that can occur across a variety of anatomical sites. In our case series, the most frequent primary locations were the esophagus and urinary bladder, with a notable number of cases also arising in the female genital tract. The disease predominantly affected older males and was frequently associated with smoking.

Histopathological and immunohistochemical evaluation remains essential for diagnosis, given the tumor's morphological overlap with other small round cell malignancies. The aggressive nature of EPSCC necessitates prompt recognition and multidisciplinary management.

LIMITATIONS

The study is limited by its small sample size, restricting generalizability. It is retrospective in nature and lacks follow-up data on treatment response or patient outcomes.
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Ethical Approval: Obtained.
Consent: Written consent secured.

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