Section: Pathology

Original Research Article

THE HISTOPATHOLOGICAL GAMUT OF NEUROENDOCRINE TUMOURS: A CROSS SECTIONAL RETROSPECTIVE STUDY AT A TERTIARY CARE HOSPITAL IN ROHILKHAND REGION OF NORTH INDIA

Shanu Gupta[1], Era Bhardwaj[2], Atul Ramdas Sonar[3], Azmat Kamal Ansari[4], Shabana Andleeb Ansari[5], Dhruv Goel[6], Abhinav Pandey[7]

[1]Assistant Professor, Department of Pathology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, India.
[2]Assistant Professor, Department of Pathology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India.
[3]Assistant Professor, Department of Pathology, Dr Ulhas Patil Medical College, Jalgaon, Maharashtra, India.
[4]Assistant Professor, Department of Biochemistry, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, Uttar Pradesh, India.
[5]Associate Professor, Uttar Pradesh University of Medical Sciences, Saifai, Etawah India.
[6]Associate Professor, Department of Orthopedics, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India.
[7]Associate Professor, Department of Community Medicine, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India.

Received *: 27/04/2025*
Received in revised form *: 13/06/2025*
Accepted *: 03/07/2025*

Corresponding Author:
Dr. Shabana Andleeb Ansari,
Associate Professor, Uttar Pradesh University of Medical Sciences, Saifai Etawah, India.
Email: shabanazulkifl@gmail.com

DOI: 10.70034/ijmedph.2025.3.52

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (3); 289-296

ABSTRACT

Background: Neuroendocrine Tumours (NETs) are a heterogeneous group of tumours with diverse biology and clinical behaviours that vary according to tumour site, type of neuroendocrine cells and grading of the tumour.

Materials and Methods: A retrospective, observational study was carried out at the Department of Pathology, Shri Ram Murti Smarak (SRMS) Institute of Medical sciences (IMS), Bareilly. All the cases diagnosed as neuroendocrine tumour or neuroendocrine carcinoma (NEC) from January 2022 to December 2024 were included. Typing of the tumour was done according to WHO classification. We used Chromogranin A (CgA), Synaptophysin, CD56 and Ki67 Immuno-histochemical markers for confirmation of neuroendocrine etiology.

Results: The study composed of total 52 cases which were archived from the Hospital Information System. The maximum number of cases were belonged to gastrointestinal tract (28.84%) followed by lung and gall bladder each comprised of 11.53%. In our study 25% cases are of grade 1 NET, 15.4% of grade 2 NET, 13.4% of grade 3 NET and 46.20% of poorly differentiated neuroendocrine carcinoma. Most of the grade 1 and 2 tumours are positive for all the three markers with strong and diffuse positivity and Ki67 proliferative index was in the range of 2-3% and 6-15% respectively. Grade 3 tumours, small cell NEC and large cell NECs were also showed positivity for all the neuroendocrine markers with somewhat reduced intensity as compared to grade 1 & 2 tumours and Ki67 proliferative index was in the range of 40-90%.

Conclusion: The effective application of WHO grading and immunomarkers like Chromogranin A, Synaptophysin, CD56, and Ki-67 proved essential for accurate diagnosis and classification. Overall, the findings offer valuable insight into regional NET patterns and call for further multicentric and longitudinal research to improve patient management.

Keywords: Neuroendocrine Tumours (NETs), Immunohistochemistry markers, Chromogranin A (CgA), Synaptophysin, CD56, Ki67.

INTRODUCTION

Neuroendocrine Tumours (NETs) are a heterogeneous group of tumours with diverse biology and clinical behaviours that vary according to tumour site, type of neuroendocrine cells and grading of the tumour.[1,2] The specific and interesting morphologic and clinical features of neuroendocrine tumours have attracted the attention of pathologists, surgeons, and physicians for many years.[3] The dense core granules (DCGs) signifies the 'neuro" characteristics of the tumour which is similar to the neurons which stores monoamines while "endocrine" property refers to the synthesis and secretion of these monoamines.[1,4,5] The neuroendocrine (NE) system includes endocrine glands, such as the pituitary, the parathyroids, and the neuroendocrine adrenal, as well as endocrine islet tissue embedded within glandular tissue (thyroid or pancreatic) and scattered cells in the exocrine parenchyma, such as endocrine cells of the digestive and respiratory tracts. If we see the distribution of neuroendocrine cells, neuroendocrine tumours have been described in the many system such as central nervous system, respiratory tract, the larynx, gastrointestinal tract, thyroid, skin, breast, and urogenital system.[6] The gastrointestinal tract and lungs are the most common primary tumor sites for neuroendocrine tumours.[7] Neuroendocrine neoplasms in various sites proved similar, since neuroendocrine, but diverse according to the secreted hormones and site of origin, pointing to the potential of almost every organ and apparatus of the human body to host such neoplastic disease.[3,8]

The biochemical evaluation of neuroendocrine tumors (NETs) plays a crucial role in their clinical assessment. The bioactive peptides and amines secreted by these tumors function as biomarkers, aiding not only in diagnosis but also in monitoring treatment response—and, in some cases, may offer prognostic insights.[9] These tumor markers are typically categorized as either specific or general. For instance, in carcinoid tumors, specific indicators include urinary 5-HIAA, neuropeptide K, substance P, and other tachykinins associated with carcinoid syndrome. In the case of endocrine pancreatic tumors (EPTs), specific markers encompass gastrin, insulin, C-peptide, proinsulin, VIP, glucagon, and somatostatin. General markers relevant to both tumor categories include chromogranins, pancreatic polypeptide, and HCG subunits.[9] Research also highlights immunohistochemical markers such as Chromogranin A (CgA), Synaptophysin, CD56, INSM1, Neuron-Specific Enolase, and PanCK as reliable indicators of neuroendocrine differentiation.[1,3,9,10,11,12,13]

MATERIALS AND METHODS

A retrospective, observational study was carried out at the Department of Pathology, at Shri Ram Murti Smarak (SRMS) Institute of Medical sciences (IMS), Bareilly. All the cases diagnosed as neuroendocrine tumour or carcinoma from January 2022 to December 2024 were included. All the cases diagnosed in this duration, irrespective of site of the lesion, were included in the present study. The data of all the patients were retrieved from Laboratory Information System (LIS) and Hospital Information System (HIS). Tumours having suspicious neuroendocrine pathology were excluded from the study. Demographic data (age, sex, clinical history etc.) were recorded from the case file of the patients. Hematoxylin and Eosin (H&E) stained slides and immunohistochemistry slides wherever done (on the basis of morphological features of tumour cells) were reviewed independently by two well trained pathologists at different time. We used the following Immune-Histochemical (IHC) markers Chromogranin A (CgA), Synaptophysin, CD56 and Ki67 for confirmation of neuroendocrine etiology. We also used other IHC panel (like CK 7, CK20, CD 45, PanCk etc) to rule out primary and common malignancy of particular site. IHC markers were performed on representative paraffin embedded section according to streptoavidine-biotin immunoperoxidase technique.

WHO grading

To establish consistency and clarity in terminology, the World Health Organization (WHO) introduced a standardized framework for classifying neuroendocrine tumors based on cellular differentiation and proliferative activity.[3,14] According to this system well-differentiated neoplasms—which preserve the morphological and molecular traits of normal neuroendocrine cells—are categorized as neuroendocrine tumors (NETs). These are further stratified into three prognostic grades: G1, G2, and G3, a system that has demonstrated reliability and applicability particularly in tumors of the respiratory and gastrointestinal tracts.[3,15,16] In contrast poorly differentiated neoplasms, characterized by pronounced cellular atypia and significantly altered molecular or genetic features, yet still expressing neuroendocrine markers, are designated as neuroendocrine carcinomas (NECs). NECs are inherently high-grade malignancies and are subclassified into small-cell (SCNEC) and large-cell (LCNEC) variants. These classification criteria have been officially incorporated into the 5th edition of the WHO classification, now titled the Classification of Endocrine and Neuroendocrine Tumors.[3,17]

For grading of the NETs, mitotic count should be evaluated in a 2 mm2 hotspot area (roughly equivalent to 10 high power fields with a 40x objective lens).[18] Ki67 index should be estimated in ≥ 500 cells in the hotspot regions,[19] If there is any discrepancy between mitotic index and Ki67 index, the higher should be considered for the classification.[20]

Sr. No.	Grading of the tumour	Mitosis	Ki67 index
I	Well differentiated NET		
A.	Low grade or grade 1 (G1)	< 2 per 2 mm^2	< 3%
B.	Intermediate grade or grade 2 (G2)	2 - 20 per 2 mm^2	3 - 20%
C.	High grade or grade 3 (G3)	> 20 per 2 mm^2	> 20%

RESULTS

The study composed of total 52 cases which were archived from the Hospital Information System from January 2022 to December 2024. Out of which 30 were (57.7%) males and 22 (42.3%) were females with male to female ratio of (1.36:1) [Table 1]. There was a wide age range (24-82 years) with peak incidence was found in the age group between 41-60 years. [Table 2]

Out of 52 cases, maximum number of cases were belonged to gastrointestinal tract (28.84%) followed by lung and gall bladder each comprised of 11.53%. Neuroendocrine tumours of liver and ovary comprised of 9.61% each. There were three cases of both urinary bladder and pancreas while two patients presented with breast lump and mediastinal mass. There were five cases belonged to unusual sites like Abdominal nodule, Pituitary gland, Vaginal swelling, Inguinal swelling and Bronchial mass. We had six cases which were not pure neuroendoocrine neoplasms rather they were associated with some other malignancies. Out of these six cases, two cases were of breast having mucinous carcinoma and invasive breast carcinoma with neuroendocrine differentiation. Single case of gall bladder having adenocarcinoma with neuroendocrine differentiation, single case of vaginal swelling diagnosed as squamous cell carcinoma with neuroendocrine differentiation, one case of urinary bladder having urothelial carcinoma with neuroendocrine differentiation and one case of lung mass having both the features of small cell carcinoma alongwith adenocarcinoma. We also had five cases of liver SOL which were diagnosed as NET grade 3 (one case), Large cell neuroendocrine carcinoma (one case) and three cases of small cell neuroendocrine carcinoma. Three of the five cases were diagnosed as metastatic neuroendocrine carcinoma after thorough clinical, biochemical and imaging analysis while rest two were considered as primary. (Table 3)

In our study 25% cases are of grade 1 NET having monotonous uniform cells with round to oval nuclei, salt and pepper chromatin and moderate cytoplasm. Mitotic count is less than 2/2mm2. The percentage of grade 2 NET are 15.4%. The cells show mild pleomorphism with round to oval nuclei, salt and pepper chromatin and moderate eosinophilic cytoplasm. Mitotic count is approximately 2-20/2mm2. Grade 3 NETs (WDNEC) comprised of 13.4% with moderate pleomorphism and mitotic count is >20/2mm2. Focal area of necrosis is also seen. We have maximum number of cases of poorly differentiated neuroendocrine carcinoma (46.20%). These tumour cells show solid sheet like proliferation with marked cellular atypia, high mitotic rates, areas of necrosis and apoptotic debris. Neuroendocrine carcinoma with small cell morphology comprised of 58.33% while large cell neuroendocrine carcinoma contributed 41.67%. Small cell NEC showed high N:C ratio, hyperchromasia, nuclear molding while large cell NEC cells are more rounded with marked pleomorphism and prominent nucleoli. (Table 4)

Grade 1 tumours are most commonly seen in GIT (Fig 1) followed by pancreas, gall bladder and ovary while Grade 2 tumours are again most commonly seen in GIT followed by ovary, breast and pituitary. In our study most common site for grade 3 tumours are GIT followed by gall bladder, liver wand ovary. Small cell NEC is most commonly seen in lung (Fig 2) followed by liver (Fig 3) and gall bladder while two cases of urinary bladdder, lung and GIT showed features of large cell NEC. (Table 5)

We applied Chromogranin, Synaptophysin, CD56 and Ki67 immunohistochemical markers in all the 52 cases. There were total 13 grade 1 NET, all of them showed positivity for Synaptophysin, 12 cases showed positivity for CD56 (Fig 4) and 11 cases were positive for chromogranin (CgA) and Ki67 proliferative index was in the range of 2-3%. There were total 8 cases of grade 2 NET, all of them were positive for CD56, six were positive for synaptophysin and seven cases showed positivity for CgA while Ki67 proliferative index was in the range of 6-15%. Out of seven grade 3 NET, all the cases were positive for CgA, synaptophysin and CD56 except single case which was negative for synaptophysin. Poorly Differentiated NEC were divided into two groups on the basis of cell morphology, small cell NEC and large cell NEC. In small cell category all the 14 cases were positive for CD56 (Fig 5), 12 cases were positive for synaptophysin (Fig 6, Fig 7) while 11 cases showed positivity for CgA and Ki67 proliferative index was in the range of 40-90% (Fig 8). There were 10 cases of large cell NEC, Nine cases were positive for synaptophysin and CD56, eight cases were positive for CgA while Ki67 proliferative index was in the range of 60-90%. In most of the cases other IHC markers like CK7, CK20 and CD45 were also applied to rule out common epithelial malignancy (of that particular organ) as well as Non Hodgkin's Lymphoma. For example we have applied CK20 which was negative in grade 1 NET of GIT to rule out adenocarcinoma of intestine (Fig 9) and PanCk positivity was shown by small cell NEC arising from liver (Fig 10). (Table 6)

Table 1: Distribution of cases according to gender of the patients

Sr. No.	Gender of the patient	Total no. of cases	Percentage (%)
1.	Male	30	57.70
2.	Female	22	42.30
	Total	52	100

Table 2: Distribution of cases according to age of the patients

Sr. No.	Age of the patient	Total no. of cases	Percentage (%)
1.	0-40 years	09	17.31
2.	41- 60 years	23	44.23
3.	> 60 years	20	38.46
	Total	52	100

Table 3: Distribution of the cases according to the site

Sr. No.	Site	No. of cases	% of cases
1	Gastrointestinal tract	15	28.84%
2	Lung	6	11.53%
3	Gall bladder	6	11.53%
4	Liver	5	9.61%
5	Ovary	5	9.61%
6	Urinary Bladder	3	5.76%
7	Pancreas	3	5.76%
8.	Breast	2	3.84%
9	Mediastinal Mass	2	3.84%
10	Abdominal nodule	1	1.92%
11	Pituitary gland	1	1.92%
12	Vaginal swelling	1	1.92%
13	Inguinal swelling	1	1.92%
14	Bronchial mass	1	1.92%
	Total	52	100%

Table 4: Distribution of cases according to grade of the tumour on histomorphological examination

Sr. No.	Grade of the tumour	Total No. of cases	% of cases
1.	Grade 1	13	25%
2.	Grade 2	08	15.4%
3.	Grade 3	07	13.4%
4.	Poorly Differentiated NEC	24	46.20%
	4a. Small cell carcinoma 4b. Large cell carcinoma	14 10	
	Total	52	100%

Table 5: Distribution of cases according to grade and site of the tumour

Sr. No.	Grade of the tumour	Site	No. of cases
1.	Grade 1 NET	GIT	06 (46.15%)
		Pancraes	03 (23.07%)
		Ovary	02 (15.38%)
		Gall Bladder	02 (15.38%)
2.	Grade 2 NET	GIT	03 (37.5%)
		Breast	02 (25%)
		Ovary	02 (25%)
		Pituitary	01 (12.5%)
3.	Grade 3 NET	GIT	03 (2.85%)
		Gall Bladder	02 (28.57%)
		Liver	01 (14.28%)
		Ovary	01 (14.28%)
4.	Small Cell NEC	Lung	04 (28.57%)
		Liver	03 (21.42%)
		Gall Bladder	02 (14.28%)
		GIT	01 (7.14%)
		Urinary Bladder	01 (7.14%)
		Bronchial Biopsy	01 (7.14%)
		Vaginal wall	01 (7.14%)
		Mediastinal Mass	01 (7.14%)
5.	Large Cell NEC	Lung	02 (20%)
		GIT	02 (20%)
		Urinary Bladder	02 (20%)
		Liver	01 (10%)
		Inguinal swelling	01 (10%)
		Abdominal nodule	01 (10%)
		Mediatinal mass	01 (10%)

Table 6: Distribution of the cases according to the grade of the tumour and positivity of IHC markers

Sr. No.	Grade of the tumour	IHC interpretation	Immunohistochemistry markers			
			CgA	Synaptophysin	CD56	Ki67
1.	Grade 1	**Positive**	11	13	12	2-3%
		Negative	02	0	01	
2.	Grade 2	**Positive**	07	06	08	6-15%
		Negative	01	02	00	
3.	Grade 3	**Positive**	07	06	07	25-30%
		Negative	00	01	00	
4.	Poorly Differentiated NEC					
4a.	Small cell carcinoma	**Positive**	11	12	14	40-90%
		Negative	03	02	00	
4b.	Large cell carcinoma	**Positive**	08	09	09	60-90%
		Negative	02	01	01	

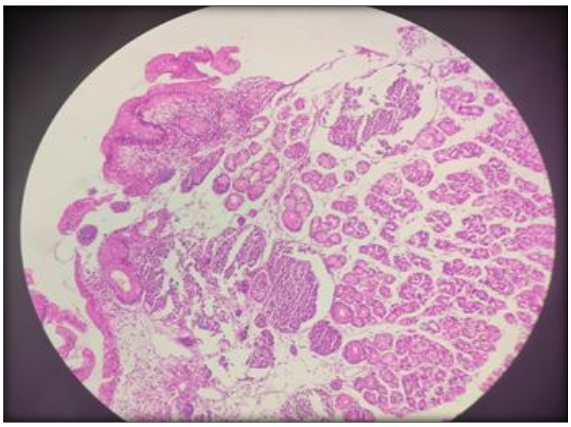

Figure 1: Carcinoid tumour of GIT (H&E, 200X)

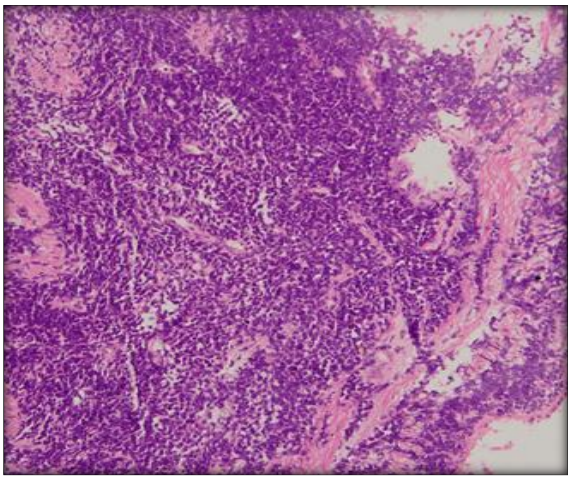

Figure 2: Small cell carcinoma lung (H&E, 100X)

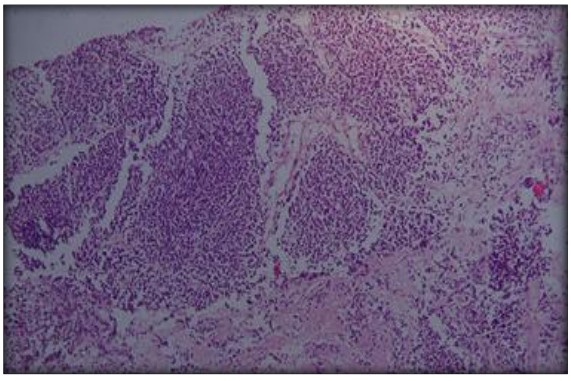

Figure 3: Small Cell Neuroendocrine carcinoma of liver (H&E, 200X)

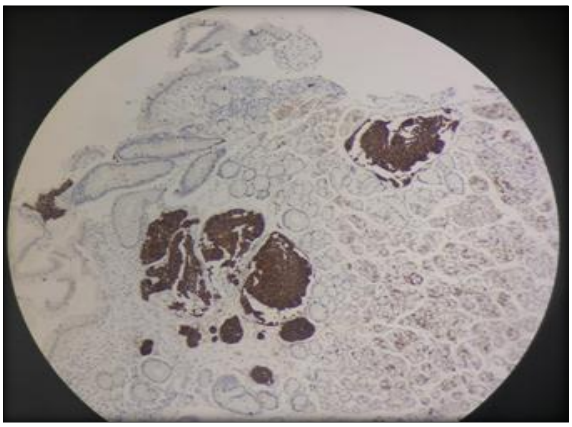

Figure 4: Carcinoid tumour of GIT showing strong and diffuse cytoplasmic positivity of CD56 (200X)

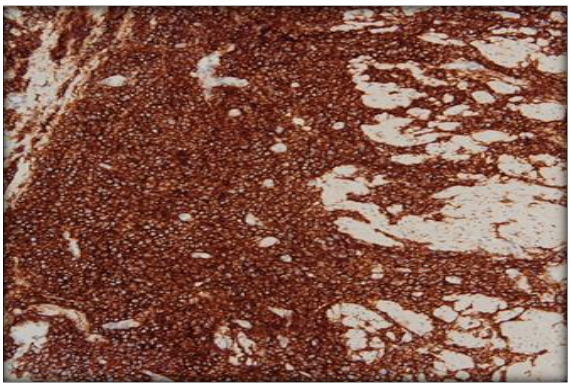

Figure 5: Small cell carcinoma– Strong cytoplasmic staining of CD56 in tumour cells (100X)

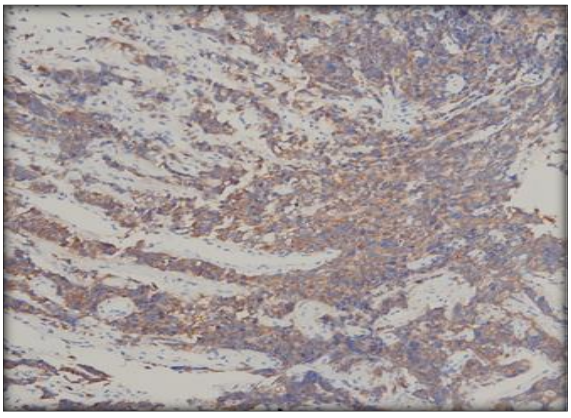

Figure 6: Small cell carcinoma– Moderate cytoplasmic staining of Synaptophysin in tumour cells (100X)

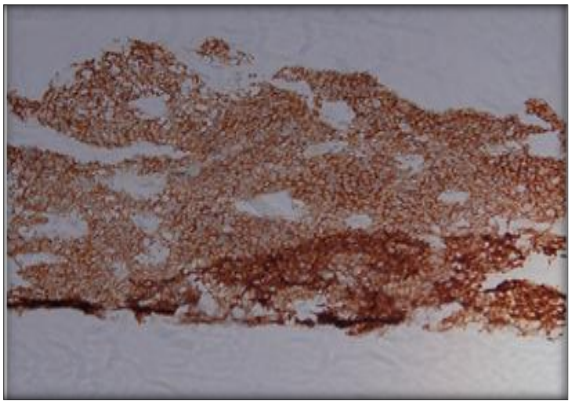

Figure 7: Neuroendocrine carcinoma of liver, showing strong positive cytoplasmic Synaptophysin staining (200X)

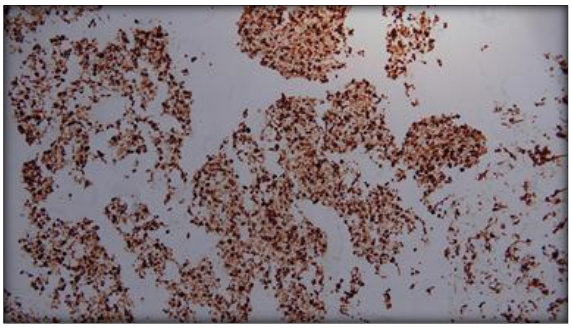

Figure 8: Neuroendocrine carcinoma of liver: showing Ki67 proliferative index of approximately 90% (200X)

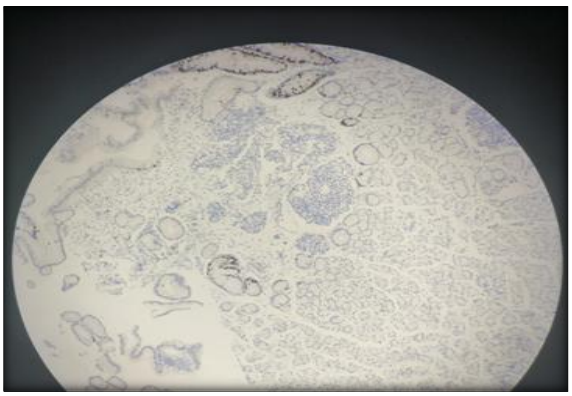

Figure 9: Carcinoid tumour of GIT showing negative CK 20 (200X)

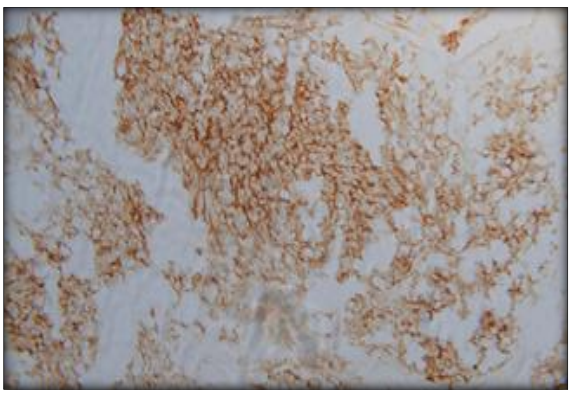

Figure 10: Neuroendocrine carcinoma of liver, showing positive cytoplasmic PanCK staining (400X)

DISCUSSION

Neuroendocrine tumours (NETs) represent a diverse spectrum of neoplasms arising from neuroendocrine cells and exhibiting a wide range of clinical and pathological behaviors.[1,2] In this retrospective analysis conducted over a three-year period at a tertiary care hospital in the Rohilkhand region of North India, we documented 52 cases, offering a cross-sectional glimpse into the histopathological landscape of NETs in this geographic population.

The male predominance (57.7%) observed aligns with trends noted in global literature, suggesting a subtle gender bias possibly linked to hormonal or environmental factors which is similar to results shown by Munita Bal et al in their study conducted in the year 2021,[21] The peak incidence in the 41–60 years age group further reflects the midlife presentation pattern frequently reported in NET epidemiology.[22]

Our study demonstrated a predilection of NETs for the gastrointestinal tract (28.84%), consistent with existing evidence highlighting the GIT as a primary site of origin. Our results are in concordance with a previous studies done by Warsinggih et al,[23] in year 2020, Oronsky B et al,[1] in the year 2017 and Estrozi B et al,[24] in the year 2011. This was followed by the lung and gall bladder (11.53% each), with the liver and ovary emerging as secondary hotspots (9.61%). Notably, this study identified NETs arising from uncommon sites such as the pituitary gland, vaginal and inguinal swellings, and bronchial and mediastinal masses—highlighting the protean nature of these tumors and the importance of heightened clinical suspicion, especially in atypical presentations.

It is interesting to note that in present study, all the cases (03/03) of pancreatic NET were of grade I which is similar to the study done by Estrozi B et al,[24] in June 2011.

A significant finding in our cohort was the high proportion (46.2%) of poorly differentiated neuroendocrine carcinomas (NECs), surpassing well-differentiated NETs (grades 1–3), which collectively comprised 53.8%. This skew suggests potential referral bias to our tertiary centre or a true regional increase in aggressive tumor biology—warranting further investigation into environmental or genetic contributors in this population.

Morphologically, small cell NECs represented the majority (58.33%) of poorly differentiated cases, largely arising from the lung and liver, while large cell NECs showed a more heterogeneous site distribution. Our histological grading correlated well with expected mitotic activity and nuclear features, reaffirming the utility of WHO classification in stratifying prognostic behavior.

Immunohistochemical analysis revealed that CD56 and synaptophysin were the most consistently expressed markers across all grades, especially in high-grade tumors, whereas chromogranin A showed variable expression, particularly in poorly

differentiated NECs. The Ki-67 proliferative index emerged as a reliable adjunct in grading, ranging from 2–3% in grade 1 NETs, 6-15% in grade 2 NETs and 40-90% in poorly differentiating NECs. The use of ancillary markers like CK20, CK7, CD45, and PanCK was pivotal in excluding differential diagnoses such as adenocarcinomas and lymphomas—reinforcing the critical role of a broad IHC panel in the diagnostic workup of NETs.

Present study shows strong expression of Chromogranin A (11/13 grade 1, 07/08 grade 2 and 07/07 grade 3) and synaptophysin (13/13 cases for grade 1, 06/08 for grade 2 and 06/07 for grade 3 tumors) which is similar to study done by Oronsky B et al,[1] which stated that well-differentiated NET cells produce abundant secretory granules with intense immunoexpression of neuroendocrine markers such as chromogranin A (CgA) and synaptophysin (Syn). Our results were in contrast, to a study done by Oronsky B et al,[1] where NECs demonstrated more limited expression of immunohistochemical markers (diffuse expression of synaptophysin, faint or focal staining for Chromogranin A (CgA) due to less cytoplasmic secretory granules. Our study reveals more positivity of CgA and synaptophysin expression in Poorly differentiated NECs.

Importantly, this study identified six cases exhibiting combined histology—neuroendocrine differentiation alongside conventional adenocarcinoma or squamous carcinoma—underscoring the diagnostic challenges posed by mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs). These hybrid tumours may have distinct clinical behaviour and therapeutic responses and should be carefully documented and studied further.

The observation of metastatic NETs, particularly among liver SOLs, highlights the imperative for robust clinical, biochemical, and imaging correlation. This also points toward the liver's dual role as both a primary and secondary site—reinforcing its central importance in NET diagnostics and staging.

Our study had certain limitations like retrospective study, a small sample size, inadequate follow-up, and lack of molecular characterization. Nonetheless, the present study provides a rare data on histopathological and epidemiological aspect of NETs that further expands the knowledge of the morphologic and clinical spectrum.

CONCLUSION

This cross-sectional retrospective study provides a comprehensive overview of the histopathological and immunohistochemical spectrum of neuroendocrine tumors (NETs) in the Rohilkhand region of North India. The findings underscore the heterogeneity of NETs in terms of anatomical distribution, tumor grade, and morphological presentation. A notable predominance of poorly differentiated NECs, particularly small cell variants, suggests an aggressive clinical profile in this cohort, emphasizing the need for early and accurate diagnosis. The study highlights the utility of a detailed histomorphological assessment supported by immunohistochemistry—including Chromogranin A, Synaptophysin, CD56, and Ki-67 index—for definitive classification and grading. The presence of combined histologies and rare anatomical sites further illustrates the diagnostic challenges associated with NETs and underscores the importance of a multidisciplinary approach integrating clinical, radiological, and pathological data. Ultimately, this research reinforces the applicability of WHO grading criteria in resource-limited settings and provides valuable epidemiological insight into NET presentation in a North Indian population. Future multicentric studies with longitudinal follow-up may help elucidate prognostic markers and therapeutic outcomes, paving the way for personalized patient management strategies.

REFERENCES

1. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing But NET: A Review of Neuroendocrine Tumors and Carcinomas. Neoplasia. 2017;19(12):991–1002. doi:10.1016/j.neo.2017.09.002
2. Oberg K. Neuroendocrine tumors (NETs): historical overview and epidemiology. Tumori. 2010 Sep-Oct;96(5):797-801. doi: 10.1177/030089161009600530. PMID: 21302634.
3. Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, Brosens LAA, Ezzat S, de Herder WW, Klimstra DS, Papotti M, Asa SL. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. Endocr Pathol. 2022 Mar;33(1):115-154. doi: 10.1007/s12022-022-09708-2. Epub 2022 Mar 16. PMID: 35294740.
4. Scalettar BA, Jacobs C, Fulwiler A, Prahl L, Simon A, Hilken L, and Lochner JE (2012). Hindered submicron mobility and long-term storage of presynaptic dense-core granules revealed by single-particle tracking. Dev Neurobiol 72(9), 1181–1195.
5. Kaltsas GA, Besser GM, and Grossman AB (2004). The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev 25, 458–511.
6. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008;9(1):61–72. doi:10.1016/S1470-2045(07)70410-2
7. Anaizi A, Rizvi-Toner A, Valestin J, and Schey R (2015). Large cell neuroendocrine carcinoma of the lung presenting as pseudoachalasia: a case report. J Med Case Reports 9, 56.
8. Asa SL, Lloyd RV, Tischler AS (2021) Neuroendocrine neoplasms: Historical background and terminologies. In: Asa SL, La Rosa S, Mete O, editors. The Spectrum of Neuroendocrine Neoplasia. Cham, Switzerland: Springer Nature. pp. 1–14.
9. Eriksson B, Oberg K, Stridsberg M. Tumor markers in neuroendocrine tumors. Digestion. 2000;62 Suppl 1:33-8. doi: 10.1159/000051853. PMID: 10940685.9th 2
10. Eriksson B, Arnberg H, Lindgren PG, Lörelius LE, Magnusson A, Lundqvist G, Skogseid B, Wide L, Wilander E, Öberg K: Neuroendocrine pancreatic tumours: Clinical presentation, biochemical and histopathological findings in 84 patients. J Intern Med 1990;228:103–113.
11. Wiedemann B, Huttner WB: Synaptophysin and chromogranins/secretogranins – Widespread constituents of distinct type of neuroendocrine vesicles and new tools in tumour diagnosis. Virchows Arch B Cell Pathol Incl Mol Pathol 1989;58:95–121
12. Eiden LE, Huttner WB, Mallet J, O’Connor DT, Winkler H, Zanini AA: A nomenclature proposal for the chromogranin/secretogranin proteins. Neuroscience

1987;21:1019–1021.https://doi.org/10.1016/0306-4522(87)90056-X
13. Wu HJ, Rozansky DJ, Parmer RJ, Gill BM, O’Connor DT: Structure and function of the chromogranin A gene. Clues to evolution and tissue specific expression. J Biol Chem 1991;266:13130–13134.
14. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol. 2018;31(12):1770–86. doi:10.1038/s41379-018-0110-y
15. Klimstra D, Kloppel G, La Rosa S, Rindi G (2019) Classification of neuroendocrine neoplasms of the digestive system. In: WHO Classification od Tumours Editorial Board, editors. Digestive System Tumours. Lyon: IARC Press. pp. 16-19.
16. Travis WD, Beasley M, Cree I, Papotti M, Rekhtman N, et al. (2022) Lung Neuroendocrine Neoplasms. In: WHO Classification of Tumours Editorial Board, editors. Thoracic Tumours. Lyon: IARC Press. pp. 109-111.
17. WHO Classification of Tumours Editorial Board. Thoracic tumours: WHO classification of tumours. 5th ed. Lyon, France: IARC, 2021.
18. Cagle PT, Allen TC, Olsen RJ. Lung cancer biomarkers: present status and future developments. Arch Pathol Lab Med. 2013 Sep;137(9):1191-8. doi: 10.5858/arpa.2013-0319-CR. PMID: 23991729.
19. Francesco Panzuto, Elettra Merola, Marianne Ellen Pavel, Anja Rinke, Patrizia Kump, Stefano Partelli, Maria Rinzivillo, Victor Rodriguez-Laval, Ulrich Frank Pape, Rainer Lipp, Thomas Gress, Bertram Wiedenmann, Massimo Falconi, Gianfranco Delle Fave, Stage IV Gastro-Entero-Pancreatic Neuroendocrine Neoplasms: A Risk Score to Predict Clinical Outcome, The Oncologist, Volume 22, Issue 4, April 2017, Pages 409–415, https://doi.org/10.1634/theoncologist.2016-0351
20. Ahmed M. Gastrointestinal neuroendocrine tumors in 2020. World J Gastrointest Oncol. 2020 Aug 15;12(8):791-807. doi: 10.4251/wjgo.v12.i8.791. PMID: 32879660; PMCID: PMC7443843.
21. Bal M, Sharma A, Rane SU, Mittal N, Chaukar D, Prabhash K, Patil A. Neuroendocrine Neoplasms of the Larynx: A Clinicopathologic Analysis of 27 Neuroendocrine Tumors and Neuroendocrine Carcinomas. Head Neck Pathol. 2022 Jun;16(2):375-387. doi: 10.1007/s12105-021-01367-9. Epub 2021 Aug 16. PMID: 34401980; PMCID: PMC9187832.
22. Yalcin, S. (2024). Introduction to Neuroendocrine Tumors. In: Yalcin, S., Öberg, K. (eds) Neuroendocrine Tumours. Springer, Cham. https://doi.org/10.1007/978-3-031-56968-5_1
23. Warsinggih, Liliyanto, Prihantono, et al. Colorectal neuroendocrine tumors: A case series. Int J Surg Case Rep. 2020;72:1–5. doi:10.1016/j.ijscr.2020.06.030
24. Estrozi B, Bacchi CE. Neuroendocrine tumors involving the gastroenteropancreatic tract: a clinicopathological evaluation of 773 cases. Clinics (Sao Paulo). 2011;66(10):1671–5. doi:10.1590/S1807-59322011001000002.