



DEMOGRAPHIC PATTERN AND HISTOPATHOLOGICAL PROFILE OF NEUROENDOCRINE NEOPLASMS DIAGNOSED AT A TERTIARY CARE CENTRE IN NORTH EAST INDIA

**Dr Bifica Sofia
Lyngdoh**

Assistant Professor, Department of Pathology, AIIMS, Guwahati.

**Dr Vandana
Raphael**

Professor & HOD, Department of Pathology, Neigrihms.

**Dr Yookarin
Khonglah**

Associate Professor, Department of Pathology, Neigrihms.

Dr Jaya Mishra

Associate Professor, Department of Pathology, Neigrihms.

**Dr Evarisalin
Marbaniang**

Assistant Professor, Department of Pathology, Neigrihms.

Dr Biswajit Dey

Assistant Professor, Department Of Pathology, Neigrihms.

ABSTRACT **Introduction:** Neuroendocrine tumors (NENs) are a heterogeneous group of tumours that can arise in any organ in the body and has a wide range of aggressiveness. **Objective:** To compare the frequency of NENs in our setup to those reported in literature in relation to age, site, degree of differentiation by doing a retrospective study. **Method:** Cases of NENs that were diagnosed in the department of Pathology, in our hospital over the past 5 years were studied considering the age, location, degree of differentiation. A fresh panel of IHC conducted for those cases where IHC was not done. **Results:** A total of 46 cases of NENs were reviewed. About 56.5% (26 cases) were males and 43.5% (20 cases) were females, with a median age of 46 years. In our study most of the tumors are found in the Gastro-entero-pancreatico-hepatobiliary (GEP) group followed by the NENs of endocrine gland (21.7%) and Broncho-pulmonary group (15.2%). NENs were graded based on mitotic count and/or Ki-67 labeling index, and/or the presence of necrosis. In total 21 cases (45.7%) had G1 grading, 7 cases (15.2%) had G2 grading, 2 cases (4.3%) had a G3 grading, and 16 cases (34.7%) were graded as NEC. **Conclusion:** As majority of the studies do not include benign NENs and those arising from the endocrine glands, therefore comparison of our results can be difficult. This is the first attempt to study the NENs from North East India and to analyze their clinicopathological features.

KEYWORDS

Neuroendocrine Tumors, Neuroendocrine carcinoma, Ki 67 labelling index

*Corresponding Author

INTRODUCTION

Neuroendocrine Neoplasms (NENs) are a heterogeneous group of tumors that can arise in any organ in the body and has a wide range of aggressiveness with a varied, confusing histology and nomenclature. The term Neuroendocrine is applied to widely dispersed cells with "neuro" and "endocrine" properties [1,2]. The annual age-adjusted incidence of NENs was 1.09 per 100 000 persons in 1973 and increased to 6.98 per 100 000 persons by 2012 [3]. In 2019, world health organization (WHO) published a uniform classification frame work for all NENs based on the 2017 WHO classification of neoplasms of the neuroendocrine of pancreas. The current classification of NENs comprises both the well differentiated Neuroendocrine Tumors (NETs) which are further graded as G1, G2 and G3 and the poorly differentiated Neuroendocrine carcinoma (NEC).

OBJECTIVE:

To study the demographic profile and pathological profile of NENs.

METHOD:

All patients of NENs diagnosed between January 2015, and December 2019, in the department of Pathology in our hospital were included in the study. Biopsy was performed either from the primary or from the metastatic lesion, and the biopsy specimens were analyzed with regard to the age, location, and degree of differentiation. IHC for confirmation including synaptophysin and chromogranin A, and other markers as deemed appropriate for exclusion of other diagnoses was done. Ki67 was also done in all the cases. We grouped the tumors according to their site of origin following the standard rules: Gastro-entero-pancreatico-hepatobiliary tumors (GEP), broncho-pulmonary tumors, skin tumors (merkel cell carcinoma), endocrine gland tumors

and other sites.

The frequencies were calculated for categorical variables and the median was calculated for continuous variable.

RESULTS

A study of 5 years from January 2015 to December 2019 was conducted in in our hospital and we found a total of 46 cases of NENs with an annual incidence of approximately 0.74%. About 56.5% (26 cases) were males and 43.5% (20 cases) were females.

The types of specimen received were biopsies in 35 cases, surgical specimen in 8 cases and review slides/blocks in 2 cases and one case had both biopsy and surgical specimen.

Age And Gender

The age of presentation ranged from 12 to 84 years. The most frequent age group was between 41 to 50 years with a median age of 46 years. The male to female ratio is 1.3:1.

Location

In our study most of the tumors are found in the GEP group (41.3%) followed by the NENs of endocrine glands and broncho-pulmonary group (Table 1). However if we consider an individual site the most frequent site in our study is the lung.

Table 1: Distribution Of NENs Diagnosed In Our Institute

Types of NET	Males	Females	Total	Percentage(%)
Broncho-pulmonary NENs				

SCLC	4	0	4	57.1
LCNC	1	0	1	14.3
Carcinoid	0	2	2	28.6
Total	5(71.4%)	2(28.6%)	7 (15.2%)	100
Gastro-entero-pancreatic NENs including the MiNENs				
Esophagus	4	2	6	31.6
Stomach	3	0	3	15.8
Small bowel	3	0	3	15.8
Colon & Rectum	2	0	2	10.5
Pancreas	1	0	1	5.3
Gall bladder	0	1	1	5.3
Liver	1	2	3	15.8
Total	14(73.6%)	5(26.3%)	19 (41.3%)	100
Endocrine gland NENs				
Thyroid	1	1	2	20
Adrenal	0	1	1	10
Parathyroid	0	1	1	10
Pituitary	2	4	6	60
Total	3 (30%)	7(70%)	10 (21.7%)	100
Paraganglioma				
Carotid body	0	3	3	50
Vagus nerve	0	1	1	16.7
Retroperitoneum	0	1	1	16.7
Spinal Mass	1	0	1	16.7
Total	1 (16.7%)	5(83.3%)	6 (13%)	100
Skin NENs				
Merkel cell carcinoma	0	1(100%)	1 (2.2%)	100
Primary unknown NENs	1(100%)	0	1(2.2%)	100
Other Origin NENs(extradural dorsal vertebral lesion)	1 (100%)	0	1(2.2%)	100
Mets with no primary tissue	1(100%)	0	1 (2.2%)	100
Total	26 (56.5%)	20 (43.5%)	46	

In the GEP group there were total of 19 cases (41.3%) out of which 4 had a mixed neuroendocrine and epithelial neoplasms (MiNENs). In the GEP group most common location is the esophagus (6 cases) out of which 2 cases had mixed NENs and squamous cell carcinoma, followed by liver (3 cases), small bowel (3 cases) and, stomach (3 cases). Out of the 3 cases in the stomach, 2 had mixed NEN and adenocarcinoma. There are 2 cases arising in the colon and rectum, and one case each from the gall bladder and, pancreas.

There were 7 cases (15.2%) in broncho-pulmonary group. In the endocrine gland NENs, there were 10 cases (21.7%) out of 6 were arising from the pituitary gland, 2 cases from the thyroid gland and one case each from the adrenal and parathyroid gland.

Six cases (13%) of paraganglioma were noted out of which 3 cases were arising from the carotid body, one case each arising from vagus nerve, spinal mass, and retroperitoneum. There was one case each arising from the skin, other origin NENs (extradural dorsal vertebral lesion), from lymph node metastasis with no primary tissue and a metastasis with known primary but no primary tissue.(Figure 1)

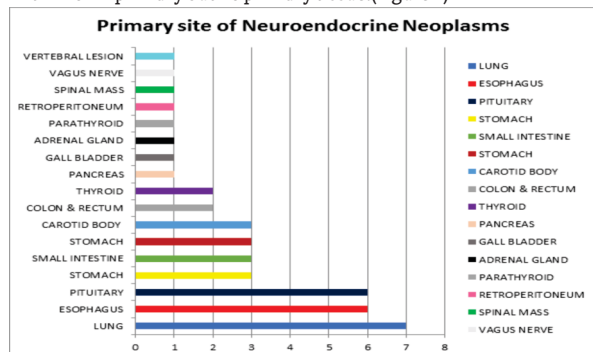


Figure 1: Showing frequency of the primary site of NENs

Degree Of Differentiation

In the GEP group around 8 cases were well differentiated, 7 cases are poorly differentiated. In the 4 MiNENs, the neuroendocrine component showed a poorly differentiated morphology in 3 cases and a well differentiated morphology in one case.

In the broncho-pulmonary group, 5 cases are poorly differentiated and 2 cases are well differentiated.

Among the NENs arising from the endocrine gland and paragangliomas all had a well differentiated appearance.

A case of Merkel cell carcinoma was classified as poorly differentiated carcinoma NEC.

The one case of NEN arising from extradural dorsal vertebral lesion showed a well differentiated tumor whereas the NEN arising from lymph node metastasis and also from a metastasis from a known case of NEN of lung but with no primary tissue showed a poor differentiation.

Grading Of The NETs

Grading of the GEP and broncho-pulmonary NENs were done as per the WHO 2019 classification.

In the GEP group, 3 cases were graded as G1, two cases as G2, 1 case as G3 and 9 cases as small cell NEC.

In the broncho-pulmonary group 3 cases were graded as G1, 2 cases as G2, and 2 cases of neuroendocrine carcinoma (NEC), out of which 1 case had small cell morphology and the other had large cell morphology. (Figure 2& 3).

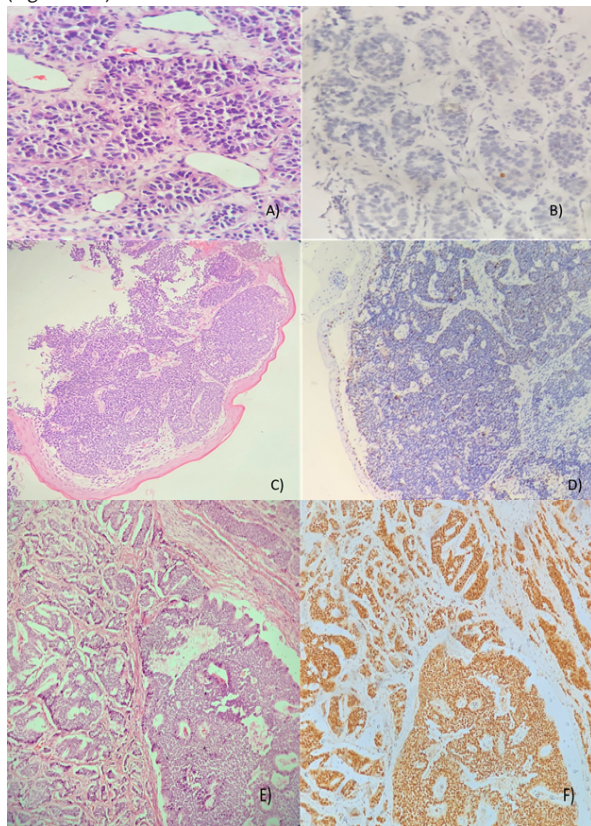


Figure 2. A) & B) Showing a Well differentiated Neuroendocrine tumor with a Ki67 <3% corresponding to Grade G1. C) & D) Showing a Well differentiated Neuroendocrine tumor with a Ki67 index between 3-20% corresponding to Grade G2. E) & F) Showing a Well differentiated Neuroendocrine tumor with a Ki67 index > 20% corresponding to Grade G3.

Ki-67 labelling index was done in all cases of NENs arising from the endocrine glands, paragangliomas, pheochromocytoma and all of them had low mitotic counts.(Table 2)

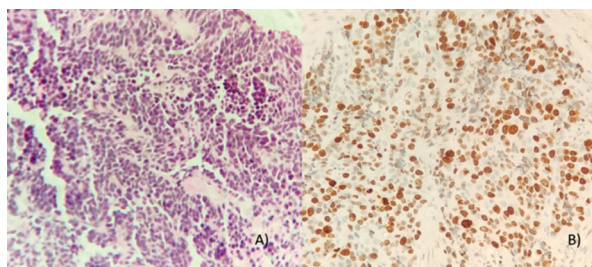


Figure 3. A) & B) Showing a Poorly differentiated Neuroendocrine carcinoma (small cell type) with a Ki67 index > 20%

Table 2: Ki-67 Labelling Index

Histological diagnosis	No of cases	Average Ki 67 index labelling
Paraganglioma	6	<1%
Medullary carcinoma thyroid	2	<1%
Phaeochromocytoma	1	<1%
Parathyroid adenoma	1	1%
Pituitary adenoma	4	2.5%
Invasive pituitary adenoma	2	6.5%

We have received 9 surgical specimens and their TNM staging is shown in Table 3

Table 3 Showing The TNM Staging Of The Surgically Resected Specimens

Serial no	Organ	TNM staging
1.	Caecum	pT ₁ N ₁ M ₁
2.	Caecum	pT ₁ N ₀ M ₀
3.	Ileum	pT ₂ N ₁ M ₀
4.	Stomach	pT ₁ N ₀ M ₀
5.	Stomach	pT ₁ N _{3a} M ₀
6.	Duodenum	pT _{1a} N ₁ M ₀
7.	Thyroidectomy	pT1N1M0
8.	Thyroidectomy	pT3N0M0
9.	Adrenalectomy	pT ₁ N ₀ M ₀

DISCUSSION

The histopathological classification of neuroendocrine tumors in different organs using site-specific terminologies and criteria has created a lot of confusion among pathologists and clinicians. From the recent WHO classification it is understood that NENs are divided into NETs and NEC. NETs are well differentiated and further graded as G1, G2 and G3 depending on the number of mitosis/hpf or based on the Ki67 labelling index and NEC are the poorly differentiated tumors with either small cell or large cell morphology.

In our study the median age of presentation was 46 years which was similar to an Indian study done by Kulkarni [4] et al where the median age of presentation was 49 years. The age at presentation in both is early compared to those found in western literature [5,6].

In our study most of the tumors were in the GEP group (41.3%) followed by NENs of the endocrine glands (21.7%) and broncho-pulmonary group (15.2%). However when you consider individual site, then the most frequent site was found in the lung (15.2%) followed by esophagus and pituitary, 13% each. A study done by Valizadeh N [7] et al found the most frequent site was the gastrointestinal (GI) system (44.11%) followed by lung in six patients (17.64%). However in a study done by Maria Alsina [1] et al it was found to be the broncho-pulmonary system (65.75%), followed by the GEP (12.75%). In a study done by Silvera [8] et al the most frequent primary site was the lung (36%), followed by the stomach (12.5%), and the small intestine (9%).

Among the GEP group in our study the most common location is the esophagus (31.6%), followed by liver, small bowel and stomach 15.8% each. In a study conducted by Arco [9] et al the most common location among the GEP group was pancreas (15.3%) followed by stomach (12.9%), colon (10.9%), and rectum (8.1%) and, small bowel (8.1%).

MinEN are defined as neoplasm in which each component represents at least 30% of the lesion. In our study, we have 4 cases of MinENs with 2 cases from esophagus, which had mixed NENs and squamous cell

carcinoma and, 2 cases from stomach, which had mixed NENs and adenocarcinoma. In literature also it is seen that the squamous cell carcinoma is the most common component in esophageal and anorectal MinENs and adenocarcinoma are more commonly observed in gastric MinENs [10].

NENs from the endocrine glands are classified differently unlike those from the GEP or broncho-pulmonary system. In the thyroid, NENs are those tumors that arise from the C-cells and are named the medullary thyroid carcinoma (MTC). Majority of these MTC are well differentiated tumors and only <1% are poorly differentiated. Ki 67 index in majority of them is <1%, even then limited studies have suggested that Ki67 alone or in combination with RET mutation have some prognostic significance [11,12,13].

According to the WHO 2004 Pituitary tumor were divided into adenoma, atypical adenoma and carcinoma. Atypical adenoma are those tumors having atypical morphological features suggestive of aggressive behaviour such as invasion growth. Other features included elevated mitotic index and a Ki-67 labeling index greater than 3%, as well as extensive nuclear p53 immunostaining. The reported incidence of atypical adenoma varies widely, ranging from 2.9% to 18.7%. Even after > 10 years of research on the utility of this classification, prognostic significance could not be established [14,15,16]. However, Ki 67 can be combined with other parameters like tumor size, clinical presentation, invasiveness on MRI, presence of metastasis or spinal spread and additional IHC to be prognostically significant.

The parathyroid tumors are classified by WHO as adenomas, atypical adenomas, or carcinomas. Malignancy is diagnosed based on invasive growth, evidenced by vascular invasion, full penetration of the tumor capsule with extension into the surrounding non-neoplastic tissues, or metastases. In parathyroid carcinomas the Ki-67 labeling index is often >5% compared with adenomas and hyperplastic nodules, even though there is a significant overlap. Therefore, although the Ki-67 labeling index, mitotic counts, and necrosis are often used as markers of aggressive behavior, they are not part of a formally defined diagnostic grading scheme [17].

Many grading system were also introduced and Ki67 index were given a cutoff value of <1%, 1-3% and >3% in pheochromocytomas and paragangliomas but the value of these scoring system still remains unclear [17].

CONCLUSION

According to our biopsy statistics the incidence of NENs in our hospital is 0.74%. There are very few Indian studies done on NENs and from the few studies including this study, it was found that the age at presentation is much early than those seen in the west. Also even though the grading system is well established in the GEP and the broncho-pulmonary system, it is not so well defined for other systems and hence a confusion exists in grading them. Therefore there is a need to create an awareness of these tumors in India and also encourage more multi-institutional studies so that there is a better understanding of the epidemiological and clinical profile of this disease in our country.

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