ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Demographic pattern and histopathological profile of neuroendocrine neoplasms diagnosed at a tertiary care center in North East India

Bifica Sofia Lyngdoh[1], Vandana Raphael[2], Yookarin Khonglah[3], Jaya Mishra[4], Evarisalin Marbaniang[5], Biswajit Dey[6]

[1]Assistant Professor, Department of Pathology, All India Institute of Medical Sciences, Guwahati, Assam [2]Professor and Head, [3]Professor, [4,5]Additional Professor, [6]Associate Professor, Department of Pathology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, NEIGRIHMS, Shillong, Meghalaya, India

Submission: 16-11-2023 Revision: 26-12-2023 Publication: 01-02-2024

ABSTRACT

Background: Neuroendocrine tumors (NENs) are a group heterogenous group of tumors that can arise in any organ in the body and have a wide range of aggressiveness. **Aims and Objective:** To compare the frequency of NENs in our setup to those reported in the literature to age, site, and degree of differentiation by doing a retrospective study. **Materials and Methods:** 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, and degree of differentiation. A fresh panel of immunohistochemistry (IHC) was 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-hepatobilliary group followed by the NENs of the 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 neuroendocrine carcinoma. **Conclusion:** As the 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.

Key words: Neuroendocrine tumors; Neuroendocrine carcinoma; Ki-67 labeling index

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v15i2.59946

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a heterogenous group of tumors that can arise in any organ in the body and have 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 1.09/100,000 persons in 1973 and increased to 6.98/100,000 persons by 2012.[3] In 2019, the World Health Organization (WHO) published a uniform classification framework for all NENs based on the 2017 WHO classification of neoplasms of the neuroendocrine 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).

Aims and Objectives

The aim of the study was to study the demographic profile and pathological profile of NENs.

Address for Correspondence:
Dr. Bifica Sofia Lyngdoh, Assistant Professor, Department of Pathology, All India Institute of Medical Sciences, Guwahati, Assam, India.
Mobile: +91-8420192563. **E-mail:** bifica1986@gmail.com

MATERIALS AND METHODS

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 the metastatic lesion, and the biopsy specimens were analyzed with regard to the age, location, and degree of differentiation. Immunohistochemistry (IHC) for confirmation including synaptophysin and chromogranin A, and other markers as deemed appropriate for exclusion of other diagnoses was done. Ki-67 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 variables.

RESULTS

A study of 5 years from January 2015 to December 2019 was conducted 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 specimens received were biopsies in 35 cases, surgical specimens in eight cases, review slides/blocks in two cases, and one case had both biopsy and surgical specimens.

Age and gender

The age of presentation ranged from 12 to 84 years. The most frequent age group was between 41 and 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 the broncho-pulmonary group (Table 1). However, if we consider an individual site the most frequent site in our study is the lung.

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

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

Six cases (13%) of paraganglioma were noted, out of which three 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 metastasis with known primary but no primary tissue (Figure 1).

Degree of differentiation

In the GEP group, around eight cases were well differentiated, and seven cases were poorly differentiated. In the four MiNENs, the neuroendocrine component showed a poorly differentiated morphology in three cases and a well-differentiated morphology in one case.

In the broncho-pulmonary group, five cases are poorly differentiated and two cases are well differentiated (Figure 2).

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

Grading of the NETS

Grading of the GEP and broncho-pulmonary NENs was done as per the WHO 2019 classification (Figures 3-5).

In the GEP group, three cases were graded as G1, two cases as G2, one case as G3, and nine cases as small cell NEC.

In the broncho-pulmonary group, three cases were graded as G1, two cases as G2, and two cases of NEC, out of which one case had small cell morphology and the other had large cell morphology.

Ki-67 labeling index was done in all cases of NENs arising from the endocrine glands, paragangliomas, and

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 and 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	

NENs: Neuroendocrine tumors, MiNENs: Mixed neuroendocrine and epithelial neoplasms

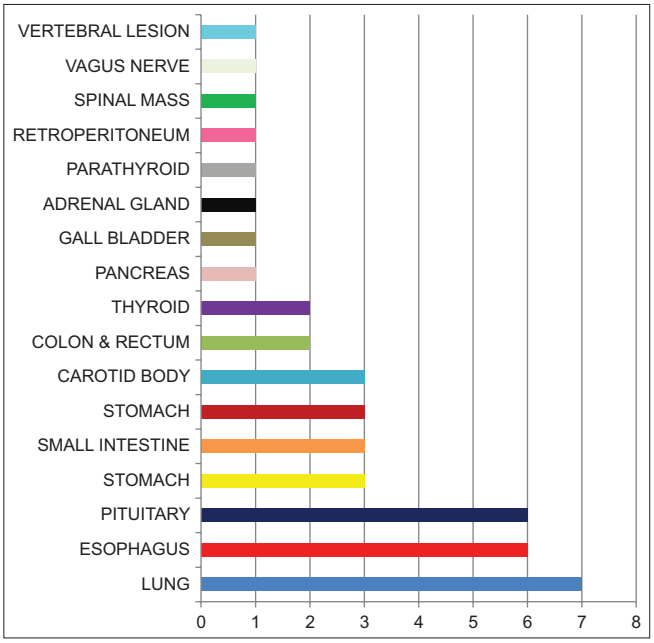

Figure 1: Frequency of the primary site of neuroendocrine tumors

pheochromocytoma and all of them had low mitotic counts (Table 2).

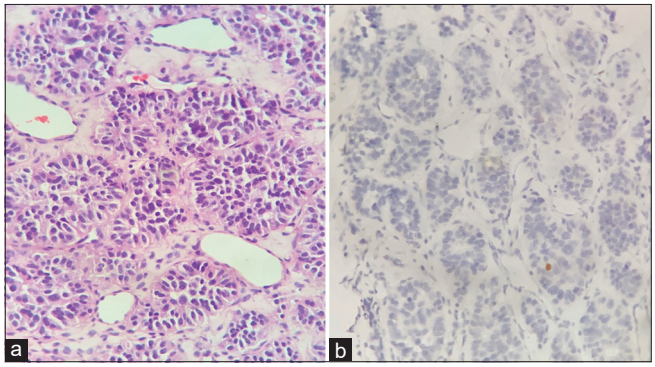

Figure 2: (a and b) A well-differentiated neuroendocrine tumor with a Ki-67 <3% corresponding to Grade G1

We have received nine surgical specimens and their tumor, node, and metastasis staging is shown in Table 3.

DISCUSSION

The histopathological classification of NETs 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

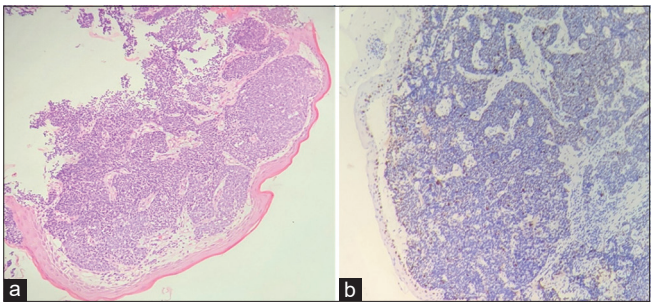

Figure 3: (a and b) A well-differentiated neuroendocrine tumor with a Ki-67 index between 3% and 20% corresponding to Grade G2

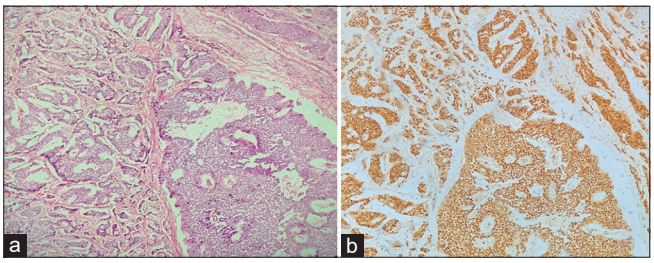

Figure 4: (a and b) A well-differentiated neuroendocrine tumor with a Ki-67 index >20% corresponding to Grade G3

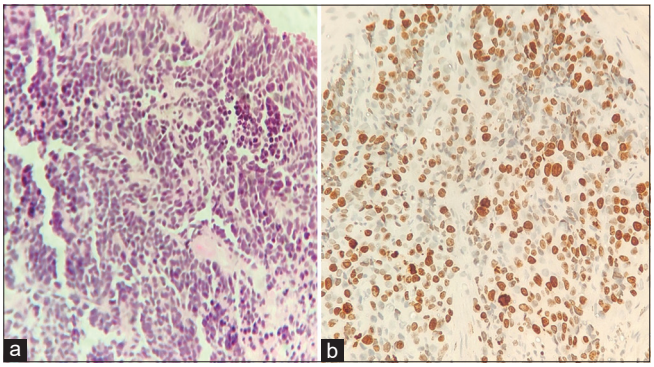

Figure 5: (a and b) A poorly differentiated neuroendocrine carcinoma (small cell type) with a Ki-67 index >20%

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 Ki-67 labeling index and NEC are 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 et al.,[4] 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 sites, the most frequent site

Table 2: Ki-67 labeling index

Histological diagnosis	No of cases	Average Ki-67 index labeling (%)
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

Table 3: The TNM staging of the surgically resected specimens

S. No.	Organ	TNM staging
1.	Caecum	$pT_4N_1M_1$
2.	Caecum	$pT_3N_0M_0$
3.	Ileum	$pT_2N_1M_0$
4.	Stomach	$pT_2N_0M_0$
5.	Stomach	$pT_3N_{3a}M_0$
6.	Duodenum	$pT_{1a}N_1M_0$
7.	Thyroidectomy	$pT1N1_bM0$
8.	Thyroidectomy	$pT3_aN_0M_0$
9.	Adrenalectomy	$pT_2N_0M_0$

TNM: Tumor, node, and metastasis

was found in the lung (15.2%) followed by the esophagus and pituitary, 13% each. A study done by Valizadeh et al.,[7] found the most frequent site was the gastrointestinal system (44.11%) followed by the lung in six patients (17.64%). However, in a study done by Alsina et al.,[1] it was found to be the bronco-pulmonary system (65.75%), followed by the GEP (12.75%). In a study done by Silveira et al.,[8] 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 the liver, small bowel, and stomach 15.8% each. In a study conducted by Del Arco et al.,[9] the most common location among the GEP group was the pancreas (15.3%) followed by the stomach (12.9%), colon (10.9%), and rectum (8.1%), and small bowel (8.1%).

MiNEN are defined as neoplasms in which each component represents at least 30% of the lesion. In our study, we have four cases of MiNENs with two cases from the esophagus, which had mixed NENs and squamous cell carcinoma, and two cases from the stomach, which had mixed NENs and adenocarcinoma. In literature also, it is seen that squamous cell carcinoma is the most common component in esophageal and anorectal MiNENs, and adenocarcinoma is 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 medullary thyroid carcinoma (MTC). The majority of these MTCs are well-differentiated tumors and only <1% are poorly differentiated. Ki-67 index in the majority of them is <1%, even then limited studies have suggested that Ki-67 alone or in combination with RET mutation has some prognostic significance.[11-13]

According to the WHO 2004, pituitary tumors were divided into adenoma, atypical adenoma, and carcinoma. Atypical adenomas are those tumors having atypical morphological features suggestive of aggressive behavior such as invasion growth. Other features included an elevated mitotic index and a Ki-67 labeling index >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.[14-16] However, Ki-67 can be combined with other parameters such as tumor size, clinical presentation, invasiveness on magnetic resonance imaging, 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 systems were also introduced and the Ki-67 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]

Limitations of the study

Limitations of the study include a small sample size and multi institutional studies from different parts of the region would have help for better understanting and generalization of the results.

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 earlier than those seen in the West. Furthermore, 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 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.

ACKNOWLEDGMENT

We would like to thank all our patients and our colleagues from the clinical branch for their participation and cooperation.

REFERENCES

1. Alsina M, Marcos-Gragera R, Capdevila J, Buxo M, Ortiz RM, Barretina P, et al. Neuroendocrine tumors: A population-based study of incidence and survival in Girona province, 1994-2004. Cancer Epidemiol. 2011;35(6):e49-e54.
   https://doi.org/10.1016/j.canep.2011.05.011
2. Basu B, Sirohi B, and Corrie P. Systemic therapy for neuroendocrine tumours of gastroenteropancreatic origin. Endocr Relat Cancer. 2010;17(1):R75-R90.
   https://doi.org/10.1677/erc-09-0108
3. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335-1342.
   https://doi.org/10.1001/jamaoncol.2017.0589
4. Kulkarni RS, Anand AS, Parikh SK, Panchal HP, Patel AA, Mehta DP, et al. Clinical and epidemiological profile of neuroendocrine tumors: An experience from a regional cancer center from Western India. South Asian J Cancer. 2019;8(3):198-202.
   https://doi.org/10.4103/sajc.sajc_364_18
5. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):3063-3072.
   https://doi.org/10.1200/jco.2007.15.4377
6. Hauso O, Gustafsson BI, Kidd M, Waldum HL, Drozdov I, Chan AK, et al. Neuroendocrine tumor epidemiology: Contrasting Norway and North America. Cancer. 2008;113(10):2655-2664.
   https://doi.org/10.1002/cncr.23883
7. Valizadeh N, Eishi Oskuie A and Mansori M. A Retrospective analysis of neuroendocrine tumors in West Azarbaijan province, Iran. Iran J Blood and Cancer. 2013;5(4):149-150.
8. Silveira F, Basile ML, Kuga FS, Próspero JD, Paes RA and Bernardi FD. Neuroendocrine tumors: An epidemiological study of 250 cases at a tertiary hospital. Rev Assoc Med Bras (1992). 2017;63(10):856-861.
   https://doi.org/10.1590/1806-9282.63.10.856
9. Del Arco CD, Sastre J, Peinado P, Díaz Á, Medina LO and Fernández Aceñero MJ. Neuroendocrine neoplasms in rare locations: Clinicopathological features and review of the

literature. Indian J Endocrinol Metab. 2018;22(3):308-315.
https://doi.org/10.4103/ijem.ijem_446_17

10. La Rosa S, Marando A, Sessa F and Capella C. Mixed adenoneuroendocrine carcinomas (MANECs) of the gastrointestinal tract: An update. Cancers (Basel). 2012;4(1): 11-30.
https://doi.org/10.3390/cancers4010011
11. Mian C, Pennelli G, Barollo S, Cavedon E, Nacamulli D, Vianello F, et al. Combined RET and Ki-67 assessment in sporadic medullary thyroid carcinoma: A useful tool for patient risk stratification. Eur J Endocrinol. 2011;164(6):971-976.
https://doi.org/10.1530/eje-11-0079
12. Tisell LE, Oden A, Muth A, Altiparmak G, Mõlne J, Ahlman H, et al. The Ki67 index a prognostic marker in medullary thyroid carcinoma. Br J Cancer. 2003;89(11):2093-2097.
https://doi.org/10.1038/sj.bjc.6601453
13. Fuchs TL, Nassour AJ, Glover A, Sywak MS, Sidhu SB, Delbridge LW, et al. A proposed grading scheme for medullary thyroid carcinoma based on proliferative activity (Ki-67 and mitotic count) and coagulative necrosis. Am J Surg Pathol. 2020;44(10):1419-1428.
https://doi.org/10.1097/pas.0000000000001505
14. Lloyd RV, Osamura RY, Kloppel G and Rosai J, editors. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: IARC; 2017.
15. Miermeister CP, Petersenn S, Buchfelder M, Fahlbusch R, Lüdecke DK, Hölsken A, et al. Histological criteria for atypical pituitary adenomas-data from the German pituitary adenoma registry suggests modifications. Acta Neuropathol Commun. 2015;3:50.
https://doi.org/10.1186/s40478-015-0229-8
16. Chiloiro S, Doglietto F, Trapasso B, Iacovazzo D, Giampietro A, Di Nardo F, et al. Typical and atypical pituitary adenomas: A single-center analysis of outcome and prognosis. Neuroendocrinology. 2015;101(2):143-150.
https://doi.org/10.1159/000375448
17. Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, 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):1770-1786.
https://doi.org/10.1038/s41379-018-0110-y

Authors Contribution:
BSL- Definition of intellectual content, literature survey, prepared the first draft of the manuscript, implementation of the study protocol, data collection, data analysis, manuscript preparation, literature survey, preparation of figures and submission of the article; **VR-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **YK-** Design of study, statistical analysis and interpretation; **JM-** Review manuscript; **EM-** Review manuscript; **BD-** Coordination and manuscript revision.

Work attributed to:
Department of Pathology, North Eastern Indira Gandhi Regional Institute of Health & Medical Sciences, NEIGRIHMS, Shillong, India.

Orcid ID:
Bifica Sofia Lyngdoh - https://orcid.org/0000-0002-2105-1347
Vandana Raphael - https://orcid.org/0000-0002-1422-2240
Yookarin Khonglah - https://orcid.org/0000-0001-7665-3372
Jaya Mishra - https://orcid.org/0000-0001-7822-9874
Evarisalin Marbaniang - https://orcid.org/0000-0002-3372-7260
Biswajit Dey - https://orcid.org/0000-0003-3332-1911

Source of Support: Nil, **Conflicts of Interest:** None declared.