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Original Research Article

Spectrum of Neuroendocrine Neoplasms – An Institutional Experience at a Tertiary Care Center

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Abstract

Background: *Neuroendocrine neoplasms (NENs) are relatively rare and heterogeneous tumor type, comprising ~2% of all malignancies. These tumours occur at various sites in the human body and are considered as one of the close differentials for many tumours. Various benign and malignant tumours undergo neuroendocrine differentiation. Its incidence is slightly increasing due to advanced imaging modalities.*

The aim of the study is to study the spectrum of neuroendocrine tumours from various sites, their clinical presentation, histomorphological features with immunohistochemistry and review of literature.

Materials and Methods: *This is a prospective study for a period of 1 year (Nov 2017-Oct 2018). Surgical resection specimens as well as biopsy were included in the study. Out of the total specimens received, 115 cases were of neuroendocrine tumours. Differential diagnosis of small round cell tumours also was considered and a panel of immunohistochemical markers were included to rule out them.*

Results: *Out of the 115 cases, 85 cases (73.9%) were benign lesions & 30 cases (26.1%) were malignant lesions. Female preponderance was noted. Peak incidence was seen in 41-60 years of age group.*

Conclusion: *Neuroendocrine tumours can occur anywhere in the body and it should be considered in one of the differential diagnosis of solid tumours. Diagnosis must be accurately made.*

Keywords: *Neuroendocrine Neoplasms, Heterogenous, Neuroendocrine Differentiation.*

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of malignancies with a varied, confusing histology and nomenclature to match. The term "neuroendocrine" is applied to widely dispersed cells with "neuro" and "endocrine" properties. The "neuro" property is based on the identification of dense core granules (DCGs) that are similar to DCGs present in serotonergic neurons, which store monoamines. (Unlike neurons, however, NE cells do not contain synapses.) The "endocrine" property refers to the synthesis and secretion of these monoamines. The neuroendocrine (NE) system includes endocrine glands, such as the pituitary, the parathyroids, and the NE 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, which belong to what is known as the diffuse endocrine system.[1] Enterochromaffin cells, which give rise to carcinoid tumours were identified in 1897 by Kulchitsky and their secretion of serotonin was established in 1953.[2] NENs have been described in pituitary, thyroid, parathyroid, thymus, breast, lung, gastrointestinal tract, urogenital tract, skin (Merkel cell carcinoma - trabecular cancer) and mediastinum.[3] Neuroendocrine tumours (NETs) account for about 0.5% of all newly diagnosed malignancies. The incidence, which is on the rise, possibly due to improved awareness is approximately 5.86/100,000 per year; with a female preponderance of around 2.5:1.[4] Based on the substances secreted and clinical syndromes, NET are divided into functioning and non-functioning tumours. For functional purposes, NENs are divided into well-differentiated, moderately-differentiated or poorly-differentiated depends on: a) Histological features, b) Size, c) Lymphovascular invasion, d) Mitotic activity, e) Ki-67 index, f) Invasion of adjacent organs, g) Presence of metastases.

Materials and Methods

This prospective study was carried out in Department Of Pathology of SMS Medical College & hospital, Jaipur; for a period of 1 year from Nov 2017 to Oct 2018. A Total of 11045 surgical and biopsy specimens were received during that period and 115 cases with histopathological diagnosis of neuroendocrine Neoplasms were included in our study. Clinical details including age, mode of presentation and pathological characteristics were analysed in all the cases. The specimens were processed routinely for histopathological examination, stained by Haematoxylin and Eosin (H&E) as well as IHC performed wherever necessary. Panel of IHC markers included were synaptophysin, Chromogranin, Neuron-Specific Enolase, Oestrogen receptor, Progesterone receptor, Her-2, CD20, Ki-67, Pan CK. The results analysed and data prepared to calculate incidence, prevalence and age and sex distribution in our area.

Results

A total of 115 cases of neuroendocrine tumours were reported which constituted 1.04% of total specimens & biopsy of during that period. [Table 1] A slight male preponderance was seen with male to female ratio of 1.27:1. [Graph 1] Our cases had varied age distribution from 9 months to 86 yrs, mean age being 44yrs. Most of cases presented in the age group 41-60 yrs (n= 39, 33.92%) followed by 21-40 yrs (n=37, 32.17%) followed by 61-80 yrs (n= 23, 20.00%) , followed by 0-20yrs (n=12yrs, 10.43%) and least common age group was >80 yrs (n=4, 3.48%). [Table 2 & Graph 2].85 [73.91%] cases were benign while 30 [26.09%] cases were malignant. Out of 85 benign cases 68 cases were of pituitary adenoma [80%] , 4[4.7%]cases of neuroblastoma, 5 [5.8%] cases of parathyroid adenoma, 4 [4.7%] cases of well differentiated pancreatic neuro endocrine tumour, 2 [2.4%] cases of collision tumour (1 being pituitary adenoma with ganglion cell tumour & other was ganglio-neuroblastoma). One [2.4%] case each of paraganglioma and bronchial carcinoid. Out of 30 malignant cases small cell carcinoma (n=20, 66.67%) was the most common malignant tumour. Two cases each of medullary carcinoma thyroid ,neuro endocrine carcinoma breast and metastatic neuroblastoma.One case each of small cell neuro endocrine carcinoma of sub glottis , poorly differentiated neuro endocrine tumour of gall bladder and metastatic neuro endocrine tumour of liver.

Clinical Features of the Tumours

1. **Pituitary Adenomas**

Pituitary adenomas constitute 10–15% of all intracranial neoplasms. All pituitary adenomas, regardless of size or hormone subtype, are WHO grade I tumors. Most adenomas usually develop in 3rd to 6th decade of life & commonly seen in males. [Figure 1A, 1B]

2. Collision tumour: Ganglioneuroblastoma composed of mixture of immature neuroblasts & ganglion cells [Figure 1C, 1D]

3. Parathyroid Adenoma: Parathyroid adenomas presented as neck mass with pressure symptoms, bony and abdominal pains. All the cases showed raised PTH, serum calcium levels.

4. Small cell carcinoma: Arise from neuro endocrine cells of basal bronchial epithelium & in histology show round to oval blue cells with minimal cytoplasm.

5. Medullary carcinoma thyroid: Neuroendocrine tumour derived from C cells of ultimobranchial body of neural crest & accounts for 1-2% of thyroid carcinoma. [Figure 2A, 2B, 2C, 2D]

6. Neuroendocrine Carcinoma of Breast: It is an uncommon tumour with incidence under 0.1%of all breast carcinoma. [3A, 3B, 3C, 3D]

7. **Pheochromocytoma:** Also called paraganglioma of adrenal medulla & causes surgically correctable hypertension.

8. Paraganglioma: It's the tumour of paraganglia with neuro endocrine expression & asymptomatic or causes symptoms due to local compression [4A, 4B]

9. Neuroblastoma: It's the primitive neoplasm of neuroectodermal origin & features depend on location and extent of tumour. [Figure 5A, 5B, 5C, 5D]

10. Pancreatic NET: It accounts for 1-2% of clinically apparent pancreatic neoplasms and demonstrate a spectrum of clinical behaviour dependent on hormone produced. [4C, 4D]

11. Gall bladder NET: The primary neuro endocrine tumors of gallbladder are very rare, representing 0.2% of all neuro endocrine tumours and diagnosed incidentally.

12. Liver metastatic NET:

13. Subglottis NET: Neuro endocrine tumours of the larynx represent a heterogeneous group of neoplasms and comprise only 0.5% of laryngeal tumours. These presents typically as a laryngeal mass.

14. Carcinoid tumour: 50% of small bowl tumours & mc in ileum, slowly growing tumour in adults in 50s.

Table 1: Incidence of Benign and Malignant Neuroendocrine Lesions

Neuroendocrine Tumours	Benign	Malignant
Pituitary Adenoma	68	0
Collision tumour	2	o
Parathyroid Adenoma	5	0
Small cell carcinoma	0	20
Medullary carcinoma- Thyroid	0	2
Neuro endocrine carcinoma Breast	0	2
Pheochromocytoma	0	1
Paraganglioma	1	0
Neuroblastoma	4	2
Pancreatic NET	4	0
GB-NET	0	1
Liver metastatic NET	0	1
Subglottis- NET	0	1
Carcinoid tumour	1	0
Total cases	85	30

Table 2: Age wise distribution

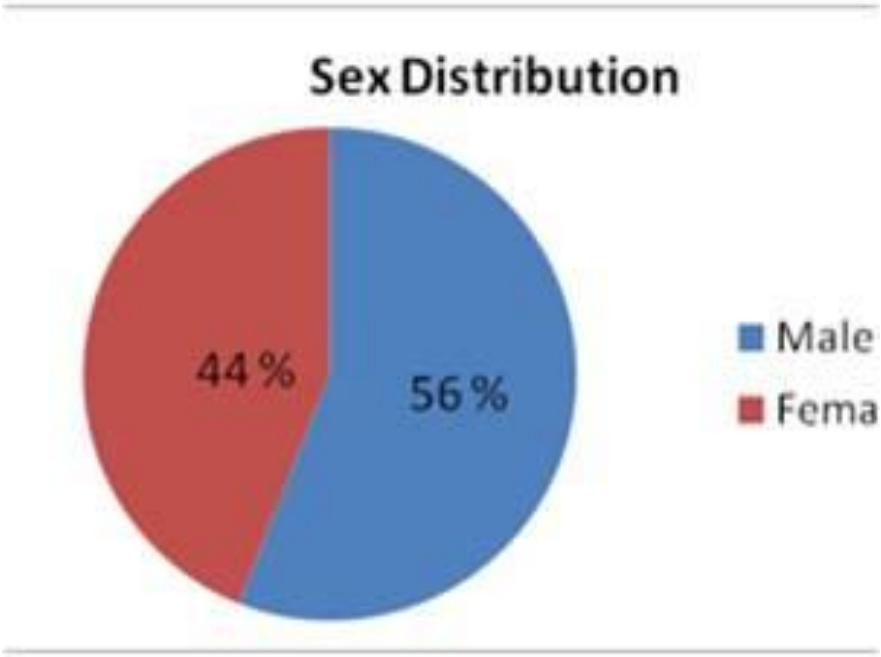
Age group	No.of cases	Frequency
0-20yrs	12	10.43%
21-40yrs	37	32.17%
41-60yrs	39	33.92%
61-80yrs	23	20.00%
>80yrs	4	3.48%
	115	100%

Table 3: Neuroendocrine tumours and clinical symptoms

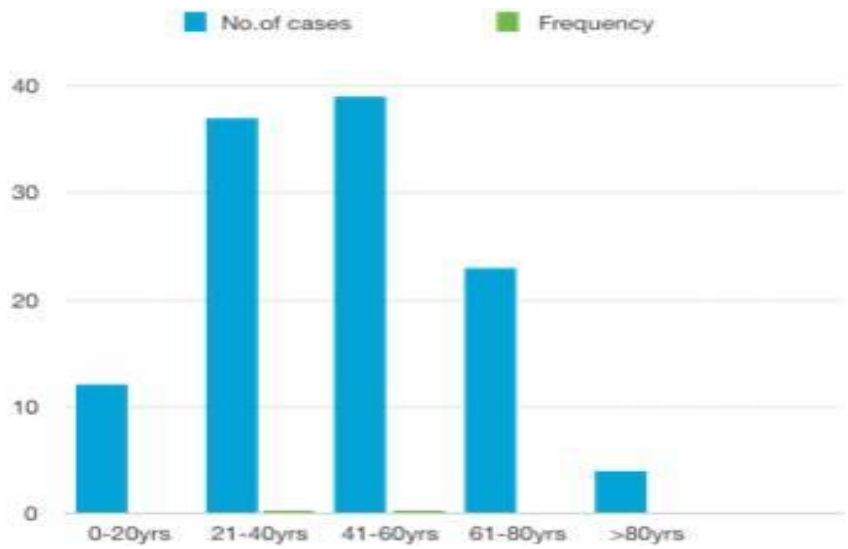
Cases	Presenting Symptoms	Hormone produced
Pituitary Adenoma	Headache, loss of vision	-
Collision tumour	-	-
Parathyroid Adenoma	Pressure symptoms	Parathyroid hormones
Small cell carcinoma	Hemoptysis	ACTH
Medullary carcinoma-Thyroid	Asymptotic	-
Neuro endocrine carcinoma- Breast	Asymptotic	-
Pheochromocytoma	Hypertension	Cortisone
Paraganglioma	Pressure symptoms	Adrenaline
Neuroblastoma	Abdominal neuroblastoma- pain. Olfactory neuroblastoma- proptosis	-
Pancreatic NET	Weight loss, Jaundice	Only in 1 case insulin production
GB-NET	Epigastric pain	-
Liver metastatic NET	Jaundice	-
Subglottis- NET	Pressure symptoms- dysphagia	-
Carcinoid tumour (Bronchial)	Pneumonia	

Table 4: NEN 2018 WHO proposed classification of selected NEN by site, category, family, and tumour type

site	Category	Family	Type	Grade	Current terminology
Lung	Neuro endocrine Neoplasm (NEN)	Neuro endocrine tumour (NET) Neuro endocrine carcinoma (NEC)	Pulmonary NET Small cell lung carcinoma (Pulmonary NEC, small cell type) Pulmonary NEC, large celltype	G1 G2	Typical carcinoid Atypical carcinoid Small cell lung carcinoma Large cell NE lung carcinoma
Uterine - cervix & corpus	Neuro endocrine neoplasm (NEN)	Neuroendocrine tumour (NET) Neuroendocrine carcinoma (NEC)	Uterine neuro endocrine tumour (NET) Uterine NEC, small cell type Uterine NEC, large cell type	G1 G2 G3	Typical carcinoid Atypical carcinoid. Atypical carcinoid Small cell NEC Large cell NEC
Pancrease	Neuro endocrine Neoplasm NEN	Neuroendocrine tumour (NET) Neuroendocrine carcinoma (NEC)	Pancreatic NET. Pancreatic NEC, Small cell type. Pancreatic NEC, Large cell type	G1 G2 G3	PanNET G1 PanNET G2. PanNET G3 Small cell NEC Large cell NEC



Graph 1: Female – Male ratio



Graph 2: Age wise distribution of cases

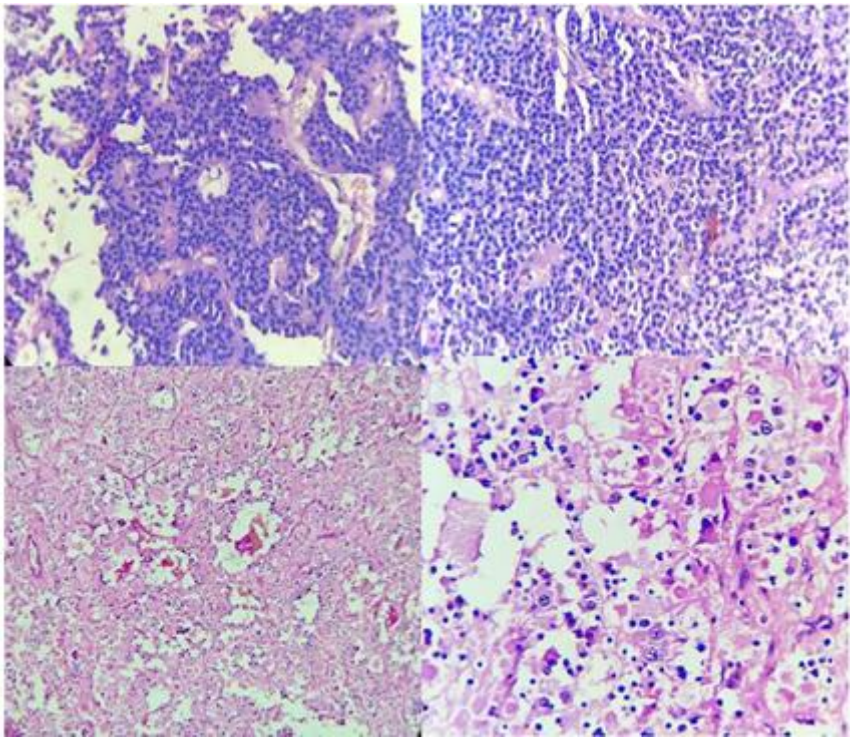


Figure: 1 Pitutary adenoma- (1A, 1B): uniform tumour cells with moderate cytoplasm, uniform nuclei with stippled chromatin (H & E, 40X, 400X); collision tumour- Ganglioneuroblastoma (1C, 1D): showing mixture of immature neuroblasts & ganglion cells. (H & E, 40X, 100X)

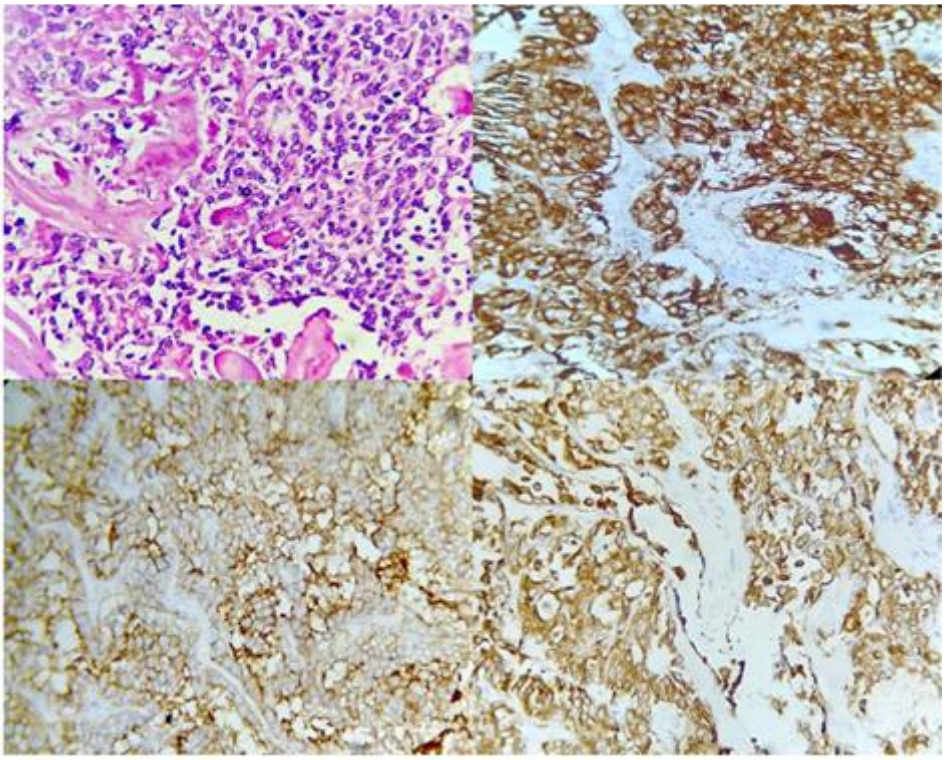


Figure: 2 Medullary carcinoma thyroid-2A, Solid sheets of tumour traversed by delicate fibrovascular septa & plump spindle cells having round to oval nuclei with finely stippled chromatin, Pink amorphous amyloid deposition in between the cells respectively (H & E, 400x); 2B: cytoplasmic immunoreactivity for calcitonin (400x); 2C: Cytoplasmic immunoreactivity of CD56 (100x); 2D: Chromgranin immuno-reactivity in cytoplasm of tumour cells (100x) ,

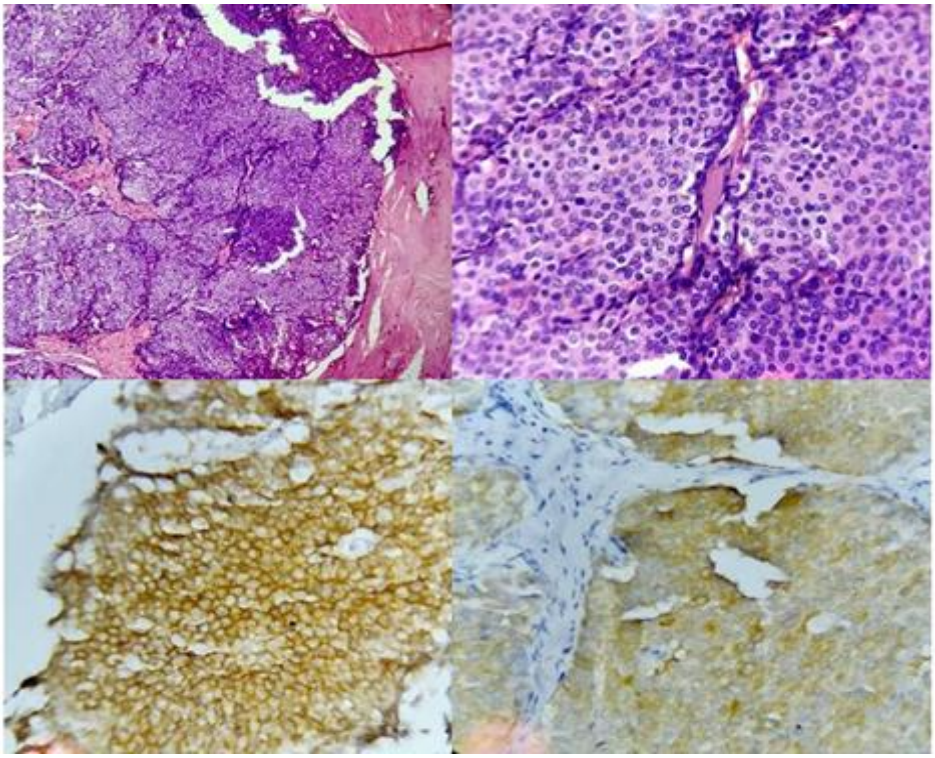


Figure: 3 Neuroendocrine carcinoma Breast – 3A, 3B: Solid nests of round to oval cells with peripheral pallisading & cells showing abundant finely granular eosinophilic cytoplasm and nuclei with salt & pepper chromatin (H & E, 400x); 3C: Synaptophysin immuno-reactivity (400x); 3D: CD56 immuno- reactivity (400x).

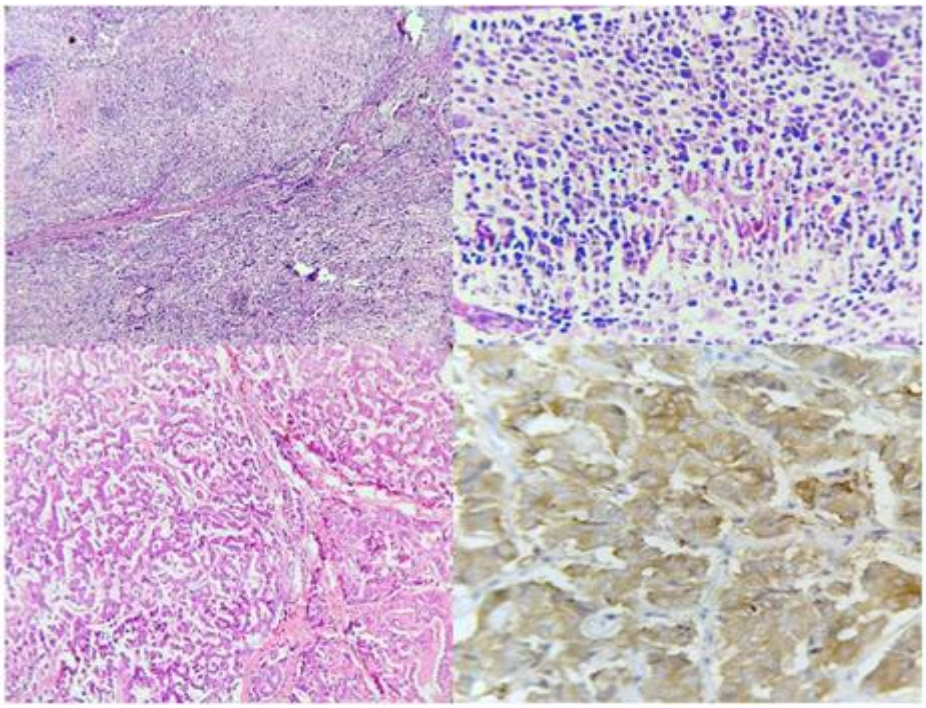


Figure 4: Paraganglioma 4A, 4B - Nesting pattern of cells within a prominent vascular network & round to oval cells with grnnular cytoplasm (H& E, 100X, 400X); Well differentiated pancreatic neuro endocrine neoplasm- 4C : well defined tumour consisting of uniform cuboidal cells arranged in solid nests and cells having moderate amount of eosinophillic cytoplasm with centrally placed nuclei with granular chromatin, tumour cells arranges in cords (H & E, 400x); 4D: Cytoplasmic immuno- reactivity for Synaptophysin (100x)

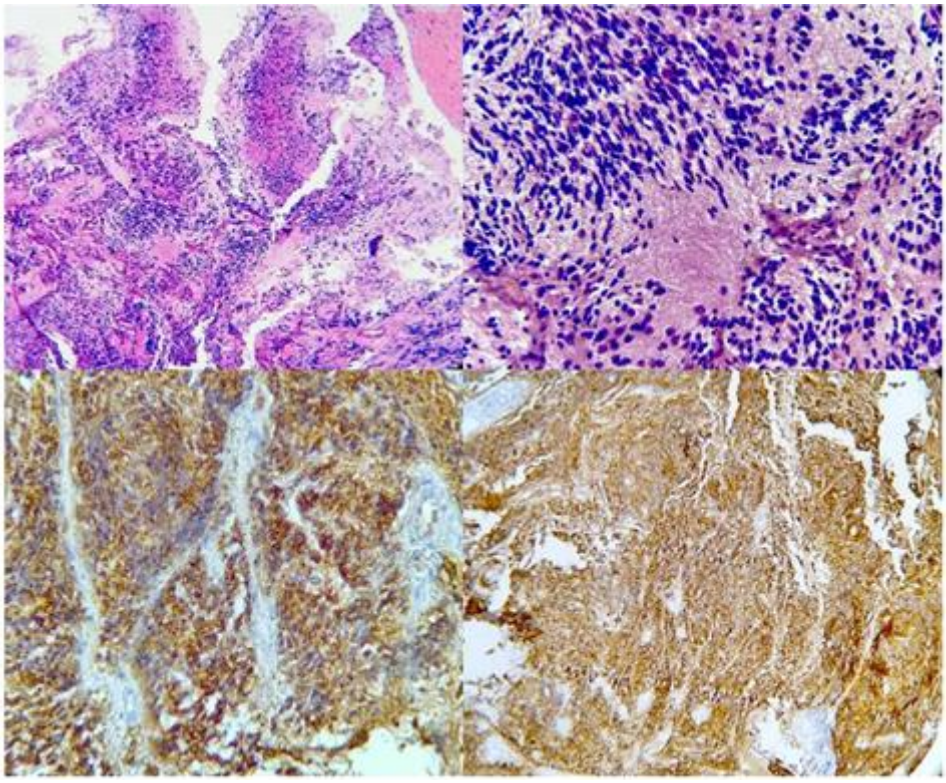


Figure 5: Neuroblastoma – 5A, 5B: Small round blue cells in a background of abundant neuropil (H & E, 100x, 400x); 5C: Cytoplasmic immuno- reactivity for Synaptophysin (100x); 5D: Cytoplasmic immuno-reactivity for NSE (400x)

Discussion

The term NENs encompasses both well-differentiated NETs and poorly differentiated NECs, as they both share common histologic, immunophenotypic and ultrastructural neuroendocrine features. A framework for NEN classification is proposed in which the term NEC is clearly indicative of high-grade malignant histology and biologic behaviour. Neuroendocrine tumour (NET), in contrast, is intended to designate a family of well differentiated neoplasms whose potential to metastasise or invade the adjacent tissues depends on tumour site, type and grade[5,6]. However well differentiated neoplasms (NETs) should usually be graded in three tiers as G1, G2, and G3, corresponding to low-grade, intermediate-grade and high-grade on the basis of mitotic count (expressed as mitosis per mm2 area; Ki 67 cell labelling index ("hotspots of at least 0.4 mm2") and presence or absence of necrosis which may be focal (punctate) or diffuse (geographic).[7] [Table 4] For the diagnosis and grading of NENs histopathology is gold standard method. Prognostic factors for NENs include primary tumour site, histological differentiation, tumour size, angioinvasion, infiltrative growth and production of hormones.[8]

Incidence of NETs has increased over the past 30 years.[9] Estimated incidence was 2%. Our study revealed incidence of 1%. NETs can be found in any location of the body, although the sites most commonly affected are the bronchopulmonary and gastrointestinal tracts as Kulchitsky cells or similar enterochromaffin-like cells are more numerous here. We have studied 115 cases of NENs in 1year with a peak in age group 41-60 yrs with a mean age of 44 yrs. Male versus female ratio was 1.27:1 but NEN had a female preponderance. The reason for this could be due to large no. of cases of pituitary adenoma & Small cell carcinoma[10] In this study 73.91% cases were benign (85 out of 115) and originated from pituitary region. There were 4 cases of well differentiated pancreatic NET (G1). In present study among 6 cases of neuroblastoma 4 cases

were well differentiated while 1 case was of poorly differentiated neuroblastoma of mandible with Ki67 of 85% & another one was metastatic neuroblastoma in cervical lymph node. In this study we encountered some uncommon cases such as 2 collision tumour- one being intrasellar pituitary adenoma with ganglion cell tumour & another one was ganglio- neuroblastoma, 2 cases of breast neuroendocrine carcinoma, 1 case of gall bladder NEC and 1 case of sub glottis NEC as only few cases of these reported in literature. neuroendocrine carcinoma of the breast is rare entity with only thirty cases reported in literature. The first case was described in 1963 by Feyrter et al.[11] For any endocrine-related carcinoma, there is an increased tendency to metastasise to the lymph nodes and the liver. In the present study, 1 case presented with metastasis to lymph nodes and 1 case of metastatic neuroendocrine carcinoma of liver. neuroendocrine tumours including neuroendocrine carcinoma of breast tend to be very slow growing. Molecular genetic studies have revealed that the development of NETs may involve different genes, each of which may be associated with several different abnormalities that include point mutations, gene deletions, DNA methylation, chromosomal losses and chromosomal gains.[13]

Conclusion

Neuroendocrine tumours can invariably occur in any region of the body. It must be considered as one of the differential diagnosis of solid tumours. As they have malignant potential, early and accurate diagnosis is necessary to aid the clinician in deciding the treatment.

Conflicts of interest- none
Funding sources - nil
Ethical approval: Not required

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