SPECTRUM OF NEUROENDOCRINE TUMOURS- A TERTIARY CARE CENTRE EXPERIENCE

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ABSTRACT

BACKGROUND

Neuroendocrine tumours occur at various sites in the human body. They 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. Although rare, they can be seen in breast, gallbladder and skin.

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 retrospective study for a period of 3 years (June 2013-June 2016). Surgical resection specimens were included in the study. Out of the total specimens received, 24 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. Biopsy specimens were excluded from the study.

RESULTS

Out of the 24 cases, 18 cases were benign lesions. 6 cases were malignant lesions. Female preponderance was noted. Peak incidence was seen in 20-30 years of age group.

CONCLUSION

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

KEYWORDS

Neuroendocrine Tumours, Carcinoids, Neuroendocrine Carcinoma of Breast, Salt and Pepper Chromatin, Neuroendocrine Differentiation.

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BACKGROUND

NETs are believed to arise from various neuroendocrine cells that are present not only in endocrine glands, but are diffusely distributed throughout the body. Enterochromaffin cells, which give rise to carcinoid tumours were identified in 1897 by Kulchitsky and their secretion of serotonin was established in 1953.[1],[2] The most common sites of neuroendocrine tumours are pituitary, thyroid, parathyroid, thymus, breast, genitourinary tract, Merkel cell carcinoma of skin (trabecular cancer) and mediastinum. The pulmonary neuroendocrine tumours are categorised as typical carcinoid, atypical carcinoid, Small Cell Lung Cancer (SCLC), Large Cell Neuroendocrine Carcinoma (LCNEC of the lung). Although, estimates vary, the annual incidence of clinically significant neuroendocrine tumours is approximately 2.5-5 per 1,00,000 cases. Two third are carcinoid tumours and one third are other NETs. Based on the substances secreted and clinical syndromes, NET are divided into functioning and non-functioning tumours.

Placing a given tumour into one of categories, i.e. 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, h) Whether they produce hormones (functioning).

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MATERIALS AND METHODS

Surgical resection specimens were received over a period of 3 years, which included 24 neuroendocrine tumours. Clinical details including age, mode of presentation, surgery performed and pathological characteristics were analysed in all the cases. The specimens were fixed in buffered formalin, routinely processed and sections cut from paraffin blocks.

Histological examination was done on Haematoxylin and Eosin (H and E) stained sections. The sections were also subjected to special stains (reticulin) and immunohistochemical stains. Panel of IHC markers included were Chromogranin (EP38), Neuron-Specific Enolase (5E2), Oestrogen receptor (EP1), Progesterone receptor (EP2), Her-2 (EP3), CD20 (L26), CD5 (EP77), Ki-67 (GM001), Pan CK (LL002).

RESULTS

Our cases had varied age distribution from 20-70 yrs. mean age being 25 yrs. Female preponderance was seen with female-to-male ratio of 1.4:1.6 cases were malignant [25%] while 18 cases were benign lesions [75%]. Out of the 18 benign cases, 6 cases [33%] were of parathyroid adenoma, 4 cases [22%] were of pituitary adenoma, 2 cases of pheochromocytoma [11%] and of 3 cases carcinoid were seen [16.6%]. One case each of adrenocortical adenoma, paraganglioma and insulinoma [5.5%] was seen, respectively. Out of the 6 malignant cases, 1 case each of malignant pheochromocytoma, periampullary carcinoma with neuroendocrine differentiation was diagnosed. Two cases [33.2%] were diagnosed as medullary carcinoma of thyroid. One case each of medullary carcinoma breast and neuroendocrine carcinoma of breast were seen.

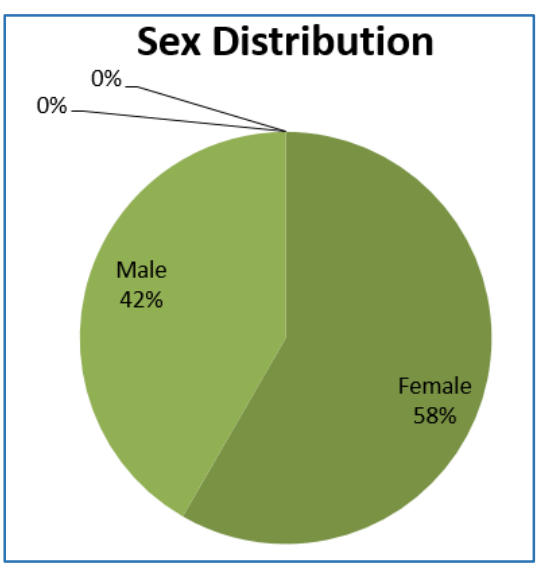


Figure 1. Female-Male Ratio 1.4:1

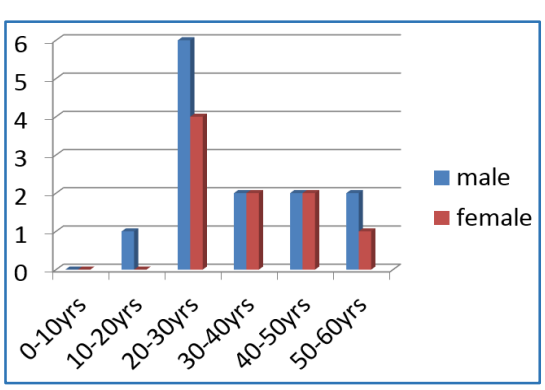


Figure 2. Age and Sex Distribution

Neuroendocrine Tumours	Malignant	Benign
Parathyroid Adenoma	0	6
Pituitary Adenoma	0	4
Pheochromocytoma	1	2
Carcinoids	0	3
Adrenal Cortical Adenoma	0	1
Insulinoma	0	1
Paraganglioma	0	1
Medullary Carcinoma Thyroid	2	0
Neuroendocrine Carcinoma of Breast	1	0
Periampullary Carcinoma with Neuroendocrine Differentiation	1	0
Medullary Carcinoma of Breast	1	0

Table 1. Incidence of Benign and Malignant Neuroendocrine Lesions

Case	Presenting Symptoms	Hormones Produced
Carcinoid Intestinal	Diarrhoea	-
Bronchial Carcinoid	Pneumonia	-
Insulinoma	Hypoglycaemia	Insulin
Parathyroid Adenoma	Pressure Symptoms	Parathyroid Hormones
Pituitary Adenoma	Headache, Loss of Vision	-
Pheochromocytoma	Hypertension	Cortisone
Medullary Carcinoma Breast	Asymptomatic	-
Medullary Carcinoma of Thyroid	Asymptomatic	-
Adrenal Cortical Adenoma	Cushing's Symptoms	Cortisone
Neuroendocrine Carcinoma of Breast	-	-
Periampullary Carcinoma with Neuroendocrine Differentiation	Weight Loss and Jaundice	-
Paraganglioma	Pressure Symptoms	-

Table 2. Neuroendocrine Tumours and Presenting Symptoms

Features of the Tumours

Parathyroid Adenoma

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

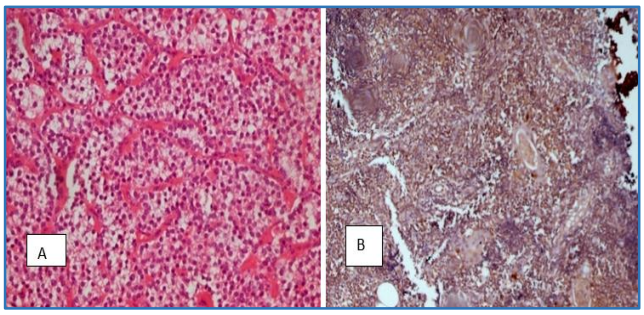


Figure 3. [A] 10x Parathyroid Adenoma [B] Chromogranin Positive

Pituitary Adenomas

Most commonly seen in males.

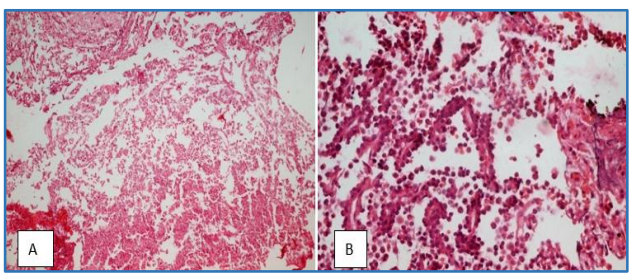


Figure 4. [A] 4x Magnification of Pituitary Adenoma [B] 10x Magnification Showing Cells around Vessels

Pheochromocytoma

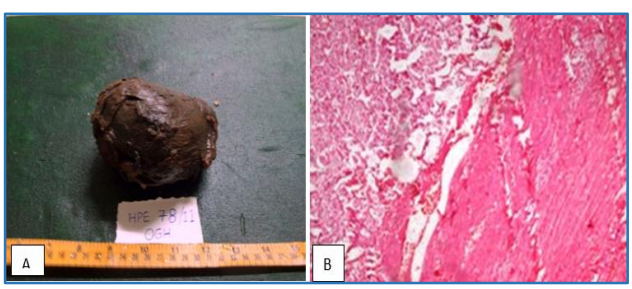


Figure 5. [A] Gross Specimen of the Adrenal Measuring 10*8*6 cm. [B] 4x Magnification showing Capsular Invasion

Medullary Carcinoma Breast

One female presented with breast mass. On HPE, lymph nodes show metastasis, Bloom-Richardson score- grade 2.

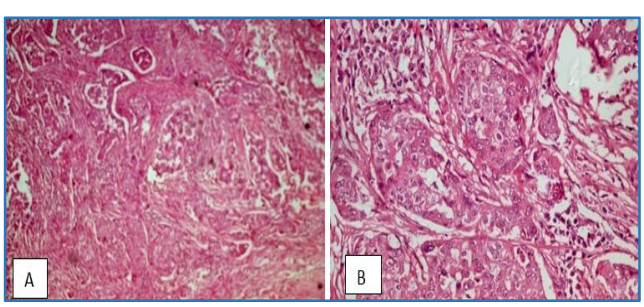


Figure 6. [A] 10x Magnification of the Tumour. [B] 40x Magnification of the Tumour with Nested Arrangement and "Salt and Pepper Chromatin"

Periampullary Carcinoma with Neuroendocrine Differentiation

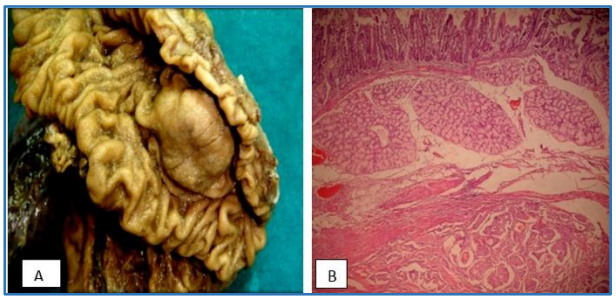
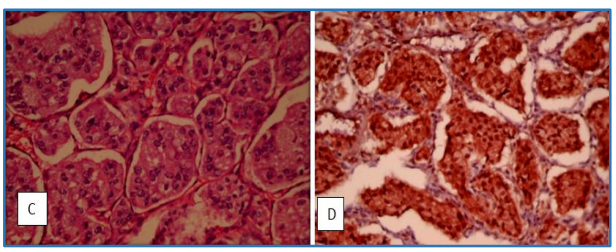


Figure 7. [A] Gross Specimen of the Tumour [B] Tumour Arranged in Nested Pattern Submucosa



[C] Higher Magnification of the Tumour Showing Zellballen Pattern. [D] Neuron Specific Enolase Positivity

Neuroendocrine Carcinoma of Breast

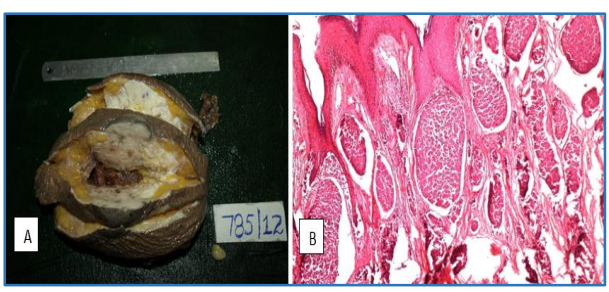
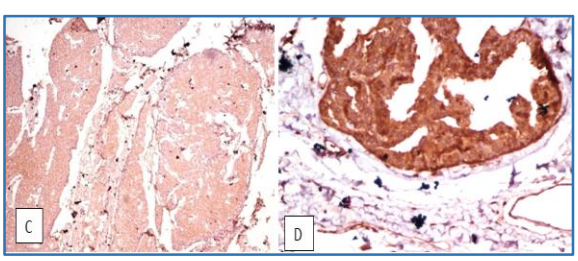


Figure 8. [A] Mastectomy Specimen Revealing Grey White Solid Tumour. [B] Tumour Arranged in Nested Pattern



[C] Her-2 [D] Chromogranin

DISCUSSION

NETs can be found in any location of the body, although the sites most commonly affected are the gastrointestinal and bronchopulmonary tracts.[3] Gastrointestinal NETs are sub-classified into foregut, midgut and hindgut tumours. Only those of midgut origin are generally argentaffin positive and secrete serotonin and hence only these should be referred to as carcinoid tumours. Many benign and malignant lesions of various organs may show neuroendocrine differentiation.[4] According to WHO 2010, neuroendocrine tumours are classified as;

Histological Classification	Well-Differentiated (Low-Grade, G1)	Moderately-Differentiated (Intermediate-Grade, G2)	Poorly-Differentiated (High-Grade, G3)
Appearance	Monomorphic population of small round cells	----------	Cellular pleomorphism
Prognosis	Prolonged survival	Intermediate	Poor
Mitotic Rate	<2	2-20	>20
Ki-67 Index	<3%	3-20%	>20%
Necrosis	Absent	----------	Present

Table 3. Histopathological Classification of Neuroendocrine Tumours

Most of the cases studied were benign (18 out of 24). Incidence of NETs has increased over the past 30 years.[4] In our study, most of the cases originated from parathyroid region and pituitary region. Estimated incidence was 2%. Our study revealed incidence of 1%. In the present study, female preponderance was seen in concordance with literature. Mean age distribution- 25 yrs. Our cases had varied age distribution from 20-70 yrs. Mean age being 25 yrs. on par with the literature. Most of the tumours were functional with hormone secretion.

According to WHO classification our cases constituted-benign-18, well-differentiated tumours- 4, poorly-differentiated- 2. Prognostic factors include primary tumour site, histological differentiation, tumour size, angioinvasion, infiltrative growth and production of hormones.[5] Many are benign, while some are malignant. Of all the neuroendocrine tumours, one case of neuroendocrine carcinoma of the breast was diagnosed, a rare entity with only thirty cases reported in literature.[6] The first case was described in 1963 by Feyrter et al.[7] It was first classified in the WHO classification of tumours of the breast 2003.[8] They are more likely to be ER/PR positive and HER-2 negative. They are usually very aggressive.[9] These tumours are usually seen in the 6th or 7th decades of life and usually have a very poor prognosis.[9] According to Sapino et al tumours, which express ER, PR have better prognosis.[10] However, neuroendocrine tumours including neuroendocrine carcinoma of breast tend to be very slow growing. In many recent studies, the incidence of neuroendocrine differentiation in breast carcinoma is said to be between 2-5%.[11]

For any endocrine-related carcinoma, there is an increased tendency to metastasise to the lymph nodes and the liver. In the present study, 2 cases presented with metastasis to lymph nodes. 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.[1] Almost all neuroendocrine tumours are considered malignant and treated aggressively usually with surgical removal.

CONCLUSION

Neuroendocrine tumours can invariably occur in any region of the body and mostly seen in the females. It must be considered as one of the differential diagnosis of solid tumours. As they have malignant potential, early and accurate diagnosis is very necessary, so as to aid in clinicians for treatment. Although, a rare entity, neuroendocrine carcinoma of breast can also occur in elderly females.

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