Section: Pathology

Original Research Article

BOUNDLESS PRESENTATION OF NEUROENDOCRINE TUMOR - FROM A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Neuroendocrine tumours (NETs) are epithelial neoplasms that can arise in many organs because of the widespread distribution of neuroendocrine cells. Their varied clinical and pathological features make timely diagnosis essential, and proper histopathological confirmation supports informed decision-making. This study aimed to describe the incidence, anatomical distribution, and presentation patterns of NETs diagnosed at a tertiary care hospital. **Materials and Methods:** A retrospective observational study was conducted over one year at the Department of Pathology of Tirunelveli Medical College. Twenty-two histopathologically confirmed NETs from biopsy and resection specimens were included. All samples were processed using routine histology and, when required, immunohistochemistry using synaptophysin, chromogranin A, and neuron-specific enolase. Demographic data, clinical details, tumour site, and microscopic features were documented and analysed descriptively. **Result:** Of the 22 patients, the male-to-female ratio was 1:1.2 (10:12). Age distribution showed 18% under 30 years, 50% between 30–50 years and 32% above 50 years. NETs were located in the breast (22.5%), stomach (18.5%), thyroid (13.5%), lungs (9%), caecum (9%), pancreas (9%), appendix (4.5%), adrenal gland (4.5%), carotid body (4.5%), and cervix (4.5%). One case was associated with MEN2B syndrome and presented with medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, and marfanoid habitus. All cases showed characteristic neuroendocrine morphology, supported by the immunohistochemical marker expression. **Conclusion:** NETs showed a wide anatomical spread, with the breast, stomach, and thyroid being the predominant sites. Middle-aged adults were the most affected. These findings highlight the importance of histopathology and immunohistochemistry in identifying both common and uncommon NET presentations in tertiary care settings.

INTRODUCTION

Neuroendocrine tumours (NETs) are epithelial neoplasms that show predominant neuroendocrine differentiation and can arise in almost any organ due to the wide distribution of neuroendocrine cells.[1] They occur most often in the gastrointestinal and pancreatic systems, followed by the lungs, thyroid, breast, adrenal gland and other uncommon sites, as described in large epidemiological studies of GEP-NETs.[2] NETs affect a broad age range and are seen in both men and women, with most cases reported between the third and fifth decades of life according to standard pathology references.[3]

The incidence of NETs has progressively increased owing to improved diagnostic awareness, better histopathology techniques, and the routine use of immunohistochemical studies. A study reported an increase in NET detection in Korea across multiple centres, showing how enhanced reporting has contributed to higher case identification.[1] This increase reflects improved endoscopy, cross-sectional imaging and recognition of small incidental lesions.[4]

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A small proportion of NETs arise in patients with hereditary syndromes. A study reported that 3.7% of NETs are linked to genetic conditions such as Multiple Endocrine Neoplasia (MEN), von Hippel–Lindau disease (VHL), neurofibromatosis type 1 (NF1), and Tuberous Sclerosis Complex, as documented in the ENETS consensus guidelines.[5] Among these, MEN2B is important because of its association with medullary thyroid carcinoma, pheochromocytoma, and mucosal neuromas.[6] Identifying syndromic associations helps guide the evaluation of additional endocrine organs and genetic counselling.

Histopathology, supported by immunohistochemistry, is essential for confirming neuroendocrine differentiation. Synaptophysin and chromogranin A are expressed in most NETs and are the most widely used markers in routine diagnosis, with CD56 providing supportive but less specific staining.[7] These markers also help confirm NETs in uncommon presentations such as breast, appendix or cervix, which have been described in earlier case reports.[8,9]

NETs may arise in typical gastrointestinal locations; however, several rare tumours, such as crypt cell carcinoma of the appendix and goblet cell carcinoid, have been documented, adding to the diagnostic spectrum.[10] These variations underline the broad pathological and clinical range of NETs, which can present as incidental findings or advanced metastatic disease. Their diverse presentation patterns emphasise the value of documentation, especially in tertiary care centres, where both common and unusual NETs are encountered. Therefore, this study aimed to assess the incidence, anatomical distribution, and presentation patterns of neuroendocrine tumours.

MATERIALS AND METHODS

This retrospective observational study was conducted on 22 histopathologically confirmed neuroendocrine tumours at the Department of Pathology, Tirunelveli Medical College, over one year between August 2023–July 2024. Institutional approval was obtained before data collection, and all specimens included were routinely processed as part of the diagnostic reporting.

Inclusion Criteria

All cases of histopathologically proven neuroendocrine tumours from various organ sites, both biopsy and resection specimens, cases with complete clinical details, gross findings, microscopic features, and immunohistochemical results were included.

Exclusion Criteria

Specimens with inadequate tissue for histological interpretation or those without complete clinical or immunohistochemical information, tumours that did not show neuroendocrine differentiation on microscopy or immunohistochemistry were excluded.

Methods: All specimens were fixed in 10% neutral buffered formalin, processed routinely, and stained with haematoxylin and eosin. Microscopic examination was performed to confirm the neuroendocrine morphology. Immunohistochemical markers, including synaptophysin, chromogranin A, and neuron-specific enolase (NSE), were used. For each case, demographic information such as age and gender, clinical presentation, organ or site of involvement, gross appearance and detailed microscopic features were recorded. Special observations, such as associated syndromes, were noted when applicable.

Statistical analysis: Data were entered into Microsoft Excel and analysed descriptively. Categorical variables were summarised as frequencies and percentages, and continuous variables were expressed as simple numerical distributions.

RESULTS

The male-to-female ratio of incidence was 1:1.2 (10:12), 18% were aged <30 years, 50% were aged 30–50 years, and 32% were aged >50 years [Table 1].

Table 1: Distribution of age group

Category	Subtypes	N (%)
Age group (years)	<30	4 (18%)
	30–50	11 (50%)
	>50	7 (32%)

Neuroendocrine tumours were most commonly located in the gastrointestinal tract (41%), followed by the breast (22.5%). Other sites included the stomach (18.5%), thyroid (13.5%), lungs (9%), caecum (9%), pancreas (9%), appendix (4.5%), adrenal gland (4.5%), carotid body (4.5%), and cervix (4.5%). One case was associated with MEN 2B syndrome, which includes medullary thyroid carcinoma, Pheochromocytoma, Marfanoid body habitus, and mucosal neuromas [Table 2 and Figure 1-5].

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Table 2: Distribution of neuroendocrine tumours by anatomical locations

Category	Location	N (%)
Neuroendocrine tumours	Stomach	4 (18.5%)
	Caecum	2 (9%)
	Appendix	1 (4.5%)
	Breast	5 (22.5%)
	Thyroid	3 (13.5%)
	Pancreas	2 (9%)
	Lungs	2 (9%)
	Adrenal	1 (4.5%)
	Carotid body	1 (4.5%)
	Cervix	1 (4.5%)

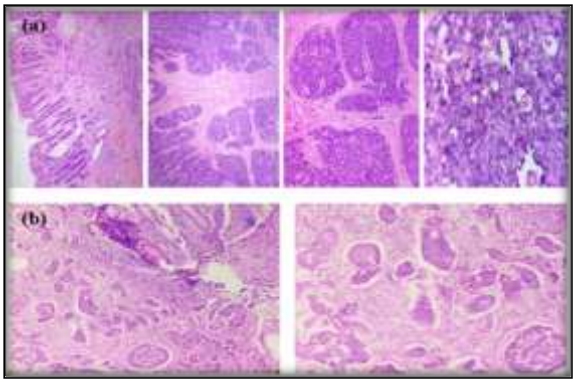

Figure 1: Histopathological image of neuroendocrine tumour of (a) stomach and (b) appendix (H&E stain, magnification x40 and x100)

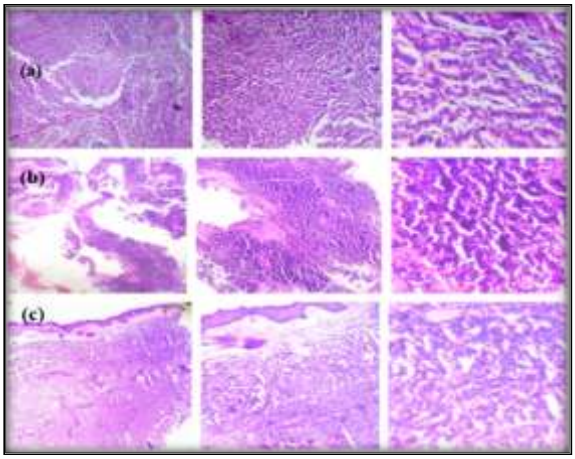

Figure 2: Histopathological image of neuroendocrine tumour of (a) pancreas, (b) lung and (c) cervical adenocarcinoma with neuroendocrine differentiation (H&E stain, magnification x40, x100 & x400).

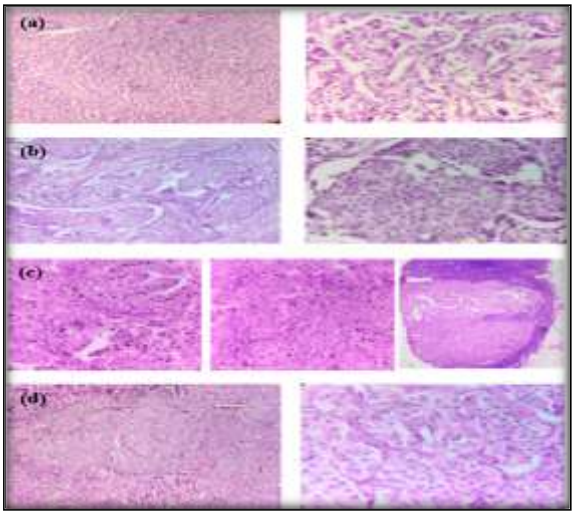

Figure 3: Histopathological image of a neuroendocrine tumour of the (a) carotid body, (b) breast, (c) medullary thyroid carcinoma with regional lymph node metastasis (stage III) and (d) adrenal pheochromocytoma (H&E stain, magnification x100 and x400)

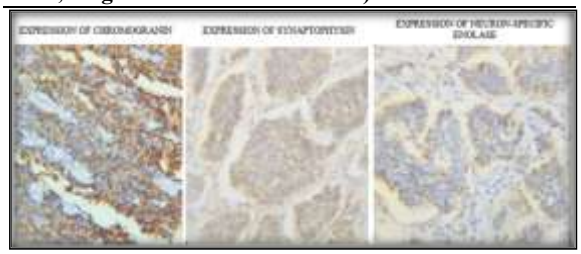

Figure 4: Expression of immunohistochemical markers

Microscopic Features: Tumour arranged in nests, trabecular and solid patterns with uniform cells showing round to oval nuclei, irregular nuclear membrane and finely stippled "salt-and-pepper" chromatin. Cytoplasm is granular and eosinophilic with inconspicuous nucleoli. Rosette-like structures may be present. Mitotic activity is generally low and necrosis, when present, assists in grading. Tumour cells showed immunoreactivity for synaptophysin and chromogranin-A confirming neuroendocrine differentiation.

Grading – WHO 2022 Neuroendocrine Neoplasm Classification.[11,12]

Well-differentiated NETs are classified into G1–G3 using mitotic activity per 2 mm² and Ki-67 proliferation index:

- G1: Mitotic <2/2 mm² and Ki-67 ≤3%
- G2: Mitotic 2–20/2 mm² or Ki-67 3–20%
- G3: Mitotic >20/2 mm² or Ki-67 >20%

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Poorly differentiated NECs (small-cell and large-cell types) show high mitosis, extensive necrosis, and aggressive biological behaviour.

DISCUSSION

NET showed a slight female predominance and was most common in middle-aged adults. The breast was the most frequent site, followed by the stomach and thyroid, with additional cases in the lungs, caecum, pancreas, and a few rare locations. One case had a syndromic association. Histologically, most tumours showed classic neuroendocrine features. Immunohistochemistry consistently confirmed neuroendocrine differentiation, reflecting the broad morphological and immunophenotypic spectrum of these tumours.

In our study, the higher occurrence in middle-aged and the spread across many organs probably mentions both the pattern and the natural biological diversity of NETs. The frequent breast involvement, although not very common in global data, may be related to our local population. The uniform immunohistochemical positivity in almost all cases also supports the reliability of the diagnosis, even though the tumour sites were quite different. Dasari et al. reported that NET incidence varies widely by anatomical site, with the highest burden in gastroenteropancreatic and pulmonary locations, along with smaller proportions arising from thyroid, cecum, appendix, and other organs also confirms that NETs commonly occur in adults.[13] In a study by Hallet et al. reported that NETs arise from multiple anatomical sites, with predominant involvement of the bronchopulmonary system (25%) and the small intestine (18%). They also observed that NETs primarily affect adults (mean age of 60.9 years).[14] While their most common sites differ from ours, this variation likely reflects geographical, genetic, and institutional differences in cases. Their findings confirm the multi-organ distribution of NETs, matching our study where tumours occurred in diverse locations.

Modlin et al. report that gastrointestinal NETs arise mainly in the small intestine (38%), appendix (18%), rectum (21%), colon (12%), and stomach (6%).[15] Fernandez et al. report that gastroenteropancreatic NETs came from multiple gut-derived endocrine cells and show classic neuroendocrine differentiation with immunohistochemical positivity for chromogranin, synaptophysin, and NSE.[16] This epidemiological pattern aligns with our findings and supports the that NETs generally share similar age demographics regardless of the primary site. This confirms our immunohistochemical results, indicating that the markers remain highly reliable across anatomical sites and tumour grades.[16]

Oronsky et al. report that the most frequent primary sites of NETs are the gastrointestinal tract (62–67%) and lungs (22–27%). Their epidemiological data show a female preponderance (2.5:1). Although their reported female-to-male ratio is higher than ours, the direction of gender bias is consistent, suggesting possible hormonal or genetic influences on NET development. NETs commonly present in adults aged 50–60 years also highlight strong immunoexpression of chromogranin A and synaptophysin, consistent with our IHC findings showing positivity for chromogranin, synaptophysin, and NSE.[17] Also, Fan et al. found that the stomach was the most common site (37.5%), followed by the colorectal tract (30.3%), oesophagus (19.1%) and pancreas (8.2%). CgA was positive in 62.2% and synaptophysin in 82% of cases. Patient mean age ranged from 49.9 to 65.4 years across tumour locations. Histologically, they describe typical neuroendocrine patterns, consistent with the morphology in our H&E images.[18] This suggests that despite different primary sites, NETs share a recognisable morphological pattern. In a study by Bellizzi et al. discuss in detail the diagnostic utility of classical neuroendocrine immunohistochemical markers, including chromogranin, synaptophysin, and NSE, as essential general markers for confirming neuroendocrine differentiation.[19]

Hasbay et al. reported 56 breast neuroendocrine tumour cases, with a mean age of 57.2 years and 73.2% of patients above 50 years. This confirmed strong immunopositivity for synaptophysin (89.3%) and chromogranin (73.2%). Histopathologically, they described nested, trabecular, mucinous and solid papillary patterns. NETs of the breast are rare but can appear alongside classic breast carcinoma types, similar to our finding that NETs arise across multiple organ systems, including the breast.[20] Chang et al. analysed 7,760 NET cases and NETs arise across multiple organ systems, with the rectum (29.65%), lung/bronchus (17.22%), pancreas (10.71%), stomach (7.69%), colon (5.79%), appendix (3.54%), and breast (1.83%) being key sites. Their result shows 58.8% males and 41.2% females, and confirms that NETs predominantly occur in adult age groups.[21] Although their sex distribution contrasts with ours, such variation is common across regions and may reflect differences in health-seeking behaviour and population characteristics.

Our study findings show that NETs mainly affect adults and can arise in many different organs, while maintaining typical histological and immunohistochemical features. The similarities between our findings and previous studies confirm the wide anatomical distribution of NETs and the consistent usefulness of markers such as chromogranin, synaptophysin, and NSE. Overall, the evidence supports the importance of morphology with IHC to avoid misclassification, particularly in tumours of unusual anatomical origin. The adult predominance supports the need for awareness programs aimed at early detection in older age groups.

The key strength of our study is the clear correlation between histology and IHC, which made the diagnosis more confident. We also included NETs

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from several organ sites, giving a wider view of their pattern. Even though the numbers are small, the variety of cases still adds useful information. Future studies should include larger, multi-centre samples to better define NET distribution across populations. Molecular and genetic analyses are needed to clarify the factors driving site variation and sex differences. Long-term follow-up would strengthen understanding of prognosis, and further research on broader IHC panels or new biomarkers may improve diagnostic accuracy, especially for NETs in uncommon sites.

Limitations

This study is limited by its single-centre, retrospective design and small sample size, which may restrict generalisability. Incomplete clinical details in some cases may have influenced the interpretation of the presentation patterns.

CONCLUSION

This study highlights the wide anatomical distribution and diverse presentations of neuroendocrine tumours, with the breast, stomach, and thyroid being the most common sites. Middle-aged adults were predominantly affected, and rare presentations, including MEN2B-associated cases, were identified. Histopathological and immunohistochemical imaging confirmed the classical neuroendocrine morphology across organs.

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