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HETEROGENICITY OF NEUROENDOCRINE TUMOURS AND ITS SIGNIFICANCE – A CASE SERIES

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ABSTRACT

Neuroendocrine neoplasms are a heterogeneous group of tumours that share characteristic neuroendocrine morphology and immunophenotype but differ considerably by anatomical site, grading, and biological behaviour. This case series was conducted in the Department of Pathology in a tertiary care health centre, Chengalpattu, Tamil Nadu, to illustrate the morphologic and immunohistochemical spectrum of neuroendocrine tumours across different organs. Five cases were studied, comprising an ileal neuroendocrine tumour, a duodenal neuroendocrine tumour, a pancreatic neuroendocrine tumour, a pituitary neuroendocrine tumour, and an adrenal pheochromocytoma. Histopathological examination in all cases showed typical neuroendocrine features, including nesting, trabecular, cord-like, lobular, rosette-like architecture. Individual tumour cells showed round to oval nuclei and finely stippled salt-and-pepper chromatin. Immunohistochemistry demonstrated synaptophysin and chromogranin positivity in all cases, confirming neuroendocrine differentiation. The ileal, duodenal, and pancreatic tumours showed low mitotic activity and low Ki-67 indices (1–2% or 2%), supporting a diagnosis of well-differentiated Grade 1 neuroendocrine tumour. The pituitary lesion also showed low proliferative activity and was classified as pituitary neuroendocrine tumour with low-grade features. In contrast, the adrenal pheochromocytoma showed larger tumour cells arranged in nests (Zell-ballen pattern), higher mitotic activity (5–10/10 HPF), and a Ki-67 index of 5–10%, correlating with its more aggressive clinical behaviour. The series highlighted both the shared diagnostic hallmarks and the site-specific heterogeneity of neuroendocrine neoplasms, underscoring the importance of integrating morphology, immunohistochemistry, and proliferation indices for accurate diagnosis and classification.

KEYWORDS: Neuroendocrine neoplasms, Neuroendocrine tumour, Synaptophysin, Chromogranin, Ki-67, Pheochromocytoma

INTRODUCTION

Neuroendocrine neoplasms (NENs) comprise a heterogeneous group of tumours derived from widely distributed neuroendocrine cells and most commonly arise in the gastro-entero-pancreatic and bronchopulmonary tracts, although they may also occur in the pituitary gland, adrenal medulla, and several other organs.(1) The epidemiology of these tumours has changed substantially over recent decades, and Sultana et al. (2023) has shown a clear rise in incidence of 7 per 1,00,000 in 2017.(2) Histologically, well-differentiated neuroendocrine tumours (NETs) typically show organoid architectural patterns such as nests, trabeculae, cords, or rosettes, and are composed of relatively uniform cells with round to oval nuclei and finely granular “salt-and-pepper” chromatin. Immunohistochemistry plays a central role in confirming neuroendocrine differentiation, with synaptophysin and chromogranin remaining the most widely used markers in routine diagnostic practice.(2)

The WHO Classification of NENs (2022) emphasize both differentiation and proliferative activity, and grading of epithelial NENs relies mainly on mitotic count and Ki-67 labelling index; indeed, Ki-67 is now regarded as standard-of-care across different NENs.(3) In the gastro-entero-pancreatic system, a well-differentiated Grade 1 NET is defined by a mitotic count of fewer than 2 per 2 mm² and a Ki-67 index below 3%.(4) This is especially relevant because small-bowel and pancreatic neuroendocrine neoplasms together constitute a major and clinically important subset of NENs, often requiring careful clinicopathological correlation for accurate diagnosis and management. However, site-specific classification remains important: pituitary tumours are now designated pituitary neuroendocrine tumours (PitNETs) in the current WHO classification, and no single clinical, radiological, or histological parameter has been shown to reliably predict aggressive behaviour in all cases.(5, 6)

Against this background, the present study is done by bringing together ileal, duodenal, pancreatic, pituitary, and adrenal neuroendocrine tumours in a single case series, the study aimed to highlight both the shared diagnostic hallmarks of neuroendocrine differentiation and the site-specific differences in architecture, grading, and biological behaviour that make these neoplasms pathologically significant.

CASE SERIES

Case 1: A 73-year-old man underwent colonoscopy, during which an incidental ileal polyp was identified, and a polypectomy specimen was received for histopathological evaluation. Microscopy showed that the lamina propria and muscularis propria were infiltrated by tumour cells arranged in nests and islands. The individual tumour cells were closely packed and displayed uniform round to oval nuclei with characteristic salt-and-pepper chromatin and moderate cytoplasm. Mitotic activity was low, at 1–2 mitotic figures per 10 high-power fields. On immunohistochemistry, the tumour cells showed strong membranous positivity for synaptophysin and chromogranin. The Ki-67 proliferation index was 1–2%, and the lesion was diagnosed as a well-differentiated neuroendocrine tumour (Grade 1) of the ileum.

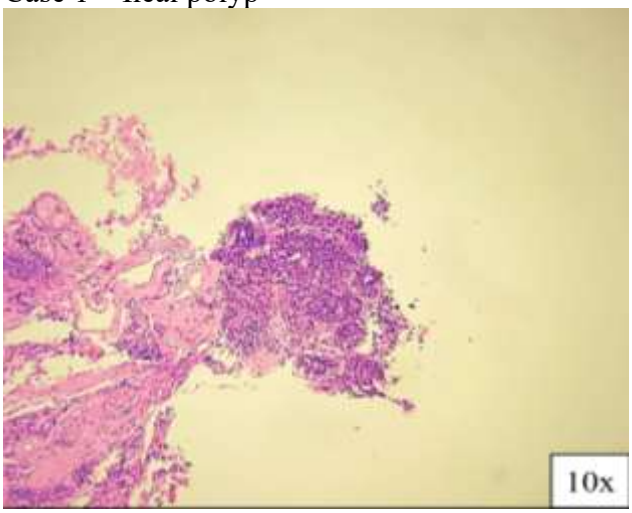
Case 2: A 60-year-old woman had an incidental D1 nodule during upper gastrointestinal scopy performed for APD, and a biopsy specimen from the nodule was submitted. Histopathological examination revealed an ill-defined lesion composed of uniform tumour cells arranged in trabeculae, cords, and nests. The individual cells had round to oval nuclei, finely granular chromatin, inconspicuous nucleoli, and moderate eosinophilic granular cytoplasm. Mitotic activity was low, at 1–2 mitotic figures per 10 high-power fields. Immunohistochemical evaluation demonstrated membranous positivity for synaptophysin and chromogranin. The Ki-67 proliferation index was 1–2%, and the lesion was diagnosed as a well-differentiated neuroendocrine tumour (Grade 1) of the duodenum.

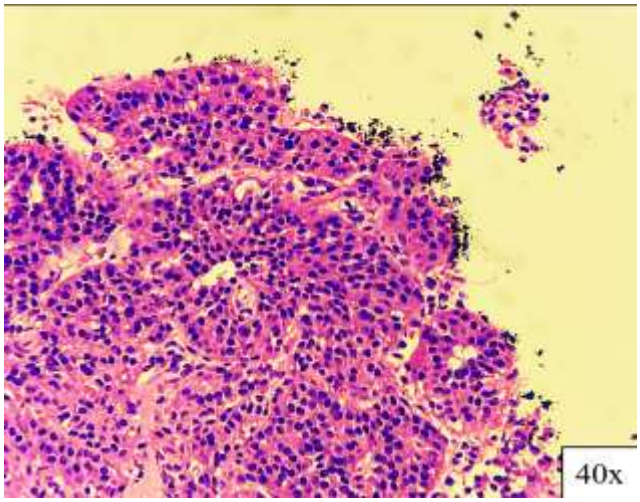
Case 3: A 54-year-old man presented with abdominal pain, on further evaluation revealed a pancreatic mass involving the body and tail of the pancreas. A distal pancreatectomy specimen was received for pathological assessment. Microscopy showed a tumour arranged in a lobular pattern of growth, with lobules separated by scant fibrous septa. The tumour cells were round and exhibited salt-and-pepper chromatin with moderate eosinophilic cytoplasm. Mitotic activity was 1–2 mitotic figures per 10 high-power fields. Immunohistochemically, the tumour showed membranous positivity for synaptophysin and chromogranin. The Ki-67 proliferation index was 2%, and the tumour was diagnosed as a well-differentiated neuroendocrine tumour (Grade 1) of the pancreas.

Case 4: A 53-year-old woman presented with headache and vomiting. Magnetic resonance imaging revealed a space-occupying lesion suggestive of pituitary adenoma. Histopathological examination showed a neoplasm composed of tumour cells arranged in solid sheets, nests, and rosette formations, separated by intervening fibrovascular stroma. The individual tumour cells were uniform in appearance and had stippled chromatin, inconspicuous nucleoli, and moderate eosinophilic to clear cytoplasm. Mitotic activity was low, at 1–2 mitotic figures per 10 high-power fields. Immunohistochemistry demonstrated positivity for synaptophysin and chromogranin. The Ki-67 proliferation index was 1–2%. Based on these findings, the lesion was diagnosed as a pituitary neuroendocrine tumour with low-grade features.

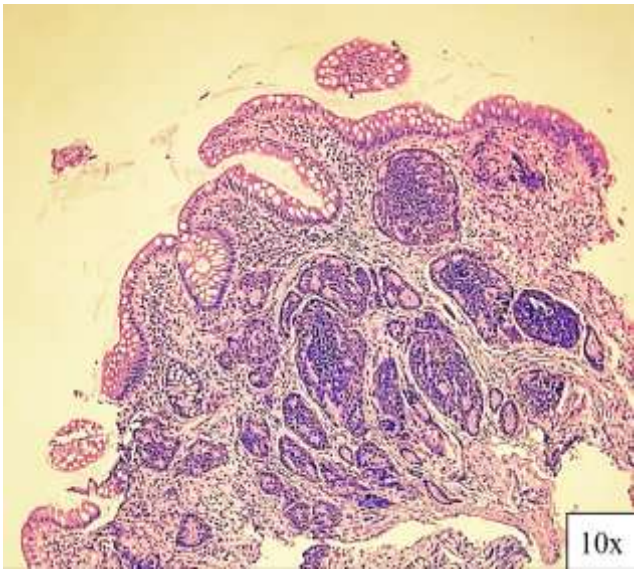
Case 5: A 21-year-old man presented with a large abdominal mass, weight loss, and severe hypertension. Imaging identified an adrenal mass measuring 20 × 15 × 11 cm, with associated inferior vena cava thrombus. Histopathological examination revealed a delineated tumour arranged in nests, trabeculae, and solid sheets, including a classical Zellballen-like pattern. The tumour cells were large and polygonal, with well-defined cell borders, round to oval nuclei, prominent nucleoli, and moderate to abundant fine granular cytoplasm. Mitotic activity was relatively higher than in the other cases, measuring 5–10 mitotic figures per 10 high-power fields. Immunohistochemical analysis showed positivity for synaptophysin and chromogranin. The Ki-67 proliferation index was 5–10%. In view of the morphology and proliferative activity, the lesion was diagnosed as pheochromocytoma, which also showed a more aggressive clinical course compared with the other tumours in the series.

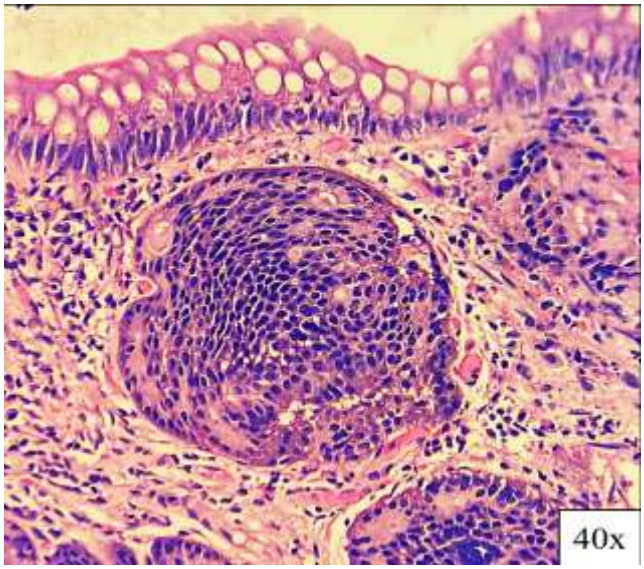
Case 1 – Ileal polyp



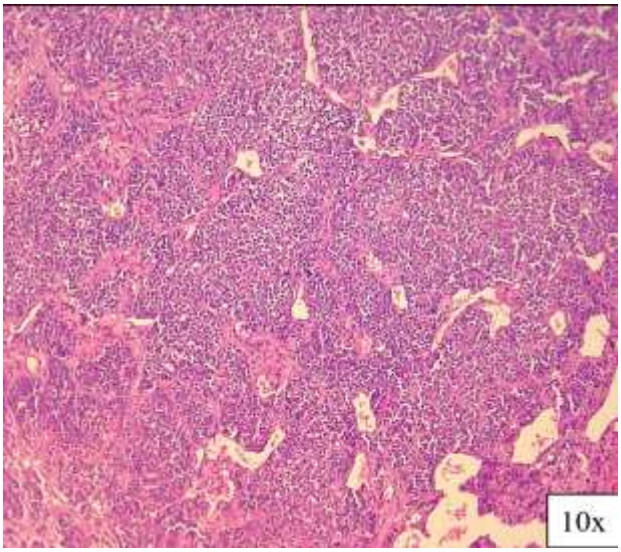


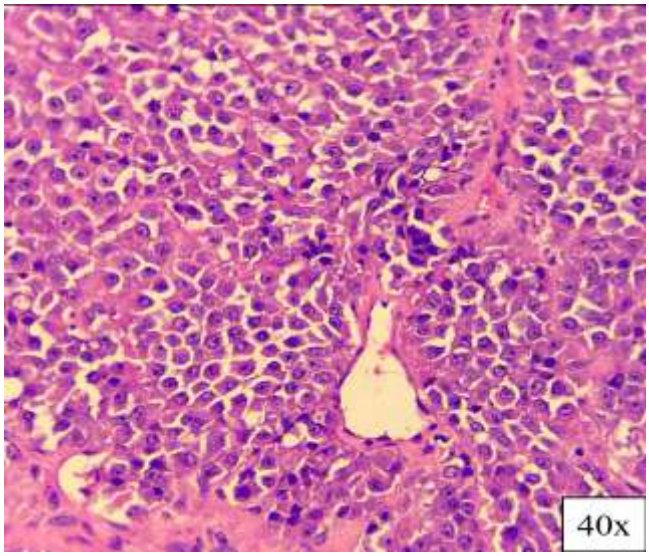
Case 2 – Duodenal D1 Nodule



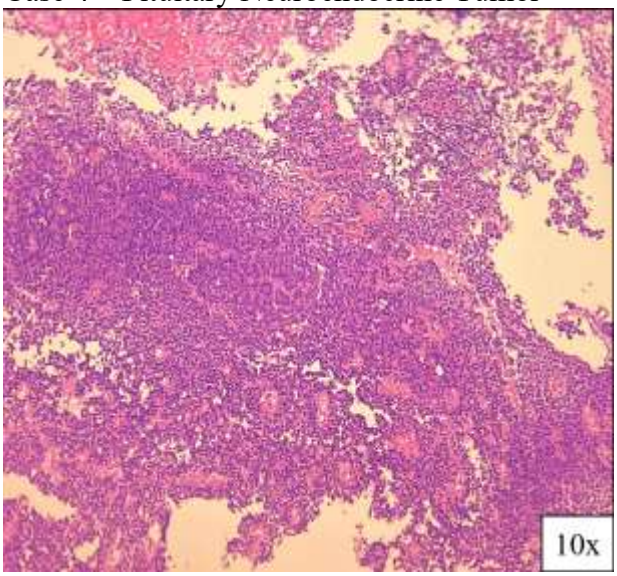


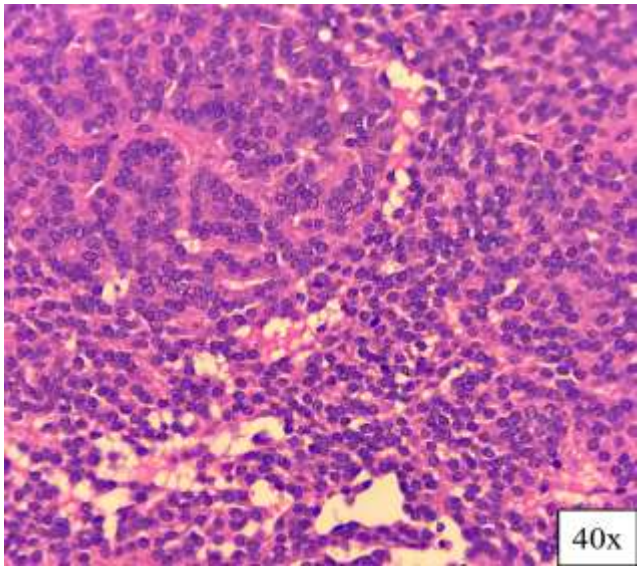
Case 3 – Pancreatic Mass





Case 4 – Pituitary Neuroendocrine Tumor





Case 5 - Pheochromocytoma

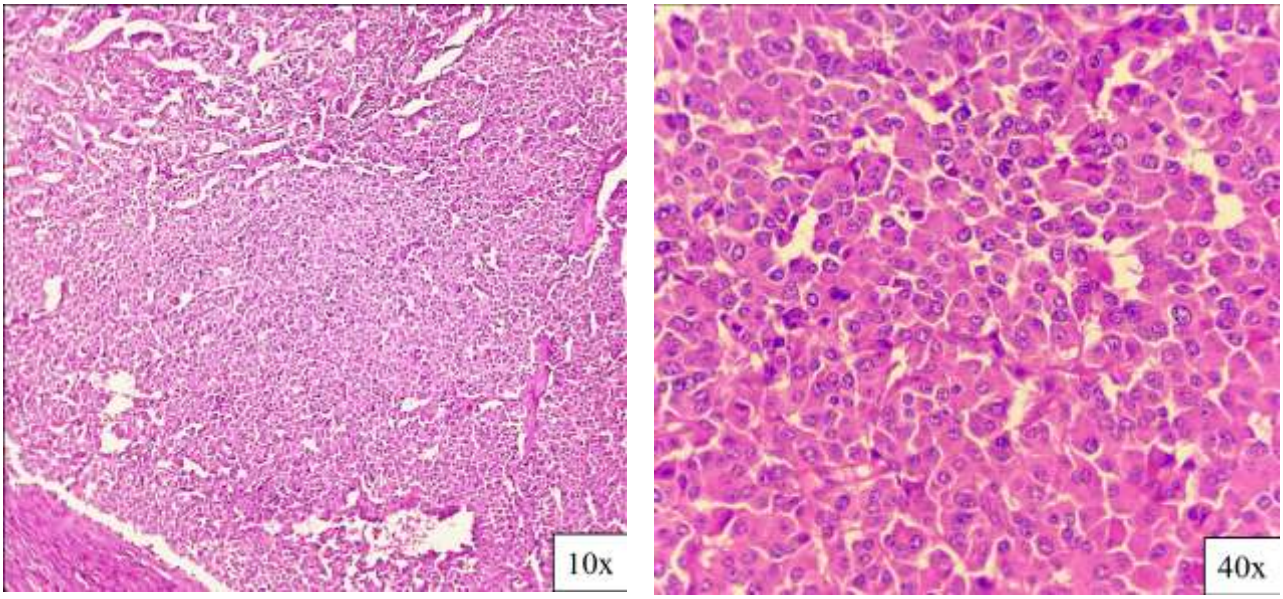


Figure 1: Photomicrographs of Haematoxylin and eosin stained slide of neuroendocrine tumours from diverse anatomical sites in the present case series

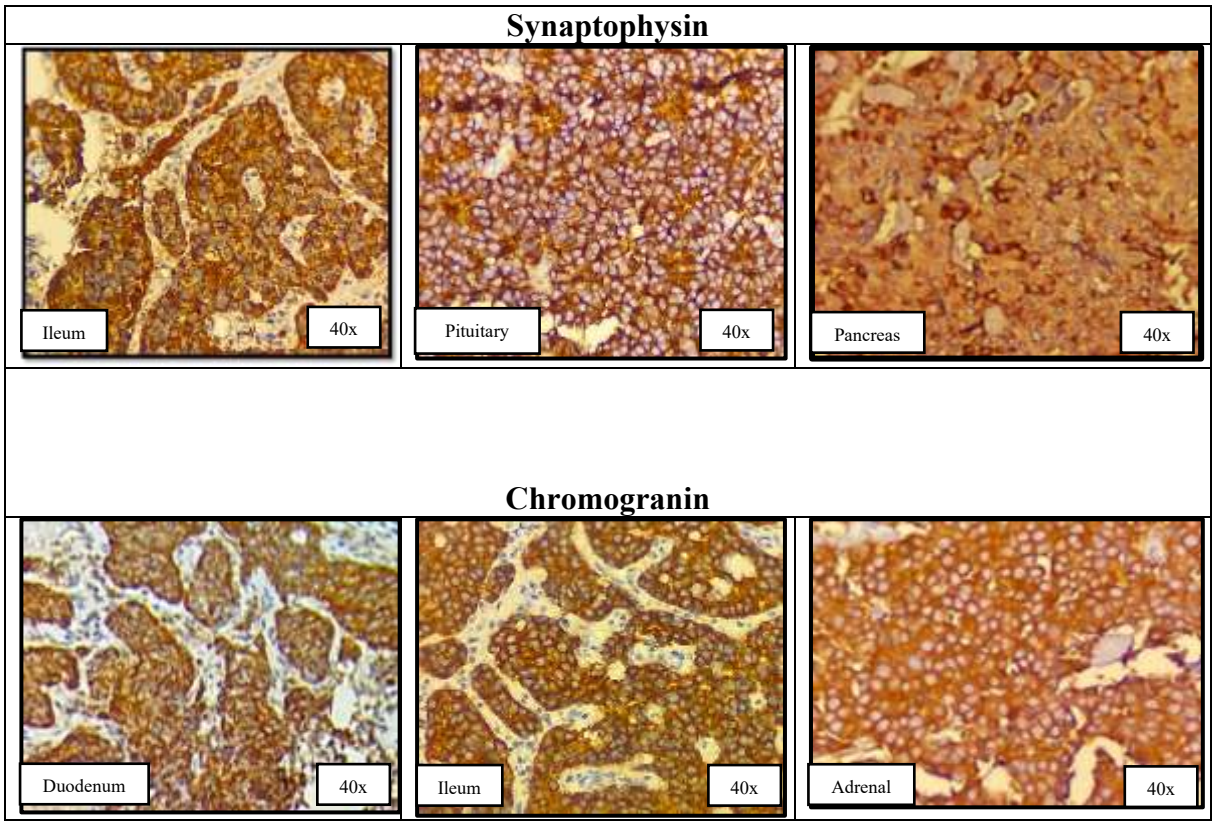


Figure 2: Photomicrographs of Synaptophysin and Chromogranin immunohistochemical pictures of neuroendocrine tumours from diverse anatomical sites in the present case series

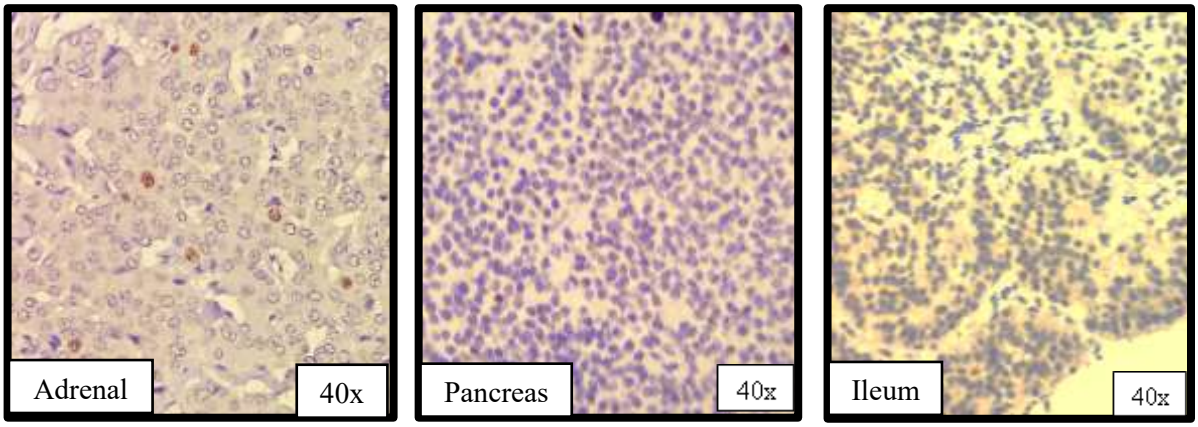


Figure 3: Photomicrographs of Ki67 immunohistochemical pictures of neuroendocrine tumours from diverse anatomical sites in the present case series

DISCUSSION

The present case series highlighted the defining paradox of neuroendocrine neoplasia: marked anatomic heterogeneity coexisting with a recognisable core morphologic phenotype. Sultana et al. (2023) added that neuroendocrine neoplasms can arise in multiple organs, most commonly in the gastrointestinal tract, but also in the pancreas, pituitary, adrenal medulla, lung, and other sites.(2) Across these locations, well-differentiated tumours typically retain an organoid growth pattern, including nests, trabeculae, cords, or rosette-like structures, and are composed of relatively uniform cells with round to oval nuclei and finely granular "salt-and-pepper" chromatin.(7, 8) This shared morphology was evident in Cases 1–4, whereas Case 5 demonstrated how site-specific variation within the neuroendocrine family can still preserve the same lineage identity while exhibiting more aggressive clinical and proliferative features.

A strength of the present series was the consistent use of morphology together with synaptophysin, chromogranin, and Ki-67 to establish neuroendocrine differentiation. In gastroenteropancreatic neuroendocrine neoplasms, current WHO/IARC framework requires assessment of both differentiation and proliferative activity, with Ki-67 index and mitotic count forming the basis of grading.(3, 9) Well-differentiated NETs are classified as G1, G2, or G3, and a G1 tumour is defined by a Ki-67 index below 3% and a mitotic count below 2 per 2 mm^2/10 high-power fields. Ki-67 is not merely ancillary in this setting; it is considered mandatory in the diagnostic work-up because it has established diagnostic and prognostic utility in gut and pancreatic neuroendocrine neoplasms, as noted by Luchini et al. (2022), Pezzilli et al. (2016) and Tracht et al. (2017).(10-12) The ileal, duodenal, and pancreatic tumours in the present study all fulfilled low-grade criteria, with Ki-67 values of 1–2% and low mitotic activity, supporting their classification as well-differentiated Grade 1 NETs.

The ileal tumour in Case 1 illustrated a classic but clinically important form of small-bowel NET. Small-bowel NETs are increasingly recognised and are now regarded as the most common primary malignancies of the small intestine, with the distal ileum representing the predominant site.(8) Their bland microscopic appearance can be deceptive because these tumours often grow slowly, present with vague symptoms, and may already have locoregional or distant spread at the time of diagnosis. Even when identified incidentally, as in the present patient, careful clinicoradiologic staging remains essential. Another practical issue is multifocality: Steinkraus et al. (2021) noted that roughly half of surgically explored small-bowel NETs may harbour multifocal lesions, many of them subcentimetre,(13) which has direct implications for intraoperative assessment and pathologic sampling. The infiltration of lamina propria and muscularis propria in this case therefore deserved attention beyond grading alone, because depth of invasion and multiplicity are important determinants of stage and subsequent management.(14)

Case 2, involving a duodenal D1 nodule found during upper gastrointestinal endoscopy, fit well with the recognised clinicopathologic profile of duodenal NETs noted by Gamboa et al. (2019).(15) These tumours are relatively uncommon and are frequently discovered incidentally during esophagogastroduodenoscopy performed for unrelated symptoms. They are often intramural or submucosal lesions, and most small lesions are localised, low grade, and biologically indolent relative to other gastrointestinal neuroendocrine neoplasms.(16) The present case showed a lamina propria-based proliferation of uniform cells in trabeculae, cords, and nests, with low mitotic activity and a Ki-67 index of 1–2%, which was entirely concordant with a localised, well-differentiated duodenal NET. This case also underscored how modest endoscopic lesions in the duodenum can still represent bona fide neuroendocrine tumours and therefore require accurate grading and correlation with lesion size, depth, and imaging findings.

The pancreatic lesion in Case 3 demonstrated the same low-grade neuroendocrine cytology in a different architectural context, namely a lobular pattern separated by delicate fibrous septa. Pancreatic neuroendocrine neoplasms are classified on the same fundamental principles of differentiation and proliferation, but their differential diagnosis is broader and includes mimics such as solid-pseudopapillary neoplasm and non-neuroendocrine tumours with focal neuroendocrine marker expression; in corroboration with Ohara et al. (2016) and Raddaoui et al. (2016).(17, 18) Konukiewitz et al. (2022) emphasise that diffuse synaptophysin and chromogranin expression, in conjunction with appropriate morphology, remains central to diagnosis, while interpretation must still be cautious because isolated neuroendocrine marker positivity is not entirely specific.(19) Clinically, nonfunctioning pancreatic NETs present with non-specific symptoms related to mass effect, including abdominal pain and weight loss, rather than a hormone hypersecretion syndrome.(20) The abdominal

pain in this patient was therefore compatible with a nonfunctioning PanNET, while the low Ki-67 index and low mitotic rate supported a well-differentiated Grade 1 tumour rather than high-grade NET or neuroendocrine carcinoma.

The immunohistochemical profile across Cases 1–5 further illustrated the practical value of combining synaptophysin and chromogranin in surgical pathology. Chromogranin A is a marker of neuroendocrine secretory granules,(21) whereas synaptophysin highlights neurosecretory vesicles;(22) together they remain the two most widely used markers of neuroendocrine differentiation in routine diagnostic practice. Their co-expression strongly supported lineage assignment in the present tumours, particularly when interpreted alongside the classic chromatin pattern and organoid architecture. At the same time, Tomita (2020) cautions that neuroendocrine markers should not be read in isolation, because synaptophysin and, less commonly, chromogranin may also be expressed in certain non-neuroendocrine neoplasms.(23) Accordingly, the diagnostic confidence in this series derived not from immunostaining alone but from concordance between histomorphology, marker profile, and site-specific clinical context.

Case 4 brought out an important taxonomic point: pituitary tumours are now formally termed pituitary neuroendocrine tumours (PitNETs) in the 2022 WHO classification, reflecting their neuroendocrine nature and broad biologic spectrum.(24) However, PitNETs are not graded using the gastroenteropancreatic G1/G2/G3 framework, and direct extrapolation of gut or pancreatic grading rules to the pituitary is inappropriate. Nasi-Kordhishti et al. (2025) emphasises that pituitary lineage assignment increasingly relies on pituitary transcription factors such as PIT-1, T-PIT, and SF-1, supplemented by pituitary hormone immunostaining, because this approach improves clinicopathologic classification and markedly reduces the category of so-called null cell tumours.(5) Although the present pituitary tumour showed synaptophysin and chromogranin positivity with a low Ki-67 index of 1–2%, that low proliferative activity should be interpreted only as supportive of relatively indolent behaviour.(6) Indeed, no single histologic or radiologic parameter reliably predicts aggressive or metastatic behaviour in PitNETs, although higher proliferation indices tend to enrich for aggressive subsets.(6)

The pheochromocytoma in Case 5 represented the most clinically aggressive lesion in the series and illustrated the distinctive pathology of adrenal medullary neuroendocrine tumours. Pacak (2011) noted that pheochromocytomas arise from chromaffin cells of the adrenal medulla and classically present with symptoms related to catecholamine excess, including headache, palpitations, diaphoresis, and hypertension; severe or sustained hypertension and weight loss, as seen in this patient.(25) Histologically, the characteristic zell-ballen pattern consists of nests of polygonal chief cells surrounded by a rich vascular network and sustentacular support cells.(26) The present tumour showed that archetypal nested/trabecular architecture, but it also displayed adverse features relative to the other cases, including marked size, inferior vena cava thrombus, higher mitotic activity, and a Ki-67 index of 5–10%. Lopes (2017) and Guilmette & Sadow (2019) added that literature no longer uses a simple benign-versus-malignant dichotomy for pheochromocytoma/paraganglioma; instead, all such tumours are considered to possess some metastatic potential.(7, 27) Risk stratification systems such as GAPP incorporate proliferative activity, and Ki-67 values above 3% contribute to higher risk scores, so the proliferative index in this case was concordant with a tumour, in corroboration with Juhlin (2021) and Kimura et al. (2014).(28, 29)

Taken together, these five cases demonstrated that the unifying diagnosis of neuroendocrine neoplasia rests on a stable triad of morphology, immunophenotype, and proliferation assessment, but that the final interpretation remains site-specific. The ileal, duodenal, and pancreatic tumours were all well-differentiated G1 NETs by Ito et al. (2021),(30) yet each carried different anatomic implications regarding multifocality, localisation, and patterns of presentation. The pituitary lesion shared neuroendocrine morphology and marker expression but required a separate classification logic grounded in lineage-based PitNET terminology. The pheochromocytoma, in contrast, highlighted how a neuroendocrine tumour can preserve classical chromaffin morphology while entering a different risk paradigm based on metastatic potential. An additional conceptual point is that the coexistence of pituitary, pancreatic, and duodenal neuroendocrine tumours in endocrine pathology should always raise awareness of inherited syndromic contexts such as MEN1 when multiple lesions occur in the same patient or family, because pituitary adenomas/PitNETs and pancreatic and duodenal NETs are recognised cardinal manifestations of that syndrome.(31)

CONCLUSION

This case series demonstrated that neuroendocrine tumours exhibited marked heterogeneity in clinical presentation, anatomical site, architectural pattern, and proliferative activity, while retaining a common core morphology characterised by organoid growth, salt-and-pepper chromatin, and neuroendocrine marker expression. The gastrointestinal and pancreatic lesions in the present series were well-differentiated low-grade neuroendocrine tumours with low mitotic activity and low Ki-67 index, whereas the adrenal pheochromocytoma showed relatively higher proliferative activity and more aggressive clinical behaviour, highlighting the biological diversity within this group of neoplasms. The study also underscored the importance of integrating histomorphology with immunohistochemistry and proliferation assessment for accurate diagnosis and site-appropriate classification. Recognition of these shared and site-specific features was essential for distinguishing low-grade indolent tumours from lesions with greater aggressive potential, thereby contributing to improved pathological interpretation and more meaningful clinicopathological correlation in neuroendocrine neoplasia.

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