Case Series

Gastrointestinal Neuroendocrine Tumours: A Comprehensive Case Series with Histomorphological Correlation at Tertiary Care Hospital, Western India

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Abstract

Background: Gastrointestinal neuroendocrine neoplasms (GI-NENs) are rare and arise from enterochromaffin/Kulchitsky cells and exhibit variable clinical, morphological, and biological behavior. Their diagnosis and grading rely heavily on histopathology and proliferation indices as per the WHO 5th edition classification. Early diagnosis and surgical resection has better outcome.
Aim: To describe the histopathological features, grading, immunohistochemical profile, and short-term outcomes of five GI-NENs.
Materials and Methods: Five cases of GI-NENs diagnosed over nine months were retrospectively analysed. Clinical details, tumour location, gross findings, histomorphology, mitotic activity, Ki-67 index, and immunohistochemistry (IHC) profiles were analyzed. All details taken from clinical case and laboratory records. Classification and grading were performed using the WHO 2022/5th edition criteria.
Results: Patients ranged from 16 to 54 years (mean 39 years) with female predominance. Duodenum was the most common site (three cases), followed by ileum (one case) and appendix (one case). Four tumours were well-differentiated NETs, low grade (three G2, one G1) and one was a poorly differentiated large-cell neuroendocrine carcinoma (NEC). Most NETs demonstrated strong Synaptophysin and Chromogranin A positivity. Ki-67 index ranged from <2% to 65%. Two patients with high-risk features (including NEC) succumbed to death within one month after surgery.
Conclusion: GI-NENs in this series primarily affected females and involved the duodenum most commonly. Well-differentiated low-grade NETs represented the predominant tumour type. Ki-67 proliferative index correlated well with histologic grade and clinical outcome, reaffirming its essential role in tumour stratification. Early diagnosis and accurate grading remain crucial for prognostication and management.
As this is a retrospective study of case series, ethical committee approval was not mandatory as per our Institutional Ethics Committee.

Keywords: gastrointestinal neuroendocrine neoplasm; histomorphology; Ki-67 proliferation index; immunohistochemistry

Introduction

Neuroendocrine neoplasms are derived predominantly from enterochromaffin or Kulchitsky cells & have diverse pathologic findings that typically correspond to the site of origin & hormone-secreting ability[1]. These tumours are found in the gastrointestinal tracts, the lung, and the ovary. Gastrointestinal neuroendocrine neoplasms (GI-NENs) are rare tumours (<2%) that come from neuroendocrine cells found mainly in the inner layers (mucosa and submucosa) of the digestive tract. Among the various GI-NENs in the gastrointestinal tract, the small intestine is the most common site of occurrence,

and carcinoid tumour is the most common pathological type[2]. They are slow-growing and asymptomatic but can present with a large mass with lymph node metastasis. Many diagnostic tools, such as CT scans, MRI, ultrasound, blood tests, and endoscopy, can help to detect these tumours, but a definite diagnosis requires examination under a microscope (pathological testing).

The World Health Organization (WHO) 5th classification of GIT-NENs introduced a new system to classify digestive tract neuroendocrine tumours[3] (Table 1).

Table 1: WHO 5th edition classification of gastrointestinal neuroendocrine neoplasms based on differentiation, grade, mitotic rate, and Ki-67 index.

Terminology	Differentiation	Grade	Mitotic rate (/2mm^2)	Ki-67 index
NET, G1	Well-differentiated	Low	<2	<3%
NET, G2		Intermediate	2–20	3–20%
NET, G3		High	>20	>20%
NEC, small cell type (SCNEC)	Poorly differentiated	High	>20	>20%
NEC, large cell type (LCNEC)			>20	>20%
MiNEN	Well/poorly differentiated	Variable	Variable	Variable

Abbreviations: NET – neuroendocrine tumor, NEC – neuroendocrine carcinoma, G – grade, MiNEN – mixed neuroendocrine non-neuroendocrine neoplasm

This classification is based on proliferative features of the tumour: The Ki-67 proliferation index and mitotic count. Ki-67 value is determined by counting at least 500 cells in the regions of highest labelling (hotspots), which are identified at scanning magnification and the mitotic count (No. of mitosis/2 mm^2). Ki-67 proliferative index has a well-documented & accepted diagnostic & prognostic role, & its evaluation is mandatory in pathological assessment[4, 5].

Well-differentiated NETs are composed of uniform, round to polygonal cells with abundant cytoplasm & 'salt & pepper' chromatin arranged in nests, ribbons, acini & trabeculae. NECs are further classified as Large Cell Neuroendocrine Carcinoma (LCNEC) & Small Cell Neuroendocrine Carcinoma (SCNEC) based on the morphology of the tumour cells. SCNECs are composed of sheets or nests of small cells with a high nuclear to cytoplasmic ratio, scant cytoplasm, hyperchromatic nuclei, finely granular chromatin & inconspicuous nucleoli. Large cell NECs are composed of round to polygonal cells with a moderate amount of cytoplasm, round nuclei, vesicular chromatin & prominent nucleoli[6, 7].

Synaptophysin and Chromogranin A are the IHC markers used for accurate characterisation of neuroendocrine neoplasms, with p53 & Retinoblastoma protein (RB) aiding in the diagnosis when there are overlapping morphological features of G3 NET & NEC. In G3 NETs, there is wild-type p53 & retained RB, while NECs exhibit diffuse positive or null staining for p53 & loss of staining for RB[4]. For Indian origin, limited data are available on these tumours, so we have tried to narrate four cases with different clinicopathological, histological and IHC expression analysis.

IHC antibodies from DAKO (Agilent) were used in this study whose clones & dilution are as follow: Synaptophysin (polyclonal, dilution 1:100, diffuse cytoplasmic staining), Chromogranin A – Chromogranin A is commonly a polyclonal antibody from Dako, used at 1:200 dilution, producing granular cytoplasmic staining. CD 56, clone 123C3, supplied by Dako, is typically used at 1:100 dilution & shows membranous staining. Ki-67, clone MIB 1 from Dako is usually used at 1:100 dilution & shows nuclear staining, which is important for tumour grading. CDX2, clone DAK-CDX2 from Dako is generally used at 1:50–1:100 dilution & shows nuclear staining. Cytokeratin, clone AE1/AE3 from Dako is usually used at 1:100 dilution & shows cytoplasmic staining. A total of 4 cases of GIT-NENs were studied for clinicopathological, histomorphological, and IHC expression. Surgical specimens were received in the pathology department of the hospital, routinely processed in paraffin and stained with H and E stain. They were reported by pathologists with reference to the WHO 5th classification. (Table 1)

Case Reports

Case 1

A 54 year male presented to department of surgery with abdominal pain, black stool since 20 days. CECT report showed a well defined intraluminal non-enhancing hypodense lesion with lobulated margins involving D1 segment of duodenum possibility of neoplastic etiology Gastrointestinal Stromal tumor likely. Surgery was performed and histopathology laboratory received specimen of tumour with distal gastrectomy (Distal part of stomach & D1 resected with tumour). Tumour measuring 3.0x2.7x1.2 cm. Cut surface was yellowish white. Microscopic examination of H & E stained sections reported it histomorphologically as Well differentiated NET, Grade 2. Later on IHC was positive for CK (epithelial marker), Synaptophysin, Chromogranin A with low Ki67 index (4–5%) confirming HPE diagnosis. Patient was followed up for one month which was uneventful, then patient was lost to follow up.

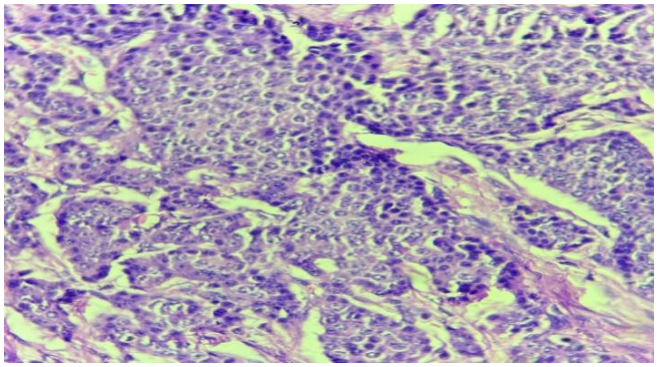

Figure 1: Neuroendocrine tumour, Grade 2, duodenum (H&E, 40x).

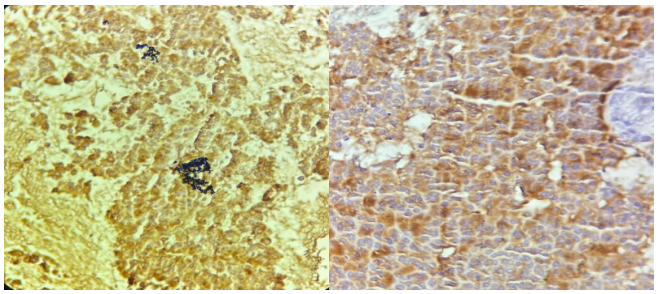

Figure 2: IHC showing positivity for Chromogranin A (left) and Synaptophysin (right) (IHC, 40x, 40x).

Case 2

A 16 year female presented to department of surgery with chief complaint of pain in right Iliac Fossa since 1 month. Ultrasonography of abdomen revealed Subacute Appendicitis, so Laproscopic Appendicectomy was performed. Specimen of Appendix was received in histopatho laboratory measuring 5.0 x 0.9 cm with incidentaloma of 0.3 cm sized, well demarcated, firm, round, yellow nodule on the tip (Fig. 3). It was histomorphologically reported as Well differentiated NET, Grade 1. IHC was not applied due to financial constraints.

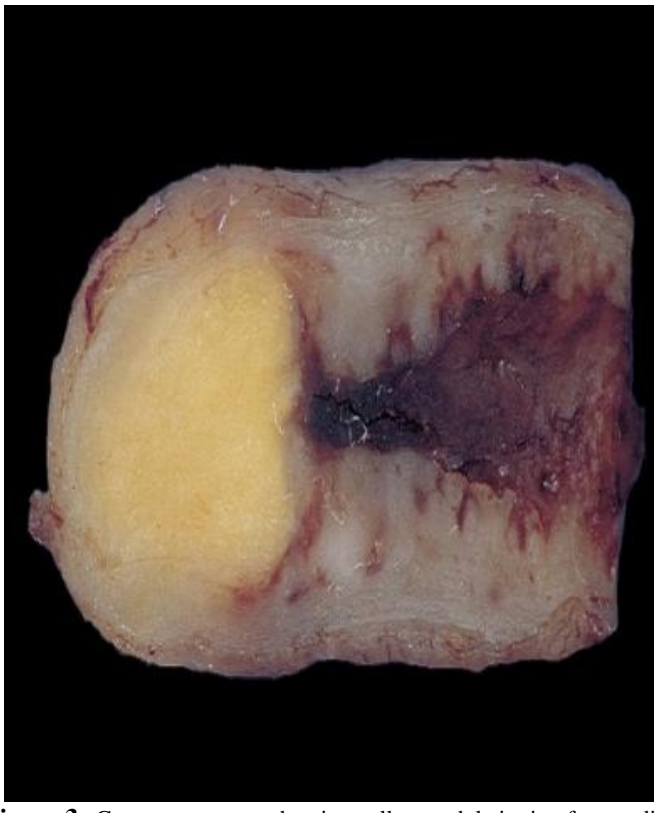

Figure 3: Gross appearance showing yellow nodule in tip of appendix.

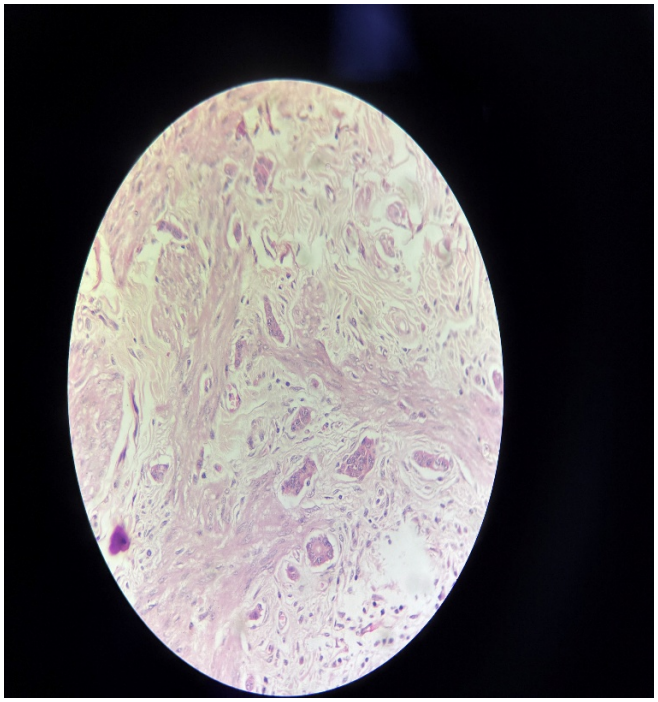

Figure 4: Neuroendocrine tumour, Grade 1, appendix (H&E, 10x).

Case 3

A 28 year female presented with right upper abdominal pain since 1 year. History of weight loss & anorexia since last 1 month. Upper GI endoscopy showed ulceroproliferative mass in duodenum. Contrast Enhanced Computed Tomography (CECT) showed a well defined lobulated hypodense lesion in second part of duodenum measuring 3.4 x 7.6 x 4.6 cm and possibility of neoplastic etiology was suggested. Patient was operated for pancreaticoduodenectomy (Whipple resection). Grossly tumour was in 2nd part of duodenum & measuring 5.2 x 2.5 x 2.3 cm. Histomorphologically reported as Well differentiated NET, Grade 2. IHC markers were positive for Synaptophysin, Chromogranin A with low Ki67 index <2%. Patients recovery was uneventful for one month after that she was lost to follow up.

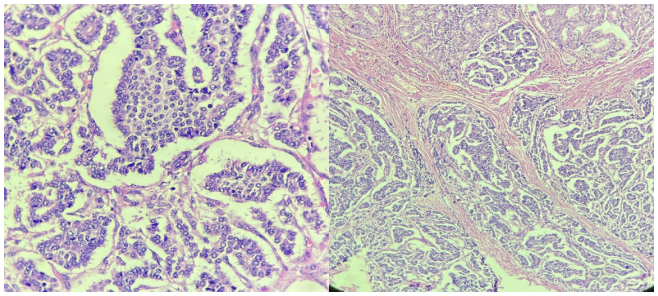

Figure 5: Neuroendocrine tumour, Grade 2, duodenum (H&E, 40x (left), 10x (right)).

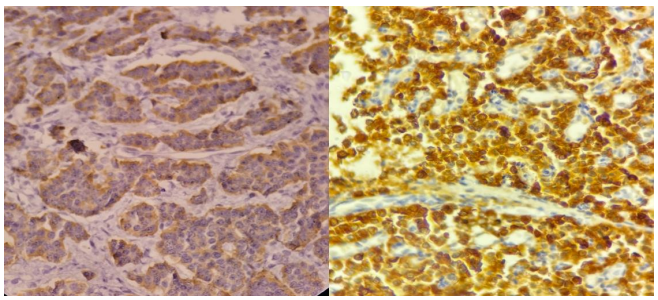

Figure 6: IHC showing positivity for Synaptophysin (left) and Chromogranin A (right) (IHC, 40x, 40x).

Case 4

A 48 year old female presented with upper abdominal pain & vomiting since 1.5 month. Upper GI endoscopy showed proliferative growth in Duodenum. CECT showed circumferential 17 mm wall thickening with 21 mm length mass in 3rd part of duodenum. Duodenal mass biopsy reported as Poorly differentiated carcinoma and IHC suggested which showed

positive for CK7, Synaptophysin, CD56, CDX 2 & negative for chromogranin A. Ki67 index was high (60–65%). Results of IHC was consistent with Large Cell NEC. Later on Whipple's specimen was received showing duodenal tumour measuring 2.3 x 2.0 x 1.3 cm in size. Histomorphologically reported as Large cell NEC with review of previous IHC results. (Fig. 8) Patient expired within one month after surgery due to aggressive behaviour of cancer.

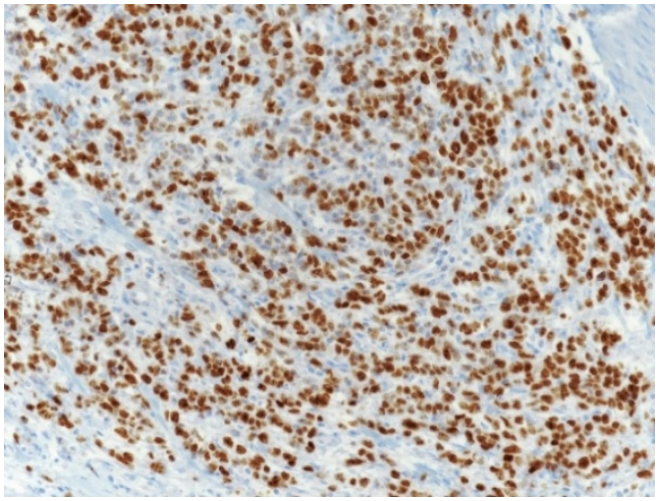

Figure 7: Ki-67 showing areas of highest proliferation (IHC, 40x).

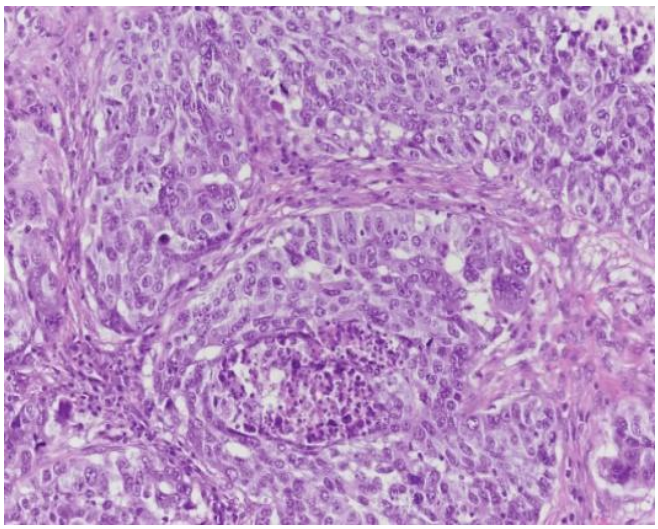

Figure 8: Large cell NEC of duodenum (H&E, 40x).

Case 5

A 51 year old female presented with abdominal pain along with vomiting, weakness & vertigo. Imaging study showed submucosal intraluminal polypoid growth in ileum suggestive of possibility of neuroendocrine tumour. Patient underwent ileal segmental resection of small intestine. Histopathology laboratory received ileal loop with a tumour measuring 1.7 x 1.5 x 0.7 cm. Histomorphologically reported as Well differentiated NET, Grade 2. IHC showed positivity for Cytokeratin 7, Synaptophysin, Chromogranin A & CD56 with 5% Ki67 proliferation index confirming HPE diagnosis. During follow up, she died within a month after the surgery.

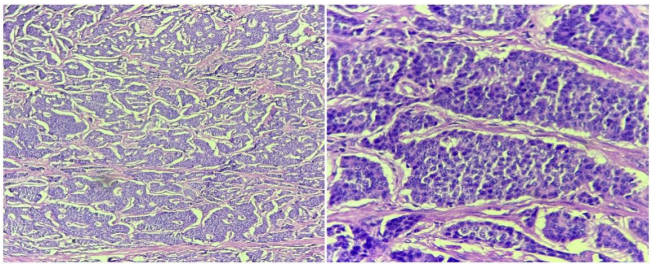

Figure 9: Neuroendocrine tumour, Grade 2, ileum (H&E, 10x (left), 40x (right)).

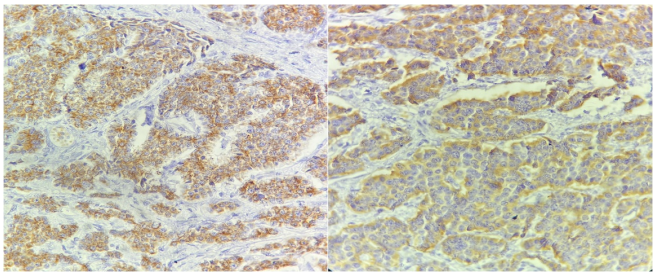

Figure 10: IHC showing positivity for Cytokeratin (left) and Synaptophysin (right) (IHC, 40x, 40x).

Table 2: Detailed analysis of clinicopathological features of five cases.

Case no.	Age (years)/Sex	Primary symptoms	Location	Tumour size	Follow up
1	54/M	Abdominal pain	Duodenum	3.0x2.7x1.2 cm	1 month then lost to f/up
2	16/F	Pain in right iliac fossa	Appendix	0.3 cm	Lost to f/up
3	28/F	Abdominal pain, weight loss	Duodenum	5.2x2.5x2.3 cm	1 month then lost to f/u
4	48/F	Abdominal pain, vomiting	Duodenum	2.3x2.0x1.3 cm	1 month after that patient died
5	51/F	Abdominal pain, vomiting	Ileum	1.7x1.5x0.7 cm	Died within month

Table 3: Detailed analysis of histopathological features with IHC expression in five cases.

Case no.	Mitosis/2mm^2	Histological grade	Ki-67 index	Synaptophysin	Chromogranin A	Cytokeratin
1	2–20	G2, Intermediate	4–5%	Positive	Positive	Positive
2	<2	G1, Low	<2%	Not done	Not done	Not done
3	4–6	G2, Intermediate	<2%	Positive	Positive	Not done
4	>20	G3, High	60–65%	Positive	Negative	Positive
5	2–3	G2, Low	5%	Positive	Positive	Positive

Discussion

Neuroendocrine cells are distributed to multiple sites in the body. NETs are most common in the lung and the GIT. Clinically, patients present vaguely, mostly asymptomatic, with an indolent course, but may present with a mass effect and metastasis. Gastrointestinal NETs are rare malignant tumours, with the stomach being the common site[1]. With advanced and improved diagnostics, the number of patients diagnosed with GIT-NET has increased, and they have gained attention over the last few years. The diagnosis includes various imaging modalities, but tumour localisation is of prime importance as surgery is the cornerstone of treatment. Endoscopy is essential for diagnosis[2].

According to the 5th WHO classification system, the term 'Neuroendocrine neoplasm' is used to describe all tumours composed of neuroendocrine cells and categorised as NET G1, G2, G3 or NEC. The grading system is based on the Ki-67 proliferation index and mitotic count. (Table 1) Chromogranin A and synaptophysin are widely used IHC markers, where Chromogranin A is positive in around 80% of cases, establishing its high sensitivity for NETs. The treatment options are outlined based on tumour (primary) site, histopathological diagnosis, grading, staging, along with clinical presentation and comorbidities[4]. In the present study, the majority of cases were observed between the third and fifth decades with a median age of 39 years. In contrast, Amarapurkar DN et al[8], Rothenstein J et al[9] showed the mean age at diagnosis as 56 & 53 years, respectively. This could be explained by the fact that the number of cases in our study was small. Female predominance in the present study aligns with reports by Zeng et al[10] & Yucel et al[11], who also reported the same. Abdominal pain was the predominant symptom, with the duodenum as the most common site in the present study. These findings were similar to observations by Muralidhar A et al[12], although Maggard et al[13] reported the small intestine as the predominant site. The present study showed low-grade NET (G1 & G2) as the most common histologic type, with only one case of NEC. These results are consistent with Amarapurkar DN et al[8], Rothenstein J et al[9], who also reported NET G1 & G2 as the most common tumour types. The above results showed that GIT-NET are usually of lower grades. Various Immunohistochemical markers were applied for confirmation of HPE diagnosis in the present study. It showed Synaptophysin & Chromogranin A are sensitive and specific, so can be used in a panel for confirming neuroendocrine differentiation. This result is in agreement with findings by Anna Fen-Yau Li et al[14].

Postoperative follow-up of patients was available in four out of five cases only. Two patients had high-risk factors for progressive disease leading to poor prognosis (death).

Limitations: As GIT-NENs are rare and the study period was of 9 months only, a limited number of cases could be studied. IHC was not performed in one patient due to financial constraints.

Conclusion

Neuroendocrine tumours of the digestive tract are rare. The mean age of presentation is 39 years, with female predominance. Duodenum is the most common site, followed by the ileum. Most of the tumours are well-differentiated and low-grade NETs (G1 and G2). On IHC, Synaptophysin & Chromogranin A were positive in most cases, establishing their reliability in the diagnosis of NETs. GIT-NENs are recognised more currently with the use of advanced diagnostic modalities, helping in early diagnosis and treatment.

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Competing Interests: None. As this is a retrospective study of case series, ethical committee approval was not mandatory as per our Institutional Ethics Committee.

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