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CASE REPORT

Gastric Large-Cell Neuroendocrine Carcinoma Presenting as Perforation Peritonitis: a Rare Case Report

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Abstract

Gastric neuroendocrine carcinomas (GNECs) are rare tumors characterized by an aggressive clinical course, rapid progression, metastatic dissemination, and poor prognosis. Due to overlapping radiological features and small pre-operative biopsy specimens, they are frequently misdiagnosed as adenocarcinoma in the pre-operative period. These tumors are generally asymptomatic or present with non-specific symptoms like epigastric pain or discomfort, weight loss, and loss of appetite. However, GNECs presenting as perforation peritonitis are rarely reported in the literature. A 60-year-old man presented to the emergency department with complaints of pain upper abdomen with loss of weight and appetite for four months. He had an endoscopic biopsy report suggestive of antral growth reported as poorly differentiated adenocarcinoma. Radiological investigations were notable for the presence of a malignant lesion in the stomach with perforation. Subtotal gastrectomy with D1 lymph node resection was done. Specimen pathology confirmed poorly differentiated high grade large cell neuroendocrine carcinoma. This article emphasizes the importance of considering GNEC as a differential diagnosis for gastric adenocarcinoma despite overlapping radiological features and challenges with pre-operative diagnosis due to its aggressive nature and to allow for appropriate management.

Keywords Neuroendocrine carcinoma · Gastric neuroendocrine carcinoma · NEC · Gastric perforation · Large-cell neuroendocrine carcinoma

Introduction

Neuroendocrine carcinomas (NECs) are rare tumors commonly reported in the pulmonary region [1]. Although rare (9%), extrapulmonary NECs are reported in various organs such as the cervix, esophagus, larynx, pancreas, and bladder [2, 3]. They are characterized by high mitotic counts and Ki-67 index and are rarely associated with hormonal syndromes. They often present in the advanced stage and have a poor prognosis, median survival being 7.7 months [2]. Gastric NECs (GNEC) account for 1.5% of stomach cancers [4–6]. This article describes a case of GNEC, presenting as perforation peritonitis, which is a rare presentation of GNECs.

Case Report

A 60-year-old gentleman with no known co-morbidities presented to the emergency department with complaints of diffuse abdominal pain associated with melena for the past three days. He gave a history of dull aching upper abdomen pain that increased with food intake and was not relieved with medications for four months. The pain was associated with weight loss (around 10 kg in the last four months), loss of appetite, and occasional episodes of non-bilious vomiting. The patient came with a one-month-old endoscopic report from a different hospital suggestive of antral growth with biopsy from the growth reported as poorly differentiated

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adenocarcinoma. On general examination, the patient was pale, dehydrated, and had tachycardia. The abdomen was distended with diffuse tenderness and guarding.

Contrast-enhanced computed tomography (CECT) of the abdomen revealed pneumoperitoneum with irregular heterogeneously enhancing circumferential wall thickening in the antropyloric region for a length of 5 cm with a rent in the body of the stomach along the greater curvature with hypodense collection in the left sub-diaphragmatic region. Multiple enlarged perigastric nodes were noted. There was no evidence of lung, liver, adrenal, or bone metastasis (Fig. 1).

The patient was taken up for emergency exploratory laparotomy with a diagnosis of malignant gastric perforation. Intra-operatively, 300 ml of bilio-purulent fluid was noted in the left hypochondrium, and perforation of size 2×2 cm was noted in the mid-body of the stomach with growth in the antropyloric region reaching the perforation site with multiple perigastric lymph nodes. There were no peritoneal or liver deposits. The peritoneal fluid was sampled for cytological examination which was negative for any malignant cells. The patient subsequently underwent subtotal gastrectomy with D1 nodal resection and Billroth-II gastrojejunostomy. An extensive D2 lymph nodal dissection was avoided in the emergency setting as the patient had hemodynamic instability during surgery, and due to the gross contamination in the peritoneal cavity.

The specimen was sent for histopathological examination. On gross examination, the cut surface of the specimen revealed a proliferative growth in the antrum measuring 4.0×3.1×0.6 cm, which was gray-white, homogenous, firm in consistency, and was seen obstructing the gastric outlet. A perforation was noted 2 cm proximal to the tumor, and mucosa around the perforation appeared unhealthy and covered with debris. Microscopically, sections from the tumor showed tumor cells arranged in nests, cords, trabeculae, and glandular patterns, exhibiting moderate to marked nuclear pleomorphism, some with bizarre nuclei, vesicular chromatin, and prominent nucleoli (Fig. 2). The glandular pattern comprised less than 30% of the tumor cells. The tumor was also seen infiltrating the serosa. Extensive necrosis and ulceration of the gastric mucosa were noted. The tumor exhibited mitotic activity of 43/10 high power fields and was poorly differentiated. Lymphovascular and perineural invasion was observed. Six out of the 16 resected lymph nodes showed metastatic deposits. On immunohistochemical staining, tumor cells were focally positive for chromogranin and synaptophysin and negative for CK 7 (Fig. 3). The Ki-67 labeling index was 85%. The above features were consistent with poorly differentiated high-grade large cell neuroendocrine carcinoma according to the WHO 2019 criteria [7]. The endoscopic biopsy from the previous hospital was wrongly reported to be adenocarcinoma, probably due to its poorly differentiated nature, the location of the tumor, and lack of immunohistochemical staining facilities. Post-operatively, the patient required ventilatory support for three days, following which he had an uneventful recovery. He was started on orals on the sixth post-operative day, which was gradually escalated, and the patient was discharged on the 12th post-operative day. Following his recovery, a FDG PET scan was done, which did not reveal any distant metastases. Ideally, this patient would have undergone adjuvant chemoradiation; however, due to his poor performance status, the tumor board decided to provide him with the best supportive care.

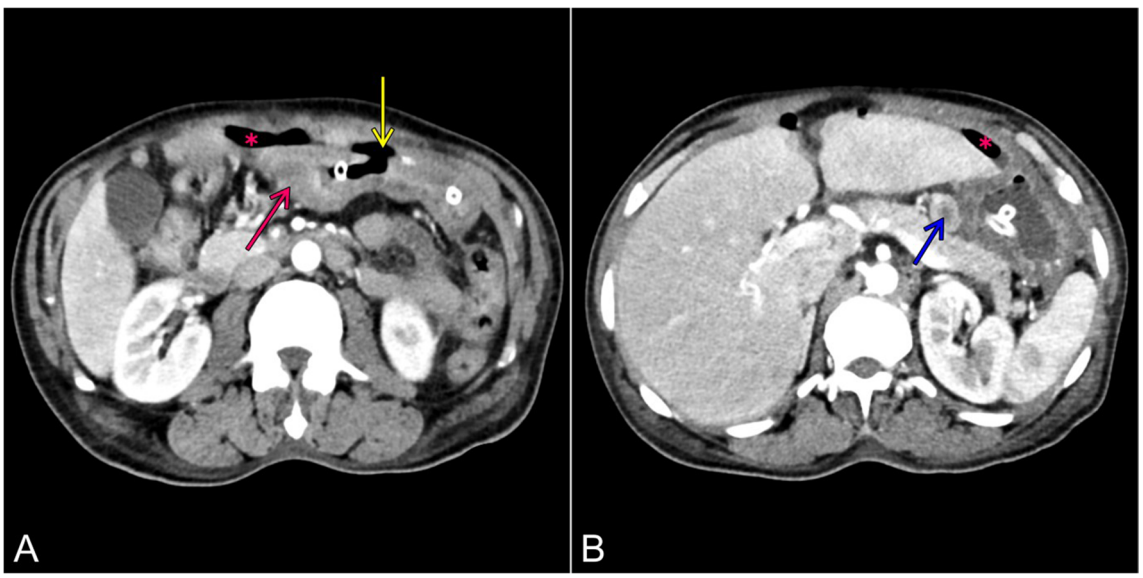

Fig. 1 Axial sections from the contrast-enhanced CT scan showing wall thickening in the antropyloric region (red arrow) with a rent in the anterior wall of the stomach (yellow arrow) with extraluminal air (red asterisk). The blue arrow shows a large perigastric lymph node

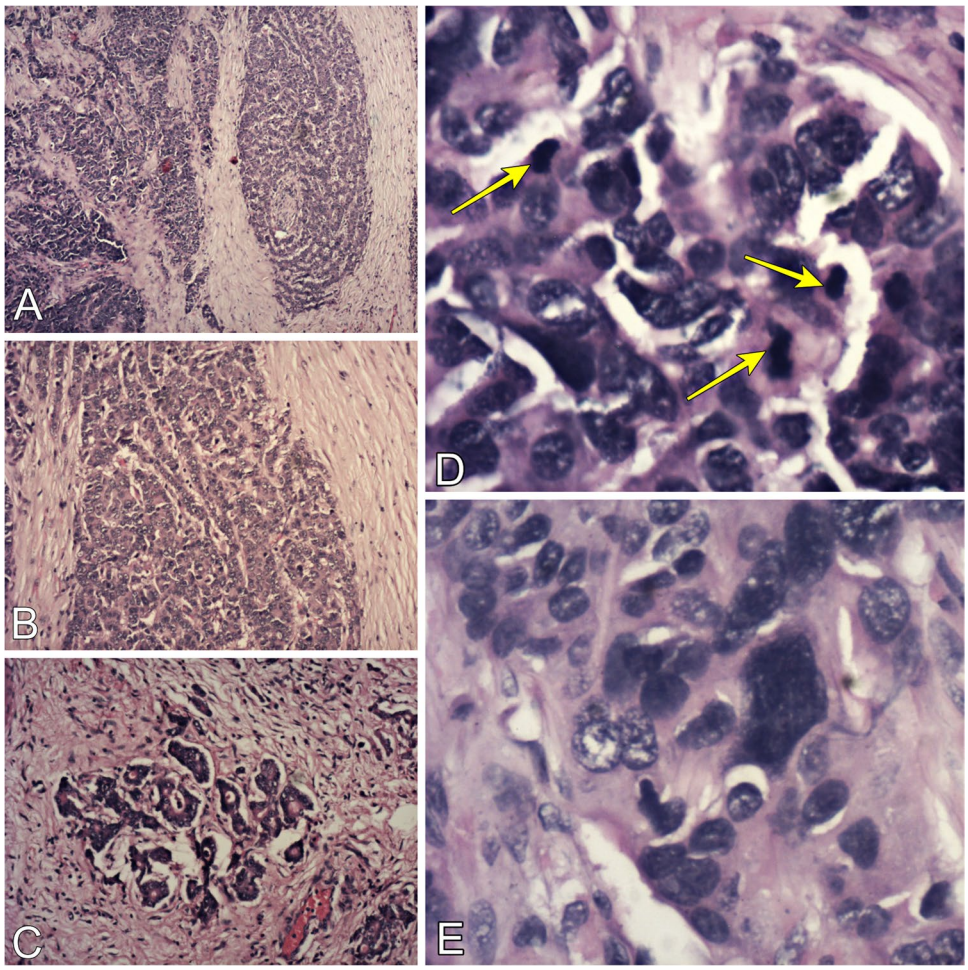

Fig. 2 **A**, **B** Histopathological sections showing tumor cells arranged in nests, cords, trabeculae (hematoxylin and eosin staining, low power ×40). **C** Sections from the tumor showing a glandular pattern of arrangement (hematoxylin and eosin staining, low power ×100). **D** Mitotic figures (hematoxylin and eosin staining, high power ×400) (yellow arrows). **E** Tumor cells with bizarre nuclei, nuclear pleomorphism, vesicular chromatin, and prominent nucleoli (hematoxylin and eosin staining, high power ×400)

Discussion

Neuroendocrine neoplasms (NENs) comprise a heterogeneous group of tumors arising from the diffuse components of the neuroendocrine system. The 2019 WHO classification, based on the morphology and proliferative rate (mitotic counts or Ki-67 labeling index), classifies NENs of the digestive system into two categories—well-differentiated neuroendocrine tumors (NETs) (low, intermediate, and high grade) and poorly differentiated NECs (small cell and large cell NEC) [7]. Some NENs can have both well or poorly differentiated components along with non-neuroendocrine pathology, like adenocarcinoma, signet ring cell carcinoma, or squamous cell carcinoma. When both components exceed 30 percent, it constitutes a mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) [7, 8].

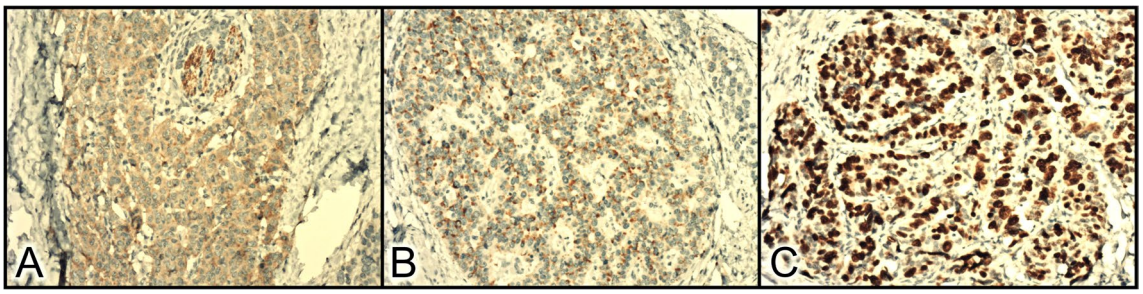

Fig. 3 **A**, **B** IHC shows positivity for synaptophysin and chromogranin (low power 100×). **C** Tumor cells with a high Ki-67 proliferation index of 85% (low power ×100). IHC, immunohistochemistry

GNECs account for only 6% of gastric NEN [9]. Incidence of gastric NEN is increasing owing to the increase in availability and expertise of endoscopy, increasing awareness and expertise in histopathology [10]. Although small cell carcinoma is more common, an increase in the incidence of large cell GNECs has been reported [11, 12]. GNECs are more common in the sixth decade (40–80 years) of life with a male predisposition [6, 9, 10]. These tumors are commonly asymptomatic with incidental detection at endoscopy or imaging. They are commonly non-functional but rare cases of secreting GNECs have been reported [6]. These patients can present with non-specific symptoms like epigastric pain or discomfort, weight loss, fatigue, and loss of appetite. Owing to this, the latency period from symptom onset to the hospital can vary from 25–240 days with a median time of presentation of 60 days [10]. Rarely, symptoms of distant metastasis may be present [10]. However, NECs presenting as perforation peritonitis is rarely reported in the literature [13–18], with only two cases of perforation in GNEC being reported [16, 18]. The clinical presentation often masquerades with other tumors commonly found at the same location; hence, diagnosis cannot be arrived at from the clinical features alone.

Diagnostic workup comprises radiological investigations like CECT and F-fluorodeoxyglucose positron emission tomography (FDG PET) and histopathological examination. Given their non-functional nature, blood investigation and serum markers are not of much use in diagnosing poorly differentiated GNECs [19]. On CECT, most GNECs are identified as a local thickening or bulky mass of the gastric wall, with a higher incidence of ulceration, irregular outer layer of the gastric wall, haziness of the perigastric fat, and metastatic perigastric lymphadenopathy, all suggestive of a high-grade nature of GNEC [9, 10]. These lesions show a moderate homogenous enhancement pattern in the arterial phase with further enhancement in the venous phase due to rich blood supply [6, 10]. However, necrotic or cystic areas causing heterogeneity in gastric mass and lymph nodes are seen in many cases [9, 10]. Unlike gastric adenocarcinoma and NETs, GNECs are hypermetabolic on FDG PET. Hence, it is a useful imaging modality for staging and monitoring response to treatment. Moreover, FDG PET has a prognostic significance; a negative FDG PET result predicts low aggressiveness and improved survival rates [19, 20]. The poorly-differentiated NECs seldom express somatostatin receptors; hence, somatostatin-receptor scintigraphy does not form part of the routine workup. However, it may be considered if the tumor is not avid on an FDG PET scan [19, 21].

On histopathology, GNEC being poorly differentiated has a sheet-like or diffuse architecture with irregular nuclei and less cytoplasmic granularity, forming nest-like structures, often with large confluent areas of necrosis and high mitotic counts. Small cell carcinomas are composed of small to medium-sized, round to oval cells with scant cytoplasm and hyperchromatic nuclei with indistinct nucleoli. In contrast, the large cell subtype comprises large cells with vesicular nuclei showing prominent nucleoli with abundant eosinophilic cytoplasm and a higher mitotic rate [9, 22]. GNEC also has a higher perineural, vascular, and lymphatic involvement than adenocarcinoma [23]. On immunohistochemical staining, markers of neuroendocrine differentiation like synaptophysin and neuron-specific enolase are usually positive, while chromogranin A may be infrequently present [3, 9, 19]. More than half of the NECs had intramucosal adenocarcinoma and/or dysplasia components suggesting the origin of GNEC from pre-existing adenocarcinoma [10, 23]. Moreover, differential localization of two histological elements has been noted; an adenocarcinoma component in the superficial mucosa and the NEC in the deeper submucosal and muscularis propria layers [10]. Therefore, as endoscopic biopsy specimens represent only a small and superficial part of the tumor, which may not be from a representative area, pre-operative diagnosis may be challenging to obtain in some cases [23]. In our case, compared with the preoperative endoscopic biopsy report of adenocarcinoma, the final histopathological report was large cell GNEC.

There is no consensus on the optimal treatment regimens for these tumors. Given clinical and histologic similarities, the existing treatment strategies are extrapolated from recommendations for small cell lung cancer [2]. Gastric NET can be endoscopically resected, whereas given their aggressive nature, GNEC requires radical surgical resection and lymph node dissection [2, 5, 23]. Systemic platinum-based chemotherapy is the mainstay of treatment for GNECs. For locoregional resectable tumors, R0 surgical resection with or without neoadjuvant chemotherapy followed by adjuvant chemotherapy or chemoradiation is recommended [2, 19]. As per the NANETS (North American Neuroendocrine Tumor Society) consensus guidelines, four to six cycles of cisplatin or carboplatin and etoposide-based adjuvant chemotherapy are recommended in such cases [19, 21]. Recommended follow-up is history and physical examination along with CECT three-monthly for the first year followed by semi-annually [2]. For locoregional unresectable or metastatic tumors, chemotherapy options include cisplatin/carboplatin-based therapy or FOLFIRINOX [3], although the optimal duration remains unspecified. The prognosis of these tumors is poor, 5-year survival being 31%, and half of the patients die within 12 months of diagnosis [6, 9].

Conclusion

GNEC is commonly asymptomatic with incidental detection at endoscopy or imaging; however, rarely they can present with gastric perforation. Due to the co-existence and differential localization of adenocarcinoma and GNEC, pre-operative diagnosis by endoscopic biopsy may be challenging. Although GNECs are rare, given their aggressive nature and overlapping radiological features, diagnosis of GNEC should be considered as a differential for gastric adenocarcinoma.

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Data Availability The data used to support the findings of this study are available from the corresponding author upon request. We will disclose all information except personal identifiable information.

Code Availability Not applicable.

Declarations

Ethics Approval The need for approval was waived for a single case report.

Consent to Participate Written informed consent was obtained from the patient for participation in this case report study.

Consent for Publication Written informed consent was obtained from the patient for publication of this report and the accompanying images, and the patient's anonymity was upheld.

Conflict of Interest The authors declare no competing interests.

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