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Case Report

Pathology Section

Amphicrine Carcinoma of the Duodenum: A Rare Entity

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ABSTRACT

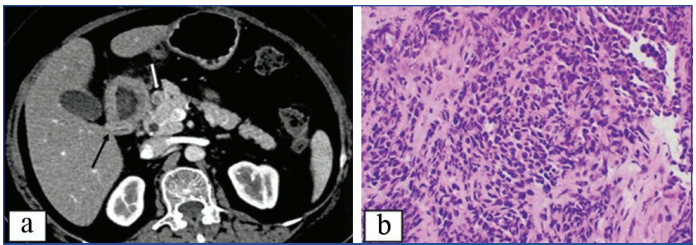
Amphicrine carcinoma, in which endocrine and epithelial cell constituents are present within the same cell, is very rare. It is different from adenocarcinoma and Mixed Neuroendocrine-Non neuroendocrine neoplasms (MiNEN). In the current World Health Organisation (WHO) classification of gastrointestinal tumours, the only mention of an amphicrine tumour is in the form of Goblet Cell Adenocarcinoma (GCA) in the appendix, which has both neuroendocrine and non neuroendocrine characteristics in the same cell. Authors hereby report the case of a 63-year-old female who presented with complaints of abdominal pain of a six-month duration. Endoscopy showed a polypoidal lesion in the duodenum. Distal radical gastrectomy was done. Microscopy of the lesion showed atypical signet-ring-like cells and goblet-like mucinous cells with fine granular chromatin. On immunohistochemistry, the tumour cells were positive for CK7, synaptophysin, and chromogranin. The cells showed Periodic Acid-Schiff stain (PAS) positive, diastase-resistant material in the cytoplasm. These cells also showed mucicarmine positivity. Considering the biphenotypic nature of tumour cells, the diagnosis of amphicrine carcinoma was given. Amphicrine carcinomas have unique features in histopathology, immunohistochemistry, special stains, and genetic profile.

Keywords: Biphenotypic nature, Goblet cell adenocarcinoma, Mixed neuroendocrine nonneuroendocrine neoplasm

CASE REPORT

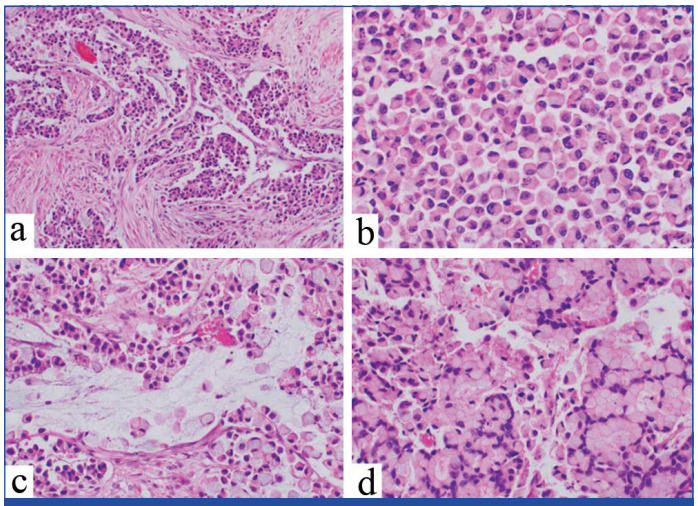
A 63-year-old female, known to have hypothyroidism and depression, was being evaluated for abdominal pain and weight loss lasting for six months. She had been taking medication for hypothyroidism (Tab. Thyroxin sodium 50 µg) for one year and antidepressants (Tab Escitalopram 5 mg) for eight months.

During an upper gastrointestinal tract endoscopy, a polypoidal lesion was discovered in the duodenum. Contrast-Enhanced Computed Tomography (CECT) revealed circumferential wall thickening predominantly in D1 extending to D2 [Table/Fig-1a]. There was no evidence of gross infiltration into the liver or pancreatic tissue. Significant lymphadenopathy was observed in the pancreatico-duodenal groove. Based on clinical and radiological findings suggestive of duodenal carcinoma, a biopsy of the lesion was performed, which showed malignant cells with crush artifacts [Table/Fig-1b]. Immunostained sections showed scant material, with atypical cells displaying patchy variable positivity for CK7, synaptophysin, and chromogranin. The MIB-1 labeling index was around 60%. These features were indicative of carcinoma with neuroendocrine differentiation.



[Table/Fig-1]: a) Axial CT sections done with neural oral contrast and intravenous iodine contrast, showing circumferential wall thickening in the D1 portion of duodenum (arrow) with a morphologically significant subcentimetric node in the pancreatoduodenal groove (Thick arrow); b) Biopsy of the lesion showing atypical cells arranged diffusely and in vague nests (H&E, 400x).

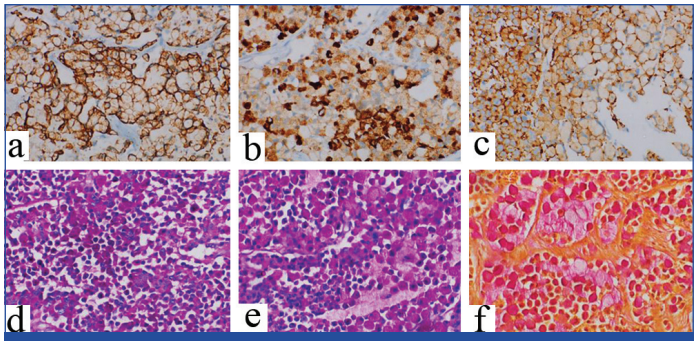
The patient underwent distal radical gastrectomy along with the first part of the duodenum and D2 lymphadenectomy. Intraoperatively, a growth was found in the proximal duodenum with a serosal nodule. Gross examination revealed a grey-white necrotic growth in the duodenum measuring 2x1.8x1.3 cm, extending almost to the serosa. Microscopically, tumour cells were arranged in lobules, nests, and sheets, consisting of atypical signet ring-like cells and goblet-like mucinous cells. These cells featured abundant pale cytoplasm, eccentrically placed nuclei with fine granular chromatin, and the presence of extracellular mucin [Table/Fig-2]. The combination of signet ring-like cells, intracellular, and extracellular mucin suggested an adenocarcinoma. However, the cell arrangement pattern, goblet cells, and granular chromatin indicated a neuroendocrine nature of the tumour cells.



[Table/Fig-2]: a) Well-formed tubules comprising of mucinous cells (H&E, 100x); b) Tumour cells with signet ring cell morphology with intracytoplasmic mucin and peripheral placement of nuclei with stippled chromatin (H&E, 400x); c) Extracytoplasmic mucin (H&E, 200x); d) Goblet cell like morphology (H&E, 400x).

Immunohistochemical examination revealed moderate positivity for CK7, diffuse positivity for synaptophysin, and patchy positivity for chromogranin in the tumour cells. The Ki-67 proliferation index was 60%. Cells positive for neuroendocrine markers displayed PAS-positive diastase-resistant material in the cytoplasm and mucicarmine positivity [Table/Fig-3].

Due to the biphenotypic nature of the tumour cells-cytokeratin positivity, neuroendocrine marker positivity, and intracellular mucin presence within the same cells-a diagnosis of amphicrine carcinoma



[Table/Fig-3]: Expression of neuroendocrine markers (a) Synaptophysin; (b) Chromogranin; and (c) Cytokeratin (IHC, 400x); (d) The cells which were positive for neuroendocrine marker showed PAS positive material in the cytoplasm; (e) Diastase resistant material in cytoplasm and (f) Mucicarmine positivity. (Special stain, 400x).

was made. The tumour cells were found infiltrating up to the subserosa. Out of the 15 lymph nodes dissected, one showed metastasis. Chemotherapy with cisplatin and irinotecan was planned, and the patient has been undergoing treatment for five months.

DISCUSSION

Amphicrine carcinoma is a distinct tumour in which the cells have both exocrine and neuroendocrine differentiation, with mucin secretion and neuroendocrine granules in the cytoplasm of the same cells [1]. Mixed exocrine-neuroendocrine tumours are rare tumours of the gastrointestinal tract. In 1938, Feyrter described the co-existence of endocrine and exocrine secretory products within the same cells. The term "amphicrine" was coined by Ratzenhofer for cells showing exocrine and endocrine differentiation. In 1987, Lewin proposed a nomenclature for classifying mixed exocrine-neuroendocrine tumours into three groups: mixed or composite tumours, collision tumours, and amphicrine tumours. In composite tumours or collision tumours, the two different cellular components are admixed or juxtaposed. In amphicrine neoplasms, the exocrine and neuroendocrine components are expressed in the same cell [2,3]. There are two possible hypotheses for the origin of mixed exocrine-neuroendocrine tumours. According to the first hypothesis, neoplastic changes occur independently and simultaneously in two different cell lines. The second hypothesis is that the tumour cells derive from one common multivalent stem cell. The latter is considered a more likely explanation for the origin of amphicrine carcinoma [3]. The 2010 WHO classification of gastrointestinal tumours classified appendiceal amphicrine neoplasms as Goblet Cell Carcinoid (GCCs) [4]. Molecular analysis conducted later revealed the aggressive clinical behaviour of GCCs and more similarities to adenocarcinomas. Hence, in the 2019 WHO classification, the term "GCC" was changed to "GCA" [5,6]. In the current WHO classification, the term amphicrine tumours were removed without any mention [6]. For non appendiceal gastrointestinal tract amphicrine tumours, the usage of different terminologies produces additional confusion. The term "amphicrine" justifies the dual expression of epithelial-neuroendocrine characteristics in the same cell [2]. Grossly, amphicrine carcinomas are indistinguishable from carcinomas. Microscopically, the tumour cells can have a wide range of morphological appearances. The morphology ranges from well-differentiated neuroendocrine tumours to poorly differentiated carcinomas with goblet cells or signet ring cells. A three-tiered grading system is followed for appendiceal GCA based on the proportion of low-grade and high-grade components. The same can be followed for amphicrine carcinoma of other sites in the gastrointestinal tract [2,3,7].

The immunohistochemistry staining pattern shows the presence of both exocrine and neuroendocrine components in the same cell. The cells diffusely express CK7 and EMA (exocrine marker) as well as synaptophysin and chromogranin (neuroendocrine markers) [2,3]. Serra S and Chetty R in their case report, described an amphicrine carcinoma arising from the duodenal mucosa and focally infiltrating the pancreas and ampulla of Vater in a 56-year-old male patient [8]. The tumour cells were arranged in small glandular structures, cords, and nests within a desmoplastic stroma. The cells were large round to oval with "salt and pepper" chromatin and showed mild pleomorphism. Focal goblet cell differentiation and extracellular mucin pools were also present, resembling a GCC of the appendix. Chromogranin and synaptophysin were positive in approximately 30% of the tumour cells, and electron microscopy showed the amphicrine differentiation with neurosecretory and mucin-type granules present in the same cells [8]. Mandoky L reported 16 cases of amphicrine carcinomas from various organs [9]. There were four sinonasal, one bronchial, one mediastinal, eight gastrointestinal, and two suprarenal gland neoplasms. The locations of gastrointestinal amphicrine carcinomas included the stomach, duodenum, ileum, and caecum. The tumours showed mucus production or glandular structures variably from 10% to more than 70%. The same range of variability was also noted for the percentage of chromogranin-positive cells. Gastric tumours were well-differentiated with minimal nuclear pleomorphism and mitotic activity. Stromal invasion was present in all cases. In one case of an ileal tumour, most of the cells were immunoreactive for chromogranin and formed glandular lumens with mucoid material. Mixed tumours arising in the caecum showed moderate to poor differentiation. In the moderately differentiated mixed tumour, glandular formation was seen in approximately 50% of the tumour. Nuclear pleomorphism, prominent nucleoli, high mitotic count (8-11/10HPF), stromal, vascular, and perineural invasion were also present. The poorly differentiated tumours were highly pleomorphic and showed 10-15% chromogranin-positive cells with scanty mucus production. The poorly differentiated tumours had an aggressive behaviour [9].

Huang D et al., studied 10 cases of amphicrine carcinoma. They classified the tumour as low-grade and high-grade. Low-grade tumours showed a predominant tubular growth pattern with intracellular mucin resembling goblet cell carcinoma of the appendix. High-grade tumours showed fusion of goblet cell clusters and showed signet ring-like cells with frequent mitosis and extracellular mucin pools. The MIB 1 labeling index ranged from 5 to 40% in low-grade tumours and 20 to 70% in high-grade tumours. The genetic data generated for amphicrine carcinomas were compared with data from a set of neuroendocrine tumours and gastric adenocarcinomas by a 90-gene real-time PCR assay. The study showed that amphicrine carcinoma shares similarity at the molecular level with conventional adenocarcinoma and shows significant diversity from neuroendocrine tumours at the molecular level [2]. In a study conducted by Sun L et al., it was seen that the copy number variation for complement C5 was higher in amphicrine carcinoma compared to both the adenocarcinomatous and neuroendocrine components of MiNEN. Thus, the use of a C5 inhibitor can be considered in patients with amphicrine carcinoma [7]. The molecular characteristics of gastric amphicrine carcinomas and MiNENs are distinct, supporting the idea that they are separate entities. GCA of the appendix has been found to have a distinct pattern of chromosomal abnormalities compared to both adenocarcinomas and neuroendocrine tumours [10]. This highlights the unique molecular characteristics of GCA. Hence, the terminology was changed from carcinoid to adenocarcinoma, and they were excluded from MiNEN in the current WHO classification for gastrointestinal tumours and placed along with adenocarcinomas to which they are more similar at the molecular level [6,11].

CONCLUSION(S)

Amphicrine tumours are characterised by the co-existence of both endocrine (neuroendocrine) and epithelial features within the same

tumour cells. Amphicrine carcinomas should be differentiated from adenocarcinoma and the neuroendocrine component of MiNEN, as their molecular origin, overall nature, and prognosis are different.

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