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Case Report

# Gastric amphicrine carcinoma: A histopathological diagnostic conundrum

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ABSTRACT

Amphicrine carcinoma is rarely reported in literature. It is characterised by dual positivity of neuroendocrine markers and mucin stain in the same cells depicting divergent differentiation. Recently published WorldHealth Organisation (WHO) classification of neuroendocrine neoplasm of 2022 differentiates it from adenocarcinoma and mixed neuroendocrine-nonneuroendocrine neoplasms (MiNEN) it shows varied histomorphology and on rare occasions neuroendocrine features may not be evident in poorly differentiated carcinoma. Hence, diagnosis based solely on histomorphology can be misleading. This is a case of amphicrine carcinoma in an elderly female which showed poorly differentiated morphology along with signet ring cells. Same cells demonstrated immunopositivity for synaptophysin, chromogranin A and were also positive for mucin stains (PAS, PAS-D and Alcian blue). This case report, thus, emphasises the importance of neuroendocrine markers as a part of routine immunohistochemistry in poorly differentiated gastric carcinomas to aid diagnosis of amphicrine carcinoma.



## 1. Introduction

Amphicrine carcinoma is exceedingly rare among gastric cancers with an aggressive behaviour.[1] Amphicrine carcinoma are characterised by co-expression of both neuro-endocrine and exocrine phenotype.[2] In the past amphicrine carcinoma was considered as a special subtype in both adenocarcinomas and neuroendocrine neoplasms.[1,3] However, recent histological, immunohistochemical and transcriptomic findings have showed amphicrine carcinoma to be a histologically and biologically distinct entity from adenocarcinomas or mixed neuroendocrine-nonneuroendocrine neoplasms (MiNEN).[4,5] Hence, this entity has been recognised by 2022 WHO classification of endocrine neoplasms.[6]

There is paucity of literature regarding its pathogenesis, histopathology and biological behaviour. Therefore, our case report with literature review aims to shed light on this unique aggressive tumour. To the best of our knowledge, this is the first case report from India.

## 2. Results

A 78-year-old lady presented with features of gastric outlet obstruction. Contrast enhanced computed tomography (CECT) abdomen showed diffuse circumferential thickening of pylorus and antrum of stomach causing luminal narrowing with few peri-gastric lymph nodes. Distal gastrectomy was done and submitted for histopathological examination.

The gross specimen showed a type 4 Borrmann lesion diffusely involving anterior and posterior wall of body and antrum. The microscopic examination revealed a poorly differentiated neoplasm composed of cords, nest and sheets of malignant cells in a background of extensive fibrosis and chronic inflammatory infiltrate. These malignant cells

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were small to medium size with moderate eosinophilic to clear cytoplasm showing moderate anisonucleosis with fine chromatin (Figure 1). These cells also showed formation of occasional rosettes (Figure 2). Many signet-ring cells were seen. Invasion into muscularis propria was observed with perineural invasion. Lymphovascular invasion was absent. Peri-gastric lymph nodes were positive for tumour.

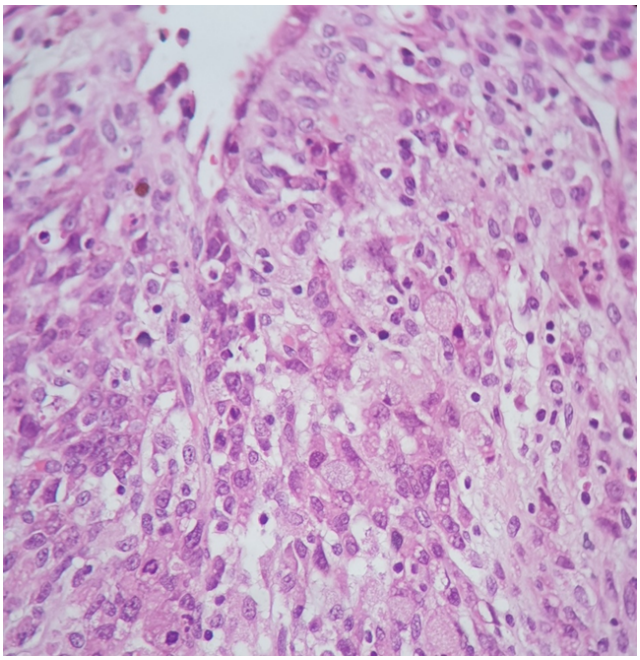

**Fig. 1:** Poorly differentiated Amphicrine carcinoma asnest like structure along with signet ring cells (HE, 400x)

On putting up special stains for mucin, same malignant cells were positive for PAS, PAS-D and Alcian blue (Figure 3). Due to the presence of occasional rosette, neuroendocrine markers were added to immunohistochemistry panel. Surprisingly these malignant cells were strongly immunopositive for synaptophysin, chromogranin A (Figure 4 A,B) in addition to epithelial marker i.e.CK7, Epithelial Membrane Antigen (EMA)and Carcinoembryonic Antigen (CEA) (Figure 4 C). They showed intact E-Catherine expression and null phenotype expression for p53. They were immunonegative for CDX2, CK20, and CD117. Ki67 was 60-70% (Figure 4). Similar histomorphology, mucin stains and immunohistochemistry was observed in lymph nodes. A final diagnosis of Gastric amphicrine carcinoma, pT2N2Mx was rendered.

## 3. Discussion

Gastric amphicrine carcinoma is a rare aggressive tumour. Concept of Amphicrine cells were first proposed by Feyrter in 1938, followed by term “amphicrine” advocated by Ratzenhofer.[7,8] Ultra structural studies support the endocrine and exocrine hybrid phenotype of amphicrine

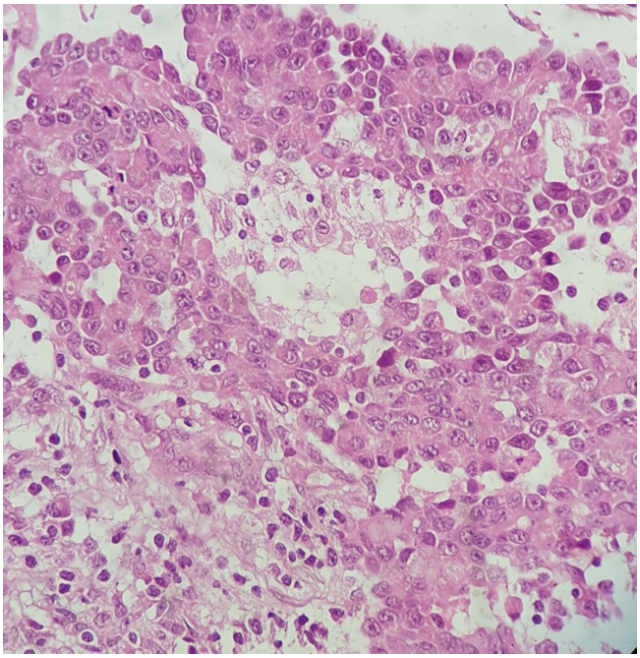

**Fig. 2:** Rosette formation (HE, 400x)

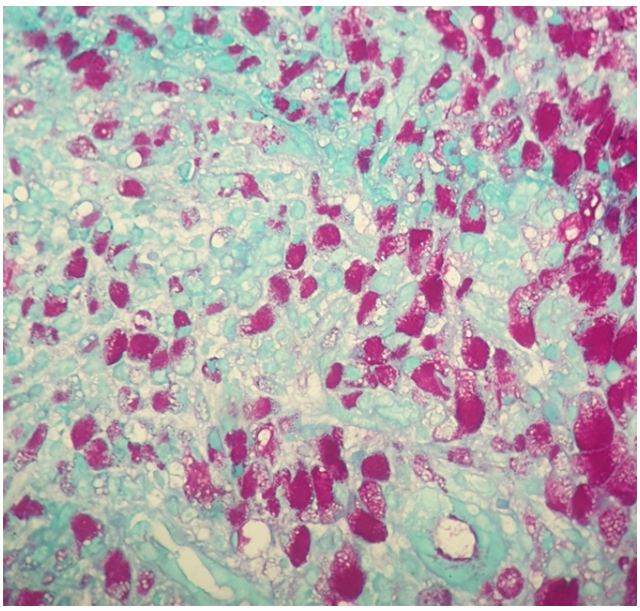

**Fig. 3:** PAS-D positive malignant cells

carcinoma by demonstrating the presence of both mucous and neuroendocrine cytoplasmic granules.[1,9] In view of co-expression of both exocrine and endocrine phenotypes it is likely to present with unique histopathology.[5] Studies have showed various architectural pattern like tubular, nest, solid sheet, scattered goblet cell or signet ring like cells.[5,10–13]

Huang et al[5] studied 10 amphicrine carcinomas in stomach and rectum. They classified tumour as low grade or high grade (both grades may mix with other components

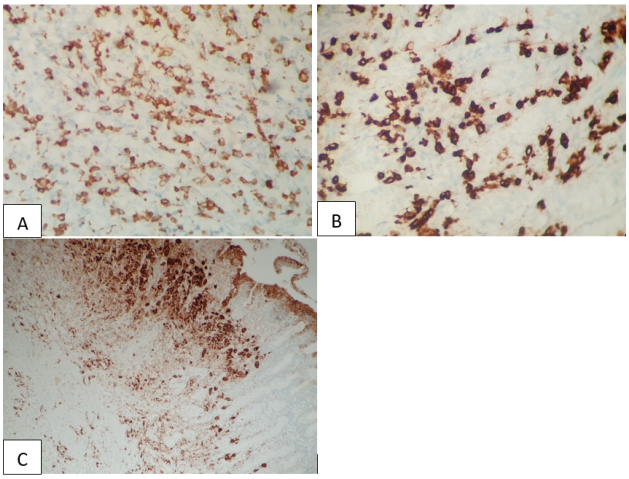


**Fig. 4:** Immunopositive stains; **A)**: Synaptophysin (400x); **B)**: Chromogranin A(400x); **C):** CEA (100x)

but less than 30% of tumour) or mixed amphicrine-neuroendocrine carcinoma with each component accounting for more than 30% of tumour. Eight cases were reported in stomach, 4 cases were low grade, 3 were high grade and one was mixed. Low grade tumors showed most commonly a tubular growth pattern with intracellular mucin resembling goblet cell carcinoma of appendix. No signet ring cells were observed in low grade group. High grade group more frequently showed fusion of goblet cell clusters with signet ring like cells. Less commonly, tumour nest of conventional adenocarcinoma in mucin poor areas or clusters of signet ring-like cells floating in mucin with frequent mitosis was seen. In mixed group, high grade amphicrine carcinoma was intermixed with conventional neuroendocrine carcinoma.

Sun et al[10] case series studies 8 cases of gastric amphicrine carcinoma. Out of 8 cases, 7 cases showed histological findings of a poorly differentiated adenocarcinoma as solid nest-like or scattered tumour cells with intracellular or intercellular mucus similar to our case. Six cases showed presence of Signet ring like cells, 3 cases of poorly differentiated adenocarcinomas were mixed with moderately differentiated adenocarcinomas.

Hamamatsu et al[11] described the lesion as a poorly cohesive carcinoma sparsely co-existing with signet ring cell carcinoma. Alipov et al[12] reported a poorly differentiated adenocarcinoma with neuroendocrine differentiation along with signet-ring cells.

Previous studies show that majority of these tumors are poorly differentiated.[5,10–13] All observed that dual positivity for neuroendocrine markers (synaptophysin and chromogranin A) and mucin stain (PAS and/ Alcian blue) in the same cells was required for the diagnosis of amphicrine carcinoma.[1–13]

Immunopositivity for EMA, CEA, low molecular Cytokeratin, Neuron specific enolase and CD56 has also been seen. Huang et al, showed Ki67 ranging from 5-40% in low grade and 20-70% in high grade. Sun et al, observed diffuse immunopositivity of p53 in two cases and immunonegative expression was also seen in one case like our case.[5,10–13]

Grossly, they may present as ulcerative lesion, fungating mass or diffusely infiltrating mass. Literature review shows involvement of any part of stomach, antrum being the most common site.[5,10–13] Size of tumour ranges from 2 to 5 cm.[5]

Sun et al[10] also compared 8 cases of gastric amphicrine carcinoma to gastric MiNEN by high resolution copy number profiling and whole expose sequencing of paraffin-embedded tissue. They showed that amphicrine carcinomas have a unique copy number and role of APC and p53 mutation in their pathogenesis, thus differentiating amphicrine carcinoma from MiNEN.

Alipov[12] demonstrated immunopositivity for CD44 variant 9, hence proposing multipotent stem cell as an origin of amphicrine carcinoma.

Amphicrine carcinoma shows increased incidence in elderly males with age ranging from 30 to 68 years.[5,10] It is rarely seen females.[14]

It can present with varied clinical features ranging from upper abdominal pain, hematochezia, hematemesis, abdominal discomfort, regurgitation, emesis, severe weight loss or anemia. Lymph node involvement is frequently seen at the time presentation similar to our case.[5,10–13]

Surgery has been suggested as mainstay of treatment. Limited data is available for role of other treatment modalities.[14] In view of aggressive nature, recognition of this tumour subtype may lead to development of specific targeted therapies in future.

## 4. Conclusion

WHO classification of neuroendocrine neoplasm of 2022 considers Amphicrine carcinoma a distinct entity from MiNEN and gastric adenocarcinoma. Histomorphological finding can be misleading and this diagnosis may be missed in the absence of characteristic neuroendocrine features. We propose that this entity must always be considered as differential of poorly differentiated carcinoma and immunohistochemistry for neuroendocrine markers must be included as part of routine IHC. Therefore, this case emphasises the essential need of including neuroendocrine markers in immunohistochemistry panel in addition to mucin stains as part of work up to arrive at diagnosis of amphicrine carcinoma.

## 5. Conflict of Interest

The authors declare no conflicts of interest.

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Nil.

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