



Case Report

# Mixed adenoneuroendocrine tumour with squamous differentiation: a case report

Irene Thomas<sup>1</sup>, Divya Surendran<sup>1</sup>, Joy Augustine<sup>1</sup>

<sup>1</sup>Department of Pathology, Amala Institute of Medical Sciences, Amala Nagar, Thrissur, Kerala, India

## Keywords:

MANEC;  
Gastrointestinal tract;  
Squamous differentiation;

## ABSTRACT

Mixed adenoneuroendocrine carcinoma is a rare neoplasm with both epithelial and neuroendocrine components. To date, only a few cases of this neoplasm have been reported in the literature among which gastric mixed adenoneuroendocrine carcinoma is very rare. We are reporting a case of gastric mixed adenoneuroendocrine carcinoma with squamous cell differentiation. Histopathological features, biological behaviour and the treatment of this rare tumour type have been discussed briefly.

## Correspondence:

Dr. Irene Thomas, MD

Department of Pathology,

Amala Institute of Medical Sciences, Amala Nagar, Thrissur,  
Kerala, India.

ORCID ID: 0000-0002-0797-5666

Email: irenethomas06@gmail.com



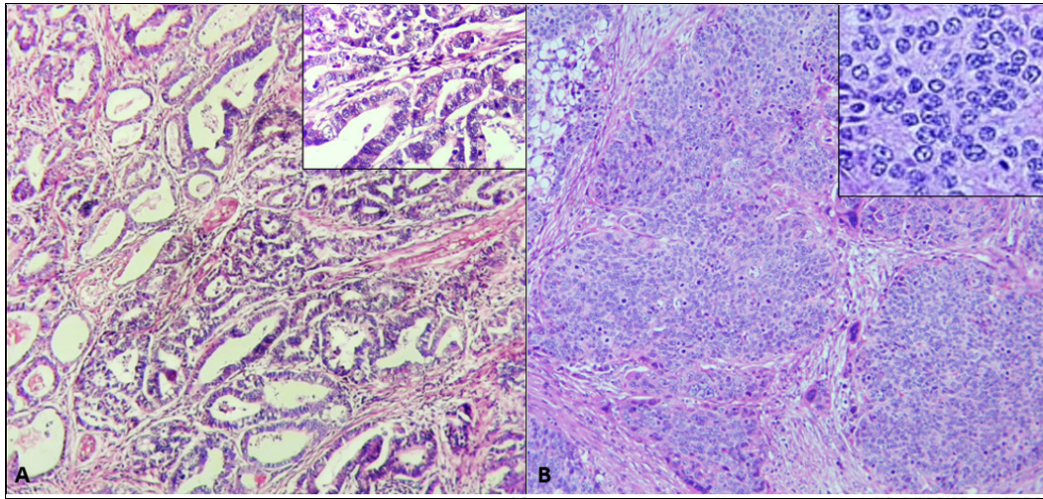
Received : May 21<sup>st</sup> 2020 ; Accepted : January 17<sup>th</sup> 2021

**Citation:** Thomas I, Surendran D, Augustine J. Mixed adenoneuroendocrine tumour with squamous differentiation: a case report. J Pathol Nep 2021;11:1891-4. DOI: 10.3126/jpn.v11i1.29031

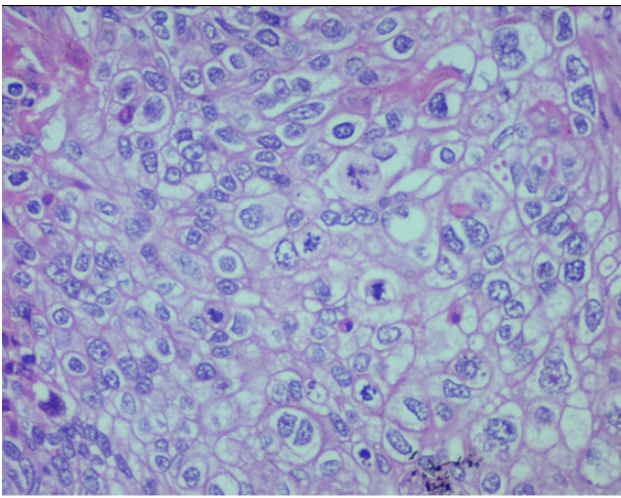
**Copyright:** This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## INTRODUCTION

Mixed adenoneuroendocrine carcinoma (MANEC) is a rare neoplasm defined by the World Health Organization (WHO) in 2010 as neoplasms consist of dual adenocarcinomatous and neuroendocrine components with a variable grade of differentiation. According to WHO these types of tumours can be classified as truly mixed only if it contains both exocrine and endocrine component with each component comprising a minimum of 30% of the tumour.<sup>1</sup> MANEC has been described in various parts of the gastrointestinal tract, pancreas, gall bladder, and cervix. The prevalence of gastric neuroendocrine carcinoma is relatively rare and accounts for only 6-16% of gastric neuroendocrine tumours, and are more common in men and present at a mean age of



**Figure 1** A. Well differentiate adenocarcinoma (HE stain, 100x) and inset showing high power view (HE stain, 400x). B. Neuroendocrine carcinoma showing nesting pattern (HE stain, 100x). Cells have scant cytoplasm and nucleus showing powdery chromatin in the inset (HE stain, 400x). Mitotic activity was high ( $>20/10$  HPF). Focal areas showed squamous differentiation (fig. 2).

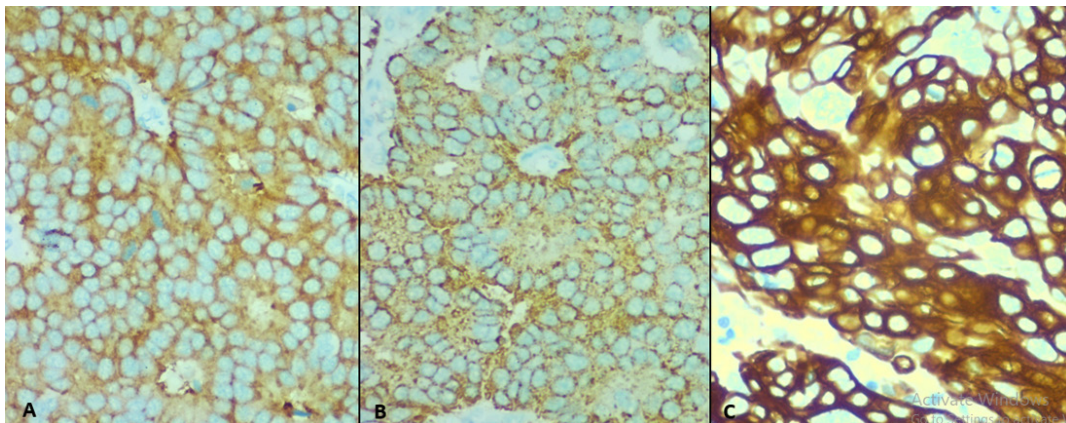


**Figure 2:** Areas showing squamous differentiation (HE stain, 400x).

63 years. No specific epidemiological data are available for MANEC.

Gastric MANEC can be categorized into three different groups based on the component having the most malignant potential. High-grade malignant MANEC are defined by an adenomatous (villous or tubulovillous) or adenocarcinomatous component with a neuroendocrine carcinoma (NEC) and the prognosis of these tumours depends on the aggressive NEC (small, intermediate, or large cell type). Intermediate-grade MANEC are formed by an adenocarcinoma component and by a neuroendocrine tumour (NET) in which the exocrine part of the tumour is more aggressive than the neuroendocrine component. Low-grade MANEC's are characterised by both adenomatous and neuroendocrine components.<sup>2</sup>

Here, we report a case of gastric MANEC with trilineage histologic differentiation, which includes an exocrine component with two different cell line differentiation in the form of moderately differentiated adenocarcinoma with areas of squamous differentiation and neuroendocrine carcinomatous endocrine component (NEC).



**Figure 3:** Neuroendocrine components showing immunoreactivity to synaptophysin (A) and chromogranin (B) and squamous areas showing immunoreactivity to CK5/6 (C) (400x).

## CASE REPORT

A 54-year lady presented with abdominal pain and weight loss. She was on treatment for systemic hypertension, diabetes mellitus, dyslipidemia, and hypothyroidism. Computerised tomography of the abdomen demonstrated focal wall thickening at the pylorus of the stomach with perigastric fat stranding- favouring primary malignancy. Endoscopy revealed an ulceroproliferative growth involving 50% of the circumference of the antrum. A biopsy was taken from the same site, the histology of which showed a moderately differentiated adenocarcinoma

The endoscopic biopsy was followed by distal subtotal gastrectomy and D2 lymphadenectomy. Grossly, the external surface of the gastrectomy specimen showed a grey-white area and on opening, an ulceroproliferative neoplasm was identified. It measured 4x2.5x0.8cm and was grey white and fleshy on the cut surface. Microscopically, the tumour comprised predominantly of moderately differentiated adenocarcinoma composed of glandular structures and areas showing neuroendocrine carcinomatous component with cells arranged in the cribriform pattern was also seen accounting >30% of the tumour (fig.1).

The tumour involved the serosal surface and 7 out of 28 lymph nodes showed metastatic deposits with both adenocarcinomatous and NEC components separately. Immunohistochemistry was done to establish the presence of neuroendocrine components and squamous differentiation, which showed strong cytoplasmic staining for synaptophysin and chromogranin in the cribriform area, and areas with squamous differentiation showed positivity for CK5/6 (fig. 3). This confirmed the neuroendocrine component and squamous differentiation and a final diagnosis of MANEC with squamous differentiation was given. Later, the patient was put on adjuvant chemotherapy. Currently, the patient is doing well and without evidence of disease recurrence.

## DISCUSSION

There is a wide spectrum of combinations of neuroendocrine and adenocarcinoma components in the gastrointestinal tract, ranging from exocrine carcinoma with interspersed neuroendocrine cells to neuroendocrine neoplasms with a focal exocrine component. Gastrointestinal tumour with both exocrine and neuroendocrine component was first described by Cordier in 1924.<sup>3</sup> Initially classification of such neoplasms was made by Lewin in 1987 into three different subtypes: collision tumours, combined tumours and amphicrine tumour.<sup>4</sup> In 2010, WHO used the term mixed adenoneuroendocrine carcinoma (MANEC).<sup>1</sup> Diagnosis is mainly based on histopathological examination along with IHC markers since there are no specific radiologic features or clinical presentation. The

pathogenesis of NEC is still unknown. Many hypotheses have been postulated regarding the histogenesis of NEC. The simultaneous proliferation of multiple cell lineages or the proliferation of stem cells capable of differentiating along multiple cell lines has been proposed.<sup>5</sup>

Gastrointestinal neoplasm displaying features of MANEC are well recognised, although uncommon. Both components can have a wide spectrum of morphological features, ranging from adenomas to adenocarcinomas and well to poorly differentiated neuroendocrine neoplasms.<sup>4,6</sup> The neuroendocrine component of the gastric MANEC usually comprises an NEC, often of large- cell type and rarely a NET.<sup>7,8</sup>

To our knowledge, among gastrointestinal MANEC only a few cases of gastric MANEC have been reported containing a squamous cell component.<sup>9-11</sup> The current case was a MANEC with squamous differentiation with regional lymph node metastasis. Zhang et al. reported a case of gastric MANEC with a squamous cell carcinoma component where the NEC component metastasized to the liver.<sup>12</sup> In addition, Bae et al. reported a gastric MANEC with squamous differentiation which is composed of only adenocarcinoma component metastasis to the regional lymph node, and distant metastasis was not detected.<sup>13</sup> In contrast, in the current case, both adenocarcinoma and NEC components metastasized to regional lymph nodes, and both were in different lymph nodes.

The optimal treatment strategy of MANECs is largely unknown due to its rarity, however, the treatment should focus on the most aggressive tumour component.<sup>14</sup> Gastrectomy, either total or subtotal according to the location along with chemotherapy is considered as the treatment of choice. Platinum-based chemotherapy should be the first-choice treatment in advanced disease.<sup>15</sup> Because of its rarity there are no data available to support the hypothesis that the presence of a third cell clone has some role in deciding the prognosis and treatment of these tumours.

## CONCLUSIONS

Gastrointestinal MANECs are a rare group of neoplasms with no definite clinical, morphological, or prognostic features. We report this case because of its rarity. Multicentre studies for these patients are required to find out the role of each cell component in the disease progression, to determine the appropriate treatment regimens, to improve the prognosis, and to prevent relapse.

**Conflict of Interest:** None

## REFERENCES

1. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. 4th ed. Lyon: IARC Press, 2010. [Website](#)

2. La Rosa S, Marando A, Sessa F et al. Mixed Adenoneuroendocrine Carcinomas (MANECs) of the Gastrointestinal Tract: An Update. *Cancers*. 2012;4:11-30. [Crossref](#)
3. Cordier R. Les cellules argentaffines dans les tumeurs intestinales. *Arch. Int. Med. Exp.* 1924; 1:5.
4. Lewin K. Carcinoid Tumors and the Mixed (Composite) Glandular-Endocrine Cell Carcinomas. *The American Journal of Surgical Pathology*. 1987;11:71-86. [Crossref](#)
5. Murata M, Takahashi H, Yamada M et al. A case of mixed adenoneuroendocrine carcinoma of the pancreas. *Medicine*. 2017;96:e6225. [Crossref](#)
6. Kitajima T, Kaida S, Lee S et al. Mixed adeno(neuro)endocrine carcinoma arising from the ectopic gastric mucosa of the upper thoracic esophagus. *World Journal of Surgical Oncology*. 2013;11:218. [Crossref](#)
7. Jiang S, Mikami T, Umezawa A et al. Gastric Large Cell Neuroendocrine Carcinomas: A Distinct Clinicopathologic Entity. *The American Journal of Surgical Pathology*. 2006;30:945-53. [Crossref](#)
8. Caruso M, Pilato F, D'Adda Tet al. Composite carcinoid-adenocarcinoma of the stomach associated with multiple gastric carcinoids and nonantral gastric atrophy. *Cancer*. 1989;64:1534-1539. [Crossref](#)
9. Haratake J, Horie A, Inoshita S. Gastric small cell carcinoma with squamous and neuroendocrine differentiation. *Pathology*. 1992;24:116-120. [Crossref](#)
10. Shibuya H, Azumi N, Abe F. Gastric small-cell undifferentiated carcinoma with adeno and squamous cell carcinoma components. *Acta Pathol Jpn* 1985;35:473-80. [Crossref](#)
11. Pericleous M, Toumpanakis C, Lungair Het al. Gastric Mixed Adenoneuroendocrine Carcinoma with a Trilineage Cell Differentiation: Case Report and Review of the Literature. *Case Reports in Oncology*. 2012;5:313-19. [Crossref](#)
12. Zhang W, Xiao W, Ma H et al. Neuroendocrine liver metastasis in gastric mixed adenoneuroendocrine carcinoma with trilineage cell differentiation: a case report. *Int J Clin Exp Pathol* 2014;7:6333-6338. [Website](#)
13. Bae H, Lee C, Jo Y et al. Gastric Mixed Adenoneuroendocrine Carcinoma with Squamous Differentiation: A Case Report. *Journal of Pathology and Translational Medicine*. 2016;50:318-321. [Crossref](#)
14. Hervieu V, Scoazec J.Y. Mixed endocrine tumors. *Ann. Pathol.* 2005;25:511-528. [Crossref](#)
15. Kwok C. Mixed Adenoneuroendocrine Carcinoma of the Stomach. *Case Reports in Gastroenterology*. 2015;9:241-245. [Crossref](#)