Gastrointestinal mixed neuroendocrine carcinoma: Case reports and review of literature

Harish Kumar Hanumappa[1], Dyan D'Souza[2], Joseph Sushil Rao[3], Faslu Rahman Naduvathkundil[4], Raghunandan Gorantlu Chowdappa[1], Elvis Peter Joseph[4]

From, [1]Assistant Professor, [2]Senior Resident, [3]Junior Resident, [4]Mch Resident, Department of Surgical Oncology, St. Johns Medical College Hospital, Bengaluru, Karnataka, India

Correspondence to: Harish Kumar Hanumappa, SV. Ashirwad Apartment, 3rd Floor, No. 420/33, 18th Main, Jayanagar 4th T Block, Bengaluru - 560 041, Karnataka, India. E-mail: harishkumarh1983@gmail.com

Received – 06 August 2018 Initial Review – 28 August 2018 Accepted – 21 September 2018

ABSTRACT

Mixed adenoneuroendocrine carcinoma (MANEC) is a rare and relatively newer entity and classified into a separate category by the WHO 2010 Classification of Tumors. Accordingly, due to its rarity of diagnosis, further oncologic management is a challenge. They contain an adenocarcinoma part and a neuroendocrine part and are further classified based on grades. We present case series with a histological diagnosis of MANEC, its management, and clinical behavior in the follow-up period. Optimum mode of the management of these tumors is yet to be proposed, as these groups of tumors are highly aggressive and associated with poor prognosis.

Key words: *Colon, Immunohistochemistry, Mixed adenoneuroendocrine carcinoma, Periampullary, Prognosis*

The World Health Organization (WHO) in the year 2010 defined mixed adenoneuroendocrine carcinoma (MANEC) as neoplasms involving both the neuroendocrine and the epithelial components. The diagnostic criteria of MANEC are as follows: Both the components must be malignant and each component has to comprise at least 30% of the tumor [1]. Cordier in the year 1924 published the first report on a mixed exocrine and a neuroendocrine tumor (NET) [2]. Since then, few developments have been made in this field. Composite carcinoid, argentaffin cell adenocarcinoma, mucin-producing carcinoid, goblet cell carcinoid, adenocarcinoid, and small cell undifferentiated carcinoma were some of the terminologies used earlier to describe this entity.

The classification of these tumors was suggested in 1987 by Lewin as collision, combined, and amphicrine tumors [3]. In the year 2000, the WHO classified these endocrine tumors as mixed exocrine-endocrine tumors when each component represents at least 30% of the lesion [4]. Finally, in 2010, the WHO classification named these tumors as MANECs [5].

It is important to note that, according to this nomenclature, if a particular component does not form 30% of the lesions, it cannot be categorized as a mixed tumor but rather an adenoma or NETs separately. This entity has been subdivided into different categories based on the degree of differentiation of each component: High-grade malignant type and intermediate-grade malignant type, (intermediate type also includes amphicrine carcinoma) [6]. We present case series with a histological diagnosis of MANEC and its management.

CASE REPORTS

Case 1

A 58-year-old gentleman presented a history of pain abdomen (dull aching) and intermittent bleeding per rectum for 4 months. On clinical examination, vital signs were stable with a pulse rate of 76/min and blood pressure of 126/84 mmHg. Pallor was present with no significant findings on per abdomen and rectal examination. Except for anemia with hemoglobin of 8 g/dL, all other blood investigations were normal. Colonoscopy revealed a nodular thick friable growth causing narrowing of the colonic lumen (ascending colon). The biopsy showed features of a poorly differentiated carcinoma, while neuroendocrine differentiation could not be excluded. Serum carcinoembryonic antigen levels were 7.19 ng/dL (normal value <5 ng/dL). Contrast-enhanced computed tomography (CECT) of the abdomen and pelvis revealed circumferential enhancing thickening of the proximal ascending colon for a length of 5 cm with significant luminal obstruction, with no evidence of distant metastases.

The patient was transfused with two units of packed red blood cells. He then underwent a right radical hemicolectomy (Fig. 1). The final histopathology report showed MANEC extending microscopically into the serosa with a pathological staging of pT3 N1a Mx. The neoplastic cells were positive to cytokeratin 20 (CK20), caudal type homeobox 2 (CDX2), and synaptophysin and were negative for chromogranin. Occasional cells were positive for CD56 with Ki proliferative index of 60–70%. The patient

was on adjuvant treatment with irinotecan and capecitabine. Response assessment was done after 4 cycles with positron emission tomography-CT (PET-CT) scan which showed multiple periportal, retroperitoneal, and mesenteric and mediastinal lymph nodes. In view of progressive disease, the regimen was changed to capecitabine and oxaliplatin. Disease remained stable after 3 cycles. Hence, three more cycles of capecitabine and oxaliplatin were planned. At present, the patient is on the same regimen.

Case 2

A 60-year-old female presented with a history of gradually increasing jaundice for 3 months associated with nausea and vomiting. On clinical examination, icterus was present with palpable gallbladder on abdomen examination. No clinical signs of cholangitis were present. No other significant findings were noted. Biochemical tests revealed a conjugated hyperbilirubinemia with serum bilirubin levels of 11 mg/dL and direct bilirubin of 8.6 mg/dL. Serum gamma-glutamyl transpeptidase and serum alkaline phosphatase levels were 72 IU/L (normal value 0–35 IU/L) and 67 IU/L (normal value 0–35 IU/L), respectively, and a serum albumin of 3.6 g/dL with other liver function test parameters within normal limits. Subsequent CECT scan revealed a dilated common bile duct (C with abrupt narrowing of distal bile duct with an ill-defined enhancing mass lesion proximal to the pancreaticobiliary junction causing dilatation of the intrahepatic biliary radicles and pancreatic duct likely a neoplastic stricture). Endoscopic retrograde cholangio pancreatography (ERCP) was done and brush cytology revealed atypical cells suspicious of malignancy.

She underwent a Whipple's pancreaticoduodenectomy and the histopathology was reported as MANEC of intermediate grade with tumor extension into the pancreas and pathologic stage of pT3b N0 Mx. A ×10 view of hematoxylin and eosin stained tissue demonstrating the neuroendocrine and adenocarcinoma component of tumor is shown in Fig. 2. Immunohistochemistry report shows positivity for CK7, synaptophysin, chromogranin, and CD56. The Ki proliferative index was 8–10% (Fig. 3). The patient is presently on adjuvant chemotherapy (cisplatin and etoposide) without any evidence of recurrence after 4 cycles of chemotherapy.

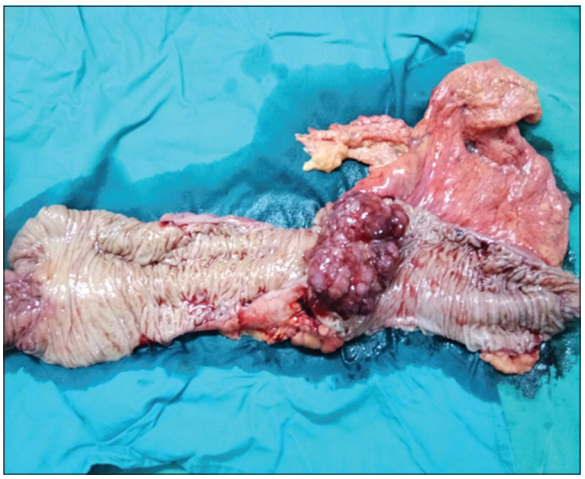

Figure 1: Specimen photograph of right hemicolectomy with tumor

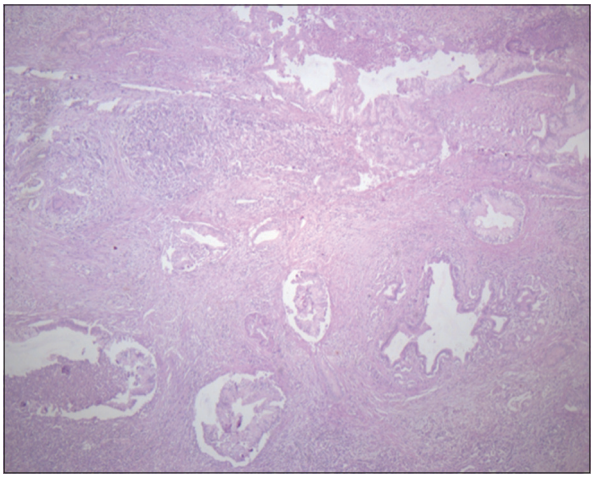

Figure 2: ×10 view of hematoxylin and eosin stained tissue demonstrating the neuroendocrine and adenocarcinoma component of tumor

Case 3

A 56-year-old gentleman presented with a complaint of jaundice of 1 month duration with loss of appetite for 15 days. On clinical examination, icterus was present with palpable gallbladder on abdomen examination. No other significant findings were noted. Biochemical tests revealed a conjugated hyperbilirubinemia with serum bilirubin levels of 8 mg/dL and direct bilirubin of 6.7 mg/dL. Other blood tests and liver function test values were within normal limits. A CECT scan revealed a dilated common bile duct with abrupt narrowing of distal bile duct with an ill-defined enhancing mass in the distal bile duct causing dilatation of the intrahepatic biliary radicles, likely a neoplastic etiology.

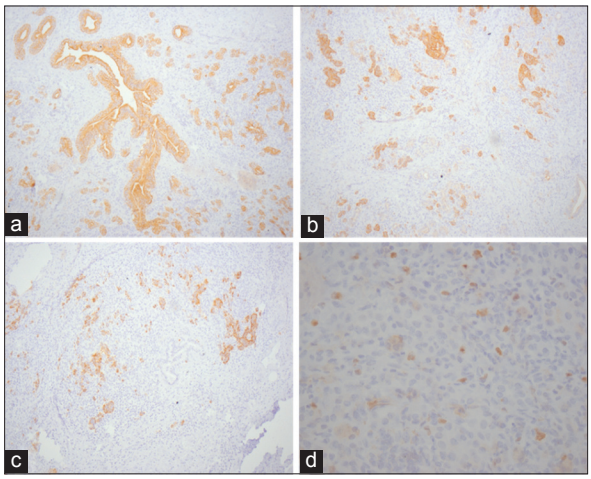

Figure 3: (a) ×10 view of cytokeratin staining demonstrating a granular pattern with 3 + positivity; (b) ×10 view of synaptophysin staining demonstrating a membranous type with 3 + positivity; (c) ×10 view of chromogranin staining demonstrating a granular cytoplasmic pattern; (d) ×40 view of Ki 67 staining demonstrating a nuclear pattern

ERCP was done and biopsy revealed atypical cells suspicious of malignancy.

He underwent Whipple's pancreaticoduodenectomy, and the final histopathology report was suggestive of MANEC with predominant adenocarcinoma component and pathologic stage of pT3b N0 Mx. The patient received 3 cycles of adjuvant gemcitabine-based chemotherapy. As he could not tolerate the treatment, further chemotherapy was not given and lost to follow up.

DISCUSSION

In the era of personalized medicine, diagnostic modality we choose and treatment decisions we make have a huge impact on prognosis. When such is the scenario, making the best use of available modern diagnostic tools and tailored therapy does influence the survival. In gastrointestinal malignancies, particularly MANEC, the neuroendocrine component does influence the biology of a tumor based on available case studies. Diagnosis of this entity is made by the use of immunohistochemistry. No particular locus is identified yet, to make use of targeted therapy, unlike in adenocarcinoma. No large studies available yet to understand the exact nature of this entity. MANEC has been described in various sites such as stomach, colon [7], pancreas [8], esophagus [9], appendix [10], rectum [11], and cervix [12]. Irrespective of a site of the tumor, prognosis and treatment have remained the same.

MANEC tumors are fluorodeoxyglucose avid, and gallium DOTANOC PET/CT has a role in staging and assessing the recurrence or progression [9]. While planning the management, the aggressiveness of this disease needs to be taken into account. For instance, MANEC of appendix needs to be treated with aggressive multimodality treatment with right hemicolectomy and adjuvant treatment rather than appendectomy alone [13]. Adjuvant chemotherapy regimen depends on higher grade and component of tumor (adeno or neuroendocrine). MANECs with a well-differentiated NET component and adenocarcinoma component can be treated as adenocarcinoma and a poorly differentiated NEC component can be treated as NECs [6].

Patta reported a high response rate to cisplatin and etoposide in patients with high-grade neuroendocrine colorectal tumors [14]. The National Comprehensive Cancer Network recommends cisplatin or carboplatin and etoposide (based on protocols for small cell lung carcinoma) [15]. In our series, treatment was based on higher component and more aggressive component. Other protocols are based on cetuximab, FOLFOX, and octreotide or bevacizumab and FOLFOX6. In the case of hepatic metastases, transarterial chemoembolization with doxorubicin has been reported [16]. Other agents such as mitomycin C or streptozocin have been used with different success rates. The role of new drugs such as everolimus or sunitinib needs to be defined. Radiotherapy could be considered in patients at high risk of local recurrence.

Research studies are required to understand the biology of the tumour, to predict the natural history of this entity. Cases reported in our series belong to elderly age group. The interval between detection of a primary tumor and metastases has been 2.5 months in one of the reports [17] when compared to 3 months in the case 1 in the case history. Reason for aggressiveness of the disease is mostly due to the neuroendocrine component of tumor [18]. Follow-up surveillance needs to be more aggressive due to the belligerent nature of the disease. Serum chromogranin levels along with a marker for epithelial component need to be used during surveillance, as they are elevated in the metastatic or recurrent setting of MANEC tumors [19]. MANECs possibly emanate from bidirectionally differentiated multipotent stem cells. No clear origin of MANEC has been proposed till date. One of the theories proposed for the transformation of the adenocarcinoma component into the neuroendocrine phenotype is the mutation in SMARCA4 [18,20].

Hence, research is needed to assess the origin of these tumors. In one of the large series, median overall survival was around 21 months, and authors reported a highly significant survival benefit with adjuvant treatment rather than surgery alone. They had also reported no significant difference in the survival between platinum compounds and etoposide when compared to platinum compounds and 5-fluorouracil [21]. Further studies are warranted to predict the responsiveness to the different line of treatment.

CONCLUSION

Histology *per se* determines prognosis in certain clinical situations. MANEC is one such condition which has a relatively poor prognosis. Optimum mode of management is yet to be proposed, as there are no clear guidelines regarding its management. Further studies are required first to assess the origin of these tumors and to find the ideal mode of management.

ACKNOWLEDGMENT

The authors would like to thank all the authors for helping us in preparing the manuscript.

REFERENCES

1. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO Classification of Tumours of the Digestive System. 4th ed. Lyon, France: IARC Press; 2010. p. 13-4.
2. Cordier R. Les cellules argentaffines dans les tumeurs intestinales. Arch Int Med Exp 1924;1:5-7.
3. Lewin K. Carcinoid tumors and the mixed (composite) glandular-endocrine cell carcinomas. Am J Surg Pathol 1987;11 Suppl 1:71-86.
4. Solcia E, Klöppel G, Sobin LH. Histological Typing of Endocrine Tumours (WHO International Histological Classification of Tumours). 2nd ed. Berlin, Germany: Springer; 2000.
5. Rindi G, Arnold R, Bosman FT, Capella C, Kilmstra DS, Kloppel G, *et al*. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO Classification of Tumours of the Digestive System. 4th ed. Lyon, France: IARC Press; 2010. p. 13-4.
6. La Rosa S, Marando A, Sessa F, Capella C. Mixed adenoneuroendocrine carcinomas (MANECs) of the gastrointestinal tract: An update. Cancers (Basel) 2012;4:11-30.
7. Gurzu S, Kadar Z, Bara T, Bara T Jr. Tamasi A, Azamfirei L, *et al.* Mixed adenoneuroendocrine carcinoma of gastrointestinal tract: Report of two cases. World J Gastroenterol 2015;21:1329-33.
8. Ogbonna OH, Garcon MC, Syrigos KN, Saif MW. Mixed

acinar-neuroendocrine carcinoma of the pancreas with neuroendocrine predominance. Case Rep Med 2013;2013:705092.
9. Kadhim MM, Jespersen ML, Pilegaard HK, Nordsmark M, Villadsen GE. Mixed adenoneuroendocrine carcinoma is a rare but important tumour found in the oesophagus. Case Rep Gastrointest Med 2016;2016:9542687.
10. Brathwaite S, Rock J, Yearsley MM, Bekaii-Saab T, Wei L, Frankel WL, *et al.* Mixed adeno-neuroendocrine carcinoma: An aggressive clinical entity. Ann Surg Oncol 2016;23:2281-6.
11. Paspala A, Machairas N, Prodromidou A, Spartalis E, Ioannidis A, Kostakis ID, *et al.* Management of MANEC of the colon and rectum: A comprehensive review of the literature. Mol Clin Oncol 2018;9:219-22.
12. Nishimura C, Naoe H, Hashigo S, Tsutsumi H, Ishii S, Konoe T, *et al.* Pancreatic metastasis from mixed adenoneuroendocrine carcinoma of the uterine cervix: A case report. Case Rep Oncol 2013;6:256-62.
13. Brathwaite S, Yearsley MM, Bekaii-Saab T, Wei L, Schmidt CR, Dillhoff ME, *et al.* Appendiceal mixed adeno-neuroendocrine carcinoma: A Population-based study of the surveillance, epidemiology, and end results registry. Front Oncol 2016;6:148.
14. Patta A, Fakih M. First-line cisplatin plus etoposide in high-grade metastatic neuroendocrine tumors of colon and rectum (MCRC NET): Review of 8 cases. Anticancer Res 2011;31:975-8.
15. NCCN Clinical Practice Guidelines in Oncology. NCCN Guidelines; 2018.
16. Ito H, Kudo A, Matsumura S, Ban D, Irie T, Ochiai T, *et al.* Mixed adenoneuroendocrine carcinoma of the colon progressed rapidly after hepatic rupture: Report of a case. Int Surg 2014;99:40-4.
17. Zhang W, Xiao W, Ma H, Sun M, Chen H, Zheng S, *et al.* Neuroendocrine liver metastasis in gastric mixed adenoneuroendocrine carcinoma with trilineage cell differentiation: A case report. Int J Clin Exp Pathol 2014;7:6333-8.
18. Ambesh P, Weissbrot J, Ratner S, Sinha A, Patti R, Balderacchi J, *et al.* Mixed adenoneuroendocrine carcinoma of the gastroesophageal junction: A Rare find. J Investig Med High Impact Case Rep 2017;5:2324709617750180.
19. Wang YH, Yang QC, Lin Y, Xue L, Chen MH, Chen J, *et al.* Chromogranin A as a marker for diagnosis, treatment, and survival in patients with gastroenteropancreatic neuroendocrine neoplasm. Medicine (Baltimore) 2014;93:e247.
20. Vanacker L, Smeets D, Hoorens A, Teugels E, Algaba R, Dehou MF, *et al.* Mixed adenoneuroendocrine carcinoma of the colon: Molecular pathogenesis and treatment. Anticancer Res 2014;34:5517-21.
21. Apostolidis L, Bergmann F, Jaeger D, Winkler EC. Treatment outcomes of patients with mixed adenoneuroendocrine carcinoma (MANEC). J Clin Oncol 2015;33:e15187.

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Hanumappa HK, D'Souza D, Rao JS, Naduvathkundil FR, Chowdappa RG, Joseph EP. Gastrointestinal mixed neuroendocrine carcinoma: Case reports and review of literature. Indian J Case Reports. 2018;4(5):340-343.

Doi: 10.32677/IJCR.2018.v04.i05.001