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Original contribution

Mixed adenoneuroendocrine carcinoma: A review of pathologic characteristics☆,☆☆

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Summary Mixed adenoneuroendocrine carcinoma (MANEC) is a rare pathologic entity defined as a tumor exhibiting both adenocarcinoma and neuroendocrine carcinoma components. Though uncommon, these tumors show aggressive behavior and generally portend a poor prognosis. This study seeks to further define clinicopathological characteristics of MANEC to aid in accurate diagnosis and properly direct clinical management. Thirty-four confirmed MANECs were identified in our 25-year retrospective review of cases arising in the gastrointestinal tract. Various gross and microscopic variables were compared to overall survival. Tumors diagnosed at advanced stage (pT4), had a prominent mucinous component and lacked goblet cell clusters, which were all significantly associated with worse overall survival. This study supports previous findings and further elucidates clinicopathologic characteristics of MANEC.
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1. Introduction

Mixed adenoneuroendocrine carcinoma (MANEC) is a rare pathologic diagnosis defined by the World Health Organization (WHO) in 2010 [1]. Previously, tumors exhibiting evidence of both goblet cell and neuroendocrine components were given a myriad of pathologic designations including "goblet cell carcinoid tumor (GCC)," "adenocarcinoma ex-GCC," "composite tumor," "adenocarcinoid tumor," "collision tumor" and "mixed endocrine-exocrine tumor" [2-4]. MANEC is defined as a tumor with both epithelial and neuroendocrine cells. Each of these components must represent at least 30% of the tumor [1]. The tumors are pathologically and clinically distinct from both their carcinoid and adenocarcinoma components. Due to the rarity of the diagnosis, limited data exist characterizing the pathological characteristics of the disease.

Previously, MANECs were felt to represent a more benign pathological entity similar to carcinoid tumors; however,

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recent evidence suggests that MANEC represents a more aggressive tumor [5,6]. Tang et al demonstrated that benign, intermediate and frankly- malignant versions of mixed adenocarcinoma and neuroendocrine tumors exist, and it is those with the frank malignancy that have the worst prognosis [7]. Clinically, true MANEC behaves more similarly to adenocarcinoma than a carcinoid tumor.

The aim of our study is to define clinicopathological characteristics of MANEC to aid in accurate diagnosis and direct clinical management.

Table 1 Clinicopathologic characteristics of cohort

Case number	Age at diagnosis (y)/sex	Anatomic location	Primary tumor size, largest dimension (cm) [c]	Final pathologic stage (AJCC 7th ed)	Sites of metastasis [c]	Clinical outcome	Survival since original diagnosis (mo)
1	58/F	Appendix	1.3	pT4b N0 M1b	O, P, Ut, B/L Ov, SB	DOD	17
2	56/F	Appendix	1.7	pT4b NX MX	–	Alive	51
3	57/F	Appendix	3.3 [b]	pT3 NX MX	None	Alive	56
4	62/F	Ileocecal valve	–	pT4b N0 M1b	B/L Ov, Ut	DOD	22
5	44/F	Appendix	4.9	pT4b NX M1a	O	DOD	36
6	56/F	Appendix	9.0	pT4a N1b M1a	M	Alive—PD	60
7	64/M	Appendix	–	pT4a NX M1b	Bladder, prostate	Alive—NED	128
8	60/F	Appendix	1.6	pT3 N0 M0	None	Alive	66
9	45/F	Appendix	4.1	pT4a NX M1b	B/L Ov, O, P	Alive—PD	66
10	71/M	Appendix	1.6	pT3 N0 MX	None	D-OC	61
11	69/F	Appendix	3.6	pT4b N2b M1b	B/L Ov, O, P, SB	DOD	2
12	54/M	Appendix	–	pT3 N0 MX	None	Alive	66
13	55/F	Cecum	3.5	pT3 N2b M1a	O	DOD	65
14	75/F	Cecum	4.8	pT4b N2b M1b	Rt Ov, Ut, P	DOD	27
15	74/M	Appendix	6.5	pT4a N0 M1a	O, SB	DOD	22
16	51/M	Appendix	6.0	pT4a NX MX	–	Alive	79
17	56/F	Appendix	10.3	pT4b N0 M1b	B/L Ov, SB, Stomach, Spleen, Ut, P, Liver	DOD	39
18	60/M	Appendix	3.0	pT3 NX MX	None	Alive	82
19	82/F	Cecum [a]	5.0	pT4a N2a MX	peritoneum	DOD	1
20	45/M	Appendix	–	pT3 N0 M0	None	Alive	89
21	47/F	Cecum [a]	2.9	pT4a N2b M1b	O, Lt Ov, P, Ut, SB	DOD	18
22	56/M	Appendix	–	pT3 N0 M0	None	Alive	95
23	56/M	Appendix	3.5	pT4b N2b M1b	O, SB	DOD	33
24	56/F	Appendix	1.0	pT3 NX MX	None	Alive	99
25	51/F	Appendix	3.5	pT4a N0 M1b	B/L Ov, Ut, O, M, rectum, liver	DOD	23
26	45/F	Appendix	2.2	pT4a N0 M1b	B/L Ov, O, P, SB, sigmoid colon	DOD	27
27	60/M	Appendix	2.2 [b]	pT4a NX MX	None	Alive	129
28	47/F	Appendix	4.3	pT4b NX M1b	B/L Ov, O, P, Ut	DOD	18
29	26/F	Appendix	2.5	pT4a N2b M1b	O, B/L Ov, U, SB, gallbladder	DOD	9
30	45/M	Appendix		pT3 N1a MX	None	Alive	170
31	30/F	Appendix	[d]	pT4a N1b M1b	O, P, B/L Ov, Ut, spleen, liver, rectosigmoid colon	DOD	9
32	56/F	Appendix	–	pT4a N0 M1b	B/L Ov, Ut, P, SB, B/L Ureters	DOD	28
33	45/M	Appendix	[d]	pT4a N0 M0	None	D-OC	88
34	60/M	Appendix	[d]	pT3 N1b M1b	SB, P, M, rectum	DOD	71

Abbreviations: O, omentum; P, peritoneum; Rt, right; Lt, left; Ov, ovary; B/L, bilateral; Ut, uterus; SB, small bowel; M, mesentery; DOD, died of disease; D-OC, died—other cause; PD, persistent disease; NED, no evidence of disease.

[a] Cases 20 and 22 had tumors that engulfed the appendix and a portion of the cecum; definitive determination of the origin between these 2 locations is not possible.

[b] Multifocal tumor; largest tumor size given.

[c] (−) indicates consult case; information not available.

[d] Due to the diffuse nature of the tumor, the maximum tumor size was not available.

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