Annals of Diagnostic Pathology 42 (2019) 69–74

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Original Contribution

Incidence of composite intestinal adenoma-microcarcinoid in 158 surgically resected polyps and its association with squamous morule☆

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ARTICLE INFO

Keywords:
Adenoma
Carcinoid
Beta-catenin
Wnt
Morule
Composite

ABSTRACT

Composite intestinal adenoma-microcarcinoid (CIAM) is a rare colorectal lesion consisting of adenoma and small well-differentiated neuroendocrine cell clusters at its base. Its incidence is unknown. Benign squamous morule may demonstrate a neuroendocrine phenotype by immunohistochemistry. We investigated the incidence and clinicopathologic features of CIAM in endoscopically unresectable, surgically removed colorectal adenomas and evaluated its association with squamous morule.

Archived pathology materials from 158 surgically resected colorectal adenomas were reviewed. 139 (88%) polyps were entirely submitted for microscopic examination. All lymph nodes were negative for adenocarcinoma and neuroendocrine tumor. CIAM was identified in 6 (3.8%) cases. The microcarcinoid (MC) was distributed over a mean of 5.8 mm (range < 1 to 12 mm), and was multifocal in 5 cases. The MC component was positive for synaptophysin in 6, CK5/6 in 4, and β-catenin in 3 cases. Two of 6 (33.3%) CIAM showed concurrent squamous morule, compared to 4.0% (6 of 152) of adenomas without MC ($p < 0.05$). At the end of the mean follow-up of 53 months, 4 were free of disease and one patient with previous history of pulmonary large cell neuroendocrine carcinoma (NEC) had a recurrence of NEC. One patient died of an unrelated disease.

The incidence of CIAM in surgically removed colorectal adenomas is 3.8%, with an indolent clinical course. Frequent co-expression of CK5/6 and β-catenin in MC combined with common co-existence of squamous morule in the same polyp suggests shared pathogenesis of MC in CIAM and squamous morule, likely representing altered Wnt/β-catenin signaling pathway.

1. Introduction

Composite intestinal adenoma-microcarcinoid (CIAM) is a rare intestinal lesion consisting of adenoma and small well-differentiated neuroendocrine cell clusters at its base. Recently the term “mixed adenoma-well differentiated neuroendocrine tumor (MANET)” has been proposed for a combined lesion of adenoma and well differentiated neuroendocrine tumor, including CIAM [1]. The microcarcinoid (MC) component of CIAM is typically located at the base of polyps, usually within the lamina propria. The MC component occupies only a minute area and forms small nests or clusters without a visible nodule or mass, and the overall architecture of the polyps is preserved [2-5]. Although this entity is increasingly recognized, its incidence is unknown, and its pathogenesis and prognosis remain uncertain due to its rarity.

Squamous morule is rarely identified within colorectal adenomas with a reported incidence of 0.4%. Microscopically, squamous morule consists of discrete nests/nodules of immature squamous epithelial cells without identifiable keratin pearls or intercellular bridges [6]. The nests may protrude into the lumen of adenomatous glands, or may be identified at the base of the polyps [7]. Recently, Lee et al. reported that squamous morule may show immunohistochemical expression of neuroendocrine markers [7]. Given the morphologic and immunohistochemical similarities between squamous morule and the MC component of CIAM, we hypothesized that these two entities may share common pathogenesis and that there would be an association between the two. In order to fully assess the base of the polyps, we studied surgically removed colorectal adenomas. The aim of the present study is to investigate the incidence and clinicopathologic features of CIAM in surgically removed colorectal adenomas and evaluate its association with squamous morule. In this manuscript, we use the term CIAM as previously used in the literature on the subject for ease of comparison

☆ The abstract of this study was presented at the 2019 USCAP annual meeting in March 2019.

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https://doi.org/10.1016/j.anndiagpath.2019.07.004

and to emphasize the small size of the MC components.

2. Materials and methods

2.1. Cases

This study was approved by the Institutional Review Board with a waiver of informed consent. Archived pathology materials from consecutive, surgically removed colorectal adenomas (2003–2018) were retrieved and reviewed. Clinicopathologic characteristics including age, gender, surgical procedure, location and size of the polyp, entirety of polyp submission for microscopic examination, and follow-up data were obtained from the electronic medical records and pathology reports. Unless specified otherwise, polyps were serially sectioned and submitted in consecutive blocks.

2.2. Microscopic examination

All the original diagnostic slides of the polyps were reviewed by two pathologists (Z.F. and H.L.). Polyps with invasive adenocarcinoma were excluded from the analysis. The polyps were classified as tubular, tubulovillous, villous, sessile serrated and traditional serrated adenomas. The presence of high grade dysplasia was assessed. The adenomatous components were evaluated for the presence of MC, and squamous morule.

In this study, squamous morules were defined as immature squamoid or spindled cells forming nests and nodules without definitive keratinization or intercellular bridges [7] [Fig. 1, Fig. 2]. MC was defined as small nests, irregular clusters or cords of cells with occasional lumina-like structure with an immunophenotypic evidence of neuroendocrine differentiation and with the morphology of well-differentiated neuroendocrine tumor, regardless of the size of the lesion [2,4,5,8] [Fig. 2]. Neuroendocrine cells within the overlying adenomatous crypts were not considered as MC [8]. All the lymph node sections were reviewed for the presence of metastatic neuroendocrine tumor or adenocarcinoma.

2.3. Cases with squamous morule (SM-1, SM-2)

The amount of squamous morules was insufficient for multiple immunohistochemical staining in many of our cases. Therefore, an additional two resection cases with sufficient amount of squamous morule (SM-1, SM-2) were evaluated by immunohistochemistry. SM-1 was from outside the search window (2019). In SM-2, squamous morules were mixed with invasive adenocarcinoma components. Thus, these two cases were not counted toward the statistical analysis.

2.4. Immunohistochemistry

Representative sections of selected cases, including SM-1 and SM-2 were subject to immunohistochemical staining for synaptophysin, chromogranin, cytokeratin 5/6, ki67 and β-catenin on Ventana BenchMark Ultra platform. For β-catenin, nuclear and/or cytoplasmic staining was considered positive [Table 1].

2.5. Statistical analysis

Fisher's exact test was performed to compare the frequencies of two parameters. Student's *t*-test was performed to compare the means of two groups. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demography and gross findings

A total of 158 cases (from 158 patients) of surgically removed polyps were retrieved (2003–2018). The polyps were removed by partial cecectomy ($n = 1$), right hemicolectomy ($n = 108$), segmental colon resection ($n = 37$), low anterior resection ($n = 7$), or transanal submucosal resection ($n = 5$). The mean age of the patients was 65 (range: 34 to 94) years, with no gender predilection (male:female = 79:79). Twenty cases had additional adenomas larger than 0.5 cm in the same specimen, which were also reviewed, but were not included in this study. The average size of the polyps was 3.0 (range: 0.5 to 11.0) cm. 139 (88%) of 158 polyps were entirely submitted for microscopic examination, with the mean number of slides examined 5.6/polyp [Table 2].

3.2. CIAM: incidence, microscopic examination and immunohistochemistry

Of the 158 cases, 6 cases showed MC components, with an overall incidence of 3.8% for CIAM in our cohort. Five cases were in the right colon, and the remaining one was in the transverse colon. All CIAMs showed tubulovillous adenomatous components (100%). High grade dysplasia was noted in 3 of 6 (50.0%) cases. There was no statistically significant difference in polyp size, polyp location (right vs. left) or the frequency of associated high grade dysplasia between adenomas with and without MC [Table 2, Table 3].

The MC component was at the base of full-thickness adenomatous components in myxoinflammatory lamina propria with conspicuous eosinophils [Fig. 2]. The nests or cords of MC were sparsely distributed and did not form mass-like lesion. Thus, they were identified only at high magnification as scattered foci, and we were unable to measure their sizes in a conventional way. Therefore, as an alternative, the "distribution" of MC was calculated by adding an average thickness (3 mm) of processed tissue when MC was seen in more than one consecutive tissue blocks. The MC was distributed over a mean 5.8 (range < 1 to 12) mm and was apparently multifocal in 5 cases. In two cases (case 9 and 12), the MC component focally extended into the superficial submucosa. The constituent cells were monotonous and bland without nuclear atypia, pleomorphism, mitotic activity, or apoptosis. The immunoprofile of the MC components is in [Table 4].

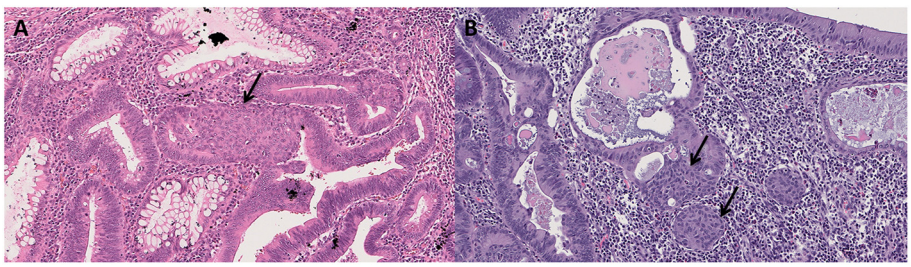

Fig. 1. Squamous morule (arrows) consisting of immature squamoid cells without identifiable keratin pearls or intercellular bridges, as shown in case 2 (A) and case 5 (B) (A, B: Hematoxylin & eosin, x200).

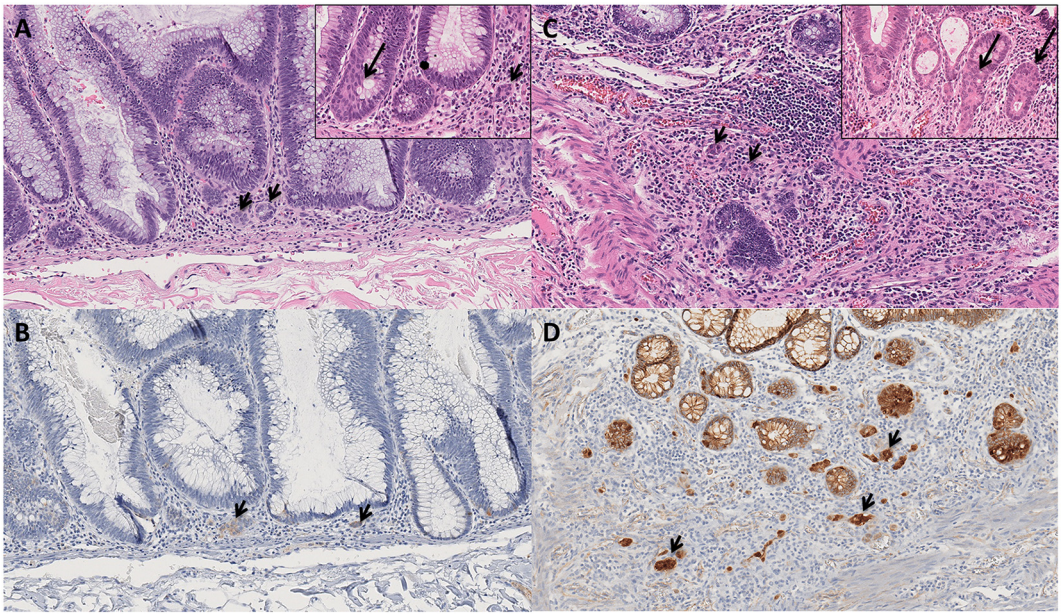

Fig. 2. Microcarcinoid (MC) of case 7 (A, B) and case 8 (C, D). MC component of composite intestinal adenoma-microcarcinoid (CIAM) is typically located at the base of polyps (short arrows), and is sparsely distributed without forming a mass lesion. MC shows immunolabeling for synaptophysin (B) and β-catenin (D). The coexisting squamous morules are demonstrated in insets (long arrows) (A, C: Hematoxylin & eosin, x200; B: Synaptophysin, X200; D: β-catenin, x200).

Table 1
Antibodies used for immunohistochemistry.

	Clone	Clonality	Dilution	Vendor	Staining localization
Synaptophysin	Synaptophysin	Rabbit P	Pre-dilute	Cell Marque, Rocklin, CA, USA	Cytoplasmic
Chromogranin	LK2H10	Mouse M	Pre-dilute	Ventana Medical Systems, Inc., Tucson, AZ, USA	Cytoplasmic
Cytokeratin 5/6	D5&16B4	Mouse M (two)	Pre-dilute	Cell Marque, Rocklin, CA, USA	Cytoplasmic
Beta-catenin	14	Mouse M	Pre-dilute	Cell Marque, Rocklin, CA, USA	Nuclear/cytoplasmic[a]
Ki67	30-9	Rabbit M	Pre-dilute	Ventana Medical Systems, Inc., Tucson, AZ, USA	Nuclear

Abbreviations: P: polyclonal; M: monoclonal.
[a] Nuclear/cytoplasmic stain is considered positive, usual localization is membranous.

Table 2
Comparison between colorectal adenoma without and with microcarcinoid.

		Adenoma (without MC)	CIAM
Number of cases		152	6
Mean age (range), years		65 (34 to 94)	67(55 to 78)
Gender (M:F)		75:77	4:2
Procedure	Partial cecectomy	1	0
	Right hemicolectomy	103	5
	Segmental resection	36	1
	Low anterior resection	7	0
	Transanal excision	5	0
Mean size of adenoma (range), cm		3.0 (0.5–11)	4.2 (2.5–6.3)
Adenoma component (# of cases)	Tubulovillous	94	6
	Tubular	47	0
	Villous	5	0
	Sessile serrated	4	0
	Traditional serrated	2	0
High grade dysplasia (%)		40.1	50.0
Squamous morule (%)		4.0*	33.3*

Abbreviations: MC, microcarcinoid; CIAM, Composite intestinal adenoma-microcarcinoid; M, male; F; female.
* The difference is statistically significant ($p < 0.05$).

3.3. Squamous morule: incidence and microscopic examination

Of the 158 cases, 8 (5.1%) had squamous morule in the adenomatous components. The squamous morules frequently protruded into the lumina of the adenomatous glands or formed a nodule that was contiguous with the glands [Fig. 1]. In 2 cases, squamous morules were also noted at the polyp base, detached from the adenomatous glands. The squamous morule was positive for CK5/6 when immunohistochemistry was performed (case 5 and 7). In the two additional cases with squamous morule (SM-1, SM-2), the squamous morules were positive for CK5/6 and β-catenin, and were negative for synaptophysin and chromogranin.

Two adenomas with squamous morule had a concurrent MC component, oftentimes in close proximity to each other. Therefore, 33.3% (2 of 6) of CIAM showed concurrent squamous morule [Fig. 2], compared to 4.0% (6 of 152) of adenomas without MC ($p < 0.05$) [Table 3].

3.4. Lymph node examination and follow-up

All lymph nodes were negative for adenocarcinoma or neuroendocrine tumor in both the CIAM and conventional adenoma group. The mean follow-up duration for the CIAM group was 53 (range: 14 to 113) months. At the end of the follow-up, 4 were free of disease and one patient with previous history of pulmonary large cell neuroendocrine carcinoma (NEC) had a recurrence of NEC. One patient died of an unrelated disease. The two patients with MC components extending to

Table 3
Characteristics of patients with polyps with squamous morule and/or microcarcinoid.

Case	Age (years)	Gender	Adenoma component	Size of polyp (cm)	Location	High grade dysplasia	Squamous morule	MC
1	66	F	Tubulovillous	3.1	Cecum	No	Yes	No
2	58	F	Tubulovillous	3.5	Sigmoid	Yes	Yes	No
3	79	F	Tubulovillous	3.0	Rectum	No	Yes	No
4	56	F	Tubulovillous	3.1	Sigmoid	Yes	Yes	No
5	83	F	Tubulovillous	4.7	Right	Yes	Yes	No
6	64	M	Tubulovillous	2.5	Left	Yes	Yes	No
7	78	M	Tubulovillous	3.8	Right	No	Yes	Yes
8	65	F	Tubulovillous	3.0	Right	No	Yes	Yes
9	61	F	Tubulovillous	6.3	Right	Yes	No	Yes
10	55	M	Tubulovillous	4.3	Right	No	No	Yes
11	70	M	Tubulovillous	5.8	Right	Yes	No	Yes
12	73	M	Tubulovillous	2.5	Transverse	Yes	No	Yes

Abbreviations: MC, Microcarcinoid; F, female; M, male.

involve the submucosa (case 9 and 12) were followed up for 14 and 15 months, respectively, with no evidence of recurrence or metastasis of neuroendocrine tumor.

4. Discussion

Neuroendocrine tumor and endocrine cell hyperplasia adjacent to glandular dysplasia has been described in inflammatory bowel disease [9,10]. Some authors have postulated that multipotent stem cells residing in adenomatous component might evolve into neuroendocrine tumor [10]. CIAM that is not associated with inflammatory bowel disease was first described by Moyana et al. in 1988 [11]. These authors hypothesized that CIAM represents either a collision tumor, or that the adenoma and carcinoid components within CIAM may be related, given the transition zone between the two components in one CIAM case [10]. The notion that adenoma and MC components may be related and share a common origin was further supported by additional reports of CIAM with endocrine immunophenotype at the base of the adenoma, and identical molecular profiles in both components [2,12].

Since its first description, CIAM has been sporadically documented as a case report or small case series in the literature. To date, the incidence of this presumably rare lesion is unknown [2-5,8,13,14]. The largest series of colorectal CIAM consisted of 24 cases that were reported in South Korea by Kim et al. in 2017. Fourteen of their cases were prospectively collected over a 38-month period. However, the authors did not report the incidence of CIAM in their cohort [3]. In the United States, Estrella at al reported 21 cases of colorectal CIAM, including 2 from the ileocecal valve. The authors retrieved the cases by "retrospective search of the surgical pathology file" over a 17.5 year period at a large cancer center. However, the incidence of colorectal CIAM in their cohort was also not documented [8]. Other studies of CIAM included consult cases and prospectively collected cases, precluding evaluation of the incidence of the lesion [2,4,5].

In order to study the incidence of rare microscopic lesion such as CIAM, a reasonably sized homogeneous cohort needs to be systemically reviewed, including histologic assessment. Moreover, the MC components of CIAM are usually situated at the base of the polyps, requiring evaluation of polyp base to detect MC components. For example, in Kim et al.'s study, 20 of the 24 polyps were removed by endoscopic submucosal dissection ($n = 11$), endoscopic mucosal resection ($n = 7$), and colectomy ($n = 2$) [3]. The adenoma component of CIAM also tends to show features of advanced/high risk polyp, with > 1 cm in size, villous component and high grade dysplasia [5,8]. Thus, in order to systemically review adenomas that are likely to have MC components at the polyp base, we targeted surgically removed polyps over a 16 year period from one tertiary medical center with active colorectal surgery service. The incidence of CIAM was 3.8% in our cohort.

The term morule, squamous morule, squamoid morule, squamous metaplasia, and squamous differentiation have been used interchangeably in the literature. While it remains unclear whether these are distinguishable or not [3,7,15-20], morules showed squamous differentiation at the ultrastructural level [20]. Squamous morule in colorectal adenoma was first described in 1981 [21], with the reported incidence of about 0.4% [6,7].

Histomorphologic and immunophenotypic resemblance between the MC component of CIAM and squamous morule has been recognized [3,5]. In Kim et al.'s cohort, 5 CIAM were initially diagnosed as tubular adenoma with squamous morule, and one as tubular adenoma with squamous metaplasia [3]. In Pulitzer et al.'s study, one CIAM was originally interpreted as adenoma with squamous metaplasia [2]. In Salaria et al.'s study, MC was interpreted as squamous morule in 5 of 10 "submitted" cases by the submitting pathologists. The MC components of CIAM were also variably immunoreactive with p63 and/or cytokeratin 5/6, suggesting squamous differentiation [5]. Lee et al. reported 5 colon polyps with squamous morules within the pseudoinvasive foci of adenomas that mimicked invasive squamous cell carcinoma. Although the authors did not compare these squamous morules with MC in the manuscript, interestingly, three cases and one case showed focal immunoreactivity for synaptophysin and chromogranin within the squamous morules, respectively, similar to MC components of CIAM.

Table 4
Characteristics of microcarcinoid components in composite intestinal adenoma-microcarcinoid.

Case	Focality	Distribution	Submucosal invasion of MC	Synaptophysin	CK5/6	Beta-catenin	Chromogranin	Ki67
7	Multifocal	12 mm[a]	No	+	f +	f +	+	< 1%
8	Multifocal	< 1 mm	No	+	f +	+	−	< 1%
9	Multifocal	5 mm	Yes	+	f+	−	−	< 1%
10	Multifocal	5 mm	No	+	−	−	+	< 1%
11	Multifocal	6 mm[a]	No	+	f +	+	−	N/A
12	Unifocal	6 mm	Yes	+	N/A	N/A	−	N/A

Abbreviations: MC, microcarcinoid; f, focal; +, positive; −, negative.
[a] Distribution of MC was measured by adding the thickness (3 mm) of consecutive tissue blocks with MC; N/A, not applicable, stain was not performed or the focus of interest was not present in the level section for the immunostain.

Moreover, the authors described isolated squamous morules forming solid nests in pseudoinvasive stroma or a myxoinflammatory stroma, unassociated with adenomatous components [7]. The description of these isolated nests of squamous morule is indeed similar to that of MC components in CIAM.

Given their immunophenotypic and morphologic resemblance, and frequent co-existence as demonstrated in our study, we hypothesize that squamous morule and MC component of CIAM may share a common pathogenesis of altered Wnt/β-catenin signaling. Wnt signaling is a pathway involved in cell proliferation and differentiation, wherein β-catenin molecule is a crucial component [22]. Squamous morules of colorectal adenomas frequently demonstrate nuclear and cytoplasmic β-catenin immunolabeling [15,17], which was the case in our study as well. Also, *β-catenin* mutation was identified within microdissected morules in pulmonary blastoma, endometrioid carcinoma, and well-differentiated fetal adenocarcinoma of the lung, though immunohistochemical stain for β-catenin was negative within the morules [23].

Likewise, cytoplasmic and/or nuclear β-catenin localization in carcinoids correlates with aberrant Wnt/β-catenin signaling [24,25]. Fujimori et al. performed both β-catenin immunohistochemistry and PCR-based direct DNA sequence analysis on 72 gastrointestinal carcinoid tumors. 57 (79%) of 72 cases showed cytoplasmic and/or nuclear β-catenin immunolabeling, of which 26 (46%) cases showed *β-catenin* mutation in exon 3 [25]. Subsequent study showed that not only genetic alterations including *β-catenin*, but also epigenetic alterations involving CpG islands of several other genes may alter Wnt/β-catenin signaling pathway. Beta-catenin immunostain was negative within these carcinoids with epigenetic alterations [24]. In our study, 5 CIAM cases were subject to β-catenin immunohistochemistry and 3 cases showed nuclear and cytoplasmic β-catenin immunolabeling within the MC components.

Wnt signaling is implicated in stem cell biology [22]. Thus, our observation of strong association between squamous morule and MC in CIAM, and other authors' speculation that the MC and adenoma component of CIAM share a common origin [2,12], appear to support a notion that all three components – squamous morule, adenoma component associated with MC, and MC of CIAM – are related and may originate from a multipotent stem cell. The significance of potential mechanistic association between the three components is unclear and warrants further study.

A majority of previous studies indicated favorable outcome of CIAM [2,3,5,12]. A single case of CIAM wherein the MC component invaded the submucosa with an infiltrative growth pattern was found to have high grade NEC in a lymph node in subsequent surgical resection [4]. In Estrella et al.'s study, 10 (40%) of 25 duodenal and colorectal CIAM showed submucosal invasion of the low grade neuroendocrine tumor and one showed lymphatic invasion. However, none of the patients showed adverse outcome related to CIAM after 2 to 128 months of follow up [8]. Similarly, after the mean follow-up period of 53 months, none of our CIAM patients developed adverse outcome related to CIAM, though MC in two cases focally involved superficial submucosa. Our data together with previous data appear to support favorable outcome of the MC component of CIAM.

Given its indolent behavior, background myxoinflammatory stroma resembling desmoplasia, and morphologic and immunohistochemical resemblance to squamous morule, awareness of CIAM and its association with squamous morule is important to avoid over-diagnosis of invasive adenocarcinoma and squamous cell carcinoma. Alternatively, adenomas harboring squamous morule at the polyp base may be interpreted as CIAM and it may be difficult or nearly impossible to distinguish the two. As Salaria et al. postulated, squamous morule and MC may, biologically, represent the same entity [5].

Nevertheless, as squamous morule is considered benign and MC of CIAM is likely indolent, there may not be a significant clinical implication if the lesion is recognized as indolent and the polyp harboring the lesion is completely excised. Lastly, MC of CIAM may be underrecognized as the lesion is situated at the base of a usually large polyp as microscopic foci. Although the MC may extend over several milimeters, the individual foci are usually subtle and scattered, and oftentimes mimic tangentially sectioned base of the adenomatous crypts. For example, MC component in 3 of 6 cases were not recognized in our cohort and were only later identified when all polyps were purposefully reviewed by the authors. In Pulitzer et al.'s study, 1 of 4 CIAM cases was initially overlooked, leading the authors to postulate that the prevalence of CIAM may be higher than supposed [2]. In Salaria et al.'s study, the impressions of the MC components were not provided in 3 of 10 “submitted” cases [5]. All the MC components in our cohort were completely excised and no patients had adverse outcome related to MC.

The limitation of our study is that molecular testing was not performed to confirm the potential common pathogenesis of MC and squamous morule. Likewise, only 2 cases of squamous morule were subject to β-catenin immunohistochemistry. Although previous studies regarding squamous morule within colorectal adenomas made a similar observation [15,17], we cannot draw a major conclusion based on small number of cases. Also, a majority of level sections that were used for ki67 immunostain had < 500 MC cells (it is recommended that 500–2000 tumor cells are to be assessed) [26], limiting the validity of the ki67 assessment. However, the MCs were bland with no mitosis, atypia, necrosis or infiltrative growth, likely representing a low grade lesion. Lastly, some MC components were negative for chromogranin, a more specific immunomarker of neuroendocrine differentiation than synaptophysin. Although our findings are in line with previous reports of immunoprofile of CIAM [2-5], this observation raises a possibility that the lesion we refer to as CIAM (or MANET) may be a heterogeneous group with a spectrum of varying morphology and immunoprofile.

In conclusion, the incidence of CIAM in surgically removed colorectal adenomas over a 16-year-period was 3.8%, with an indolent clinical course. Frequent co-expression of CK5/6 and β-catenin in MC combined with common co-existence of squamous morule in the same polyp suggests shared pathogenesis of MC in CIAM and squamous morule, likely reflecting altered Wnt/β-catenin signaling pathway.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of Competing Interest

None.

Acknowledgements

None.

References

[1] La Rosa S, Marando A, Sessa F, Capella C. Mixed adenomeuroendocrine carcinomas (MANECs) of the gastrointestinal tract: an update. Cancers 2012;4:11–30.
[2] Pulitzer M, Xu R, Suriawinata AA, Waye JD, Harpaz N. Microcarcinoids in large intestinal adenomas. Am J Surg Pathol 2006;30:1531–6.
[3] Kim MJ, Lee EJ, Kim DS, Lee DH, Youk EG, Kim HJ. Composite intestinal adenoma microcarcinoid in the colon and rectum: a case series and historical review. Diagn Pathol 2017;12:78https://doi.org/10.1186/s13000-017-0665-9.
[4] Lin J, Goldblum JR, Bennett AE, Bronner MP, Liu X. Composite intestinal adenoma-microcarcinoid. Am J Surg Pathol 2012;36:292–5. https://doi.org/10.1097/PAS.0b013e318236e4d2.
[5] Salaria SN, Abu Alfa AK, Alsaigh NY, Montgomery E, Arnold CA. Composite intestinal adenoma-microcarcinoid clues to diagnosing an under-recognised mimic of invasive adenocarcinoma. J Clin Pathol 2013;66:302–6. https://doi.org/10.1136/jclinpath-2012-201314.
[6] Bansal M, Fenoglio CM, Robboy SJ, King DW. Are metaplasias in colorectal adenomas truly metaplasias? Am J Pathol 1984;115:253–65.
[7] Lee HE, Chandan VS, Lee CT, Wu TT. Squamoid morules in the pseudoinvasive foci of colonic polyp morphologically mimic invasive carcinoma. Hum Pathol

2017;68:54–60. https://doi.org/10.1016/j.humpath.2017.08.019.
[8] Estrella JS, Taggart MW, Rashid A, Abraham SC. Low-grade neuroendocrine tumors arising in intestinal adenomas: evidence for alterations in the adenomatous polyposis coli/β-catenin pathway. Hum Pathol 2014;45:2051–8. https://doi.org/10.1016/j.humpath.2014.07.001.
[9] Gledhill A, Hall PA, Cruse JP, Pollock DJ. Enteroendocrine cell hyperplasia, carcinoid tumors and adenocarcinoma in long-standing ulcerative colitis. Histopathology 1986;10:501–8.
[10] Sigel JE, Goldblum JR. Neuroendocrine neoplasms arising in inflammatory bowel disease: a report of 14 cases. Mod Pathol 1998;11(6):537–42.
[11] Moyana TN, Qizilbash AH, Murphy F. Composite glandular-carcinoid tumors of the colon and rectum report of two cases. Am J Surg Pathol 1988;12:607–11.
[12] La Rosa S, Uccella S, Molinari F, Savio A, Mete O, Vanoli A, et al. Mixed adenoma well-differentiated neuroendocrine tumor (MANET) of the digestive system: an indolent subtype of mixed neuroendocrine-non neuroendocrine neoplasm (MiNEN). Am J Surg Pathol 2018;42:1503–12. https://doi.org/10.1097/PAS.0000000000001123.
[13] Thosani N, Rao B, Ertan A, Guha S. Wide spectrum of neuroendocrine differentiation in identical appearing colon polyps: a report of 2 mixed endocrine-glandular polyps. Turk J Gastroenterol 2014;25(Suppl. 1):242–3. https://doi.org/10.5152/tjg.2014.5193.
[14] Lyda MH, Fenoglio-Preiser CM. Adenoma-carcinoid tumors of the colon. Arch Pathol Lab Med 1998;122:262–5.
[15] Pantanowitz L. Colonic adenoma with squamous metaplasia. Int J Surg Pathol 2009;17:340–2. https://doi.org/10.1177/1066896908322551.
[16] Mochizuki K, Kondo T, Oishi N, Tahara I, Inoue T, Kasai K, et al. Squamous morula formation in colorectal adenoma: immunohistochemical and molecular analyses. Pathol Res Pract 2015;211:797–800. https://doi.org/10.1016/j.prp.2015.05.002.
[17] Ueo T, Kashima K, Daa T, Kondo Y, Sasaki A, Yokoyama S. Immunohistochemical analysis of morules in colonic neoplasms: morules are morphologically and qualitatively different from squamous metaplasia. Pathobiology 2005;72:269–78.
[18] Sasaki A, Yokoyama S, Arita T, Inomata M, Kashima K, Nakayama I. Morules with biotin-containing optically clear nuclei in colonic tubular adenoma. Am J Surg Pathol 1999;23:336–41.
[19] Sarlin JG, Mori K. Morules in epithelial tumors of the colon and rectum. Am J Surg Pathol 1984;8:281–5.
[20] Hendrickson MR, Kempson RL. Endometrial epithelial metaplasias: proliferations frequently misdiagnosed as adenocarcinoma. Report of 89 cases and proposed classification. Am J Surg Pathol 1980;4:525–42.
[21] Chen KT. Colonic adenomatous polyp with focal squamous metaplasia. Hum Pathol 1981;12:848–9.
[22] Nusse R, Clevers H. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. Cell 2017;169:985–99. https://doi.org/10.1016/j.cell.2017.05.016.
[23] Makishi S, Kinjo T, Sawada S, Chinen K, Hirayasu T, Hamada T, et al. Morules and morule-like features associated with carcinomas in various organs: report with immunohistochemical and molecular studies. J Clin Pathol 2006;59:95–100.
[24] Kim JT, Li J, Jang ER, Gulhati P, Rychahou PG, Napier DL, et al. Deregulation of Wnt/β-catenin signaling through genetic or epigenetic alterations in human neuroendocrine tumors. Carcinogenesis 2013;34:953–61. https://doi.org/10.1093/carcin/bgt018.
[25] Fujimori M, Ikeda S, Shimizu Y, Okajima M, Asahara T. Accumulation of β-catenin protein and mutations in exon 3 of β-catenin gene in gastrointestinal carcinoid tumor. Cancer Res 2001;61:6656–9.
[26] Rindi G, Arnold R, Bosman FT, Capella C, Klimstra 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. World Health Organization classification of tumours of the digestive system. 4th ed.Lyon: IARC Press; 2010. p. 13–4.