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Adenocarcinoma ex-goblet cell carcinoid (appendiceal-type crypt cell adenocarcinoma) is a morphologically distinct entity with highly aggressive behavior and frequent association with peritoneal/intra-abdominal dissemination: an analysis of 77 cases

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High-grade versions of appendiceal goblet cell carcinoids ('adenocarcinoma ex-goblet cell carcinoids') are poorly characterized. We herein document 77 examples. Tumors occurred predominantly in females (74%), mean age 55 years (29–84), most with disseminated abdominal (77% peritoneal, 58% gynecologic tract involvement) and stage IV (65%) disease. Many presented to gynecologic oncologists, and nine had a working diagnosis of ovarian carcinoma. Metastases to liver ($n=3$) and lung ($n=1$) were uncommon and none arose in adenomatous lesions. Tumors had various histologic patterns, in variable combinations, most of which were fairly specific, making them recognizable as appendiceal in origin, even at metastatic sites: I: Ordinary goblet cell carcinoid/crypt pattern (rounded, non-luminal acini with well-oriented goblet cells), in variable amounts in all cases. II: Poorly cohesive goblet cell pattern (diffusely infiltrative cords/single files of signet ring-like/goblet cells). III: Poorly cohesive non-mucinous cell (diffuse-infiltrative growth of non-mucinous cells). IV: Microglandular (rosette-like glandular) pattern without goblet cells. V: Mixed 'other' carcinoma foci (including ordinary intestinal/mucinous). VI: goblet cell carcinoid pattern with high-grade morphology (marked nuclear atypia). VII: Solid sheet-like pattern punctuated by goblet cells/microglandular units. Ordinary nested/trabecular ('carcinoid pattern') was very uncommon. In total, 33(52%) died of disease, with median overall survival 38 months and 5-year survival 32%. On multivariate analysis perineural invasion and younger age (<55) were independently associated with worse outcome while lymph-vascular invasion, stage, and nodal status trended toward, but failed to reach, statistical significance. Worse behavior in younger patients combined with female predilection and ovarian-affinity raise the possibility of hormone-assisted tumor progression. In conclusion, 'adenocarcinoma ex-goblet cell carcinoid' is an appendix-specific, high-grade malignant neoplasm with distinctive morphology that is

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recognizable at metastatic sites and recapitulates crypt cells (appendiceal crypt cell adenocarcinoma). Unlike intestinal-type adenocarcinoma, it occurs predominantly in women, is disguised as gynecologic malignancy, and spreads along peritoneal surfaces with only rare hematogenous metastasis. It appears to be significantly more aggressive than appendiceal mucinous neoplasms.
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Goblet cell carcinoid is a rare and distinctive appendiceal neoplasm that accounts for $<5\%$ of all appendiceal tumors and has peculiar morphologic characteristics. It is believed to be a chimeric tumor with amphicrine lineage and shows both glandular/mucinous and neuroendocrine differentiation (albeit limited).[1–4] To emphasize its glandular nature numerous names have been ascribed to it, including adenocarcinoid, mucinous-carcinoid, microglandular goblet cell carcinoma, composite goblet cell carcinoid-adenocarcinoma, and (perhaps the most morphologically descriptive), crypt cell adenocarcinoma.[4–9] Despite having some glandular differentiation, it has been shown that once the classical, well-differentiated appendix-confined examples are removed by appendectomy, they are reportedly curable, placing them closer to well-differentiated neuroendocrine neoplasms (carcinoids), at least in behavior.[10–12]

It has recently been recognized that these tumors may also transform into, or be associated with, other high-grade, non-goblet cell carcinoid-adenocarcinoma patterns.[3,10–13] For such cases, gastrointestinal pathology experts Tang and Klimstra *et al*[3] proposed the name adenocarcinoma ex-goblet cell carcinoid in their analysis, whereas Taggart *et al*[14] used the term 'mixed goblet cell carcinoid-adenocarcinoma'. Meanwhile, gynecologic pathologists and oncologists see a somewhat different facet of this tumor, which often manifests as gynecologic tract metastases. Hristov *et al*[15] documented their experience with these tumors in gynecologic pathology practice at Johns Hopkins and Massachusetts General Hospitals and highlighted their highly aggressive behavior in the manuscript 'ovarian metastases of appendiceal tumors with goblet cell carcinoid-like and signet ring cell patterns: a report of 30 cases'.

The clinicopathologic characteristics and behavior of these high-grade versions of goblet cell carcinoid termed adenocarcinoma ex-goblet cell carcinoid have not been fully elucidated. In this study, 77 examples of this entity were analyzed and found to have distinctive morphologic characteristics that render them recognizable as appendiceal primaries even at metastatic sites. They were also found to be highly aggressive with a tendency for spread along peritoneal surfaces, and limited hematogenous metastasis. For this entity, the category designation 'appendiceal crypt cell adenocarcinoma' initially proposed by Isaacson and more recently endorsed by Van Eeden *et al*,[6,16] may be more applicable, at least at a conceptual level, as it emphasizes their appendix-specific morphologic repertoire and distinctive biologic behavior compared with that of other carcinoma types and 'carcinoids'.

Materials and methods

The study was conducted in accordance with the Institutional Review Board requirements of each participating institution.

Case Selection

Surgical pathology files of Wayne State University Detroit, MI, USA, and Emory University Hospital, Atlanta, GA, USA as well as the authors' consultation files were reviewed for cases qualifying as adenocarcinoma ex-goblet cell carcinoid as defined by Tang *et al*[3] and also reported as mixed goblet cell adenocarcinoma–by Taggart *et al*,[14] or the ovarian metastatic cases presented by Hristov *et al*.[12,15] Cases of pure goblet cell carcinoid were excluded from analysis. The 77 adenocarcinoma ex-goblet cell carcinoid cases identified accordingly were subjected to detailed clinicopathologic review. Only cases with slides available for histopathologic verification were included in the study.

Evaluation of Clinical Parameters

Demographic data (age and gender), tumor location, tumor spread, and macroscopic findings were extracted from surgical pathology reports and chart review. Follow-up information was obtained through contact with primary physicians or chart review. For some cases, follow-up information was obtained from the Surveillance Epidemiology End Results database.

Histopathological Analysis

All the slides of the cases were re-analyzed by the authors to determine the tumor characteristics. The mean number of slides examined per case was 16 (range 1–80). The distribution of the tumors, the presence or absence of perineural invasion, vascular invasion, lymph node metastasis, and involvement of organs were analyzed. An attempt was also made to classify the cases based on the morphologic 'A, B, C' and '1, 2, 3' categories proposed by Tang *et al*[3] and Taggart *et al*[14] (respectively).

Statistical Analysis

Descriptive data analyses were performed by calculating frequencies and percentages for categorical variables, or measures of central tendency (means or medians) for continuous variables. Survival analyses were performed to examine factors associated with post-diagnosis mortality. We constructed Kaplan–Meier curves with corresponding log-rank tests for statistical significance to examine patient survival according to various demographic and disease-related characteristics. In addition, we used multivariable Cox proportional hazards models and extended Cox models, when the proportional hazards assumption was violated, to examine the association between survival and various factors taken together. Backwards elimination was used to construct the most parsimonious model. Owing to the smaller sample size, variables were retained in the model if their *P*-value was < 0.1. The results of survival analyses were expressed as hazard ratios and reported along with the corresponding 95% confidence intervals. Proportional hazard assumptions were tested by examining log minus log plots for each variable in the model. In addition, all models were examined for interactions and co-linearity among covariates.

Results

Clinical Findings

Of the 77 patients, 57(74%) were females and 20(26%) were males with a F:M ratio of 2.9:1. The median patient age was 55 years (range 25–84). The details of the clinicopathologic findings and surgical procedures performed are summarized in Table 1.

In total, 33/57 (58%) females had disseminated gynecologic tract disease. The appendiceal primary was confirmed histologically in 50 cases. In an additional 10 right hemicolectomy specimens, extensive peritoneal disease was found and the appendiceal fossa was filled entirely with carcinoma leaving no identifiable normal appendiceal tissue.

Histologic Findings

None of the cases were associated with a detectable mucosal adenomatous lesion. The appendiceal wall was diffusely and circumferentially infiltrated by tumor cells extending to the serosal surface, often with relative preservation of the layers of the wall (Figure 1). In 10 patients who presented with disseminated disease and underwent right hemicolectomy, the appendix was entirely replaced by carcinoma.

Upon review of the slides from both the primary and metastatic tumors, it was determined that there were eight histologic patterns that were fairly distinctive and typically occurred in combination. In fact, because the volume of each pattern often varied from section to section and organ to organ within the patients, it was impossible to obtain accurate estimates of their relative proportions, and thus the morphologic 'A, B, C' and '1, 2, 3' categories proposed by Tang *et al*[3] and Taggart *et al*[14] (respectively) could not be reliably obtained in this cohort in which most cases had widely disseminated tumors.

Table 1 Clinicopathologic characteristics in patients ($n = 77$)

Characteristic	N	%
Sex		
Female	57	74
Male	20	26
Median age, years (range)	55 (29–84)	
Type of surgical procedure		
Appendectomy	27	35
Appendectomy only	11	41
Appendectomy +/− omentectomy, salpingo-oophorectomy and/or total abdominal hysterectomy	16	59
Colon resection	35	46
Right hemicolectomy +/− omentectomy, salpingo-oophorectomy and/or total abdominal hysterectomy	34	97
Sigmoid colectomy	1	3
Small bowel resection	1	1
Primary salpingo-oophorectomy[a]	3	5
Ovarian biopsy	2	4
Liver biopsy	1	1
Falciform ligament biopsy	1	1
Pathologic findings		
Lymph-vascular invasion	30	39
Perineural invasion	19	25
Carcinomatosis	59	77
Gynecologic tract involvement	33/57	58
pT		
T2	1	1
T3	17	22
T4	48	63
Tx	10	13
pN		
N0	13	27
N1/2	36	73
pM		
M0	23	30
M1a	12	16
M1b	34	44
Mx	6	8
Liver metastasis	3	4
Lung metastasis	1	1
Final stage		
I	0	0
II (T3-4b, N0, M0)[21]	19	28
III (Any T, N1-2, M0)[21]	5	7
IV (Any T, N0-2, M1a/b)[21]	45	65
Unknown	8	10
Overall survival, median months (range)	38 (2–45)	

+/−, plus or minus.
[a]These patients had a preoperative suspicion of ovarian carcinoma.

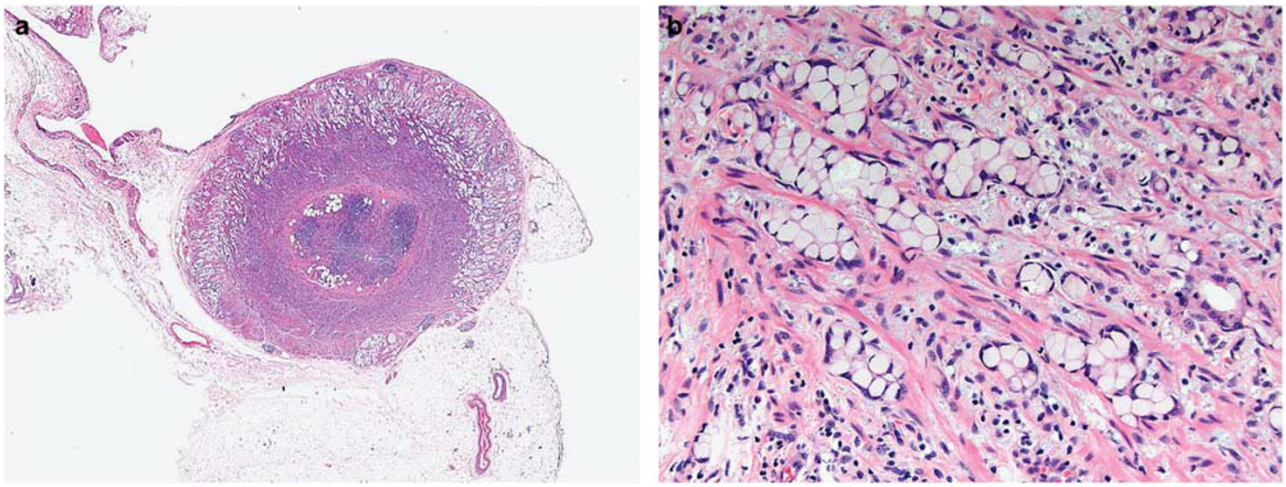

Figure 1 (**a**) Cross-section of appendix showing concentric mural infiltration by tumor with preservation of the layers of the appendiceal wall. (**b**) 'Conventional goblet cell carcinoid/crypt cell pattern' is characterized by small round collections of goblet cells with acinar configuration, closely resembling colonic crypts, but lacking distinct lumina.

Although these histologic patterns were not found to have any specific clinical associations, at the same time they had distinctive characteristics that allowed their diagnosis even at metastatic sites and their differentiation from other appendiceal and abdominal cancer types:

(I) Conventional goblet cell carcinoid/ crypt pattern. All cases had at least some foci of this pattern (by definition), which was characterized by small round collections of goblet cells in an acinar configuration, closely resembling colonic crypts, but typically without overt lumen formation, and composed only of goblet cells (Figure 1).

(II) Poorly cohesive goblet cell pattern. Goblet-type cells in non-glandular, diffusely infiltrative pattern akin to 'poorly cohesive cell' carcinomas as defined by 2010-World Health Organization;[17] ie, forming chains or individual goblet-type cells lying independently in the stroma without overt gland formation or accompanying mucin (Figure 2). These were somewhat similar to other signet ring carcinomas of the gastrointestinal tract, but were distinguishable by their voluminous cytoplasm and basophilic mucin unlike the pale, acidophilic (foveolar-like) mucin more commonly seen in gastric signet ring cell carcinomas (Figure 2). Invariably, this poorly cohesive cell pattern transitioned to more clustered versions of similar cells with small collections representing abortive forms of ordinary goblet cell carcinoid/crypt pattern.

(III) Poorly cohesive non-mucinous cell pattern. Non-mucinous cells with hyperchromatic nuclei growing in a diffusely infiltrative (poorly cohesive cell) pattern dissecting through normal structures in a manner similar to that of poorly cohesive gastric carcinomas,[18] mammary lobular carcinomas,[19] or plasmacytoid urothelial carcinomas[20] (Figure 2). In isolation, these were indistinguishable from the aforementioned carcinoma subtypes, but cases with this pattern had other patterns admixed.

(IV) Microglandular pattern without goblet cells was characterized by relatively small, round rosette-like tubules lined by well-polarized, cuboidal-columnar nuclei (Figure 2). These could be distinguished from tubular-intestinal-type adenocarcinomas by the roundness and smaller size of tubules, lack of branching interconnecting glands and absence of luminal necrosis. Tubule rigidity was characteristic.

(V) Mixed component of other non-specific carcinoma types: ordinary intestinal pattern or extracellular stromal mucin deposition. Ordinary intestinal pattern was very uncommon, and typically a very small component of the tumor and transitioned into microglandular pattern that is more specific of goblet cell carcinoid. Areas with profuse stromal mucin production predominated in some cases, but invariably these mucinous areas had some foci with distinctive small tubule-like goblet cell clusters with hints of goblet cell carcinoid-type crypts floating within the mucin (Figure 3). Of note, this distinctive clustering allowed us to suggest the diagnosis of this entity in metastatic foci and small biopsies and was confirmed on resection.

(VI) Goblet cell carcinoid pattern with high-grade cytomorphology (Figure 2) was characterized by ill-defined small acini or typical goblet cell carcinoid clusters but with marked nuclear atypia consisting of enlarged, round, and pleomorphic nuclei, in contrast with the ordinary goblet cell carcinoid pattern (crypts) in which the nuclei are compressed at the periphery.

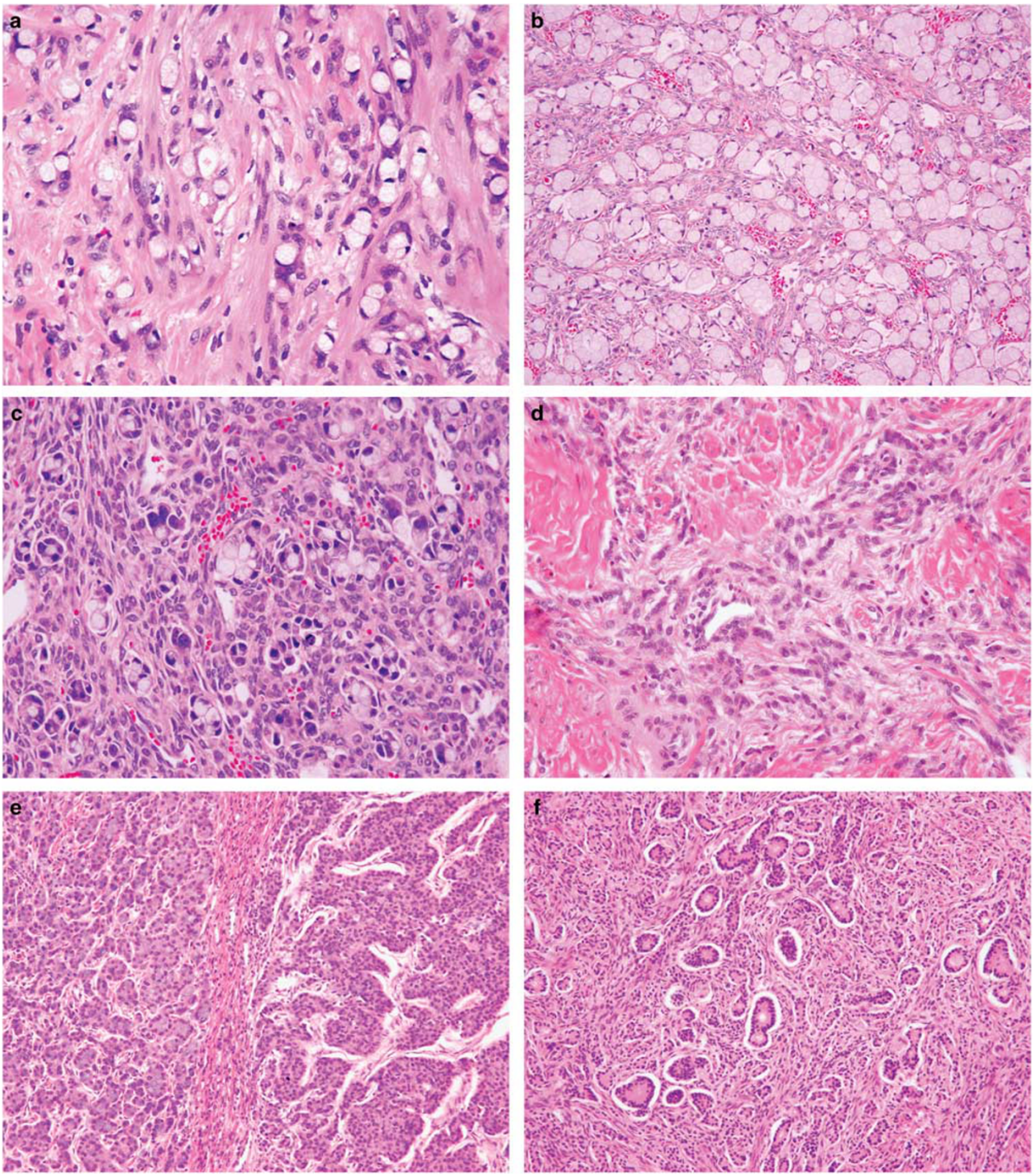

Figure 2 Images are from two patients (**a–c** (one patient) and **d–f** (another patient)), each with multiple tumor patterns. (**a**) 'Poorly cohesive goblet cell pattern' with non-gland forming, diffusely infiltrative pattern of stromal invasion by goblet-type cells in a manner akin to 'poorly cohesive cell' carcinoma. (**b**) These tumor cells have voluminous cytoplasm containing more basophilic mucin unlike the pale, acidophilic (foveolar-like) mucin more frequently seen in gastric signet ring cell carcinoma. (**c**) Within the same patient tumor cells showed a 'Goblet cell carcinoid pattern with high-grade morphology' characterized by ill-defined acini with marked nuclear enlargement, pleomorphism and hyperchromasia. (**d**) 'Poorly cohesive non-mucinous cell pattern' is composed of small, non-mucinous cells distributed as thin, diffusely infiltrative cords. (**e**) Note the focus of 'ordinary carcinoid-like pattern (well-differentiated neuroendocrine tumor)' with nested/trabecular growth on the right and the more solid goblet cell carcinoid tumor clusters with isolated goblet cells on the left. (**f**) The same tumor (shown in **d** and **e**) also showed a 'microglandular pattern' composed of polarized cuboidal-columnar cells forming small, punched-out, rosette-like tubules with interspersed goblet-type cells.

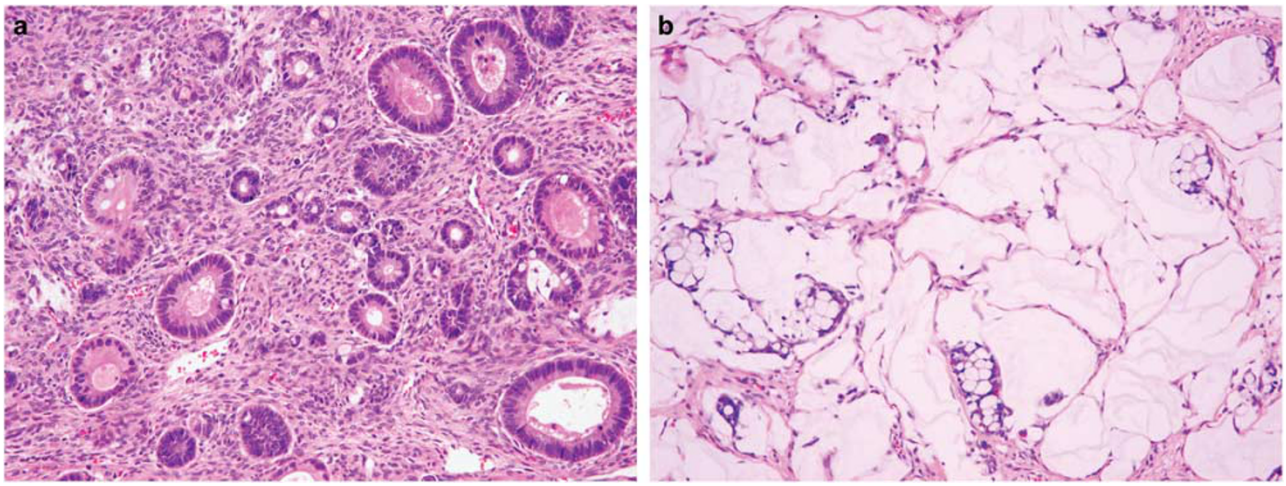

Figure 3 (**a**) 'Microglandular pattern' composed of tumor cells dispersed as punched-out rosette-like tubules with rigid luminal borders and lined by polarized cuboidal-columnar cells. Single goblet-type tumor cells are interspersed between tubules. (**b**) Mixed mucinous type carcinoma pattern' with abundant stromal mucin containing small clusters of floating goblet cell carcinoid-type crypts within it.

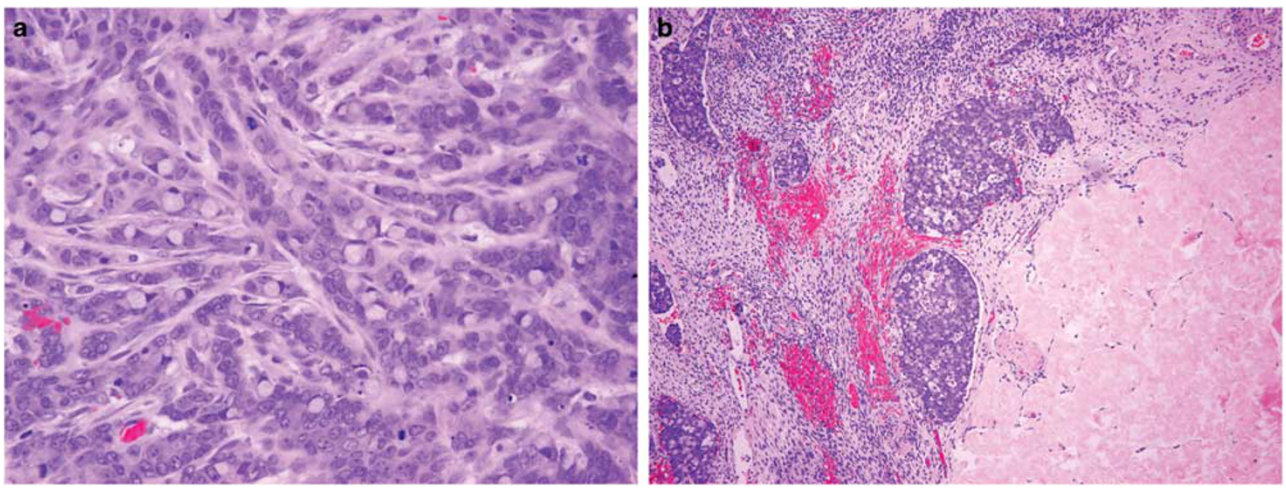

Figure 4 (**a**) 'Solid sheet-like growth pattern' is characterized by islands and cords of mitotically active tumor cells with high nuclear to cytoplasmic ratio, scant mucin, and interspersed singly distributed signet ring-like goblet cells. (**b**) Metastatic tumor deposits were seen in ovarian stroma and lymphatic spaces adjacent to a corpus albicans within the same patient.

These also often had more irregular and stretched tubular architecture and displayed transitions to more poorly cohesive cell patterns.

(VII) Ordinary 'carcinoid-like' pattern (well-differentiated neuroendocrine tumor) characterized by nested/trabecular growth was noted in only 1 case (Figure 2).

(VIII) Solid sheet-like growth pattern, often punctuated by goblet cells or microglandular units (Figure 4).

None of the cases had a pure histologic pattern and in any given case there was a mixture of at least two or more of these patterns. The proportion of these patterns within each tumor and its corresponding metastatic foci was also found to be highly variable and in most instances, a mixture of patterns was observed within a given organ (Figure 2 illustrates the combination of these patterns in two different cases). In some cases, for example, although the ovary showed a solid sheet-like pattern (Figure 4), there was a poorly cohesive non-signet ring pattern in the uterus of the same case, and this was a very common occurrence.

Fifty-nine (59) patients had disseminated transcoelomic abdominal disease involving serosal and/or peritoneal surfaces ($n=16$), omentum ($n=10$), and/or gynecologic tract (including ovaries ($n=30$; 24 (31%) of which were bilateral and 6 (8%) unilateral), uterus ($n=1$), vagina ($n=1$), and cervix ($n=1$)). Lymph-vascular invasion was present in 30/77 (39%) and extensive in 6 (8%). Perineural invasion

Table 2 Survival in our cohort compared with others in the literature

Study cohort (n = *77*)		*Tang et al*[3] (n = *33*)		*Hristov et al*[15]	*Taggert et al*[14] (n = *74*)		
		Group B	*Group C*	(n = *30*)	*Group 1*	*Group 2*	*Group 3*
Total *N*	63	26	7	25	23	27	24
Dead *N* (%)	33 (52)	7 (27)	6 (86)	17 (68)			
Alive *N* (%)	30 (48%)	19 (73)	1 (14)	8 (32)			
Median survival (mths)	38						
Mean survival (mths)		43 ± 6	31 ± 6	19	83.8	60.6	45.6
1 year (%)	87			63			
3 year (%)	55	85	17	34 (2-year survival)			
5 year (%)	32	36	0	0			

[3]Group B, adenocarcinoma ex-goblet cell carcinoid, signet ring cell type; Group C, adenocarcinoma ex-goblet cell carcinoid, poorly differentiated carcinoma type; [14]Group 1, goblet cell carcinoid tumor with $<25\%$ adenocarcinoma; Group 2, goblet cell carcinoid tumor with 25–50% adenocarcinoma; Group 3, goblet cell carcinoid tumor with $>50\%$ adenocarcinoma; N, number; Mths, months.

was present in 19/77 (25%) cases and was extensive in 5 (7%).

Tumor Stage

By 2010-World Health Organization and American Joint Committee on Cancer guidelines[10,21] 48/77 (63%) tumors were pathologic T4 (T4a (penetrating visceral peritoneum), $n=12$ and T4b (directly invading other organs/structures), $n=36$);[21] 17/77 (22%) were T3, 1/77 (1%) was T2 and 10/77 (13%) were Tx. Of the 49 patients with lymph node sampling, lymph node metastasis was found in 36/49 (73%) patients, whereas 13/49 (27%) had negative lymph nodes; 46/77 (60%) tumors were metastatic (M1a (peritoneal) = 12; M1b (parenchymal/organ) = 34), 23/77 (30%) tumors had no metastasis and the 'M' status was unknown in 6 (8%) tumors; 59 tumors (77%) displayed abdominal/pelvic carcinomatosis with regional spread to serosal surfaces and peritoneum either at the time of diagnosis or shortly thereafter. Interestingly 58% (33/57) of females had gynecologic tract involvement by disease. However, visceral metastases to organs other than the gynecologic tract and peritoneum were only rarely seen and involved the liver ($n=3$), lung ($n=1$), and other unusual sites such as gallbladder (subserosal involvement) and pericardium, (one case each). Even in cases with liver involvement, in 2/3 cases the tumors appeared to be more capsular rather than forming a distinct intra-parenchymal mass. Of the 69 patients with pathologic staging the overall clinical stage distribution was: 65% stage IV, 7% stage III and 28% stage II disease at diagnosis. Despite the frequency of widely metastatic stage IV disease (any T, N0-2, M1a/b), lymph node metastases were relatively low, hence there were more stage II (T3-4b, N0, M0) than stage III (any T, N1-2, M0) patients.[21]

The clinicopathologic findings are summarized in Table 1.

Follow-Up Information

Follow-up data were available for 63/77 (82%) patients for whom no standard therapy was employed. As these patients were retrospectively identified, and this entity is still not fully characterized or recognized, they had been diagnosed and treated differently. On the other hand there did not appear to be any treatment bias generated by the pathology report or patient characteristics.

Of the 63 patients with survival data 30 (48%) were alive and 33 (52%) were dead at last follow-up. Follow-up information could not be obtained for the remainder of the study cohort. Fifty-seven of 63 patients (91% of those with follow-up) had active disease at last follow-up. All 33 deaths (33/63) were cancer-related at a median of 23 months (6–79 months), 3 of them peri-operative (within 3 months of surgery). Thirty (30) patients were alive at last follow-up (median follow-up 18 months (1–154 months)) and 24 of these were alive with disease and six without. The median overall survival was 38 months (range: 2–45 months) with 1-, 3- and 5-year survival rates of 87%, 55%, and 32%, respectively (Table 2).

Correlation of Clinicopathologic Characteristics with Survival

The initial multivariate model included age, sex, tumor stage, extent of lymph node involvement, presence of metastasis, lymph-vascular invasion, and perineural invasion. The final model (Table 3) included the following variables that remained associated with survival: (1) age ≥ 55 versus <55 (hazard ratio = 0.06, $P<0.01$, 95% confidence interval: 0.02–0.25), (2) extent of lymph node metastasis, highest level of metastasis (pN2) versus none (pN0), (hazard ratio = 3.49, $P=0.06$, 95% confidence interval: 0.93–13.06), (3) presence of lymph-vascular invasion (at ≤ 25 months: hazard ratio = 0.29, $P=0.06$, 95% confidence interval: 0.08–1.07,

and at >25 months: hazard ratio = 5.53, $P = 0.06$, 95% confidence interval: 0.94–32.57) and (4) presence of perineural invasion (hazard ratio = 0.12, $P = 0.01$, 95% confidence interval: 0.02–0.63) (Table 3). Age ($P < 0.01$) and perineural invasion ($P = 0.01$) were found to be independent, statistically significant prognostic factors. The age difference was no longer evident by 70 months of follow-up. Although female gender was associated with lower survival on univariate analysis this association was no longer statistically significant on multivariate analysis (Figure 5).

Table 3 Multivariate analysis of clinicopathologic factors affecting overall survival

Characteristic	*Hazard ratio*	*95% Confidence interval*	P-*value*
Age			
≥55	0.063	0.02–0.25	<0.01
<55	ref.		
pN			
0	ref.		
1	1.96	0.53–7.30	0.32
2	3.49	0.93–13.06	0.06
Lymph-vascular invasion			
≤25 months			
Yes	0.29	0.08–1.07	0.06
No	ref.		
>25 months			
Yes	5.53	0.94–32.57	0.06
No	ref.		
Perineural invasion			
Yes	0.12	0.02–0.63	0.01
No	ref.		

Abbreviations: pN, pathologic nodal status; ref. reference group.

Discussion

This study elucidates that the high-grade version of the enigmatic entity goblet cell carcinoid is a distinctive tumor with fairly specific (albeit subtle) morphologic features unique to the appendix, and has a variety of distinguishing clinicopathologic characteristics.

Specific Morphologic Characteristics Allow its Recognition as an Appendiceal Primary Even at Metastatic Sites

It has been shown in the literature that the characteristic histology that defines ordinary goblet cell carcinoid is seldom, if ever, displayed by tumors arising in any other organ. These include the formation of small round uniform glandular units composed of goblet cells that closely mimic small colonic crypts, with extremely well-polarized and often compressed peripheral nuclei.

Our study illustrates that the dedifferentiated or high-grade version of goblet cell carcinoid (adenocarcinoma ex-goblet cell carcinoid) also has fairly specific, trademark histologic characteristics, albeit with much more versatility in its morphologic repertoire than its low-grade or well-differentiated counterpart. In addition to the ordinary goblet cell carcinoid/crypt pattern these dedifferentiated examples are characteristically less organized and contain irregular and cytologically high-grade crypt cell patterns. There are also patterns other than ordinary goblet cell carcinoid. For example, in many cases, there are diffusely infiltrative patterns with signet ring-like cells similar to other poorly cohesive gastrointestinal carcinomas, but in most of these the cells exhibit a more 'goblet cell' morphology, with

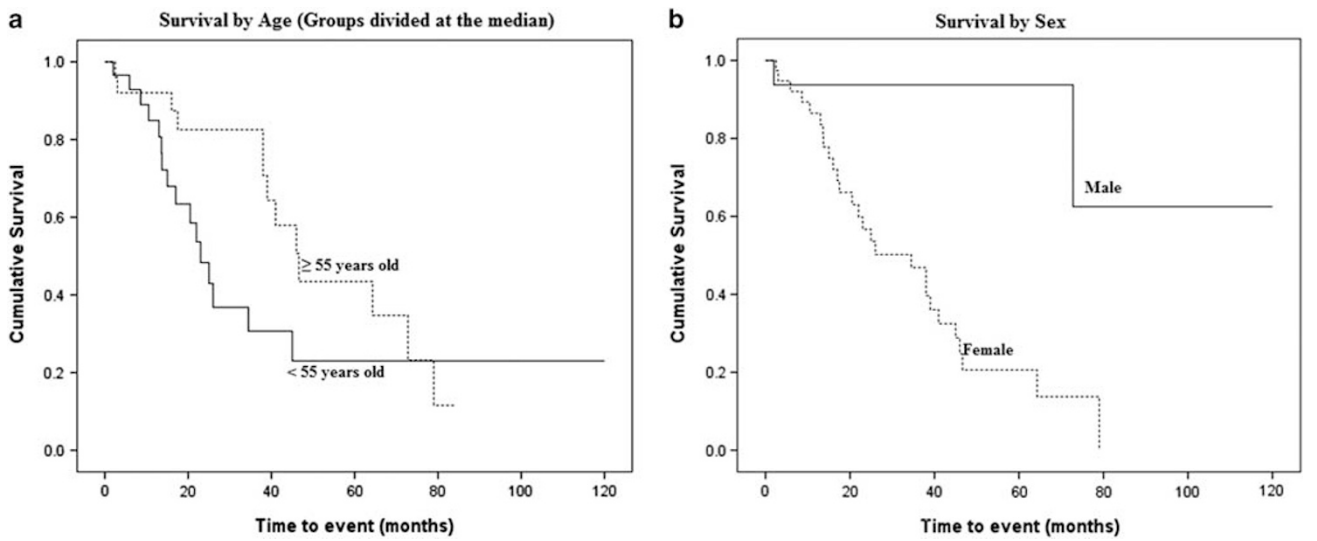

Figure 5 Kaplan–Meier survival curves show that patients <55 years of age (**a**) and women (**b**) had lower survival than their respective counterparts. However, the gender difference was no longer statistically significant after controlling for other variables, and the age difference was no longer evident by 70 months of follow-up.

voluminous basophilic cytoplasm instead of the more acidophilic/foveolar morphology that typifies gastric examples. Furthermore, the frequent abortive crypt-like clustering allows their recognition as appendiceal primaries. Similarly, some cases exhibit a tubular pattern of non-mucinous cells that may be mistaken for other tubular-type carcinomas of the gastrointestinal tract; however, these tubules are more distinctive because of their relatively round, non-complex, rosette-like architecture, and rigid luminal borders. Occasionally, other carcinoma types such as 'intestinal' may be admixed, but this is rare, and when present, they often transition to the more microglandular or rosette-like pattern of dedifferentiated goblet cell carcinoid. Similarly, some cases have excessive stromal mucin production, but typically, even within these mucinous areas the goblet cell cytology and abortive small crypts are a give-away to their true 'appendiceal' nature. The frequent mixing of a variety of morphologic patterns is also helpful in diagnosis.

Of note, over the years, as we have gained experience with these distinctive histologic patterns in our practice we were often able to suggest appendiceal origin in peritoneal and ovarian metastases that showed this morphology. In fact, in many cases the metastatic tumors had developed more atypical foci that were composed of patterns diverging from those of the primary. However, they were nonetheless still recognizable as adenocarcinoma ex-goblet cell carcinoid. In their 2007 paper examining the ovarian metastases of these tumors, Hristov *et al*[15] also emphasized this phenomenon.

Observations Pertinent to the Category Designation

These recurring histologic patterns with overt glandular differentiation were seen in all 77 cases and support the notion that these tumors are indeed adenocarcinomas (adenocarcinoma ex-goblet cell carcinoids) as proposed by Tang *et al*,[3] and not high-grade neuroendocrine carcinomas. The paucity and focality of chromogranin A and other neuroendocrine markers immunohistochemically also supports this impression.[3,12,14,15] Moreover, in most of the patterns displayed by these adenocarcinomas there appears to be an attempt to recapitulate appendiceal crypt cells as evidenced by their propensity for goblet cell production (often different than ordinary 'signet ring cells') and the distinctive microglandular pattern, supporting the concept of 'crypt cell adenocarcinomas' as initially suggested by Isaacson[6] and recently by van Eeden.[16]

This name also assigns an identity to this tumor that distinguishes it from other 'adenocarcinoma' types arising from this organ (such as mucinous carcinomas or the occasional ordinary tubular-type adenocarcinomas) as well as from non-appendiceal signet ring cell and tubule-forming adenocarcinomas (such as intestinal or pancreatobiliary). Essentially it establishes it as an 'appendiceal-type' adenocarcinoma with its own trademark histologic characteristics.

Regardless of name, this study as well as others[3,14,15] demonstrates that once the morphologic characteristics of this tumor are widely recognized by pathologists, they will be accurately diagnosed as appendiceal in origin, and can be distinguished from other carcinomas perhaps even more easily than other gastrointestinal, pancreatobiliary or mullerian type carcinomas.

Clinicopathologic Characteristics

In addition to their trademark histomorphology, these tumors also have important clinical associations. As with ordinary goblet cell carcinoids, there is a strong predilection for females (accounting for 74% of our cohort) with a F:M ratio of almost 3:1. This female preponderance has also been noted by others.[3,22] Although Warkel *et al*[7] in a study of ordinary goblet cell carcinoids at the Armed Forces Institute of Pathology found a 2:1 male predominance, they attributed this to predominant enlistment of males in the military. Hristov's study not only highlighted the gynecologic pathologists' perspective on these high-grade examples (hence their exclusive female cohort) but it also demonstrates another intriguing aspect of this tumor, and that is its propensity for transcoelomic pelvic dissemination and gynecologic tract involvement,[14,15,22] which is similar to our findings with 58% of the cases showing gynecologic tract involvement, sometimes as the first sign of disease.

Whether this tumor's female predilection, relatively young patient age (mean 55 years, almost a decade younger than that of most typical organ cancers) and propensity for ovarian involvement signify any potential link to a hormonal etiology/pathogenetic role in their development and/or progression is uncertain.[3,14,15,23] It is noteworthy that females (on univariate analysis) and patients < 55 years (on all analyses) appeared to have more aggressive disease. In general, younger patients with common organ cancers usually have a better prognosis except for hormone-driven organs like breast and prostate, in which a subset of younger patients have a more biologically aggressive form of disease. Of course this is all speculative and needs to be further investigated and verified with hormone receptor and other mechanistic studies.

This tumor also shows distinctive behavioral characteristics from other gastrointestinal tract adenocarcinomas. First, it is significantly more aggressive than ordinary carcinoid (well-differentiated neuroendocrine tumors). On the other hand, unlike intestinal-type adenocarcinoma, it is often (84%) transmural (T3/4) at diagnosis, has no associated *in situ* or adenomatous component, frequently spreads in a transcoelomic fashion sometimes bypassing local lymph

nodes, and seems to have conspicuous disinterest in hematogenous metastasis to liver and lungs, despite being widely disseminated on the abdominal surfaces. In this regard (in its pattern of spread) it is similar to appendiceal mucinous neoplasms; however, its behavior is significantly more aggressive than low-grade appendiceal mucinous neoplasms (of the so-called disseminated peritoneal adenomucinosis type) but is comparable to that of high-grade appendiceal mucinous adenocarcinoma that produces 'peritoneal mucinous carcinomatosis'.[24,25]

Because almost half the patients with goblet cell carcinoid-related tumors have residual disease on right colectomy, most authors recommend a right hemicolectomy even for ordinary goblet cell carcinoid,[14] which would be even more applicable to this high-grade, mixed, adenocarcinoma ex version of goblet cell carcinoid. The proclivity for peritoneal spread and recurrence in pelvic organs (including the gynecologic tract) raises the additional issue of management after cytoreductive surgery.[23,26] Although hemicolectomy with adequate surgical margins is an established goal,[3,14] patients would benefit from peritoneal and omental exploration, perhaps even with prophylactic salpingo-oophorectomy and hysterectomy in post-menopausal women.[12,23,27] Additional hyperthermic intraperitoneal chemotherapy in a manner similar to appendiceal mucinous neoplasms[28,29] warrants further exploration as it has been linked to improved survival when compared with systemic chemotherapy.[26] The paucity of hematogenous metastasis (to organs such as liver) provides an additional argument for this approach.

Prognosis

For ordinary goblet cell carcinoids as well as adenocarcinoma ex-goblet cell carcinoid (or 'mixed adenocarcinoma-goblet cell carcinoid') several predictable poor prognostic features have been identified including lymph node metastases, margin positivity, increased mitotic activity (>2/10 high power fields), extra-appendiceal spread and a large ($>50\%$) component of adenocarcinoma.[4,12] However, most of these studies were mainly focused on appendectomy specimens reviewed by gastrointestinal pathology experts.[3,14] Assessment of the amount of 'adenocarcinoma' component[12,14] or the extent of the different patterns of adenocarcinoma[3] have also been investigated as potential prognosticators in survival (Table 2).[3,12,14] In our cohort that consisted of a large number of high-stage and disseminated cases (77%) we have been unable to confidently utilize these criteria because most of our tumors showed an exuberant mixture of various histologic patterns not only within a given case, but varying greatly from slide to slide and organ to organ, making it impossible for us to apply these proposed classification schemes[3,14] (Figure 2). In fact, in 10 of our cases, the appendix itself was entirely replaced by cancer. This morphologic variability as well as the heterogeneity that occurs in more advanced forms of this entity was also noted by Hristov *et al* in their study focusing on gynecologic metastasis of these tumors.

Among potential prognosticators in our cohort, we found that younger age (<55 years) and perineural invasion correlated significantly with survival on multivariate analysis. Extent of nodal involvement and lymph-vascular invasion were also associated with survival in univariate analysis although they did not reach statistical significance in multivariate analysis. Interestingly, although not statistically significant, the majority of patients (65%) also had stage IV disease making their overall prognosis dismal, irrespective of tumor volume, even when tumors appeared more localized.

Summary

This study demonstrates that adenocarcinoma ex-goblet cell carcinoid, the high-grade (dedifferentiated) version of appendiceal goblet cell carcinoids, is a carcinoma with a spectrum of morphologic patterns and subtle but trademark histologic features that make it recognizable as 'appendiceal type,' even at metastatic sites and in small specimens. For this entity, which has been studied under a plethora of names including 'mixed goblet cell carcinoid-adenocarcinoma' and 'appendiceal tumors with goblet cell carcinoid-like and signet ring cell patterns', the category designation of adenocarcinoma ex-goblet cell carcinoid or 'appendiceal crypt cell adenocarcinoma' may be more appropriate. These highly aggressive tumors are seen predominantly in females in their early to mid-fifties, have a predilection for transcoelomic dissemination with frequent gynecologic tract involvement, while seldom showing hepatic metastasis, and have a median survival of only 38 months.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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