Annals of Diagnostic Pathology 43 (2019) 151401

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

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

Goblet cell tumors of the appendix: A review

Sara A.J. Sinno, Nawaf M.H. Jurdi*

Department of Pathology and Laboratory Medicine, American University of Beirut Medical Center, Beirut, Lebanon

ARTICLE INFO

Keywords:
Appendix
Goblet cell carcinoid
Adenocarcinoma ex-goblet cell carcinoid
Mixed adenoneuroendocrine carcinoma
Crypt cell adenocarcinoma
Goblet cell adenocarcinoma

ABSTRACT

Goblet cell tumors are rare tumors of the appendix that exhibit both neuroendocrine and mucinous differentiation. This dual differentiation has led to a controversy regarding the proper classification of these neoplasms as to whether they should be considered neuroendocrine tumors or adenocarcinomas. Multiple grading systems have been proposed that were able to segregate these tumors into prognostically significant groups. Many of these grading systems rely on identifying and/or quantifying the carcinomatous growth pattern. Goblet cell tumors show patchy and focal expression of neuroendocrine markers and are characterized by a mutational profile that is different from both appendiceal adenocarcinomas and neuroendocrine tumors. They exhibit a more aggressive behavior than neuroendocrine tumors, and as such, many authors recommend that they be approached and treated as adenocarcinomas.

1. Introduction

Goblet cell tumors are rare and distinctive neoplasms that occur almost exclusively in the appendix. They were first described by Gagné et al. in 1969 [1]. They exhibit both neuroendocrine and mucinous differentiation [2] and are composed predominantly of goblet cells with occasional neuroendocrine cells and Paneth cells [3]. Much controversy exists regarding the proper classification and grading of these neoplasms and to whether they should be considered as neuroendocrine tumors or as adenocarcinomas. This controversy is reflected in the various names that have been used in referring to these tumors, including: goblet cell carcinoid, adenocarcinoid, crypt cell carcinoma, mucinous carcinoid, microglandular goblet cell carcinoma, mixed carcinoid-adenocarcinoma, mixed adenoneuroendocrine carcinoma, and adenocarcinoma ex-goblet cell carcinoid [3-5]. The proper characterization of these tumors has important clinical significance in predicting prognosis and in guiding clinical management.

2. Clinical features and gross pathology

Goblet cell tumors occur in adults. The patients range from 18 to 89 years of age with a reported mean age in the fifth to sixth decades [3,5-8]. The tumors occur in roughly equal percentages between men and women [3,8,9]. One study, however, reported a slight female predominance with a male to female ratio of 1:2.2 [7]. Presenting symptoms vary and include symptoms suggestive of acute appendicitis, acute or chronic abdominal pain, abdominal mass or fullness, or the tumor may be discovered incidentally [3,5,7]. Female patients with advanced disease stage may present with ovarian masses leading to a preoperative diagnosis of a primary ovarian neoplasm [7].

Gross examination of the appendix does not reveal a distinct mass in many of the cases [7]. A mass was seen in only 28% of the cases in one study [5]. Goblet cell tumors usually cause thickening of the appendiceal wall by involving it circumferentially and may extend longitudinally along the length of the appendix [7]. The greatest tumor dimension, thus, may be determined by measuring the length of extension of the tumor along the appendix and is estimated to be > 2 cm in the majority of the cases [7].

3. Histopathology

Goblet cell tumors characteristically do not involve the appendiceal mucosa, except in areas where the tumor nests are connected to the base of the crypts [10]. The mucosa does not exhibit adenomatous or dysplastic changes or changes suggestive of a mucinous cystic neoplasm [7].

Many classification systems have been proposed in order to stratify goblet cell neoplasms into prognostically relevant groups. In 1990, Burke et al. proposed a grading system based on the amount of associated carcinoma [4]. Carcinomatous growth was defined as having fused or cribriform glands, diffusely infiltrating signet ring cells, tumor cells arranged in a single-file pattern, or in solid sheets [4]. Tumors that

* Corresponding author at: American University of Beirut Medical Center, Department of Pathology and Laboratory Medicine, Cairo Street, 3rd floor, Beirut, Lebanon.
E-mail address: nj14@aub.edu.lb (N.M.H. Jurdi).

https://doi.org/10.1016/j.anndiagpath.2019.151401

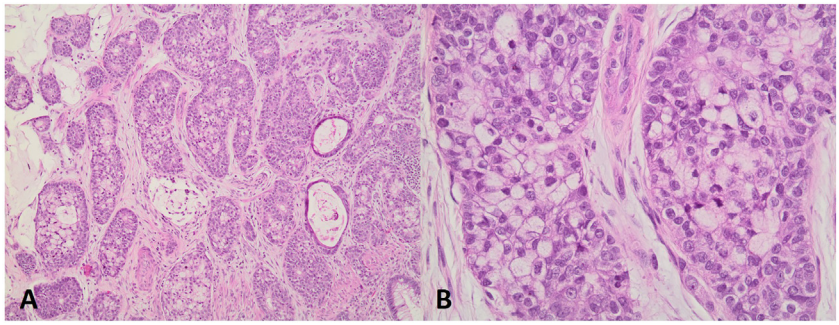

Fig. 1. Goblet cell carcinoid. A. The tumor cells are arranged in cohesive clusters. Pools of extracellular mucin are noted (left side) (original magnification ×100). B. The tumor cells have low grade cytologic features and contain intracellular mucin vacuoles (original magnification ×400).

contained < 25% carcinomatous growth were classified as goblet cell carcinoids, while those that had > 50% carcinomatous growth had a worse prognosis and were classified as mixed carcinoid-adenocarcinoma [4].

In 2008, Tang et al. classified goblet cell tumors based on the type of the carcinomatous component [7]. As such, the tumors were grouped into three categories: typical goblet cell carcinoid (group A), adenocarcinoma ex goblet cell carcinoid, signet ring cell type (group B), and adenocarcinoma ex goblet cell carcinoid, poorly differentiated carcinoma type (group C). In typical goblet cell carcinoids (group A), the tumor cells are arranged in cohesive groups and clusters (Fig. 1A). This clustering arrangement is maintained as the tumor invades through the muscularis propria into adipose tissue in higher stage examples. The tumor cells have bland cytologic features and contain intracellular mucin vacuoles which cause displacement of the nuclei to the periphery (Fig. 1B). Desmoplasia is minimal to absent and there is minimal architectural distortion of the appendiceal wall. Mitotic activity is rare. Perineural invasion, however, may be prominent. Pools of extracellular mucin can be seen [7]. Adenocarcinoma ex goblet cell carcinoid, signet ring cell type (group B) is characterized by the focal presence of areas of typical goblet cell carcinoid in addition to the adenocarcinoma. The carcinomatous component demonstrates partial or complete loss of the goblet cell clustered architecture and infiltrates the appendix discohesively as single cells or single files. The tumor cells have signet ring cell features with significant cytologic atypia. A desmoplastic stromal reaction is often present [7]. In adenocarcinoma ex goblet cell carcinoid, poorly differentiated adenocarcinoma type (group C), a typical goblet cell carcinoid component is present focally (Fig. 2A). The carcinomatous element may be gland-forming (Fig. 2B) or may form confluent sheets of malignant cells that may have signet ring cell features. It can also have features of a high grade neuroendocrine carcinoma or an undifferentiated carcinoma [7].

The 2010 World Health Organization classification of tumors of the appendix divided goblet cell tumors into two categories: goblet cell carcinoids and mixed adenoneuroendocrine carcinomas which referred to carcinomas arising from preexisting goblet cell carcinoids [10].

In 2015, Lee et al. proposed a two-tier histologic grading system [9]. This grading scheme relies on assessing three histologic features: cytologic atypia, peritumoral stromal desmoplasia, and the presence of a solid growth pattern. Cytologic atypia is defined as having enlarged, hyperchromatic nuclei, with irregular contours. The nuclear to cytoplasmic ratio is increased and there is decrease or loss in intracellular mucin. The atypia must be present in an area that is > 1 mm^2 [9]. Stromal desmoplasia is defined as having dense fibrous connective tissue surrounding the tumor cells and replacing the smooth muscle in the muscularis propria [9]. The solid growth pattern is characterized by tightly packed cells with loss of cell clustering and absent to minimal intervening stroma. It must be present in an area > 1 mm^2 [9]. Each feature is given a score of 1 if present and a score of 0 if absent. Tumors with a total score of 0 or 1 are considered low grade and those with a total score of 2 or 3 are considered high grade [9].

Later, Nonaka et al. regarded that goblet cell tumors, irrespective of their grades, are a distinctive variant of adenocarcinoma and proposed that the term crypt cell adenocarcinoma to be used [5]. The authors grouped the tumors by the percentage of the high grade component: < 40%, 40%–89%, and ≥ 90%. Low grade areas were defined as having organoid nests with rounded smooth contours or a compressed linear appearance when they are in the muscularis propria. The high grade component, on the other hand, is characterized by having irregular nests with loss of the organoid arrangement. It includes branching cords, fused glands, solid sheets, confluent glands, and discohesive single cells [5].

In a similar context, Yozu et al. proposed that goblet cell tumors should be approached as adenocarcinomas and should be graded and staged as such [8]. The authors classified all goblet cell tumors as goblet cell adenocarcinomas and proposed a three-tier grading system that is similar to that set by Burke et al. The grading system relies on quantifying the low grade component within the tumor. Low grade goblet

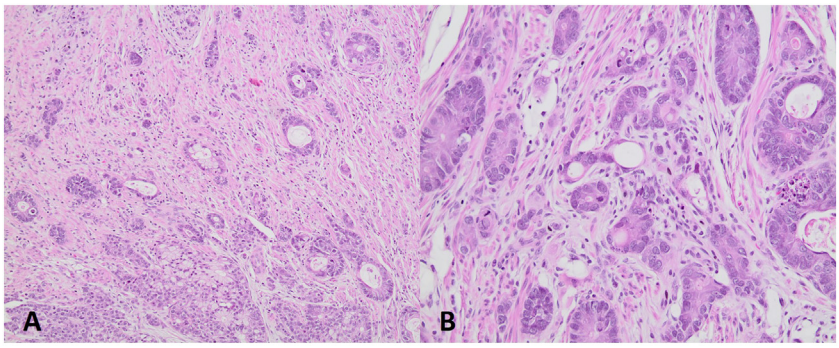

Fig. 2. Adenocarcinoma ex goblet cell carcinoid, group C, according to the Tang classification. A. A goblet cell carcinoid (bottom) is present adjacent to an infiltrative adenocarcinoma (original magnification ×100). B. The adenocarcinoma is gland-forming and is mitotically active (original magnification ×200).

cell adenocarcinomas (grade 1) exhibit > 75% tubular or clustered growth, whereas high grade goblet cell adenocarcinomas (grade 3) show < 50% tubular growth. Tumors exhibiting 50–75% tubular or clustered growth are classified as intermediate grade (grade 2) goblet cell adenocarcinomas. Tubular or clustered growth is defined as the presence of small, discrete, cohesive clusters of tumor cells that include goblet cells, cuboidal glandular cells, and Paneth cells. The clusters may or may not have lumina and may be present within extracellular mucin pools. In low grade goblet cell adenocarcinomas, the tumor cells have low grade cytologic features and low nuclear to cytoplasmic ratio. Mitoses are infrequent. On the other hand, the non-tubular and non-clustered growth patterns seen in high grade goblet cell adenocarcinomas (grade 3) include: single cells, single-files, solid sheets, abortive tubules, and complex anastomosing cords. The tumor cells have high grade cytologic features and a high nuclear to cytoplasmic ratio [8].

4. Ancillary studies

The goblet cells are positive with mucin stains, including mucicarmine, Alcian blue, and PAS after diastase digestion [10,11]. By immunohistochemistry, goblet cell tumors show focal and patchy expression of neuroendocrine markers, synaptophysin and chromogranin [3,7]. In addition, goblet cell tumors show diffuse positivity for CEA, CDX-2, and CAM5.2 [12]. They are characterized by frequent coexpression of CK7 and CK20, with CK20 being positive in almost all cases and CK7 being positive in 70–75% of cases (positivity ranging from focal to diffuse) [12,13]. According to the Tang classification, group C tumors (adenocarcinoma ex goblet cell carcinoid, poorly differentiated carcinoma type) show diffuse positivity for p53 in the adenocarcinoma component, unlike groups A (typical goblet cell carcinoid) and B (adenocarcinoma ex goblet cell carcinoid, signet ring cell type) [7]. Furthermore, group C tumors show loss of mucin glycoprotein (MUC)2 and expression of MUC1, unlike groups A and B which have an opposite expression profile [7]. Ki-67 proliferative index is significantly higher in the adenocarcinoma component in group C tumors (80%) than in groups A and B (11–16%) [7]. All three groups in the Tang classification have normal staining with beta-catenin (membranous), E-cadherin, and Rb [7]. Both goblet cell carcinoids and adenocarcinomas ex-goblet cell carcinoid show absence of microsatellite instability with retained nuclear expression of MLH1, PMS2, MSH2, and MSH6 [14].

5. Pathogenesis

Goblet cell tumors are considered amphicrine tumors, with both exocrine and endocrine characteristics [2]. They are believed to arise from a pluripotent progenitor stem cell located at the base of the intestinal crypt that exhibits divergent dual mucinous and neuroendocrine differentiation [2,15]. Ultrastructural analysis reveals that the tumor cells contain variably-sized mucinous vacuoles and occasional membrane-bound, electron-dense granules present in between the mucinous globules [2]. Unlike neuroendocrine tumors, the electron-dense granules are few and may be difficult to find [2].

Molecular studies reveal that goblet cell tumors are a distinctive type of tumors that is different from neuroendocrine tumors of the appendix and colorectal-type appendiceal adenocarcinomas [14,16]. TP53, KRAS, BRAF, and APC mutations, which are frequently seen in colorectal-type adenocarcinomas, are rare or absent in goblet cell carcinoids and adenocarcinomas ex goblet cell carcinoid [14,16]. Goblet cell carcinoids, also, lack EGFR gene mutations [17]. Goblet cell carcinoids and adenocarcinomas ex goblet cell carcinoid have been shown to harbor similar mutational profiles thereby confirming that the two entities belong to the same category of tumors and that the adenocarcinoma may represent a higher grade transformation of the goblet cell carcinoid [14,16]. Both goblet cell carcinoids and adenocarcinomas ex goblet cell carcinoid show alterations in the Wnt-signaling associated genes (USP9X, NOTCH1, CTNNA1, CTNNB1, TRRAP) [14]. In addition, mutations in chromatin remodeling genes ARID1A and ARID2, CDH1, RHPN2, MLL2, SOX9, and RHOA have been reported to occur in goblet cell tumors [16,18].

6. Differential diagnosis

6.1. Goblet cell tumor versus neuroendocrine tumor

Even though goblet cell tumors share some similarities with neuroendocrine tumors of the appendix, such as exhibiting features of neuroendocrine differentiation, important differences exist between the two tumors. Goblet cell tumors consist, at least focally, of clusters of goblet cells or signet ring-like cells. These cells, while being a defining feature of goblet cell neoplasms, are absent in neuroendocrine tumors. Immunohistochemically, neuroendocrine tumors show diffuse immunoreactivity for the neuroendocrine markers, synaptophysin and chromogranin [7]. Goblet cell tumors, on the other hand, show focal staining with these markers [7]. While goblet cell tumors are positive for CEA and demonstrate frequent coexpression of CK7 and CK20, neuroendocrine tumors are negative for these markers [12,13].

6.2. Goblet cell tumor versus colorectal-type appendiceal adenocarcinoma and signet ring cell carcinoma

Goblet cell tumors may exhibit areas that are morphologically indistinguishable from colorectal-type appendiceal adenocarcinomas or signet ring cell carcinomas. The presence of well-cohesive clusters of goblet cells, at least focally, is a main criterion in distinguishing the two tumors. Moreover, the mucosa in goblet cell tumors does not exhibit adenomatous or dysplastic changes [7]. Immunohistochemically, both colorectal-type appendiceal adenocarcinomas and goblet cell tumors express CK7, CK20, and CDX-2 [10,12,13]. Expression of neuroendocrine markers (synaptophysin and chromogranin) can be of diagnostic utility as they are mostly negative in right-sided colonic adenocarcinomas [12]. At the molecular level, goblet cell tumors lack mutations seen in colorectal-type adenocarcinomas, such as TP53, KRAS, BRAF, and APC gene mutations [14,16].

7. Prognosis and current treatment

Based on the American Joint Committee on Cancer (AJCC) staging system, goblet cell carcinoids are staged according to the criteria for appendiceal adenocarcinomas and not neuroendocrine tumors because their behavior is closer to that of adenocarcinomas [19]. As such, the pT classification is based on the extent of invasion through the appendiceal wall, rather than tumor size which is used in staging neuroendocrine tumors [19].

Goblet cell tumors pursue a more aggressive course than neuroendocrine tumors of the appendix [5]. The most common pattern of spread is direct extension into the right colon and ileum [7]. 20–63% of patients present with metastatic disease [7,9]. Common metastatic sites include the peritoneum and omentum [7]. The ovary is a common metastatic site in women [7]. Lymph node metastases have been detected in 22–38% of cases [7,9]. Metastasis to solid organs, such as the liver, bone, and brain, is uncommon [5].

The various classification systems that have been proposed were able to stratify goblet cell tumors into prognostically significant groups [3-5,7-9]. Higher grade tumors, with a predominant carcinomatous growth, are more likely to present at an advanced stage and exhibit a more aggressive clinical course than lower grade tumors [3-5,7,8]. The overall mean survival for all goblet cell tumors was 43 months in one study [7]. According to the study done by Yozu et al., the 10-year survival rate for low grade, intermediate grade, and high grade tumors was 78%, 33%, and 4% respectively [8].

The management of patients diagnosed with goblet cell tumors on appendectomy specimens is controversial. Some authors, on one hand,

suggest that appendectomy alone is sufficient in cases of localized disease, absence of cecal involvement, and in low grade tumors [20]. Others, on the other hand, recommend that right hemicolectomy to be performed in all patients with goblet cell tumors, in order to ensure absence of residual disease and for accurate disease staging [3,21]. Since the ovaries are a common metastatic site in women, some studies advocate performing prophylactic oophorectomy in postmenopausal women [3]. Patients with advanced tumors are also treated with adjuvant chemotherapy, mainly 5-fluorouracil-based regimens, similar to that used in colorectal adenocarcinomas [21]. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy have been used in cases of peritoneal carcinomatosis [22]. However, the effectiveness of these chemotherapy regimens remains controversial [3].

8. Conclusions

Goblet cell tumors are a distinctive type of appendiceal tumors that exhibit both mucinous and neuroendocrine differentiation. Even though their behavior more closely resembles colorectal adenocarcinomas than neuroendocrine tumors, goblet cell neoplasms are characterized by a mutational profile that is distinct from both tumors. Currently, there is no consensus regarding the appropriate terminology to be used in referring to these tumors and which grading system to adopt. Many authors, however, agree that these tumors should be approached and treated as adenocarcinomas.

Funding

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

References

[1] Gagné F, Fortin P, Dufour V, Delage C. Tumors of the appendix associating histologic features of carcinoid and adenocarcinoma [in French]. Ann Anat Pathol (Paris) 1969;14(4):393–406.
[2] Kanthan R, Saxena A, Kanthan SC. Goblet cell carcinoids of the appendix: immunophenotype and ultrastructural study. Arch Pathol Lab Med 2001;125(3):386–90.
[3] Taggart MW, Abraham SC, Overman MJ, Mansfield PF, Rashid A. Goblet cell carcinoid tumor, mixed goblet cell carcinoid-adenocarcinoma, and adenocarcinoma of the appendix: comparison of clinicopathologic features and prognosis. Arch Pathol Lab Med 2015;139(6):782–90.
[4] Burke AP, Sobin LH, Federspiel BH, Shekitka KM, Helwig EB. Goblet cell carcinoids and related tumors of the vermiform appendix. Am J Clin Pathol 1990;94(1):27–35.
[5] Nonaka D, Papaxoinis G, Lamarca A, Fulford P, Valle J, Chakrabarty B. A study of appendiceal crypt cell adenocarcinoma (so-called goblet cell carcinoid and its related adenocarcinoma). Hum Pathol 2018;72:18–27.
[6] McCusker ME, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973–1998. Cancer 2002;94(12):3307–12.
[7] Tang LH, Shia J, Soslow RA, et al. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. Am J Surg Pathol 2008;32(10):1429–43.
[8] Yozu M, Johncilla ME, Srivastava A, et al. Histologic and outcome study supports reclassifying appendiceal goblet cell carcinoids as goblet cell adenocarcinomas, and grading and staging similarly to colonic adenocarcinomas. Am J Surg Pathol 2018;42(7):898–910.
[9] Lee LH, McConnell YJ, Tsang E, et al. Simplified 2-tier histologic grading system accurately predicts outcomes in goblet cell carcinoid of the appendix. Hum Pathol 2015;46(12):1881–9.
[10] Carr NJ, Sobin LH. Adenocarcinoma of the appendix. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. 4th edvol 3. Lyon, France: IARC Press; 2010. p. 122–5. World Health Organization Classification of Tumours.
[11] Roy P, Chetty R. Goblet cell carcinoid tumors of the appendix: an overview. World J Gastrointest Oncol 2010;2(6):251–8.
[12] van Eeden S, Offerhaus GJ, Hart AA, et al. Goblet cell carcinoid of the appendix: a specific type of carcinoma. Histopathology 2007;51:763–73.
[13] Alsaad KO, Serra S, Schmitt A, Perren A, Chetty R. Cytokeratins 7 and 20 immunoexpression profile in goblet cell and classical carcinoids of appendix. Endocr Pathol 2007;18(1):16–22.
[14] Jesinghaus M, Konukiewitz B, Foersch S, et al. Appendiceal goblet cell carcinoids and adenocarcinomas ex-goblet cell carcinoid are genetically distinct from primary colorectal-type adenocarcinoma of the appendix. Mod Pathol 2018;31(5):829–39.
[15] Isaacson P. Crypt cell carcinoma of the appendix (so-called adenocarcinoid tumor). Am J Surg Pathol 1981;5(3):213–24.
[16] Johncilla M, Stachler M, Misdraji J, et al. Mutational landscape of goblet cell carcinoids and adenocarcinoma ex goblet cell carcinoids of the appendix is distinct from typical carcinoids and colorectal adenocarcinomas. Mod Pathol 2018;31(6):989–96.
[17] Dimmler A, Geddert H, Faller G. EGFR, KRAS, BRAF-mutations and microsatellite instability are absent in goblet cell carcinoids of the appendix. Pathol Res Pract 2014;210(5):274–8.
[18] Wen KW, Grenert JP, Joseph NM, et al. Genomic profile of appendiceal goblet cell carcinoid is distinct compared to appendiceal neuroendocrine tumor and conventional adenocarcinoma. Hum Pathol 2018;77:166–74.
[19] Overman MJ, Asare EA, Compton CC, et al. Appendix–carcinoma. In: Amin MB, Edge SB, Greene FL, editors. AJCC cancer staging manual. 8th edChicago: The American Joint Committee on Cancer and Springer; 2017. p. 237–50.
[20] Varisco B, McAlvin B, Dias J, Franga D. Adenocarcinoid of the appendix: is right hemicolectomy necessary? A meta-analysis of retrospective chart reviews. Am Surg 2004;70(7):593–9.
[21] Pape UF, Perren A, Niederle B, et al. ENETS consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology 2012;95(2):135–56.
[22] McConnell YJ, Mack LA, Gui X, et al. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: an emerging treatment option for advanced goblet cell tumors of the appendix. Ann Surg Oncol 2014;21(6):1975–82.