Neuroendocrine Neoplasms of the Appendix

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According to the latest World Health Organization (WHO) classification [1], the neuroendocrine neoplasms of the appendix showing neuroendocrine differentiation include neuroendocrine tumors (NETs), neuroendocrine carcinomas (NECs), and mixed adenoneuroendocrine carcinomas (MANECs), including goblet cell carcinoids.

Neuroendocrine Tumors (NETs)

Neuroendocrine tumors are the most common primary malignant neoplasms of the appendix and are found in 0.3–0.9 % of patients undergoing appendectomy [2, 3]. Langhans first described a gut carcinoid tumor in 1867 [4]. The term "carcinoid" was introduced by Oberndorfer in 1907 for carcinoma-like lesions of the gastrointestinal tract, which showed a more benign behavior than conventional carcinomas. By definition, "carcinoid" is a neoplasm that arises in the neuroendocrine tissues of the GI tract and lung. Originally, carcinoids were grouped into foregut (respiratory tract, thymus, stomach, duodenum, and pancreas), midgut (small intestine, appendix, and right colon), and hindgut (transverse and descending colon, sigmoid, and rectum) tumors.

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Pathogenesis

In 1928 Masson identified the subepithelial "Kultschitzky" cells as the origin of appendiceal carcinoid tumors and demonstrated their endocrine and neural characteristics [5]. He also proposed that appendiceal carcinoids originated from subepithelial neuroendocrine cells (SNC), whereas other located NETs originated from epithelial neuroendocrine cells (ENC) [5].

Epidemiology

Primary appendiceal neoplasms are uncommon, comprising 0.4–1 % of all gastrointestinal malignancies [6]. In pediatric patients, the rate is 0.08–0.5 % [2, 7]. The overall incidence of carcinoid tumors in surgical specimens has been estimated to 1–2 cases per 1000 appendectomies [4]. Most frequently, the tumor is localized at the tip of the appendix and is diagnosed as an incidental finding in the appendectomy specimens [8]. Less frequently it may be found in the middle or the base. Frequently this tumor occurs in girls aged 12–13 years [4]. The incidence of appendiceal carcinoids peaks between 15 and 19 years of age in female patients and 20 and 29 years in men [9], while malignancies of the appendix are most frequent between the ages of 38 and 49 years [10–12].

Clinical Presentation

Most appendiceal NETs are clinically silent [4, 6]. When symptomatic, the clinical presentation of appendiceal carcinoids is similar to that of acute appendicitis, with intermittent abdominal pain or pain localized in the right lower abdominal quadrant. A carcinoid syndrome in association with a metastatic well-differentiated appendiceal NETs is exceedingly rare [13], except in the presence of widespread liver or retroperitoneal metastases [1, 14].

Diagnosis

Most appendiceal neoplasms are clinically silent [6], and the majority of appendiceal carcinoids are discovered during incidental histologic examination of the appendectomy specimen [15]. Obstruction of the tumor causes symptom of appendicitis, but histopathologic analysis confirms an obstructing factor in only 25 % of cases [16]. Even a symptomatic obstructive NET of an appendix will usually be identified during computed tomography scans or ultrasound as appendicitis [17].

Pathologic Findings

The tip of the organ is the preferred site of the appendiceal NETs that are mainly observed in women at an age of 40–50 years. Children may be also affected. The tumors are mostly between 1 and 2 cm in size and infiltrate the appendix wall. Occasionally, these tumors may involve and obstruct more proximal part of the appendix and may present as acute appendicitis.

EC Cell NETs

Majority of appendiceal NETs are EC cell NETs with uniform tumor cells arranged in solid nests, sometime with peripheral palisading [1]. Tumor cells are uniform with little or no pleomorphism or mitoses (Fig. 1) and Ki67 proliferative index of <2 % (Fig. 2), consistent with well-differentiated, histologic grade G1 NETs [18]. The tumor cells stain positive for CgA, Syn, CAM5.2 (Figs. 3, 4, and 5), CK8/CK19, CD56, and CDX2 and usually negative for CK7/CK20, CEA, and TTF-1 [18–20]. These tumors are also immunoreactive for serotonin and substance P and may contain S100-positive sustentacular cells [1]. Occasionally, clear cell pattern may predominate that may resemble goblet cell carcinoid (GCC).

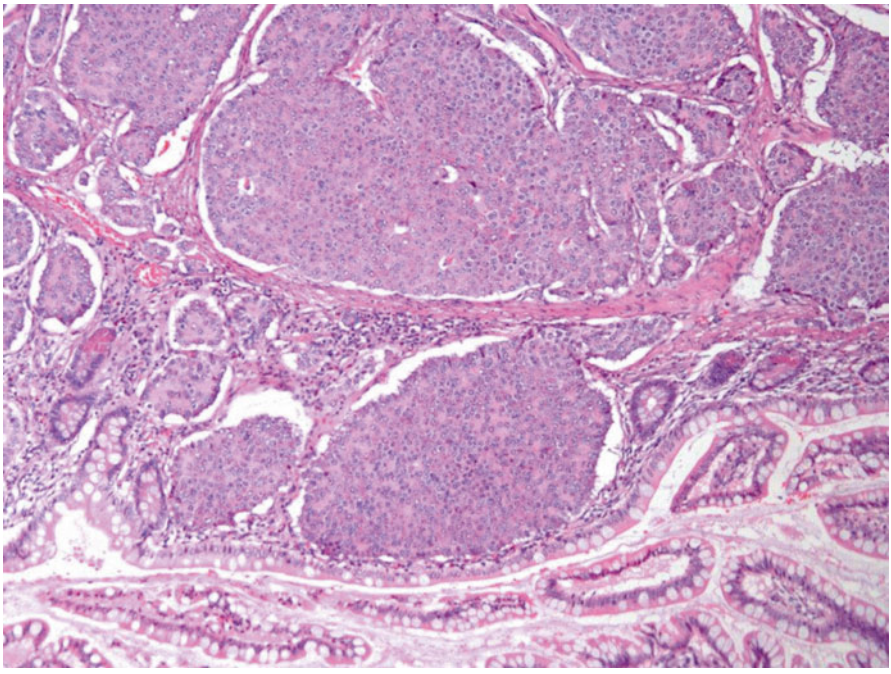

Fig. 1 Well-differentiated NET showing nested pattern of uniform neoplastic cells, infiltrating the wall of the appendix [H&E Original magnification 100×]

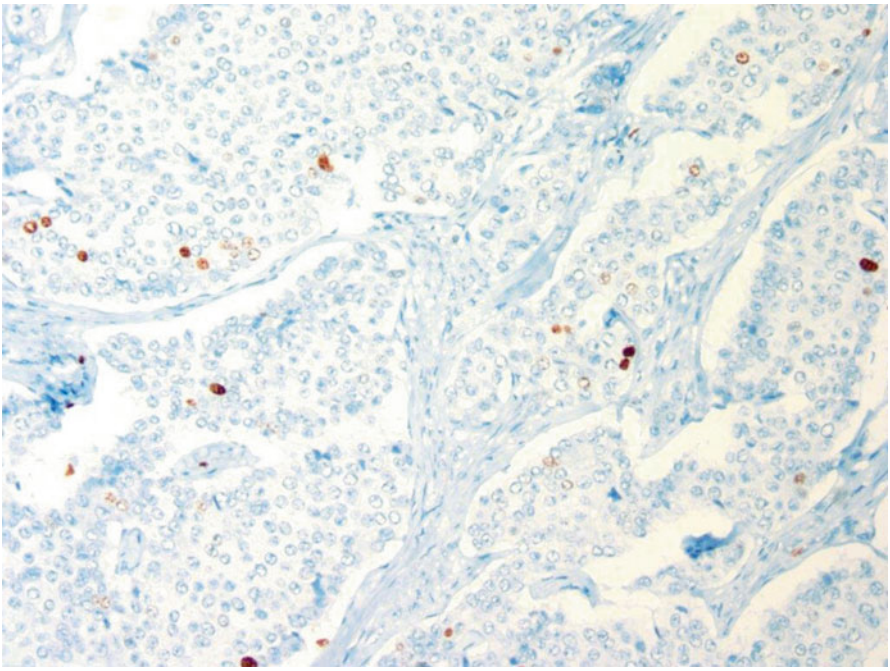

Fig. 2 Well-differentiated NET showing low Ki67 (<5 %) index [Ki67 IHC. Original magnification 200×]

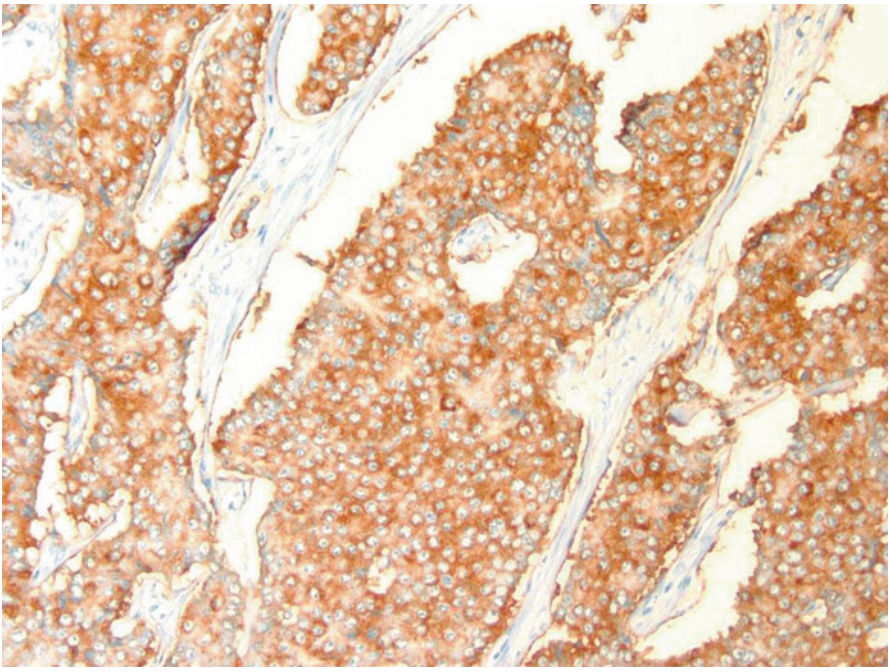

Fig. 3 Well-differentiated NET showing CgA-positive tumor cells [CgA IHC. Original magnification 200×]

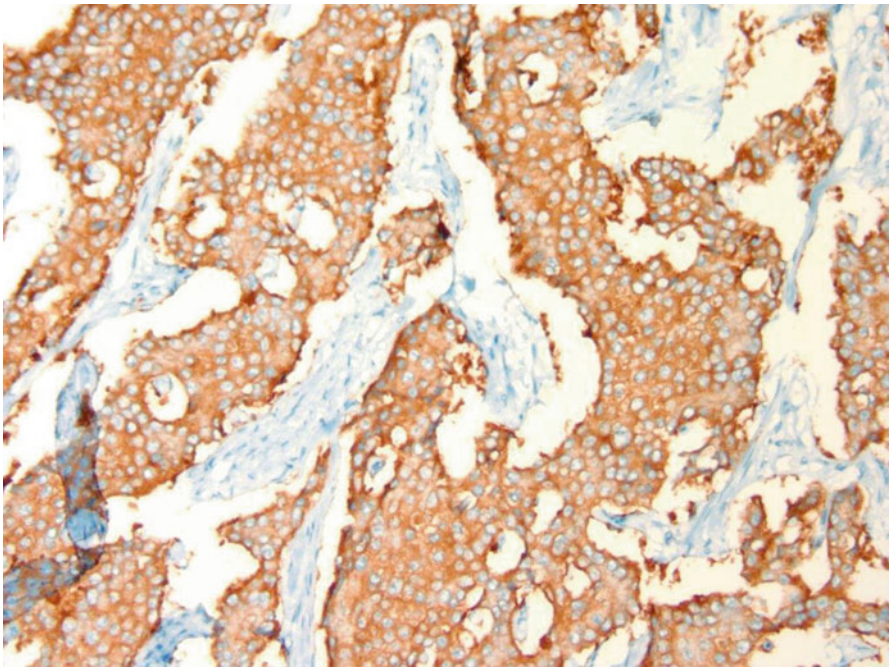

Fig. 4 Well-differentiated NET showing synaptophysin-positive tumor cells [Syn IHC. Original magnification 200×]

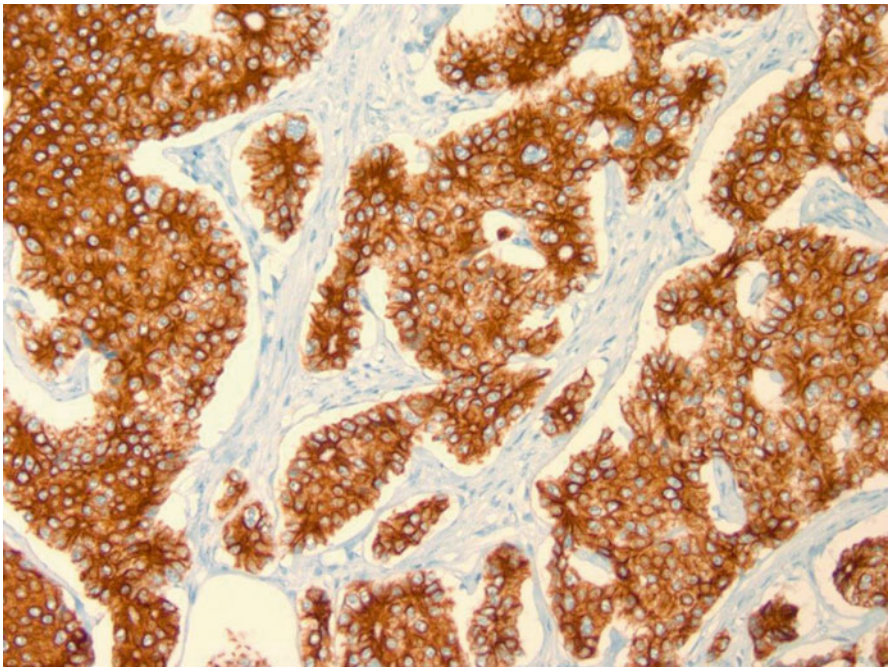

Fig. 5 Well-differentiated NET showing CAM5.2-positive tumor cells [CAM5.2 IHC. Original magnification 200×]

L Cell NETs

These form a minority of primary appendiceal NETs, produce glucagon-like peptides (GLP1, GLP2) and PP/PPY, measure 2–3 mm in size and exhibit tubular or trabecular histologic pattern [1], and resemble similar NETs in the rectum.

Tubular Carcinoid

These affect younger patients and consist of an infiltrative pattern of small tubules with luminal mucin and uniform tumor cells, without any typical nested pattern or mitoses. Tumor cells are often positive for CgA, glucagon, and serotonin but negative for S100 [1]. These tumors originate from basal parts of mucosal crypts and spare primary involvement of the appendiceal mucosa.

The immunologic characterization of gastrointestinal NETs demonstrated a different β-catenin level in appendiceal NETs as compared to NETs localized elsewhere [21].

Molecular Pathology

In contrast to other GI-NETs, loss of heterozygosity (LOH) at the MEN1 gene locus is rare in NETs of the appendix [22–24]. Unlike colonic adenocarcinomas, KRAS mutations are uncommon in appendiceal NETs or GCCs, while immunohistochemical expression of p53 protein or TP53 gene mutations were detected in a fraction (25–31 %) of GCCs [18, 25]. Gene expression profiling has shown overexpression of NAP1L1, MAGED2, and MTA1 as novel markers of aggressive behavior in appendiceal NETs with lymph node or liver metastases, and also in GCCs, but not in incidentally detected small NETs [1].

Prognosis and Postoperative Monitoring

Overall prognosis of small appendiceal NETs is excellent in all ages [3, 4]. Long-term follow-up has revealed that no patient treated by appendectomy died of appendiceal NETs with a diameter <2 cm [8, 26]. Although carcinoid tumors of the appendix rarely metastasize [14, 15, 27], many factors may be associated with increased metastatic potential, the size of the appendiceal NET being the best prognostic factor [2, 16, 26].

According to the North American Neuroendocrine Tumor Society (NANETS) guidelines (2009), low-grade, well-differentiated NETs smaller than 1 cm have a low recurrence rate and do not require further monitoring [4], while in tumors with a diameter of 1–2 cm and presence of aggravating factors (localization at the base,

infiltration of the mesoappendix >3 mm, vessel infiltration, grade 2 NET), in which a simple appendectomy was performed, a regular monitoring is recommended [4]. For tumors larger than 2 cm, the National Comprehensive Cancer Network (NCCN) 2013 guidelines propose monitoring by history, physical examination, and imaging every 3 months in the first year and every 6–12 months in the next 10 years and measuring 5-HIAA and CgA [4].

Other prognostic factors include Ki67 index, reduced E-cadherin level, or angioinvasion, but need further investigation [6]. Also, patients with carcinoids of the appendix have up to 33 % risk of developing a synchronous or metachronous colorectal neoplasm [2, 14, 28, 29] and warrant colonoscopic screening as part of their postoperative follow-up [30].

Treatment

Treatment of choice for appendiceal NETs is surgical, and the type of operative procedure is determined by histology and metastatic risk [6]. The majority of patients with an incidental carcinoid are cured by appendectomy [30]. Tumors <1 cm hardly ever metastasize and are treated by appendectomy; tumors >2 cm require right hemicolectomy because of a significant risk of metastatic spread [3, 4]. Treatment for lesions 1–2 cm is controversial and needs further tumor characterization, i.e., mesoappendiceal invasion, vascular invasion, mitotic activity, proliferation markers, and careful patient risk evaluation [3]. Cases with tumor at the base of the appendix with involvement of the surgical margin or cecum are prognostically unfavorable and require at least partial cecal resection to avoid residual tumor or subsequent recurrence [1]. Similarly, transmural infiltration or infiltration of mesoappendix, tumor >2 cm, any high-grade malignant carcinoid (including those with a high mitotic index), and GCC histology require right hemicolectomy or ileocecal resection [2, 26, 31]. Absolute indication for reoperation is the existence of local lymph nodes and the presence of tumor rupture [4].

Appendiceal Carcinoids in Children

Although carcinoids are rare in children, these are the most frequent tumors of the gastrointestinal tract in childhood and adolescence [32].

Demographics

In children the tumor is usually smaller than 2 cm in diameter [33] with a reported incidence of 0.2–0.5 % in surgically removed appendices in children [34]. The tumor is more common in white females with a mean age of 12–13 years [33, 35].

Clinical Features

Generally, carcinoid tumors measuring <10 mm, located at the tip of the appendix, present as acute appendicitis, while tumors measuring more than 20 mm and located at the base of the appendix may present with clinical signs of peritonitis [33]. Metastasis of an appendiceal carcinoid is very rare in children probably because most reported tumors in this age group are small and less aggressive [7].

Prognosis

The appendiceal carcinoids are usually benign, and localized disease has an excellent prognosis. The uncommon occurrence of metastasis is related to the primary tumor size and depth [27]. Clinical awareness and early diagnosis of CT of the appendix may significantly decrease morbidity and mortality [7].

Treatment

The treatment of the carcinoid tumors in the appendix depends on the size and the site of the tumor [7]. Tumors smaller than 2 cm can be adequately treated by appendectomy, while right hemicolectomy is recommended for pediatric patients with appendiceal carcinoid tumors larger than 2 cm, especially when the mesoappendix is involved or if residual tumor is present at the surgical resection margin [36].

Mixed Adenoneuroendocrine Carcinomas (MANECs)

As the name implies, these consist of a mixture of exocrine (signet ring type or poorly differentiated) and endocrine carcinoma components, with one component exceeding 30 % [1]. These are primary carcinomas of the appendix that arise by progression of a pre-existing GCC [37], as explained in a later section. These may involve any part of the appendix; appear as whitish, mucoid induration, 1–5 cm; and exhibit a diffuse infiltrative growth pattern [19, 38]. They generally affect older patients with an average age of 52 years [1]. These are characterized by submucosal concentric growth, mucin positivity, and immunoreactivity of tumor cells for serotonin, somatostatin, and CEA [1]. Histologically, these malignancies are signet ring type or poorly differentiated adenocarcinoma type [37, 39]. The latter tumor type is positive for p53 and MUC1, but negative for MUC2 [37]. These carcinomas usually form in the apparent absence of neoplastic changes in the mucosal epithelium [38]. In a comprehensive GCC and carcinoma study by Tang et al. [37], GCCs were classified as typical GCC (group A) and adenocarcinoma ex-GCC on the basis of the histologic features at the

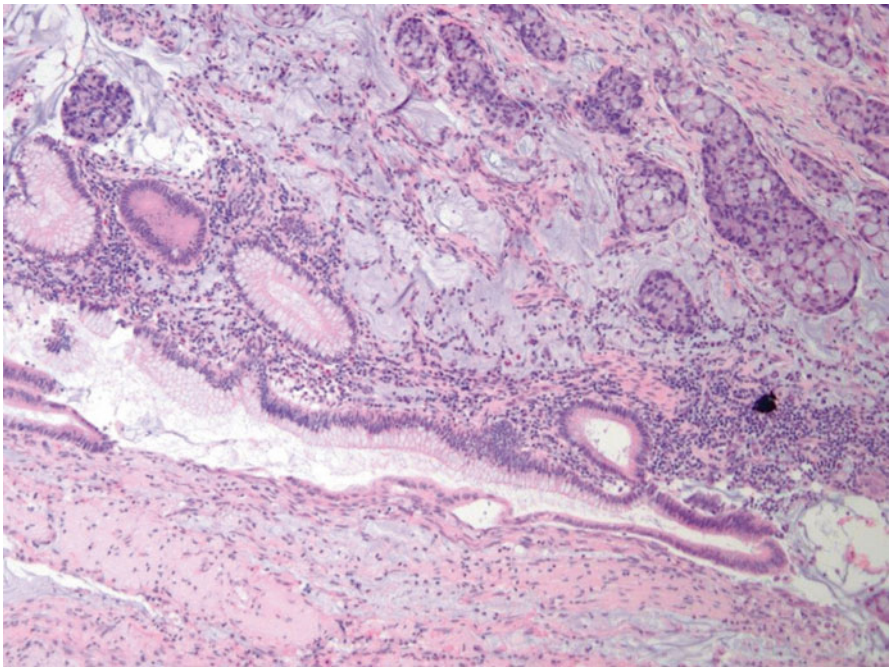

Fig. 6 Adenocarcinoma ex goblet cell carcinoid infiltrating the wall of the appendix [H&E Original magnification 100×]

primary site to help assess prognosis. The adenocarcinoma ex-GCC group was further divided into signet ring cell type (group B) and poorly differentiated adenocarcinoma type (group C). The typical GCC (group A) comprises well-defined goblet cells arranged in clusters with cohesive linear pattern, minimal cytologic atypia, or architectural distortion of appendiceal wall but no desmoplasia. Group B has goblet cells or signet ring cells arranged in irregular large clusters (Figs. 6 and 7), but lacks confluent sheets of cells, discohesive single file, or single cell infiltrating pattern, significant cytologic atypia, stromal desmoplasia, and associated destruction of the appendiceal wall. Group C has at least focal evidence of goblet cell morphology, a component (>1 low-power field or 1 mm^2) not otherwise distinguishable from poorly differentiated adenocarcinoma, which may appear as either (a) gland forming or (b) confluent sheets or signet ring cells or (c) undifferentiated carcinoma.

Primary Neuroendocrine Carcinomas (NECs)

NECs of the appendix, pure or mixed, have been reported [40], but are exceedingly rare [41, 42]. The case described by Rossi et al. [42] was a 35-year-old female with a biphasic malignancy composed of a non-mucinous adenocarcinoma closely juxtaposed with a poorly differentiated (small cell) endocrine carcinoma, who was

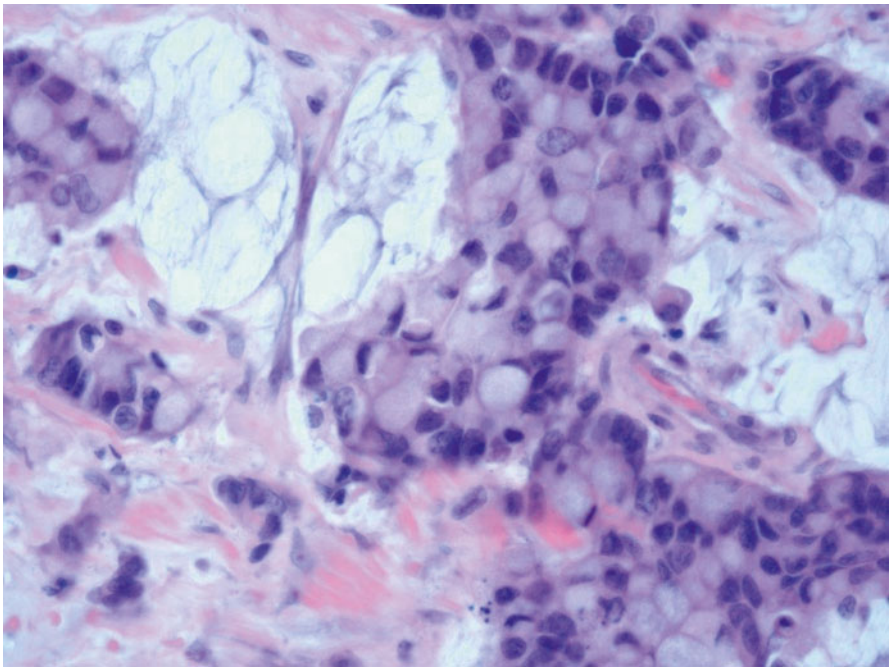

Fig. 7 Adenocarcinoma ex goblet cell carcinoid of the appendix, featuring clusters of signet ring carcinoma cells with highly atypical nuclei in a background of dissecting mucin pools and a few scattered goblet-like cells with smaller, less atypical nuclei [H&E Original magnification 400×]

treated by right hemicolectomy and chemotherapy and was reported to be alive at 65 months of follow-up. Immunohistochemically, the adenocarcinoma component strongly stained for CK20 and CEA, while the endocrine component displayed a dot-like positivity for pan-cytokeratins and Cg. Both components were negative for CDX2 and p53. Genotypic analysis by microsatellite instability showed many microsatellite alterations as well as a normal p53 gene setup. The authors thought of this lesion as a clonal tumor in which the endocrine component was derived from a progressive differentiation of the adenocarcinoma following a glandular-to-endocrine sequence. In general, immunohistopathologic features of primary appendiceal NECs are similar to NECs elsewhere in the GI tract [1]. While these malignancies have aggressive histology, since only a few cases have been reported so far, it is difficult to predict their outcome.

Goblet Cell Carcinoids

The term goblet cell carcinoid was coined by SG Subbuswamy in 1974 for a series of 12 cases of a new entity, in which the principal cell type morphologically resembled goblet cells of the gastrointestinal tract and had a significant population of

argentaffin cells [43]. Subsequently, Cooper and Warkel reported a large series of 39 cases using the term "adenocarcinoid" [44] and documented distinct prognostic value for this new entity to be intermediate between carcinoids and the classical adenocarcinoma [45].

Demographics

GCC of the appendix comprises 5 % of all primary appendiceal neoplasms and is more common in Caucasians [11]. The age of presentation ranges from 18 to 89 years with peak incidence in fifth or sixth decades [11, 23, 46]. The reported male to female ratio is 1.4:1–1:2.2 [37, 47]. In a clinicopathologic study of 55 Chinese patients, GCC was more frequent in males and older age and had significantly larger tumor size and greater frequency of mesoappendix infiltration than typical carcinoids (TCs) [48].

Clinical Presentation

Most commonly, GCCs present as acute appendicitis [16, 49, 50]. They may also present as abdominal pain and a palpable lower abdominal mass [37]. Up to 10–20 % of patients may present with distant metastases [51]. About 50 % of the female patients present with metastases to the ovary [50]. Less frequent presentations may be bowel obstruction, intussusception, gastrointestinal bleeding, chronic intermittent lower abdominal pain, and rarely mesenteric adenitis or iron deficiency anemia due to cecal ulceration [47, 50]. In 3 % of cases, it may be an incidental finding [37]. Rarely GCC coexists with conventional mucinous tumors of the appendix [47, 52–54].

Pathogenesis

GCCs are thought to arise from pluripotent intestinal stem cells that reside in appendiceal crypts and can differentiate into mucus cells and also neuroendocrine cells [47, 55]. Initially, they were considered a subtype of carcinoid tumor, based on their basal-glandular/mural location, its well-differentiated nature, and the absence of dysplasia in the surrounding epithelial lining of the appendix [43]. Some cases of GCCs have been reported in patients with appendiceal mucinous neoplasms [56] and schistosomiasis [57]. The latter can lead to GCC by inducing persistent proliferation of pluripotent stem cells in the crypt epithelium. To date no consensus has been reached if GCC is a variant of neuroendocrine tumor or a subtype of mucin-producing adenocarcinoma with neuroendocrine differentiation [45, 48].

Histopathologic Findings

Gross

GCCs generally appear as ill-defined firm nodular thickening of the appendix. Majority of the tumors are >2 cm in size (average 2.4 cm) [37, 58]. Most common location is the tip of the appendix, followed by the base [45]. Circumferential involvement of the appendix wall with longitudinal extension is the most common growth pattern [45], resulting in the formation of an ill-defined tumor mass [38]. For full histopathologic evaluation of this neoplasm and to rule out the presence of adenocarcinoma within the GCC, the entire appendix should be submitted for histopathologic review [37].

Microscopic

In his original description of GCC, Subbuswamy [43] referred to a neoplasm in which mucin-filled cells with crescentic nuclei were arranged in small clumps or rosettes, with no definite lumen, but with striking resemblance to goblet cells or signet ring cells, with the tumor cell clusters resembling Brunner's glands. The bulk of the tumor is in the lamina propria or submucosa of the appendix, surrounding the basal parts of the mucosal crypts. Occasionally goblet cell nests are found in large pools of mucin in the muscularis propria of the appendix. The tumor consists of small, rounded nests of signet ring-like cells, resembling intestinal goblet cells, with mild to moderate atypia, low mitotic activity, and Ki67 index of <20 % [37]. Goblet-like tumor cells and extracellular pools of mucin stain positive with mucin stains [Bosman]. Vascular and perineural invasion and infiltration of the periappendiceal fat are common. The surrounding epithelium either is well preserved or shows fibrous obliteration of the lumen without evidence of adenomatous change. Associated acute appendicitis has been reported in some cases [44].

An unusual mucoid variant of GCC with well-differentiated microacini and rosettes of neuroendocrine cells infiltrating the base of the mucosal glands or the deeper muscle layers without any stromal reaction have been described. In this study an association was found between GCCs and primary carcinomas, which occurred either before or after the appendicular neoplasms [59].

Special Stains

Most neoplastic cell GCCs are argyrophil positive (Sevier-Munger stain), but rarely argentaffin positive (with Fontana-Masson stain) [45]. The vacuolated (goblet-like) cells tend to be positive for mucicarmine, PAS, PAS with diastase, and alcian blue [56].

Immunohistochemistry

Neuroendocrine Markers

Most GCCs show scattered and variable tumor cell positivity for chromogranin A and synaptophysin [25, 37, 55], in contrast to classic appendix carcinoids, in which staining for chromogranin A and synaptophysin is most often homogeneous [60]. The endocrine cell component may also be positive for CD56, serotonin, enteroglucagon, somatostatin, and/or pancreatic polypeptide (PP) [1]. The goblet-like cells express CEA, CK19/CK20, and MUC2 [18, 37], which is also a marker of colonic adenocarcinoma.

Differentiation Markers

Generally GCCs also show strong immunoreactivity for CEA, CDX-2, CAM 5.2, and cytokeratin [18, 55, 61]. CK20 immunoreactivity is present in 100 % and CK7 in 70.5 % of GCCs, while classical appendix carcinoids are CK7 negative and may be CK20 positive in up to 16 % of cases [18, 19]. Based on similar CK7/CK20 immunoprofiles in GCC and colorectal carcinoma, GCCs have also been called crypt cell or amphicrine carcinomas [19], while other authors have proposed the term mucin-producing neuroendocrine tumor of the appendix [62]. Based on their distinctive histology and immunohistochemical profile, GCCs have also been termed term "low-grade adenocarcinoma with neuroendocrine differentiation" [48].

Ki67 Index

Generally, Ki67 index is higher in GCC (4.7 %) relative to classic carcinoids (0.9 %). Using the proliferation index, based on Ki67 immunoreactivity, Tang et al. categorized GCCs in three groups according to histology (groups A, B, and C) and found that the average Ki67 index increases within the groups and that the survival rate is significantly reduced with increasing Ki67 index [37]. In contrast, a more recent study found that Ki67 had no prognostic significance in GCCs [63].

Other Immunohistochemical Markers

Similar to carcinoids and in contrast to adenocarcinoma (E-cadherin negative), E-cadherin staining shows strong membranous staining in GCC [45, 64]. β-catenin staining in GCC is similar to normal appendiceal mucosa and typical carcinoid, with strong membranous staining but without nuclear or cytoplasmic staining, while in adenocarcinoma, β-catenin stain is usually nuclear [64].

Electron Microscopy

The neoplastic cells of GCCs contain both mucin droplets and electron-dense neurosecretory granules [44, 55, 65].

Molecular Pathology

Generally, molecular studies have shown conflicting results in GCCs, although a similarity has been shown between ileal carcinoids and GCCs [45]. Allelic loss of chromosome 11q, 16q, and 18q has been found in 11 %, 11 %, and 39 % of GCCs [23]. This is similar to ileal carcinoids (27, 37, and 56 %), but distinct from appendix carcinoids [45]. Among other molecular alterations, no KRAS, beta-catenin (CTNNB1), or DPC4/SMAD4 mutations or p53 overexpression or loss of DPC4 staining was identified in GCCs [23, 45]. Most GCCs are p53 negative/p16 negative, suggesting its control by a p53 independent pathway [45]. Dysregulation of the cell cycle pathway is likely to be involved, as suggested by overexpression of cyclin D1 (30–70 %) and p21 (40–60 %) [23, 25, 55]. Rb protein expression is preserved in GCCs [37]. Gene expression profiling analysis showed malignant appendiceal carcinoids (APCs) and GCCs to have elevated expression of NAP1L1, MAGE-D2, and MTA1 compared with APCs identified at surgery for appendicitis [66]. These findings and differences in NALP1 gene expression (decreased in GCCs) provide a series of molecular signatures that differentiate various carcinoids of the appendix. The molecular delineation of malignant appendiceal tumor potential provides a scientific basis to define the appropriate surgical management as opposed to morphologic assessment alone [66]. Despite several recent advances, however, molecular studies have failed to settle the controversy around histogenesis of GCCs [45].

Imaging

Computer tomography (CT) scanning or magnetic resonance imaging (MRI) may have low sensitivity for locally advanced disease, but may be used for lymph node and liver metastases [67]. Indium-labeled octreotide scintigraphy is the most sensitive imaging modality for metastasis [45]. FDG-PET is useful for high-grade GCC [45]. Lifelong screening for synchronous or metachronous malignancies is recommended [60], and there may be an increased risk of secondary neoplasms [67, 68].

Diagnosis

The diagnosis of GCC is histologic, which in majority of patients is made during surgery or histopathologic examination of resected specimen for acute appendicitis [60, 69]. A combination of histologic and immunohistopathologic features is needed to confirm the diagnosis [48]. Because of the potential to metastasize to distant sites, including the lungs, contrast CT of the chest, abdomen, and pelvis is recommended for all patients with a GCC regardless of its histologic grade. In equivocal cases, FDG-PET or even guided biopsy of the suspicious lesion may be considered to confirm the diagnosis [51].

Metastatic Spread

The most common route of metastases from GCCs is trans-celomic/peritoneal invasion, and the most common metastatic sites are the ovaries, peritoneal surfaces of the pelvis, and abdominal cavity [45]. Other metastatic sites include the ribs, vertebrae, lymph nodes [70], and rarely prostate [71] and the lung [55]. GCC cells have also been reported in the pleural fluid [72]. In cases of metastatic GCCs [29], the Ki67 proliferation index was >20 %, which, according to the new GCC classification, will be designated as "adenocarcinomas ex-GCC" of "signet ring cell type" or "poorly differentiated adenocarcinoma type" [51]. These authors [51] have also described a first histologically proven lung metastasis and unfavorable outcome from a "typical" GCC with Ki67 index of <5 %.

Prognosis

The prognosis of GCC is intermediate between carcinoids and appendiceal adenocarcinomas with an overall 5-year survival of 76 % [45]. The corresponding survival rates for localized, regional, and distant metastatic disease were 86 %, 74 %, and 18 %, respectively [58]. Stage is the most important prognostic factor, with 5-year disease-specific survival rates of 100 %, 76 %, 22 %, and 14 % for AJCC stages I, II, III, and IV, respectively [50]. Histologic grade is also an important prognostic factor [45], with reported mean survival rates of 119, 43, and 31 months for GCCs in groups A, B, and C, respectively [37]. Histologic features predictive of aggressive behavior in GCCs are high mitotic count (>2/10 hpf), high Ki67 index (>3 %), serosal or mesoappendiceal extension, angioinvasion, lymph node metastases, increased number of Paneth cells, increased mucin secretion, and production of pancreatic polypeptide [29, 38, 64]. Perineural and lymphatic invasion do not correlate with prognosis [49]. Most common cause of death in GCC patients is peritoneal carcinomatosis [45].

Treatment

Primary treatment for GCC is surgical resection. Complete removal of the tumor is recommended because of the unpredictable biological behavior of this tumor, which includes delayed local recurrences and lung metastases [55]. Localized GCCs can be treated with appendectomy, while right hemicolectomy is recommended for higher stage disease due to its unpredictable clinical course and higher risk of nodal metastases [37, 45, 69]. Prophylactic oophorectomy is an option, especially for postmenopausal females due to high incidence of ovarian metastases [37, 50, 73]. Similarly, appendectomy is recommended in females presenting with Krukenberg tumors with unknown primary [74].

Other treatment options include cytoreductive surgery with intraperitoneal chemotherapy for patients with peritoneal carcinomatosis [56, 75], debulking surgery, and adjuvant chemotherapy as for colorectal adenocarcinoma [2], including 5-flourouracil (5FU), leucovorin [50], FOLFOX/FOLFIRI combination (5FU/leucovorin, irinotecan, and oxaliplatin) [60], or streptozotocin with 5FU, cisplatin with etoposide, and interferon [29]. Recent European Neuroendocrine Tumor Society (ENETS) guidelines advocate 5-FU-based combination regimen as first-line therapy for GCCs [67].

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Abbreviations

CEA	Carcinoembryonic antigen
CgA	Chromogranin A
CT	Computer tomography
EC	Enterochromaffin cell
ENC	Epithelial neuroendocrine cells
ENETS	European Neuroendocrine Tumor Society
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCC	Goblet cell carcinoid
GI	Gastrointestinal
GLP	Glucagon-like peptide
5-HIAA	5-Hydroxyindoleacetic acid
HIPEC	Hyperthermic intraperitoneal chemotherapy
MANEC	Mixed adenoneuroendocrine carcinoma
MEN1	Multiple endocrine neoplasia syndrome 1
MRI	Magnetic resonance imaging
NANETS	The North American Neuroendocrine Tumor Society
NCCN	The National Comprehensive Cancer Network
NETs	Neuroendocrine tumors

PP	Pancreatic polypeptide
RH	Right hemicolectomy
SDHD	Succinate dehydrogenase complex subunit D, integral membrane protein
SNC	Subepithelial neuroendocrine cells
TC	Typical carcinoid
WHO	World Health Organization

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