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REVIEW

Appendiceal neuroendocrine tumors: Recent insights and clinical implications

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Abstract

New insights emerged last decade that enriched our knowledge regarding the biological behavior of appendiceal neuroendocrine tumors (NETs), which range from totally benign tumors less than 1cm to goblet cell carcinomas which behave similarly to colorectal adenocarcinoma. The clinical implication of that knowledge reflected to surgical strategies which also vary from simple appendicectomy to radical abdominal procedures based on specific clinical and histological characteristics. Since the diagnosis is usually established post-appendicectomy, current recommendations focus on the early detection of: (1) the subgroup of patients who require further therapy; (2) the recurrence based on the chromogranin a plasma levels; and (3) other malignancies which are commonly developed in patients with appendiceal NETs.

Key words: Appendiceal carcinoids; Neuroendocrine tumors; Goblet cell carcinoma; Right hemicolectomy

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INTRODUCTION

In 1907, Oberndorfer[1] first introduced the term "carcinoid" to describe "little carcinomas" of the small intestine which were thought (by him at that time) to be probably benign.

However, the continuous knowledge which was added by studying these tumors for nearly a century strengthen the notion that the above term was inaccurate or inadequate to describe several parameters of this heterogeneous group of gastrointestinal tumors (including the appendiceal one). Thus, the term "carcinoid" was replaced by the term "gastroenteropancreatic neuroendocrine tumors, GEP-NETs"[2]. The term "appendiceal NET" will be used hereafter.

According to the current WHO classification[3], appendiceal NETs are classified as: (1a) Well differentiated NETs with benign biological behaviour or (1b) Well differentiated NETs with uncertain malignant potential; (2) Well differentiated neuroendocrine carcinoma (with low malignant potential); and (3) Mixed exocrine-neuroendocrine carcinoma. Goblet cell carcinoma (synonyms: adenocarcinoid, mucous adenocarcinoid) belongs to the last category.

BENIGN AND MALIGNANT APPENDICEAL NETs

Epidemiology

Although appendiceal NETs constitute an unusual and sporadic entity, it accounts for more than 50% of all primary tumors of the appendix[4].

Benign appendiceal NETs represent the second commonest neuroendocrine neoplasms of the gastrointestinal tract (small bowel NETs being the commonest) and their histological diagnosis is established, usually incidentally, in 0.3%-0.9% of patients undergoing appendicectomy. This means that the probability of a surgeon coming across an appendiceal NET is once for every 100 to 300 appendectomies performed by him. The annual incidence is about 2-3 newly diagnosed cases per million of general population although post-mortem studies increase the incidence to 170 cases per 100 000. The mean age of patients at the time of diagnosis is at end of the second decade of life with an increased incidence among females[5-8]. The last finding probably reflects the increased use of diagnostic laparoscopy among females for atypical lower abdominal pain and the concomitant laparoscopic appendectomies performed[9].

Malignant appendiceal NETs represent the third commonest (after small bowel and rectum) malignant neuroendocrine neoplasms of the gastrointestinal tract with an annual incidence of 0.63 cases per million of the general population and the mean age of the patients at time of the diagnosis in the 5th decade of life[8].

Clinical presentation

Normally, appendiceal NETs remain asymptomatic. Although accurate preoperative diagnosis using abdominal computed tomography (CT)[10] or ultrasound[11] scans has been reported, the total number of the enrolled patients is extremely small (only case reports have been published) and thus is not suitable for definite conclusions. Therefore, for the vast majority of cases, the diagnosis of appendiceal NETs is established incidentally postoperatively in the specimens of appendectomies which had been performed due to either acute appendicitis or recurrent, chronic, dull, nonspecific lower right quadrant abdominal pain[6,12]. Carcinoid syndrome is very uncommon (< 1%).

Diagnosis

Since most appendiceal NETs are diagnosed postoperatively, any effort to be diagnosed preoperatively is practically unrealistic so the diagnostic work-up should focus on the early detection of recurrence in patients who have already had surgery.

The use of plasma chromogranin-A levels as a tumor marker contributes to the differential diagnosis from goblet cell carcinoma, the early detection of recurrence and the long term follow-up of metastatic disease. All patients should be investigated 6 and 12 mo postoperatively and then annually while the follow-up should be lifelong[13].

Especially for tumors > 2 cm, a CT scan and somatostatin receptor scintigraphy (SRS) is recommended at 6 mo and 12 mo postoperatively and then annually. Colonoscopy is advised for the early detection of synchronously present or metachronously developed large bowel tumors[13].

Biological behavior

Approximately 80% of appendiceal NETs have a maximum diameter of < 1 cm, 15% have a diameter 1-2 cm and only 5% have a diameter greater than 2 cm[14]. Tumor size greater than 2 cm strongly correlates both to metastatic potential[15] and to an unfavourable 5 years survival rate[16].

Approximately 70%-75% of the tumors are located in the apex, 15%-20% in the body and 5%-10% in the base of the organ[14]. Although there is not enough evidence to support the theory that the location of the tumor correlates to the overall survival, cecum invasion or positive resection margins should be considered for planned future therapeutic strategies[17].

A multifocal pattern of the disease along the appendix has not been described yet. However, the coexistence of appendiceal NET with small bowel or rectal NETs[15], colorectal cancer[18], Crohn's disease[19] and synchronous or metachronous development of malignancies outside the gastrointestinal tract[15] are well documented.

The possibility of lymph node metastases from appendiceal NETs with vascular invasion is estimated as high as 30%[7] but only 1% for tumors with appendiceal mesentery invasion[20]. However, the prognostic significance of appendiceal mesentery invasion remains controversial since its relationship to distant metastases development has been reported as between 0[20] and 4.1%[15]. To date, there have been no reports correlating lymph node metastases to appendiceal serosa invasion.

The rate of cellular proliferation (as it expressed by the Ki-67) does not seem to be of prognostic value.

Table 1 Classification and staging of appendiceal NETs according to the TNM system

Stage	T	N	M
I	T1	N0	M0
II	T1	N1	M0
	T2	N0	M0
III	T2	N1	M0
	T3	Any N	M0
IV	Any T	Any N	M1

NETs: Neuroendocrine tumors; T1: Tumor < 2 cm; T2: Tumor ⩾ 2 cm but < 3 cm; T3: Tumor ⩾ 3 cm; N0: No lymph node metastases; N1: Regional lymph node metastases; M0: No metastases; M1: Distant metastases.

Classification and staging

Based on the analysis of the published report from the SEER database between 1977-2004, it is suggested that the first proposed TNM classification and staging systems for appendiceal NETs (which was based on the report from the SEER database between 1973-1999)[21] should be modified[22] according to Table 1.

Treatment

Current guidelines[13,22,23] propose simple appendectomy as adequate and curative for the treatment of appendiceal NETs < 1 cm, while for tumors 1-2 cm, a simple appendectomy followed by periodic postoperative follow-up for 5 years is recommended.

Right hemicolectomy (within 3 mo from the appen-

dicectomy) should be reserved for patients in whom at least one of the following criteria is present: tumor size > 2 cm, location of the tumor at the base of the appendix, infiltration of the cecum, positive surgical resection margins, appendiceal mesentery invasion, metastatically infiltrated mesoappendiceal lymph node, presence of undifferentiated or low differentiated cells or presence of goblet cells.

Serosal, vascular, lymphatic or perineural invasion alone does not constitute inclusion criteria for right hemicolectomy.

GOBLET CELL CARCINOMA

Epidemiology

Goblet cell carcinomas (GCC) constitute less than 5% of all primary appendiceal tumors[24] and, similar to the appendiceal NETs, their diagnosis is established usually incidentally in 0.3%-0.9% of patients undergoing appendicectomy. Its annual incidence is 0.05 new cases per 100000 of general population[23] with an equal distribution between the sexes and the mean age of the patients at the time of diagnosis in the 6th decade of life, nearly 20 years later than the mean age of the diagnosis of malignant appendiceal NETs and almost 10 years earlier than the mean age of the diagnosis of the appendiceal adenocarcinoma[25].

Histology

GCC is derived from undifferentiated stem cells which are completely different from the endocrine cells in the mucosal stroma. The degree of integration of the goblet cells versus APUD cells varies from pure GCC to pure carcinoid tumor. GCC cells have two type of granules which are mainly acid mucinous, are not mixed and can be recognized by different histochemical staining[26].

In their recent study, Tang *et al*[27] tried to answer the long-standing question: "Should GCCs be classified as NETs or as *de novo* mucous adenocarcinomas of the appendix?" Based on histological findings, they proposed classification of GCCs in: (1) Typical GCC (type A); (2) adenocarcinoma ex GCC, signet ring cell type (Type B); and (3) adenocarcinoma ex GCC, poorly differentiated carcinoma type (Type C).

On one hand, GCCs are developed in epithelium without dysplasia and this development is not related to the adenoma-carcinoma sequence of carcinogenesis. The immuno-phenotype of typical GCCs is different from the immuno-phenotype of adenocarcinoma and genetic alterations of neuroendocrine origin, completely different from the genetic alterations which lead to adenocarcinoma formation, are responsible for that[28]. Moreover, both NETs and GCCs of the appendix express chromogranin-A[29].

On the other hand, the positive expression of p53 range from 0% in type A GCC to 100% in type C GCC, findings suggestive that for the transformation to the adenocarcinoma phenotype in type C, the immunohistochemical expression of Cytokeratins (CK) 7 and 20 in appendiceal NETs and GCCs disclosed that GCCs express CKs similarly to colonic adenocarcinomas, while NETs do not[30]. Immunohistochemical expression of Math1 and HD5 is observed in GCCs but not in NETs[31] while the biological behavior of GCCs is identical to adenocarcinomas but not to NETs.

Based on the above findings, it is proposed that GCCs should constitute a distinct histological and clinical entity different from the appendiceal NETs, while the classification which is proposed by Wang *et al*[32] seems to comply to the biological behavior of the tumors and with the prognosis of the patients.

Clinical presentation

In the majority of cases, the disease remains asymptomatic. Acute appendicitis (due to luminal obstruction by the tumor) is the main symptom followed by atypical abdominal pain and abdominal mass. Unusual symptoms are intussusception, gastrointestinal bleeding, bowel obstruction, anemia and miscellaneous urinary manifestations[26].

In 11% of cases the disease is already metastatic at the time of diagnosis, mainly to the ovaries and peritoneum[23]. However, studies[33] propose that the ovarian metastases should be considered as secondary to adenocarcinoma rather than to appendiceal GCC, further supporting the proposed by Tang *et al* classification.

Diagnosis

In fact, most appendiceal GCCs are diagnosed postoperatively so any effort for accurate preoperative diagnosis is unrealistic. The diagnostic work-up should focus on the early detection of recurrence in patients who have already had surgery.

Magnetic resonance imaging is more sensitive than CT and CT more sensitive than SRS in the early detection of pulmonary, hepatic and peritoneal metastases[34]. Plasma chromogranin-A levels have no diagnostic value while the periodic measurement of tumor markers related to the mucinous characteristics of the tumor such as CEA, CA 19-9 and CA 125 is recommended[23]. Lifelong screening for synchronous or metachronous malignancies is also recommended[13].

Treatment

Right hemicolectomy (usually performed after the initial appendectomy) is recommended as the treatment of choice after the histological confirmation of GCC independent of the size of the primary tumor[13]. In female patients with GCC of the appendix, regardless of age, bilateral salpingo-oophorectomy is also advocated. In cases with advanced peritoneal dissemination, cytoreductive surgery with adjuvant intraperitoneal chemotherapy may offer prolonged survival[35]. Adjuvant chemotherapy is usually not effective although it can be used in patients with obvious spread of the disease[36]. Chemotherapeutic protocols are the same as those used in the treatment of colorectal adenocarcinoma.

CONCLUSION

Based on new insights that emerged last decade, the biological behavior of appendiceal NETs ranges from totally

Table 2 Recommended surgical strategies for appendiceal NETs based on specific clinical and histological characteristics

Indications	Type of operation
Tumor size < 1 cm	Appendicectomy
Tumor size 1-2 cm	Appendicectomy + Regular F/Up for 5 years
Tumor size > 2 cm	Right hemicolectomy
Location of the tumor at the base of the appendix	Right hemicolectomy
Infiltration of the cecum	Right hemicolectomy
Positive surgical resection margins	Right hemicolectomy
Appendiceal mesentery invasion	Right hemicolectomy
Metastatically infiltrated mesoappendiceal lymph node	Right hemicolectomy
Presence of undifferentiated or low differentiated cells	Right hemicolectomy
Presence of goblet cells	
Goblet cell carcinoma in males	Right hemicolectomy
Goblet cell carcinoma in females (regardless of age)	Right hemicolectomy + Bilateral salpingo-oophorectomy
Peritoneal dissemination from goblet cell carcinoma	Cytoreductive surgery + Adjuvant intraperitoneal chemotherapy

benign tumors less than 1 cm to goblet cell carcinomas which behave similarly to colorectal adenocarcinoma. Depending on specific clinical and histological characteristics, surgical strategies also vary from simple appendicectomy to radical abdominal procedures (Table 2). Since, in the vast majority of cases, the diagnosis is usually established post-appendicectomy, it is crucial for clinicians to identify the subgroup of patients who require further therapy, to detect early the recurrence based on the chromogranin A plasma levels and to detect early other malignancies which are commonly developed in patients with appendiceal NETs.

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