APPENDICEAL NEUROENDOCRINE TUMORS – REPORT OF TWO CASES AND REVIEW OF LITERATURE

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ABSTRACT

Background: Appendiceal neuroendocrine tumors are the second most common neuroendocrine tumors of the gastrointestinal tract, after small bowel neuroendocrine tumors.

Case Reports: We are reporting two cases of appendiceal neuroendocrine tumors, both of male patients aged 24 and 34, respectively, experiencing pain in the right iliac fossa. After preoperative evaluation and confirming the diagnosis of acute appendicitis, both the patients underwent a laparoscopic appendectomy. A histopathology examination of the specimen in both cases revealed a neuroendocrine (carcinoid) tumor of the appendix.

Discussion: Appendiceal neuroendocrine tumors are primarily diagnosed postoperatively. As a tumor marker, the plasma chromogranin A level should be investigated postoperatively at 6–12 months. An annual CT scan and a biannual somatostatin receptor scintigraphy are recommended. For tumors larger than 2 cm in size, a colonoscopy is advised annually for the early detection of synchronously present or metachronously developed large bowel tumors.

Keywords: Neuroendocrine tumors, carcinoid, appendicitis, appendectomy, chromogranin A

INTRODUCTION

Carcinoid tumor is the most common tumor in the appendix and accounts for more than 50% of the cases of primary appendix tumors, usually discovered after the appendectomy has been conducted1–4.

The diameter of the tumor is between 1 cm and 2 cm. The larger the tumor, the lower the five-year survival rate5–7.

Most of these type of tumors are located in the apex (70–75%), followed by the body (15–20%) and base (5–10%)5.

Carcinoid tumors are the most prevalent among people aged between 40 and 50 years. Males are less affected by such tumors than females, maybe due to a higher rate of appendectomies conducted in females who undergo pelvic surgery8.

Carcinoid tumors are located within the submucosa at the tip of the appendix, hence they do not cause obstruction4.

Small tumors are usually asymptomatic, larger tumors may be symptomatic (with distant metastasis to lymph nodes), and tumors located at the base could lead to an obstructed appendix. The larger the tumor size, the more likely the metastasis and more evident the symptoms of carcinoid tumor9,10.

A rare type of appendiceal tumor, sometimes referred to as an adenocarcinoid (also termed goblet cell or mucous carcinoid), contains chromogranin A and is composed largely of goblet cells4,11.

In their study, U. Plöckinger et al. discuss the staging, prognosis, and treatment of appendiceal carcinoids in detail4.
The treatment of choice for appendiceal neuroendocrine tumors depends on the size and location of the primary tumor and likelihood of regional and distant metastases. If the primary tumor is smaller than 1 cm in size and located at the apex, it can be cured with a simple appendectomy. Conversely, a hemicolectomy is required if the tumor is larger than 2 cm in size, located at the base, or smaller than 2 cm in size and invading the mesoappendix.4,6,12.

CASE REPORTS

Case 1

A 24-year-old male was admitted to the emergency department with lower abdominal pain since two days. On examination, positive rebound tenderness was observed in the right iliac fossa. The patient was diagnosed for acute appendicitis and operated. The histopathology examination displayed an appendix measuring 6 cm in length and 1 cm in diameter. The cross-section yellowish tip was 0.8 cm in diameter and 1.5 cm in length. Three sections were stored in two cassettes. Two additional sections were submitted.

In a microscopic examination, the section revealed the obliteration of the lumen and replacement of the mucosa with solid islands of uniform polygonal cells with minimal pleomorphism and granular cytoplasm in a predominantly acinar pattern. Retraction of the tumor islands was witnessed from the surrounding stroma, and the wall was thickened. No definite angioinvasion/neuroinvasion was found. The mitotic rate was observed to be less than 1/10 HPF. Seemingly normal entrapped mucosal glands and residual lymphoid follicle were also observed. The serosa appeared to be free of tumor involvement. Other sections filled with the mucosa were infiltrated with foamy histocytes (consistent with a mucocele) and had thickened walls and calcification areas.

Diagnosis

The patient was diagnosed with acute appendicitis, and a laparoscopic appendectomy was performed. The features of the affected appendix were found to be consistent with those of a well-differentiated endocrine carcinoid tumor. Surgical margins were free of tumor involvement.

Ancillary studies found that the chromogranin A stain displayed diffuse positivity with the diagnosis of the neuroendocrine differentiation.

Figure 1. Histopathology report (Case 1)

Case 2

A 43-year-old male was admitted with right lower quadrant abdominal pain since one day, which aggravated with movement. On examination, positive rebound tenderness was observed in the right iliac fossa. Blood investigation displayed leukocytosis. The patient was diagnosed with acute appendicitis, and a laparoscopic appendectomy was performed.

Histopathology Examination

The appendix was found to be 6 cm in length and 1.5 cm in maximum diameter. The serosa appeared to be noticeably congested. Sections from the tip and other parts were stored in three cassettes.

Sections of the appendix displayed features of acute suppurative appendicitis along with focal necrosis of the appendix wall and...
extension of inflammation to the periappendicular tissue. Solid nests of tubular and gland-like structures were detected at the tip of the appendix invading the muscular wall, just reaching the serosal layer.

**Diagnosis**

The patient was diagnosed with acute suppurative appendicitis and periappendicitis. A laparoscopic appendectomy was performed. The histopathology report displayed a well-differentiated endocrine carcinoid tumor of the appendix (classic and tubular) at the tip of the appendix, extending to the mesoappendix. Surgical margins were free of tumor involvement.

**DISCUSSION**

The term “carcinoids,” used to describe “little carcinomas,” was first introduced in 1907 by Oberndorfer (German physician and pathologist)\(^\text{13}\). The term “carcinoid” was replaced with “gastroenteropancreatic neuroendocrine tumors” after nearly a century of continued study\(^\text{14}\).

After small bowel neuroendocrine tumors, the second most common neuroendocrine tumors of the gastrointestinal tract are appendiceal neuroendocrine tumors. For 0.3–0.9% of patients who undergo appendectomies, this type of tumor is usually diagnosed during the histopathology examination\(^\text{10}\). Malignant appendiceal neuroendocrine tumors represent the third most common malignant neuroendocrine neoplasms of the gastrointestinal tract. The possibility of lymph node metastasis from appendiceal tumors with neuroendocrine tumors that have a vascular invasion is as high as 30%. However, just 1% of such tumors have an appendiceal mesentery invasion\(^\text{9, 10}\).

Appendiceal neuroendocrine tumors are largely diagnosed postoperatively\(^\text{2, 3}\); the plasma chromogranin A level as a tumor marker should be investigated at 6–12 months postoperatively\(^\text{4}\). An annual CT scan and a somatostatin receptor scintigraphy are recommended at 6 and 12 months postoperatively. For tumors larger than 2 cm in size, a colonoscopy is advised annually for the early detection of synchronously present or metachronously developed large bowel tumors\(^\text{4, 15}\).

**Clinical Presentation**

As with other intestinal neuroendocrine tumors, those found in the appendix can secrete serotonin and other vasoactive substances (5-hydroxytryptophan, norepinephrine, dopamine, histamine, polypeptides, and prostaglandins). These substances are responsible for episodic flushing, wheezing, diarrhea, and right-sided valvular heart disease.

Depending on the stage of the disease, surgery (appendectomy or hemicolecotomy) is
the treatment of choice for appendiceal neuroendocrine tumors\textsuperscript{4, 6, 12}.

The majority of neuroendocrine tumors are located in the distal one-third of the appendix, where they are unlikely to cause obstruction\textsuperscript{2, 3}. As a result, most patients are asymptomatic. Symptoms are more likely when large tumors are present and metastasis occurs beyond the regional lymph nodes. Approximately 10\% of appendiceal neuroendocrine tumors are located at the base of the appendix, where they can cause obstruction, leading to appendicitis\textsuperscript{5, 16}.

\textbf{Figure 4.} Endoscopic appearance of appendiceal NETs

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{TNM staging of appendiceal carcinoid} & \\
\hline
\textbf{Primary tumor (T)} & \\
\hline
T0 & Tumor cannot be assessed & \\
T1 & Tumor 2 cm or less in greatest dimension & \\
T2 & Tumor more than 2 cm but not more than 4 cm & \\
T3 & Tumor more than 4 cm or with extension to cecum or ascending colon & \\
T4 & Tumor directly invades other adjacent organs or structures, e.g., abdominal wall and ileocolic introitus & \\
\hline
\textbf{Regional lymph nodes (N)} & \\
\hline
N0 & No regional lymph nodes can be assessed & \\
N1 & Regional lymph node metastasis & \\
\hline
\textbf{Distant metastases (M)} & \\
\hline
M0 & No distant metastases & \\
M1 & Distant metastases & \\
\hline
\end{tabular}
\caption{TNM staging of appendiceal carcinoid}
\end{table}

\textbf{Treatment and Prognosis}

As carcinoid tumors are detected after the appendectomy, the best treatment for them is still debatable. Whether the patient should undergo a right hemicolectomy depends on the site and size of the tumor. A tumor located at the base of the appendix that is larger than 2 cm in size is preferably treated through a right hemicolectomy\textsuperscript{4, 6, 12}.

\textbf{Post-treatment Follow-up}

Follow-up is not required for a tumor smaller than 2 cm in size. Unless clinically indicated, 3- and 12-month follow-ups are required for a tumor larger than 2 cm in size. These are carried out through historical and physical examinations using a tumor marker (5-HIAA and chromogranin A) and abdominal imaging\textsuperscript{4, 15}.

\textbf{REFERENCES}


