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NEUROENDOCRINE TUMOR OF APPENDIX A CASE REPORT AND LITERATURE REVIEW

Surgery

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ABSTRACT

The immense majority of neuroendocrine neoplasms of the appendix are carcinoid tumors. Most are of enterochromaffin (EC) cell type, although rare examples are of L cell type. New discernments occurred last decade that enriched our knowledge regarding the biological performance of appendiceal neuroendocrine tumors (NETs), which range from totally benign tumors less than 1cm to goblet cell carcinomas which behave correspondingly 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. We present a rare case of neuroendocrine tumor of appendix diagnosed after appendectomy in young patient.

KEYWORDS

Appendiceal carcinoids, Neuroendocrine tumors, Goblet cell carcinoma, Post Appendectomy, Surgical approaches

Background

First it is a rare disease classified as such in the journal ORPHA under the number 100079. While appendiceal NETs constitute an unusual and sporadic entity, it accounts for more than 50% of all primary tumors of the appendix. [1]. In 1907, Oberndorfer 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 [2]. Nevertheless, 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"[3]. The term "appendiceal NET" will be used hereafter. The distinction between goblet cell carcinoid and other types of tumor is of great importance because of the implications for treatment and prognosis. Frank adenocarcinoma can arise from goblet cell carcinoids, and tumors with both components are classified as mixed goblet cell carcinoid-adenocarcinoma. The carcinoma component of the latter determines their prognosis, which would be worse than for a goblet cell carcinoid alone. Since the diagnosis is usually established post-appendicectomy, current recommendations focus on the early detection of: (a) the subgroup of patients who require further therapy; (b) the recurrence based on the chromogranin a plasma levels; and (c) other malignancies which are commonly developed in patients with appendiceal NETs. According to the current WHO classification [4], 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.

Case report

A 17-year-old young man presented with tender in right lower abdomen associated with vomiting and fever. Physical examinations revealed a localized pain at the right iliac fossa associated with rebound tenderness, no palpable mass. Blood investigations were within normal values except WBC (hyperleucocytosis = 12000/mm3). Chest x-ray and ECG were with no abnormalities. Abdominal ultrasound revealed acute appendicitis. The patient underwent operation it was a phlegmonous appendix.

An appendectomy was performed by laparotomy (Mac Burney incision) He passed a smooth post-operative period and he was discharged on the 2nd post-operative day in good condition. The histopathological result of the appendix revealed histopathological aspect in favor of a differentiated neuroendocrine tumor grade I of the appendix classified pT3 according to the WHO 2010 classification The immunohistochemical study showed high positivity of tumor cells to anti-A chromogranin. Histopathological result shown aspect of a well differentiated neuroendocrine tumor grade I of the appendix

Discussion

The appendicular neuroendocrine tumors account for 20% of all digestive endocrine tumors; these are the most frequent digestive endocrine tumors after small bowel tumors. Most of the tumors are located at the tip of the appendix and in the vast majority of cases the tumors behave very little aggressively. Neuroendocrine carcinomas, which are very rare in the appendix, are almost exclusively well differentiated. The 5-year survival of patients treated for endocrine tumor of the appendix is excellent for localized forms. Goblet cell carcinomas (GCC) constitute less than 5% of all primary appendiceal tumors [5] and, similar to the appendiceal NETs, their 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. The annual incidence is about 2-3 newly diagnosed cases per million of general population (170 cases per 100000). The mean age of patients is at the end of the second decade of life with an increased incidence amongst females [6-7]. Malignant appendiceal NETs (NeuroEndocrine Tumors) 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 [7]. The last finding probably reflects the increased use of diagnostic laparoscopy among females for atypical lower abdominal pain and the concomitant laparoscopic appendectomies performed [8].Normally, appendiceal NETs remain asymptomatic. While accurate preoperative diagnosis using abdominal computed tomography (CT)[9] or ultrasound[10] 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. Consequently, 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, non-specific lower right quadrant abdominal pain[11,12]. As found in our patient. GCC is derived from undifferentiated stem cells which are completely different from the endocrine cells in the mucosal stroma. In their recent study, Tang et al 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) [13]. Carcinoid syndrome is very uncommon (< 1%). In Goblet cell carcinomas 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 [14]. In 11% of cases the disease is already metastatic at the time of diagnosis, mainly to the ovaries and peritoneum [15]. However, studies propose that the ovarian metastases should be considered as secondary to adenocarcinoma rather than to appendiceal GCC, further supporting the proposed classification by Tang et al. [16]. 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 examined 6 and 12 months postoperatively and then annually while the follow-up should be lifelong. Especially for tumors > 2 cm, a CT scan and somatostatin receptor scintigraphy (SRS) is recommended at 6 months and 12 months postoperatively and then annually. Colonoscopy is advised for the early detection of synchronously present or metachronously developed large bowel tumors [17]. 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 [18]. Tumor size greater than 2 cm strongly correlates both to metastatic potential [19] and to a disapproving 5 years survival rate [20]. Around 70%-75% of the tumors are located in the apex, 15%-20% in the body and 5%-10% in the base of the organ [18]. While 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[21]. The possibility of lymph node metastases from appendiceal NETs with vascular invasion is estimated as high as 30%[22] but only 1% for tumors with appendiceal mesentery invasion[23]. However, the prognostic significance of appendiceal mesentery invasion remains controversial since its relationship to distant metastases development has been reported as between 0 and 4.1% [19, 23]. To date, there have been no reports correlating lymph node metastases to appendiceal serosa invasion.

Classification and staging of appendiceal NETs according to the TNM system [24].

Stage	T	N	M
I	T1	N0	M0
Stage	T	N	M
Ii	T1	N1	M0
	T2	N0	M0
III	T2	N1	M0
	T3	Any	NM0
IV	Any	TAny	NM1

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 metastasis.

The National Comprehensive Cancer Network 2013 Guidelines for appendiceal carcinoids ≤2 cm in diameter call for surveillance "as clinically indicated", but offer no specific criteria on which to base this decision [25]. Only for tumors >2 cm is scheduled surveillance recommended. This includes a history and physical 3–12 months post-resection and every 6–12 months thereafter up to 10 years, with consideration of follow-up imaging or laboratory markers 5-hydroxyindoleacetic acid or chromogranin A. In 2012 the European Neuroendocrine Tumor Society published consensus guidelines on the follow-up of neuroendocrine tumors, including appendiceal carcinoids [26]. These consensus guidelines state that follow-up investigations are not routinely indicated for appendiceal endocrine tumors <1 cm after simple appendectomy resulting in an R0 resection. Follow-up for carcinoid tumors 1 to 2 cm in diameter and an R0 resection was more controversial, though most participants at the conference suggested no further surveillance was necessary. The North American Neuroendocrine Tumor Society also released consensus guidelines regarding follow-up and surveillance of gastrointestinal neuroendocrine tumors in 2009 [27]. They concluded that low-grade well-differentiated appendiceal carcinoids <1 cm have a low recurrence risk and require no surveillance. Tumors 1 to 2 cm in size should be followed if poor prognostic factors such as nodal metastasis, lymphovascular invasion, mesoappendiceal invasion, or mixed pathology are identified. Concerning treatment recent recommendations [17,25,15] 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. (Therapeutic strategy applied to our patient). Right hemicolectomy (within 3 months from the appendicectomy) 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. 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 [17]. 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 [28]. Adjuvant chemotherapy is usually not effective although it can be used in patients with obvious spread of the disease [29]. Chemotherapeutic protocols are the same as those used in the treatment of colorectal adenocarcinoma

Conclusion

The appendicular neuroendocrine tumors account for 20% of all digestive endocrine tumors.Based on new comprehensions that occurred last decade, the biological behavior of appendiceal NETs ranges from totally 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. Since, in the vast majority of cases, the diagnosis is usually established post-appendicectomy, it is fundamental for physicians to find the subgroup of patients who necessitate additional therapy and to detect early the recurrence suspected on the elevation of plasma levels of chromogranin A.

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