Neuroendocrine Tumour, Mucinous Adenocarcinoma and Signet-Ring Cell Carcinoma of the Appendix: Three Cases and Review of Literature

T. Ploenes · N. Börner · C. J. Kirkpatrick · A. Heintz

Received: 12 April 2012 / Accepted: 28 June 2012 / Published online: 12 July 2012
© Association of Surgeons of India 2012

Abstract Appendiceal neoplasms are relatively common tumours. Although these tumours are often associated with signs and symptoms of acute appendicitis, most appendiceal neoplasms are clinically silent. Appendiceal neoplasms are found in 0.7 to 1.4 per cent of all appendectomy specimens. The classification of these tumours is still confusing and precise treatment methods for these neoplasms remain unclear. First choice therapy of these neoplasms is still a surgical treatment and the type of operative procedure is determined by histology and metastatic risk. Here, we report three cases of appendiceal neoplasms and make a short review of literature.

Keywords Appendix · Carcinoma · NET · Carcinoid · Surgery

Introduction

Primary appendiceal neoplasms are unusual but not rare, and appendiceal tumors account for 0.4–1 % of all gastrointestinal malignancies. Unfortunately, these neoplasms are grouped with colorectal malignancies, although clinical and histopathological features differentiate between colorectal

cancer and appendiceal neoplasms. Appendiceal tumors are often associated with signs and symptoms of an acute appendicitis and are found in 0.7–1.4 % of all appendectomy specimens. Most appendiceal neoplasms are clinically silent and the diagnosis can only be made by formal histology. The classification of these tumors is confusing and, since their first description in 1882, precise treatment methods for these neoplasms remain unclear. The clinical and pathological features are unusually varied as compared to other gastrointestinal malignancies and require expert clinical judgment for optimal treatment. In this article we present three cases of appendiceal malignancies (neuroendocrine tumor, mucinous adenocarcinoma, and signet-ring cell carcinoma) and discuss their optimal treatment with respect to relevant literature and our own experiences.

Case 1

A 69-year-old man experienced an acute onset of pain in the lower right quadrant for 1 day and a raised white blood cell count (17,700/ μ l). There was no history of fever, vomiting, nausea, or diarrhea. He had no surgical history and the only significant medical condition was systemic hypertension. On physical examination, we found tenderness at McBurney's point with no rebound tenderness. Abdominal ultrasonic sonography demonstrated a swollen appendix with wall thickening. Acute appendicitis was diagnosed and an appendectomy was performed. Intraoperatively there was an inflamed appendix with local peritonitis. The histopathological examination demonstrated a NET (neuroendocrine tumors) (pT3 pN0 M0 R0) with infiltration of the mesoappendix (Fig. 1). It was decided to perform a right hemicolectomy in the course of a second operation.

T. Ploenes (✉) · A. Heintz
Department of Visceral Surgery,
Hildegardis Academic Teaching Hospital,
Hildegardisstraße 2,
5513 Mainz, Germany
e-mail: Till_ploenes@gmx.de

N. Börner
Gastroenterology Practice,
Mainz, Germany

C. J. Kirkpatrick
Institute of Pathology, Medical University Center Mainz,
Mainz, Germany

Case 2

A 68-year-old man underwent a screening colonoscopy and a 2×3 cm submucous tumor at the appendix base was found (Fig. 2). Histological examination of samples taken from the surface showed no malignancy. Preoperative evaluation did not reveal any abdominal pain, fever, vomiting, hematemesis, melaena, or diarrhea. Abdominal ultrasound sonography demonstrated an intramural tumor at the appendiceal base only. We performed a laparotomy and after intraoperative histopathological examination a right hemicolectomy was performed. Histopathological analysis revealed a mucinous adenocarcinoma (pT1 pN0 M0 R0).

Case 3

A 56-year-old female patient presented with severe pain in the lower right quadrant localized to McBurney's point underwent emergency appendectomy. The operation revealed an inflamed and perforated appendix with localized peritonitis. Microscopy revealed an adenocarcinoma of the appendix with signet ring cells and mesoappendiceal invasion (pT3 pN0 cM0 G3 R0) (Fig. 3). Due to the perforated appendix and the classification of the tumor, it was decided to perform an adjuvant chemotherapy after right hemicolectomy according to the FOLFOX scheme.

Discussion

In 1907, Oberndorfer introduced the term “carcinoid” for carcinoma-like lesions of the gastrointestinal tract, which

Fig. 2 Submucous tumor of the appendix base found during a screening colonoscopy

showed a more benign behavior than conventional carcinomas. He called these lesions carcinoids. The carcinoid is a neoplasm originating in the neuroendocrine tissue found especially in the gastrointestinal tract and the lung. Traditionally carcinoids were divided 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. In 2000, the WHO classification termed carcinoids of the appendix as (well-differentiated) neuroendocrine tumors (NET).

Neuroendocrine tumors of the appendix are the most common primary malignant lesion originating in the appendix and are found in 0.3–0.9 % of patients undergoing appendectomy [1, 2].

Fig. 1 Histologic findings in Case 1. Neuroendocrine cells arranged in cords and spindle-shaped configuration infiltrating the submucosa (a, CK 20 immunostain 4×; b, CK 20 immunostain 40×; c, hematoxylin-eosin stain 40×; d, synaptophysin immunostain 40×)

Fig. 3 The adenocarcinoma of the appendix with the signet ring cell and mesoappendiceal invasion found in Case 3. Histologic examination shows carcinoma cells infiltrating vermiform appendix (a, hematoxylin-eosin stain 4×; b, hematoxylin-eosin stain 40×; c, periodic acid-Schiff reaction 4×; d, periodic acid-Schiff reaction 10×)

Generally neoplasms of the appendix are found in 0.9–1.4 % of all appendectomy specimens [3], and the carcinoid tumors have the highest prevalence accounting for 32–57 % (up to 85 %) of all appendiceal neoplasms [4–6].

Interestingly, epidemiological studies have reported a slightly higher incidence of female patients [5, 7, 8], which some authors ascribed to the higher laparoscopy and appendectomy rate. This allows detection of more lesions, but McCusker et al. reported that the higher rate of operations could not fully explain the higher prevalence of carcinoids in female patients. The peak incidence of diagnosed carcinoids of the appendix ranges between 15 and 19 years of age for female patients and 20 and 29 years of age for men [8]. However, diagnoses of malignant lesions of the appendix are concentrated in patients between the ages of 38 and 49 years [5, 7, 9].

Carcinoid neoplasms have their roots in the same progeny as other gastrointestinal cells and not, as suggested earlier, in neural tissue. However, carcinoids are generally suspected to be malignant, but there is evidence that appendiceal carcinoids have a much better prognosis compared to other gastrointestinal NET. This may indicate a different cell derivation of appendiceal compared to other gastrointestinal carcinoids. In 1928, Mason proposed that appendiceal carcinoids originated from subepithelial neuroendocrine cells (SNC), whereas other located NETs originated from epithelial neuroendocrine cells (ENC). The immunological characterization of gastrointestinal NETs demonstrated a different β -catenin level in appendiceal NETs as compared to NETs localized elsewhere [10]. The expressed pattern of catestatin-A, a novel 21-amino acid peptide, differs in appendiceal NETs compared to other localized NETs as well [11].

There is no specific clinical sign or symptom associated with carcinoids of the appendix. Most NETs of the appendix are asymptomatic and usually incidental findings during appendectomy or other benign pelvic surgery and cholecystectomy.

Over 50 % of carcinoids mimic acute appendicitis with the classical right lower quadrant abdominal pain, which leads to appendectomy [1, 3, 12, 13].

Some authors suggest that the obstruction of the tumor causes the symptom of appendicitis, but histopathological analysis confirms an obstructing factor in only 25 % [3].

NETs of the appendix are usually discovered during surgery or by pathologists. Even a symptomatic obstructive NET of an appendix will usually be identified during computed tomography scans or ultrasound as appendicitis [14], and there is only one case reported presenting the sonographic diagnosis of an appendiceal NET in a 14-year-old boy [15]. However, it is very doubtful that routine application of these techniques will increase preoperative diagnosis of this entity. Hematological, biochemical, or urinary

investigations are only indicated by the rare carcinoid syndrome to monitor the progression of the disease.

The first-choice therapy is surgical treatment and the type of operative procedure is determined by metastatic risk. Although there are many factors correlating with increased metastatic potential, the size of the appendiceal NET is the best prognostic factor [1, 3, 16]. The risk of metastases in tumors less than 1 cm is near zero, and it is a matter of general agreement that appendectomy alone is justified. For tumors greater than 2 cm of diameter right hemicolectomy is indicated. For NETs of the intermediate type between 1 and 2 cm of diameter further criteria are needed. Only the location (at base vs. mid-appendix or at tip), metastases, and invasion/mesoappendiceal involvement appear to be reliable criteria. Ki67 index, reduced E-cadherin level, or angioinvasion needs further investigation but may be important future prognostic markers. However, the intermediate type demands a decision on tumor risk versus procedural patient risk, and some authors even discuss a cutoff for appendiceal NETs of 2 cm diameter for appendectomy [17].

Adenocarcinomas of the appendix are less common than appendiceal NETs, and since the first case was reported by Berger in 1882, there have been only a few hundred cases described in the literature. Because of the low incidence, there is still controversy concerning the optimal treatment for this cancer.

Appendiceal adenocarcinomas are very rare and an age-adjusted incidence rate for these tumors is reported to be 0.12 up to 0.95 per 1,000,000 people [18]. The mean age at presentation is 63 years and men are, with 58 %, more affected than women. In 1995, Cortina et al. reviewed 13 patients with adenocarcinoma of the appendix and demonstrated that 77 % had metastatic disease on examination. About 83 % of female patients had synchronous ovarian lesions, and in 15 % of patients, a second primary malignancy was found.

According to the WHO classification, carcinomas of the appendix were divided into adenocarcinoma, mucinous adenocarcinomas, which were mucinous and mostly well differentiated, signet-ring cell adenocarcinomas (if more than 50 % of cells are signet-ring cells), small cell carcinomas, and undifferentiated carcinomas. Well-differentiated and mucinous carcinomas with cystic structures were termed mucinous cystadenocarcinomas [19].

The clinical presentation of an appendiceal adenocarcinoma is usually not specific, and in the most cases initial symptoms are the result of the neoplasm invading the peritoneal cavity. In 69 % cases abdominal pain in the lower right quadrant was reported, in 19 % a palpable abdominal mass was found. Other described symptoms are vomiting, nausea, ascites, change in bowel habits, chronic pelvic pain, or weight loss [18, 20].

Based on these reported signs and symptoms, acute abdomen, acute appendicitis, hernia or ovarian mass is most commonly diagnosed [18, 19].

Correct diagnosis is usually not made preoperatively. However, radiologic findings of appendiceal adenocarcinomas are often dependent on the detection of a resulting mucocele, but a mucocele is only the description of an obstructive mass by intraluminal accumulation of mucoid material and does not contribute to a pathologic diagnosis. The causes of a mucocele may also be benign and only the diameter may suggest the dignity of the process [14, 20, 21].

In some cases a soft tissue mass in the lower right quadrant can be detected and calcification increases the specificity. Computer tomography, ultrasound, and magnetic resonance can also be useful, but preoperative detection is still rare. Colonoscopy can be an important tool for diagnosing submucosal lesions, although necrosis may impede diagnosis.

Due to the rarity of the adenocarcinoma of the appendix, it is very difficult to carry out studies on which surgeons can base their therapeutic decisions and some of the older literature regards these neoplasms as a basically slow-growing noninvasive process. Thus, it is not surprising that some early authors claim that appendectomy alone is a suitable treatment. During the 1990th, a controversy existed on the optimal surgical therapy and some authors advocated right hemicolectomy as the therapy of choice. According to new literature and based on our own experience, we agree with these authors that patients are best served by the more aggressive treatment even if a second operation is needed. After all, the presence of metastases in the ovaries in female patients is very frequent and routine oophorectomy is also indicated. If nodal metastases are detected, patients may benefit from adjuvant chemotherapy based on 5-fluorouracil and levamisole. Finally, there is a high incidence (up to 35 %) of synchronous and metachronous neoplasms (especially in the large intestine), and computer tomography and colonoscopy should be performed during follow-up to detect these lesions. Metastatic disease of appendiceal adenocarcinomas is common, and it is a well-known fact that perforated appendices with adenocarcinoma may result in pseudomyxoma peritonei caused by malignant cells seeding on the omentum and implanting in the peritoneal cavity. In this case optimal treatment includes right hemicolectomy with lymph node dissection, oophorectomy, omentectomy, peritoneotomy, and removal of malignant ascites. Systemic chemotherapy does not improve survival, but intraperitoneal chemotherapy or radiation may be beneficial in these patients.

References

- Goede AC, Caplin ME, Winslet MC (2003) Carcinoids tumour of the appendix. *Br J Surg* 90:1317–1322
- Stinner B, Rothmund M (2005) Neuroendocrine tumours (carcinoids) of the appendix. *Best Pract Res Clin Gastroenterol* 19(5):729–738
- O'Donnell ME, Carson J, Garstin WIH (2007) Surgical treatment of malignant carcinoid tumours of the appendix. *Int J Clin Pract* 61(3):431–437
- Connor SJ, Hanna GB, Frizelle FA (1998) Appendical tumour: retrospective clinicopathologic analysis of appendiceal tumours from 7970 appendectomies. *Dis Colon Rectum* 41:75–80
- Sandor A, Modlin IM (1998) A retrospective Analysis of 1570 appendiceal carcinoids. *Am J Gastroenterol* 93:422–428
- McGory ML, Maggard MA, Kang H, O'Connell JB, Ko CY (2005) Malignancies of the appendix: beyond case series report. *Dis Colon Rectum* 48(12):2264–2271
- McCusker ME, Cote TR, Clegg LX, Sobin LH (2002) Primary malignant neoplasms of the appendix. *Cancer* 94:3307–3312
- Hemminki K, Li X (2001) Incidence trends and risk factors of carcinoid tumors. A nationwide epidemiological study from Sweden. *Cancer* 92:2204–2210
- Modlin IM, Lye KD, Kidd M (2003) A 5-decade analysis of 13715 carcinoid tumors. *Cancer* 97:934–959
- Barshack I, Goldberg I, Chowers Y et al (2002) Different beta-catenin immunoreexpression in carcinoid tumors of the appendix in comparison to other gastrointestinal carcinoid tumors. *Pathol Res Pract* 198:531–536
- Prommeger R, Ensinger C, Adlassnig C et al (2004) Catestatin—a novel neuropeptide in carcinoid tumours of the appendix. *Anticancer Res* 24:311–316
- Moertel CL, Weiland LH, Telander RL (1990) Carcinoid tumors of the appendix in the first two decades of life. *J Pediatr Surg* 25:1073–1075
- Roggo A, Wood WC, Ottinger LW (1993) Carcinoid tumors of the appendix. *Ann Surg* 217:385–390
- Pickhardt PJ, Levy AD, Rohrmann CA Jr, Kende AI (2003) Primary neoplasms of the appendix: radiologic spectrum of disease with pathologic correlation. *Radiographics* 23:645–662
- Deeg KH, Reisig A, Seitz G (2003) Sonographic diagnosis of a carcinoid tumour of the appendix in 14-year-old boy. *Ultraschall Med* 24:120–122
- Stinner B, Kisker O, Zielke A, Rothmund M (1996) Surgical management for carcinoid tumours of small bowel, appendix, colon and rectum. *World J Surg* 20:183–186
- Bamboot ZM, Berger DL (2006) Is right hemicolectomy for 2.0-cm appendiceal carcinoids justified? *Arch Surg* 141:349–352
- Ito H, Osteen RT, Bleday R, Zinner MJ, Ashley SW, Whang EF (2004) Appendiceal adenocarcinoma: long-term outcomes after surgical therapy. *Dis Colon Rectum* 47(4):474–480
- Hamilton SR (2000) Pathology and genetics of tumours of the digestive system. IARC, Lyon
- Gonzalez-Moreno S, Sugarbaker PH (2004) Right hemicolectomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding. *Wiley Interscience*
- Deans GT, Spencer RA (1995) Neoplastic lesions of the appendix. *Br J Surg* 82:229–306