

Carcinoid tumour of the appendix: problems of diagnosis and treatment

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Rezumat

Tumorile carcinoide apendiculare: probleme de diagnostic și tratament

Tumorile carcinoide neuroendocrine sunt considerate cele mai frecvente tumori apendiculare primare. Tumorile apendiculare primare sunt neobișnuite. Examinarea histopatologică de rutină a pieselor operatorii de apendicectomie este justificată datorită constatărilor nu rare de tumori apendiculare. În cazurile de apendicită la vârstnici, indexul de suspiciune pentru tumorile epiteliale ale apendicelui vermiform va fi crescut. Mai mult, odată ce este stabilit diagnosticul unei leziuni adenomatoase, examinarea colonoscopică a întregului cadru colic este recomandată datorită frecvenței neoplasmelor colo-rectale sincrone. În studiul nostru, noi prezentăm 3 cazuri de tumori carcinoide apendiculare și descriem tratamentul și rezultatele obținute. Ele au fost diagnosticate incidental după examinarea histopatologică a apendicelui vermiform supus examinării în cursul conduitei terapeutice pentru alt diagnostic clinic. Apendicectomia este suficientă pentru leziunile < 1 cm, dar pentru leziunile peste 2 cm în diamteru există o creștere semnificativă a diseminării metastatice și astfel hemicolectomia dreaptă este recomandată în astfel de cazuri. Tumorile carcinoide apendiculare sunt găsite în 0,3 – 0,9% din pacienții ce au suferit apendicectomie. Controverse există în ce privește conduita terapeutică urmând apendicectomiei, în special cu privire la

rolul hemicolectomiei drepte la pacienții cu tumori mai mici de 2 cm în diametru.

Cuvinte cheie: tumori apendiculare, carcinoid, leziuni adenomatoase, apendicită

Abstract

Carcinoids (neuroendocrine tumours) are considered the most common primary appendiceal neoplasm. Primary appendiceal tumours are uncommon. Routine histopathological examination of appendectomy specimens is justified given the not infrequent incidental finding of appendiceal tumours. In cases of appendicitis in the elderly, the index of suspicion for epithelial tumours of the appendix should be raised. Moreover, once the diagnosis of an adenomatous lesion is made, colonoscopic examination of the entire large bowel is mandatory given the frequency of synchronous colorectal neoplasia in our population. In our study, we review 3 cases of carcinoid tumor of the appendix and describe their presentation, treatment and outcome. They are often diagnosed incidentally after histopathological examination of the vermiform appendix submitted in the course of the management of another clinical diagnosis. Appendectomy is appropriate for lesions < 1 cm but for lesions over 2 cm in diameter there is a significant increase in metastatic spread and thus right hemicolectomy is required in such cases. Appendiceal carcinoid tumours are found in 0,3 - 0,9 per cent of patients undergoing appendicectomy. Controversy exists over the management following appendicectomy, especially with regard to the role of right hemicolectomy in patients with tumours smaller than 2 cm in diameter.

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Key words: appendiceal tumours, carcinoid, adenoma, appendicitis.

Introduction

Carcinoid tumours are among the most common primary malignant lesions arising from the appendix, accounting for up to 60% of all appendiceal tumours (1). They are present in approximately 0.3% (2) of patients undergoing appendectomy and are often found incidentally during surgery for other indications. Although most appendiceal carcinoids are clinically silent and behave benignly, they do have the potential to metastasize. Extensive investigation into the molecular, biological, and clinical characteristics of the tumour since its recognition early in the 20th century has resulted in a management algorithm that has seen little change since initial proposals were made in landmark articles by Moertel and colleagues in 1968 (2) and 1987 (3). Surgical resection remains the mainstay of treatment and the only means by which complete cure may be achieved. During the past decade, there has been extensive investigation into the importance of characteristics other than tumour size that might have an association with metastasis and poorer prognosis. The prognostic data on characteristics such as vascular, muscular, mesoappendiceal, and periappendiceal lymphatic invasion have been conflicting (4,5). Tumour size, in contrast, is considered the most important prognostic factor, with a proposed increase in the risk of metastasis for tumors greater than 2.0 cm (3).

Presentation of cases

In January 2009 we examined a 20-year-old male patient who was admitted to the Second Surgical Clinic of Emergency Hospital of Craiova for pain in the right iliac fossa, fever, nausea. Routine hematological and biochemical investigations included blood sugar, urea nitrogen, hemoglobin, urine analysis, T. Quick, T. Howell, levels that were within normal limits. Leucocytes = 10.800/mm³.

On the physical examination the patient present pain to the lower right side of the abdomen, rebound tenderness. Digital rectal examination, elicits tenderness in the rectovesical pouch.

The patient underwent emergency surgical intervention for acute appendicitis, CO no. 79/10.03.2009 and we found turbid peritoneal fluid approximate 20-30 ml, who was to harvest for bacterial culture and sensitivity testing. We found the medio-cecal descendent appendix coated of the great omentum. We performed appendicectomy, omentectomy, drainage with two drain tube, situated in the rectovesical pouch and in the retro-cecal space.

Macroscopic examen of the appendix emphasized of the tumor mass to the apex 1,2 cm in the diameter and 2 cm of the lenght, the thickening of the omentum (Fig. 1 and 2).

Histological examination after surgery showed carcinoid

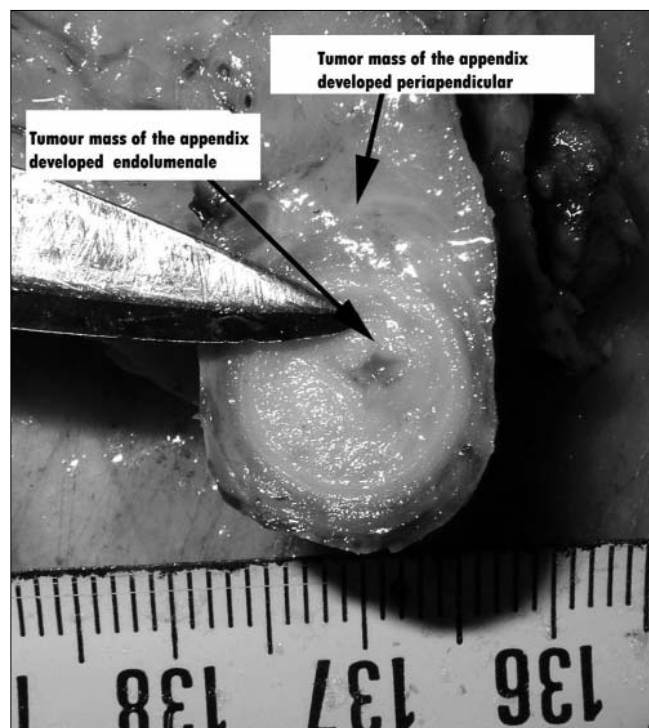


Figure 1. Tumour mass of the appendix cross-sections fixed in formalin. It is noted that the tumour mass of the appendix has developed endolumenale and periapendicular

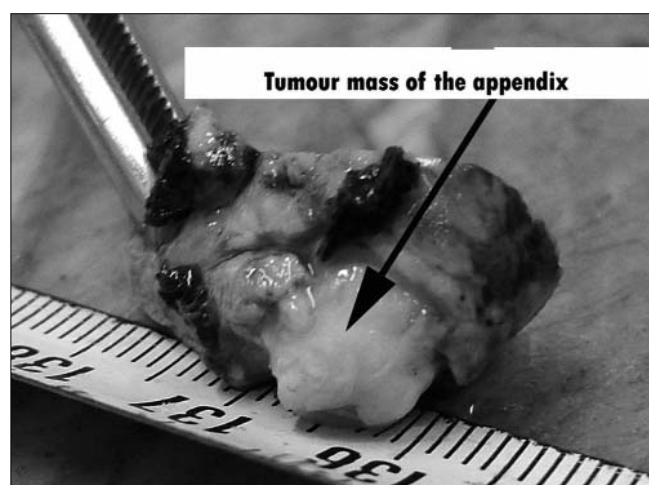


Figure 2. Macroscopic appearance of tumour mass of the appendix (operative piece fixed in formalin)

tumour of the appendix invading muscle wall of the appendix and diffusely inflamed appendix (Fig. 3). Luminal obstruction of the appendix by the neuroendocrine tumour with 1,2 cm diameter and 1,5 cm in the lenght.

Immunohistochemistry: chromogranin A (clone DAK-3) in the cytoplasm of the tumor cells located in the submucosa muscle wall of the appendix and in the periapppendicular adipose tissue (Fig. 4). Synaptophysine (Clona SY 38) was positive in the cytoplasm of the tumor cells (Fig. 5).

After the histopathologically examen the patient was

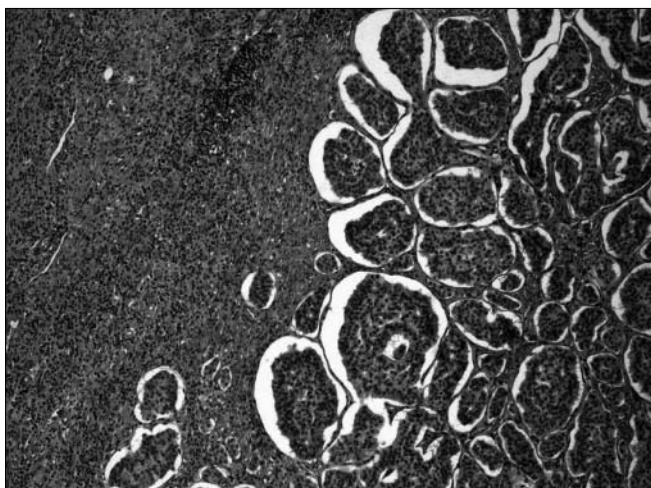


Figure 3. H&E staining (ob.x20), Appendix with neuroendocrine tumor

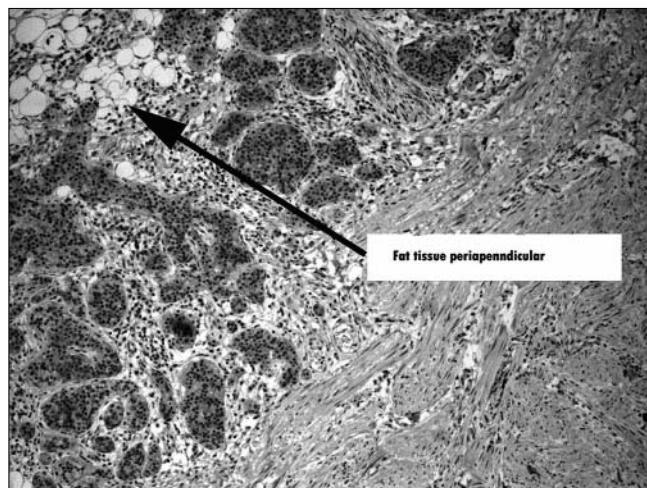


Figure 4. Immunohistochemistry: Synaptophysine x10 (clone SY 38) positive in the cytoplasm of tumor cells, located in submucosa, muscle layer and fat tissues periapendicular

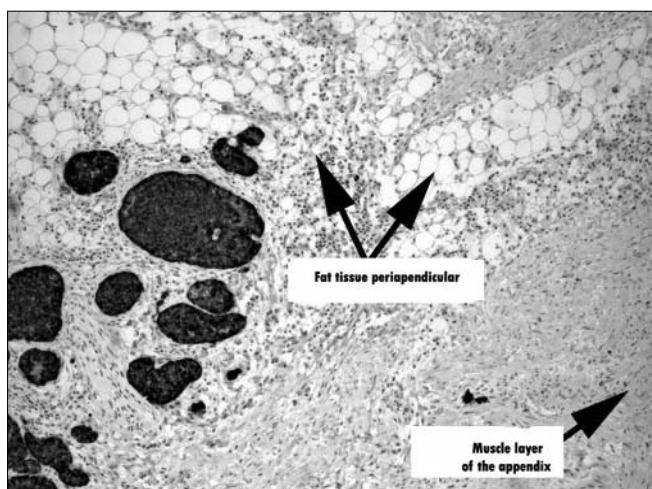


Figure 5. Immunohistochemistry: Chromogranin A x20 (clone DAK-A3) mostly positive in the cytoplasm of tumor cells located in submucosa, muscle layer and fat tissues periapendicular

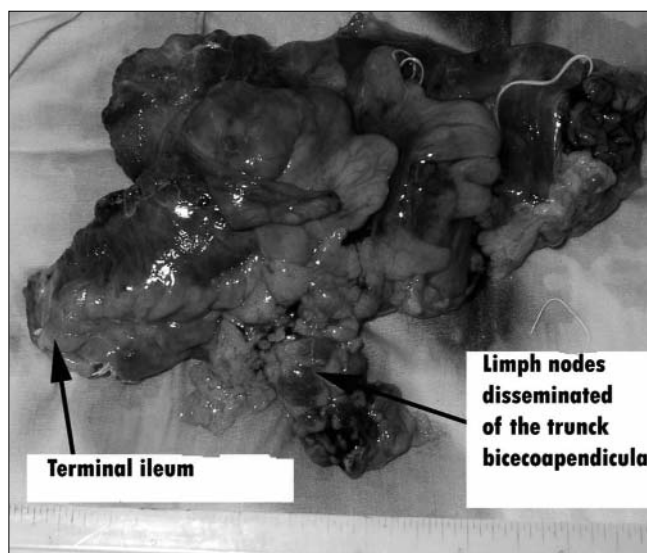


Figure 6. Operative piece (terminal ileum, right colon) – right hemicolectomy. Observe the many lymph nodes disseminated of the trunk bicecopendicular

admitted in Second Surgical Clinic. Computerized tomography (CT): liver with normal dimension, normal structure, left lobe = 5,4 cm, right lobe = 15 cm, gall bladder without stone. Pancreas normal. Urinary bladder without parietal lesions. Colon without parietal modifications. It wasn't limphadenopathy in the examined area.

The laboratory data on admission: Hb=12,3 g/dl, L = 7700/mm³, glicemia=87 mg%, urea=21 mg%, T.Q=80%, INR=1,15, APTT=24 sec., ASAT=14u/l, ALAT=13 u/l. The concentration of 24 – h urinary levels of 5 hidroxyindolacetic acid was 3,6 mg/24 h (N=2-9), level of seric serotonin was 88,2 µg/l (N=117-190) and level of chromogranin A was 24 µg/l (N=19-98).

Ecg: normal, Rx chest: normal.

On the data 09.04.2009 (CO 486), the patient underwent surgery and we found ileon and sigmoid colon adherent to the parietal wall and to the rectovezical pouch. We found tumor mass of the basis of the appendix, with 1 cm diameter (Fig. 6 and 7). A right hemicolectomy with ileotransverso-anastomosis end-side was performed.

Postoperative evolution was favorable. It was discharged in a good condition.

The patient C.A., 18 years old, female, admitted in Second Surgical Clinic of Emergency Hospital of Craiova, on the data of 17.01.2007, for pain in the right iliac fossa. Physical examination showed pain in the right iliac fossa of the abdomen, abdominal rebound tenderness. Rectal examination: anal canal and rectal ampulla normal aspect.

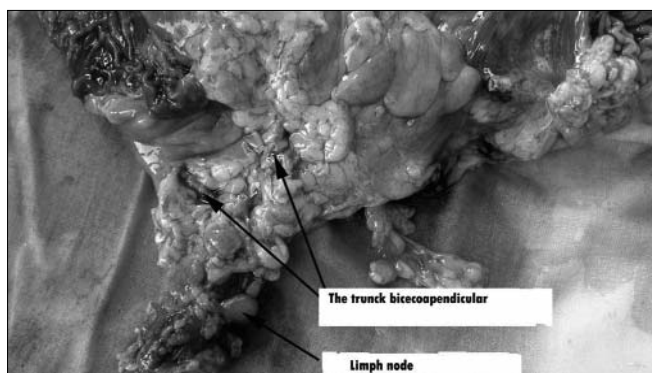


Figure 7. Detail that shows multiple lymph nodes on the path trunk bicecocolic

The laboratory data on admission: Hb=12,5 g/dl, L=8300/mm³, glicemia=83mg%, urea=23 mg%, ASAT= 12 ui, ALAT= 14 ui, Urine analysis: normal.

On the data 17.01.2007, CO no. 112, we perform the surgical treatment and we found the serosa of the appendix congested with yellow plaques of exudates. Appendix was situated mediocecal descendent, with 11 cm length. It was appreciated that acute appendicitis. The surgical treatment was appendectomy.

Gross description: the cross sectioned end appears dilated and the wall appears thickened and adenomatous.

Postoperative evolution was favorable and the patient was discharged in a good condition.

Histopathological analysis showed classical carcinoid tumour of the appendix invading muscle wall. Luminal obstruction of the appendix by the neuroendocrine tumour with 0,75 cm diameter.

Immunocytochemistry: chromogranin A (clone DAK-3) in the cytoplasm of the tumoral cells located in the submucosa muscle wall of the appendix. Synaptophysin (Clon SY 38) was positive in the cytoplasm of the tumoral cells.

Postoperative colonoscopy and computerized tomography were normal.

The patient M.P., 67 years old, male, was admitted in Surgical Clinic of Emergency Hospital of Craiova on the 23.04.1997 for right lower quadrant pain and abnormal intestinal transit.

The laboratory data on admission: Hb=12,4 g/dl, Leucocytes=8600/mm³, glicemia=97mg%, urea=45mg%, ASAT=23 ui, ALAT = 14 ui, Urinary analysis: normal.

Irigography: cecal lacunar image.

Ecography: liver, pancreas, kidney normal aspect. Without liquid collection in the peritoneal cavity.

We perform the surgical treatment and intraoperative finding was the tumoral mass in the appendix zone (transformation of the appendix in the tumoral mass what included cecum, adjacent of the base of the implanting of the appendix), the tumor had approximate 6 cm in diameter and didn't invaded other organs, but was invaded the peritoneal wall and the mesenteric peritoneum. The liver and other organs haven't been invaded.

The patient underwent right hemicolectomy with ileo-transverso-anastomosis end to side and peritonectomy in the invaded zone.

Operative piece: tumoral mass outset the appendix. The tumour had 6 cm in the diameter and invaded the cecum around of the basis of the appendix. The mucosa of the cecum was invaded by the tumor upon of 3 cm surface. Ileocecal valve wasn't affected.

Histopathological analysis showed classical carcinoid tumor of the appendix invading the wall of the appendix and cecum. The peritoneum of the abdominal wall and the mesenteric peritoneum were invaded.

No adjuvant therapy was administered. Seven years later the patient was operated for high intestinal obstruction and intraoperative we found multiple nodular dissemination upon the peritoneum of abdominal wall with invasion of the small bowel, determined intestinal obstruction of the small bowel. We practiced entero-enterale derivation. The biopsy of the peritoneal tumoral mass emphasized microscopic structure of carcinoid tumour. The patient died 8 month later from bronchopneumonia.

Discussion

Epidemiological studies show a slight but consistently higher incidence among female patients (6,7,8). Some authors have ascribed this to the higher appendectomy and laparoscopy rate among young women, which allows more incidental small lesions to be detected (9). McCusker and colleagues (10) and others (11,3) found that the incidence is increased to a greater extent than can be explained by the appendectomy rate alone, suggesting a true higher incidence.

These neuroendocrine tumours are more often diagnosed in the young, with a reported peak incidence between 15 and 19 years of age for female patients (11) and 20–29 years for men (8). In our study the age of female patient was 18 years old and to the young male patient the age was 20 years old.

Large epidemiological studies, however, suggest an average diagnostic age of between 38 and 49 years for malignant lesions (6,10,8). Goblet cell carcinoids tend to present at a later age of about 52 years (10). The differences noted between databases probably represent differences in the histological criteria used, and the exclusion or inclusion of small benign lesions, which are more common among the young (6). The situation may perhaps be misrepresented in the young as they are more likely to undergo appendectomy, resulting in an incidental finding of a carcinoid tumour.

Carcinoid tumours are of neuroendocrine origin and derived from primitive stem cells, which can give rise to multiple cell lineages. In the intestinal tract, these tumours develop deep in the mucosa, growing slowly and extending into the underlying submucosa and mucosal surface. This results in the formation of small firm nodules, which bulge into the intestinal lumen. These tumours have a yellow, tan, or gray-brown appearance that can be observed through the intact mucosa. The yellow color is a result of cholesterol and

lipid accumulation within the tumor. Tumours can have a polypoid appearance and occasionally become ulcerated (12). With expansion and infiltration through the submucosa into the muscularis propria and serosa, carcinoid tumors can involve the mesentery. Metastases to the mesenteric lymph node and liver, ovaries, peritoneum, and spleen can occur (13). Upon histologic examination, carcinoid tumours have 5 distinctive patterns: (1) solid, nodular, and insular cords; (2) trabecular or ribbons with anastomosing features; (3) tubules and glands or rosette like patterns; (4) poorly differentiated or atypical patterns; and (5) mixed patterns. A combination of these patterns is often observed. Tubules can contain mucinous secretions, and individual tumour cells can contain mucin-positive material, which includes the various acidic and neutral intestinal mucin. Tumors rarely have eosinophilic stroma. Capillaries are often prominent. Cells are uniformly round or polygonal with a central nucleus and punctate chromatin as well as small nucleoli and infrequent mitosis. The cytoplasm can be slightly acidophilic, basophilic, or amphophilic. Eosinophilic granules may be present. Immunohistochemically, these tumours have a strong positive reaction to keratin and neuroendocrine markers. These include chromogranin and synaptophysin. In our cases, immunohistochemistry exam emphasized: chromogranin A (clone DAK-A3) mostly positive in the cytoplasm of tumor cells located in submucosa, muscular layer of the appendix and peripendicular fat tissues; synaptophysin (clone SY 38) was positive in the cytoplasm of tumour cells. In midgut carcinoids, cells are arranged in closely packed, round, regular, monomorphous masses. In the appendix, carcinoids appear as discrete yellow nodules in the lumen. Lesions associated with diffuse wall thickening are relatively uncommon. Carcinoid tumours commonly affect the tip of the appendix. Most carcinoid tumours invade the wall of the appendix, and lymphatic involvement is nearly universal. About 75% of patients have evidence of peritoneal involvement. However, only a few patients have regional or distant dissemination. The size of the tumour can be correlated with outcome of the disease; tumors smaller than 1.5 cm in diameter (after formalin fixation) rarely result in distant metastases or recurrences. Carcinoid tumors can be associated with concentric and elastic vascular sclerosis that results in obliteration of vascular lumina and ischemia. A common finding is elastosis and fibrosis that surround nests of the tumor cells and that result in matting of the involved tissues and lymph nodes. Fibroblastic proliferation may result from the stimulation of fibroblast cells by growth factor. This stimulation may be a result of a local release of tumor growth factor (TGF)- β , β -fibroblast growth factor (β -FGF), and platelet-derived growth factor. Classic carcinoid tumor cells are argentaffinic and argyrophilic. At present, immunostain and hormonal markers are used for diagnosis. Carcinoids may have somatostatin receptors. Five identified somatostatin receptors are members of the G-protein receptor family.

Clinical presentation and factors predicting metastatic potential

Carcinoid tumours of the appendix are usually asymptomatic

and an incidental finding; they rarely present with metastases (14). They can cause appendicitis as a result of luminal obstruction, but this is not common as they are most often located at the tip of the organ. Connor and colleagues (1) found the majority of presentations to be as an incidental finding associated with acute appendicitis. Of the carcinoids in their series, 62 per cent were located in the distal third of the appendix. Roggo and colleagues (114) demonstrated similar features, with 54 per cent presenting in association with acute appendicitis and 78 per cent found at the tip of the appendix. Several other studies have confirmed this pattern of presentation (3,11,15). Moertel and colleagues (2) reported that tumours were most commonly diagnosed during benign pelvic surgery or at cholecystectomy. Goblet cell carcinoids often present clinically as a diffusely inflamed appendix, with the diagnosis made by histological examination after surgery (16,15).

Tumour characteristics that predict aggressive behaviour include size, histological subtype and mesoappendiceal involvement. Virtually all studies support the predictive value of tumour size. Moertel and colleagues (2) first indicated in 1968 that metastatic disease from lesions smaller than 2 cm was unlikely. This was corroborated in their follow-up study reported in 1987 (3). Of 150 patients, 127 had lesions of less than 2 cm in diameter and none had metastases; three of 14 patients with lesions larger than 2 cm but smaller than 3 cm had metastatic disease, and four of nine patients with lesions greater than 4 cm had metastatic disease. In our cases, the size of the tumor was 1.2 cm for young male patient and 0.75 cm for female patient (the old male patient, the tumor had 6 cm in diameter). Based on these observations, the authors considered that the risk of metastatic disease in tumours smaller than 2 cm was sufficiently low to treat them by local resection alone (appendicectomy).

Lymphatic invasion was an almost universal finding in the same series. Moertel and colleagues, found no difference in histological architecture or morphology of cells between metastatic and non-metastatic carcinoids larger than 1 cm. Vascular invasion, uncommon in this study, was not significantly related to outcome (3), although it has been cited as an indicator favoring a more aggressive approach. Angioinvasion was regarded as a feature of highly malignant neuroendocrine lesions by Capella and colleagues (17). The number of Ki67 (a proliferation marker)-positive cells correlated with mitotic activity and the proportion of positive nuclei per square millimeter was always greater than 2 per cent in high-grade tumors. No significant difference in Ki67 expression between prognostic groups in low grade malignant tumors was noted. Sokmensusuer and colleagues (18) evaluated 37 gut carcinoids. The Ki67 proliferation index was significantly increased in all tumours greater than 2 cm in diameter. There were no appendiceal tumors larger than 2 cm in this study. Kawahara and colleagues (19) demonstrated that overexpression of p21 and reduced staining of E-cadherin correlated with malignant behavior, and that Ki67 did not. The prognostic value of proliferation markers in pancreatic and a gastric (foregut) neuroendocrine tumour is well established (20). The evidence

in midgut and hindgut lesions, excluding the appendix, also suggests that a high proliferative index may correlate with more aggressive behavior (21), but in the appendix there is currently little evidence for or against this. Despite this lack of evidence, an appendiceal carcinoid with high mitotic and Ki67 indices should be considered a potentially aggressive neuroendocrine tumor, as is the case for other gastrointestinal carcinoids. The present authors therefore regard these immunohistological markers as a complementary tool in decision-making.

The vast majority of patients do not require any further procedure or investigation relating to a carcinoid tumor following appendectomy. Lesions smaller than 1 cm require no staging unless recognized as high-grade malignant. Patients with tumors of between 1 and 2 cm may benefit from additional screening. Plasma chromogranin A is currently the most important blood marker available, the level being raised in 80-100 per cent of patients with neuroendocrine tumors (22,23). Chromogranin A levels correspond to tumour load and levels above 5000 $\mu\text{g/l}$ predict a poor outcome (24).

Patients with raised levels of chromogranin A require further imaging. Intra-abdominal or mesenteric disease may require preoperative computed tomography with contrast agent. ^{111}In -labelled octreotide scintigraphy is the most sensitive imaging modality in the diagnosis and staging of metastatic disease. Those with tumors larger than 2 cm, incomplete resections, and metastatic disease or goblet cell carcinoids warrant further investigation, including determination of plasma chromogranin A concentration, 24-h urinary levels of 5-hydroxyindoleacetic acid, computed tomography and ^{111}In -labelled octreotide scintigraphy.

In our case the concentration of 24-h urinary levels of 5 hydroxyindolacetic acid was 3,6 mg/24 h ($N=2-9$), level of seric serotonin was 88,2 $\mu\text{g/l}$ ($N=117-190$) and level of chromogranin A was 24 $\mu\text{g/l}$ ($N=19-98$).

Patients with appendiceal carcinoids have a good prognosis overall. The vast majority are cured by simple appendectomy as the primary and final procedure, the diagnosis often being made subsequently. With only a handful of small lesions having ever been reported as metastasizing (25), patients with a tumor smaller than 1 cm will almost certainly have no future problem from the lesion. This accounts for at least 70 per cent of patients in most studies (2) and the vast majority of situations that general surgeons will encounter. It is nevertheless true that in patients with metastatic disease the primary site is often not identified. Therefore the true relationship to an appendix primary is difficult to determine. When series of patients with malignant carcinoid from large centers are studied (26,27), deaths are rare. Most patients survive many years of close follow-up, even those with metastases at presentation. Appendiceal carcinoids usually metastasize to the regional lymph nodes rather than to the liver (8,25). Patients with local disease are reported to have a 5-year survival rate of 92 per cent, those with regional metastases 81 per cent, and the few with distant metastases 31 per cent (8). Lesions at the base of the appendix are more likely to produce local recurrence than those at the tip if treated only by simple appendectomy.

Problems of treatment

The accepted treatment of malignant carcinoid tumours of the appendix is a primary right hemicolectomy (RHC) or an interval RHC following appendectomy and histological confirmation of a carcinoid greater than 2.0 cm (28). Although there have been reports of recurrent disease in patients with tumors greater than 2.0 cm treated by simple appendectomy alone, the literature (3,11) suggests that recurrence occurs as late as 25 years after the initial diagnosis, and death from metastases occurs even later. This raises the question of whether RHC should be considered for appendiceal carcinoids greater than 2.0 cm in diameter. Right hemicolectomy is a significant abdominal procedure with an associated risk, especially in the elderly or infirm. Reported morbidity rates for elective right hemicolectomy are close to 40 per cent. Respiratory and cardiovascular complications predominate, putting the elderly at particular risk (29), although this should not preclude operation in those with a clear indication for surgery.

Comparing the risk of right hemicolectomy with the survival figures for patients with lesions smaller than 2 cm, a conservative approach seems appropriate in most circumstances. In those with tumors of 1-2 cm towards the tip of the appendix, with typical carcinoid histology, no angiolymphatic or mesoappendiceal invasion (8) and a low proliferative index, a right hemicolectomy does not appear justified. For larger lesions or positive margins only about 20 per cent of specimens show any residual or lymphatic disease, but on a risk basis hemicolectomy can be justified if cure is achieved (27).

Syracuse and colleagues (15) emphasized the value of close examination of the mesoappendix for invasion, particularly for lesions of 1-2 cm. If the mesoappendix is involved, a prophylactic right hemicolectomy is indicated. A raised mitotic index (more than 2 cells per mm^2) and high Ki67 index (more than 2 per cent of positive cells per mm^2) may be indicative of more malignant behaviour and again a formal right hemicolectomy should be considered. Reduced E-cadherin staining and over-expression of p21 needs further assessment in appendiceal lesions and may be a useful future prognostic marker. Angioinvasion should be regarded as a feature of more malignant behavior. In the presence of advanced disease a formal right hemicolectomy to remove the primary and lymph node secondary may be of value as a staged procedure, as part of an overall treatment regimen. However, at present there is no evidence to show that it improves symptom control or survival. There is also no good evidence to show that a right hemicolectomy prevents additional distant metastases from occurring in patients with distant metastatic disease at presentation (30).

Most goblet cell appendiceal carcinoids require planned surgery, as the metastatic risk is high (30). Localized discrete small tumours are treated locally, but diffuse inflammatory lesions may warrant more radical surgery. Unfortunately, intraperitoneal spread is a common occurrence. As is the case with other carcinoids, aggressive debulking of intra-abdominal metastases may improve symptom control and

survival (31,32). Bilateral oophorectomy has also been advocated (30,33). Any mucin-producing cells should prompt histological review, which may indicate a need for right hemicolectomy (27).

Conclusions

1. Malignant carcinoid tumours of the appendix are rare and are difficult to identify preoperatively.
2. The right hemicolectomy is recommend as the treatment of choice for all malignant carcinoid tumours except for small classical carcinoid tumours less than 2 cm in diameter at the tip of the appendix with low proliferative index, without angiolymphatic or meso-appendiceal extension.

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