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Chapter 5

ABDOMINAL ANGINA IN PATIENTS WITH A MIDGUT CARCINOID, A SIGN OF SEVERE PATHOLOGY

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Abstract

In 36 consecutive patients with a foregut carcinoid with extensive local tumor growth and liver metastases with a carcinoid syndrome, six patients had complaints of postprandial abdominal pain and attacks of subileus based on segmental intestinal ischemia. A diagnosis of abdominal angina was supported by a positive response to nitroglycerin in two and ischemia of the ileum demonstrated by angiography in two other patients. Complaints improved in all patients by surgery. Histopathology of the resected small bowel specimens showed elastic vascular sclerosis in three and ischemic changes in three other patients, confirming the clinical diagnosis. Resection of ischemic bowel can provide relief in patients with segmental intestinal ischemia due to carcinoid-induced vascular sclerosis.

Introduction

Carcinoid of the midgut has an incidence between 0.46 and 1.13 per 100,000 persons per year.^{1,2}

Abdominal pain is a frequent presenting symptom in these patients. Abdominal pain in carcinoid patients can also be due to bowel ischemia apart from bowel obstruction due to e.g. the primary tumor.

Reviewing 209 patients with a midgut carcinoid, Moertel in 1961 was one of the first to report bowel ischemia in four carcinoid patients.³ Ten years later Anthony and Drury described elastic vascular sclerosis as a morphologic substrate for this disorder in carcinoid patients.⁴ Due to its rare occurrence intestinal ischemia at diagnosis and during the course of the disease is not always considered as the main cause of abdominal pain in these patients. Mesenteric fibrosis, nodular involvement, progressive tumor growth and peritoneal adhesions causing intermittent subileus are other well known complicating factors. An exploratory laparotomy, following failure of conservative treatment of a subileus often does not disclose the bowel ischemia, which can be the origin of the problem. Abdominal angina can be diagnosed by a response to sublingual nitroglycerin.⁵ A superior mesenteric artery (SMA) angiography prior to surgery can assist in making decisions before and during laparotomy. Over the last decades, new treatment modalities such as octreotide and interferon have been shown to suppress the release of vaso-active substances by carcinoid tumors. These improvements may have led to a longer survival, potentially resulting in more late vascular symptoms in these patients.^{6,7} In a series of 36 consecutive patients with a carcinoid syndrome with extensive tumor growth and liver metastases, six patients complained of abdominal pain and episodes of subileus and underwent surgery based on definite criteria. The diagnostic work up and results are discussed.

Patient 1

A 67-year-old man with a metastatic carcinoid tumor had a history of left ventricular failure and a coronary bypass graft 10 years ago. He had experienced flushes for some months and an abdominal CT scan showed multiple hepatic metastases. A small bowel ileus required a laparotomy disclosing a 30 cm segment of purple-colored ileum, bearing a small, stenosing tumor and massive involvement of the liver. The mesentery of the small bowel was shortened by fibrosis and metastatic nodes causing kinking and twisting of the bowel. Segmental resection was considered hazardous because of vascular complications and a bypass of the stenosis was thought to be sufficient. The patient recovered uneventfully but was readmitted 2 weeks later for acute peritonitis. Laparotomy revealed necrosis of the bypassed small bowel segment requiring resection of 80 cm ileum followed by end-to-end anastomosis. Five days later a third laparotomy was needed to drain an anastomotic leak. Twenty days postoperatively the patients, while on total parenteral nutrition (TPN), died of left sided cardiac failure. The bowel necrosis was most likely caused by total inadequate bowel circulation, which was not recognized during the first laparotomy and subsequently leads to full blown necrosis.

Patient 2

A 61-year-old man presented with severe abdominal pain. Gallstones were diagnosed but a laparoscopic cholecystectomy did not alleviate his abdominal discomfort. Two months later an exploratory laparotomy showed a tumor in a Meckel's diverticulum with venous congestion and partial necrosis of the ileal wall, invading the mesentery and resection of 15 cm of the small bowel disclosed a carcinoid tumor with metastatic nodes in the mesentery. A few months later he was referred for continuous severe abdominal pain intolerable during the first few hours after each meal. Opioids did not sufficiently relieve the pain and the patient, having lost 21 kg in a few months time was put on TPN. Ultrasound of the abdomen and a small bowel series showed no abnormalities. The CT scan showed a mass anterior to the mesentery of the small bowel. An octreotide scan showed activity medially of the right kidney. A subtraction angiography of the SMA showed the ileocolic artery to be absent, resulting from the previous operation (Figure 1). The distal ileal arteries were not visible. At laparotomy, the distal ileum was pale and covered with distended veins. Multiple enlarged lymph nodes were seen in the small bowel mesentery. After resection of 80 cm of the distal ileum, the patient recovered uneventfully and resumed enteral nutrition. Pathology showed ischemic enteritis with multiple distended veins. The routine

stains showed no vascular abnormalities in the specimen. Nine years later the patient can eat normally and is able to maintain his body weight.

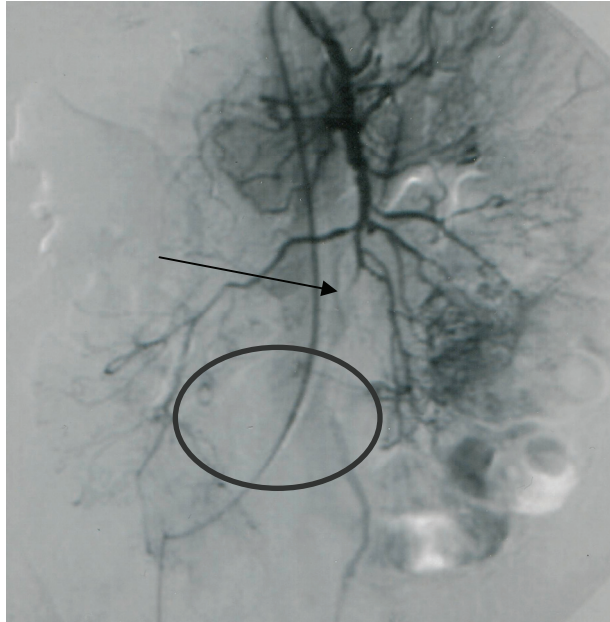


Figure 1:

Angiography of the SMA of patient 2. The ileocolic artery is absent (arrow) as a result of the first operation. The distal ileal arteries are not visible (oval).

Patient 3

A 48-year-old female underwent resection of the terminal ileum for a carcinoid tumor in another hospital, but a metastatic mass was left in situ. During the subsequent 2 years the patient underwent two laparotomies, one to relieve a mechanical ileus and one to bypass the duodenum compressed by metastatic nodes. Two years later abdominal complaints developed in a pattern suggesting abdominal angina; an angiography however was normal. At laparotomy an ileal loop adherent to the metastatic mass in the mesentery was resected, but showed no microscopic abnormalities. After some months the abdominal pain recurred and the patient could tolerate only liquids while using uploads. A carcinoid syndrome became apparent and the CT scan showed liver metastases.

Abdominal pain worsened by meals and subsided after sublingual administration of nitroglycerin. An angiography of the SMA showed compromised circulation in the distal ileal arteries, which deteriorated during tube feeding and improved during administration of nitroglycerin. Another laparotomy confirmed the absence of palpative ileal arteries in the distal 70 cm of the ileum. After resection of 60 cm the patient recovered uneventfully and normal enteral feeding was resumed. Microscopy, however, showed normal small bowel without evidence of ischemic

alterations. The absence of vascular abnormalities in the specimen and the beneficial effect of nitroglycerin suggested a compromised circulation by the combination of mechanical compression and vascular spasms. Three years later the patient is still doing well.

Patient 4

A 51-year-old man was referred with a carcinoid syndrome with flushes and diarrhea up to 10 times a day, which had progressed slowly over the last 5 years. He was treated with interferon- α . The history was consistent with partial obstruction of the small bowel. At laparotomy the mesentery contained numerous metastatic nodes and was shortened by fibrosis. The primary tumor was situated in a Meckel's diverticulum and removed by a segmental resection. The patient visited our outpatient clinic one year later with a small bowel ileus prior to which he could tolerate liquids only. At laparotomy adhesive segments of the terminal ileum with an aspect similar to radiation enteritis were resected. After resection of the affected small bowel segment we were concerned by the marginal circulation of the proximal side but further resection was not carried out in fear of causing a short bowel syndrome. Pathology showed ischemic enteritis reaching into the resection margins with increased elastin in the vascular adventitia. Postoperatively the patient developed a small bowel fistula refractory to conservative treatment. At subsequent laparotomy extensive adhesion prohibited access to the peritoneal cavity. The patient succumbed several weeks later.

Patient 5

A 69-year-old female was seen with a history of diarrhea and flushing caused by a carcinoid tumor with hepatic metastases. Over the past decade her weight had steadily decreased. At referral her body weight was 54 kg with a 1.76 m length. An octreotide scan showed lesions of metastases in the liver and both lungs. Subcutaneous octreotide was started and the diarrhea subsided. One year later she was admitted because of deteriorating condition and progressive weight loss, but she denied cramps or abdominal angina related to meals. A small bowel transit examination showed slow passage and inertia of the small bowel. Angiography of the SMA showed (probably congenital) absence of both the right and middle colic artery and equivocal circulation in both ileal arteries. A laparotomy was mandatory with the anatomy and circulation of the terminal ileum compromising the function of the intestinal tract. The terminal ileum showed venous congestion and was considerably narrowed and kinked due to shortening of the mesentery with several

metastatic foci. An ileocecal resection was performed and microscopy showed a small carcinoid tumor, metastatic nodes in the mesentery and tumor deposits on the surface of the mesentery without ischemic changes. The vessels showed sclerotic changes with thickening of the adventitia caused by elastic vascular sclerosis (Figure 2). After initial recovery the patient developed a small bowel ileus requiring a second laparotomy. The ileocolic anastomosis was trapped in an adhesive mass in the right upper abdominal quadrant, which necessitated a resection of the anastomosis. Histopathology showed serositis but no ischemia. An enterocutaneous fistula required TPN but cardiac condition deteriorated progressively and she died of cardiac failure. Post-mortem examination disclosed the presence of metastatic carcinoid tumor and valve abnormalities consistent with carcinoid heart disease.



Figure 2

Microscopic aspect of the mesentery of the small bowel of patient 5. Extensive deposition of elastic fibers in the adventitia of the arterial wall with narrowing of the lumen (left upper corner). The elastin staining is responsible for the dark color of the elastic fibers in the arterial wall and in the surrounding soft tissue (enlargement 25:1).

patient	clinical presentation			investigation			pathology		outcome	remarks
	weight loss	ileus	angina	angiogram	nitroglycerin	ischemia	EVS			
1	-	+	-	ND	ND	yes	-	improved	died, cardiac failure	
2	+	-	+	positive	ND	yes	-	yes		
3	+	-	+	positive	+	-	-	yes		
4	-	+	-	ND	ND	yes	yes	-	died, leaking anastomosis	
5	+	-	-	not conclusive	ND	-	yes	-	died, cardiac failure	
6	+	-	-	not conclusive	+	-	yes	yes		
total	4	2	2	2	2	3	3	3	3	

Table 1

Clinical presentation, procedures and pathology, of the 6 patients in chronological sequence

ND = not done,

EVS = elastic vascular sclerosis,

+ = present

Patient 6

A 70-year-old female with a rectal adenocarcinoma underwent pre-operative radiotherapy followed by rectosigmoid resection and colorectal anastomosis in another institution. During re-laparotomy for post-operative hemorrhage the surgeon encountered and excised a small tumor of the terminal ileum, which proved to be a carcinoid. Post-operatively, food intake elicited intolerable abdominal pain lasting for about 20 minutes. The patient was admitted to our institution and placed on TPN. Angiography of the SMA revealed equivocal circulation of the terminal ileum. The abdominal pain promptly disappeared after sublingual administration of nitroglycerin. At re-laparotomy dense adhesions were found between the loops of the terminal ileum. The mesentery contained several enlarged lymph nodes. A 100 cm segment of terminal ileum was resected and continuity was restored by means of an ileocecostomy. Pathology showed multiple carcinoid tumors, metastatic nodes, peri-vascular fibrosis and elastosis of the vessel wall. The patient recovered and proved to be able to eat without any abdominal discomfort.

Discussion

These six cases demonstrate that postprandial abdominal pain in patients with a midgut carcinoid can be caused by segmental intestinal ischemia. The data about the clinical presentation, diagnostic procedures and pathology of the specimens are summarized in Table 1. Ultimately 3 patients died post-operatively from complications of enteric ischemia and end stage carcinoid syndrome. The initial symptoms are too aspecific to differentiate bowel ischemia from obstruction due to adhesions and/or mesenteric fibrosis. However, a history of pain occurring directly after meals or an intolerance for food with severe weight loss, as in patients 2, 3, 5 and 6, are suggestive for ischemic bowel disease. We earlier described the sublingual administration of nitroglycerin for the temporary relief of the pain to confirm bowel ischemia.⁵ In some patients ileal transit is impeded by the intestinal stenosis. Plain X-rays, ultrasound, CT scanning and MRI do not help to differentiate between obstruction and ischemia. Only a selective angiography of the SMA with food challenge can distinguish between these two.⁸ Angiography can confirm the diagnosis and informs about the appropriate segment to be resected. This will enable the patient to resume adequate feeding. Inadequate resection or a bypass procedure will leave the patient with (intolerable) pain (e.g. patient 2) and the hazard of subsequent necrosis of the compromised bowel segments, as happened to patient 1. There is still

much to be elucidated about the pathophysiology of intestinal ischemia in carcinoid disease. After the description of Anthony and Drury several authors have confirmed their observations.^{4,9-16} Intestinal ischemia in carcinoid disease is only seen when the primary tumor is located in the midgut. They hypothesize that the fibrosis originating from serotonin release causes fibrosis with shortening and kinking of the mesentery and narrowing of the vessels by means of elastic vascular elastosis. The mechanical effect of metastatic nodes in the mesentery may be a third factor. Other authors postulate a direct effect of serotonin on the smooth muscle cells and the fibroblast of the vessel wall. The effect of nitroglycerin on abdominal angina is suggestive for reversible vasoconstriction. The authors agree that ischemia is only seen in patients with residual metastatic disease in the mesentery, consistent with a loco-regional biochemical effect.⁹⁻¹⁶ Overexpression of acidic fibroblast growth factor (aFGF) in stroma of a carcinoid tumor might be another, additional local factor.¹⁷ In 2004 Modlin et al surveyed the literature over the last 40 years covering the incidence, diagnosis, therapy and biological basis for carcinoid-associated fibrosis. Surgery remains the cornerstone of therapy. They conclude that the mechanism of fibrosis is still poorly understood and there are no means by which this complication can be predicted or monitored.¹⁸ These six patients have taught us to consider the possibility of intestinal ischemia. In a patient with carcinoid syndrome, abdominal complaints inconsistent with ileus should be an indication for a nitroglycerin test and selective angiography to evaluate whether ischemia plays a role. Moreover, angiography can help the surgeon decide to operate or not. Prior to any surgery for residual carcinoid of the midgut, an angiography of the SMA should seriously be considered. Patients with carcinoid syndrome with abdominal angina due to a midgut carcinoid with loco-regional extension can only be helped by surgical resection even though the complication rate is high.

References

1. Modlin IM, Sandor A: An analysis of 8305 cases of carcinoid tumors. *Cancer* 1997;79:813-829.
2. Neary PC, Redmond PH, Houghton T, Watson GR, Bouchier Hayes D: Carcinoid disease: review of the literature. *Dis Colon Rectum* 1997;40:349-362.
3. Moertel CG, Sauer WG, Dockerty MB, Baggenstros AH: Life history of the carcinoid in the small intestine. *Cancer* 1961;14:901-912.
4. Anthony PP, Drury RA: Elastic vascular sclerosis of mesenteric blood vessels in argentaffin carcinoma. *J Clin Pathol* 1970;23:110-118.
5. Brada SJ, Wijffels RT, Kahraman T, de Vries EGE: Sublingual nitrate provides cause for fear of food in a carcinoid patient. *Ann Oncol* 1997;8:1053-1054.
6. Frank M, Klose KJ, Wied M, Ishaque N, Schade BC, Arnold R: Combination therapy with octreotide and alpha-interferon: effect on tumor growth in metastatic endocrine gastroenteropancreatic tumors. *Am J Gastroenterol* 1999; 94:1381-1387.
7. Kolby L, Persson G, Franzen S, Ahren B: Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. *Br J Surg* 2003;90:687-693.
8. Wallace S, Ajani JA, Charnsangavej C, DuBrow R, Yang DJ, Chuang VP, Carrasco CH, Dodd GD, Jr.: Carcinoid tumors: imaging procedures and interventional radiology. *World J Surg* 1996;20:147-156.
9. Bessell JR, Karatassas A, Allen PW: Intestinal ischaemia associated with carcinoid tumour: a case report with review of the pathogenesis. *J Gastroenterol Hepatol* 1994;9:304-307.
10. Harvey JN, Denyer ME, DaCosta P: Intestinal infarction caused by carcinoid associated elastic vascular sclerosis: early presentation of a small ileal carcinoid tumour. *Gut* 1989;30:691-694.
11. Payne James JJ, de Gara CJ, Lovell D, Misiewicz JJ, Gow NM: Metastatic carcinoid tumour in association with small bowel ischaemia and infarction. *J R Soc Med* 1990;83:54.
12. Qizilbash AH: Carcinoid tumors, vascular elastosis, and ischemic disease of the small intestine. *Dis Colon Rectum* 1977;20:554-560.
13. Strobbe L, D'Hondt E, Ramboer C, Ceuppens H, Hinnekens P, Verhamme M: Ileal carcinoid tumors and intestinal ischemia. *Hepatogastroenterology* 1994;41:499-502.
14. Sworn MJ, Reasbeck P, Buchanan R: Intestinal ischaemia associated with ileal carcinoid tumours. *Br J Surg* 1978;65:313-315.
15. Warner TF, O'Reilly G, Lee GA: Mesenteric occlusive lesion and ileal carcinoids. *Cancer* 1979;44:758-762.
16. La Rosa S, Chiaravalli AM, Capella C, Uccella S, Sessa F: Immunohistochemical localization of acidic fibroblast growth factor in normal human enterochromaffin cells and related gastrointestinal tumours. *Virchows Arch* 1997;430:117-124.
17. Modlin IM, Shapiro MD, Kidd M: Carcinoid tumors and fibrosis: an association with no explanation. *Am J Gastroenterol* 2004;99:2466-2478.

