The paper presents a case report of coexisting multifocal colorectal cancer and multifocal carcinoid of the small intestine. Our literature review did not demonstrate any report of such case. We emphasize necessity of careful inspection of abdominal cavity during any surgical procedure since small lesions, in particular in the small intestine, may be omitted – as was the case during the initial colectomy in our case. Current epidemiological data are also presented and standards of management for diagnosis and treatment of gastrointestinal carcinoid.

**Key words:** carcinoid, colorectal cancer, synchronous tumors

Carcinoid is a malignant tumor of the neuroendocrine system. According to data from 2009, its incidence is 1-4/1 000 000 per year (1). Carcinoid cells secrete whole variety of bioactive peptides, including 5-hydroxytryptamine (5-HT, serotonin), chromogranin-A and chromogranin-C. This tumor most often is found in the bronchus (25.3-30.2%), jejunum (13.4-17.6%), rectum (10-18.5%), colon (7.6-9.5%), and vermiform appendix (2.4-7.6%) (2, 3, 4). Overall 67.5% of carcinoid cases are found in the gastrointestinal tract (1).

This paper presents a case of a 53-year old patient who underwent a selective surgical procedure due to a multifocal colorectal adenocarcinoma and multifocal carcinoid of the small intestine. We did not find any report of synchronous multifocal colorectal adenocarcinoma and multifocal carcinoid of the small intestine in the available literature.

CASE REPORT

Colonoscopy was done in a regional hospital (patient J.D., medical record: L2268/08) due to persistent diarrhea with sporadic admixture of blood. A circular infiltration was found in the region of splenic flexure that did not allow the rest of the large intestine to be examined. A flat polyp was found approximately 8 cm distally to the infiltration and was completely removed. Histopathology confirmed a diagnosis of adenocarcinoma both in the specimen from the infiltration, and in the polyp (the polyp was resected along with a 1 mm margin). The patient was referred to an oncological center where no evidence of metastatic disease was found at admission basing on clinical examination and imaging studies of the abdominal cavity and the chest. Laboratory tests (hematology, electrolytes, liver tests, renal tests, clotting system) were unremarkable.

After the abdominal cavity was opened, no palpable lesions were found in the liver, retroperitoneal space or other abdominal organs. A 4 cm large intestine mass was found in the region of the splenic flexure (that was seen and verified by colonoscopy) and a second 8 cm mass in the region of hepatic flexure (previously not detected since a colonoscope could
Multifocal colorectal adenocarcinoma with a synchronous multifocal carcinoid of the small intestine

not be passed through the mass in the splenic flexure). Since 3 malignant foci were found in the colon, the whole colon was resected and “side-to-side” manual anastomosis was done between the ileum and the sigmoid colon.

Histopathology demonstrated two foci of G2 adenocarcinome of the colon. The surgical procedure was radical and resected mesenteric lymph nodes were found to be free of metastases. The tumor was classified as B2 according to Astler-Coller classification and pT3N0M0 according to TNM classification.

On day 6 after the surgical procedure laparotomy was done due to signs and symptoms of prolonged postoperative gastrointestinal obstruction. Distended small intestine loops were found and ileosigmoid anastomosis was patent and leak-proof. During inspection and decompression of distended small intestine loops, a flat, intramural, off-white mass, 1.5 cm in diameter, was found approximately 60 cm from the anastomosis (fig. 1) and a second, slightly smaller mass was found approximately 12 cm in the direction of Treitz ligament (these both masses were overlooked during the initial surgical procedure and could only be clearly seen with distended intestinal loops). Only specimens were collected from both these masses in the small intestine and no attempt to resect them was made since it was a surgical procedure done in an urgent setting due to paralytic ileus (neither of these masses caused ileus). Carcinoid was diagnosed (immunochemistry profile: cytokeratin CAM 5.2 +, cytokeratin 20 -, chromogranin +, synaptophysin +). The postoperative period was uncomplicated.

Due to carcinoid diagnosis, whole body scintigraphy with labeled somatostatin analogues (SRS) was done and demonstrated pathological accumulation of the tracer below the lower margin of the right liver lobe and in the midline, in the naval region (only 2 foci were found). They could have corresponded to small intestine masses found during re-laparotomy. The patient was qualified to resection of the above mentioned lesions in the small intestine following completion of endocrinological diagnostic workup. Two months after the previous surgical procedure, the abdominal cavity was opened and a small intestinal fragment, approximately 20 cm in length, containing both these masses, was resected. The whole small intestine was palpated and no other concerning sites were found. After sectioning of the resected intestinal fragment (fig. 2), 2 other masses, approximately 0.5 cm in diameter, were found but were not previously felt. Histological examination confirmed presence of a total of 4 carcinoid tumors in the resected fragment of the small intestine.

Currenty the patient undergoes ongoing endocrinological and surgical follow-up. Two and half years passed since the surgical procedure had been done and no evidence of local recurrence or distant metastases were found in CT imaging of abdominal cavity, chest x-ray or scintigraphy.

DISCUSSION

Incidence of gastrointestinal carcinoid has increased over the past 30 years (1973-2004) from 1.09/1 000 000 to 4/1 000 000 (1, 5, 6). Autopsy reveals carcinoid more often (21 cases per 1 000 000 autopsies, most commonly in the small intestine) (7).
Clinically, gastrointestinal carcinoid most often (50-60%) is asymptomatic. If the disease is symptomatic, the following are observed: periodic abdominal pain (51%), intestinal obstruction (31%), palpable mass (17%) and gastrointestinal bleeding (11%) (6). Classic carcinoid syndrome occurs in 8% of cases and is associated with distant metastases at the time of diagnosis in 91% of cases. These metastases are particularly common in the liver (biologically active metabolic products, especially 5-HT, are released directly to the systemic circulation through hepatic veins) (7). Classic signs and symptoms of carcinoid syndrome include: sudden reddening of the facial skin (flushing), diarrhea, spasmodic abdominal pain and spastic bronchial constriction.

A screening test for carcinoid syndrome is assay of 5-hydroxyindoloacetic acid (5-HIaa) level in 24-hour urine. In this context we must remind that 5-HIaa level is elevated by certain foods and drugs (e.g. bananas, pineapples, kiwi, salicylates, L-dopa).

Endoscopic procedures (along with endoscopic ultrasound imaging), ultrasound imaging (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and radiolabeled somatostatin receptor scintigraphy (SRS, OctreoScan) are most commonly used to detect carcinoid foci (8, 9). SRS has the highest sensitivity in the diagnosis of carcinoid: it demonstrates the tumor in 73-89% of cases (5).

Gastrointestinal carcinoids can be multifocal (in 20-30% of cases). Tumor are most often located in the small intestine (70-87% of cases), and 40-70% of them are located within 60 cm from the ileocecal valve. Distant metastases are most often found in the liver (22-66%), lungs (4%) and bones (3%). Prevalence of distant metastases is closely related to the tumor size. If a tumor is smaller than 1 cm, metastases are found in 10-25% of cases. If size of the tumor is 1-2 cm, metastases are found in 58-60% of cases, while when the tumor is larger than 2 cm, metastases are found in 70% of cases (10).

Five year survival depends predominantly on the presence of distant metastases (in particular in the liver) and tumor location. Five year survival is 88% for patients with no more than locally advance disease, while it is markedly worse (25%) for patients with liver metastases (11). Five year survival is more than 95% for patients with carcinoid of the vermiform appendix and 70-80% for patients with carcinoid of the small intestine (12).

Radical resection of an intestinal fragment with the tumor is the recommended therapy. When tumors are smaller than 2 cm and located in the large intestine, rectum or stomach, local endoscopic resection with collection of specimen from the adjacent mucosa is possible (16). Chemotherapy (both neoadjuvant and postoperative) with 5-FU and/or streptozotocin, doxorubicin rarely results in more than 20% response rate and therefore is not routinely used (13). Somatostatin analogues have not consistently resulted in reduction of the tumor size. In generalized disease, somatostatin analogues have seemed to stabilize the disease and prolong life – however these results still have not been definitely confirmed (14, 15). When treatment with somatostatin analogues is planned, cholecystectomy is recommended since the risk of cholecystolithiasis is greatly increased (16). Surgical treatment of the primary tumor is also used when distant metastases are found since it reduces the risk of intestinal obstruction and alleviates abdominal pain.

Current recommendations by NCCN (National Comperhensive Cancer Network) from 2008 concerning follow-up of patients diagnosed with gastrointestinal carcinoid that have received radical treatment provide: 3 months after the surgical treatment – endoscopic procedure with collection of specimen for histopathology, assessment of marker levels (chromogranin-A, 5-HIaa) and CT or MRI. Then these procedures should be repeated every 6 months for the first 3 years after the surgical treatment, while every year thereafter. Further follow-up is not required only for carcinoid of the vermiform appendix smaller than 2 cm (16).

First report of coexistence of a carcinoid with an additional non-carcinoid tumor was presented by Pearson and Fitzgerald in 1949 (17). In a study by Gerstle et al. (20) in 1995, synchronous second primary tumor was fund in 29 among 69 (42%) patients with gastrointestinal carcinoid. Data collected by Habal et al. (18) in 2000 that included almost 5000 cases of gastrointestinal carcinoid, second coexisting tumor was found in 12-46% of cases (average 17%). Such coexistence was most common for carcinoid of the small intestine (29-52%), vermiform appendix (13-32%) and colorectal (5-32%) (18).
In a report prepared on the basis of database SEER (Surveillance, Epidemiology and End Results Program, National Cancer Institute, USA), 29% of patients with gastrointestinal carcinoid had an additional malignancy (19). The most common association was coexistence of carcinoid and colorectal cancer. Due to higher aggressiveness of this second primary tumor, majority of carcinoid patients died of this synchronous tumor (20).

Diagnosis of gastrointestinal carcinoid is difficult due to its predominantly asymptomatic nature. Standard detailed inspection of abdominal cavity should not be limited to searching for metastases in the liver or regional lymph nodes but should involve assessment of the whole large and small intestine. Asymptomatic carcinoid most often is not advanced and therefore it is possible to perform a segmental intestinal resection with the tumor. Such management will not significantly affect the outcome of treatment of the colorectal adenocarcinoma (21).

Table 1 summarizes literature data concerning reported cases of colorectal adenocarcinoma with a synchronous multifocal carcinoid of the small intestine.

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Cause of surgery / dominant symptom</th>
<th>Location of the adenocarcinoma</th>
<th>Location of the carcinoid</th>
<th>Treatment</th>
<th>Treatment outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cioffi Ugo et al. (23)</td>
<td>a 64-year old female patient with abdominal pain, nausea, weight loss and recurrent constipation episodes</td>
<td>ileum</td>
<td>ileum</td>
<td>surgical – resection of distal segment of the ileum with the cecum.</td>
<td>18-month follow-up – no evidence of recurrence or metastatic disease</td>
</tr>
<tr>
<td>2</td>
<td>Habal N et al. (19)</td>
<td>a 55-year old patient admitted in an urgent setting with abdominal pain, bloating and nausea</td>
<td>sigmoid colon</td>
<td>rectum and metastases in the liver</td>
<td>surgical – resection of the sigmoid colon and rectum, biopsy of liver metastases</td>
<td>follow-up ongoing</td>
</tr>
<tr>
<td>3</td>
<td>Sacchi G. et al. (24)</td>
<td>a 57-year old patient with colic abdominal pain on the right side and mucous diarrhea</td>
<td>ascending colon</td>
<td>ileum</td>
<td>surgical – anterior rectal resection</td>
<td>recurrence of adenocarcinoma 2 years after surgical treatment; the patient died 4 months after the recurrence</td>
</tr>
<tr>
<td>4</td>
<td>Khuchchandani M. et al. (25)</td>
<td>a 53-year old patient with diarrhea, bleeding from the rectum and abdominal pain persisting for 2 weeks</td>
<td>rectum</td>
<td>rectum</td>
<td>surgical – anterior rectal resection</td>
<td>the patient died after 5 months with signs and symptoms of cachexia. Autopsy demonstrated numerous, massive metastases in the liver</td>
</tr>
<tr>
<td>5</td>
<td>McHugh M. S. et al. (26)</td>
<td>a 74-year old female patient with bloating and diarrhea</td>
<td>rectum</td>
<td>ileum (3 foci)</td>
<td>surgical – anterior rectal resection with segmental resection of the ileum</td>
<td>follow-up ongoing</td>
</tr>
<tr>
<td>6</td>
<td>Tse V. et al. (27)</td>
<td>a 72-year old patient with loss of body weight and anemia</td>
<td>hepatic flexure of the colon</td>
<td>ileum (2 foci that could not be palpated), a metastasis to a lymph node located along the ileocecal artery</td>
<td>surgical – right hemicolecotomy</td>
<td>follow-up ongoing</td>
</tr>
<tr>
<td>7</td>
<td>Klucinski A. et al. (28)</td>
<td>a 72-year old female patient with signs and symptoms of gastrointestinal obstruction</td>
<td>transverse colon</td>
<td>ileum (a tumor was not detected during the surgical procedure, fund in histopathological examination)</td>
<td>surgical – extended right hemicolecotomy</td>
<td>no data</td>
</tr>
</tbody>
</table>
cinoma coexisting with gastrointestinal carcinoid.

We did not find a report in the literature that would document occurrence of multifocal colorectal adenocarcinoma (3 foci) synchronous with multifocal carcinoid of the small intestine (4 foci).

CONCLUSIONS

Coexistence of colorectal adenocarcinoma and carcinoid of the small intestine is relatively common (approximately 12-46% of cases). Multifocal tumor and only locally advanced are rare, which is underlined by only few reports in the literature. Conventional surgical practice that requires inspection of the whole abdominal cavity with oncological surgical procedure, will usually result in easy diagnosis of other bowel disease and therefore it should not be omitted despite development of imaging studies. Furthermore, the reported case illustrates that unexpected intraoperative findings (three-focal colorectal adenocarcinoma) can hamper detection of synchronous, multifocal small lesions in the small intestine.

REFERENCES

Multifocal colorectal adenocarcinoma with a synchronous multifocal carcinoid of the small intestine


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