Neuroendocrine carcinomas of the colon and rectum. 
A unit’s experience over six years

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RESUMEN

Introducción: los tumores neuroendocrinos de colon y recto son poco frecuentes. Suelen ser tumores poco diferenciados, diagnosticados por el patólogo y de especial agresividad en su comportamiento clínico. El pronóstico suele ser malo, con tendencia a la rápida metastatización.

Material y métodos: se ha revisado la experiencia de una Unidad de Coloproctología durante un periodo de seis años. Se han revisado de manera retrospectiva los pacientes con un tumor de espira neuroendocrina. Se han excluido los tumores carcinoides.

Resultados: durante este periodo, se han intervenido 2.155 pacientes por cáncer de colon y recto y se han hallado cinco pacientes con tumores neuroendocrinos. La edad media fue de 66 años, tres varones y dos hembras. Se localizaron uno en ciego, dos en recto y dos en sigma. Dos pacientes presentaban diseminación del tumor a distancia. Se realizó cirugía en todos los pacientes con quimioterapia posterior en dos de ellos. Un paciente falleció por insuficiencia hepática postoperatoria, otro a los dos meses y otro al año. Dos pacientes siguen vivos con un seguimiento medio de ocho meses.

Conclusiones: los tumores neuroendocrinos son unos tumores de aparición rara en el colon y recto. La clínica de presentación no difiere de la que podrían tener los adenocarcinomas. En el momento del diagnóstico estos tumores suelen presentar enfermedad a distancia, como en dos de los cinco casos presentados, relacionándose con un mal pronóstico para el enfermo. El tratamiento quirúrgico y quimioterápico combinado es el que puede alargar más la supervivencia de los pacientes.


ABSTRACT

Introduction: neuroendocrine tumours of the colon and rectum are infrequent. They are usually undifferentiated, easy to diagnose for the pathologist and are especially aggressive in their clinical behaviour. Prognosis is usually poor and they have a high tendency to metastase early.

Material and methods: we have reviewed our experience in a Colorectal Unit during a period of six years. Patients with neuroendocrine tumours have been reviewed retrospectively. Carcinoïd tumours have not been included in this study.

Results: during this period, 2,155 patients have been operated for colorectal cancer and in five patients a neuroendocrine tumour has been found in the specimen. Mean age was 66 years, three male and two female. One tumour was located in the caecum, two in the rectum and two in the sigmoid colon. Two patients had hepatic metastasis at diagnosis. Surgery was performed in all patients and two patients received adjuvant chemotherapy. A patient died because of post-operative hepatic insufficiency, another at 2 months and another after one year. Two patients are still alive after eight months’ follow-up.

Conclusions: neuroendocrine tumours appear to be rare in the colon and rectum. Clinical manifestations are not different from standard adenocarcinoma. When these tumours are diagnosed, they have distance disease, as in two of the five cases, related to a poor prognosis for the patient. Surgery is the treatment that can offer a greater chance of survival to these patients.

Key words: Tumour. Neuroendocrine. Colon. Rectum. Undifferentiated carcinoma.


INTRODUCTION

The finding of a neuroendocrine tumor of the colon and rectum is infrequent even if neuroendocrine cells are present in the body (1). Most of these cells are located in
the intestinal tract, and tumors can arise in any location, have a low incidence, and are usually poorly differentiat-
ed (2). The classification and nomenclature of these tu-
mors is still controversial for pathologists. Neuroen-
docrine tumors of the colon and rectum, however, are
divided into low-grade or carcinoid tumors, and high-
grade tumors. Pathological findings such as presence of
nuclear pleomorphism with multiple mitoses, and posi-
tive Ki-67 and synaptophysin staining help in the diagno-
sis. In general, carcinoid tumors have a benign behavior
but high-grade neuroendocrine tumors are especially ag-
gressive with a high tendency to metastatization. We
have reviewed our experience with neuroendocrine tu-
mors of the colon and rectum in a specialized colopro-
tology unit for a period of six years.

PATIENTS AND METHOD

A retrospective review was performed of all patients
who underwent surgery for colorectal cancer in our unit.
Our study period was six years long, and patients with a
neuroendocrine tumor diagnosed in a pathology sample
were reviewed. Neuroendocrine tumors not located in the
colon or rectum were excluded. We report the cases in-
volved.

Patient number 1

A 68-year-old female who consulted for fever, toxic
syndrome, anorexia, and loss of weight was admitted and
studied with barium enema, which showed a stenotic le-
sion with infiltration in the rectosigmoid region that en-
abled us to study the rest of the colon. An ultrasonography
was performed, which revealed cholelithiasis without he-
patic lesions. CEA and CA 19.9 were normal. Surgery was
performed, and revealed a big tumor in the rectosigmoid
junction, exteriorized, with uterine posterior wall invasion
and left ureter dilation. A low anterior resection was per-
formed with annexial and uterus resection. A cholecistec-
tomy was also performed. The patient was discharged un-
eventfully. The pathology report described a 13 x 9 cm
ulcerated tumor with macroscopic infiltration of the uter-
ine wall. Microscopically the tumor showed high cellular
density with diffuse sheets of small-intermediate size,
round hyperchromatic cells exhibiting scant cytoplasm,
nuclear moulding, granular chromatin, and prominent nu-
cleoli. Extensive necrotic areas were present. Neoplastic
cells expressed immunohistochemical positivity for cyto-
queratin 7, cytoqueratin 20, and CAM 5.2. The pa-
tient had 52 out of 58 adenopathies affected, and a liver
biopsy was positive for metastasis. Lymphatic, venous,
and perineural invasion was present. After 2 months
the patient was admitted to the emergency room with
vomiting, hematemesis, jaundice, and abdominal dis-
tension, and died.

Patient number 2

A 69-year-old male presented with tenesmus and
rectorhagia, which had lasted for over one month. A
fibrocolonoscopy was performed and a tumor was evi-
denced at 10 cm from the anal sphincter with infiltra-
tion and a 5-cm diameter that occupied ¾ of the lumen.
An abdominal CT scan was performed, which showed a
rectal neof ormation with perirectal invasion and adenopa-
thies. Multiple hepatic lesions were found. CEA was 1.2 ng/mL and an endorectal ultrasonography
showed a neoformation occupying 100% of the lumen
without adenopathies at 8 cm from the anus. Biopsies
demonstrated a high-grade carcinoma with neuroen-
docrine differentiation. Neither radiotherapy nor
chemotherapy was given. A big tumor of the mid third
of the rectum was observed at 6-8 cm from anal mar-
gin, exteriorized to the minor pelvis basically on the
anterior and lateral aspects. The liver had multiple le-
sions. A Hartman’s procedure was performed with
proctectomy and total mesorectal excision. The patient
was discharged uneventfully. The pathology report de-
scribed a poorly differentiated neuroendocrine carcino-
ma. Neoplastic cells expressed immunohistochemical
positivity for synaptophysin and were negative for cyto-
queratin 7, cytoqueratin 20, and CAM 5.2. The pa-
tient had 52 out of 58 adenopathies affected, and a liver
biopsy was positive for metastasis. Lymphatic, venous,
and perineural invasion was present. After 2 months
the patient was admitted to the emergency room with
vomiting, hematemesis, jaundice, and abdominal dis-
tension, and died.

Patient number 3

A 69-year-old male was admitted for study after 2
months’ weight loss, toxic syndrome, abdominal pain,
and then blood in feces for the past 7 days. A mass was
palpable on the right flank, and ultrasounds revealed mul-
tiple hepatic lesions. A CT scan demonstrated a cecal
mass with probable peritoneal carcinomatosis and multi-
ple hepatic metastases. Surgery was performed and an exterio-
erized neoplasm with peritoneal carcinomatosis and
ascites was seen. A right hemicolecction with ileo-
colic termino-terminal anastomosis was performed.
After surgery the patient developed severe liver failure,
which resulted in death after 11 days. The pathological
analysis showed a morphology similar to that of neuroen-
docrine tumors with immunohistochemical positivity for
chromogranin and synaptophysin. The tumoral pro-
life index (Ki-67) was elevated. Hepatic and peritoneal
biopsies were positive for neuroendocrine tumor.
Patient number 4

A 75-year-old male patient with no relevant clinical history was admitted for study because of tenesmus and occasional rectorrhagia. A fibrocolonoscopy was performed up to the cecum, and a 2.2-cm rectal tumoral polypoid, nodular, well-delimited lesion was observed. A transanal resection was performed. The pathology report described a carcinoid tumor with immunohistochemical positivity for keratine CAM 5.2, synaptophysin, and chromogranin. No expression of p53 was found, and the proliferation index for protein Ki-67 showed nuclear expression in 10-15% of tumor cells. No local or distant recurrence has been found after 10 months, and he is currently under treatment with 5-fluorouracil and streptomycin.

Patient number 5

A 54-year-old female with a 2-month hematochezia history was studied by fibrocolonoscopy, which found a tumor in the sigmoid colon. No metastatic disease was found. A laparoscopic sigmoidectomy with colorectal termino-terminal anastomosis was performed. The pathology report described a neuroendocrine poorly differentiated tumor with big cells, vascular invasion, and immunohistochemical positivity for synaptophysin, chromogranin, enolase, and CD56, with a proliferative index of 75% as assessed with Ki-67 (Fig. 1). Follow-up has shown no local or distant recurrences after 10 months.

DISCUSSION

These tumors derive from the neuroendocrine (NE) system and can be found all over the body, in the lung, skin, urogenital system, digestive tract, thyroid, parathyroid, and suprarenal glands (1,2). They can synthesize, secrete, and store more than 40 pharmacologically-active substances. Serotonin, vasoactive intestinal peptide, calcireine, substance P, and histamine are most commonly synthesized (3,4).

Initial descriptions of these undifferentiated small-cell tumors of the colon and rectum were provided by Gould and Chejfec in 1978 (5).

Their most frequent localization in the digestive tract is the appendix, ileum, and rectum, even if they have been described in the stomach, colon, esophagus, and duodenum. Undifferentiated small-cell carcinomas of the colon and rectum are rare and morphologically similar to those of the lung (6). The most frequent localization of these tumors is the cecum, rectum and sigmoid colon, with the anal localization of these rare tumors being linked to poor prognosis (1,2,5,7). These less frequent localizations have, however, been found in our patients.

A histological or immunohistochemical analysis of neuroendocrine colorectal tumors shows that they account for 1 to 4% in the various series. Prevalence is difficult to establish (1). In a study that included a significant number of patients (988 colorectal resections in more than 10 years) an incidence of 3.9% was found for “neuroendocrine cancers of the colon and rectum” (4).

According, however, to the American National Cancer Institute, only 0.3% of colorectal cancers will be neuroendocrine in type (8), which is consistent with our series of 2,155 patients who underwent surgery (0.23% = 5/2,155). Primary histological colorectal cancers are more aggressive, with fast dissemination and the worst prognosis (9).

The origin and growth of neuroendocrine tumors is still controversial (5,10,11). It is thought that neuroendocrine tumors and low-grade carcinomas may originate from the same epithelial neuroendocrine cells, after damage to the stem cell (11,12). On the other hand, high-grade neuroendocrine carcinoma may originate from APUD tissue (13). It is thought that these tumors can be stimulated by their own growth through neuroendocrine substance secretion. Some amines and polypeptidic hormones also play an important role in the normal growth of the intestinal epithelium (14). The term carcinoid is used only for well-differentiated neuroendocrine tumors, with low or no malignant potential (1). On the other hand, undifferentiated small-cell tumors are uncommon in the digestive tract. These tumors are very infrequent and do not account for more than 1% of all colonic tumors (2,15).

Three tumoral varieties have been described: Pure neuroendocrine, predominant neuroendocrine, and tumors with similar neuroendocrine and exocrine expression (4), according to the histological pattern found.

Small-cell tumors of the colon and rectum are classified as high-grade malignant neuroendocrine carcinomas, and recently a new classification has been proposed according to prognosis (16,17). A neuroendocrine variety has been described, which is rare and aggressive with multidirectional differentiation, and with neuroendocrine, adenocarcinoma, and squamous-cell carcinoma foci (18).

Their clinical presentation is not different from that of colonic adenocarcinoma. At diagnosis, however, a poorer stage may be found. They usually present with abdominal pain, hematochezia, fecal occult blood, or presence of a mass—the signs and symptoms that alert the physician—and rarely other symptoms such as paraneoplastic syndrome, and carcinoid or metabolic abnormalities (3, 5). All patients in our series had a paraneoplastic or carcinoid syndrome. The liver is the first place where metastasis is found, as with colonic adenocarcinoma.

Survival rates as described by different authors show that these tumors are very aggressive and associated with poor prognosis (Table I).

Prognosis is worst for purely NE tumors and the small-cell pattern, and is better for the intermediate-cell type (5,19).
It has been proven that adenocarcinomatous differentiation to neuroendocrine tumor is a poor prognostic factor in terms of survival for patients in stages II and IV (20). Thomas and Sobin (8) found a survival rate of 27% at 5 years after combining stage II (48.8% survival rate at 5 years) and stage IV tumors (5.6% survival rate at 5 years) with adenocarcinoma pattern. However, only 3 of the 51 patients with stage III and IV NE undifferentiated tumors were alive after 2 years.

Tumor stage at diagnosis is very important for prognosis and survival. The median survival rate is estimated between 6 and 15 months. These survival rates are similar to those found in our review, which are close to 7 months. Longer survival rates are related to earlier diagnosis and a better histological pattern (2,5,7). Treatment is mainly surgical, and adjuvant therapies such as chemotherapy or radiotherapy play a minor role in terms of survival (21). New, aggressive chemotherapy courses using either streptozotocin and 5-fluoroouracil or doxorubicin and 5-fluoroouracil have, however, been proposed (21,22).

NE tumors of the colon and rectum are rare, and have a tendency to local invasion and dissemination. Diagnosis must be early in order to increase survival rates. Surgery is still the only effective treatment but new chemotherapy drugs have been tried. Palliative measures such as surgery with colostomies or radiotherapy must be evaluated in order to increase quality of life for these patients.

REFERENCES

Table I. References found about neuroendocrine tumours of the colon and rectum

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Year</th>
<th>n</th>
<th>Age (R)</th>
<th>Sex</th>
<th>Localization</th>
<th>Stage</th>
<th>M1</th>
<th>Treatment</th>
<th>Post-operative quimiotherapy</th>
<th>Radiotherapy</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hung SS (27)</td>
<td>1989</td>
<td>1</td>
<td>69</td>
<td>♀</td>
<td>C5</td>
<td>M1</td>
<td>Liver</td>
<td>QT alone</td>
<td>No</td>
<td>No</td>
<td>1 month</td>
</tr>
<tr>
<td>Saclarides (4)</td>
<td>1994</td>
<td>39</td>
<td>65.5 (28-80)</td>
<td>♀: 14, ♂: 25</td>
<td>RC: 19, LC: 11, R: 9</td>
<td>DUKES A: 7, B: 8, C: 16, DUKES D: 15</td>
<td>L: 8, CARC: 3, MULTIP: 2, PUL: 1, GG: 1</td>
<td>CIR: 20, biopsy diagnostic: 2, RAB o Miles: 6, local reaction: 1</td>
<td>NC</td>
<td>NC</td>
<td>10% pure NE pattern and 20% mixed-exocrine pattern, after 2 years</td>
</tr>
<tr>
<td>Acea (28)</td>
<td>1996</td>
<td>4</td>
<td>55 (40-66)</td>
<td>♀: 2, ♂: 2</td>
<td>RC: 2, SC: 2</td>
<td>IV: 4</td>
<td>L: 4</td>
<td>Surgery: 3, QT: 4</td>
<td>Yes</td>
<td>No</td>
<td>0% after 1 year</td>
</tr>
<tr>
<td>Vázquez Ruiz (25)</td>
<td>2000</td>
<td>1</td>
<td>76</td>
<td>♂</td>
<td>C: 1</td>
<td>T4N1M0</td>
<td>OS</td>
<td>Surgery and QT</td>
<td>Yes</td>
<td>No</td>
<td>Alive after 20 months</td>
</tr>
<tr>
<td>Andrés Marín (26)</td>
<td>2003</td>
<td>1</td>
<td>44</td>
<td>♀</td>
<td>R: 1</td>
<td>T4N2M1</td>
<td>L</td>
<td>Surgery</td>
<td>Yes</td>
<td>Yes</td>
<td>Dead at 18 months</td>
</tr>
<tr>
<td>Grabowski (21)</td>
<td>2002</td>
<td>20</td>
<td>58.3</td>
<td>♀: 6, ♂: 14</td>
<td>RC: 9, LC: 4, R: 7</td>
<td>EST I: 2, EST II: 8, EST IV: 10 (T2, T3, 12, T4, 6)</td>
<td>L: 9, CARC: 1, PULM: 1, PAN: 1</td>
<td>QT PRE: 6</td>
<td>Yes: 15</td>
<td>NC</td>
<td>11% after 2 year</td>
</tr>
<tr>
<td>Bernick (24)</td>
<td>2004</td>
<td>38</td>
<td>57 (52.8, 61.6)</td>
<td>♀: 21, ♂: 17</td>
<td>CO: 17, R: 21, AC: 6, A: 1</td>
<td>EST I: 6, EST II: 7, EST IV: 25</td>
<td>25</td>
<td>CIR: 31, without treatment: 1</td>
<td>Yes: 28</td>
<td>Yes: 11</td>
<td>Global: 10.5 months 46% after 1 year 26% after 2 years 12% after 3 years</td>
</tr>
<tr>
<td>Kang (29)</td>
<td>2006</td>
<td>455</td>
<td>67.9</td>
<td>♀: 233, ♂: 222</td>
<td>RC: 44.9%, TC: 6.9%, LC: 3.9%, R: 29.6%</td>
<td>Local: 10.8%, Regional: 27.1%, Distant: 62.1%</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>Global: 21.4% after 5 years 72.6% in local stages 39.7% in regional stages 5.5% with distant disease</td>
</tr>
<tr>
<td>Jung (23)</td>
<td>2006</td>
<td>13</td>
<td>60 (41-83)</td>
<td>♀: 7, ♂: 6</td>
<td>C: 1, TC: 1, SC: 2, R:9</td>
<td>EST IB: 2, EST IC: 3, EST IV: 8, PULM: 2</td>
<td>L: 9, CARC: 2, PULM: 2</td>
<td>QT: 5</td>
<td>Yes</td>
<td>NC</td>
<td>With QT: 16.4% in stage III and 17.5% in stage IV after 32 months Without QT (5 patients): mean 62 months</td>
</tr>
</tbody>
</table>

CO: Colon; C: Caecum, RC: Right colon; TC: Transverse colon; LC: Left colon; SC: Sigmoid colon; R: Rectum; CA: Anal canal; A: Caecal appendix; L: Liver; CARC: Carcinomatosis; MULTIP: Multiple; PUL: Pulmonar; GG: Gangliomatous; CER: Cerebral; PAN: Pancreatic; OS: Bone.