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Research Article

Rectal Neuroendocrine Tumors. Our Experience and Review of the Literature

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Abstract

Background: Neuroendocrine tumors (NETs) of the rectum are a rare entity in malignant colorectal neoplasms. They account for 1 - 2% of all rectal cancers. However its incidence has increased due to the screening and prevention programs of colorectal cancer in the last years. We report a series of cases of NETs evaluated in our General and Digestive Surgery Department and a review of the literature.

Material and Methods: Between the period of June 2008 and June 2017, all patients diagnosed with neuroendocrine tumor (NET) of the rectum who required assessment and/or surgical treatment were analyzed. All the patients underwent a colonoscopy with a neuroendocrine tumor biopsy In the cases that required surgical intervention, the definitive histology identified in the piece was neuroendocrine tumor of the rectum. All the histological pieces were analyzed by the same pathologist.

Results: Fourteen patients with neuroendocrine tumor histology of the rectum were described. There were 8 women and 6 men aged between 32 and 68 years with an average of 52 +/- 9 years. All neuroendocrine tumors were classified according to the 2010 WHO classification of NETs. Surgical intervention was performed in six of the patients, while in the rest, due to their size and casual finding in the colonoscopy, they could be resected endoscopically. Eight patients (57.1%) with well differentiated neuroendocrine tumor (G1) were identified, five patients (35.7%) in whom a poorly differentiated neuroendocrine tumor (G3) was identified and only one case (7.1%) was found to have a moderately differentiated neuroendocrine tumor (G2). Of the six patients who required surgery, in two cases the tumor debuted with intestinal obstruction requiring urgent surgery. Survival by groups within the surgically treated patients who presented a G3 stage was 26 months while in the patient who presented a G2 tumor it was 67 months. In the cases of those patients who were resected endoscopically, survival was 100%.

Conclusion: NETs have a low incidence within malignant neoplasms of the rectum. Its diagnosis is usually as an incidental finding during screening for colorectal cancer. The histological characteristics of the tumor (lymphovascular invasion and proliferation index) as well as its size are fundamental for the choice of the corresponding treatment. The treatment of rectal NETs requires a multidisciplinary approach where the correct staging influences the prognosis and survival of each patient.

Keywords: *Rectal Neuroendocrine Tumor; Carcinoid; Rectum; Endoscopic Resection; Rectal Neoplasms; Ki-67*

Abbreviations

NETs: Neuroendocrine Tumors; APUD: Amine Precursor Uptake Descarboxilase; ENETS: European Neuroendocrine Tumor Society; 5HIA: 5-Hydroxyindoleacetic Acid; TAMIS: Transanal Minimally Invasive Surgery; TEM: Transanal Endoscopic Microsurgery; WHO: World Health Organization

Introduction

Neuroendocrine tumors (NETs) of the rectum are a rare entity in malignant colorectal neoplasms. They account for 1-2% of all rectal cancers. They represent 20% of the total NETs of the digestive tract [1]. Its incidence has increased around the world in recent years [2,3]. In Asia, rectal localization of the NETs is the most frequent [4]. They have a slight predisposition for males and their highest incidence occurs in the sixth decade of life [5-7].

NETs are derived from Kulchitsky cells or enterochromaffin cells (from the neural crest) found in the digestive tract epithelium (Lieberkühn crypts) and respiratory system. These cells belong to the APUD system (Amine Precursor Uptake Descarboxilase) and have particular molecular characteristics such as their positivity for enolase and synaptophysin as well as their ability to secrete peptides or hormones such as histamine, adrenaline, noradrenaline, dopamine, VIP or ATCH, among others [1,8].

Concept, historical evolution and classification

Historically, the term carcinoid was reserved for those tumors of the digestive system with a less aggressive behavior than carcinomas. Langhans was the first to describe the term intestinal carcinoid in 1867. In 1888, his histology was described by Lubarsch and they are defined as carcinomas. It was in 1907 Oberndorfer designated the name carcinoid for those which showed a benign behavior. Gasset and Masson relate them to the endocrine system in 1914 without any sort of classification. It is not until 1963 when, Williams and Sandier proposed the first classification according to the embryonic origin and the part of the digestive tract where they are located (anterior, middle or posterior intestine) [9-11].

However, it is not until the year 2000 when World Health Organization (WHO) appointed the concept of neuroendocrine tumor or neuroendocrine carcinoma to replace the old and confusing term "carcinoid" and classify them according to their histological grade. This new classification was modified in 2010 by the WHO again, based on both morphological and histological criteria by differentiating three different grades: Grade 1 or differentiated for those with an expression of the lower Ki67 nuclear protein. or equal to 2% together with a mitosis number per field of less than 2 per 10 high-power fields. Grade 2 or moderately differentiated with a Ki 67 between 3 and 20% and between 2 and 20 mitoses per field and finally Grade 3 or poorly differentiated for an Ki67 expressivity higher than 20% or a higher number of 20 mitoses per field [12] (Table 1).

WHO grade	Mitotic count	Ki 67 index
G1	< 2	< 2%
G2	2 - 20	3% - 20%
G3	> 20	> 20%

Table 1: *Classification of TNE (WHO).*

In 2012, the European Neuroendocrine Tumor Society (ENETS) established a guide on the management and treatment of these tumors [13].

Sypmtoms and signs

Most rectal NETs are asymptomatic at the time of diagnosis and are usually discovered incidentally during colonoscopy or other tests that are part of the patient's study. Early screening and screening programs for colorectal cancer have played an important role in increas-

ing the incidence of these tumors in recent years as incidental findings in screening colonoscopies. Its presentation form in colonoscopy is characteristic, as small polypoid lesions of small size usually less than 10 mm (Figure 1). In those patients who produce symptoms, gastrointestinal bleeding type rectorragia, alterations of the intestinal rhythm as diarrhea or constipation, pain or tenesmus are the most frequent. They can be associated with multiple endocrine neoplasia syndrome type I, neurofibromatosis type I or Von Hippel Lindau [1,8].

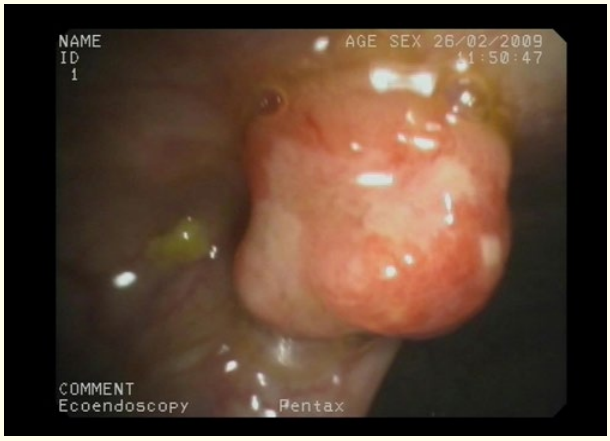

Figure 1: *Endoscopic feature of a NET in lower rectum.*

The carcinoid syndrome characterized by flushing or diarrhea and, to a lesser extent, bronchospasm and heart failure, is rare. It was not found in any patient in our series. In cases in which rectal NETs develop as intestinal obstruction as in patients with rectal adenocarcinoma, they usually indicate advanced disease with a worse prognosis [10].

Diagnosis and complementary tests

Screnning programs and advances in diagnostic techniques have increased the number of rectal NET cases. The realization of colonoscopy is basic in the treatment and management of these tumors. The finding of these tumors is usually incidental due to the few symptoms rectal NETs produce.

Rectal NETs present a polypoid aspect in general of small size becoming confused with polyps until their anatomopathological examination. Currently the presence of ulceration is not related to its aggressiveness and degree of metastatization. The colonoscopy should be complete since the presence of other polyps or even other tumors in a synchronous manner is possible.

Computed axial tomography: This is the test most used to complete the preoperative tumor staging. In addition, advances in the processing of images and their subsequent reconstruction have resulted in virtual colonoscopy displacing the barium enema as a morphological test for the assessment of the entire colon and rectum in those patients who have not been able to perform a complete colonoscopy.

Magnetic Resonance Imaging: Due to its greater sensitivity and specificity is the test of choice to determine the characteristics of liver injury. It also constitutes a good study for local staging (organ affectation, lymphadenopathy, etc.) at the level of the pelvis.

Abdominal ultrasound: It presents low sensitivity for the evaluation of neuroendocrine tumors but it presents a useful tool for performing punctures and/or biopsies of guided liver lesions.

Endoanal ultrasound: High sensitivity test to assess the rectal involvement of these tumors, distinguishing them from stages with muscle layer involvement, also assessing the presence of locoregional adenopathies.

Octreo-Scan In111: This nuclear medicine test in which the element Indio111 is used as a radiopharmaceutical presents a sensitivity discussed due to the low frequency of these tumors. However, it can be a useful tool for the assessment of metastatic disease.

Biochemical markers

The values of serotonin as its most active metabolite, 5-hydroxaloacetic acid (5HIA) are usually found elevated in urine of 24 hours up to 50% of its normal value in the presence of these tumors. The 5HIA presents a sensitivity of approximately 70% with a specificity between 88 and 100% depending on the series [10].

The true biochemical marker of neuroendocrine tumor, considered by some authors as the gold standard, is chromogranin A. Despite their low specificity (62.9%), they show good specificity (98.4%) depending on the series. Its value is identified higher in those tumors that are functional and are related to the degree of metastasis, demonstrating the usefulness of monitoring it in the follow-up of the G2-G3 level NETs [8,10].

Histology of NETs

The anatomopathological study has become a fundamental part of neuroendocrine tumors. The aggressiveness of these tumors as well as its stage is given by the amount of mitosis that its cells present and the greater or lesser expression of cell proliferation markers such as Ki67.

The tumor cells of the NETs present an extraordinary capacity to produce and store peptides in neurosecretion granules, identifiable to electron microscopy as electron dense granules. These cells have been called argentaffin cells due to the content of these granules and the different way of reacting to silver or argyrophilic salts if necessary for the staining of some external exogenous agent. The name of enterochromaffin cells is originated in the positivity that the cells of said tumors presented to salts such as potassium chromate, staining techniques prior to the development of immunohistochemistry.

After the development of immunohistochemical techniques at the end of the 20th century, proteins linked to cytoplasmic structures (enolase, synaptophysin, chromogranin, etc.) or nuclear structures (Ki67) characteristic of neuroendocrine tumors were discovered.

Ki67: Marker of cell proliferation detected by monoclonal antibodies (located in the cell nucleus but that during mitosis is located on the surface of the chromosome) that indicates the degree of aggressiveness of these tumors.

Synaptophysin: Membrane glycoprotein expressed by neurons and some neuroendocrine cells (Figure 2).

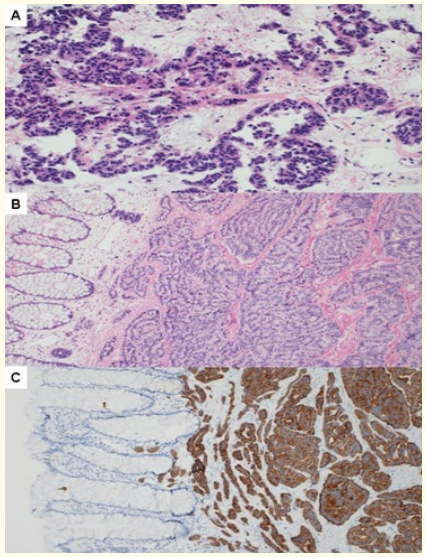

Figure 2: *A) NET metastasis in liver B) Rectal NET hematoxylin eosin positive C) Rectal NET synaptophysin positive.*

Treatment

The only curative treatment is complete resection with free resection margins. It has not been demonstrated that radical surgery increases survival in those cases of metastatic disease.

The tumor size as well as the invasion of the muscularis propria are the factors that best predict tumor aggressiveness and the ability to spread at a distance.

Neuroendocrine tumors of the rectum less than 10 mm: They present a low risk of metastasis (< 3%). Complete resection by endoscopy or transanal resection with free margins represents the curtative treatment of choice [14].

Neuroendocrine tumors of the rectum between 10 and 20 mm: Most authors find no difference between local resection versus abdominal surgery due to the risk of metastasis (10 - 15%) of these lesions [15].

Neuroendocrine tumors of rectum greater than 20 mm: They are the most aggressive, reaching rates of metastasis between 60 - 80% [11]. The invasion of the muscularis propria is frequent in these tumors. The only curative treatment is radical rectal surgery (low anterior resection or abdominoperineal amputation according to its distance to the anal margin) with complete excision of the mesorectum.

Local resections may be indicated in palliatively selected patients by reducing burden and tumor symptomatology [16].

Adjuvance

Adjuvant treatment after surgery is discussed by many authors and may be reserved for patients with poorly differentiated neuroendocrine tumors with incomplete resection. The somatoestatin analogues have been used in patients with neuroendocrine tumors that present carcinoid syndrome with significant improvement.

However in the rectum this syndrome as well as the functionality of these tumors is rare [10]. Systemic chemotherapy is not usually used for NETs G1-G2. In those patients who have presented progression of the disease, the schemes with 5 fluoracil and doxorubicin have come to show regression rates of around 25% [17].

Prognosis and survival

The prognosis, as well as the survival of rectal NETs depend on tumor staging. The stages with better prognosis and superior survival are G1-G2 (well or moderately differentiated). In addition, certain factors such as tumor size, lymphovascular and / or perineural infiltration and the involvement of different layers have an important influence on prognosis and survival. Apparently, according to the series contemplated in the literature, size is the parameter with the greatest weight to predict the tumor's dissemination capacity. For tumors with a size smaller than 10 mm and without lymphovascular involvement whose extension does not reach beyond the mucosa or submucosa they present a good prognosis. These results change, increasing almost up to 20% when the lesion is greater than 20 mm and penetrates the muscle layer.

For those well-differentiated neuroendocrine tumors type G1 and G2 smaller than 10 mm without invasion of the muscularis propria nor ganglion involvement, no follow-up is required. For tumors with a size between 10 and 20 mm of any histological grade (G1, G2 and G3), an annual follow-up by colonoscopy and CT is sufficient.

For those older than 20 mm, follow-up should be routine for the G3colonoscopy every 4 - 6 months the first year and then at least annually.

Materials and Methods

Following a small series of cases of rectal NETs, we reviewed the literature and compared results. From June 2008 to June 2017, 14 cases of rectal NETs were obtained, which required assessment by our service.

It is a retrospective observational study. The following variables were studied: sex, age, tumor location, type of resection, survival and aspects related to the tumor (size, lymphovascular involvement, free margins, mitotic index, Ki67 expression) and tabulated in a Microsoft Excel spreadsheet 2016.

The histological study as well as the immunohistochemical techniques (preoperative by colonoscopy as well as those performed on the surgical piece) were analyzed by the same pathologist.

In the cases of those patients who could undergo endoscopic resection, the presence of free margins was confirmed by histological study of the specimen analyzed, as well as the biopsy of the endoscopic resection scar.

Results and Discussion

There were 6 men and 8 women between the ages of 32 and 68 with an average of 52 +/- 9 years. All of them underwent a complete colonoscopy as part of the initial study. The referred symptoms were: rectal bleeding (50%), anemia (14.3%) or as a casual finding after screening for colorectal cancer (14.3%). The most frequent location in our series was in the superior rectus (7 cases), followed by the middle rectus (5 cases) and the inferior rectus (2 cases).

Due to the degree of tumor differentiation and its size, six of the patients required surgical intervention. In four of the patients, scheduled surgery was performed, choosing the surgical technique based on the tumor location. In all these cases, a radical surgery of the R0 type tumor consisting of tumor resection, lymphadenectomy and excision of the mesorectum was performed. Five of the patients presented a histology of poorly differentiated neuroendocrine tumor (G3) so, depending on their location and distance to the anal margin, a low anterior resection or abdominoperineal amputation was performed. In the patient diagnosed with a well-differentiated neuroendocrine tumor (G1) whose margins of resection after colonoscopy were affected, a transanal resection was performed due to the patient rejected an abdominoperineal amputation. None of the patients had metastatic tumor disease at the time of diagnosis, nor was it evident during the surgical intervention. The end result of the piece confirmed the diagnosis of NET of rectum with a cell proliferation index or Ki67 > 95% in three of them and in the other less than 10% that corresponded with previous biopsies.

During follow-up, five of the patients who underwent surgery developed tumoral progression consisting of unresectable liver metastases, so they received complementary chemotherapy treatment (4 - 6 cycles) with etoposide and cisplatin together with radiotherapy (24 - 30 sessions of 1.8cGys). Despite treatment during follow-up, all patients died. Survival according to tumor differentiation within the surgically treated patients who presented a G3 stage was 26.9 months while in the only patient who presented with a G1 tumor who underwent surgery, it was 106 months, being currently free of disease (Table 2).

	Sex	Age	Location	Grade	Ki 67	Survival
Patient 1	Male	53	Lower	G3	100%	64 months (deceased)
Patient 2	Female	49	Intermediate	G3	> 90%	7 months (deceased)
Patient 3	Female	48	Lower	G3	> 95%	15 months (deceased)
Patient 4	Female	56	Superior	G3	> 90%	43 months (deceased)
Patient 5	Male	51	Intermediate	G3	> 95%	1 month (deceased)
Patient 6	Female	68	Lower	G1	< 10%	103 months (not deceased)

Table 2

On the other hand, in the series of patients not surgically treated, eight patients (6 women and two men) presented a neuroendocrine tumor of the rectum whose treatment was endoscopic resection. The average age was 55 +/- 12.2 years. Seven cases of well differentiated tumor (G1) were obtained (87.5%) and only one case of moderately differentiated neuroendocrine tumor (G2) (16.7%). The tumor size

ranged from 0.2 to 20 mm with an average of 10 +/- 6.7 mm. Endoscopic resection was performed in all patients and no progression of the disease was observed, with 100% survival in all patients. All patients were followed up with colonoscopy and annual abdominal-pelvic CT without pathological findings.

Discussion

Neuroendocrine tumors of the rectum are rare malignancies that represent around 16% of the total NETs in the literature. In our experience, they represented 21.8%, being the second place in frequency behind the pancreatic neuroendocrine tumors.

Its incidence has tripled in the last 30 years, mainly due to two causes, the development of screening programs for colorectal cancer and improvements in imaging techniques [12]. Scherübl., *et al*. in their work establishes that the realization of colonoscopies to the population as a form of these screening programs helps to diagnose earlier stages [18].

The prognosis of neuroendocrine tumors of the rectum is not only conditioned by its size. 80% of G3 patients had lymphatic or vascular involvement in our study after the subsequent analysis of the piece, developing further metastases. In only one case, in which lymphovascular infiltration was demonstrated, did not develop metastasis in the follow-up.

According to Louis de Mestie., *et al*. those tumors smaller than 10 mm completely resected do not require follow-up because probability of recurrence and/or metastatization is very low [19]. In USA and Japan, rectal NETs smaller than 10 mm that do not present submucosal invasion or lymphovascular infiltration have 100% survival [20,21]. However, authors such as Konishi and Soga establish a risk of lymphatic spread between 7-9.7% [22,23].

For those less than 15 mm without invasion of the muscularis mucosae layer, without lymphovascular infiltration, low proliferation index and free margins there are no clear guidelines for follow-up. Nonetheless, Nobuhisa states that those rectal NETs greater than 10 mm that present lymphovascular invasion have a risk of metastasizing similar to that of adenocarcinomas [12]. For Zhang, endoscopic resection of tumors smaller than 16 mm is sufficient and has a good prognosis [4]. Sekiguchi describes that endoscopic resection achieves 96.7% of a complete resection with 96% survival at 5 years, establishing colonoscopy as an effective method of treatment [24].

Holinga., *et al.* described 8.3% of positive adenopathies after 26 months of resection, so this working group establishes an endorectal ultrasound every 6 months during the first three years for patients over 50 years of age [25].

In our series, endoscopic resection was performed for those tumors that presented a size between 0.2 and 20 cm. During the follow-up, was performed by colonoscopy and annual abdominal-pelvic CT. In the case of the patient who underwent a transanal resection, the tumor size was 0.8 mm due to the fact that endoscopic resection could not be performed. For some authors, the possibility of surgery based on TAMIS (transanal minimally invasive surgery) or TEM (transanal endoscopic microsurgery) may be a non-aggressive alternative in which endoscopic resection can not be performed.

Most of the rectal NETs are smaller than 10 mm (79%) and most are limited to the submucosa [26,27]. In our series, patients who presented a size greater than 20 mm were operated on with complete excision of the mesorectum, performing the follow-up consisting of annual colonoscopy and abdominal-pelvic CT every 6 months.

Sun-Hye., *et al*. associates as risk factors for developing a NET, those individuals with a previous oncological history or who present with hypertriglyceridemia or metabolic syndrome [1].

The performance of a scintigraphy and the detection of serum levels of chromogranin A are recommended according to ENENTS guidelines. In our series, no patient required scintigraphy and chromogranin A levels were not elevated in any patient.

Tumor differentiation is intimately related to the survival of patients. Thus for the G1, figures are established in the 5-year survival literature between 94% -100%, 54% -74% for the G2 stages and between 15% and 37% for the G3 [28]. In our series we obtained a 100% survival for G1 and G2.

Conclusion

Neuroendocrine tumors have a low incidence within malignant neoplasms of the rectum. The histological characteristics of the tumor (lymphovascular invasion and proliferation index) as well as its size influence the patient's prognosis. In lesions smaller than 10 mm and low grade, endoscopic resection is recommended as treatment. For poorly differentiated or larger tumors, complete resection of the rectum associated with complete excision of the mesorectum is necessary.

The treatment of rectal NETs requires a multidisciplinary approach where the correct staging influences the prognosis and survival of each patient.

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Conflict of Interest

The authors declare that they have no conflict of interests.

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