Watch-an-wait strategy for multiple rectal neuroendocrine tumors with widespread invasion

N. Torres[1], M. El Moussaoui[2], S. Basbous[3], V. Fridman[4], I. Borbath[5], J. Deflandre[6]

(1) Department of Gastroenterology, Cliniques universitaires St Luc, Yvoir, Belgium.; (2) Department of Infectious Diseases and General Internal Medicine, University Hospital of Liège, Liège, Belgium; (3) Department of Gastroenterology, University Hospital of Charleroi, Charleroi, Belgium; (4) Department of Anatomopathology, University Hospital of Liège, Liège, Belgium; (5) Department of Gastroenterology, Cliniques universitaires St Luc, Brussels, Belgium; (6) Department of Gastroenterology, Centre Hospitalier Régional (CHR) de Liège, Liège, Belgium.

Abstract

A 57-year-old man with a history of surgical resection for subocclusive small bowel Crohn's disease, was referred for endoscopic follow-up. Rectal neuroendocrine tumor(rNETs) was found during screening colonoscopy in the form of a centimetric polyp. A post-polypectomy endoscopy was reassuring while random biopsies performed showed low grade multiple rNETs diffusely infiltrating the mucosa and submucosa. Both abdominal-pelvic computed tomography (CT) and endoscopic ultrasonography echoendoscopy (EUS) did not identify any lymph node or distant lesion. Watch-and-wait strategy was performed by regular colonoscopy and EUS. As far as we know, this case is the unique case reported of non-progressive diffuse multiple rectal neuroendocrine tumors after a very long-term follow-up of 20 years. This case further supports that "Watch and wait" could be a safe alternative management strategy for selected rNETs, specially in patients for whom the surgical risk is increased with a potentially significant impact on the quality of life. (Acta gastroenterol. belg., **2023,** 86, **563-565**).

Keywords: Neuroendocrine neoplasm, staging, neuroendocrine carcinoma, endocrine cell micronests.

Introduction

Although neuroendocrine tumors (NETs) are rarely found (1), their frequency have risen over the last years, mainly due to the increased detection rates provided by accurate endoscopy and the accessibility of colonoscopy (1,2,3). The rectum is the second most frequent localization (1,4) and their presentation range from asymptomatic indolent tumor to aggressive metastatic disease (1,4,5). Rectal neuroendocrine tumors (rNETs) are commonly situated in the frontal or lateral mid-rectal wall, on average between 4 and 8 cm from the anorectal junction (1,4). rNETs are usually diagnosed incidentally during colorectal cancer screening endoscopy. They appear as small yellowish lesions, usually less than 10 mm in diameter (1,4), making them sometimes difficult to discriminate from the more usual polypoid lesions (1,4).

Although rNETs have an excellent prognosis compared to all other neuroendocrine gastrointestinal neoplasms, they have a potential of malignant degeneration (1). Therefore, it is necessary to evaluate this risk to determine the management strategy.

According to the European Neuroendocrine Tumor Society (ENETS) consensus, rNETs are classified according to grading and pTNM classification of malignant tumors (1,4). Grading is based on the expression of Ki67: low grade (G1) with Ki67 expression lower than 2%, intermediate grade (G2) with Ki67 expression between 3 and 20%, high grade (G3) with Ki67 expression greater than 20% (4).

EUS is a key element to guide the therapeutic management so it should be performed before treatment to determine the size of the tumor, the depth of invasion and the lymphatic invasion (LI) to make a better therapeutic decision (1,4). The management of rNETs consists of an endoscopic or surgical resection to obtain a completely oncological resection with safe margins (1). The type of resection depends on the size, depth of invasion, lymphatic and vascular invasion (LVI), grade of differentiation and risk of metastasis (1,4).

We report a case of a patient with multiple rNETs, an even more rare situation, for which a "watch-and-wait" strategy was chosen.

Case report

A 57-year-old Caucasian man with a history of small bowel resection, in 1976, for a subocclusion in a context of latent ileal Crohn's disease, was referred 22 years later to our hospital for endoscopic follow-up. During the colonoscopy, a 7 mm sessile polyp was resected in the rectum.

The histological and immuno-histological analysis revealed a low grade rNET (G1) infiltrating the mucosa and submucosa with clear resection margins.

Chromogranin A, Neuron Specific Enolase, Synaptophysin, Epithelial Membrane Antigen, pankeratin, and CD56 were positive (Fig.1). The patient was asymptomatic.

Expression of Ki67 was low (less than 1%) and no mitosis was demonstrated. Both abdominal-pelvic CT and EUS showed no evidence of lymph node or distant

Correspondence to: N. Torres, Avenue du Docteur Gaston Thérasse 1, 5530 Yvoir, Cliniques universitaires St Luc, Yvoir, Belgium, Phone: +32 81 42 21 11.
Email: nadia.torres@student.uliege.be

Submission date: 01/05/2022
Acceptance date: 07/01/2023

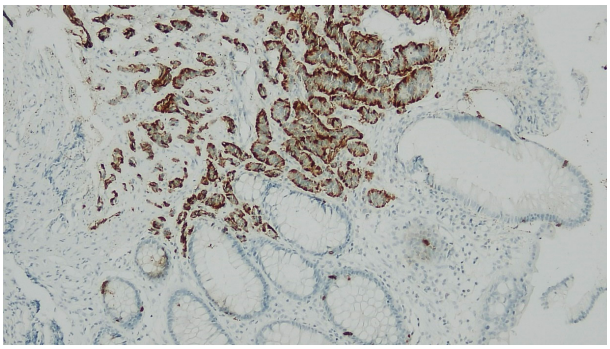

Figure 1. — Immunohistochemical study of the biopsied specimen. Neuroendocrine tumoral cells are chromogranin-positive.

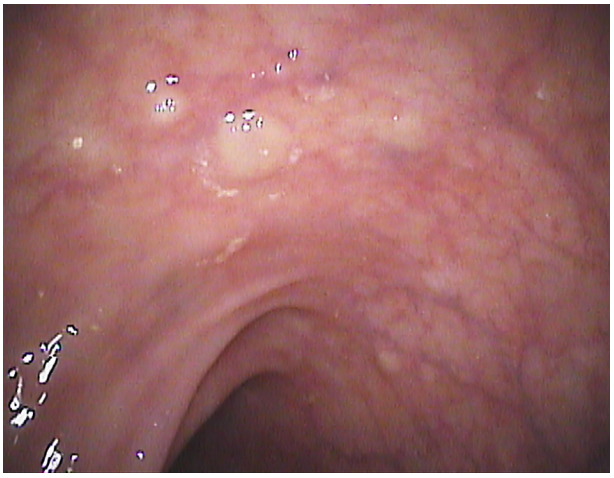

Figure 2. — Colonoscopy (7 March 2007). Endoscopic findings of multiple neuroendocrine tumors in the rectum.

organ metastasis. The somatostatin receptor scintigraphy performed in 1998 was negative.

Because the small tumor size, the low histological grade (G1), the absence of LI, complete resection, and negative extension work-up, a watch-and-wait strategy was decided.

During the first endoscopic follow-up performed 6 months later, multiple, more than 8 small (less than 10 mm) yellowish and discreetly nodular lesions scattered in the form of spots in the middle and upper third of the rectum, were identified (Fig 2). Anatomical pathological samples were consistent with clusters of G1 rNETs diffusely infiltrating the mucosa and muscularis mucosae.

Endoscopic follow-up consisted in regular colonoscopy performed by the same operator every 6 months the first two years, then every year during 11 years and later every 3 years. Histopathological analyses of all biopsies performed, repeated abdomino-pelvic CT and EUS remained absolutely stable over time. EUS showed no tumor infiltration. The chromogranin A assays performed were systematically normal.

Whole-body [^{18}F]-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) requested for another indication did not detect any suspect tumor lesions. At the time of the most recent follow-up visit, 20 years after multiple rNETs diagnosis, random rectal biopsies revealed exactly the same characteristics as it has been described at the diagnosis. A follow-up every 3 years was expected but the patient died of SARS-CoV-2 pneumonia in the meantime. No autopsy was performed.

Discussion

RNETs are uncommon and multiple rNETs even less so, therefore the management strategies are not clearly established (2,3,6).

As reported by others, the risk factors for disease extension are tumor size, depth invasion, mitotic index and expression of Ki67, LVI and the number of lesions (1,2,4). The most relevant factors are probably the histological grade and the size of the tumor as reported by ENETS consensus (1,4).

Indeed, according to the ENETS guidelines, well-differentiated tumors and lesions smaller than 10 mm have a low risk of LVI, muscularis invasion with a metastatic risk less than 3%. On the contrary, rNETs larger than 20 mm have a high risk of involvement of the muscularis propria and metastatic risk estimated at 60 to 80%, and require surgical management (1,4). RNETs with an intermediate size between 10 and 19 mm have an estimated metastatic potential of 10 to 15%. In these cases, the assessment in endoscopy associated with an EUS will guide our choice between endoscopic or surgical resection (1,4).

When a rNETs is suspected at colonoscopy, an EUS should be performed before treatment to determine the best therapeutic option for the patient (1,3,4).

After, the ENETS guidelines recommend CT/magnetic resonance imaging(MRI) staging if the size of the lesion exceeds 10mm(1), if the resection is incomplete or when metastatic lesions are suspected (1,4).

As for all rectal tumors, the best imaging is MRI (4,7), which allows precise staging of the disease and is mandatory before surgery (4).

Regarding the follow-up, the ENETS guidelines are based on the size of the tumor and the clear resection margins. Hence, a single rNETs smaller than 10 mm with complete resection do not require regular follow-up (1,4,7). Tumors larger than 10 mm with complete resection require endoscopic surveillance at 1 year, 3 years and then every 5 years. If there is one risk factor of local or distant recurrence, a surveillance by rectosigmoidoscopy or EUS should be performed every 6 months during 3 years and then every year (1).

Regarding conventional imaging, the ENETS guidelines recommend a CT/MRI every 3 to 12 months for G1 and G2 over 1 cm and every 3 months for G3 (7).

The place of functional imaging, mainly somatostatin receptor scintigraphy (SRS) and gallium-68 DOTA octreotide PET/CT, in follow-up is unclear due to the paucity of data available. Therefore, the ENETS guidelines recommend SRS for G1/G2 exceeding 1cm every 12 to 24 months and every year for G3 (7).

However, the PET imaging technique seems to be superior (4,7) and the guidelines will probably be reviewed accordingly.

Chromogranin A follow-up is controversial as fluctuations in plasma concentration are frequent. Moreover, chromogranin A is often normal in small rectal tumors, like in our case (7).

On the other hand, a case of a single 5 mm grade G1 rNET with LI has also been described (8). In the same way, a case of a 8 mm grade G1 rNET with complete submucosal resection and initial negative extension workup, presented hepatic metastasis 5 years later (5).

No somatostatin analogue was used as our patient was asymptomatic and his chromogranin A normal. This treatment is only used to reduce symptoms and the ENETS guidelines do not recommend this therapy for non-secreting tumors (4).

Our patient presented a low grade rNETs smaller than 10 mm with a complete resection and no distant lesion, but the EUS was performed afterwards. We adopted a surveillance strategy in view of the persistence of multiple of rNETs while guidelines were lacking at this time (2,3).

There are very few data available regarding the management of multiple, diffuse rNETs and their prognosis. A recent Japanese single-center retrospective study showed no significant difference between LI in single rectal and multiple rNETs. However, there was a significantly higher rate of LI in the sub-group of multiple NETs with more than 8 lesions (only 3 patients in this group) so they recommend a surgical resection with lymphadenectomy (2).

Otherwise, the management of multiple rNETs (less than 8 lesions) could probably be similar to single NETs based on this unique report.

Another paper, reporting a small case series (5 cases) of multiple grade G1 rNETs (3 lesions), all endoscopically resected, with no sign of progression during a short follow-up of 24 months (3).

Several cases reports have been published in the literature of multiple rNETs with submucosal spread, not visible, so surgery was performed even for small lesions because of the increasing LI risk (6).

This rarity explains the lack of consensus on endoscopic versus surgical management and the interval period of endoscopic control if a wait-an-watch strategy is decided in multiple rNETs (3,6).

In conclusion, our patient's case is the unique case reported of a multiple rectal, diffuse type NETs without progression with a very long follow-up of 20 years. Our report exhibits the possibility to avoid systematic resection approach and to promote follow-up strategies.

Small localised G1 neoplasms mostly have a favourable prognosis, so a "watch-and-wait" strategy may be a safe alternative for patients for whom the surgical risk is high with a potential major impact on their quality of life.

Nevertheless, our observation needs to be supported by further data to implement new strategies. If a watch-and-wait strategy is adopted, the interval between every endoscopy appointment remains to be defined.

Conflict of interest statement

The authors declare no conflict of interest.

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