Single brain metastasis from a minute, well differentiated, but invading beyond the tunica muscularis mucosa rectal carcinoid

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Abstract

We report the case of a 48-year-old woman with small-sized (< 10 mm), highly differentiated, aggressive rectal carcinoid, who developed a solitary distant metastasis to the brain. The primary lesion, initially removed by conventional polypectomy, invaded the mucosa/tunica muscularis mucosa and had positive resection margins. Afterwards, an assessment of 5-hydroxyindoloacetic acid (5-HIAA) 24 h urine excretion revealed a significantly increased level. Thus, a partial rectal resection was performed. Because of constantly elevated carcinoid markers : serum chromogranin A (CGA) and 5-HIAA, a somatostatin receptor scintigraphy was performed, which disclosed a focus of pathological marker accumulation in the left frontal area. The pathological finding after neurosurgical excision was meningioma. An unexpected normalization of the biochemical markers prompted us to verify this diagnosis. The final histopathological report was a well-differentiated neuroendocrine brain metastasis.

Our case shows that in well differentiated, of diameter < 10 mm rectal carcinoids, an invasion even beyond the mucosa/tunica muscularis mucosa seems to be an independent factor predicting a malignant metastatic potential of these tumors. Hence, in such cases, behind the endoscopic submucosal resection with ligation device a more radical surgery should be considered. Additionally, a systematic CGA and 5-HIAA follow-up assessment and whole body somatostatin receptor scintigraphy, if necessary, are required. (Acta gastroenterol. belg., **2009**, 72, **63-66**).

Key words : small sized, rectal carcinoid, brain metastasis, invasion depth, ki67.

Introduction

Rectal neuroendocrine neoplasms are rare and constitute approximately 20% of gastro-intestinal carcinoids and 1.3% of all rectal tumors (1). According to the Carcinoid of the Rectum Risk Stratification score, introduced by Fahy *et al*., tumors characterized by the size of < 1 cm, invasion confined to the mucosa/submucosa, no lymphnode metastases and mitotic rate < 2/50 HPF (number of mitosis per high power fields), appear to have an indolent course and low risk of distant metastasis (2). Metastases from neuroendocrine cancers mainly occur in the lymph nodes, lungs, liver and bones, whereas they are very rare in the brain (3,4). In the latter, the primary tumors are usually large-sized > 20 mm, poorly differentiated (Ki-67 > 2%), localized in the lungs, ileum, colon, mediastinum, stomach, and extremely rarely in the rectum (3,5,6).

We report the first case of a small-sized (< 10 mm), highly differentiated, but invading further than the mucosa rectal carcinoid, which developed a single distant metastatic lesion to the central nervous system.

Case report

A 48-year-old woman presented to Gastroenterological Outpatient Clinic in October 2003 complaining of abdominal pain and change in bowel movement. The interview revealed that the symptoms started about three years before. The abdominal pain was localized mainly in the left lower area and was accompanied by diarrhea alternating with constipation. The patient's past medical history included arterial hypertension and miastenia. A rectoscopy performed revealed a small (< 10 mm), singular polyp nine cm from the anal verge. Cytological evaluation of the material received by biopsy showed nests of neuroendocrine cells with no atypical features. Consequently, the patient underwent a complete colonoscopy, in which apart from the polyp mentioned above, no other abnormalities were noted. The histopathological finding in the polypectomy specimens was a carcinoid : positive expression of chromogranin A and synaptophysin (Fig. 1-2), which invaded beyond the mucosa/tunica muscularis mucosa -positive resection margins (Fig. 3). The proliferation index Ki-67 was found to be negative in the carcinoid cell nuclei (< 1%) (Fig. 4). The evaluation of 24 hours urine 5-hydroxyindolacetic acid (5-HIAA) excretion following conventional polyp resection showed significantly increased level 27 mg/24 h (N 2-6 mg/24 h). Taking in consideration the positive resection margins and elevated biochemical marker level (5HIAA) a partial Dixon's resection of the rectum was performed. No further neoplastic lesions were found. During this time the patient received only symptomatic treatment (Mebeverine hydrochloride). Due to mild symptoms and short period between the diagnosis and the Dixon's resection no somatostatin analog treatment was given.

The postoperative assessment of the biochemical carcinoid markers showed an elevated serum chromogranin A (CGA) level 63 U/l (N 2-18 U/l, DAKO

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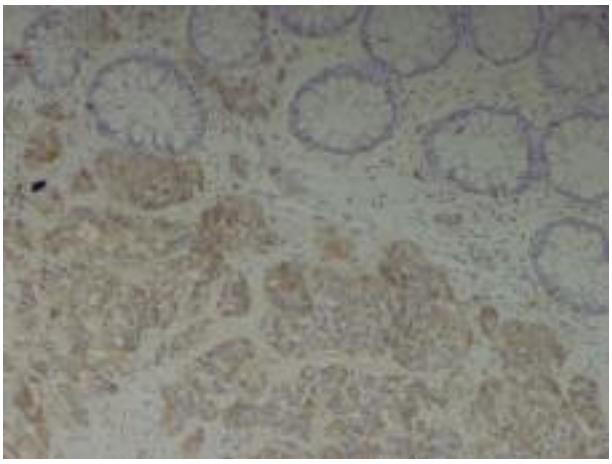

Fig. 1. — Histopathological evaluation of rectal carcinoid : positive expression of chromogranin in neuroendocrine tumor cells demonstrated with immunohistochemical technique (objective 100×).

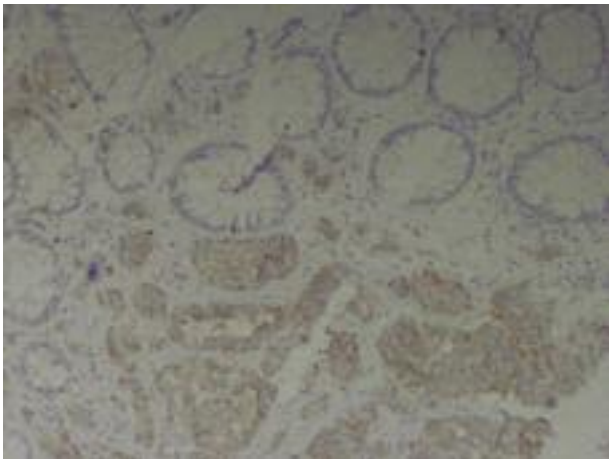

Fig. 2. — Histopathological evaluation of rectal carcinoid : positive expression of synaptophysin in neuroendocrine tumor cells demonstrated with immunohistochemical technique (objective 100×).

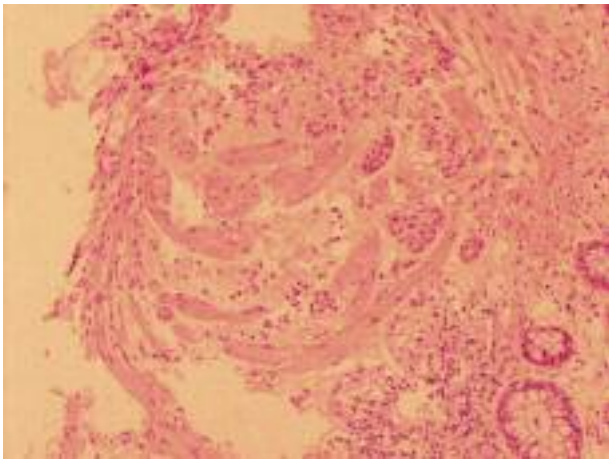

Fig. 3. — Histopathological evaluation of rectal carcinoid showing the invasion beyond the mucosa/tunica muscularis mucosa, H + E (objective 100×).

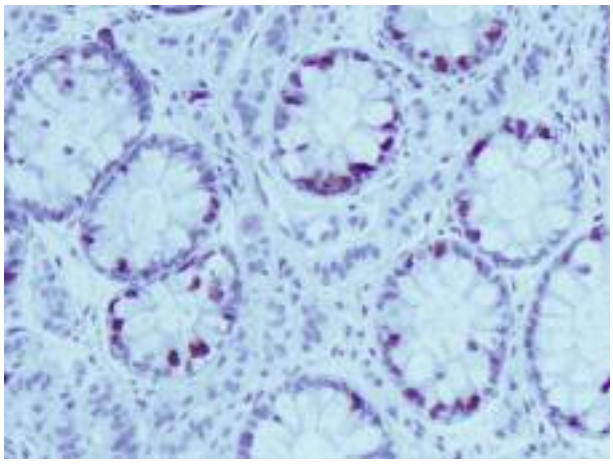

Fig. 4. — Histopathological evaluation of rectal carcinoid showing negative expression of Ki-67 tumor cell nuclei (< 1%) demonstrated with immunohistochemical technique.

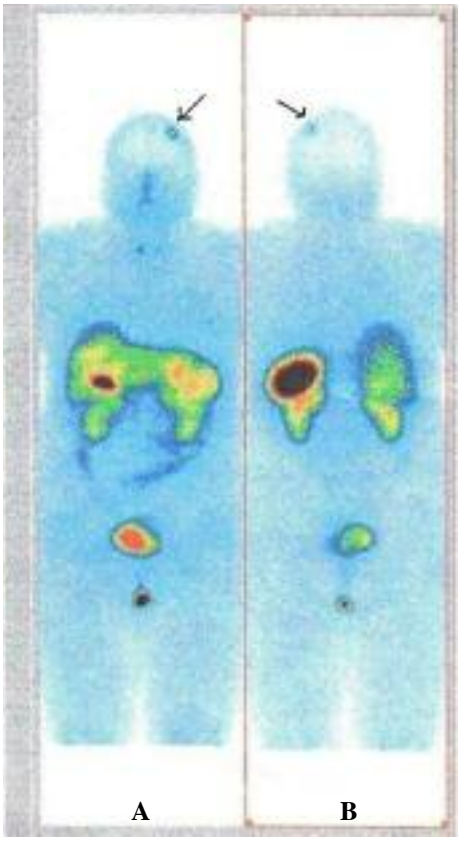

Fig. 5. — Whole body somatostatin receptor scintigraphy shows a focus of pathological marker accumulation in the left fronto-parietal area, visible on the anterior (A) and posterior (B) projection (arrow).

Chromogranin A ELISA kit) and still highly increased urine 5-HIAA excretion 39.4 mg/24 h. In order to explain the elevation of these markers, a whole body somatostatin receptor scintigraphy SRS using 99mTc-EDDA-HYNIC was performed. The scanning showed a single focus of pathological marker accumulation in the left fronto-parietal area (Fig. 5).

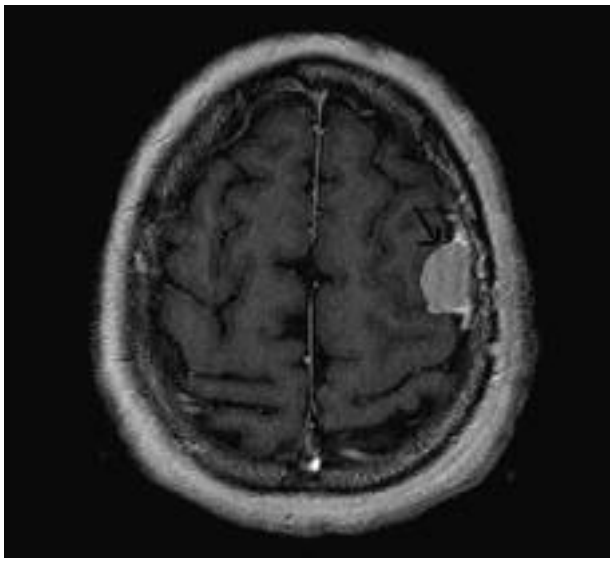

Fig. 6. — MRI of the head showing a mass, localized in the left frontal area (arrow).

Magnetic Resonance Imaging (MRI) of the head revealed 2 cm, highly contrast enhanced mass, localized in the left frontal area and presumably originating from the dura mater (Fig. 6).

A total removal of the brain tumor was performed and the initial diagnosis was meningothelial meningioma. Two months later, a control of the serum CGA level showed decrease to 9.7 U/l. Due to the unexpected normalization of this carcinoid marker (CGA) a decision to verify the diagnosis of meningioma was made. The final rapport obtained from our Department of Pathology revealed a brain neuroendocrine lesion, probably metastasis from a highly differentiated neuroendocrine tumor. Immunohistochemically, the brain tumor cells stained positive for chromogranin and synaptophysin (Fig. 7-8). The proliferation index Ki-67 was found to be positive only in a few cell nuclei < 2%, indicating that the primary neoplasm belongs to the type IB according to the WHO 2000 classification ; well differentiated neuroendocrine tumors with uncertain behavior (Fig. 9).

The latest follow-up medical assessment showed : serum CGA level and urine 5-HIAA excretion in the normal ranges, 100 ng/ml (N 20-100 ng/ml, Cis Bio International Kit) and 3.6 mg/24h respectively. The clinical, imaging and endoscopic examinations (head MRI, CT of the abdomen , chest X-ray, colonoscopy) showed no signs of disease recurrence.

Discussion

Neuroendocrine cancers rarely metastasize to the brain. The largest series of the literature published to date on brain carcinoids was reported by Hlatky *et al*. In the study of 1633 patients with carcinoid tumors the authors found 24 cases (1.5%, median age 60 years) with brain metastases. A single brain lesion was found in

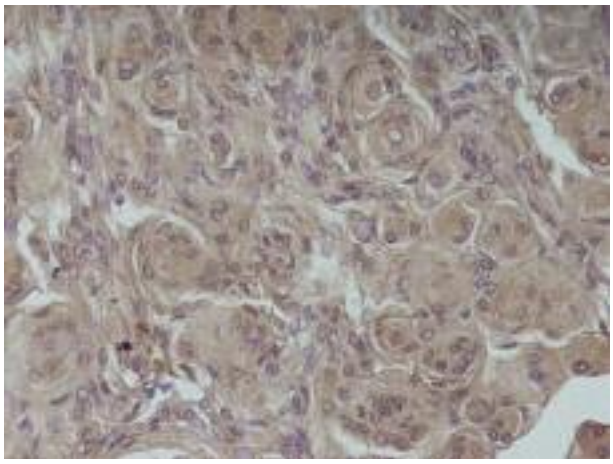

Fig. 7. — Immunohistochemical evaluation of the brain tumor initially diagnosed as meningioma : positive chromogranin expression in tumor cells (objective 200×).

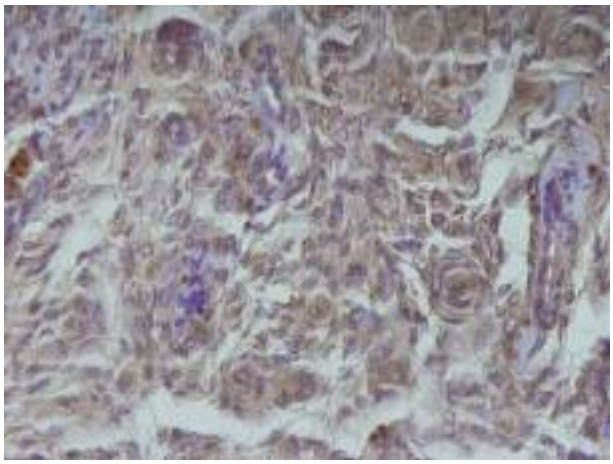

Fig. 8. — Immunohistochemical evaluation of the brain tumor initially diagnosed as meningioma : positive synaptophysin expression in tumor cells (objective 200×).

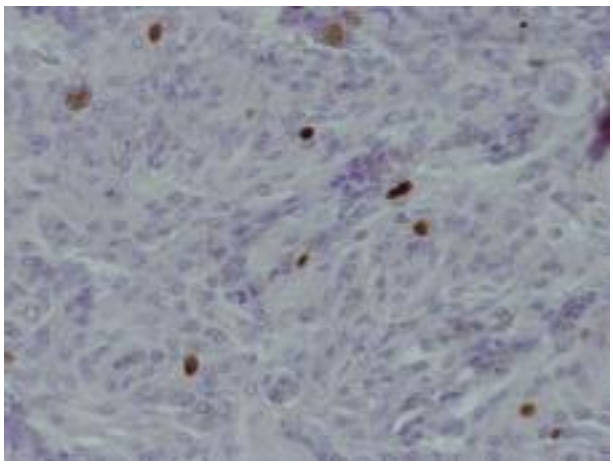

Fig. 9. — Immunohistochemical evaluation of the brain tumor initially diagnosed as meningioma : positive Ki-67 expression in < 2% of tumor cells (objective 200×).

11 patients (46%), the remaining 13 presented multiple cerebral metastases. All subjects had disseminated neoplastic disease at the time of diagnosis of the brain tumor. In 10 patients (42%) the metastatic lesions were dural based mimicking a meningioma (5).

Brain metastases from rectal neuroendocrine tumors are unusual. The majority of rectal carcinoids are localized (75-85%) and incidence of distant metastases at diagnosis ranges between 1.7 and 8.1% (1). The risk of metastasis have been shown to correlate with the tumor size by several authors. Mani *et al*. reported that metastases was found in 2% of patients with tumors < 1.0 cm, 10-15% in patients with tumors measuring 1.0-1.9 cm, and 60-80% in patients with tumors measuring > 2 cm (6). A large meta-analysis of rectal carcinoid, by Soga, showed that the rate of metastasis according to tumor size was 77% (≥ 21 mm), 30% (11-20 mm), and 5.5% (< 10 mm), respectively (7).

On the other hand, the depth of invasion has also been implicated as an important prognosis factor in rectal carcinoids. Heah et al found that tumor size can not predict malignant potential of rectal carcinoids as even small tumors (< 1 cm) can develop metastases (8).

It has been demonstrated also that in patients with tumors < 2 cm metastases were seen in 2% if the tumor was confined to the submucosa, the risk of metastases rose to 48% if the tumor invaded the muscularis propria (9). Another factor, the cell proliferation index Ki-67, has also been investigated. Hotta *et al*. assed the usefulness of Ki-67 for predicting the metastatic potential of rectal carcinoids and found a significantly higher Ki-67 ratio in metastatic group than non-metastatic group.

Moreover, the authors reported that Ki-67 ratio > 1.5% was superior to other histological parameters such as invasion depth, variation in nuclear size, and degree of vessel permeation (10).

In well-differentiated (Ki-67 < 2%) rectal carcinoids, less than or equal to 10 mm in diameter standard polypectomy or conventional submucosal resection are commonly performed. However, according to some authors, complete resection of rectal carcinoid tumors is very difficult using these techniques, as these tumors, even though small in diameter, are located in the submucosal layer of the rectal wall (11). Recently, Mashimo et al. reported a novel technique named endoscopic submucosal resection with a ligation device. The authors demonstrated that this method could be safely performed in small rectal carcinoids and it provided a higher complete resection rate (12).

In our patient a highly differentiated carcinoid tumor (Ki-67 < 1%) was diagnosed in a minute polyp (< 10 mm) of the rectum. For this reason the risk of metastases was thought to be very low. The assessment of specimens obtained by standard polypectomy revealed neuroendocrine tumor cells in one of the lateral lines of resection and in the tunica muscularis mucosa. This suggested high probability that the tumor had penetrated the submucosa.

Because of increased 5 HIAA 24 h excretion first of all we decided to perform a partial resection of the rectum. Unexpectedly, the biochemical follow-up investigations revealed a constantly increased 5 HIAA and significantly elevated serum chromogranin A level. Then a whole body somatostatin receptor scintigraphy was performed, which revealed a singular focus of pathological tracer accumulation in the central nervous system. This turned out to be a well-differentiated (ki-67 < 2%) neuroendocrine brain lesion. The common pathological and immunohistochemical features of the rectal and cerebral tumors suggest that the most probable primary origin of the brain metastasis is the minute rectal carcinoid diagnosed before. The only way to provide evidence that the brain tumor was a metastasis and not a second primary is to perform genetic studies of the both (rectal and cerebral) lesions. Such analyses are not routinely carried out.

The reported case suggests that in well-differentiated rectal carcinoids, of size less that 10 mm, an invasion even beyond the mucosa/tunica muscularis mucosa may be an independent factor predicting a malignant metastatic potential of these tumors. Hence, in such cases, behind the endoscopic submucosal resection with ligation device, a more radical surgery should be considered. Additionally, in patients with meningioma-like lesion the history of carcinoid tumor is of high importance, and therefore in such cases the CGA, 5-HIAA follow-up assessment and whole body somatostatin receptor scintigraphy, if necessary, are required.

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