Everolimus in a Patient with Metastatic Neuroendocrine Tumor of the Rectum

Introduction

In a 56 years old woman, a neuroendocrine tumor (NET) of the rectum with about 2 cm in diameter was found during colonoscopy. Computed tomography of the abdomen and pelvis was performed, revealing at least one suspicious lymph node with an intensive contrast medium enhancement. Somatostatin-receptor scintigraphy in fusion with computed tomography showed an increased tracer uptake of both, the primary tumor and two lymph nodes. After completion of staging, anterior resection and mesorectal excision were performed. The tumor was classified pT3, pN1 (1/12), R0 with a proliferation (Ki67) of 15% (G2).

About one year later, suspicious liver lesions were detected in abdominal ultrasound. Percutaneous biopsy was performed, confirming metastases of a NET with a proliferation index (Ki67) as high as 10% with a high tracer uptake in somatostatin-receptor scintigraphy. The patient was subsequently treated with multiple sessions of $^{90}$Y-DOTATOC radio-receptor therapy and two cycles of $^{90}$Y-SIRT therapy. After initial disease stabilization, the disease progressed further.

At that time, five years after initial diagnosis, the patient first presented at our endocrine department for further treatment. $^{68}$Ga-DOTANOC-PET/CT revealed progressive, systemic disease with hepatic, lymphatic, and pulmonal metastases, without relevant tracer uptake. The patient was not willing to undergo systemic chemotherapy. We therefore discussed an off-label use of everolimus 10mg daily with the patient who agreed on this option.

In the first assessment of treatment efficacy after three months of treatment, we saw a stable disease with a marked necrosis of the largest as well as some other metastases (Figure 1). The patient reported a relief of right upper abdominal pain that she had complained about constantly before. Unfortunately, she kept on experiencing several adverse effects of the medication, so we had to taper and finally withdraw everolimus after about 4.5 months. The re-assessment of the tumor burden, about 3 months after the previous MRI scan, showed progressive disease again (Figure 1).

Discussion

NET of the rectum are often found coincidentally during colonoscopy [1], are often small (< 10 mm) without deep invasion or metastases, and can, in many cases, be removed completely by endoscopic means [2-5]. Therefore, they are sometimes considered to be of rather benign nature. This case demonstrates a rare, unfavourable course of a rectal NET. Given its size, high

Figure 1: In the left part of the figure, the situation at baseline can be found, focusing on the biggest hepatic lesion with an already remarkable inhomogeneous appearance. At first assessment, 3 months after initiation of everolimus therapy, necrotic degradation in the biggest one as well as some other hepatic lesions was found (middle), that showed solid reorganisation about 45 days after withdrawal of the therapy (right).
proliferation, and presence of suspicious lymph nodes in initial imaging, this was a high-risk constellation from the beginning [1-3], highlighting the need for thorough surgery as the only potential cure [6]. The unusual early recurrence and following metastatic spread was presumably forwarded by insufficient lymph node dissection, since review of available documents revealed discrepancy of preoperative imaging and pathologic report, that only identified one metastatic lymph node. Since metastatic rectal NET are a rather rare entity, current guidelines provide few therapeutic options only, with systemic chemotherapy being the recommended approach for progressive, systemic disease [2,3]. Based on the patient’s decision against chemotherapy, we decided for an off-label use of everolimus. The patient who presented with progressive disease demonstrated pain relief and disease stabilization per objective measures following initiation of therapy. One might argue whether the necrotic degradation of some of the metastases should be considered as an even partial response. Yet, we cannot prove that this was a consequence of antitumor medication since spontaneous cystic and necrotic degradation has also been described in both, NET and neuroendocrine carcinoma (NEC) [7]. Regardless, it addresses the necessity to expand our knowledge of the influence of morphologic changes following antitumor-therapy in NET and to investigate whether or not we have to integrate those into our current tumor response assessment tools, as for example in gastrointestinal stromal tumors (GIST) [8].

Taken together, this case draws attention to the malign potential of all NET regardless of the primary site. It demonstrates that due to sparse evidence on the treatment of rare NET, individual approaches are important where guidelines fail to provide us suitable options for individual patients. Last, even though often considered to be an alternative in patients with slowly proliferating NET only, everolimus also seems to be a suitable option in higher proliferation, even in other than the approved primary tumor sites, at least in selected patients.

**Funding:** This work was supported by the German Research Foundation (DFG) and the Technische Universität München within the funding programme Open Access Publishing

**References**


