Intramyocardial Metastasis of a Neuroendocrine Neoplasm of the Small Intestine: a Case Report.

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ABSTRACT

Neuroendocrine neoplasms of the small intestine are often an incidental finding on imaging studies or diagnosed when already metastasized. Symptoms originate from secreted hormones or mass-effect of the tumor. A 68-year-old man presented with palpitations. He had a history of a metastasized carcinoid and carcinoid syndrome for which he was treated with somatostatin. Upon physical examination he had a normal blood pressure, heartbeat and cardiac auscultation. An electrocardiogram showed no abnormalities. The echocardiography was non-conclusive and a cardiac MRI revealed a nodular thickening in the basal infero-septal wall, indicative for intracardial metastasis. Indeed, a 18F-fluorodihydroxyphenylalanine PET-CT scan showed uptake in the known liver metastasis, but in the myocardium as well. Since the patient did not have arrhythmias or evidence of heart failure, no changes in therapy were made and imaging studies are to be repeated annually. Cardiac metastasis is a rare complication of neuroendocrine neoplasms of the small intestine and should not be confused with carcinoid heart disease. Whenever a patient with a history of a neuroendocrine neoplasm has cardiac complaints, cardiac metastasis should be considered. The therapy of cardiac metastasis is dependent on the location and symptoms. Somatostatin analogue treatment should be considered to halt progression.
INTRODUCTION

Neuroendocrine neoplasms of the small intestine arise from serotonin-producing enterochromaffin cells and are characterized by a low proliferation. The reported incidence is between 0.32/100,000 and 1.12/100,000/year with the majority of cases occurring in the 7th Decade. Commonly it is found in the ileum and if metastasized, it is mainly to the liver or regional lymph nodes. Symptoms originate from mass-effect of the primary tumor or from secreted hormones. Less than 20% of the tumors secrete those biologically active hormones, which are responsible for the so-called carcinoid syndrome. About 50-60% of the patients with carcinoid syndrome develop carcinoid heart disease, which is right-sided valvular heart disease due to endocardial plaques of fibrous tissue. It is thought that elevated concentrations of serotonin plays a major role in the pathogenesis of carcinoid heart disease. Since the humoral substances are usually inactivated in the pulmonary circulation, left-sided heart involvement is uncommon. The average age of diagnosis is between 60 and 65 years and there might be a slight male preponderance. Pre-operative diagnosis is made by cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI), which can serve for initial staging as well. Following the discovery of prominent molecular biomarkers in neuroendocrine neoplasms, the role of functional imaging is increasing, but limited due to the availability. Still, a pathological diagnosis remains mandatory.

The grading is mainly based on the immunohistochemical determination of the proliferation marker, Ki67. Staging is usually done by CT or MRI. All patients with Grade 1 or 2 tumor should be considered for curative surgery, even if liver or regional lymph-node metastasis are present.

The 5-year survival rate depends on staging and grading with a 5-year survival of up to 100% in grade I stage I tumors, with reduced survival numbers in patients with grade II or III tumors, extensive metastasized disease or carcinoid heart disease. In contrast with carcinoid heart disease, actual cardiac metastases are very rare.

CASE PRESENTATION

A 68-year-old man presented at the out-patient clinic with palpitations. The patient had a past history of a neuroendocrine neoplasms of the small intestine (ileal carcinoid tumor), which was resected 22 years ago. Two years later he had a recurrence in a mesenteric lymph node and liver for which an expectant management was chosen. Fourteen years after the initial surgery, he developed diarrhea and flushes. The diagnosis carcinoid syndrome was made for which somatostatin was started. The remaining medical history includes hypertension, paroxysmal atrium fibrillation, and prostate cancer in 2010 for which he had a transurethral resection of the prostate.

Three weeks before presentation he had paroxysmal complaints of palpitations for up to ten minutes. He did not have angina pectoris, nor was there a provocative moment.

Upon physical examination the patient had a normal blood pressure and heartbeat. Cardiac auscultation demonstrated normal sounding tones without extra tones or murmurs. An electrocardiogram showed a normal sinus rhythm with an intermediary axis and normal conduction without ST-segment deviations. A preliminary diagnosis of recurrent paroxysmal atrium fibrillation was made and a follow-up visit was arranged with an ambulant ECG-registration and echocardiography in advance. The echocardiography (Fig. 1) showed a dilated left atrium, hypokinetic septum and akinetic apex, possibly due to an old infarction for which further imaging studies were scheduled. A cardiac MRI (Fig. 2 and 3) was performed to evaluate the cardiac situation. It showed a normal systolic function with an ejection fraction of 52%. There was a nodular thickening in the basal infero-septal wall, as made visible with first pass gadolinium enhancement. The delayed enhancement series showed, in this nodular thickening, diffuse enhancement in a non-ischemic distribution. This lesion is indicative for an intracardial metastasis. There was no delayed enhancement in a typical sub-endocardial distribution, which would fit with
infarction. Consequently, a 18F-fluorodihydroxyphenylalanine (18F-DOPA), positron emission tomography (PET) CT scan (18F-DOPA PET-CT) (Fig. 4) showed uptake in the known liver metastases, but in the myocardium as well, indicative for cardiac metastasis. Because of the location of the metastasis, patient is at risk for macro-reentrant ventricular tachycardia by disruption of the cardiac conduction system. Fortunately, these were not detected on ambulatory ECG registration. The palpitations disappeared spontaneously without intervention.

**Figure 1.** Echocardiography short axis showing infero-septal sharply circumscribed hyperdense structure

**Figure 2.** Cardiac MRI short axis showing a nodular thickening in the basal inferoseptal wall
Since the patient did not have any other complaints besides palpitations, no arrhythmias, no evidence of heart failure, and surgical resection was not without risks, no changes in therapy were made. Imaging studies will be repeated annually and ambulatory ECG on indication.
Neuroendocrine neoplasms of the small intestine were originally described as ‘carcinoid’ tumors by Oberndorfer in 1907, but the nomenclature has been changed in 2010 by the World Health Organization. Regardless of the nomenclature, a pathological diagnosis is mandatory in all patients with suspected neuroendocrine neoplasms of the small intestine.

Since neuroendocrine tumors frequently have a high level of somatostatin receptor (SSTR) expression, labelled somatostatine analogues can be used for staging properties. For many years somatostatin-receptor scintigraphy (SRS) with 111In-pentetreotide has been used for staging of NETs in combination with CT. Over the last years new staging methods have become available.

18F-DOPA PET-CT is based on the property of neuroendocrine cells to take up amine precursors like 18F-DOPA, which makes it an excellent modality for detecting neuroendocrine metastases. As described by Koopmans et al. 18F-DOPA PET-CT is successfully used in the detection of carcinoid lesions with a per-patient sensitivity of 96% and per-lesion sensitivity of 98%. The per-patient sensitivity and per-lesion sensitivity were 79% and 66% respectively for SRS with CT.

Cardiac metastases are rare, with only a few reports in the last years (table 1). Detection methods vary and usually biopsy is performed to confirm the diagnosis.

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients with cardiac metastasis</th>
<th>Localization of primary tumor</th>
<th>Other metastases</th>
<th>Cardiac symptoms</th>
<th>Detection method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rueda et al</td>
<td>2014</td>
<td>Right bronchus</td>
<td>no</td>
<td>Palpitations</td>
<td>Cardiac MRI biopsy</td>
</tr>
<tr>
<td>Bukowczan et al</td>
<td>2015</td>
<td>Terminal ileum</td>
<td>Ovaries, liver</td>
<td>None</td>
<td>111In-pentetreotide biopsy</td>
</tr>
<tr>
<td>Makis et al</td>
<td>2015</td>
<td>Small bowel</td>
<td>Liver, lymph nodes, breast</td>
<td>None</td>
<td>111In-pentetreotide 123I-MIBG</td>
</tr>
<tr>
<td>Yan et al</td>
<td>2016</td>
<td>Small bowel</td>
<td>Liver</td>
<td>Palpitations, AF</td>
<td>111In-pentetreotide Cardiac MRI</td>
</tr>
<tr>
<td>Bonsen et al</td>
<td>2016</td>
<td>Retrospective report: 6 out of 273</td>
<td>NA</td>
<td>NA</td>
<td>68Ga-DOTATATE PET/CT</td>
</tr>
<tr>
<td>Castello et al</td>
<td>2016</td>
<td>Terminal ileum</td>
<td>Liver, pancreas,</td>
<td>None</td>
<td>111In-pentetreotide Cardiac MRI biopsy</td>
</tr>
<tr>
<td>Studer et al</td>
<td>2017</td>
<td>Terminal ileum</td>
<td>Liver</td>
<td>Edema, dyspnea</td>
<td>111In-pentetreotide Cardiac MRI biopsy</td>
</tr>
</tbody>
</table>
Recently, $^{68}$Ga-DOTA-octreotate (DOTATATE), another radiolabelled somatostatin analogue, has been introduced. As shown by Haug et al., $^{68}$Ga-DOTATATE in combination with PET/CT had a patient-based sensitivity of 96% in the detection of metastases, but the sensitivity of $^{18}$F-DOPA PET-CT was only 56% in this study. However, in this study with 25 patients, no cardiac metastases were detected. In a more recent report by Bonsen et al. with 273 patients, cardiac metastasis were detected with $^{68}$Ga-DOTATATE PET-CT in six patients. However, since these patients did not have cardiac complaints or symptoms, the clinical impact of this result was limited.

The therapy of cardiac metastasis should be patient-tailored depending on the localization(s) of the metastases and performance status of the patient. Options include surgery, somatostatin analogues, protein kinase inhibitors or watchful waiting, but evidence to support those options is lacking. If complications like arrhythmias or heart failure occur, antiarrhythmic or heart failure agents should be administered.

Ultrasound follow-up should be annually performed with attention to arrhythmias or heart failure.

**CONCLUSION**

This case shows the additive value of $^{18}$F-DOPA PET-CT to evaluate metastatic disease in a patient with a neuroendocrine neoplasm of the small intestine. With the new imaging methods, the detection of cardiac metastasis is more accurate than before. The clinical impact of cardiac metastases might be serious, since severe complications like ventricular arrhythmias or heart failure might occur. Therefore these patients should be monitored carefully.

**DECLARATION OF CONFLICTING INTEREST**

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**REFERENCES**


