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^{111}In-pentetreotide and ^{123}I-MIBG for detection and resection of lymph node metastases of a carcinoid not visualized by CT, MRI or FDG-PET

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A patient with a history of a jejunal carcinoid and resection of liver metastases underwent CT, MRI and FDG-PET as well as somatostatin receptor scintigraphy using ^{111}In-pentetreotide during follow-up. Octreoscan demonstrated one extrahepatic abdominal lesion with pathologic uptake, while the other imaging modalities failed to show a corresponding abnormality. For verification of this finding ^{123}I-MIBG scintigraphy was performed. The MIBG scan confirmed the octreotide positive lesion and showed an additional abdominal lesion in the SPECT study. According to the scintigraphic results, radioguided surgery (RGS) was implemented using ^{123}I-MIBG. This resulted in the intra-operative detection of two para- and pre-aortic lymph node metastases by the gamma probe and successful resection. An additional preaortal lymph node, suspicious by palpation, was also removed. Histopathology revealed metastases of a carcinoid tumor in all three specimens. In conclusion, the use of RGS facilitates successful removal of carcinoid metastatic lesions despite negative conventional imaging results. Secondly, ^{123}I-MIBG scintigraphy may provide advantages over octreoscan for preoperative localization as well as radio-guided surgery of neuroendocrine metastatic lesions, if the involved site is located in proximity to highly octreotide-avid organs such as the kidneys or spleen.

Key words: ^{111}In-pentetreotide, ^{123}I-MIBG, radioguided surgery, carcinoid metastases, neuroendocrine tumor

INTRODUCTION

CARCINOID TUMORS are neuroendocrine neoplasms that arise from the bronchus, appendix, small intestine, colon, rectum, larynx, thymus, kidney, ovary, prostate and skin.[1] They are mostly located in the appendix and ileum,[2] and often metastasis to the liver. Although functioning carcinoid tumors can be diagnosed by characteristic symptoms and signs described as carcinoid syndrome, and by the increased serotonin metabolite 5-hydroxy-indol acetic acid (5-HIAA) in the urine, non-functioning carcinoids are found incidentally or after mechanical symptoms such as obstruction. The primary tumor and possible metastases may be localized by ultrasound, chest X-ray, gastrointestinal endoscopy, computed tomography (CT), magnetic resonance imaging (MRI), and by nuclear medicine procedures using ^{131}I- or ^{123}I-metaiodobenzylguanidine (MIBG) and ^{111}In-pentetreotide in combination with CT and/or MRI.[3–8]

The primary treatment of carcinoid tumors requires surgery as the only possible curative approach, and the success of primary surgery is closely related to patient survival. Intra-operative use of gamma probes increases the success rate of surgery with more lesions found undetected by palpation during surgery due to their smaller size. In previous series, it has been shown that by using gamma probes intraoperatively surgeons removed 57%

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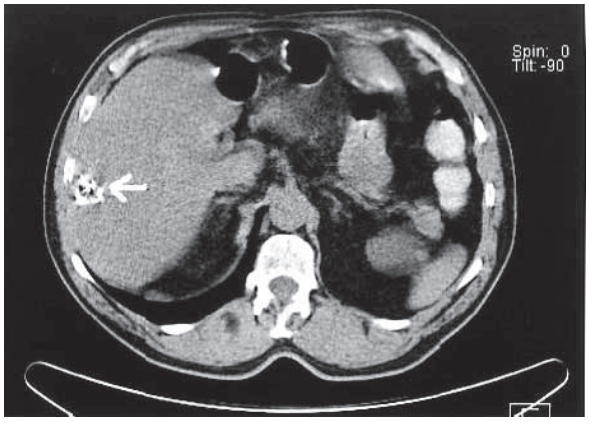

Fig. 1 Abdomen CT image showing a contrast absorbed lesion in the right liver lobe at the site of a removed liver metastasis.

Fig. 2 Twenty-four hour ^{111}In-pentetreotide SPECT coronal images show one lesion on the mid-abdomen and one additional non-specific lesion with faint tracer uptake (*black arrows*).

more lesions compared to palpation in gastroenteropancreatic tumors.[9] Radio-guided surgery (RGS) allows detection and resection of tumors and/or metastases according to the increased uptake of radiopharmaceuticals such as ^{111}In-pentetreotide, ^{123}I-MIBG or radio-labeled monoclonal antibodies.

With this case report, we aimed to emphasize the clinical role of RGS for intra-operative localization and removal of metastatic and/or recurrent lesions of carcinoid tumors not detected with conventional radiological techniques. We also point out, that in some cases MIBG may provide advantages over octreoscan according to the site of interest and the interference by organs with high physiological tracer uptake.

CASE REPORT

A 54-year-old man had surgery for a well differentiated jejunal carcinoid with metastases to the liver and mesenterial lymph node. The patient was free of disease after surgery and underwent regular follow-up examinations. Three years later during routine follow-up the abdominal CT scan (Siemens, 16 slices CT) showed an obscure finding in the right liver lobe (Fig. 1), potentially suggestive of a liver metastasis, with no extrahepatic

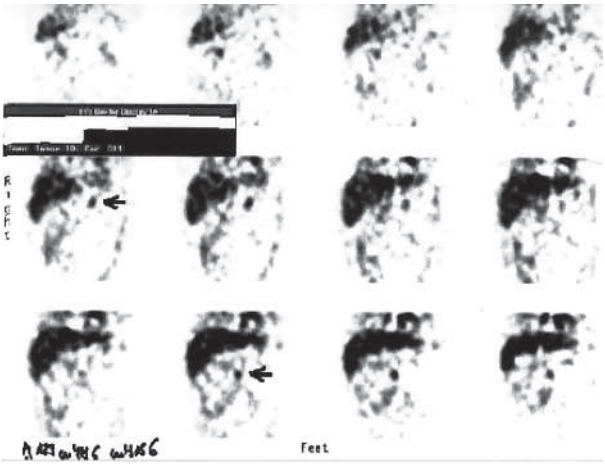

Fig. 3 Twenty-four hour ^{123}I-MIBG SPECT coronal images show two lesions in mid-abdomen (*black arrows*).

suspicious findings. The patient had no abdominal or carcinoid related symptoms and no weight loss. The results of the laboratory work-up including liver function tests were within the normal range. The physical examination provided no relevant finding regarding tumor recurrence or metastases. MRI (Intera 1.5 Tesla system, PHILLIPS Medical System) was performed to further evaluate the patient, but turned out to be normal. Somatostatin receptor scintigraphy showed one clearly pathologic intra-abdominal lesion while an additional site of faint tracer accumulation was regarded as non-specific intestinal uptake (Fig. 2), and no hepatic abnormality was demonstrated. For verification of the marked intra-abdominal finding and detection of possible other metastases, ^{123}I-MIBG scintigraphy was performed after intravenous injection of 250 MBq of the radiotracer. Four and 24 hour planar images and 24 hour SPECT of the thorax and abdomen were acquired. ^{123}I-MIBG SPECT images revealed two focal lesions with prominent tracer uptake in the mid-abdomen (Fig. 3). For further evaluation of the patient and potential anatomical correlation of these scintigraphic findings, a F-18-FDG PET/CT (Siemens Biograph), study was performed. However, the PET/CT imaging acquired 90 min after injection of 380 MBq ^{18}F-FDG was normal. Figure 4 shows the coronal PET images. According to the results of ^{111}In-pentetreotide and ^{123}I-MIBG scintigraphy, RGS was planned using ^{123}I-MIBG, since the superiority of MIBG lesion detection was accompanied by interfering renal background activity in the octreoscan.

Twenty-four hours after intravenous injection of 280 MBq ^{123}I-MIBG, explorative abdominal surgery with RGS was performed. A gamma probe (C-TRAK, AEA Technology, Braunschweig/Germany) equipped with a snap-on standard collimator was used. The energy window was adjusted to 145–175 keV. The surgeon was advised to avoid directing the gamma probe towards the

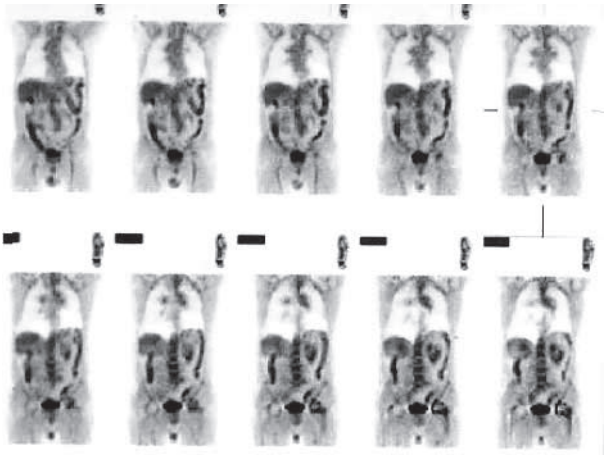

Fig. 4 The ^{18}F-FDG PET coronal images were normal.

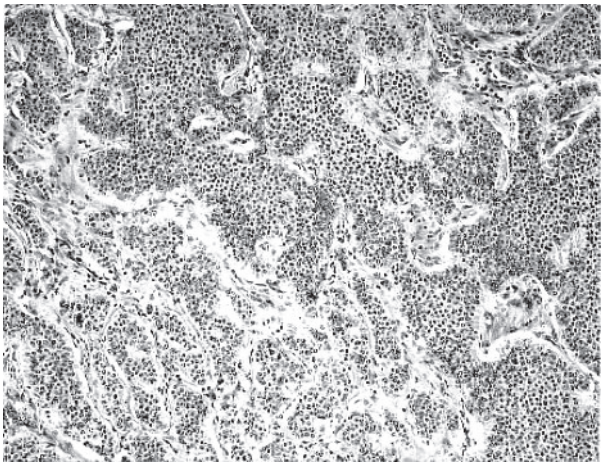

Fig. 5 Histologic image of the para-aortic metastatic lymph node showing the classic carcinoid appearance in hematoxylin-eosin staining.

liver because of the hepatic background activity. During explorative abdominal surgery the gamma probe guided the detection of one para-aortic lymph node metastasis (1.8 cm in greatest diameter) close to the hilus of the left kidney with successful resection. Subsequently, the probe led to another site of increased activity located ventral to the aorta. Here, another two lymph node metastases were found and removed, being 1.8 and 1.0 cm in greatest diameter, respectively. The larger one was clearly suspicious by palpation because of hard consistency and provided a smaller signal for the gamma probe. All three specimens, one para-aortic and two pre-aortic lymph nodes, turned out to be well-differentiated metastases of a carcinoid tumor by histopathology (Fig. 5).

DISCUSSION

Carcinoid tumors of the gastrointestinal tract differ in their clinical and histopathologic features depending on the insite of origin. Jejunoileal carcinoid tumors are usually insular and largely argentaffin, with a high rate of chromogranin and serotonin positivity.[10] These features differentiate jejunoileal carcinoids from other gastrointestinal carcinoids. They have a relatively high rate of transmural invasion and aggressive clinical behavior, and a poor long term prognosis when metastasized. Five year survival of the jejunoileal carcinoids is 47–65%.[10–13] Carcinoid tumors have somatostatin receptors which allow performing somatostatin receptor scintigraphy.

^{111}In-pentetreotide is used for the evaluation and therapy planning of somatostatin receptor positive neuroendocrine tumors (NET) and their metastases due to its affinity to somatostatin receptors. Since ^{123}I-MIBG is an analogue of noradrenaline, it accumulates in NET via the reuptake mechanism and consecutively by vesicular monoamine transporters. Except for neuroblastoma and pheochromocytoma, ^{111}In-pentetreotide is the tracer of choice for evaluation of NET. In carcinoid tumors, ^{111}In-pentetreotide was found to be more sensitive than ^{123}I-MIBG in detecting the metastases demonstrated by CT and/or MRI.[7,14–16] However, in comparative studies using both agents a complementary role or a comparable specificity of ^{123}I-MIBG was reported for the detection of metastatic lesions having faint uptake or not detected with ^{111}In-pentetreotide.[7,14] Additionally, ^{123}I-MIBG uptake of tumor lesions is a prerequisite when planning ^{131}I-MIBG therapy. The most significant imaging time point is at 24 h post injection and generally regarded sufficient for diagnosis. Nevertheless, dual-time point imaging may aid in differentiating specific from non-specific findings such as contamination. Ohrvall et al.[17] designed a gamma probe detector for the energy level of ^{111}In, and suggested that endocrine tumors as small as 2–3 mm in greatest diameter could be detected with this gamma probe. However, the smallest lesion hereby identified intra-operatively was reported to have a size of 5 mm.[18] Ohrvall et al. added that the high background activity from liver, spleen and kidneys is a major drawback for its use. Accumulation of ^{111}In-pentetreotide in spleen, liver, kidney, urinary bladder and colon, as well as in pathologic tissue such as sarcoidosis, tuberculosis or other granuloma forms, ventral hernia, and parapelvic renal cyst, could limit the use of this agent for RGS to detect metastatic lesions in the area of the above mentioned organs.[8,19] Therefore, the use of ^{123}I-MIBG seems more appropriate for the intra-operative gamma probe detection of neuroendocrine tumors and their metastases located in proximity to the kidneys due to the absent physiologic renal MIBG accumulation and only faint corresponding intestinal activity.

Atypical carcinoids may show increased mitotic activity and cellular pleomorphism, as well as a lack of somatostatin receptor overexpression.[20] As FDG is expected to accumulate in the undifferentiated rather than the well-differentiated neuroendocrine tumors,[21] it could provide positive imaging in such an atypical carcinoid tumor.

Therefore, evaluating a carcinoid patient using another imaging modality with the capability of detecting aggressive tumors, such as ^{18}F-FDG PET, seems reasonable in the case of a negative ^{111}In-pentetreotide scan. However, conflicting results about the role of ^{18}F-FDG PET for evaluating neuroendocrine tumors were reported.[21–24] While some authors suggested that ^{18}F-FDG PET should be used in the case of a negative ^{111}In-pentetreotide study,[21,22] others stated that ^{18}F-FDG PET in combination with ^{111}In-pentetreotide and CT plays an important role for the diagnosis, management and follow-up of neuroendocrine tumors.[23,24] Since the resected lymph node metastases in our patient were of the well-differentiated type, it comes not unexpected that ^{18}F-FDG PET/CT imaging was normal. Also, our findings support the studies stating that ^{111}In-pentetreotide scintigraphy is superior to ^{18}F-FDG PET imaging in evaluating neuroendocrine tumors whereas ^{18}F-FDG PET is useful in carcinoid tumors with high proliferative activity.[21]

In our patient, MIBG scintigraphy clearly revealed two sites of lymph node metastases (pre- and para-aortic), while octreoscan only demonstrated one site (pre-aortic). Apparently the other site, in close proximity to the hilus of the left kidney, was overshadowed by adjacent renal activity in the octreoscan. This highlights the disadvantage of the otherwise superior somatostatin receptor imaging compared to MIBG in terms of interference by organs with high physiological tracer uptake, such as the spleen, kidneys and to a much lesser extent intestine. High background activity of these sites may obscure tumor lesions in their proximity. As for the liver, both tracers provide high background activity whereas in case of sites close to the kidneys or spleen, MIBG has a clear advantage over ^{111}In-pentetreotide, if taken up by the tumor.

In our case where intra-operative localization of mid-abdominal lesions was needed, it was advantageous to use ^{123}I-MIBG instead of ^{111}In-pentetreotide because of the issue of renal background activity in light of prior successful MIBG imaging. Since two of the three metastatic lymph nodes were located at one site (pre-aortic), it remains unclear, whether both lesions contributed to scintigraphic visualization of the site or whether only one of them was depicted in the pentetreotide and MIBG scans while the other lesion was negative. However, all three metastatic lesions proved to be of the well-differentiated histologic type and lacked any diagnostic FDG uptake. In conclusion, the use of RGS permits successful removal of carcinoid metastatic lesions despite negative conventional imaging results and therefore unavailable preoperative anatomical localization. Secondly, ^{123}I-MIBG may provide advantages over ^{111}In-pentetreotide in the pre- and intra-operative localization of carcinoid tumors according to the region of interest which is due to less interfering background activity in organs such as the kidneys or spleen.

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