Carcinoid Syndrome Caused by a Small Intestinal Neuroendocrine Tumor

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Contents

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Opening

The neuroendocrine system is a complex system comprised of neuroendocrine organs (e.g., the adrenal medulla, pituitary, and parathyroids) and widely dispersed neuroendocrine cells that are found in various organs, most notably in the mucosa of the gastrointestinal and respiratory tracts. Neuroendocrine tumors (NETs) can arise both in neuroendocrine organs (e.g., pheochromocytoma) and from dispersed neuroendocrine cells in other organs. The term neuroendocrine tumor that is widely used in clinical practice is mostly related to tumors arising from the dispersed neuroendocrine cells, and the well-differentiated forms of these neuroendocrine tumors were formerly termed carcinoids. The term neuroendocrine neoplasm (NEN) comprises both neuroendocrine tumors and neuroendocrine carcinoma (NEC). Carcinoid syndrome is a paraneoplastic endocrine syndrome mostly observed in patients suffering from neuroendocrine tumors of small intestinal (midgut) origin.

Definition of the Disease

Carcinoid syndrome is a paraneoplastic endocrine syndrome typically observed in patients with neuroendocrine tumors of gastrointestinal or less frequently of bronchial origin. Several humoral factors (serotonin, histamine, kallikreins, and prostaglandins) might contribute to its pathogenesis, but the biogenic amine serotonin is the most important. Serotonin is synthesized from the amino acid tryptophan. Neuroendocrine tumors of the gastrointestinal tract are relatively rare with an incidence of about 3.5/100.000/year in studies conducted in the United States. Gastrointestinal neuroendocrine tumors can arise at many sites. Characteristic locations include the small intestine, appendix, stomach, pancreas, colon, and rectum. The incidence of lung neuroendocrine tumors varies between 0.2 and 2/100.000/year. The incidence of NET is increasing. The classification of neuroendocrine tumors has been modified extensively in the past decades. The latest World Health Organization (WHO)-based classification of gastrointestinal NET is presented in ◘ Table 44.1. Well-differentiated neuroendocrine tumors (with grades 1–2) were formerly termed carcinoid tumors as their histological morphology resembles carcinomas, but their biological behavior is much more benign. It must be stressed that even tumors with the lowest proliferation rates can metastasize. About two-thirds of the neuroendocrine tumors are not associated with clear hormonal overproduction and are thus hormonally inactive, whereas one-third are hormone-producing. Carcinoid syndrome is most often observed in tumors arising from the midgut, mostly in the small intestine, and it is typically seen in patients with multiple liver metastases. Carcinoid syndrome is the most frequent paraneoplastic endocrine syndrome in NET patients being observed in almost 20% of cases.

Pancreatic neuroendocrine tumors include hormone-producing tumors such as insulinoma (► Chap. 46), gastrinoma (► Chap. 48), and very rare tumors such as glucagonoma (incidence: 1:20 million/year), VIP-oma (incidence: 1:10 million/year), and somatostatinoma (incidence: 1:40 million/year). Glucagonoma is associated with an impaired glucose homeostasis or diabetes mellitus, and non-endocrine paraneoplastic syndromes such as migrating thrombophlebitis and a severe necrotizing skin disease, necrolytic migrating erythema (◘ Fig. 44.1). VIP-oma secretes VIP (vasoactive intestinal peptide) and is associated with severe diarrhea and hypokalemia (its alternative names include Verner–Morrison syndrome, WDHA syndrome—watery diarrhea hypokalemia achlorhydria—and pancreatic cholera). Somatostatinoma often does not have typical clinical features, but the triad of diabetes mellitus/impaired glucose homeostasis, recurrent cholelithiasis, and diarrhea or steatorrhea (fatty stool) can occur.

Case Presentation

A 60-year-old female patient was referred to our center because of flushing, abdominal pains, and diarrhea that could not be explained by routine gastroenterological examinations. Her history included appendectomy and tonsillectomy. Her current complaints started 3 years earlier. Abdominal imaging showed multiple liver lesions, the largest having a diameter of 5 cm.

What is the typical flush like in carcinoid syndrome?

The flush usually involves the upper body, and it is most commonly seen on the face. About 80–85% of patients with carcinoid syndrome have flushing. The typical flush associated with carcinoid syndrome is not accompanied by sweating (Fig. 44.2a). Emotional stress and alcohol can provoke flushes. If the carcinoid syndrome is active for a long time (usually several years), a chronic flush can develop (Fig. 44.2b). Other conditions associated with flushing are presented in Table 44.2.

What kind of other symptoms and complications might occur in carcinoid syndrome?

Secretory diarrhea is seen in about 80% of patients, and this can be very disturbing. Bronchospasm leading to dyspnea is more infrequent, observed in 10–20%.

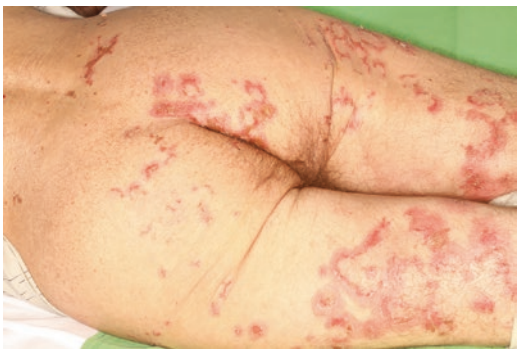

Fig. 44.1 Necrolytic migratory erythema. Necrotic, eroded, crusted and scaling, annular, red plaques on the skin of a 75-year-old male with a glucagon-producing tumor. He was first misdiagnosed as contagious impetigo in diabetes mellitus. After surgical removal of the tumor, the skin lesions healed spontaneously. (Courtesy of Prof. Miklós Sárdy, Department of Dermatology, Venereology and Dermatooncology, Semmelweis University, Budapest, Hungary)

Table 44.1 Classification of gastrointestinal neuroendocrine tumors based on the recent (2019) World Health Organization classification (WHO Classification of Tumours)

	NET-G1	NET-G2	NET-G3	NEC (small or large cell)	MINEN
Differentiation	Well-differentiated	Well-differentiated	Well-differentiated	Poorly differentiated	Well- or poorly differentiated
Grade	Low	Intermediate	High	High	Variable
Ki-67 index (%)	<3	3–20	>20	>20	Variable
Mitotic index	<2	2–20	>20	>20	Variable

Klimstra DS, Kloppel G, La Rosa S, Rindi G, Digestive system tumours, 5th ed: The WHO Classification of Tumours Editorial Board (Ed), the WHO classification of neuroendocrine neoplasms of the digestive system)
NEC neuroendocrine cancer, *MINEN* mixed neuroendocrine-non neuroendocrine neoplasm, Ki-67 is an immunostaining used to show proliferation activity, *Mitotic index* mitoses/2 mm^2, NET-G1 can be corresponded to the former term typical carcinoid, whereas NET-G2 to atypical or malignant carcinoid

Fig. 44.2 Flush in carcinoid syndrome. **a** An acute flush. **b** Chronic flush with facial venous telangiectasia

Table 44.2 Differential diagnosis of conditions associated with flushing

Physiological conditions	Diseases	Drugs
Perimenopausal syndrome Food containing capsaicin	*Neuroendocrine tumors:* pheochromocytoma, medullary thyroid cancer, VIP-oma *Hematological diseases:* systemic mastocytosis, chronic myelogenous leukemia Tumors, e.g., renal cancer Panic syndrome	Alcohol Alcohol + disulfiram Nicotinic acid Levodopa

The most frequently observed conditions are perimenopausal and panic syndromes. Pheochromocytoma is mostly associated with hypertension that is not a feature of carcinoid syndrome. Medullary thyroid cancer can secrete several different biologically active compounds resulting in flushing

A very rare phenomenon is associated to the intensive serotonin biosynthesis needing the vitamin niacin, and thus niacin deficiency can develop. Niacin deficiency can manifest itself as pellagra (a disease of 4Ds if left untreated: dermatitis, dementia, diarrhea, and death).

What is carcinoid heart disease?

Approximately 50% of patients with carcinoid syndrome suffer from carcinoid heart disease that is related to the development endocardial fibrosis mostly due to serotonin action. As serotonin is extensively metabolized by the lungs, valves of the right side of the heart are mostly involved while the left is usually spared. Tricuspid insufficiency and pulmonary stenosis can be observed. Regular (e.g., every 6 months) echocardiography is needed in patients with carcinoid syndrome.

Very rarely, retroperitoneal fibrosis can develop in severe cases of carcinoid syndrome.

What kind of other neuroendocrine neoplasms can be associated with severe diarrhea?

Besides carcinoid syndrome, severe diarrhea can also occur in pancreatic NET such as in gastrinoma (▶ Chap. 48), VIP-oma, or glucagonoma. Diarrhea might also be severe in medullary thyroid cancer, a neuroendocrine neoplasm originating from the calcitonin-producing neuroendocrine C-cells of the thyroid (▶ Chap. 19).

Which hormonal measurements should be used to confirm the diagnosis of carcinoid syndrome?

The serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) can be measured from the urine, and its significant elevation has high sensitivity and specificity. In patients with carcinoid syndrome, 5-HIAA is usually considerably elevated exceeding two or three times the upper normal reference value. Urine should be collected for 24 hours in a dark bottle in an acidic environment (similarly to urinary catecholamines, see the chapter on pheochromocytoma [▶ Chap. 37]). Several false positive and negative conditions can occur with 5-HIAA. False positive results can be seen with malabsorption and several foods (e.g., pineapple, banana, kiwi, eggplant, tomato, and nuts) containing serotonin or tryptophan. Drugs can also lead to false positive (e.g., acetaminophen, coumaric acid, and phenobarbital) or negative results (e.g., levodopa, imipramine, aspirin, and isoniazid).

The 5-HIAA measurement in this case gave 100.8 mg/24 h (normal <8.2), so it was significantly elevated.

Recently, serotonin levels can also be measured in the blood.

The other major biomarker of value in carcinoid syndrome is chromogranin A (CgA), which is a general marker of neuroendocrine tumors. In contrast with 5-HIAA, CgA is also associated with tumor burden and can be used for the follow-up of neuroendocrine tumor patients, even in patients without hormonal activity. CgA was 369.2 ng/mL (normal range: 19.4–98.1).

Which conditions could lead to false positive CgA?

CgA can be elevated in severe hypertension, pregnancy, renal insufficiency, chronic atrophic gastritis, inflammatory bowel disease, non-neuroendocrine tumors, and several other pathologies. In chronic atrophic gastritis, high gastrin stimulates CgA release. Pharmacological inhibition of gastric acid production by histamine H2 receptor-blockers and to a larger extent by proton pump inhibitors can result in sometimes significant CgA elevation, and therefore, these drugs should be omitted before CgA measurement (3 days for H2-blockers, 10–14 days for proton pump inhibitors in general). Glucocorticoids can also lead to CgA elevation.

How should we proceed?

A histological diagnosis is needed, and therefore, an ultrasound-guided liver biopsy from a metastatic lesion was performed. The liver biopsy showed a NET-G1 with a Ki-67 <1%.

Is the imaging diagnosis of liver metastases of neuroendocrine neoplasm easy?

Unfortunately, NET-metastases are often mistakenly diagnosed as hemangiomas by ultrasound, and even their computed tomography (CT) or magnetic resonance imaging (MRI) diagnosis needs expertise.

What can we infer from the histological diagnosis?

As shown in Table 44.1, this is a well-differentiated neuroendocrine tumor with a low proliferation rate. The prognosis of these tumors is good, and patients with proper treatment can survive even decades after the diagnosis. Many different treatment regimens can be tried.

Whereas the prognosis of well-differentiated NET-G1 and NET-G2 is good, neuroendocrine cancer with proliferation rates over 20% (either by Ki-67 immunostaining or by the mitotic rate) has poor prognosis. Most recently, a NET-G3 category has been established (first for pancreatic NET) that has rather high proliferation rate but shows well-differentiated morphology.

Should we look for the primary tumor?

In such patients having multiple liver metastases and carcinoid syndrome, the primary tumor is usually small and located in the small intestine. We could argue that a small tumor in comparison to the several liver metastases is of little importance, but even such small tumors can lead to intestinal obstruction. Moreover, reduction of the tumor burden (tumor debulking) in well-differentiated NET is an important treatment option, and operative procedures are thus often used in NET-G1 and NET-G2.

Which imaging techniques should be performed to find the primary tumor?

Nowadays, functional imaging based on the expression of somatostatin receptors (SSR) by NET is considered to be the most sensitive imaging modality. Neuroendocrine neoplasms express receptors for somatostatin, and marked somatostatin analogues can be used by nuclear medicine for imaging. There are five somatostatin receptors (SSR) in humans, and the somatostatin analogue used for imaging (octreotide) binds mostly receptor types

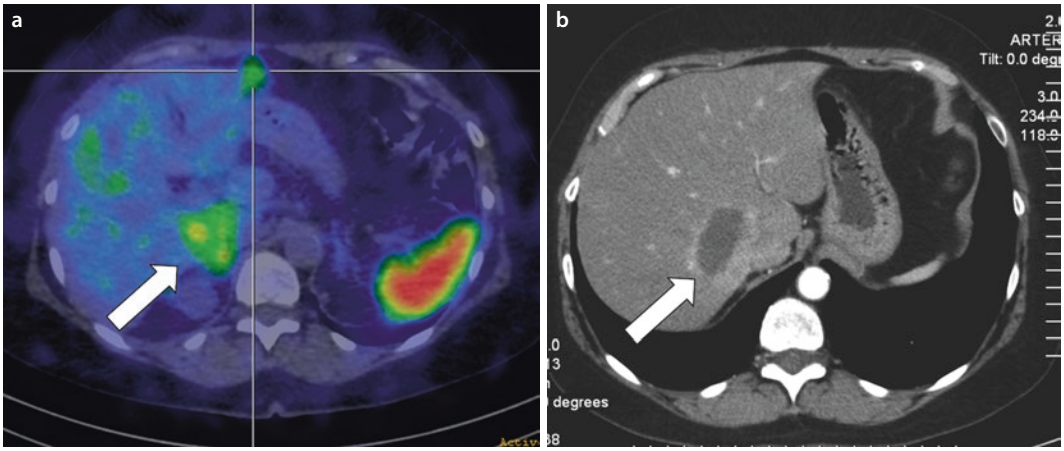

Fig. 44.3 **a** Octreotide scintigraphy SPECT-CT showing multiple metastases in the liver (green) with a large metastasis in the right lobe (arrow). **b** Necrosis in the large metastasis following TACE (transarterial chemoembolization)

2 and 5. (Native somatostatin has a very short half-life, and therefore, somatostatin analogues have been developed, e.g., octreotide and lanreotide.) Radiolabeled (^{111}In) octreotide is used in classic somatostatin receptor scintigraphy that can be combined with SPECT-CT (single photon emission computed tomography), but recently ^{68}Ga-DOTATATE PET-CT (positron emission computed tomography) with sensitivity and specificity over 90% is considered to be the most appropriate imaging.

- Ultrasound, CT, MRI, and endoscopies also belong to the standard imaging techniques of NET.

- In this case, octreotide scintigraphy was performed, which showed the SSR-positive lesions of the liver but failed to show the primary tumor (Fig. 44.3a). The primary tumor could be localized by using CT-enterography that showed the tumor in the terminal ileum.

- Laparotomy was performed and an ileal tumor with a diameter of 1 cm was removed. Histology was the same as from the liver metastasis (NET-G1, Ki-67 <1%).

? What should be the treatment strategy?

- The treatment strategy is primarily based on the pathological characteristics of the tumor. Whereas NET-G1 and NET-G2 have good prognosis and a wide array of treatment modalities are available, NEC (neuroendocrine cancer) is treated by systemic chemotherapy. General treatment options for NEN are summarized in Table 44.3.

- NET-G1 small intestinal tumors are usually slowly growing tumors, and there are reports that in hormonally inactive tumors even observation could be sufficient. However, recent findings (PROMID [octreotide] and CLARINET [lanreotide] studies) show that somatostatin analogues (SSAs) are not only useful for alleviating hormonal symptoms but also for inhibiting tumor growth. Therefore, SSAs are considered as the primary treatment option for patients with well-differentiated G1 and G2 tumors. (In G3 tumors and cancer, SSA is indicated only for alleviating hormonal symptoms.) Along with interferon-α (IFN-α), SSA therapy can be regarded as a biological treatment option for NET.

? How can somatostatin analogues be used in patients with carcinoid syndrome?

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Table 44.3 Treatment strategies for metastatic small intestinal NET based on the pathological classification

NET-G1	NET-G2	NET-G3	NEC
Tumor debulking and interventional radiological techniques (e.g., TACE and RFA)			–
SSA		PRRT[a]	Systemic chemotherapy: platinum-based (cisplatin/carboplatin) + etoposide FOLFOX FOLFIRI
PRRT		Systemic chemotherapy (FOLFOX, FOLFIRI)	
Everolimus			
IFN-α			

RFA radiofrequency ablation, *TACE* transarterial chemoembolization, *FOLFOX* Oxaliplatin-Fluorouracil-Leucovorin, *FOLFIRI* Irinotecan Fluorouracil Leucovorin
[a]If the Ki-67 index of the tumor is <50%

SSAs can alleviate symptoms associated with carcinoid syndrome in about 80% of patients. The two mainly used analogues, octreotide and lanreotide, are similarly effective, and both can be used in monthly depot injections that are very comfortable for the patient. Octreotide is also available in short-acting injections that can be used by subcutaneous or intravenous administration. In metastatic NET patients, monthly 30 mg octreotide or 120 mg lanreotide are the standard doses, but there are reports on the effectivity of even larger doses.

What is carcinoid crisis?

Carcinoid crisis is a rare condition in carcinoid syndrome patients that is most often provoked by the manipulation or treatment of the tumor (e.g., operation, interventional radiological treatment, biopsy, and peptide receptor radionuclide therapy [PRRT]). Due to excessive mediator release, significant hypotension and cardiovascular instability can occur. It should be treated with high dose intravenous octreotide (500–1000 μg) in infusion. In patients suffering from carcinoid syndrome, subcutaneous octreotide should be given before interventions (e.g., 3 × 200 μg s.c.) in addition to the depot SSA preparations to prevent carcinoid crisis.

What are the main side effects of SSAs?

As SSAs inhibit the secretion of cholecystokinin and thus gallbladder contraction, gallstones can develop in these patients. Our patient also developed gallstones and had symptoms associated with them after 5 years of SSA use and cholecystectomy had to be performed. Further side effects include diarrhea and impairment of glucose homeostasis. The most significant impairment of glucose homeostasis is seen with the most novel somatostatin analogue pasireotide that binds four somatostatin receptors (SSR1, 2, 3, and 5) and is mainly used in the treatment of acromegaly and Cushing's disease (see ▶ Chaps. 2 and 3).

What about interferon-α (IFN-α)?

IFN-α has similar efficacy as SSAs in alleviating symptoms and reducing tumor proliferation in carcinoid syndrome patients, but is much less tolerated. Major side effects of interferon therapy include flu-like symptoms (headache, muscle pains, and fever), hematologic alterations (leukopenia and anemia), and elevated transaminases. The usual dose of IFN-α in NET patients is 3 × 3 million units/week. Due to their different ways of actions, SSA and IFN-α can be combined.

We tried IFN-α in our patient and the combination with SSA was more effective than SSA alone in alleviating symptoms; moreover, both 5-HIAA excretion and CgA were reduced. However, the patient could not tolerate IFN-α, and it had to be stopped 3 months after its initiation.

If the patient still complains about diarrhea, are there further treatment options?

First, it should be examined whether it is really carcinoid syndrome that is responsible for the diarrhea. Other causes of diarrhea (e.g., dysbacteriosis, bacterial contamination, malabsorption, and pancreatic insufficiency) should be ruled out. A novel agent inhibiting tryptophan hydroxylase, telotristat, can be tried, which reduces bowel movements and can contribute to symptomatic relief in carcinoid syndrome.

What could be the next treatment step?

SSA treatment was initiated with monthly 120 mg lanreotide, but she continued to complain about diarrhea and flushing. As the tumor was progressive, we decided for a somatostatin peptide receptor radionuclide therapy.

What is PRRT (peptide receptor radionuclide therapy)?

Neuroendocrine neoplasms can be targeted by exploiting their high expression of somatostatin receptors (SSR) using radioisotopes. Radioisotope-bound SSA (mostly octreotide) is internalized by tumor cells, and the radiation kills the neighboring cells as well. Nowadays, mostly ^{177}Lutetium (^{177}Lu) is used in therapy (^{177}Lu-DOTATATE) that emits both β- and γ-radiation and is much better tolerated than the previously used ^{90}Yttrium (^{90}Y). (These radiolabeled SSA can be termed theranostics, as the same molecule can be used for diagnostic and treatment purposes.) PRRT can be used in a wide variety of NET, but the first randomized trial (NETTER-1) was performed in midgut NET.

What are the conditions needed for performing PRRT?

Patients should be in a relatively good overall condition (Karnofsky performance scale over 50), should have good renal function and blood cell counts, and should have an expected survival of at least over 3–6 months. The tumor must display higher somatostatin receptor (SSTR) expression on nuclear imaging than the liver.

What major side effects could occur related to PRRT?

Major side effects include renal, hematologic, and liver toxicity that are altogether rare. Renal toxicity was more common with ^{90}Y than with the currently used ^{177}Lu. Hematologic toxicity is a major concern. Mild forms include transient leukopenia and thrombocytopenia, but severe hematologic complications such as myelodysplastic syndrome and acute myelogenous leukemia can develop in about 1–2% of treated cases.

What kind of other treatments could be envisaged?

As shown in Table 44.3, there are still several options to be tried. Ablative treatments including interventional radiological techniques like transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) are rather effective as in our patient's case shown in Fig. 44.3b displaying necrosis after TACE. Everolimus as an mammalian target of rapamycin (mTOR) inhibitor can also be tried in small intestinal NET, but it is often poorly tolerated due to many side effects including stomatitis, rash, fatigue, infections, and so on. (Everolimus and sunitinib [a tyrosine kinase inhibitor] were first shown to be effective in pancreatic NET.) These treatment options are also effective against refractory carcinoid syndrome.

Is there a role for liver transplantation for treating metastatic NET?

Very rarely, in selected cases, if the primary tumor was removed and there are no metastases outside the liver, liver transplantation can be envisaged in well-differentiated NET.

What are the treatment options for neuroendocrine carcinomas?

Neuroendocrine carcinomas (NEC) have generally poor prognosis and require systemic chemotherapy. In NEC of small intestinal origin, platinum-based chemotherapy + etoposide is the standard regimen, but other regimens (Table 44.3) can also be tried. Novel findings show that PRRT can be tried even in NEC, mostly in patients with tumors having Ki-67 index <55%. The systemic treatment of NEC of pancreatic origin includes streptozotocin + 5-fluorouracil, but the oral capecitabine/temozolomide combination (CAPTEM) is also increasingly used.

Epilogue

Our patient is in a relatively good overall condition after more than 10 years of treatment. The management of neuroendocrine neoplasms necessitates a multidisciplinary approach involving pathology, endocrinology, gastroenterology, surgery, oncology, nuclear medicine, and radiology. Patients should be treated by centers having expertise in the management of this disease.

Tips

- The reader is advised to read the next chapter presenting a bronchial neuroendocrine tumor associated with an ectopic ACTH syndrome (▶ Chap. 45) and the chapters dealing with pancreatic neuroendocrine tumors (insulinoma [▶ Chap. 46] and gastrinoma [▶ Chap. 48]).

Take Home Messages

- Carcinoid syndrome is a rare paraneoplastic syndrome associated with hormonally active neuroendocrine neoplasms (NETs), most frequently observed in patients with small intestinal NET giving multiple liver metastases.
- NETs have different histological subtypes that are very important to know for planning treatment.
- Useful biomarkers for diagnosis include 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, and chromogranin A as a general NET-marker.
- High expression of somatostatin receptors by NET is exploited in both the diagnosis and the treatment.
- Somatostatin analogues are efficient in reducing hormonal symptoms, and these have also antitumoral activity.
- Radiolabeled somatostatin analogues can be used for diagnosis by nuclear medicine and also for treatment (peptide receptor radionuclide treatment) (theranostics).
- In well-differentiated small intestinal neuroendocrine tumors (grades 1 and 2), other treatment modalities include surgery (debulking), ablative interventional radiological treatments (e.g., transarterial chemoembolization and radiofrequency ablation), and targeted treatment (everolimus).
- Poorly differentiated small intestinal neuroendocrine cancer (grade 3) should be treated with systemic chemotherapy.

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