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【 CASE REPORT 】

Cardiac Metastasis Caused Fatal Ventricular Arrhythmia in a Patient with a Rectal Neuroendocrine Tumor

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Abstract:

A 60-year-old man had received octreotide for a metastatic neuroendocrine tumor (NET) in the rectum. Computed tomography and ultrasonography revealed a cardiac tumor, diffuse thickness of the ventricular wall and pericardial effusion, which was diagnosed as cardiac metastasis. The metastatic lesions continued to grow despite the alteration of chemotherapy, and the patient complained of repeated syncope and was admitted to our hospital at 11 months after the diagnosis of cardiac metastasis. An electrocardiogram during syncope showed sustained ventricular tachycardia, which was considered to be caused by the cardiac metastasis. We herein report a case of NET with cardiac metastasis which caused lethal arrhythmia along with a review of the pertinent literature.

Key words: cardiac metastasis, neuroendocrine tumor, ventricular arrhythmia

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Introduction

Neuroendocrine tumors (NETs) are relatively rare, but their incidence is reportedly 3.51 and 6.98 per 100,000 persons-year in nationwide cohorts of Japan and the United States, respectively, with 2- to 3-fold increases noted in the last several decades (1, 2). NETs originate mainly in the gastrointestinal tract, pancreas and pulmonary tract. Metastases of NET generally occur in the liver, lung and bone, with other sites suggested to be rare (3). However, despite their rare frequency, metastases to sites such as the heart and brain still occur and can cause serious complications in patients with metastatic NET. While quite a few cases of cardiac metastases in NET with fatal arrhythmia have been reported (4, 5), the clinical course and optimal therapeutic strategy remain unclear.

We herein report a rare case of cardiac metastases in a rectal NET patient with fatal arrhythmia.

Case Report

A 60-year-old man who complained of bloody stool was diagnosed to have a rectal NET (WHO classification grade 2) with multiple metastases to the lymph node, liver and bone three years previously (Fig. 1). He had no relevant medical or familial history. In addition, he had no typical symptoms of carcinoid syndrome, hyperparathyroidism, hyperthyroidism or hyperepinephrinemia. The laboratory data at the time of the initial diagnosis are shown in Table 1. The electrolyte and hormone values were within the normal ranges. The serum carcinoembryonic antigen (CEA) level had increased at the time of the initial diagnosis; however, this abnormality was not considered to be due to the tumor because the change was not proportional to the degree of tumor progression, and there were no other tumorous lesions on CT or endoscopic examinations. The patient's smoking history was thought to have caused the high level of CEA. Furthermore, computed tomography showed no abnormal

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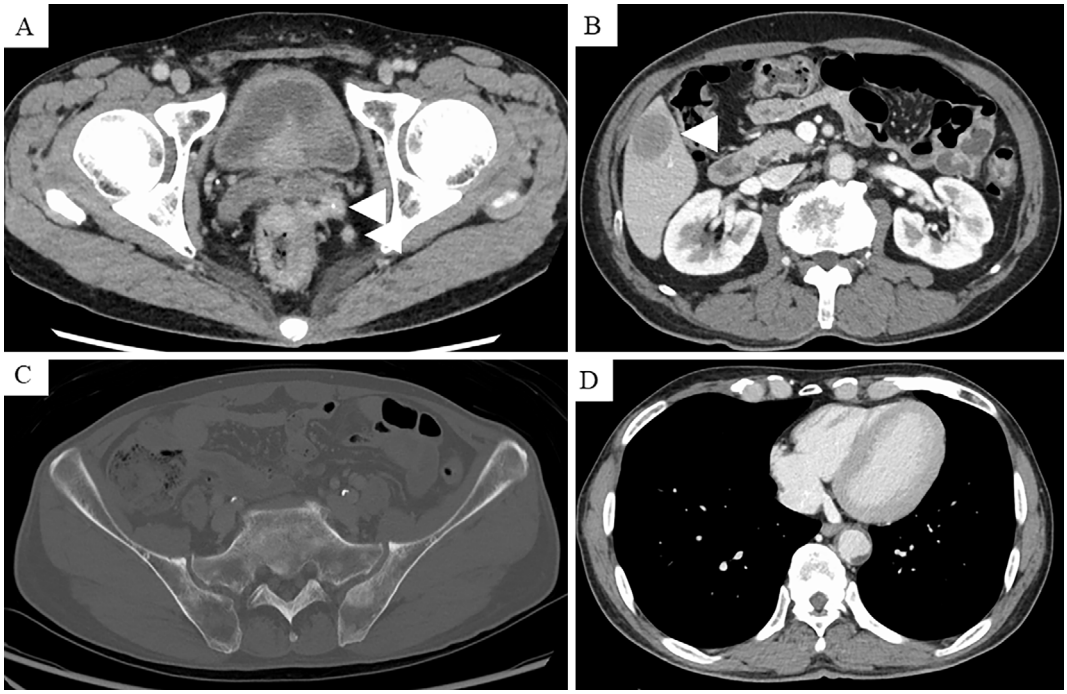

Figure 1. **CT findings at the initial diagnosis of NET. Computed tomography at the initial diagnosis showed swelling of multiple lymph nodes (A: arrowheads) without the detection of the primary lesion and liver metastasis (B: arrowhead), consolidation of the vertebra and iliac bone (C), and findings of a tumor and an abnormal enhancement in the left ventricle and septum (D).**

Table 1. **Laboratory Data at the Initial Diagnosis.**

	Measured value	Normal range		Measured value	Normal range
WBC	6,070 /μL	3,500-8,500	FT3	2.44 pg/mL	2.30-4.00
Hb	12.3 g/dL	13.5-17.0	FT4	1.28 ng/dL	0.90-1.70
Plt	20.2 10^4/μL	15.0-35.0	TSH	2.12 μIU/mL	0.50-5.00
Alb	3.8 g/dL	3.9-4.9	i-PTH	60.9 pg/mL	15.0-65.0
Na	141 mmol/L	135-150	IRI	<0.20 μU/mL	0.0-18.7
K	4.3 mmol/L	3.5-5.0	Glucagon	81 pg/mL	70-174
Cl	103 mmol/L	96-110	Gastrin	95 pg/mL	≤ 200
Ca	9.0 mg/dL	8.7-11.0	CEA	17.4 ng/mL	≤ 5.0
CRP	0.37 mg/dL	≤ 0.30	NSE	14.9 ng/mL	≤ 16.3

WBC: white blood cell count, Hb: hemoglobin, Plt: Platelet, Alb: serum albumin, Na: sodium, K: potassium, Cl: chlorine, Ca: calcium, CRP: C-reactive protein, FT3: free T3, FT4: free T4, TSH: thyroid stimulating hormone, i-PTH: intact parathyroid hormone, IRI: immunoreactive insulin, CEA: carcinoembryonic antigen, NSE: neuron-specific enolase

findings of the endocrine organs, which excluded functional NET and multiple endocrine neoplasia. The endoscopic, histologic and immunohistochemical findings at the initial diagnosis are shown in Fig. 2. He had been treated with octreotide for 17 months after the first diagnosis; however, the liver metastases increased, and lung metastases were newly detected with computed tomography (CT). Therefore, chemotherapy was changed to everolimus.

He complained of dyspnea and general fatigue six months after starting chemotherapy with everolimus. CT showed bilateral pleural effusion, pericardial effusion, wall thickening in the ventricular septum and areas of poor enhancement in the left ventricle (Fig. 3A, B) in addition to the progression of liver and lung metastases and the appearance of new metastases in the right kidney. Transthoracic echocardiography (TTE) revealed pericardial effusion, a tumor measuring 15 mm in diameter in the ventricular septum (Fig. 3C) and heterogenous thickening of the left ventricular wall (Fig. 3D) at 24 months after the initial diagnosis. In addition, TTE revealed no right-sided valvular disease (tricuspid and pulmonary arterial valve), which excluded carcinoid heart syndrome. The pericardial effusion fluid obtained by a puncture was bloody, but negative for neuroendocrine cells. While the tumor in the heart was not biopsied, both the tumor and the irregular thickening of the ventricular wall were diagnosed as cardiac metastases derived from the rectal NET based on

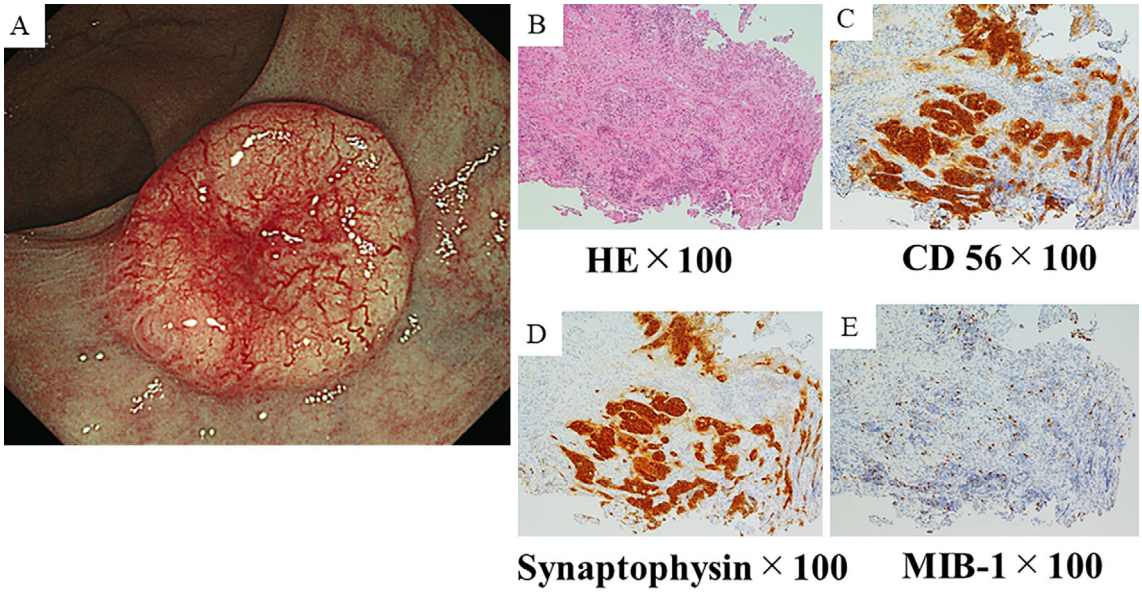

Figure 2. **Endoscopic, histological and immunohistochemical findings at the initial diagnosis of the rectal tumor. Colonoscopy revealed a yellowish submucosal tumor measuring 25 mm in diameter, accompanied by dilated vessels at the surface and depression in the central part (A). Histological findings of the biopsied specimen (Hematoxylin and Eosin staining; B ×100) showed a rope-shaped or ribbon-like arrangement of cells with elliptic nuclei and eosinophilic cytoplasm, and the immunohistochemical findings were positive for CD56 (C ×100) and synaptophysin (D ×100), with about 10% of cells positively reactive for MIB-1 (E ×100), consistent with NET grade 2 according to the WHO classification 2010.**

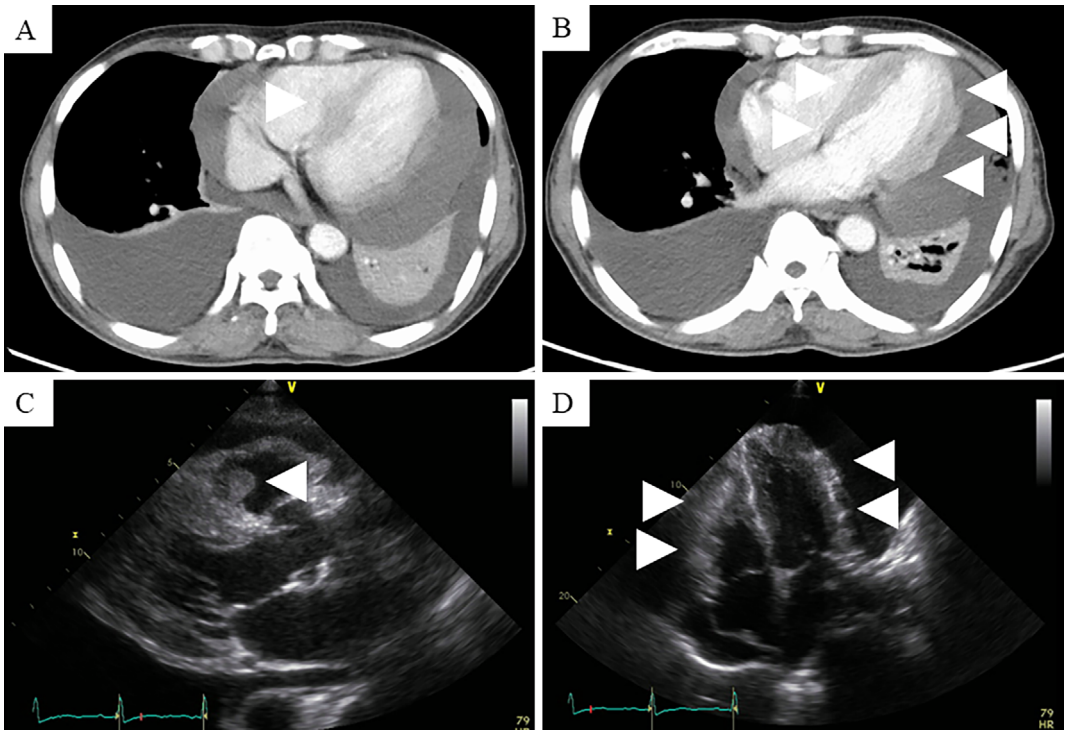

Figure 3. **CT and TTE findings in the heart at the time of the detection of cardiac metastases. Contrast-enhanced CT revealed a tumor with a poor enhancement in the ventricular septum (A; arrowhead) and heterogenous wall thickening of the left ventricle (B; arrowheads) along with pericardial effusion (A, B). TTE showed that the mass originated from the ventricular septum and protruded into the right ventricle lumen on a parasternal long-axis tomogram (C; arrowhead), and diffuse wall thickening of the left and right ventricle was noted on an apical 4-chamber tomogram (D; arrowheads).**

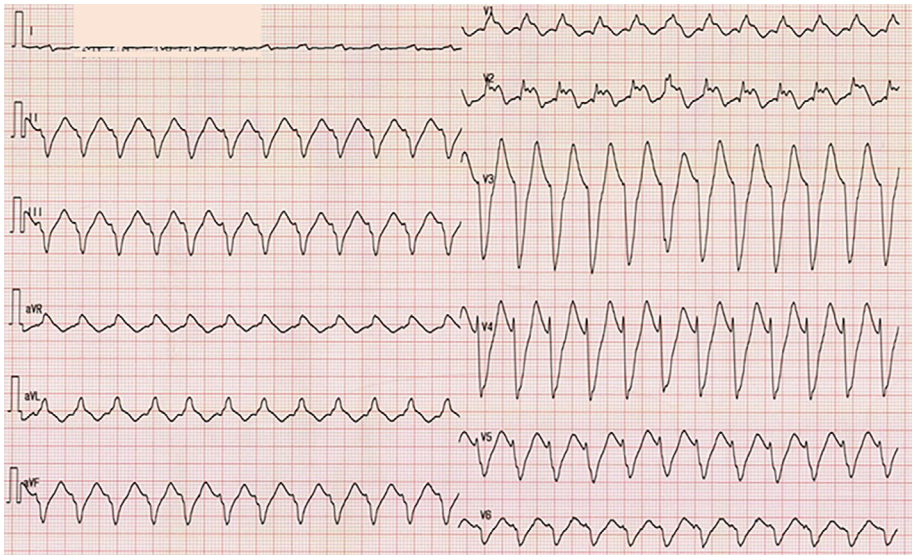

Figure 4. **Electrocardiogram recorded at syncope. An electrocardiogram recorded at syncope showed ventricular tachycardia.**

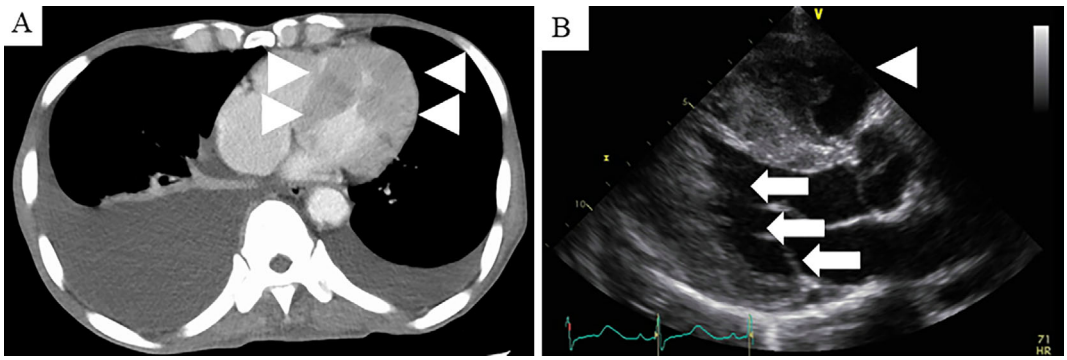

Figure 5. **CT and TTE findings in the heart when complicated with ventricular arrhythmia. The progression of the tumor and wall thickening with the poor enhancement in the ventricular septum and wall are observed on CT (A; arrowheads), and the progression of the protruding mass in the ventricular septum (B; arrowhead) and exacerbation of diffuse thickening of the ventricular wall were detected with TTE (B; arrows).**

the progression of metastases in other organs. The bilateral pleural effusion was thought to represent leakage due to a low serum albumin level rather than pleural metastasis or diastolic dysfunction because of the rapid improvement after the intake of a diuretic drug and albumin supplementation. However, although a cytological examination was negative for pleural metastasis, the coexistence of pleural metastasis could not be ruled out.

The cardiac metastases continued to grow regardless of the chemotherapy being changed to streptozocin and lanreotide. He complained of repeated syncope and was admitted to our hospital at 34 months after the initial diagnosis (which was 11 months after the diagnosis of cardiac metastases). An electrocardiogram during syncope showed ventricular tachycardia (VT) (Fig. 4). In addition, the patient's pulse was not detected on palpation while VT was detected on the monitor and electrocardiogram. VT successfully recovered by defibrillation; however, CT and TTE showed progression of the ventricular tumor and wall thickening, which by now had invaded almost the entire ventricular wall (Fig. 5). Thereafter, pulseless VT occurred repeatedly and the patient died on the following day. An autopsy was not performed based on his family's request. Sustained pulseless VT was considered to be the final cause of death.

Discussion

We herein report a rare case of cardiac metastases in a patient with rectal NET causing fatal ventricular arrhythmia. The incidence of metastatic cardiac tumor in patients with malignant tumor has been reported to range from 2.3% to 18.3%, the main primary sites of which consisted of malignant melanoma and mediastinal tumor (6). According to the European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines for the Management of Brain, Cardiac and Ovarian Metastases from Neuroendocrine Tumors (3), car-

Table 2. Summary of the Reported Cases of Cardiac Metastasis Causing Fatal Arrhythmia in Patients with NETs.

No.	Age (years)	gender	Location	PE	Diagnostic procedure	Primary site	Tumor grade	Carcinoid syndrome	Distant metastasis	Types of arrhythmia	Treatment	Prognosis after the diagnosis (or treatment) of cardiac metastases	Reference
1	78	F	LV wall RV wall Septum	+	TTE CT MRI	Bronchus	-	-	ND	VA	Somatostatin	Dead 1 year after diagnosis	4
2	54	M	RV wall	-	TTE CT Scintigraphy	Ileo-ecum	-	+	Per LN	VA	Resection, Sandostatin therapy after resection	Survive at least 2 years after the resection	5
3	60	M	LV wall RV wall Septum	+	TTE CT	Rectum	G2	-	Liver Lung Bone	VT	Everolimus Storeptozocin lanreotide	Dead at 11 months after the diagnosis	Present case

LV: left ventricle, RV: right ventricle, PE: pericardial effusion, TTE: transthoracic echocardiography, CT: computed tomography, MRI: magnetic resonance imaging, ND: not described, Per: peritoneum, LN: lymph node, VA: ventricular arrhythmia, VT: ventricular tachycardia

diac metastases are extremely rare, with only 36 previously reported cases. Most cases with cardiac metastases in NETs have been reported to be derived from the mid-gut, such as ileo-cecal NETs, while in our case, the primary tumor existed in the hindgut rectum.

Only two NET patients with cardiac metastases causing arrhythmia have been previously reported (Table 2) (4, 5). In these three cases, including our own, the primary sites consisted of the bronchus, ileo-cecum and rectum, and two cases (excluding one with no description) had previously and/or synchronously multiple distant metastases in addition to those in the heart. Cardiac metastases were detected in the ventricular wall and/or septum in the heart in all cases. The lesions were diagnosed with US and CT, and one case was diagnosed with somatostatin scintigraphy plus US and CT. Chemotherapy was performed in two cases, while a solitary cardiac metastasis was surgically removed in one case who exhibited a long-term survival after resection.

While detecting cardiac metastases measuring less than 10 mm in a diameter has been difficult using CT and/or TTE, somatostatin receptor-positron emission CT has demonstrated a high efficacy for detecting small cardiac metastases in NET patients (7-9). Following the development of this CT procedure, the incidence of cardiac metastases has increased from 0.7% to 4.3%. Because cardiac metastases might cause severe complications, such as heart failure, lethal arrhythmia and cardiac tamponade, surveillance of cardiac metastases in NET patients using somatostatin receptor-positron emission CT is recommended.

Recently, multidisciplinary therapeutic approaches, including chemotherapy, such as somatostatin analogue, molecular-targeted drugs and cytotoxic agents, have been rapidly developed for the treatment of patients with metastatic NETs (10), thus contributing to a prolonged survival of such patients (11). However, in our case, somatostatin analogues, molecular-targeted drugs and cytotoxic agents were not sufficiently effective as the cardiac metastasis had already markedly progressed by the time that it was detected. The establishment of appropriate therapeutic strategies for cardiac metastases as well as an aggressive screening program for small cardiac metastasis using somatostatin receptor-positron emission CT are expected to improve the outcomes of NET patients.

NETs have been reported to cause carcinoid heart disease in more than 50% of the patients with carcinoid syndrome, which is present in about 20% of patients with NETs at the time of diagnosis (12, 13). Carcinoid heart disease was suggested to induce atrial fibrillation and ventricular tachycardia due to right-sided heart failure, valvular disease and serotonin-associated diseases (14, 15). According to previous reports, the incidence of cardiac metastases in NETs was suggested to be rarer than that of carcinoid heart disease (16). However, given the differences in the treatment plan, we need to accurately distinguish cardiac metastases from carcinoid-associated heart diseases when NET patients have chest symptoms, cardiac effusion, arrhythmia and heart failure. In our case, normal hormone levels and the absence of any concomitant symptoms indicated a non-functional NET without carcinoid syndrome. TTE revealed signs of right-sided heart failure which was suggested to have resulted from bloody pericardial effusion, while TTE revealed no right-sided valvular disease or dysfunction associated with carcinoid heart syndrome. On the other hand, a tumor and heterogenous wall thickening were detected in the right and left ventricular walls and septa. Furthermore, the patient had no history of heart disease and other factors which were possible to cause ventricular arrhythmia such as abnormal electrolyte. These findings strongly suggested that the patient's ventricular tachycardia had been caused by cardiac metastases from the rectal NET.

In conclusion, we encountered a rare case of cardiac metastases in a patient with a rectal NET causing fatal ventricular arrhythmia. Because of the risk of severe complications, such as fatal arrhythmia and pericardial effusion, appropriate screening and optimal therapeutic approaches for NET patients with cardiac metastases need to be established based on studies in a large number of such patients.

Author's disclosure of potential Conflicts of Interest (COI).
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