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# Synchronous neuroendocrine tumors in both the pancreas and ileum: A case report

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ABSTRACT

*INTRODUCTION:* Although it is well-known that in multiple endocrine neoplasia type 1 (MEN 1) disease, multiple endocrine lesions frequently occur, synchronous or metachronous neuroendocrine tumors (NETs) in non-MEN 1 patients are extremely rare.
*PRESENTATION OF CASE:* An asymptomatic 72-year-old woman with an ileal NET was referred to our hospital. Abdominal computed tomography revealed another circular tumor within the pancreatic head. She was classified as a non-MEN 1 patient. An operative procedure was performed with a preoperative diagnosis of synchronous NET, which was confirmed by pathological examination.
*DISCUSSION:* Both morphologic and immunophenotypic findings were different between in the ileum and pancreas. Therefore, it was reasonable to consider that both tumors were primary tumors. The synchronous occurrence of these tumors is unusual, and it may be considered as a chance occurrence.
*CONCLUSION:* We here report the first case of synchronous pancreatic NET and ileal NET in a non-MEN 1 patient.



## 1. Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) account for approximately 2% of all neoplasms [1,2]. Although it is well-known that in multiple endocrine neoplasia type 1 (MEN 1) disease, multiple endocrine lesions in the pituitary, parathyroid, and embryological foregut organs (lung, stomach, duodenum, upper jejunum, and pancreas) frequently occur [3], synchronous or metachronous NETs in non-MEN 1 patients are extremely rare. To the best of our knowledge, no case of synchronous NETs in non-MEN 1 disease has been previously reported in the English literature. Here we present the first case of synchronous pancreatic NET (PNET) and ileal (midgut) NET in a non-MEN 1 patient.

## 2. Presentation of the case

A 72-year-old woman was found to have an ileal polypoid tumor by colonoscopy, which was performed because of positive results from an occult blood test of the stool. Histology of the biopsy specimens taken from the tumor revealed it was a NET. The patient was referred to our hospital. On admission, she did not have any symptoms. Her medical and family history was unremarkable. The laboratory findings were as follows: white blood cell count = 5600/μl, hemoglobin = 12.2 g/dl, hematocrit = 35.6%, platelets = 235 × $10^3$/μl, aspartate aminotransferase (AST) = 15 IU/l (normal <30), alanine aminotransferase (ALT) = 15 IU (normal <35), and amylase = 64 IU/l (normal <132). HbA1c was 7.1%, suggestive of a mild glucose intolerance. The tumor-markers were within normal limits. Her insulin level was slightly elevated at 18.7 U/ml (1.1–9.0), but gastrin level was within the normal ranges (190 pg/ml; normal <200). Neither pituitary tumor nor parathyroid tumor were detected. Dynamic contrast-enhanced computed tomography (CT) revealed another enhanced round mass within the pancreatic head, in addition to the ileal tumor. On dynamic contrast-enhanced magnetic resonance imaging (MRI), the pancreatic mass showed rapid contrast enhancement at arterial phase on the fat suppression T1-weighted image. Fluorodeoxyglucose positron emission tomography-CT (FDG-PET/CT) showed abnormal fluorodeoxyglucose-uptake in both lesions of the pancreas and ileum alone, without evidence of other metastatic deposits

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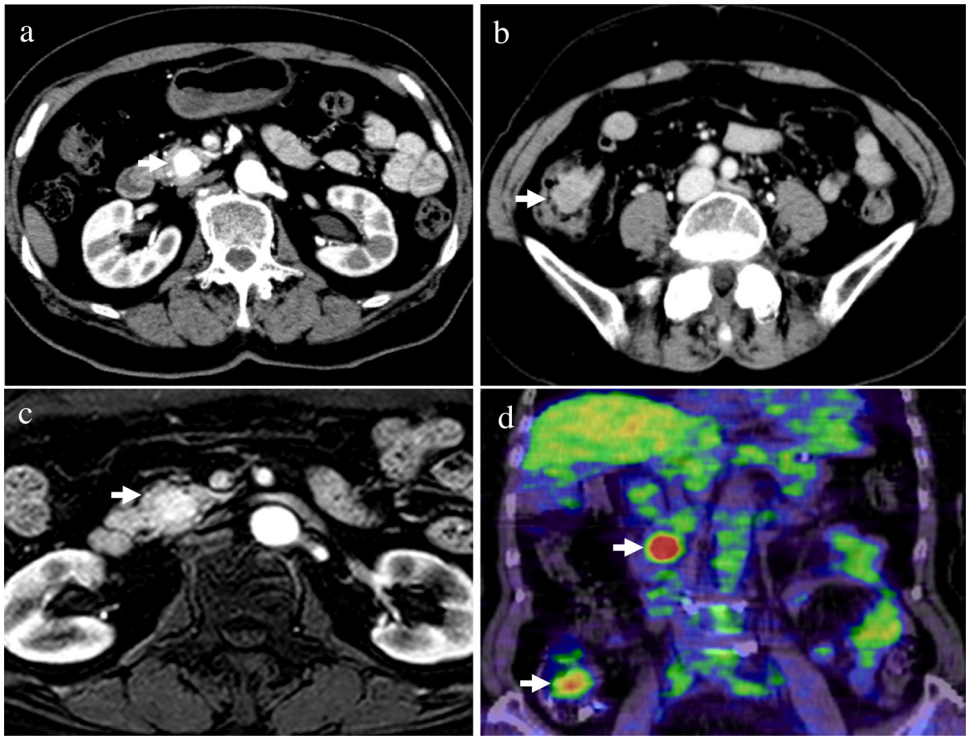


**Fig. 1.** Computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) images. (a) arterial phase of dynamic CT revealed the enhanced tumor measuring 20 × 15 mm in size located in the head of the pancreas. (b) portal phase of dynamic CT also revealed the enhanced tumor measuring 20 × 20 mm in size. (c) arterial phase of dynamic MRI showed the rapid enhanced tumor in the head of the pancreas. (d) FDG-PET/CT revealed abnormal uptake only in the pancreas and the ileocecal lesions.

or endocrine lesions (Fig. 1). A subtotal stomach-preserving pancreaticoduodenectomy and an ileocecal resection were performed simultaneously. The duration of the operation was 9 h and 15 min and the total amount of blood loss was 322 ml.

In the resected specimens, a whitish solid-nodular tumor in the pancreas head, measuring 14 × 13 × 12 mm size, and a yellowish solid-protruding tumor in the terminal ileum, measuring 21 × 7 × 15 mm size were found (Fig. 2). Histologically, both tumors were composed of relatively monotonous growth of tumor cells with round nuclei. The tumor cells in the pancreas proliferated in small-size cell-nests and had thin trabecular architectures. The tumor cells in the ileum proliferated in round cell-nests and tumor cells tended to have a palisade periphery. Both tumors were immunohistochemically positive for neuroendocrine markers (i.e., chromogranin A, synaptophysin, and CD56), and negative for insulin, glucagon, somatostatin, and gastrin. However, serotonin was positive only in the ileal tumor alone, whereas pancreatic polypeptide (PP) positivity was only observed in the pancreas tumor (Fig. 2). The Ki-67 labeling indexes of both tumors were below 2%. The ileal tumor had a metastatic deposit in a regional lymph node. From the morphologic and immunophenotypic differences, these tumors were considered to be both primary NETs G1, according to the WHO 2010 classification [4]. The pancreatic tumor was categorized as a non-functional PNET (so-called PPoma), pT2, pN0, M0, pStage Ib, and the ileal tumor categorized as an enterochromaffin (EC) cell, serotonin-producing NET (previously designated EC cell-midgut carcinoid), pT2, pN1, M0, pStage IIIb.

The patient's post-operative course was uneventful, and the patient has been free from tumor recurrence for 20 months since surgery without any adjuvant therapy.

## 3. Discussion

The incidence rate of GEP-NETs in the United States increased five-fold (from 1.09 per 100,000 people to 5.25 per 100,000) from 1973 to 2004 [5]. A similar tendency in the incidence of GEP-NETs was observed in Japan [6]. In the near future, with advances in both practitioner knowledge and imaging technology, synchronous or metachronous such as that demonstrated here, may be reported more often. At the initial diagnosis, 19.9% of PNETs patients and 6.0% of GI-NETs patients were reported to have distant metastasis [6]. Although the liver is the predominant site for NETs metastases [7,8], the present case did not show liver metastasis. Furthermore, both morphologic and immunophenotypic findings were different between in the ileum and pancreas. Therefore, we believe it was reasonable to consider that both tumors were primary tumors.

Some GEP-NETs may be associated with genetic syndromes, particularly MEN 1 [6,9,10]. Non-functioning PNETs and gastric (foregut) NETs have been observed in 20% and 10% of MEN 1 patients at age 40 years, respectively [11]. However, EC cell, serotonin-producing NETs, which were observed in the present case, were not consistent the sequence of MEN 1 pathogenesis [3,6,12]. In non-MEN patients, synchronous or metachronous NETs in the plural embryologic regions have not been reported in the literature, although EC cell, multiple serotonin-producing NETs can occur within the midgut [13]. Moreover, differences between gene expression profiles of PNETs and those of EC cell serotonin-producing NETs in recent studies [14,15] suggested that these NETs did not share the same tumorigenic pathway. Thus, the synchronous occurrence of a PNET and GI-NET observed in the present case may be a coincidental finding.