# Misleading clinical presentation of carcinoid syndrome

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## Abstract

**Rare cases of carcinoid syndromes can develop from either gastrointestinal neuroendocrine tumors (NETs) without liver metastasis or large retroperitoneal involvement. We report a case of a patient with isolated flushing highly suggestive of carcinoid syndrome caused by an ileal NET with adjacent lymph node metastases but with no liver metastases. The final diagnose was delayed for this patient due to a combination of misleading clinical presentation and negative usual screening tests (urinary 5-HIAA and serum chromogranine A). Given its high sensitivity and specificity, $^{68}$Ga-DOTATATE PET confirmed the diagnosis of neuroendocrine tumor. Therefore, this case reminds clinicians that carcinoid syndrome may manifest as flushing only and highlights that imaging is a major aspect of the evaluation and diagnosis of patients with suspected gastrointestinal NETs.** (Acta gastroenterol. belg., **2021**, 84, **501-503**).

**Key words**: carcinoid syndrome, neuroendocrine tumors (NET), flushing, 5-HIAA, chromogranin A, $^{68}$Ga-DOTATATE PET/CT.

## Introduction

Carcinoid syndrome is a rare manifestation of neuroendocrine tumors (NETs) that usually only affects patients with liver metastases of gastro-intestinal NETs, patients with extra gastro-intestinal NETs such as ovaries, testis, lungs/bronchus, or patients with extensive retroperitoneal involvement of midgut NETs. Typical clinical features of carcinoid syndrome are flushing (60-85%), secretory diarrhea (60-80%), abdominal pain (40%), telangiectasia (25%), vascular heart disease (20%), intermittent bronchial wheezing (<10%) and pellagra (5%) (1). Urinary 5-HIAA and serum chromogranine A are sensitive screening tests (2,3). However, imaging, and in particular Ga-DOTATATE PET/CT, is also important for the evaluation and diagnosis of patients with suspected gastrointestinal NETs (4).

## Case

We report the case of a 25-year-old woman, with no particular personal or familial medical history, who attended our dermatology outpatient clinic at the Cliniques universitaires Saint-Luc, Brussels, Belgium, complaining of facial flushing occurring a few minutes after meals for the last 6 months. She described episodes of hot flushes with transient non-pruritic, macular erythematous rash, mainly localized on the face and trunk and associated with heart palpitations. These manifestations usually began about 5 to 10 minutes after food intake at least once a day, but not necessarily at every meal, resolved spontaneously after 1 to 5 minutes and were not associated with a specific aliment. The phenomenon was never accompanied by dyspnea,

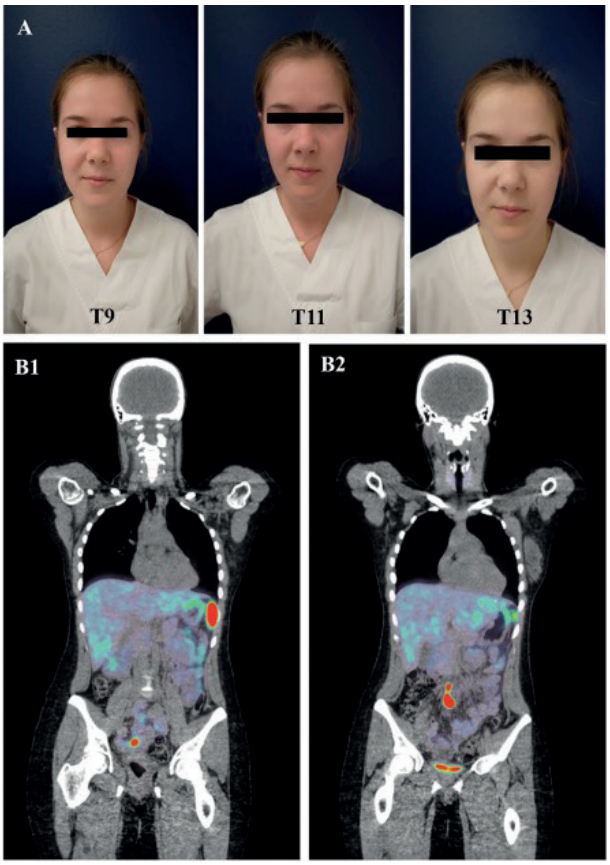


Fig 1. — (A) Oral provocation test. Nine minutes after food intake (T9): flushing starts. Eleven minutes after food intake (T11): flush increases, associated with palpitations and slight elevation of blood pressure. Thirteen minutes after food intake (T13): spontaneous resolution with relative skin pallor. (B) $^{68}$Ga-DOTATATE PET. Focal uptake in the terminal small bowel (B1), as well as in two metastatic right common iliac lymph nodes but with no liver lesions identified (B2).

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swelling, abdominal pain, diarrhea or other systemic complaints. No improvement was observed despite initial treatment with antihistamines (bilastine 20 mg b.i.d) and propranolol 10 mg a day. Clinical examination was normal. Prick tests with food were negative. About 9 minutes (T9) after oral provocation test with milk and cereals, flushing of the face, trunk and arms was observed. The patient's blood pressure was 120-80 mmHg. Two minutes later (T11), the flush increased, she felt heart palpitations and her systolic blood pressure increased slightly (130-80 mmHg). Spontaneous resolution of the eruption and normalization of the blood pressure were observed 2 minutes later (T13) (Fig.1A). A 24-Hour Holter monitoring was normal. Laboratory tests including white blood cell counts, electrolytes, kidney and liver function, CRP, TSH, total IgE and plasmatic tryptase level were within normal ranges. Plasma gastrin and chromogranin A were also within normal ranges as well as catecholamine urine test. Esophago-gastro-duodenoscopy was unremarkable. An abnormal hypervascularized small bowel lesion in the right pelvis and a right common iliac lymphadenopathy were seen on MRI images of the abdomen with no suspicious lesions seen in the liver. Lower endoscopy confirmed an ileal submucosal lesion located 50cm from the ileo-caecal valve. Finally, $^{68}$Ga-DOTATATE PET images demonstrated focal uptake in the terminal small bowel, as well as in two regional right common iliac lymph nodes but with no liver lesions identified (Fig.1B). This confirmed the diagnosis of neuroendocrine tumor (NET) and regional lymphadenopathy with an overexpression of somatostatin receptors.

Resection of the midgut lesion with superior mesenteric axis lymph node dissection was performed. Although positive lymph nodes have been described along the right iliac axis on MRI and $^{68}$Ga-DOTATATE PET, surgical exploration did not find any lymphadenopathy in this region. The positive lymph nodes were actually located along the distality of the superior mesenteric vessels. Histological examination showed a well differentiated tumor of the midgut (Ki67 4,3%, G2, WHO classification) infiltrating the entire intestinal wall without effraction and five regional lymph nodes. All the flushing symptoms disappeared after surgery. Moreover, 3 months post-surgery $^{68}$Ga-DOTATATE PET was negative.

## Discussion

Carcinoid syndrome only occurs in about 10% of patients with carcinoid tumors (5). It develops when sufficient amounts of vasoactive substances reach the systemic circulation. This explains why carcinoid syndrome usually affects patients with liver metastases of gastro-intestinal NETs, patients with extra gastro-intestinal NETs such as ovaries, testis, lungs/bronchus, or patients with extensive retroperitoneal involvement of midgut NETs (6). Our patient presented with symptoms highly suggestive of carcinoid syndrome caused by an ileal NET with adjacent positive lymph nodes but with no liver metastases. This presentation, with only regional lymphadenopathy, is extremely rare with only a few cases having been reported in literature (6,7). Isolated flushing with transient macular erythematous rash in our patient was also misleading.

Furthermore, urinary 5-HIAA levels were normal. However, sensitivity and specificity of 5-HIAA urinary quantification for detecting carcinoid syndrome are only 70 and 90% respectively (2). Chromogranin A, which has a sensitivity of 84% for identifying patients with NETs, was also normal (3). Due to the combination of rare manifestations, the patient's young age and the negative screening tests (especially 5-HIAA), final diagnosis was delayed for this patient.

Therefore, imaging remains a key factor in the diagnosis of NETs, and given its high sensitivity and specificity, $^{68}$Ga-DOTATATE PET/CT should be the preferred imaging modality (4).

To conclude, clinicians should know that rare cases of carcinoid syndromes can develop from either gastrointestinal NETs without liver metastasis or large retroperitoneal involvement. Urinary 5-HIAA and serum chromogranine A levels could be normal. Therefore, imaging is a major aspect of the evaluation and diagnosis of patients with suspected gastrointestinal NETs.

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## Author's contributions

LF contributed as the first author for the manuscript. CVL helped in the writing of the paper. MB, IB, HY and JL reviewed and corrected the manuscript. All authors have read the manuscript and have confirmed that they have no conflict of interest.

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