Clinical features of carcinoid syndrome

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INTRODUCTION

"Carcinoid syndrome" is the term applied to a constellation of symptoms mediated by various humoral factors elaborated by some well-differentiated neuroendocrine tumors (NETs) of the digestive tract and lungs, which synthesize, store, and release a variety of polypeptides, biogenic amines, and prostaglandins (table 1). Some of these tumor products are responsible for carcinoid syndrome, but the relative contributions of each and the specificity of any for particular components of the syndrome are uncertain (table 2).

The pathophysiology and clinical manifestations of carcinoid syndrome will be reviewed here. The diagnosis and treatment of this disorder are discussed separately. (See "Diagnosis of carcinoid syndrome and tumor localization" and "Staging, treatment, and post-treatment surveillance of non-metastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors" and "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring".)

FREQUENCY

Neuroendocrine tumors (NETs) may arise anywhere in the gastrointestinal tract, in the lungs, and occasionally, elsewhere (table 3). Carcinoid syndrome is most common in the setting of disseminated disease, particularly liver metastases, but it can occur in apparently locoregional

disease. One reason may be understaging. Unappreciated hepatic metastases may be more common than previously reported [1-3], especially in small bowel primaries.

The liver inactivates bioactive products secreted into the portal circulation. This may explain why patients with gastrointestinal NETs most often develop carcinoid syndrome if they have hepatic metastases, resulting in the secretion of tumor products into the systemic circulation [4]. In the large majority of cases, carcinoid syndrome is associated with metastatic tumors originating in the midgut (jejunum, ileum, and cecum); however, the expression is variable in individual patients [5]. Less often, carcinoid syndrome is caused by a NET arising in the lung or in the distal colon or rectum (foregut and hindgut embryologic origin, respectively) [6]. Gastric and lung NETs may be associated with atypical carcinoid syndromes. (See 'Variant syndromes' below.)

Approximately 1 percent of pancreatic NETs secrete excess serotonin and other vasoactive substances that produce carcinoid syndrome. (See "Clinical characteristics of well-differentiated neuroendocrine (carcinoid) tumors arising in the gastrointestinal and genitourinary tracts".)

PATHOPHYSIOLOGY

As many as 40 secretory products have been identified in various gastroenteropancreatic neuroendocrine tumors (NETs) [4]. The most prominent of these are serotonin, histamine, tachykinins, kallikrein, and prostaglandins (table 1).

Tryptophan metabolism — Altered metabolism of tryptophan occurs in almost all patients with carcinoid syndrome. In normal subjects, approximately 1 percent of dietary tryptophan is converted to serotonin; however, this value may increase to 70 percent or more in patients with carcinoid syndrome [7]. Serotonin is then metabolized to 5-hydroxyindoleacetic acid (5-HIAA) (figure 1).

However, some foregut NETs (gastric, lung (figure 2)) lack the aromatic amino acid decarboxylase that converts 5-hydroxytryptophan to serotonin [5]; these tumors produce 5-hydroxytryptophan (and histamine) instead of serotonin. Hindgut NETs (distal colon and rectum) rarely secrete serotonin or any other bioactive hormones and are, therefore, unassociated with hormonal syndromes, even when metastatic (table 3) [5].

These alterations in tryptophan metabolism can explain many of the findings in carcinoid syndrome:

- The diversion of tryptophan to the synthesis of serotonin in patients with widely metastatic tumors may result in niacin deficiency. This disorder may be characterized by decreased

protein synthesis and hypoalbuminemia, with or without the clinical manifestations of pellagra (rough scaly skin, glossitis, angular stomatitis, and mental confusion) [8].

- Tumor production of serotonin is the most likely cause of the diarrhea in carcinoid syndrome. Serotonin stimulates intestinal secretion and motility and inhibits intestinal absorption [9,10].

Serotonin may also stimulate fibroblast growth and fibrogenesis. These effects can lead to the peritoneal and cardiac valvular fibrosis associated with carcinoid syndrome [11]. (See 'Cardiac valvular lesions' below.)

Serotonin does not cause flushing [12]. Among the potential mediators are bradykinins, prostaglandins, tachykinins, substance P, and/or histamine [13].

Histamine — Primary gastric NETs can produce histamine, which may be responsible for the atypical flushing and pruritus associated with these tumors (see 'Gastric NET variant syndrome' below). The observation that such flushing can be ameliorated by combined H1 and H2 antagonism is compatible with this hypothesis [12].

Kallikrein — Some NETs produce kallikrein, a protein that cleaves kinin from plasma kininogens. Bradykinin, a short-lived product of this cleavage, is a potent vasodilator and may be responsible for flushing in some carcinoid patients [14]. Kinins also stimulate intestinal motility and increase vascular permeability [15].

Prostaglandins — Prostaglandins E and F stimulate intestinal motility and fluid secretion in the normal gastrointestinal tract [16]. Although elevated serum prostaglandin concentrations are found in patients with carcinoid syndrome, their role in the symptomatology of this disorder is uncertain [17].

Tachykinins — Some NETs secrete tachykinins (substance P, neurokinin A, neuropeptide K). Elevations in the serum concentrations of these latter polypeptides may contribute to flushing and diarrhea [18-20].

CLINICAL FEATURES

Cutaneous flushing — Episodic flushing is the clinical hallmark of carcinoid syndrome and occurs in 85 percent of patients. The typical flush associated with midgut neuroendocrine tumors (NETs; jejunum, ileum, cecum, appendix) begins suddenly and lasts from 30 seconds to as long as 30 minutes. It primarily involves the face, neck, and upper chest, which become red to violaceous or purple, and is associated with a mild burning sensation (picture 1). Severe

flushes are accompanied by a fall in blood pressure and rise in pulse rate. As the disease progresses, the episodes may last longer, and the flushing may be more diffuse. The differential diagnosis of flushing is listed in the table (table 4).

Most flushing episodes occur spontaneously, but they can be provoked by eating, drinking alcohol, defecation, emotional events, palpation of the liver, and anesthesia [21-23]. (See "Treatment of the carcinoid syndrome", section on 'Carcinoid crisis: prevention and management'.)

Venous telangiectasia — These purplish vascular lesions, similar to those seen in acne rosacea, appear late in the course of carcinoid syndrome. They are due to prolonged vasodilatation and most often occur on the nose, upper lip, and malar areas.

Diarrhea — Secretory diarrhea occurs in 80 percent of patients and is often the most debilitating component of the syndrome. Stools may vary from few to more than 30 per day, are typically watery and nonbloody, and can be explosive and accompanied by abdominal cramping. The abdominal cramps may be a consequence of mesenteric fibrosis or intestinal blockage by the primary tumor. The diarrhea is usually unrelated to flushing episodes. Transit time through the intestine may be extremely short [10].

Bronchospasm — Ten to 20 percent of patients with carcinoid syndrome have wheezing and dyspnea, often during flushing episodes. Carcinoid wheezing should not be mistaken for bronchial asthma because treatment with beta agonists can trigger intense, prolonged vasodilation [24].

Cardiac valvular lesions — Carcinoid heart disease is characterized by pathognomonic plaque-like deposits of fibrous tissue. These deposits occur most commonly on the endocardium of valvular cusps, the cardiac chambers, and occasionally, the intima of the pulmonary arteries or aorta (figure 3). The valves and endocardium of the right side of the heart are most often affected because inactivation of humoral substances by the lung protects the left heart. Left-sided valve disease may be caused by right-to-left shunting (eg, through a patent foramen ovale [PFO]) or with high levels of circulating vasoactive substances. The clinical manifestations and treatment of carcinoid heart disease are discussed separately. (See "Carcinoid heart disease".)

Minor manifestations — There are a number of minor manifestations associated with carcinoid syndrome:

- As noted above, diversion of dietary tryptophan for synthesis of large amounts of serotonin can very rarely result in the development of pellagra [8], manifested by rough

scaly skin, glossitis, angular stomatitis, and mental confusion. Poor dietary intake, and diarrhea or malabsorption can augment this process.

- Muscle wasting may occur as a result of poor protein synthesis.
- In addition to the mesenteric fibrosis associated with NETs, extensive fibrosis can occur in the retroperitoneal area and other sites, causing ureteral obstruction [25,26].
- Persistent brawny edema of the face and, to a lesser degree, of the extremities may be an advanced manifestation of the syndrome in some patients with severe flushing attacks. This is particularly true for those with foregut NETs [27].

VARIANT SYNDROMES

Some patients with functioning gastric or lung neuroendocrine tumors (NETs) have clinical and biochemical variations from the classic syndrome.

Gastric NET variant syndrome — In patients with the gastric NET variant, the flushes may be patchy, sharply demarcated, serpiginous, and cherry red; they are also intensely pruritic. Diarrhea or cardiac lesions are unusual. The tumors that cause this variant syndrome secrete histamine [28,29].

Lung NET variant syndrome — In patients with the lung NET variant, the flushes can be very severe and prolonged, lasting hours to days [27]. They may be associated with disorientation, anxiety, and tremor. Periorbital edema, lacrimation, salivation, hypotension, tachycardia, diarrhea, dyspnea, asthma, edema, and oliguria are other components of this variant. The specific hormone mediator of flushing in patients with lung NETs is unclear, but it could be histamine. In some cases, blood serotonin or urine 5-hydroxyindoleacetic acid (5-HIAA) levels are normal. (See "Lung neuroendocrine (carcinoid) tumors: Epidemiology, risk factors, classification, histology, diagnosis, and staging".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more

sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Carcinoid syndrome (The Basics)")

SUMMARY

- **Frequency**
  - Neuroendocrine tumors (NETs) may arise anywhere in the gastrointestinal tract, in the lungs, and occasionally, elsewhere (table 3). Carcinoid syndrome is most common in the setting of disseminated disease from a small intestinal primary tumor, particularly liver metastases, but it can occur in apparently locoregional disease. (See 'Frequency' above.)
  - Carcinoid syndrome is less common overall with gastric and lung NETs, and almost never occurs in NETs arising in the hindgut (distal colon and rectum). Gastric and lung NETs are sometimes associated with atypical carcinoid syndromes. (See 'Variant syndromes' above.)
- **Pathophysiology**
  - As many as 40 secretory products have been identified in various gastroenteropancreatic NETs. The most prominent of these are serotonin, histamine, tachykinins, kallikrein, and prostaglandins (table 1). (See 'Pathophysiology' above.)
  - Tumor production of serotonin is the most likely cause of the diarrhea in carcinoid syndrome.
- **Clinical features**
  - Episodic flushing is the clinical hallmark of carcinoid syndrome and occurs in 85 percent of patients. The typical flush associated with midgut NETs (jejunum, ileum, cecum, appendix) begins suddenly and often lasts 20 to 30 seconds. It primarily involves the face, neck, and upper chest, which become red to violaceous or purple, and is

associated with a mild burning sensation (picture 1). Severe flushes are accompanied by a fall in blood pressure and rise in pulse rate. As the disease progresses, the episodes may last longer, and the flushing may be more diffuse. The differential diagnosis of flushing is listed in the table (table 4). (See 'Clinical features' above.)

- Diarrhea is a prominent complaint in the majority of patients with carcinoid syndrome and is due to rapid intestinal transit time. (See 'Diarrhea' above.)
- Right-sided valvular heart disease affects as many as 40 percent of patients. (See 'Cardiac valvular lesions' above.)
- A minority may experience bronchospasm. (See 'Bronchospasm' above.)
- Some patients with functioning gastric or lung NETs have clinical and biochemical variations from the classic syndrome. (See 'Variant syndromes' above.)

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Topic 2614 Version 30.0

GRAPHICS

Products of well-differentiated neuroendocrine tumors

Amines
Serotonin
5-Hydroxytryptophan
Norepinephrine
Dopamine
Histamine
Polypeptides
Kallikrein
Pancreatic polypeptide
Bradykinin
Motilin
Somatostatin
Vasoactive intestinal peptide
Neuropeptide K
Substance P

Neurokinin A
Neurokinin B
Corticotropin (ACTH)
Gastrin
Growth hormone
Peptide YY
Glucagon
Beta-endorphin
Neurotensin
Chromogranin A
Prostaglandins

Graphic 79329 Version 2.0

Carcinoid symptoms and their putative mediators

Organ	Symptom	Frequency (%)	Putative mediator
Skin	Flushing	85	Kinins, histamine, kallikreins, other
	Telangiectasia	25	
	Cyanosis	18	
	Pellagra	7	Excess tryptophan metabolism
Gastrointestinal tract	Diarrhea and cramping	75 to 85	Serotonin
Heart	Valvular lesions		Serotonin
	Right heart	40	
	Left heart	13	
Respiratory tract	Bronchoconstriction	19	Unknown

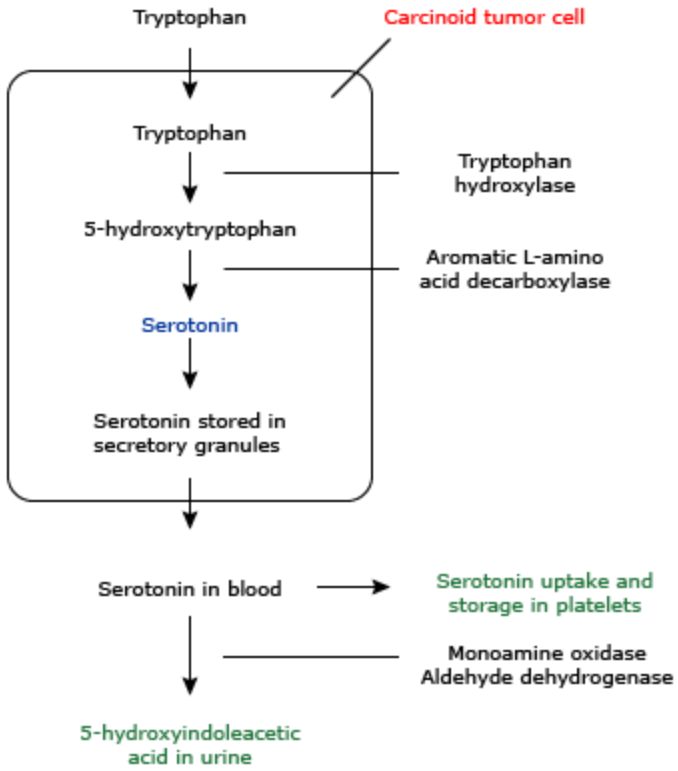
Graphic 63079 Version 9.0

Characteristics of gastroenteropancreatic neuroendocrine tumors

	Foregut	Midgut	Hindgut
Localization	Stomach, duodenum, bronchus, thymus	Jejunum, ileum, appendix, ascending colon	Transverse, descending, and sigmoid colon, rectum, genitourinary
Secretory products	5-hydroxytryptophan, histamine, multiple polypeptides	Serotonin prostaglandins, polypeptides	Variable
Carcinoid syndrome	Rare, and atypical when it happens	Classic	Rare

Graphic 56015 Version 10.0

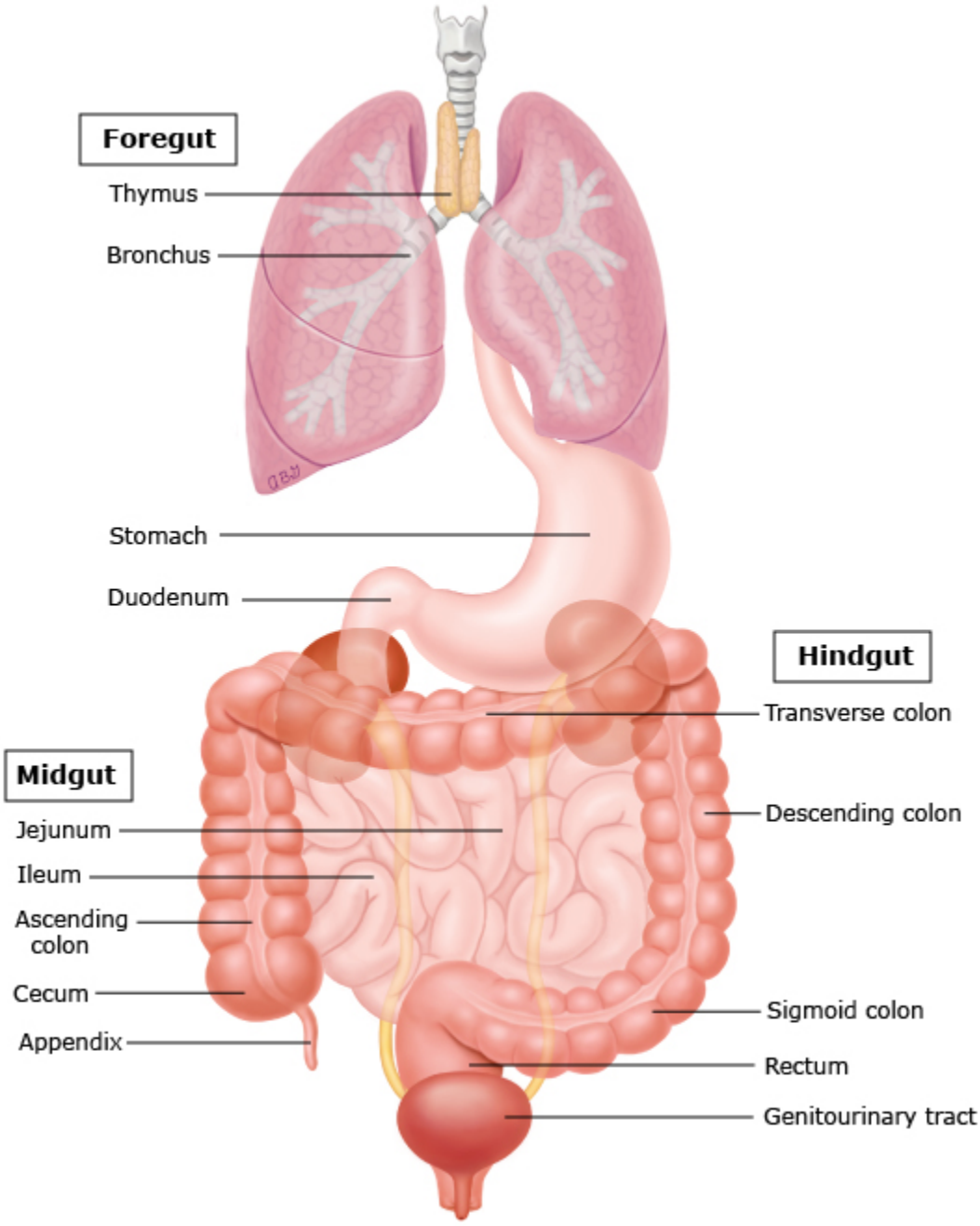
Tryptophan and serotonin metabolism



Pathways of tryptophan and serotonin metabolism in the carcinoid tumor cell. Patients with the carcinoid syndrome often have increased levels of 5-hydroxyindoleacetic acid (5-HIAA) excretion in the urine and serotonin in the blood; urinary serotonin excretion is either normal or slightly increased.

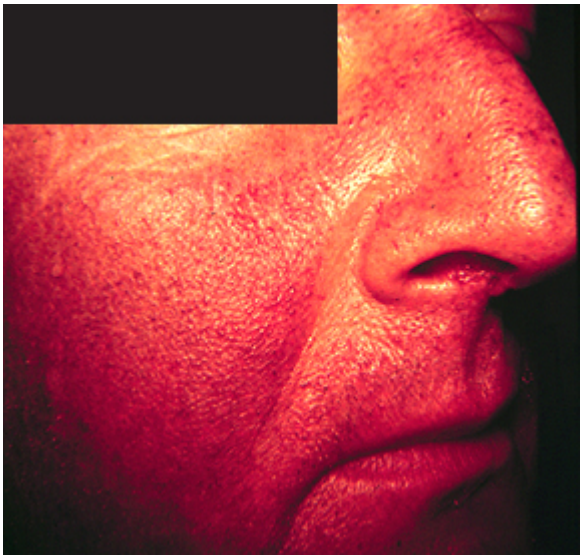
Graphic 51368 Version 4.0

Anatomic location of neuroendocrine tumors based upon embryonic divisions of the alimentary tract



Graphic 83185 Version 3.0

Carcinoid flush



Marked facial flushing in a patient with the carcinoid syndrome.

Courtesy of Stephen E Goldfinger, MD.

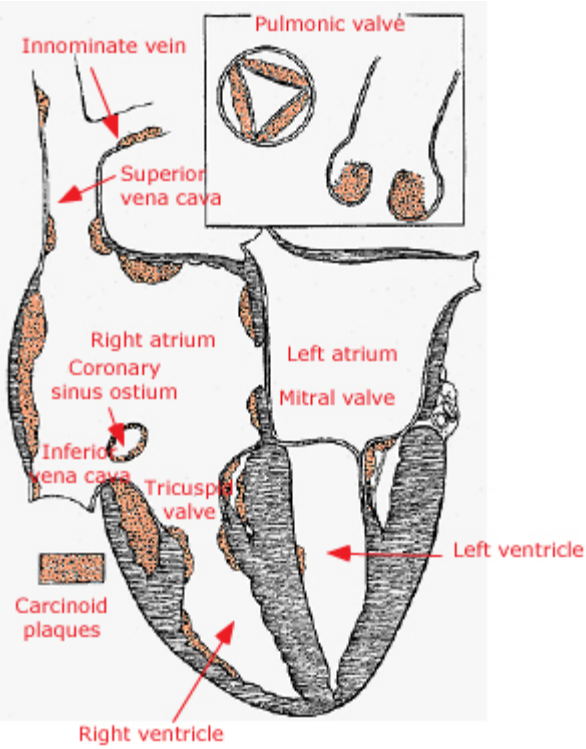
Graphic 55493 Version 2.0

Causes of flushing

Type	Causes
Physiologic	Menopause
	Hot drinks
	Emotional distress
	Anaphylaxis
Drugs	Alcohol
	Alcohol plus chlorpromazine or disulfuram
	Diltiazem
	Amyl nitrate
	Nicotinic acid (niacin)
	Levodopa
	Bromocriptine
Diseases	Carcinoid syndrome
	Systemic mastocytosis
	Basophilic chronic granulocytic leukemia
	VIPoma
	Pheochromocytoma
	Medullary carcinoma of the thyroid
	Renal cell carcinoma
	Diencephalic seizures
	Postural Orthostatic Tachycardia Syndrome (POTS)

Graphic 78237 Version 3.0

Location of fibrous plaques in carcinoid heart disease



In patients with carcinoid heart disease, distinctive lesions, termed carcinoid plaques, develop on the right side of the heart (tricuspid and/or pulmonic valves); such plaques are occasionally found on the left side of the heart.

Adapted from Roberts WC. Am J Cardiol 1997; 80:251.

Graphic 74687 Version 3.0

Contributor Disclosures

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