The carcinoid syndrome describes the signs and symptoms associated with unregulated vasoactive hormone production by neuroendocrine tumors. Though carcinoid tumors can be found anywhere throughout the body, carcinoid syndrome does not develop unless the primary tumor first originates in the liver prior to metastasis. Symptoms of carcinoid syndrome include flushing, diarrhea, and wheezing. Conversely, VIPomas usually form in the pancreas and release vasoactive intestinal peptide (VIP) which results in profound chronic diarrhea with concomitant hypokalemia and dehydration, wheezing, and flushing (similar to carcinoid syndrome). VIPomas are often associated with multiple endocrine neoplasia type 1. Diagnosis is based off blood or urine measurements of serotonin and VIP. Treatment consists of minimizing symptoms with medication and complete surgical removal of the tumor.
Definition of Carcinoid Syndrome

Carcinoid tumors are slow-growing neuroendocrine tumors. The neuroendocrine system helps regulate a variety of systems throughout the body. Neuroendocrine cells release hormones in response to environmental and neural signals. Specialized neuroendocrine cells are found throughout the GI tract, such as the pancreas, but also the small and large intestine and appendix. Carcinoid tumors and VIPomas are derived from neuroendocrine cells that replicate without regulation due to a genetic mutation. These neoplasms release a variety of different hormones into the bloodstream.

Epidemiology of Carcinoid Syndrome

Spread of the carcinoid syndrome

Neuroendocrine tumors are found throughout the body. They are often asymptomatic, especially those found in the pancreas. Carcinoid tumors are the most common type of neuroendocrine tumors of the gut while VIPomas are the third most common neuroendocrine tumor of the pancreas (after insulinoma and gastrinoma). These tumors can be found in all age groups, but there is a great incidence with older age, with a peak between 50–70 years old. There is no difference between men and women or across ethnicity.

Etiology of Carcinoid Syndrome

Causes of the carcinoid syndrome

Both carcinoid tumors and VIPomas arise from abnormal cell development resulting in unregulated cell replication. Carcinoid tumors can be found anywhere in the body including the lungs, thymus, pancreas, GI tract, and liver. They are slow growing and usually asymptomatic.

Symptomatic carcinoid tumors are known for producing serotonin, but they can produce other hormones including dopamine, catecholamine, glucagon, insulin, and histamine. VIPomas are associated with multiple endocrine neoplasia type I (MENI) and are often found with neoplasms of the pituitary and parathyroid gland. They are most frequently found in the body and tail of the pancreas. Carcinoid syndrome is the result of unregulated overproduction of hormones by these tumors.

Pathology and Pathophysiology of Carcinoid Syndrome

VIPomas release large amounts of vasoactive intestinal peptide (VIP). Under normal circumstances, VIP relaxes the GI tract and increases secretion of pancreatic bicarbonate and digestive enzymes. VIP causes non-GI changes as well, such as stimulating vaginal secretion, increasing cardiac contraction, and dilation of coronary arteries. However, a VIPoma secretes far too much VIP in an unregulated process, also known as the Verner-Morrison syndrome.

Verner-Morrison syndrome causes chronic diarrhea and concomitant dehydration, metabolic alkalosis, and elevated bicarbonate. Though these symptoms may seem
counterintuitive as the body loses bicarbonate during diarrhea, there are other mechanisms in the body when the diarrhea is chronic; in cases of chronic diarrhea with dehydration, there is an increase of aldosterone which results in an increased secretion of potassium and reabsorption of sodium and bicarbonate. VIPomas can also occasionally cause flushing similar to carcinoid syndrome.

Carcinoid tumors can release a variety of different hormones including **insulin**, **glucagon**, **gastrin**, and **histamine**, but are most commonly known to release **serotonin**. Carcinoid tumors can form in many parts of the body such as lungs, GI tract, appendix, and thymus. In these areas, the hormones produced by the carcinoid tumor are inactivated and the tumors are virtually asymptomatic.

Theoretically, the hormones released by carcinoid tumors are inactivated by the liver. However, if a carcinoid tumor develops in the liver or metastasizes to the liver, it usually causes symptoms. The usual symptoms associated with the carcinoid tumor in the liver are diarrhea, wheezing, and flushing due to the release of vasoactive serotonin. There is one exception to this rule; a carcinoid tumor forming on the ovary will be symptomatic.

### Symptoms of Carcinoid Syndrome

**Carcinoid syndrome**

**Heart**
- pulmonic and tricuspid valve thickening and stenosis
- endocardial fibrosis

**Liver**
- hepatomegaly

**Gastrointestinal**
- diarrhea
- cramps
- nausea
- vomiting

**Skin**
- cutaneous flushes
- apparent cyanosis

**Respiratory**
- cough
- wheezing
- dyspnea

**RETROPERITONEAL AND PELVIC FIBROSIS**
Signs and symptoms of VIPomas

**Verner-Morrison syndrome** consists of **profuse, chronic diarrhea** (more than 10 watery stools per day) that is non-bloody and without mucus, which results in dehydration, hypokalemia, and non-ion gap metabolic alkalosis. Volume depletion may result in weight loss, loss of skin turgor, and **tachycardia**. Hypokalemia may cause muscle cramps and weakness and cardiac complications. VIPomas also may cause **facial flushing, profuse sweating**, and **achlorhydria**.

Signs and symptoms of carcinoid tumors

Most carcinoid tumors are **asymptomatic** and are found incidentally during surgery or imaging. Some tumors cause symptoms due to mass effect or kinking or partial obstruction of the intestine. Carcinoid tumors of the liver or ovary produce malignant carcinoid syndrome spontaneously or under stress (surgery, chemotherapy, exercise, emotional, etc.). Symptoms may be intermittent or constant and vary in severity and primarily consist of **diarrhea, wheezing**, and **flushing** of the head and neck.

**Diagnosis of Carcinoid Syndrome**

When a patient’s history points towards carcinoid syndrome or Verner-Morrison syndrome, several steps are required for disease diagnoses and confirmation prior to initiating treatment; **confirmatory labs** are taken to evaluate the condition, **elevated levels of 5-HIAA** (5-hydroxyindoleacetic acid) or other hormones in urine or plasma can indicate carcinoid tumor, and **elevated VIP levels** in blood is indicative of VIPoma.

Samples for both conditions should be collected when symptoms are present. Once a tumor is suspected, a **CT scan** is used to locate the tumor. An alternate and very sensitive technique involves **somatostatin receptor scintigraphy** which utilizes a positron emission tomography (PET) scan coupled with indium-labeled octreotide. The octreotide will target the tumor and mark it on the PET scan.

Though a biopsy is often impossible for VIPomas in the pancreas, carcinoid tumors in the large intestine or upper GI can be biopsied endoscopically. Patients with a VIPoma should be evaluated by a genetic test for MEN I.

**Differential Diagnoses of Carcinoid Syndrome**

Clinical pictures similar to the carcinoid syndrome

- Celiac disease (sprue)
- Gastroenteritis
- Intestinal motility disorders
- Irritable bowel syndrome
- Zollinger-Ellison syndrome
- Ogilvie syndrome

**Therapy of Carcinoid Syndrome**
Treatment of the carcinoid syndrome

The first concern for patients with carcinoid syndrome is **rehydration and electrolyte restoration**. Once they are stable, further treatment can be attempted. Both conditions respond to **octreotide therapy. Serotonin antagonists** can also be used in the treatment of carcinoid syndrome. Tumor resection is reserved for severe and non-responsive conditions. Unresectable tumors can be managed with yttrium-90 labeled octreotide which targets the tumor and doses it with radioactivity from inside the body.

### Progression and Prognosis of Carcinoid Syndrome

Profuse volume depletion may result in **renal failure**. VIPomas in young children and infants may result in failure to thrive due to malnutrition and dehydration. Carcinoid tumors may metastasize anywhere throughout the body and are commonly found in the liver and lungs. Most symptoms respond well to medical therapy and surgical treatment is curative in about half of all patients. **The metastatic disease only slightly increases mortality.**

### Review Questions

The correct answers can be found below the references.

1. **What is the first line of medical treatment for carcinoid syndrome or Verner-Morrison syndrome?**
   - A. Amitriptyline
   - B. Quetiapine
   - C. Octreotide
   - D. Chlordiazepoxide

2. **Which is the least invasive method to test for a carcinoid tumor?**
   - A. Urine tests for 5-HIAA
3. A 59-year-old man presents to your clinic with a history of intermittent diarrhea, flushing, and occasional wheezing. A mass is detected in the pancreas. What tumor is most likely associated with this condition?

A. VIPoma
B. Carcinoid tumor
C. Adenocarcinoma
D. A or B

References


**Correct answers:** 1C, 2A, 3D

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