

# The Carcinoid Syndrome

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## Citation

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## Abstract

A case is presented of a small bowel carcinoid tumor with hepatic metastases causing the carcinoid syndrome. Pathophysiology, epidemiology, clinical presentation, and therapeutic modalities are discussed.

## CASE PRESENTATION

A 73 year old white male with a past medical history significant for duodenal and gastric ulcers status post pyloroplasty presented to the emergency department complaining of nausea, vomiting, and right upper quadrant abdominal pain for two months. The patient stated the pain did not change with food or position and was not accompanied by any fevers, chills, jaundice, diarrhea, melena, or bright red blood per rectum. The patient's social history included remote alcohol and tobacco use. Physical exam was pertinent for tender hepatomegaly with a liver span of 18 centimeters. Laboratories revealed a normal complete blood count, normal chemistries, and normal liver function tests except for an elevated GGT of 162 and alkaline phosphatase of 221. A CT scan of the abdomen revealed multiple, enhancing solid masses in the liver, the largest at the junction of the anterior segment of the right lobe and the medial segment of the left lobe, measuring 6.4 centimeters in greatest diameter. Smaller satellite lesions were also identified in the lateral segment of the left lobe and in the right lobe.

The initial differential diagnosis of the hepatic lesions included cysts, either congenital, echinococcal, or secondary to adult polycystic liver disease, abscess, either pyogenic or amebic, or benign or malignant neoplasms. Benign neoplastic possibilities included hemangiomas, focal nodular hyperplasia, or hepatic adenoma. The differential diagnosis or malignant disease included metastatic disease, most commonly from colon, stomach, pancreas, or breast, or primary malignancy such as hepatocellular carcinoma or cholangiocarcinoma. To narrow the differential diagnosis, tumor markers such as alpha fetoprotein, carcinoembryonic antigen, and prostatic antigen were sent and were all normal. A hepatitis B surface antigen and hepatitis C antibody were

negative.

The interventional radiology service was eventually consulted for a liver biopsy. The procedure was performed but several minutes after the administration of dissociative anesthetic the patient became hypotensive and bradycardic, requiring intravenous fluid resuscitation and overnight observation in the medical intensive care unit. Pathology on the fine needle aspiration and core biopsies of the liver revealed nests of neoplastic cells surrounded by a dense fibrous stroma. The cells had a moderate amount of cytoplasm and medium to large nuclei with "salt-and-pepper" chromatin and occasional large nucleoli. Immunohistochemical stains were positive for synaptophysin, chromogranin, NSE, and AE1/AE3, a pattern consistent with a neuroendocrine tumor such as a gastrointestinal carcinoid or a pancreatic islet cell tumor. A 24 hour urine collection for 5-hydroxyindoleacetic acid was dramatically elevated at 384 milligrams, confirming the diagnosis of a carcinoid tumor. An octreotide scan revealed increased uptake in the ileum and within the liver. The patient did well clinically and was discharged home with follow up in hematology/oncology clinic.

## DISCUSSION

Carcinoid syndrome is the term applied to a diffuse group of symptoms caused by the production of various polypeptides, prostaglandins, and biogenic amines. They may arise anywhere in the gastrointestinal tract, in the bronchi, and occasionally elsewhere. The pathophysiology of the syndrome is secondary to altered tryptophan metabolism. Basically, in normal subjects only one percent of dietary tryptophan is converted to serotonin; however, in the carcinoid syndrome this value may increase to 70% or more. The serotonin is subsequently metabolized to 5-hydroxyindoleacetic acid (HIAA).

Some hindgut (transverse and descending colon and rectum) carcinoids cannot convert tryptophan to serotonin and its subsequent metabolites and thus are not associated with the carcinoid syndrome.

The carcinoid syndrome is most commonly seen with small bowel carcinoid tumors. Approximately 10% of small bowel carcinoids, less than one percent of appendiceal carcinoids, and virtually no rectal carcinoids are associated with the syndrome. Importantly, among patients with intestinal carcinoids, as in the case report, the carcinoid syndrome is not seen until the tumor has metastasized to the liver. The classic symptoms and their relative frequencies in the carcinoid syndrome are as follows : flushing (85%), telangiectasias (25%), cyanosis (18%), pellagra (8%), diarrhea and cramping (75-85%), valvular lesions (right-sided 40% and left-sided 13%), and bronchoconstriction (19%). Interestingly, the patient in the case presentation may have had a “carcinoid crisis” during his liver biopsy, defined by severe hypotension and often precipitated by anesthetics.

The patient in the case presentation had a small bowel carcinoid tumor with hepatic metastases. The preferred modality for following these patients is with contrast enhanced CT scans. Another useful test is somatostatin receptor scintigraphy. This is because over 90% of neuroendocrine tumors contain high concentrations of somatostatin receptors and can thus be imaged with a radiolabeled form of the somatostatin analogue octreotide. The uptake of radiolabeled contrast is also predictive of good response to therapy with octreotide. 5-HIAA levels are also useful in following patients with metastatic carcinoid tumors and although highly specific, are not particularly sensitive. This test is best used on patients with midgut carcinoids and is generally less useful for foregut and hindgut carcinoids. A more sensitive test than 5-HIAA for metastatic carcinoid tumors is plasma chromogranin A. This test also can be of prognostic value, with a level higher than

5000 mcg/ml associated with a poor prognosis.

Treatment for carcinoid tumors are extremely variable because of the tumor's unpredictability. Most signs and symptoms of the carcinoid syndrome, episodic flushing, wheezing, diarrhea, and carcinoid heart disease, can be controlled with somatostatin analogues, i.e. octreotide. However, actual tumor regression occurs in less than 5%. If a patient is refractory to octreotide, another option is interferon alfa. IFN $\alpha$  improves symptoms of hormonal hypersecretion in 40-50%, induces tumor stabilization in 20-40%, and achieves tumor regression in 15%. The major adverse effect that limits its utility is myelosuppression. Treatment for hepatic metastases include surgery, radiofrequency ablation, liver transplantation, hepatic artery chemoembolization, or cytotoxic chemotherapy. Surgery is most useful with a limited number of metastases and can effectively palliate symptoms of hormonal hypersecretion. Radiofrequency ablation can often be used as an adjunct to surgical resection. The role of orthotopic liver transplantation is very controversial given the fact that the tumor can be very indolent. Hepatic artery chemoembolization is a very intriguing therapy. The principle is that the tumor derives most of its blood supply from the hepatic artery whereas normal hepatocytes use oxygen from the portal vein. Response rates with this therapy have generally been greater than 50% but have often been transient, lasting only 4 to 24 months. A final option for patients refractory to all other modalities is cytotoxic chemotherapy. Diverse agents such as fluorouracil, dacarbazine, streptozocin, cyclophosphamide, and doxorubicin have been tried in various combinations, but none have been shown to have significant activity against carcinoid tumors. These agents should be administered with extreme caution because some may be cardiotoxic, thereby worsening possible carcinoid heart disease.

## References

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