Carcinoid Syndrome from Gastrointestinal Carcinoids without Liver Metastasis

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Although patients with bronchial and ovarian carcinoid tumors can develop the carcinoid syndrome (diarrhea and/or flushing) in the absence of hepatic metastasis, it is believed that development of the carcinoid syndrome in patients with carcinoid tumors of gastrointestinal origin occurs only after the patient has hepatic metastasis. This is explained by hepatic inactivation of most of the serotonin in the portal circulation or by the fact that hepatic metastases are larger than the primary tumor in the gastrointestinal tract. Three patients with ileal and jejunal carcinoid tumors who developed the carcinoid syndrome without obvious hepatic metastasis are described. Two of the patients had intra-abdominal, but extrahepatic, metastasis that probably drained directly into the systemic circulation. The third patient had an ileal carcinoid with clinical involvement limited to adjacent mesenteric lymph nodes. Following resection of her tumor, her urinary 5-HIAA excretion and platelet serotonin level returned to normal, and her attacks of carcinoid flushing virtually ceased. She has occasional spells of "blushing" that are thought to be benign; however, further close follow-up study will be needed to be certain that she is free of disease. It is suggested that each patient with the carcinoid syndrome be evaluated with CT and technetium-99 pertechnetate liver scans. If there is no liver involvement detected with these studies, one should consider hepatic arteriogram or laparotomy to determine if the patient's tumor might be totally resectable.

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IT IS THOUGHT that patients with bronchial and ovarian carcinoid tumors may have the carcinoid syndrome in the absence of liver metastasis, while patients with carcinoid tumors arising in the gastrointestinal tract must have hepatic metastasis before they develop this syndrome.[1-3] The usual explanation for this phenomenon is that bronchial and ovarian carcinoid tumors drain directly into the systemic circulation, while blood draining gastrointestinal carcinoid tumors is carried to the liver by the portal vein (Fig. 1). Two suggestions have been proposed to explain why gastrointestinal carcinoid tumors do not produce the carcinoid syndrome in the absence of hepatic metastasis.[1] First, the liver, which contains a large amount of monoamine oxidase activity, inactivates most of the serotonin released by the tumor, preventing it from reaching the systemic circulation. Second, primary gastrointestinal carcinoids are usually small, and the amount of humoral material they secrete is likely to be substantially less than that secreted by the much larger hepatic metastases that are frequently present when there is liver involvement. Patients with the carcinoid syndrome from carcinoid tumors arising in the gastrointestinal tract are thus thought to be incurable and, therefore, may not undergo resection of the primary tumor.

Three patients with carcinoid tumors of gastrointestinal origin who had the carcinoid syndrome in the absence of hepatic metastasis were treated. Two of the patients had unresectable tumors in extrahepatic areas in the peritoneal cavity. However, following resection of her jejunal carcinoid tumor, the third patient seems to be free of disease by both clinical and laboratory criteria.

Materials and Methods

Twenty-four-hour urine specimens were collected under refrigeration (2 C). Blood samples were drawn from an antecubital vein. Urinary 5-hydroxyindoleacetic acid (5-HIAA) was measured by a colorimetric technique[4]; serotonin and histamine were measured by highly specific radioenzymatic techniques (5,6).

Report of Cases

Case 1. This 57-year-old man had episodes of crampy midabdominal pain in 1969. In 1974, results of upper GI series with small-bowel follow through revealed a constricting lesion in the midjejunum. A jejunal carcinoid was resected, and the bowel was reconstituted by jejunojejunostomy. Although the margins of the resection were free of tumor, metastasis to mesenteric lymph nodes and perineural invasion were present in the resected specimen. In May 1976, urinary 5-HIAA excretion was 7.6 mg/24 hr (normal 2-9 mg/24 hr). In February 1980, the patient again developed episodes of crampy abdominal pain. In May 1981, an abdominal CT scan demonstrated a

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Submitted for publication: December 17, 1981.

0003-4932/82/0700/0033 $00.80

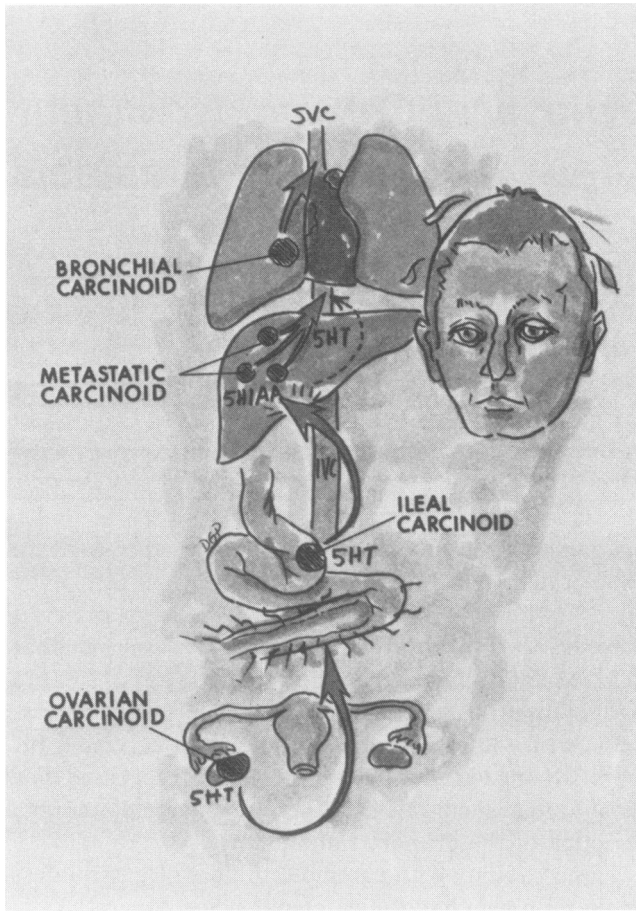

FIG. 1. Mechanism of the carcinoid syndrome. Blood from ovarian and bronchial carcinoid tumors drains directly into the systemic circulation, resulting in the carcinoid syndrome in the absence of hepatic metastasis. Blood from ileal carcinoids drains into the portal circulation to the liver, where the serotonin is inactivated. Thus, hepatic metastases are usually present when carcinoid tumors of gastrointestinal origin produce the carcinoid syndrome.

mass near the head of the pancreas, between the aorta and the inferior vena cava (Fig. 2). There were no abnormalities in the liver on either the CT or technetium-99 pertechnetate liver scan. There were no abnormalities found in the liver during surgical exploration. Biopsy of the unresectable retroperitoneal mass revealed a carcinoid tumor that contained 550 μg of serotonin per gram of tumor. One month after operation, the patient's urinary 5-HIAA excretion was elevated to 35 mg/24 hr, his urinary histamine excretion was 28 μg/24 hr (normal 15–60 μg/24 hr), and his platelet serotonin was 1,030 pmol/mg platelet protein (normal 300–1,800 pmol/mg platelet protein). Questioning of the patient revealed that he had been taking 0.25 mg of reserpine for hypertension for the preceding three months. One month after discontinuing the reserpine, his platelet serotonin had increased to 6,630 pmol/mg protein, and his urinary 5-HIAA excretion was 42 mg/24 hr.

In response to careful questioning, the patient described episodes of facial flushing every two to three weeks. Although he did not have diarrhea, he described his abdominal pain as cramping in nature, sometimes relieved by passing flatus. A trial of the serotonin antagonist cyproheptadine (4 mg qid) resulted in marked amelioration of the abdominal pain. The patient had four monthly treatments of streptozotocin, with no clinical improvement.[7] In September 1981, he developed obstructive jaundice, with a serum bilirubin level of 12.7 mg/dl. Results of transhepatic cholangiogram demonstrated a dilated common bile duct. At laparotomy there was no evidence of metastasis to the liver. The patient had a cholycystoduodenostomy, with a resulting fall in serum bilirubin to normal. One month after operation, a CT scan demonstrated no change in the size of the retroperitoneal mass and no evidence of metastasis in the liver. The patient is now receiving radiation therapy to the retroperitoneal tumor mass.[8]

Case 2. After developing acute abdominal pain, this 60-year-old man underwent exploratory laparotomy in 1977. A carcinoid tumor was resected from the terminal ileum, and the terminal ileum was reunited. Lymph nodes in the region contained carcinoid tumor. The patient felt well until early in 1980, when he began to experience diarrhea with production of five to six watery stools per day. At that time, he also had bouts of spontaneous and alcohol-induced facial flushing. In July 1980, he experienced persistent right upper quadrant pain. Some small, ill-defined focal areas of decreased tracer uptake in the liver were shown with ^{99m}TC pertechnetate liver scan. However, abdominal CT scan, abdominal aortogram, and selective hepatic arteriogram showed no liver abnormalities (Fig. 3). The patient's preoperative 5-HIAA excretion on two successive days was elevated to 59 and 46 mg/24 hr, and his platelet serotonin concentration was elevated to 4,400 pmol/mg platelet protein. In July 1980, the patient underwent exploratory laparotomy. Carcinoid tumor was found in the terminal ileum at the anastomosis line, as well as in the adjacent mesentery. There were many 3–5-mm tumor implants on the peritoneal surface and in the cul-de-sac. The masses in the terminal ileum and the adjacent mesentery were excised, as well as 6–8 inches of right colon. Careful examination of the liver revealed no hepatic metastasis. His carcinoid tumor contained 6,460 μg of serotonin per gram of tumor.

After operation, the patient's 5-HIAA excretion was reduced to 42 and 28 mg/24 hr, and his platelet serotonin level was reduced to 2,130 pmol/mg platelet protein. His urinary histamine excretion was elevated to 119 μg/24 hr. The patient received a course of streptozotocin without clinical benefit.[7] In July 1981, the patient developed gross hematuria. IVP and retrograde showed some dilatation of the upper right kidney collecting system that may have been present in a mild form the preceding year (Fig. 3). This remained stable for the next five months. Because of increasing diarrhea with an increase in urinary 5-HIAA excretion (55 mg/24 hr) and platelet serotonin (5,770 pmol/

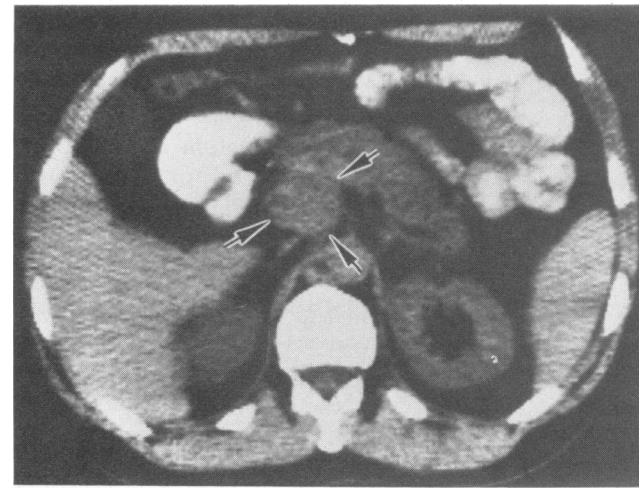

FIG. 2. Abdominal CT scan of patient 1. This scan, made in May 1981, demonstrated a retroperitoneal mass near the head of the pancreas (arrow). The liver was normal.

mg platelet protein), the patient was treated with parachlorophenylalanine (Fenclonine®), an inhibitor of serotonin synthesis, with reduction in diarrhea.[9] At present he still has no clinical or laboratory evidence of liver metastases.

Case 3. In June 1980, this 28-year-old woman experienced bouts of facial flushing provoked by eating food or drinking alcoholic beverages. The attacks of facial flushing were accompanied by conjunctival injection, headache, lack of energy, and feelings of apprehension. In April 1981, the flushing began to appear also on the arms, legs, and trunk. The flushed areas had the appearance of red patches with smooth borders and were not pruritic. The patient did not have diarrhea or other changes in bowel habits. In June 1981, she experienced some bouts of crampy right lower quadrant pain.

In July 1981, the patient's urinary 5-HIAA excretion was noted to be elevated to 14.8 and 16.5 mg/24 hr, and her platelet serotonin level was elevated to 5,230 pmol/mg platelet protein. Her urinary histamine excretion of 34 μg was normal. Results of upper GI x-ray with small bowel follow through, air contrast barium enema, gastroscopy, and proctoscopy were normal. CT and ultrasound examination of the abdomen and pelvis revealed only a right ovarian cyst, with no abnormalities in the liver. A superior mesenteric arteriogram demonstrated a hypervascular mass 4 × 2.5 cm in the midportion of the small intestine (Fig. 4). When epinephrine was injected with the contrast material into the superior mesenteric artery, the patient had a generalized flush. However, when epinephrine was injected with contrast material into the hepatic artery, there was no abnormality seen and the patient did not flush.

At laparotomy a 1-cm ileal carcinoid and a 4-cm group of adjacent lymph nodes that contained carcinoid tumor were resected. A corpus luteum and follicular cyst of the right ovary were also removed. Careful examination revealed no other abnormalities in the abdomen. In particular, the liver showed no evidence of metastatic disease. The ileal carcinoid tumor contained 718 μg of serotonin per gram of tumor.

By the third and sixth postoperative day, respectively, the patient's urinary 5-HIAA excretion (3.1 mg/24 hr) and platelet serotonin concentration (1,290 pmol/mg platelet protein) had fallen to normal (Fig. 5). Her urinary histamine excretion remained normal (37 μg/24 hr). The patient was totally free of flushing episodes for the next six weeks.

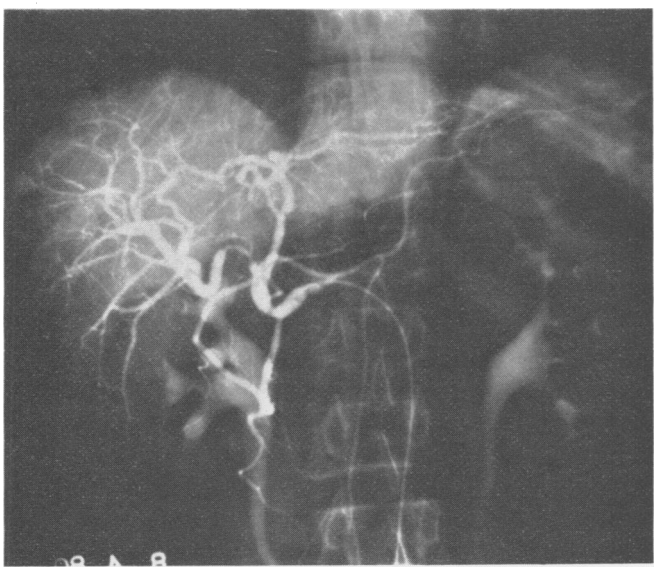

FIG. 3. Hepatic arteriogram of patient 2. This arteriogram made in July 1980 demonstrates a normal liver. There was mild dilatation of the collecting system of the right kidney.

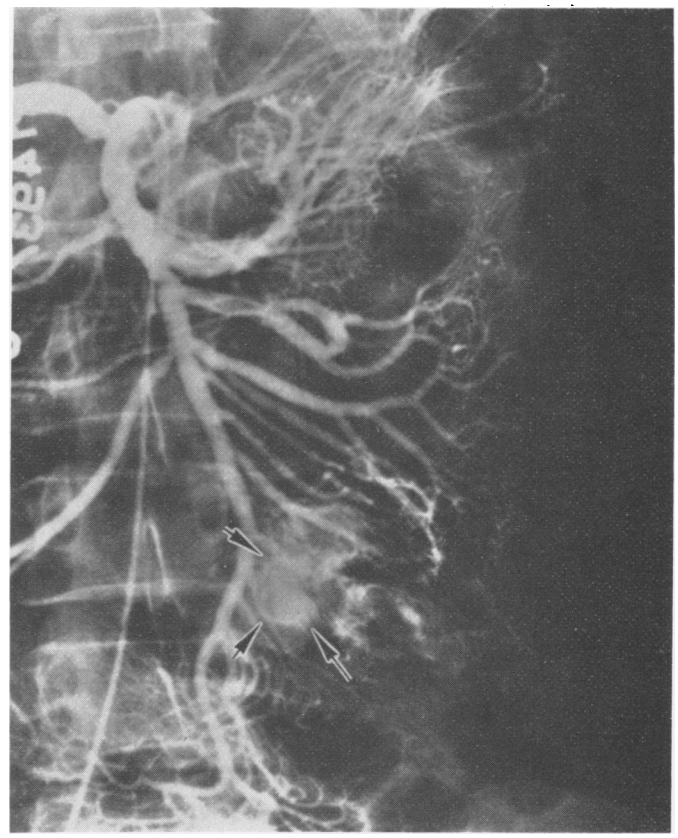

FIG. 4. Superior mesenteric arteriogram of patient 3. This arteriogram, made in July 1981, demonstrates a 4 × 2.5 cm hypervascular mass in the midportion of the small intestine (arrow).

Subsequently, she has had several episodes of flushing of her face and ears. They have not been accompanied by headache, and they are not provoked by alcohol. Because the patient's 5-HIAA excretion and platelet serotonin concentration remain normal, it is believed that they are benign blushing episodes (Fig. 5).

Discussion

Three patients with serotonin-producing carcinoid tumors who developed the carcinoid syndrome in the absence of hepatic metastasis are described. Patient 1 developed a large retroperitoneal tumor mass that probably drained directly into the systemic circulation (Fig. 6). Patient 2 had multiple small tumor implants on the parietal peritoneum, as well as a larger implant in the cul-de-sac that also drained into the systemic circulation (Fig. 6). The explanation for the carcinoid syndrome of patient 3 is more puzzling, as her tumor seemed to be limited to the proximal ileum and its adjacent lymph nodes, with no obvious implants draining into the systemic circulation (Fig. 6).

Patient 2 had a minimal defect on his ^{99m}Tc pertechnetate liver scan. This questionable defect could not be confirmed on the more sensitive techniques of CT scan, hepatic arteriogram, and careful examination at sur-

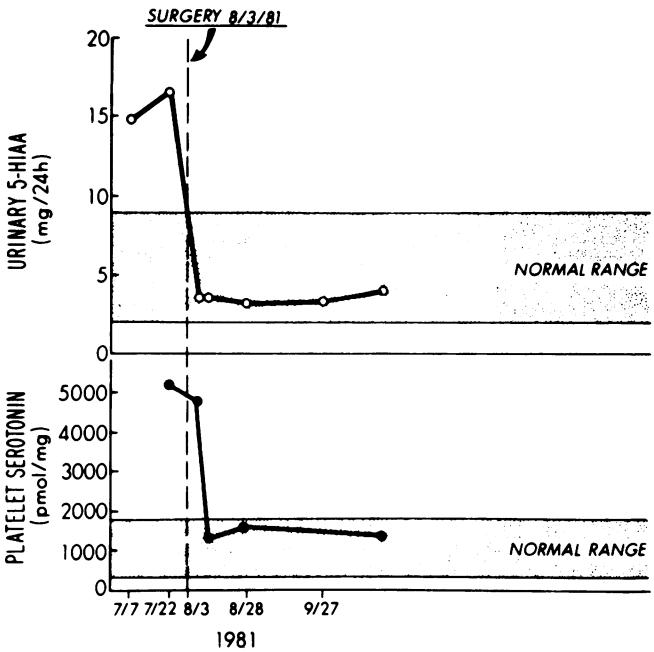

FIG. 5. Urinary 5-HIAA excretion and platelet serotonin level of patient 3. Three days after resection of the carcinoid tumor, the patient's 5-HIAA excretion had fallen to normal, while her platelet serotonin level remained elevated. Six days after surgery, both 5-HIAA excretion and platelet serotonin level had fallen to normal.

gery. Despite the fact that all three patients had normal liver function tests, and a normal liver by both CT examination and examination at surgery, one cannot rule out microscopic foci of tumor in the liver. This tumor has not become evident over time in patients 1 and 2. In the case of patient 3, tumor was not seen on hepatic arteriogram, even with the sensitive technique of epinephrine enhancement.[10] Epinephrine releases vasoactive materials such as kallikrein and serotonin from carcinoid tumors.[11] Epinephrine injection into the superior mesenteric artery to the tumor provoked a flush; epinephrine injection into the hepatic artery to the liver did not provoke a flush, suggesting that carcinoid tumor was not present in the liver.

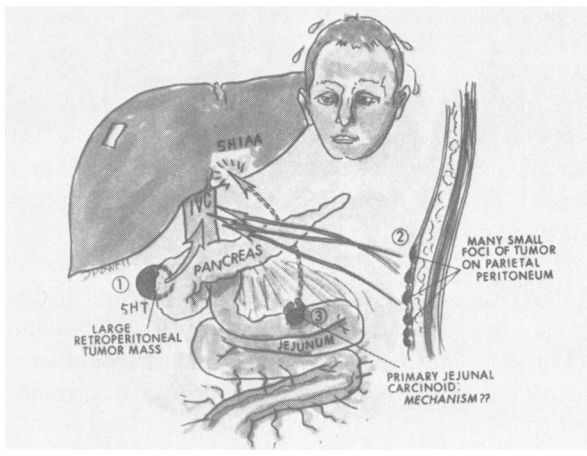

FIG. 6. Mechanism of carcinoid syndrome in three patients in this report. In patients 1 and 2, blood from the carcinoid tumor probably drained directly into the systemic rather than the portal circulation. In patient 3, blood from the carcinoid tumor should have drained directly in the portal circulation. Thus the mechanism of her carcinoid syndrome is not yet clear.

Serotonin is thought to be inactivated by monoamine oxidase during its passage through the liver. Carcinoid tumors secrete other vasoactive materials, such as histamine, kallikrein, prostaglandins, and substance P.[1] Urinary histamine excretion was measured and found to be normal in patients 1 and 3, but elevated in patient 2. Administration of the histamine antagonists did not prevent the flushing episodes of patient 2, suggesting that this amine is not responsible for his carcinoid syndrome. It is not possible at this time to make statements on the possible role of kallikrein, prostaglandins, and substance P in carcinoid syndrome from gastrointestinal carcinoids in the absence of hepatic metastasis.

Serotonin is concentrated and stored in the dense granules of the platelets.[1] Patient 2, who was receiving reserpine for hypertension, had a normal platelet serotonin concentration. Reserpine is known to impair the ability of the platelets to concentrate serotonin.[12] It is of interest that, despite the administration of reserpine, the patient's carcinoid tumor was able to store a large amount of serotonin. It is known that reserpine can decrease serotonin in the platelets and brain of rabbits without altering the serotonin in the gastrointestinal tract of the animals.[13] Carcinoid tumors may also be resistant to serotonin depletion by reserpine. It is clear that if one used platelet measurements to screen for serotonin-producing carcinoid tumors in patients receiving reserpine, one would not detect these tumors. The physician should either have the patient discontinue reserpine for two weeks or use urinary 5-HIAA excretion to detect serotonin overproduction.

It is of interest that although the 5-HIAA excretion of patient 3 had fallen to normal by the third postoperative day, her platelet serotonin concentration remained elevated (Fig. 5). This probably occurred because the elevated platelet serotonin persists during the life span of the platelets. After the serotonin rich platelets leave the circulation, the platelet concentration of serotonin returns to the normal range.

During the past 11 years, one of the authors (JMF) has participated in the care of 52 patients with serotonin-producing carcinoid tumors and the carcinoid syndrome. The primary tumors of the patients were bronchus (5), stomach (2), pancreas (1), jejunum (3), ileum (32), caecum (3), and unknown origin (6). One patient had the carcinoid syndrome in the absence of proven hepatic metastasis. Although his CT scan re-

mained normal, he did not undergo arteriogram or a second laparotomy. Thus, the present three patients represent only 6% of the patients with the carcinoid syndrome who do not have apparent hepatic metastasis. Patients 1 and 2 were not curable, due to extrahepatic metastasis. A more prolonged period of observation will be required to be certain that patient 3 is now free of carcinoid tumor. It is suggested that each patient with the carcinoid syndrome be evaluated with CT and ^{99m}Tc pertechnetate liver scans. If these studies show no liver involvement, one might consider hepatic arteriogram or laparotomy to determine if the patient's tumor might be totally resectable.

Acknowledgments

Supported by the Veterans Administration, The Caroline H. Stewart Memorial Carcinoid Fund and a grant from the American Cancer Society. The authors acknowledge the technical assistance of Ms. Judith Davis and the secretarial assistance of Ms. Vee Bunch.

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