Carcinoid Heart Disease with Severe Hypoxia due to Interatrial Shunt through Patent Foramen Ovale

Carcinoid heart disease occurs in approximately half of patients who have carcinoid syndrome and is the leading cause of death among these patients. It is typically manifest as right-sided valvular lesions, usually tricuspid insufficiency and pulmonary valve stenosis. This case report describes the unusual presentation of a patient with carcinoid heart disease and a large right-to-left shunt through a patent foramen ovale. (Tex Heart Inst J 1997;24:125-8)

A 43-year-old man with metastatic carcinoid syndrome was transferred to the Johns Hopkins Hospital for evaluation of hypoxia and tricuspid and pulmonary valve disease. Two years before admission, the patient had experienced facial flushing, diaphoresis, and diarrhea. Carcinoid syndrome was diagnosed and H2-blockers and somatostatin were prescribed. Six months later, he developed malaise, lethargy, and pedal edema; he became dyspneic on exertion. He also experienced nagging right upper-quadrant abdominal pain on deep inspiration and had a productive morning cough. There was no history of cigarette smoking, lung disease, or occupational exposure.

Seven days before admission, the patient’s symptoms worsened dramatically. Dyspnea and syncope were accompanied by nausea, vomiting, and right upper-quadrant pain. He was admitted to another hospital, at which time he was cyanotic and delirious. An echocardiogram showed tricuspid insufficiency, pulmonary insufficiency, right ventricular dilatation, aortic valve thickening, and aortic insufficiency. A bubble contrast echocardiogram revealed a large right-to-left interatrial shunt.

The patient was transferred to the Johns Hopkins Hospital for cardiac surgical intervention. On admission, his vital signs were unremarkable. Intense facial flushing was noted. Jugular venous distention rose 12 cm above the sternal notch. There was a prominent sternal lift, intensified 1st heart sound, 3rd and 4th heart sounds, and a 2/6 holosystolic murmur at the left sternal border radiating to the right sternal border, consistent with tricuspid insufficiency. Distal pulses were poor. The liver was tender, firm, and pulsatile with a 20-cm span. The spleen was not palpable. The extremities had 2+ pitting edema to the level of the knees. Neurologic examination revealed no focal deficits.

A sample of arterial blood yielded a pH of 7.34, a pO2 of 75 mmHg, and a pCO2 of 40 mmHg while the patient was breathing 100% oxygen. Serum electrolytes
were normal. Aspartate aminotransferase was 44 U/L and alanine aminotransferase was 27 U/L. There was a leukocytosis of $17.5 \times 10^9/L$ with a leftward shift. Because of severe right upper-quadrant pain, a peritoneal tap was performed; the white cell count of the aspirate was $4.4 \times 10^9/L$ with 87% polymorphonuclear leukocytes. Empiric antibiotic therapy (vancomycin, cefotaxime, and metronidazole) was begun for presumed sepsis. An abdominal computed tomographic scan showed liver metastases, ascites, and no abscess. Cerebrospinal fluid was clear.

Echocardiography revealed severe tricuspid insufficiency, pulmonary insufficiency, paradoxic septal motion, right ventricular dilatation, right-to-left interatrial shunt, and fair-to-poor left ventricular function. By Doppler echocardiographic study, the mean pulmonary valve pressure gradient was found to be 35 mmHg and the mean aortic valve pressure gradient was 20 mmHg. Cardiac catheterization indicated severe tricuspid insufficiency and a large shunt across a patent foramen ovale. The coronary arteries were free of disease.

The patient was referred for urgent surgical intervention because of hypoxia and low cardiac output. He underwent tricuspid and pulmonary valve replacements with porcine bioprostheses. A 1.0-cm patent foramen ovale was closed. Other findings included marked right ventricular hypertrophy, an “Ebsteinoid” scarred tricuspid valve with severe insufficiency, mild-to-moderate pulmonary valve stenosis, and an unsuspected anterior right ventricular wall infarction, probably due to a coronary embolus visible in a large anterior right ventricular marginal coronary artery. After the valve replacements, the patient could not be weaned from cardiopulmonary bypass due to right heart failure. Left ventricular function was satisfactory. The aortic valve was inspected, in order to exclude the presence of aortic stenosis, during a 2nd brief period of cross-clamping. No significant stenosis was seen, but involvement of the valve by the carcinoid process was noted. An intraventricular balloon pump was placed via the right groin, and the patient was eventually weaned from cardiopulmonary bypass with high-dose inotropic support (epinephrine, dobutamine, and isoproterenol). Because of massive cardiac and pulmonary edema, the sternum and subcutaneous tissues could not be closed. The wound was packed and plans were made for delayed primary closure.

On the 1st postoperative day, the patient remained mechanically ventilated on 100% oxygen but was partially weaned from inotropic support. The intra-aortic balloon pump was removed on the 2nd postoperative day. The patient was 20 kg above preoperative weight, so slow continuous ultra-filtration was begun for fluid removal. By the 4th postoperative day, the patient was improving and was near extubation. Later that day, he suddenly developed a left tension pneumothorax, which herniated the heart through the sternal wound resulting in cardiac arrest. The pneumothorax was promptly decompressed with a left chest catheter and cardiopulmonary resuscitation was begun, but neither a cardiac rhythm nor blood pressure could be reestablished. Permission for postmortem examination was denied by the family.

Discussion

Carcinoid tumors are rare, slow-growing, neuroendocrine neoplasms typically arising from argentaffin (Kulchitsky) cells of the gastrointestinal tract.\(^5\)\(^{10}\) Though capable of distant metastases, they have a favorable prognosis if discovered early.\(^8\) Carcinoid tumors never arise primarily in the heart, though infrequently they can metastasize to the heart or pericardium.

Approximately 4% of patients with carcinoid tumors develop carcinoid syndrome.\(^2\)\(^8\)\(^{11-14}\) The carcinoid tumor is manifest as episodic flushing of the skin, telangiectasia, diarrhea, cardiac valvular lesions, and bronchospasm.\(^1\)\(^2\)\(^4\)\(^9\)\(^{11-15}\) Characteristic facial flushing and a precordial systolic murmur of tricuspid insufficiency are often the presenting signs. The carcinoid syndrome is usually indicative of hepatic metastases whose products are not inactivated by the liver.

Carcinoid heart disease occurs as a late complication in approximately half of patients with the carcinoid syndrome.\(^1\)\(^5\)\(^{16-17}\) The most common cardiac manifestation is valvular heart disease.\(^18\)\(^{19}\) The valvular lesions lead to cardiac failure, which is the most common cause of death in patients with carcinoid syndrome.\(^12\)\(^{14}\)\(^{20-22}\)

The association of right-sided valvular heart lesions with carcinoid tumors was 1st reported in 1952.\(^23\) These lesions are typically tricuspid insufficiency and pulmonary valve stenosis.\(^5\)\(^6\)\(^{16}\)\(^{17}\)\(^{20}\)\(^{24}\) Pulmonary valve stenosis tends to increase the degree of tricuspid insufficiency and exacerbate right heart failure.\(^18\)

Left-sided lesions are rare and have been reported mainly in patients with longstanding carcinoid syndrome.\(^15\)\(^{22}\) It has been postulated that carcinoid syndrome results from release of 5-hydroxytryptamine (5-HIAA) or serotonin from the carcinoid cell.\(^11\)\(^{13}\)\(^{21}\)\(^{22}\) Serotonin is metabolized to 5-HIAA in the vascular endothelium of the lung and liver.\(^2\) The sparing of the left heart may be due to clearance by the monoamine oxidase (MAO) system in lung parenchyma.\(^17\)\(^{22}\)

The usual treatment for symptomatic carcinoid syndrome is surgical removal of as much tumor as
possible.\textsuperscript{25,27} Patients with metastatic carcinoid tumors may survive 12 to 13 years after resection of the primary lesion;\textsuperscript{14} therefore, surgical resection should be considered in all patients with carcinoid tumors, with or without carcinoid syndrome. Cardiac surgical intervention for carcinoid heart disease is usually indicated for symptomatic tricuspid and pulmonary valve disease. Such intervention can substantially improve the symptoms of right heart failure, and will most likely improve survival. The 1st patient with carcinoid heart disease treated successfully by surgery underwent tricuspid valve replacement and pulmonary valvotomy with single pulmonary valve cusp excision.\textsuperscript{6} In a review by Ross and Roberts\textsuperscript{28} of 15 surgically treated patients, the operative mortality rate was 20\%, but there were several long-term survivors (greater than 2 years); 1 patient lived more than 11 years after pulmonary and tricuspid valve replacement.\textsuperscript{28} At operation, valve replacement rather than repair is generally necessary. Bioprosthetic valves are usually preferred over mechanical valves, but accelerated degeneration of the bioprosthetic valves has been observed.\textsuperscript{28}

The case reported herein is believed to be the 4th case in the literature of an atrial-level shunt producing hypoxia in a patient with carcinoid heart disease. In 1956, McKusick\textsuperscript{29} reported the 1st case; his patient presented with dyspnea on exertion and cyanosis. At autopsy, a patent foramen ovale was found, with carcinoid involvement of the pulmonary, tricuspid, mitral, and aortic valves in decreasing order of severity. In 1958, Fischer and Lindenberg\textsuperscript{29} described a similar case in which a slit-like foramen ovale was diagnosed at autopsy. The 1st surgical closure of a patent foramen ovale with tricuspid and pulmonary valve replacement in a patient with carcinoid heart disease\textsuperscript{24} was performed in 1988. Stewart and co-authors\textsuperscript{30} described a case of cyanosis attributed to a right-to-left shunt. They speculated that the cause might be microscopic pulmonary fistulae, but did not consider the possibility of a patent foramen ovale.\textsuperscript{31}

The reported case is remarkable for several features. First, it demonstrates the interaction of severe tricuspid insufficiency, pulmonary valve stenosis, and a patent foramen ovale to produce hypoxia. Elevated right atrial pressure due to tricuspid insufficiency and pulmonary valve stenosis presumably stretched the foramen ovale and led to the right-to-left shunt. The shunt may have been increased further by poor right atrial compliance secondary to carcinoid involvement. Second, the case demonstrates left heart involvement by the carcinoid process, presumably because blood containing tumor products had direct access to the left side of the heart via the patent foramen ovale. Third, there was a paradoxical coronary embolus, which caused right ventricular infarction and may have further increased the shunt by reducing right ventricular compliance. The embolus might have been a dislodged tumor particle or a venous clot that entered the systemic arterial circulation via the foramen ovale. Regrettably, a postmortem examination was not performed, so the presence of embolus could not be demonstrated conclusively.

The authors recommend that an atrial-level shunt be considered in hypoxic patients with the carcinoid syndrome and suggest that surgical closure is indicated in such cases.

**Acknowledgment**

The authors wish to acknowledge the assistance of Mrs. Lori Garrison in the preparation of this manuscript.

**References**

13. Lundin I, Norheim L, Landelius J, Oberg K, Theodorsson-Noorheim E. Carcinoid heart disease: relationship of circulat-


128 Carcinoid Heart Disease with Hypoxia due to Interatrial Shunt Volume 24, Number 2, 1997