FUNCTIONING MALIGNANT CARCINOID: A REVIEW OF NINE CASES

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THE malignant appearance but benign course of tumors arising from the argentaffin cells of the small intestine was emphasized by Oberndorfer[1] in 1907 when he named these tumors 'carcinoids.'

In 1954, Thorsen and associates[2] described a syndrome that consisted of malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis. They reported 16 cases that partially or fully demonstrated these criteria and concluded that, "In view of the rarity of both pulmonary stenosis and malignant carcinoid of the small intestine . . . the fact that several cases have been reported to suffer from both conditions simultaneously makes this rather unsuspected combination a clinical and pathologic syndrome . . . ".

In the 10 years immediately following the published report of the carcinoid syndrome, nine patients with functioning malignant carcinoid have been treated and studied at the Cleveland Clinic. One patient with a malignant adenoma of the bronchus and functioning metastases to the liver was previously reported[3] as having a variant of the typical carcinoid syndrome. A review of the case material illustrates the protean manifestations of the syndrome, and the validity of Sjoerdsma and Melmon's[4] recent suggestion that the term *carcinoid spectrum* be used to designate functioning and disseminated malignant carcinoids.

Clinical Material

The clinical data of the nine patients examined at the Cleveland Clinic in the years 1955 through 1964 are summarized in *Table 1*.

Age and sex. The ages of the patients ranged from 11 to 65 years, the mean age being 47 and the median age 53 years. The 11-year-old patient is believed to be the youngest person known to have a functioning malignant carcinoid; this case has been previously reported.[5] The series comprised six males and three females.

Site of primary carcinoid. The most common site of the primary tumor (six patients) was in the distal ileum (*Fig. 1*). One patient, in whom the carcinoid arose from the gastric antrum, did not show the vivid, patchy-red flush described as typical of a metastatic gastric carcinoid.[6]

Two additional patients have been examined who are not included in this series. In each of these patients a carcinoid was found incidentally at laparotomy for

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Table 1.—*Data of nine patients who had functioning malignant carcinoid, Cleveland Clinic series, 1955-1964*

Patient no.	Sex	Age at time of diagnosis, yr.	Site of primary carcinoid	Metastasis to		Heart lesions, type	5-hydroxyindoleacetic acid in urine, mg./24 hr.	Signs and symptoms			Status after treatment	Duration of survival or of follow-up
				Liver	Other areas			Diarrhea	'Asthmatic' attacks	Flushes		
1	M	11	Ileum	Yes	Omentum	None	32	No	No	No	Asymptomatic	12 mo.
2	M	28	Stomach	Yes	Omentum	None	'Positive'	Yes	Yes	Yes	(Living?)	Lost, since 1957
3	M	45	Bronchus	Yes	Hilar nodes	Murmur	107	Yes	No	Yes	Dead	21 mo.
4	M	53	Ileum	Yes	Omentum	None	66	No	No	No	Asymptomatic	9 yr.
5	M	53	Ileum	Yes	Not known	None	56	Yes	Yes	Yes	Dead	5 yr.
6	F	51	Ileum	Yes	Omentum, ovary	None	206	Yes	No	Yes	Dead	5 mo.
7	F	61	Ileum	Yes	Retroperitoneal fibrosis	Tricuspid valve, pulmonic valve	35	Yes	No	Plethoric face	Dead	14 days
8	F	57	Ileum	Yes	Omentum	None	'Positive'	Yes	Yes	Yes	Dead	10 yr.
9	M	65	Not determined	Yes	Not determined	None	367.5	Yes	No	Plethoric face	Dead	1 mo.

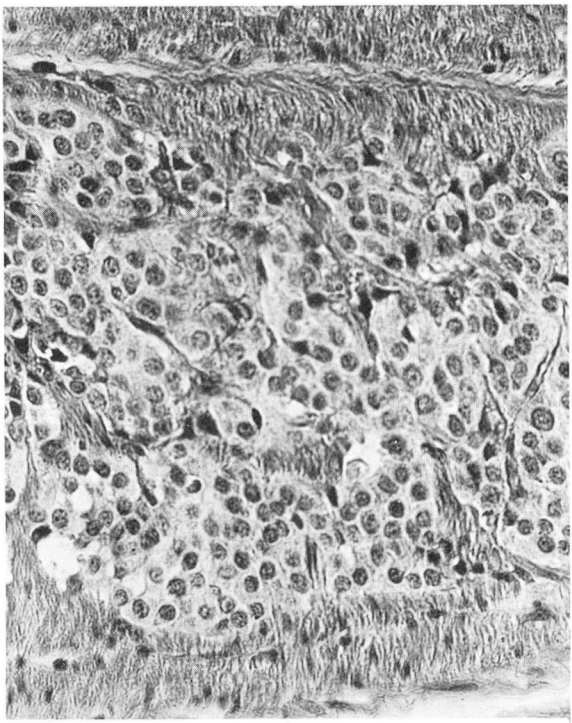

Fig. 1. Photomicrograph of a malignant carcinoid (functioning) in intestinal wall (distal ileum). Hematoxylin-eosin stain; magnification X380.

another condition and resected. One lesion was in the ileum and the other in the gastric antrum; neither lesion had metastasized. These two patients had never had symptoms of the carcinoid syndrome.

Metastases. Each patient included in this series had hepatic metastases; in six patients, metastases were proved at laparotomy, in two at postmortem examination, and in one patient by needle biopsy of the liver. In addition to hepatic metastases there was extensive local spread of all tumors. One tumor was believed responsible for diffuse retroperitoneal fibrosis that led to obstructive uropathy and death. One primary tumor in the ileum was metastatic also to the ovary.

Right heart lesions. Two of the patients had right-sided heart murmurs; at autopsy the lesion in one patient was found to be a nodular and septic valvulitis of the pulmonary valve (*Fig. 2*). This lesion is similar to those described by Roberts and Sjoerdsma[7] as pathognomic carcinoid heart lesions, seen most commonly on the tricuspid and pulmonic valves.

Symptoms. Seven of the nine patients experienced symptoms of a functioning carcinoid; the most common of which was diarrhea. In several patients, the diarrhea was caused by partial intestinal obstruction and by circulating serotonin.

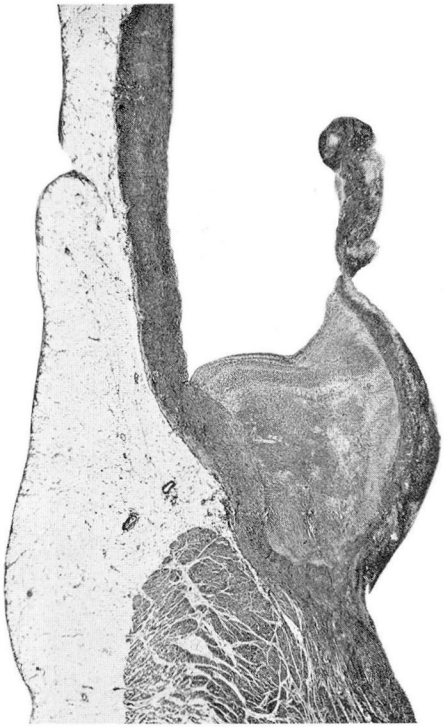

Fig. 2. Photomicrograph of a section of pulmonic valve cusp, demonstrating typical fibrotic lesion of carcinoid heart disease as well as the vegetations of acute bacterial valvulitis, Masson stain; magnification X10.

Episodes of bronchoconstriction, simulating attacks of asthma, were experienced by three patients. In each case the episode was heralded by peripheral vasodilation and a feeling of flushing warmth throughout the body. Such flushes were experienced by five of the nine patients several times daily. Two patients had a plethoric appearance constantly, without superimposed flushing.

The metabolic breakdown product of serotonin, 5-hydroxyindoleacetic acid, was excreted in the urine of all nine patients. In seven of these patients the 5-hydroxyindoleacetic acid urine levels ranged from 32 mg. to 367.5 mg. per 24 hr. (normal in our laboratory is less than 16 mg. per 24 hr.). In two patients, examined in 1956 and in 1957, respectively, special quantitative values were not determined, but the qualitative tests were positive. The two asymptomatic patients have increased urinary concentrations of 32 and 66 mg. per 24 hr., respectively, at the present time (August 1965). Two symptomatic patients had values of 35 and 56 mg. per 24 hr., respectively, at the time of active symptoms. These low values in symptomatic patients support the thesis put forth by Oates and associates,[8] that in addition to serotonin, the kinin peptides, kalledins and perhaps other substances may be responsible for some symptomatic aspects of the conditions.

Treatment

The therapy undertaken in seven of the nine patients comprised surgical resection of the segment of ileum containing the primary tumor, and the involved mesenteric lymph nodes. In addition, in one patient, a left hepatic lobectomy was performed. Six of the patients received various serotonin antagonists by parenteral administration. The value of these compounds is not apparent from study of this limited group.

Results

Progress reports have been completed for eight of the nine patients. One patient is alive according to the records of the United States Veterans Administration, but has been lost to follow-up since 1957. Two of the nine patients are asymptomatic nine years, and seven months, respectively, after diagnosis and initial treatment of the lesions. In those patients who were symptomatic, mean survival has been 34.9 months (almost three years) from the time of diagnosis. The range of survival has been from 14 days to 10 years. Long survivals, even of patients with metastases in the liver at the time of laparotomy, indicate the slowly growing nature of the malignant functioning carcinoid, and emphasize the value of palliative resection of the tumor whenever possible.

Summary

Nine cases of functioning malignant carcinoid representative of the carcinoid spectrum were treated and studied at the Cleveland Clinic during the 10 years since the recognition of the carcinoid syndrome in this country. The protean manifestations of malignant carcinoid tumors are reviewed; and the relatively long-term survival of patients surgically treated, even in the presence of widespread metastases, is noted.

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