Carcinoid heart disease: successful tricuspid valve replacement

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Honey, M. and Paneth, M. (1975). Thorax, 30, 464-469. Carcinoid heart disease: successful tricuspid valve replacement. A woman aged 46 was found to have severe tricuspid valve disease 14 years after the diagnosis of a malignant carcinoid tumour of the ileum and 33 years after the onset of symptoms attributable to the disease. Increasing ascites requiring repeated paracentesis had not responded to chemotherapy including infusion of 5-fluorouracil and vincristine into the coeliac artery. The tricuspid valve was replaced by a Björk-Shiley prosthesis. After operation there was no recurrence of ascites or oedema. She remains well one year and 11 months later. It is suggested that valve replacement surgery should be considered more often in patients with carcinoid heart disease. Hepatomegaly and ascites should not be attributed too readily to advancing malignant disease without careful consideration of the role of right-sided valvar lesions in the production of these signs.

The carcinoid syndrome (Thorson et al., 1954; MacDonald, 1956; Sjoerdsma, Weissbach, and Udenfriend, 1956; Thorson, 1958) occurs in patients with malignant argentaffinoma of the small bowel and hepatic metastases (and occasionally other primary sites), and results from the secretion of 5-hydroxytryptamine (serotonin) and kallikrein by the tumour (Grahame-Smith, 1968). In addition to the hormonal effects (flushing, diarrhoea, oedema, bronchoconstriction) these patients may also show a characteristic deposition of fibrous tissue on the heart valves and endocardium, with resulting pulmonary stenosis, tricuspid stenosis and regurgitation, and occasionally left-sided valve disease (Thorson, 1958; Cosh, Cates, and Pugh, 1959; Roberts and Sjoerdsma, 1964). Though cardiac valve lesions may ultimately lead to the death of the patient (Thorson, 1958; Trell et al., 1973), there have been very few attempts to correct these surgically. We report here the third case of successful valve surgery (tricuspid valve replacement) in the carcinoid syndrome.

CASE REPORT

A married woman aged 32 was referred to the Royal Marsden Hospital in 1959 with a history of flushes since the age of 13, and intermittent colic with watery diarrhoea. Flushes occurred many times a day, spontaneously or provoked by food or alcohol or by cold or emotional stimuli. During mild attacks, which lasted about 10 minutes, there was a widespread carrotty-red flush, sometimes with mauve blotches; more severe attacks were followed by peripheral vasoconstriction with pallor or cyanosis of the extremities. Attacks of diarrhoea preceded by abdominal pain were less frequent. At this time a systolic murmur was heard at the left border of the sternum, but there were no other abnormal signs. An electrocardiogram was normal. Urinary 5-hydroxyindole acetic acid (5-HIAA) was 114 mg in 24 hours (normal 2-8 mg). The free plasma serotonin (Robertson and Andrews, 1961) was 60-75 ng/ml (normal 0-5 ng/ml). Flushes, accompanied by a fall in blood pressure and swelling of the lips, were precipitated by intravenous noradrenaline1.

At laparotomy (Mr. R. W. Raven) there were several yellowish submucous nodules in the ileum (1-5 mm), with one enlarged lymph node in the adjoining mesentery, and multiple small hepatic metastases (up to 1 cm diameter). A 25 cm segment of ileum was resected with adjoining mesentery and lymph node, and a wedge of liver tissue was removed for histological examination. The ileal and hepatic nodules showed islands of poly-

1Case 9 of Robertson, Peart, and Andrews (1962)
gonal cells with lightly staining nuclei and argyrophil granules in the cytoplasm, within a fibrous stroma, the appearances being typical of argentaffin carcinoma (Fig. 1). After operation flushes continued but were less frequent. Urinary 5-HIAA was less but still abnormal (41 mg in 24 hours) one week after operation.

She continued to have typical flushes and occasional bouts of diarrhoea. In 1961 she had a normal pregnancy. In 1962 she received methysergide with doubtful benefit, but otherwise no treatment was given and her condition remained unchanged for a further 10 years. During this time 5-HIAA excretion remained high. A systolic murmur was still audible, but there were no signs of heart failure. Clinical examination and scintiscan showed a normal-sized liver.

In January 1973 she reported abdominal swelling and increasingly frequent attacks of diarrhoea. Flushes continued. Hepatomegaly and ascites were noted. A liver scintigram (4.6 mCi 99mTc colloid) showed an enlarged liver with multiple cold areas consistent with metastases. Urinary 5-HIAA was 29 mg and 35 mg in 24 hours on two occasions. She was then treated by infusion of 5-fluorouracil into the coeliac artery (1 g daily for 3 days) followed by intra-arterial vincristine (2 mg). Despite this treatment, and intraperitoneal mustine (10 mg), ascites recurred repeatedly after abdominal paracentesis. No malignant cells were seen in the ascitic fluid. Swelling of the right leg was attributed to venous thrombosis, but a phlebogram showed no evidence of this. Subsequently, increasing swelling of both legs was treated with diuretics, including frusemide and spironolactone. In June 1973, when aged 46, she was referred for cardiological opinion.

She then complained of increasing breathlessness, rapid palpitation, and swelling of the legs and abdomen. Diarrhoea was effectively controlled with codeine, and flushes were infrequent. There was facial telangiectasia and cyanosis. She was in rapid atrial fibrillation, with a high venous pressure and oedema of the legs. The liver was enlarged and pulsatile and there was ascites. There was clinical evidence of right ventricular hypertrophy and a delayed diastolic murmur in the left fourth intercostal space increased on inspiration. With continued diuretic therapy and digitalization, oedema cleared and ascites became less. The venous pressure remained high with slow 'y' descent.

A chest radiograph showed slight cardiac enlargement with prominence of the right atrium.

FIG. 1. Carcinoid tumour of ileum (Haematoxylin and eosin ×190).
but no pulmonary venous distension. An electrocardiogram showed atrial fibrillation, low voltage QRS complexes in the standard leads, and dominant R in V1, suggesting right ventricular hypertrophy. An echocardiogram showed a large right ventricle and paradoxical septal movement, but no tricuspid echo was identified.

The clinical diagnosis of tricuspid stenosis and regurgitation was confirmed by cardiac catheterization (Table). The right atrial pressure pulse suggested severe tricuspid regurgitation and with simultaneously recorded right ventricular pressure showed a 0-5 kPa (4 mm) tricuspid diastolic mean gradient (Fig. 2). A right atrial cineangiogram showed slow passage of contrast from the right atrium into the right ventricle, which was moderately dilated but contracted well. The inferior portion of the tricuspid valve appeared rigid and the orifice narrowed, with contrast passing only through the upper part of the valve. A 1-3 kPa (10 mm) systolic gradient across the pulmonary valve indicated mild pulmonary valvar stenosis. Arterial desaturation suggested right-to-left shunting through a patent foramen ovale, though this was not crossed by the catheter.

The demonstration of organic tricuspid valve disease accounted for the development of clinical signs of right heart failure. Though hepatomegaly and ascites could be attributed to malignant metastasis, the failure of the ascites to respond to intensive cytotoxic drug therapy suggested that these features were probably secondary to carcinoid heart disease. Tricuspid valve replacement was therefore advised.

At operation in July 1973, the right atrium was found to be tense but not enlarged, and there was a marked diastolic thrill over the right ventricle. The tricuspid valve was grossly abnormal, with thickened leaflets, virtually absent chordae, and commissural fusion. The valve was excised and replaced by a 31 mm Björk-Shiley prosthesis. A patent foramen ovale was closed.

The histological appearances of the excised valve cusps and papillary muscles were typical of the carcinoid syndrome (Fig. 3). The cusps were thickened by the deposition of a relatively acellular collagen deposit with preservation of normal cusp architecture; mast cells were seen in the papillary muscle but not in the cusps. There was no endocardial thickening over the muscle.

| TABLE |
| CARDIAC CATHETERIZATION DATA |
| Site | Pressure (mmHg) | Oxygen Saturation (per cent) |
| Right atrium | 17 | 5 Z 7 mean 10 |
| Right ventricle | 27/0-5 |
| Pulmonary artery | 19/10 mean 14 |
| Pulmonary artery wedge | 27/0-5 mean 6 |
| Femoral artery | 120/85 |

Tricuspid diastolic mean gradient 4 mmHg
Cardiac index 1.9 litres/min per sq m
Right-to-left shunt 0.6 litres/min per sq m (32%)

1Mid-thorax reference level; 1 mmHg = 0.133 kPa.
2Assumed basal oxygen uptake.
3Assumed pulmonary venous saturation (96%).

FIG. 2. Simultaneous recording of pressure in right atrium and right ventricle.
Following tricuspid valve replacement, right heart failure required further intensive treatment with frusemide and amiloride, but within two weeks of operation the venous pressure was normal and all oedema had disappeared. It was later possible to reduce the dosage of frusemide and eventually discontinue all diuretics without recurrence of venous pressure elevation, oedema, or ascites. The liver was no longer enlarged. In addition to the prosthetic valve sounds, a pulmonary ejection systolic murmur (grade 2/6) was still present. Postoperative electrocardiograms show right bundle-branch block. Dipyridamole (Persantin) was given for its effect in inhibiting platelet deposition and so reducing the risk of thromboembolic complications of valve replacement by prosthesis. Sinus rhythm was restored by DC countershock. Mild flushes still occur almost every day, but severe flushes are infrequent. Variable mild diarrhoea is controlled with codeine. Urinary 5-HIAA (March 1974) was 55 mg in 24 hours.

**DISCUSSION**

Patients with malignant carcinoid tumours and liver metastasis may survive for many years after the appearance of the first signs of the disease (Thorson, 1958; Trell et al., 1973). In addition to the hormonal effects of increased circulating serotonin, these patients may also develop signs of tricuspid and pulmonary valve disease which may be the cause of death. The rarity of the disease and the long survival of patients may account for the paucity of information about the cause of death. Furthermore, the cause of death may not be apparent even in published reports. Thorson (1958) reviewed 12 cases of his own and 67 from the literature, of whom 56 had died. Information was available about the cause of death in 48, though details were often vague. He commented on the difficulty in distinguishing cachexia due to heart failure from that of metastatic liver disease. It appeared that heart failure was a contributory cause of death in 27 and the major cause in 16. Trell et al. (1973) also stressed the importance of cardiac lesions as a cause of death in a review of 11 cases of carcinoid heart disease. Roberts (1967) observed that in his series the total duration of illness from onset of symptoms to death was unaffected by the presence of carcinoid heart disease. This surprising observation probably reflects the tendency for cardiac lesions

**FIG. 3.** Tricuspid valve (Elastic—Van Gieson X240), showing relatively acellular collagenous deposit (right) on tricuspid leaflet (left).
to develop in patients whose malignant disease is of longer duration and more slowly progressive.

There have been only three published reports of attempted valve replacement, two successful (Arroyo et al., 1966; Carpena et al., 1973) and one unsuccessful (Wright and Mulder, 1963). Arroyo et al. (1966) replaced the tricuspid valve by a Starr-Edwards prosthesis and performed a pulmonary valvotomy in May 1965, and the patient survived for over six years (Carpena et al., 1973). Carpena et al. (1973) also reported pulmonary valvotomy and tricuspid valve replacement (with Kay-Shiley disc valve), the patient remaining well at the time of the report one year after operation in January 1972.

Our patient illustrates well the features of this disease. It seems likely that this has been present for over 30 years, and hepatic and lymph node metastases were observed at laparotomy 14 years before valve replacement; there were multiple primary ileal tumours (MacDonald, 1956; Moertel et al., 1961). Though the presence of a cardiac murmur at that time suggested that a valve lesion was already present, she did not develop any further manifestations of carcinoid heart disease for 13 years. The unusually protracted course may be related to the extent of the fibrous tissue proliferation noted on histological examination. The appearance of the excised tricuspid valve was also typical (Roberts and Sjoerdsma, 1964): the observed changes had resulted in combined stenosis and regurgitation, and there was also clinical and haemodynamic evidence of mild pulmonary valve stenosis. Though there is still evidence of hepatic metastasis, as shown by liver scintigram and increased excretion of the serotonin metabolite 5-HIAA, there has been little evidence of progression of the malignant process and the patient’s present state following tricuspid valve replacement is certainly no worse than it has been at any time since the original bowel resection in 1959. Before operation it was not possible to be certain that liver enlargement and ascites were not directly due to the malignant process, though examination of the peritoneal fluid had shown no malignant cells. Her subsequent progress shows that her clinical deterioration was entirely attributable to the cardiac effects of carcinoid disease, aggravated by the onset of atrial fibrillation. There has been no clinical or haemodynamic evidence of involvement of left-sided valves despite patency of the foramen ovale.

The long-term prognosis remains uncertain: there is already evidence of pulmonary valve involvement, as yet trivial; but the condition may progress, demanding further surgical intervention. The genesis of the cardiac manifestations of carcinoid disease is still obscure but, in the presence of increased circulating serotonin levels, it is possible that fibrin and platelet deposition induced by serotonin, bradykinin or other circulating substance may lead to dysfunction of the prosthetic valve despite the administration of dipyridamole. Finally, her death may result from progression of the malignant process. Nevertheless it is clearly well worthwhile to treat the valve lesions on their own merits in such patients. It is surprising that this has not been attempted more often; this suggests a lack of sufficient awareness of the effects of the cardiac manifestations of carcinoid disease on its natural history.

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