Case Report

CARCINOID DISEASE: AN EVER-WIDENING SPECTRUM

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The ever-widening spectrum of carcinoid disease necessitates a radical change in our original thoughts about this disorder. It is now widely recognized that tumours producing this syndrome may arise from varying foci (Calvert, Karlsh, Wells, 1963) and recently an attempt has been made (Williams and Sandler, 1963) to classify them under various headings according to the site of origin. An embryological basis was used by these authors to group the various carcinoids according to associated histological and biochemical characteristics. They are careful to point out that there is no evidence that this distinction is of fundamental importance and, as our knowledge increases, it seems obvious that we shall constantly have to reappraise the situation.

Peart, Porter, Robertson, Sandler and Baldock (1963) have described the carcinoid syndrome due to a pancreatic duct neoplasm secreting 5-hydroxytryptophan (5-HTP) and 5-hydroxytryptamine (5-HT). They demonstrate that during the terminal phase of their patient's illness the excretion of indole derivatives decreased and the free plasma-5-HT fell below detectable levels. However, post-mortem tissue from a secondary deposit in the liver was found to contain (per g. wet weight) 22 µg. histamine, 40 µg. 5-HTP and 32 µg. 5-HT.

The following case of a pancreatic neoplasm is presented because it contains many features of clinical and biochemical interest within this context. If it be agreed that the diagnosis of carcinoid syndrome is substantiated by the data presented, then the spectrum of this disease appears to need widening still further.

Case Report

The patient, a housewife aged 48 years, first came under medical care in early 1961. At that time she had sustained a left hemiparesis of sudden onset without loss of consciousness. Her blood-pressure was found to be 170/105 mm. Hg. without cardiac enlargement. She made a good recovery after three weeks in hospital, although left with a minimal hemiparesis on examination. There was no residual disability.

Following discharge it was noted that the blood-pressure had risen to 200/130 mm. Hg. Four months after the onset of her illness she first complained of diarrhea to her medical practitioner, although on direct questioning she admitted that this symptom had first appeared whilst an in-patient with her neurological disability. She had withheld the information, but with onset of these bowel symptoms had been passing four to eight pale offensive motions daily. In spite of large doses of mecamylamine for the attempted control of her blood-pressure, the diarrhea persisted and eight months after her initial hospital admission she had lost 1 stone (6.38 kg.) in weight.

At this juncture her diarrhea was investigated. The stools were found to be pale, with a fecal fat excretion of 16.6 g./24 hours. A barium meal and follow-through showed some degree of clumping in the ileum. It was also noted on the barium meal that the stomach appeared to be displaced to the right.

No satisfactory explanation for this was found. An IVP was normal. Despite a fat-free diet she continued to lose weight and 12 months after the onset of symptoms had lost 20 lb. (9 kg.). Re-admission to hospital at this time failed to produce any improvement. She continued to have mild diarrhea (bowel open two to four times daily) and the substitution of a gluten-free diet was unavailing. In view of the steady deterioration, she was transferred to the Westminster Hospital for further study in April 1962.

Further questioning at this time revealed several interesting facts. Since the onset of her diarrhea she had suffered from extreme abdominal borborygmi. These had been so pronounced that she had been forced to give up Sunday worship because of them. The noise that rumbled through the quiet of her village church had been the source of such personal embarrassment that her religious beliefs had been subordinated to her physical disability. Flushing attacks and dyspnnea on effort had been prominent for some considerable time. The latter symptom had been present for at least three years and was becoming progressively worse. Recently she had been unable to perform everyday tasks without stopping for breath at short intervals. She denied wheezing or attacks suggestive of asthma.

Neither she nor her family was aware of any change in her mental status. The past and family history were irrelevant.

On examination she looked ill with evidence of wasting and dehydration. She was a peculiar cyanotic colour with dilated venules on the face and neck. There was dyspnnea on the slightest exertion. Superficial mobile lymph nodes could be palpated in all fields, including the left supraclavicular region. BP 140/80 mm. Hg.

The classical systolic murmur of tricuspid incompetence...
was heard at the lower end of the sternum, with an associated early blowing diastolic murmur heard in the second left interspace, which was thought to be compatible with pulmonary incompetence. The pulmonary second sound was normally split. In the abdomen there was a vague mass palpable in the left hypochondrium, the exact nature of which was not apparent on clinical grounds. Examination of the central nervous system confirmed the presence of a mild residual hemiparesis. There was generalized hirsutism with a masculine distribution of pubic hair, but the patient was confident that this had always been present and that no change had occurred during the course of her present illness. At this stage a diagnosis of carcinoid disease was postulated, on the basis of cyanosis, flushing attacks, diarrhoea and the cardiac lesions.

Investigations

X-ray of the chest showed grade 2 cardiac enlargement, due mainly to a large right atrium and dilated ascending aorta (Fig. 1). A barium enema showed a sluggish flow of the barium with marked dilatation of the rectum and sigmoid colon. A volvulus of a loop of the sigmoid colon was demonstrated. After evacuation the volvulus appeared to have untwisted itself and the gaseous distension had disappeared. The steatorrhoea was confirmed with a faecal fat excretion in five days of 174 g. Radio-active fat studies showed 33.5% of the radiotriolein to have been unabsorbed and 8.3% of the radio-oleic acid. These figures suggested a pancreatic element to the steatorrhoea. Faecal trypsin was estimated on two occasions and found to be 0 units and 80 units respectively. The FIGLU test was negative, serum B12 270 µg./ml, serum calcium 9.4 mg./100 ml and phosphate 3.2 mg./100 ml. Alkaline phosphatase 48 K.A. units. Remainder of the liver function tests were normal. A glucose tolerance test showed figures of 66, 120, 132 and 84 mg./100 ml over two and a half hours. The urine was negative for glucose throughout, but revealed an unidentified reducing substance when tested with Benedict's reagent. Urea and electrolytes were within normal limits with the exception of a low

FIG. 1.—Chest X-ray showing cardiac enlargement due mainly to a right atrium and dilated ascending aorta.

FIG. 2.—Pancreatic tumour × 50. H. and E. Showing carcinoma with a cylindromatous pattern and strands of cells linked in a network surrounding thick cylinders of hyalinized collagen.

FIG. 3.—Lung × 76. H. and E. Intima almost completely occluded by cellular intimal thickening.

FIG. 4.—Lung × 76. H. and E. Pulmonary arterioles completely occluded by cellular intimal thickening.
serum bicarbonate (18.5 mEq/l) compatible with her diarrhoea. The serum proteins were normal. BSR retention was slightly elevated at 20% at 45 minutes, as was the urinary urobilinogen at 1.6 Ehrlich units. No L.E. cells were found in the peripheral blood, latex and Rose-Waaler tests negative. Thryoglobulin-sensitized-tanned-red-cell test negative and Coombs test negative. Spectroscopy failed to demonstrate any abnormal blood pigments. The latent antithyroglobulin test was positive at 1/20. Repeated blood-counts prior to operation were within normal limits. Blood WR and Kahn negative. ECG consistent with RVTH. Chromatography of the urinary aminocids showed a normal pattern. Examination of the urine for 5-hydroxyindole acetic acid (5-HIAA) showed figures of 12.8, 12.1, 8 and 6.4 mg./24 hours on four separate occasions. (Normal: less than 10 mg./24 hours.) The urinary HMMA was normal at 1 mg./24 hours. Estimation of the urinary ketosteroids and hydroxysteroids showed an excretion of 5.0 g. and 3.5 mg./24 hours respectively. Respiratory function tests did not show any evidence of obstructive lung disease. 1 oz. of brandy failed to provoke a flush. The intravenous effect of 0.5 µg. and 1.0 µg. of noradrenaline (Pearl, Porter, Robertson, Sandler, Baldock, 1963) was studied without convincing evidence of a flush being produced. Methoxamine 3 mg. i.v. increased the blood-pressure from 130/100 to 170/110 mm. Hg. On oral administration the diastolic murmur diminished as bradycardia appeared. There was no change in the systolic murmur and during this investigation a definite flush appeared. Amyl nitrate by inhalation caused marked vasodilatation and as tachycardia appeared the systolic murmur became distinctly louder and the diastolic murmur appeared to increase slightly as recovery ensued. An injection of 2 mg. of serotonin i.v. produced definite accentuation of the pulmonary diastolic and tricuspid systolic murmurs accompanied by a facial flush similar to, but less than, her spontaneous attacks. Cardiac catheterisation revealed severe pulmonary hypertension with a P.A. pressure of 95/42 and a mean of 54 mm. Hg. No gradient across either the pulmonary or the tricuspid valves could be demonstrated. There was no evidence of a shunt and the left atrial pressure was normal.

Course

As biochemical evidence was not forthcoming in support of the clinical diagnosis of carcinoid disease, it was decided to perform an exploratory laparotomy, to elucidate the nature of the abdominal mass.

At operation, a large tumour about 4 in. in diameter was found occupying the body of the pancreas and projecting from its infero-anterior aspect. The nake-eyed appearance suggested a cystadenoma and the body and tail of the pancreas were excised together with the spleen.

Post-operatively the patient’s condition remained satisfactory until the eighth day. Massive alimentary haemorrhage then occurred and re-exploration failed to localise a source for this. During the second operation cardiac arrest intervened with subsequent death.

Autopsy

The striking feature was the presence of several large intrahepatic secondaries which were not obvious until the liver was cut across. The remaining pancreas was normal. The heart weighed 500 gm., with dilatation of the right auricle and ventricle. The tricuspid valve ring was 13 cm. and pulmonary valve 9 cm. in circumference. The pulmonary artery showed minimal atherosclerosis only and the cusps of all the valves were completely normal. Remainder of heart normal. Lungs macroscopically normal. Many lymph nodes were obviously affected by tumour. Remainder of the examination was essentially normal with the exception of massive haemorrhage into the distal small gut and colon, for which no obvious source was found.

Both the primary tumour and secondary deposits revealed a similar histological picture (see Fig. 2). It was that of a carcinoma with a cylindromatous pattern. Strands of cells linked in a network surrounding thick cylinders of hyalinized collagen. The cells showed great variation in size, shape and staining character. The cytoplasm was opaque and eosinophilic; very finely granular, but did not contain argentaffin granules. Diaz and Fontanato methods were negative and there was no fluorescence.

Microscopy of the lungs showed an unusual form of proliferative endarteritis affecting quite small arterioles; there was a varying degree of cellular proliferation in these, causing thickening to one side of the vessel and, in some cases, complete occlusion. The elastica in these vessels was increased and the whole appearance was thought to be that of chronic pulmonary hypertension (see Fig. 3 and 4). No tumour cells were found.

The only other histological abnormality found on a widespread organ survey was in the pituitary gland. Here there appeared to be mild hypertrophy of the pars anterior, although the proportion of cell types was unaltered. Examination of the hepatic secondaries (Dr. A. S. Azatoor) failed to demonstrate any evidence of 5-HT or 5-HTP.

Discussion

Clinically this case presents many features of the carcinoid syndrome. The extreme borborygmi, diarrhoea and steatorrhoea are some of the more clinical manifestations of this disease and the flushes and dilated facial venules are further evidence in support of this diagnosis. The clinical signs of tricuspid and pulmonary incompetence led us to suspect that the valves were directly involved in a carcinoid process. Confirmation of this was not obtained by cardiac catheterisation and necropsy revealed severe pulmonary hypertension only. 5-hydroxytryptamine has a powerful vasoconstrictor effect on the pulmonary circulation (Daws and Comroe, 1954; Comroe, van Lingen, Stroud, Roncoroni, 1953) which is usually largely unresponsive to most substances affecting systemic vasculature. 5-HT is an important exception and appears to operate by a direct vasoconstrictor action on the pulmonary vessels. Its effects on systemic blood-pressure are unpredictable (Page, 1957) but our patient’s previous hypertension is of interest in this context. It could conceivably have been mediated by 5-HT produced by the tumour during the initial phase of the disease and the subsequent fall in pressure due either to its known variability of action or to the extreme diarrhoea or to both of these influences.

The histological difficulty in this field has been re-emphasised by Pearl, Porter, Robertson, Sandler, Baldock (1963), and an atypical appearance is by no means inconsistent with a diagnosis of carcinoid; neither is the absence of intracellular granules nor of silver staining. Both Peart and others (1963) and Dengler (1959) failed to demonstrate these latter features in the cases they present in spite of positive
biochemical evidence. Furthermore, preoccupation with those histological evidence has undoubtedly led to false diagnoses being made to and the clinical picture being ignored (Arnett and Long, 1931; McMullen and Hanson, 1958). There is a pronounced affinity between argentaffin cells and the alpha cells of the pancreatic islets. This has prompted some observers to incriminate 5-HT as a factor producing the diarrhoea associated with non-specific islet-cell tumours. 5-HT increases intestinal motility in the experimental animal (Roche e Silva, Valle and Picarelli, 1963) and man (Hendrix, Atkinson, Clifton and Ingelfinger, 1957). Facial flushing accompanying diarrhoea due to an islet-cell tumour has been reported (Murray, Paton and Pope, 1961) and in this case there was no biochemical evidence of increased 5-HT production and both the flushing and diarrhoea ceased after removal of the neoplasm. Espiner and Beach (1962) came to the conclusion that the tumour itself could not be the source of an increase in blood 5-HT and that this is unlikely to be important in the causation of refractory diarrhoea associated with islet-cell tumours.

In our case no biochemical support was obtained for the clinical diagnosis of carcinoid. The slight increase in 5-hydroxyindole acetic acid (5-HIAA) excretion observed in this case on two occasions is not incompatible with diarrhoeal states in general (Kowlessar, Williams, Law and Sleisinger, 1958) and is therefore of no help in the diagnosis. The persistent excretion of a reducing substance in the urine (other than glucose) raised the possibility of some other metabolite being concerned in the production of this syndrome, although at present this is pure speculation. Analysis of a liver metastasis in Dengler's case (1959) showed a very small quantity of 5-HT only and furthermore the tumour was not found to be a 5-HTP secretor. It was suggested that the tumour was able to convert 5-HTP to 5-HT very readily but had little storage capacity for 5-HT. The urine of this patient contained a gross excess of 5-HIAA. Unfortunately, the free plasma 5-HT was not estimated in our case and histamine studies were not performed.

It might be argued that the clinical diagnosis is at fault in the case described in this paper. This contention can only be supported on the grounds that the patient had two separate diseases, both of them rare, i.e. islet-cell tumour of the pancreas (with secondary steatorrhoea, facial flushing, etc.) and idiopathic pulmonary hypertension. Another solution would be to ascribe the pulmonary hypertension to multiple tumour emboli from the pancreatic tumour to the lungs. However, no histological evidence of tumour emboli was found and this seems unlikely. Absence of hypokalaemia and peptic ulceration are further points against the diagnosis of a typical islet-cell tumour. The possibility must remain that multiple emboli occurred at the time of onset of her dyspnoea only, with subsequent reactive pulmonary hypertension.

The gradation of the indole-secreting tumours from the biochemically inactive hindgut variety, via the histologically typical midgut 5-HT secretors to the foregut type which often show atypical histological appearances and secrete 5-HTP, is of great interest. However, the many facets of the biochemical abnormality in this disease are still not fully understood and the present case appears to be a variant of this disorder in which the classical biochemical changes could not be elicited. Furthermore, Eccleston, Crawford and Ashcroft (1963) have recently described a carcinoid syndrome in which 5-hydroxyindole compounds were not found but the blood and urine contained an excess of tryptamine instead.

Support for this widening concept of what was initially thought to be a clear-cut entity has come from Gowenlock, Platt, Campbell and Wormsley (1964) who describe an oat-cell carcinoma of the bronchus showing several features of the malignant carcinoid syndrome. Also, a kinin peptide has now been implicated in the mechanism underlying the flushes in this disorder (Oates, Melmon, Sjoerdma, Gillespie and Mason, 1964) and an attempt made to correlate the presence of this compound with the various systemic and endothelial manifestations. We believe that there is now sufficient evidence to justify discarding the term hyperserotonism used by so many authors and that the variability of the biochemical findings in the carcinoid syndrome may ultimately be shown to be due to a disorder of metabolic function as yet undetermined.

Summary

A case of pancreatic neoplasm is presented in which the clinical features strongly suggested a carcinoid tumour.

No biochemical evidence was obtained in support of this diagnosis, although the patient's urine contained an unidentified reducing substance.

It is suggested that this case represents a variant of the carcinoid syndrome occupying a position between classical cases of this type on the one hand and islet-cell tumours on the other. Furthermore, that this disorder may ultimately be shown to be due to a disorder of metabolic function as yet undetermined.

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REFERENCES


