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(Accepted 11 November 1987)

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Infective endocarditis complicating tricuspid valve disease in the carcinoid syndrome

A distinct form of heart disease has been described in patients with the carcinoid syndrome. Disease of the cardiac valves occurs as a late complication in about half of the patients.¹ Though abnormal cardiac valves are more susceptible to infection than normal valves, we believe that no cases of infective endocarditis have been reported in association with carcinoid heart disease. We report a case of streptococcal endocarditis affecting a regurgitant and stenotic tricuspid valve in the carcinoid syndrome.

Case history

A 65 year old man presented with a six month history of increasing lassitude, weight loss of 6.4 kg, and intermittent watery diarrhoea. He had a history of prostatectomy for a benignly enlarged prostate and hypertension controlled with bendroflumazide. He denied having had rheumatic fever. He had a ruddy complexion and was feverish. Lymphadenopathy and finger clubbing were absent. The pulse was regular, and blood pressure was 130/85 mm Hg. A harsh mid-systolic murmur was heard, maximal at the apex. The murmur had not been present one year previously. The liver was smooth and non-tender, and its lower edge was palpable two fingerbreadths below the costal margin. There was no splenomegaly. The cardiac murmur changed over several days, becoming maximal at the lower left sternal edge.

The white cell count was $13.8 \times 10^9/l$ with 69% neutrophils. An electrocardiogram showed sinus rhythm with right ventricular hypertrophy, and there was slight prominence of the left border of the heart in a chest x ray film. Serial blood cultures grew *Streptococcus viridans*. Echocardiography showed thickened tricuspid valve leaflets with doming of the septal leaflet compatible with tricuspid stenosis. The right atrium and right ventricle were dilated. Contrast two dimensional echocardiography suggested tricuspid regurgitation. No vegetations were seen on the tricuspid valve. The mitral valve was normal; the pulmonary valve was not visualised. Computed tomography of the abdomen showed an 8×10 cm mass posterolaterally in the right lobe of the liver and multiple smaller low density areas throughout the liver, suggesting metastases. No primary tumour was identified. The urinary 5-hydroxyindole acetic acid excretion was $385 \mu\text{mol}/24 \text{ h}$ (normal $10-45 \mu\text{mol}/24 \text{ h}$), confirming the carcinoid syndrome.

Intravenous benzylpenicillin and gentamicin were given for six weeks. The patient's fever settled rapidly, and his cardiovascular state did not deteriorate. The diarrhoea and facial flushing, characteristic features of the carcinoid syndrome, were treated with oral chlorpheniramine maleate and cimetidine. This produced a prolonged period of normal bowel function, but the flushing, although improved, was incompletely abolished.

Comment

The carcinoid syndrome is a rare cause of acquired cardiac disease, causing predominantly right sided lesions, but valvular heart disease is a frequent finding.^{1,2} Not until 1954, however, was carcinoid heart disease recognised as part of the full clinical and pathological syndrome.² Pathognomonic fibrous plaques cover the pulmonary and tricuspid valves, the endocardium of the right atrium and ventricle, and the intimal surfaces of the vessels draining the right ventricle.³ The commonest valvular lesions are tricuspid regurgitation and stenosis with mild pulmonary stenosis.⁴ The two dimensional echocardiographic features of carcinoid heart disease

are distinctive: the tricuspid valve leaflets appear diffusely thickened, shortened, and stiff without evidence of commissural fusion.⁴

Carcinoid tumours and their metastases grow slowly, and morbidity largely derives from their endocrine effects. Cardiac lesions progress slowly but can result in appreciable morbidity and mortality as congestive cardiac failure develops.¹ Intractable heart failure has been successfully treated by replacement of the tricuspid valve.⁵ We believe that the association of carcinoid heart disease and infective endocarditis has not been documented previously.

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(Accepted 9 November 1987)

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Inhibitory effects of ranitidine on flushing and serum serotonin concentrations in carcinoid syndrome

Dramatic reductions in the frequency, duration, and intensity of flushing attacks in the carcinoid syndrome have been reported during combined treatment with H_1 and H_2 receptor antagonists.^{1,2} We report a patient with a metastatic pancreatic carcinoid tumour in whom administration of ranitidine alone led to cessation of flushing attacks, together with a significant reduction in serum serotonin concentrations.

Case report

A 73 year old man was admitted with flushing, and nausea and epigastric pain after meals. Physical examination showed no abnormality. Laboratory investigations showed that he had non-insulin dependent diabetes as well as an appreciably raised serum concentration of carcinoembryonic antigen and increased neuron specific enolase, serum lactic acid dehydrogenase, and transaminase activities.

Ultrasound scan and computed tomogram of the abdomen and retroperitoneum showed a small nodule in the head of the pancreas 1 cm in diameter and a solitary liver mass 5 cm in diameter. Histological examination of needle biopsy specimens from both lesions showed a metastatic endocrine pancreatic tumour. Serum serotonin concentrations were measured using high performance liquid chromatography and electrochemical techniques as described by Korpi (normal range 0.03 to 0.20 mg/l).³ The concentrations of serotonin in the serum were above normal when he was not having a flushing attack, and repeated measurements varied between 0.80 and 1.0 mg/l . During flushing attacks the concentration rose to $1.30 \mu\text{g/l}$. Because of his nausea and epigastric pain after meals gastroduodenoscopy was carried out and biopsy specimens taken. Histological examination showed non-specific haemorrhagic gastritis and superficial ulceration in the duodenal bulb for which he was given ranitidine 150 mg orally twice daily. This treatment resulted in immediate cessation of his flushing attacks.

We therefore carried out a single blind crossover study of ranitidine 150 mg orally twice daily followed by three days when he received only antacids (the placebo period was limited to three days for ethical reasons) and then a further period when he received ranitidine as before. The frequency of flushing attacks was recorded and serum serotonin concentrations were measured daily.

The results are shown in the figure. There was immediate cessation of flushing during both periods of ranitidine administration and recurrence of symptoms during the placebo period. The serum serotonin concentration fell as soon as he started taking ranitidine. During the placebo period there was a progressive rise to pretreatment values. One tailed unpaired analysis by the Mann-Whitney test showed that serum serotonin concentrations were significantly lower when he was receiving ranitidine than when he was receiving placebo ($p < 0.05$).

Frequency of flushing and blood serotonin concentrations during administration of ranitidine and placebo.

Comment

The cause of flushing attacks in patients with carcinoid syndrome is unknown. In a subgroup of patients (many of whom have metastatic gastric carcinoid tumours) histamine excretion is frequently and consistently raised.^{4,5} Two reports have shown significant reductions in both frequency and duration of flushing attacks during combined treatment with H₁ and H₂ receptor antagonists in two patients with metastatic gastric and ileal carcinoid tumours.^{1,2} In one of these patients,¹ the duration (but not the frequency) of flushing attacks was reduced by cimetidine alone. The authors concluded that in some patients with carcinoid tumours histamine may be the cause of the flushing attacks. In one patient,² however, histamine excretion in the urine was normal during the flushing attacks, whereas the serum serotonin concentration was raised. We know of no data on serum serotonin concentrations during treatment with antihistamines.

In our patient administration of ranitidine alone caused prompt cessation of flushing attacks and a significant reduction in serum serotonin concentrations. This suggests that the beneficial effects of H₂ receptor antagonists seen in some patients with the carcinoid syndrome, may not necessarily be caused by inhibition of the action of histamine but may be partially mediated by a reduction in serum serotonin concentrations.

We thank Dr E Moerman (J F & C Heymans Institute, Ghent, Belgium) for carrying out the measurements of serum serotonin concentrations and Mrs S Goossens for secretarial help.

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(Accepted 9 November 1987)

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Buerger's disease associated with IgA nephropathy: report of two cases

Buerger's disease is a non-atherosclerotic, segmental, inflammatory, occlusive vascular disease of unknown aetiology that affects male smokers under the age of 50. It is characterised by multiple occlusions of small and medium sized arteries and veins in both hands and feet. We describe for the first time two cases of Buerger's disease associated with IgA nephritis. Buerger's disease was diagnosed according to the clinical and angiographic criteria described by Adar,¹ and IgA nephritis by examination of a percutaneous renal biopsy specimen with an immunofluorescence technique.

Case reports

Case 1—A 21 year old Algerian had had severe Buerger's disease for five years and had had several toes amputated (figure). Over six months he developed renal failure with a serum creatinine concentration of 200 µmol/l, nephrotic syndrome, macroscopic haematuria, and high blood pressure. His Buerger's disease worsened. Histological examination of a renal biopsy specimen showed necrotic glomerulonephritis with mesangial deposition of IgA, and endocapillary proliferation with segmental crescents. His serum IgA concentration was 3.2 g/l (normal range 0.8-5.0 g/l). The serum creatinine concentration reached a peak of 500 µmol/l before spontaneous improvement occurred. Six months later his serum creatinine concentration had fallen to 200 µmol/l and his vascular disease had improved with healing of the previous amputation scars.

Case 1: Angiogram showing amputation of toes and multiple distal arterial occlusions.

Case 2—Buerger's disease and IgA glomerulonephritis were diagnosed at the same time in a 21 year old man with a five year history of thrombophlebitis migrans, Raynaud's phenomenon, high blood pressure (180/110 mm Hg), proteinuria (0.50 g/24 hours), and microscopic haematuria but no renal failure. The serum IgA concentration was 1.9 g/l. Seventeen years later his condition was unchanged; he did not have renal failure or the nephrotic syndrome and had not required any amputations. His blood pressure was well controlled with treatment.

Comment

Circulating antibodies to collagen are present in the blood of 45% of patients with Buerger's disease, and limited data have recently been published that suggest that these are accompanied by increased cellular sensitivity to human type I or type III collagen, or both.² An immune