Haemolytic-uraemic syndrome complicating long-term mitomycin C and 5-fluorouracil therapy for gastric carcinoma

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SUMMARY Three cases of acute renal toxicity in patients receiving long-term therapy with mitomycin C and 5-fluorouracil are reported. Two of the patients (1 and 3) are from a multi-centre trial of adjuvant chemotherapy for gastric carcinoma. All three cases showed extensive fibrin deposition in the kidneys and lungs, the appearances of the renal lesions being similar to those seen in the haemolytic-uraemic syndrome. Two of the three cases had received blood transfusions, and attention is drawn to the possibility that mitomycin C may sensitise the kidneys to minor mismatches. With the increasing use of these antimitotic agents, great vigilance should be exercised with regard to renal function and haemolytic status.

Mitomycin C, one of a series of mitomycins, is a comparatively recently introduced antimitotic agent. It had been extracted from *Streptomyces caespitosus* in soil collected in Japan. The structure of mitomycin C is shown in Fig. 1.

The drug effects its cytotoxic action by means of its alkylating properties and in both rhesus monkeys and man, gastrointestinal and bone marrow toxicity have been demonstrated.^{1,2} More recently pulmonary fibrosis,^{3,4} has been recorded, as has renal damage.⁵ In the latter report, the renal changes were those of focal glomerular necrosis, atrophy of tubules and chronic inflammatory cell infiltration. In addition there was glomerular basement membrane thickening and swelling of nuclei, with occasional eosinophilic intranuclear inclusions. These findings were also noted in the subsequent paper which described a rapidly progressive and a more chronic form of renal impairment in patients receiving mitomycin C treatment.⁶

The present paper reports three patients treated with mitomycin C and 5-fluorouracil for gastric malignancy. In each of them there were acute renal changes differing from those described before, with superimposed acute pulmonary damage. The clinical history and management of two of these patients are reported elsewhere;⁷ in this paper we describe the pathological findings in greater detail.

Fig. 1 Chemical structure of mitomycin C

Patients and methods

CASE 1

A 60-year-old woman underwent total gastrectomy for a well differentiated node-positive adenocarcinoma. She was entered into a multicentre adjuvant chemotherapy trial and received treatment every three weeks with mitomycin C and 5-fluorouracil. She remained well until course 15 but then developed progressive macrocytic anaemia associated with a rising serum urea and creatinine.

At this stage chemotherapy was stopped and she was admitted for blood transfusion eight days later. Four units of packed cells were given slowly and she was discharged 48 h later. She was readmitted six days later with persistent right-sided headaches and vomiting. Investigations showed evidence of a disseminated intravascular coagulation state and a ris-

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ing blood urea. She deteriorated with increasing pulmonary oedema and loss of consciousness culminating in death three days after admission.

Necropsy findings

Bilateral serous pleural effusions were present. The lungs were firm and heavy due to extensive acute pulmonary oedema. Confluent haemorrhagic areas were noted in all lobes. The kidneys (combined wt 240 g) were macroscopically normal. The brain (1330 g) was swollen and an intracerebral haemorrhage was present in the left occipital lobe. Multiple "punctate" haemorrhages were seen in the pons, mid-brain, basal ganglia and cerebellar white matter. There was no macroscopic evidence of recurrent tumour.

Histological findings

The lungs showed intra-alveolar proteinaceous oedema fluid. Many alveoli were lined by fibrin "hyaline membranes." There was no evidence of an interstitial fibrosis. The alveolar lining cells were hyperplastic. The smaller pulmonary arteries and arterioles showed fibrocellular intimal thickening. The kidneys showed extensive glomerular lesions of varying ages. Many glomeruli showed recent thrombosis and infarction of the glomerular tufts (Fig. 2). Others showed haemorrhage and partial necrosis of the glomerular tufts with occlusion of the afferent arterioles and capillaries by fibrin thrombi (Fig. 3). A few glomeruli showed older ischaemic lesions, characterised by shrinkage and fibrosis. Some glomeruli showed segmental cellular proliferation and fibrous crescent formation. Marked recent and old ischaemic tubular changes were seen ranging from tubular necrosis with intratubular haemorrhages to tubular loss and interstitial fibrosis. The interlobular arteries showed intimal cellular fibrosis. The appearances were those of a microangiopathic haemolytic anaemia producing fibrin deposition in small vessels leading to a haemolytic-uraemic syndrome. The brain showed multiple old and recent microinfarcts with focal "ball and ring" type haemorrhages around small vessels occluded by fibrin thrombi. A small lymph node from close to the pancreas contained a few metastatic carcinoma cells. Adjacent perineural lymphatics contained mucin-positive carcinoma cells.

CASE 2

A 38-year-old woman underwent a total gastrectomy one year prior to death for an undifferentiated carcinoma. She was treated with mitomycin C and 5-fluorouracil in several courses, as described before (case 1). The final course of these drugs commenced three months prior to her death. A month later she

developed severe anaemia with an increased reticulocyte and schistocyte count in the peripheral blood. There was also mild impairment of renal function. A diagnosis of haemolytic-uraemic syndrome was made and fibrin deposition was demonstrated by immunofluorescence in a skin biopsy. The patient was transfused with washed red cells. Over the final three weeks the patient developed rapidly progressive renal failure, cardiac failure and cerebral oedema.

Necropsy findings

Bilateral straw coloured pleural effusions (each approximately 200 ml.) were present. The lungs were very firm and congested with prominent pleural lymphatics. There was fibrinous pleurisy. Both kidneys (combined wt 210 g) were of normal size but on slicing there was a patchy mottled yellow-white appearance to most of the cortices. No renal papillary necrosis was present. There was no evidence of lymph node enlargement or residual neoplasia. The spleen (170 g) was of normal size. Red marrow was plentiful in the ribs, vertebrae, and femur. The brain showed gyral flattening.

Histological findings

There was extensive fibrin deposition and haemorrhage within respiratory bronchioles and alveolar spaces in the lung. The kidneys showed fibrin deposition and necrosis within glomeruli and fibrin within the walls and lumina of arterioles (including glomerular afferents). Fibrin was also present in the tubular lumina. Some glomeruli showed varying degrees of fibrosis and sclerosis with formation of crescents (Fig. 4). Intranuclear inclusions were not seen. Bone marrow from the vertebrae, ribs and femur was hypocellular but showed a relative excess of erythroid precursor cells. There was no evidence of residual neoplasm in any organ.

CASE 3

A 67-year-old man underwent partial gastrectomy for node-positive carcinoma. He was entered into a palliative chemotherapy trial and treated with mitomycin C and 5-fluorouracil every three weeks. He remained clinically recurrence-free but developed anaemia and progressively rising urea after 20 cycles of treatment. According to protocol regulation, chemotherapy was discontinued but follow-up continued once every three weeks. Four months later his condition appeared to be progressing in spite of cessation of treatment and he was readmitted to hospital for further investigations of his haemolytic anaemia and renal failure. The anaemia and renal failure progressed and he became acutely breathless with signs of acute pulmonary oedema from which he died.

Fig. 2 Glomerulus showing thrombosis and infarction of the tufts. Periodic acid-methenamine silver $\times 400$

Fig. 3 Glomerulus showing occlusion of the afferent arteriole and capillaries by fibrin thrombi. Martius Scarlet Blue $\times 400$

Fig. 4 One glomerulus shows necrosis of the tuft and the other shows shrinkage and sclerosis of the tuft with the formation of a fibrocellular crescent. Haematoxylin and eosin $\times 160$

Fig. 5 Secondary ischaemic tubular damage with loss of tubules and interstitial fibrosis. Haematoxylin and eosin $\times 160$

Fig. 6 Interlobular artery with marked fibrocellular intimal proliferation and oedema. Haematoxylin and eosin $\times 160$

Necropsy findings

Bilateral serous pleural effusions were present. The trachea and main bronchi contained a large amount of frothy haemorrhagic oedema fluid. The lungs were heavy (left lung 980 g, right lung 990 g). There was marked distension of the subpleural lymphatics. On slicing they showed confluent haemorrhagic pulmonary oedema.

The kidneys (combined wt 200 g) were small but equal in size. The capsular surfaces were finely granular. No capsular haemorrhages were seen. On slicing they showed thin cortices. No cortico-medullary haemorrhages were present.

There was no macroscopic evidence of recurrent tumour.

Histological findings

The lungs showed extensive haemorrhagic pulmonary oedema with deposition of intra-alveolar fibrin and desquamation of alveolar lining cells. The alveolar septal capillaries were intensely congested. There was no evidence of interstitial fibrosis. The pulmonary arterioles and small muscular pulmonary arteries showed intimal fibrosis. No fibrinoid necrosis of pulmonary arteries was seen.

Examination of the kidneys revealed varying degrees of glomerular damage. Some glomeruli showed total necrosis and infarction with rupture of glomerular capillaries and extravasation of red blood cells. Other glomeruli showed fibrinoid necrosis of the afferent arterioles with the necrosis extending into the glomerular tufts. Other glomeruli showed recent eosinophilic fibrin capillary thrombi.

A few glomeruli showed older lesions with varying degrees of glomerular ischaemia leading to glomerular shrinkage and fibrous destruction. The tubules showed extensive secondary ischaemic damage with loss of proximal tubules and associated interstitial fibrosis (Fig. 5). Some tubules showed recent necrosis. The interlobular arteries (Fig. 6) showed subintimal oedema and concentric cellular intimal proliferation. There was no evidence of residual neoplasm in any organ.

The appearances were those of a microangiopathic haemolytic anaemia leading to fibrin thrombi deposition in glomerular afferent arterioles and capillaries leading to glomerular ischaemia and a haemolytic-uraemic syndrome.

Discussion

The haemolytic-uraemic syndrome is now a well-recognised entity and has been described both in children and in adults. Excellent reviews^{8,9} list a primary syndrome in children and thrombotic thrombocytopenic purpura in adults. In addition, secondary haemolytic-uraemic syndrome can occur as a response to various factors, including renal transplantation, eclampsia and malignant hypertension. Of particular relevance to our reported cases, the syndrome has been observed with disseminated gastric malignancy^{10,11} and in one patient with inoperable gastric carcinoma treated by mitomycin C and 5-fluorouracil.¹²

The histological changes in the three cases described are typical of haemolytic-uraemic syn-

drome; these changes included, in the kidneys, fibrin deposition and erythrocyte clumping in glomerular tufts, fibrin deposition in the lumina of arterioles (including glomerular afferent arterioles) and in the lumina of renal tubules. In addition, in the lungs, there was fibrin deposition in the alveolar spaces and within vascular lumina.

In our three cases the renal failure was rapidly progressive; this is of interest, as two clinical varieties of renal impairment in patients receiving mitomycin C have recently been described.⁶ These include an acutely progressive form with microangiopathic haemolytic anaemia, and a more chronic form without microangiopathic haemolytic anaemia which resulted in death within three to eight months. In five cases examined histologically, which comprised examples of both clinical types, the changes were essentially the same, with "musculomucoid intimal hyperplasia" of arteries and occasional fibrin thrombi in arterioles. Interstitial fibrosis, tubular atrophy and glomerular necrosis were also described.

It is most unlikely that this coagulopathy resulted from disseminate malignancy, as in two of the cases there was no evidence of recurrent or metastatic carcinoma, despite a rigorous histological search and in one case (case 1) there was only a solitary micro-deposit of gastric carcinoma in a pancreatic lymph node.

It seems likely, then, that mitomycin C (itself or in combination with 5-fluorouracil) can in some way lead to the haemolytic-uraemic syndrome. The pathogenesis of this effect is obscure, but the drug may in some way sensitise the patient to minor mismatches during blood transfusion, and clearly clinical vigilance of renal function should be exercised in patients receiving mitomycin C.

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