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MITOMYCIN-INDUCED RENAL INJURY

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Summary

Haemolytic uraemic syndrome reported in some patients treated for cancer with mitomycin is of unknown pathogenesis and evidence implicating mitomycin inconclusive. To determine whether mitomycin can induce direct renal damage, left kidneys in Lewis rats were perfused with mitomycin (60–4000μg). Control rats received saline-only perfusions. Renal tissue was examined from one hour up to one month later. Twenty-nine out of 31 rats, developed left renal pathology: nine (mitomycin 1000–4000μg) – severe cortical infarction, 20 (mitomycin 60–500μg) – lesions indistinguishable from human haemolytic uraemic syndrome. Glomerular endothelial damage was the earliest detectable abnormality, followed by platelet accumulation and later capillary wall splitting typical of micro-angiopathy. Some kidneys had interlobular artery necrosis and thrombosis. Bizarre tubular cells with giant nuclei similar to those reported in human kidneys with mitomycin-induced haemolytic uraemic syndrome were seen. Right kidneys were normal. No rats in the control group (10) developed haemolytic uraemic syndrome-like lesions. Thus mitomycin directly produced renal lesions indistinguishable from those of human haemolytic uraemic syndrome, suggesting a mechanism for injury seen in mitomycin-treated patients, and providing a new model of haemolytic uraemic syndrome in the rat.

Introduction

A haemolytic uraemic syndrome is being increasingly reported as a complication of mitomycin cancer chemotherapy. There is strong clinical evidence implicating mitomycin: cases are reported where mitomycin was given as the sole therapeutic agent [1–3]; a positive relationship exists between the total dose of mitomycin administered and the likelihood of haemolytic uraemic syndrome [4]; in many cases recurrence of malignancy was convincingly excluded as a cause of the haemolytic uraemic syndrome [5–7]. Despite this, there has been no conclusive

evidence that mitomycin can trigger a haemolytic uraemic syndrome and no indication of the possible pathogenesis of the lesions. Early toxicological studies did not reveal nephrotoxicity in most species tested, although a necrotising nephrosis was reported in monkeys [8]. The experiments to be described were designed to see whether mitomycin itself will induce renal endothelial damage, as current evidence suggests that endothelial damage is the primary lesion in haemolytic uraemic syndrome [9].

Methods

Mitomycin (Laboratoire Choay, Paris, France) was administered to Lewis rats by isolated perfusion of the left kidney [10]. In this technique the left renal circulation is isolated by clamping the aorta and inferior vena cava above and below the origin of the renal vessels, and ligation of adrenal, spermatic and lumbar vessels. A needle is introduced into the section of aorta enclosed by the clamp to perfuse the kidney, and the perfusion drains through a hole in the renal vein. After perfusion the aortic and renal vein punctures are surgically repaired and the clamp removed. In these experiments 31 rats received doses of between 60–4000μg mitomycin in saline. The volume of each dose was 4ml, the time in contact with the kidney 10 minutes. Blood was flushed from the kidneys with saline before mitomycin infusion, and the drug was similarly flushed out before removing the clamps. A group of 10 control rats were similarly treated with saline-only perfusions.

Renal biopsies and nephrectomies were taken at intervals from one hour up to one month after perfusion, and processed by standard methods for light and electron microscopy.

Results

In mitomycin-perfused kidneys the renal lesions were dose dependent: 1000–4000μg, nine out of nine developed cortical infarction which with the highest dose was a nearly total cortical necrosis, with areas of medulla infarction occurring within 24 hours of perfusion.

250–500μg Twelve out of 14 developed extensive lesions closely resembling those of haemolytic uraemic syndrome which will be described in greater detail. The two remaining cases had necrotic lesions which were considered due to technical failure.

60–120μg Seven out of eight developed milder haemolytic uraemic syndrome-like lesions, and one showed no abnormality. In the control group eight out of 10 showed no significant abnormality by light or electron microscopy, one had mild ischaemic tubular damage, and one was necrotic, considered technical failure.

Haemolytic uraemic syndrome-like lesions

No changes were detected by light microscopy before 24 hours after perfusion. By electron microscopy the earliest change was seen in *six hours,* where there was early evidence of endothelial damage in glomerular capillaries, with lifting endothelium, loss of fenestrations, and small numbers of platelets adhering to basement membranes. By *24 hours,* in kidneys perfused with 250–500μg mitomycin by light microscopy focal thrombosis and necrosis were seen in glomeruli and arterioles (Figure 1) and in occasional interlobular arteries. There was severe acute tubular damage and some peritubular capillary haemorrhage. By electron microscopy there was severe glomerular injury, with large platelet aggregates and endothelial damage (Figure 2). At *one week,* changes were also seen in kidneys perfused with lower doses of mitomycin (60–120μg) which had appeared normal at 24 hours. By light microscopy glomerular thromboses persisted. Tubular damage was extensive, and abnormal mitoses and large cells with bizarre nuclei were seen in tubules, occasionally in glomeruli (Figure 3), and in perirenal connective tissue cells. Interlobular arteries showed fibrinoid necrosis. By electron microscopy glomerular capillaries were narrowed by a subendothelial lucent zone which in some areas contained trapped platelets and granular material (Figure 3). At *one month,* when nephrectomy specimens were obtained, the lesions were patchy, with normal areas and abnormal areas in which glomeruli showed sclerosis and capillary wall splitting. In these areas

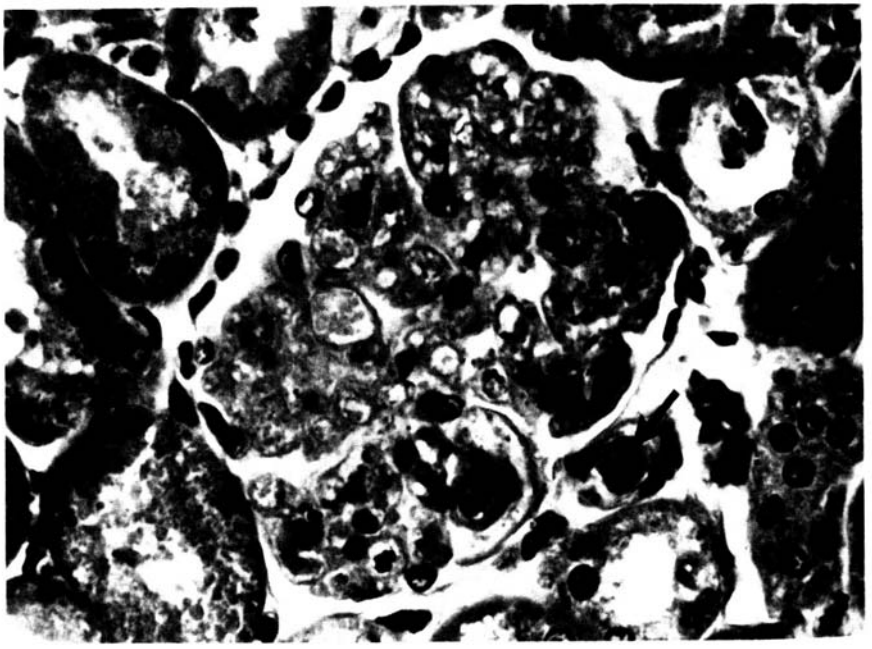

Figure 1. Glomerulus 24 hours after 250μg mitomycin. There are areas of necrosis, glomerular thrombi and a thrombus in the afferent arteriole (arrow). x 500

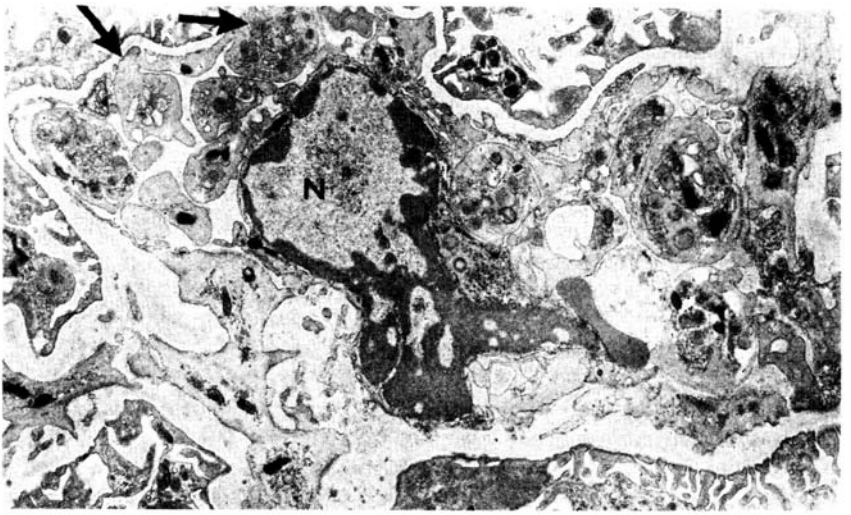

Figure 2. Electron micrograph of part of a glomerular capillary 24 hours after 250μg mitomycin. There are intraluminal platelets, and platelets adhering to exposed basement membrane (arrows). N = nucleus of a damaged endothelial cell. x 7,300

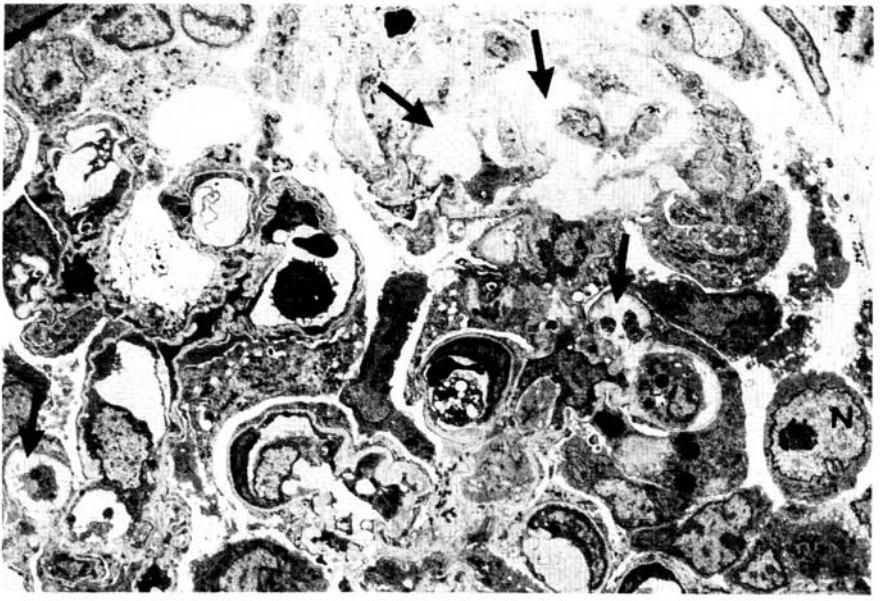

Figure 3. Low power electron micrograph of part of a glomerulus one week after mitomycin. Capillaries are narrowed by a lucent subendothelial zone (arrows). A cell with bizarre nuclear appearance (N) and giant nucleolus is present on the right. x 1,600

there was tubular atrophy, persistence of abnormal nuclei and interstitial mononuclear cell infiltration. A few arteries showed some intimal thickening. By electron microscopy glomerular capillary wall thickening and collapse were confirmed, with subendothelial lucent widening and areas of interposition.

Discussion

These results show that mitomycin directly perfused into the rat kidney will induce haemolytic uraemic syndrome-like lesions. The first identifiable abnormality is endothelial damage with platelet adhesion to basement membranes, and intraluminal aggregation. These changes are rarely seen in human biopsies of haemolytic uraemic syndrome, as this must represent a very early change. The later lesions in the model, namely glomerular platelet thrombi, and capillary wall thickening due to subendothelial widening and mesangial cell interposition are very similar to human haemolytic uraemic syndrome [9]. The patchy nature of the lesions is also consistent with a haemolytic uraemic syndrome kidney.

The appearances in the model suggest that a cumulative action of mitomycin on vascular endothelium could be responsible for the haemolytic uraemic syndrome occurring during mitomycin therapy. It may lead to endothelial dysfunction which is not manifest unless a further triggering insult is encountered, such as bacteraemia. This would account for the latent period often observed between the cessation of mitomycin treatment and the development of haemolytic uraemic syndrome, and the minority of all treated patients affected by haemolytic uraemic syndrome.

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