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Case report

Glomerular tuft ballooning in mitomycin-C-induced renal impairment

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Summary. Severe ballooning of the glomerular tufts was observed in a 65-year-old man who was treated with mitomycin C (MMC) and had typical MMC-induced renal lesions. He developed renal failure and severe anaemia 6 months after initiation of chemotherapy. Ballooned tufts were caused by enormous expansion of the sub-endothelial space simultaneously associated with mesangiolysis. Glomerular cysts, described in a variety of disorders including thrombotic microangiopathy and diabetes mellitus, are derived from cystically dilated and united capillary luminae secondary to mesangiolysis. The morphogenesis of this unusual lesion when induced by MMC differs from that of the glomerular cysts previously reported.

Key words: Glomerular tuft ballooning – Mitomycin C – Mesangiolysis – Morphogenesis

Introduction

Mitomycin C (MMC), an antibiotic isolated from *Streptomyces caespitosus*, is currently in widespread use for chemotherapy of a variety of solid tumours. Nephrotoxicity from MMC is an uncommon finding but may be fatal (Liu et al. 1971; Hanna et al. 1981; Giroux et al. 1985; Verweij et al. 1987); renal failure often begins several months after initiation of chemotherapy and is frequently accompanied by microangiopathic haemolytic anaemia (MAHA). The characteristics of the renal pathology reported previously are generally similar to those observed in thrombotic microangiopathy: glomerular mesangiolytic changes, double contour of the capillary wall due to widening of the sub-endothelial space, fibrin thrombi and onion-skinning and fibrinoid necrosis of arterioles (Liu et al. 1971; Hanna et al. 1981; Hamner et al. 1983; Giroux et al. 1985). In addition, nuclear degeneration of mesangial cells has been reported (Mazzucco et al. 1982; Giroux et al. 1985; Cordonnier et al. 1986).

It is a general consensus that segmental ballooning of the capillaries in thrombotic microangiopathy is a change secondary to mesangiolysis. This, in turn, is defined as dissolution or attenuation of mesangial matrix and degeneration of mesangial cells (Shigematsu et al. 1976; Morita and Churg 1983). We describe here the morphogenesis of ballooning of the glomerular tufts in MMC-induced renal lesions. Tuft ballooning was caused principally by prodigious expansion of the sub-endothelial space concurrently involving the mesangial area.

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Case report

A 65-year-old man who underwent a total gastrectomy in March 1989 for leiomyosarcoma of the stomach was referred to our department for evaluation of oedema and renal dysfunction in November 1989. Adjuvant chemotherapy was begun following surgery in April, at which time his renal function was normal and there was no proteinuria. MMC was given every week (10 mg) and the cumulative dose of MMC was 70 mg. He was well until late September 1989 when he developed general fatigue, shortness of breath and oedema. He was pale and his face was puffed. Physical examination on admission revealed a blood pressure of 170/80 mmHg, severe anaemia, a grade II/VI systolic ejection murmur at the apex, and oedema. There was no evidence of tumour recurrence or metastasis.

Admission laboratory values included: red blood cells (RBCs), 217×10^4; haemoglobin, 6.9 g/dl; haematocrit, 22.4%; white blood cells (WBCs), 7000 with normal differential; platelets, 15×10^4; reticulocytes, 18‰; fragmented red cells on a peripheral smear; fibrin/fibrinogen degradation products (FDP), 10 μg/ml; fibrinogen, 301 mg/dl; blood urea nitrogen, 41 mg/dl; creatinine, 1.9 mg/dl; serum albumin, 2.8 mg/dl; total bilirubin, 0.9 mg/dl; lactate dehydrogenase, 568 IU/l. Urinalysis revealed proteinuria, haematuria and cylindruria. A 24-h urine collection contained 0.8 g protein. Renal function test showed a moderate impairment; creatinine clearance was 49 ml/min.

Because there were no progressive signs of renal dysfunction and anaemia, he was treated with furosemide for oedema. Renal function and anaemia improved gradually but at re-admission in

September 1990 he had low-grade fever, dyspnoea on effort and loss of appetite. Abdominal ultrasonography revealed multiple liver metastasis. He received a total of 62.3 g 5-fluorouracil without effect. His condition deteriorated gradually, while his serum creatinine level remained 1.0 mg/dl. He died of hepatic failure on 26 January 1991 and autopsy was performed.

Renal pathology

Both biopsy and autopsy specimens were prepared by standard techniques for light and electron microscopy as previously described (Shiiki et al. 1990). Biopsy tissue was also examined by immunofluorescence. For light microscopy, sections were stained with haematoxylin and eosin, periodic acid-Schiff (PAS), periodic acid silver methenamine (PAM) and Masson's trichrome.

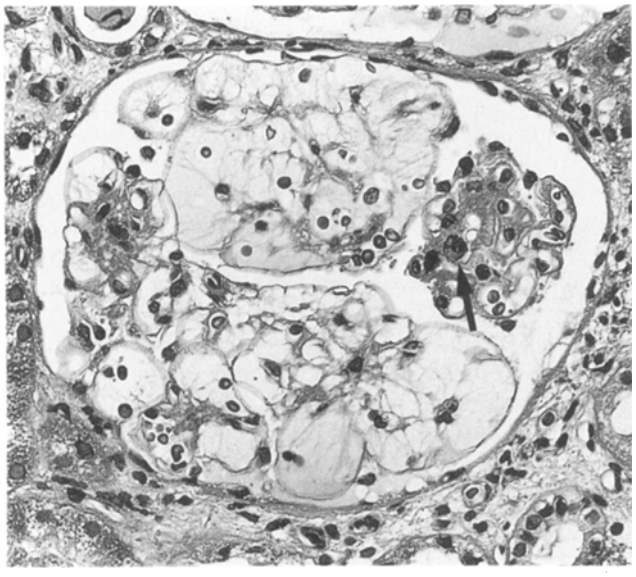

Fig. 1. Ballooning of the glomerular tufts occupying about three-quarters of the glomerular space. Ballooned tufts contain several fragmented red blood cells. *Arrow* indicates a bizarre nucleus in a mesangial cell. H & E, ×250

Twenty-five glomeruli were included in the light microscopic specimen. All showed thickening of the capillary wall with a "double contour" pale space. The mesangial area was occasionally enlarged, where the matrix was loose and reticulated on PAM staining. Some mesangial cells possessed bizarre nuclei, which have been described as morphological evidence of nuclear damage caused by interference of MMC with purine synthesis (Mazzucco et al. 1982; Cordonnier et al. 1986) (Fig. 1). In addition, 20% of glomeruli exhibited balloon-like dilatation of the glomerular tufts, in which some fragmented RBCs, a few attenuated mesangial cells and slit-like capillaries were observed (Fig. 1). The interstitium was diffusely widened due to oedema. Some tubules contained PAS-positive casts. There were no fibrin thrombi and no fibrinoid necrosis in the glomeruli and arterioles.

Immunofluorescent microscopy showed diffuse, faint deposition of fibrinogen and segmental deposition of IgM along the capillary wall.

Electron microscopy revealed extensive widening of the sub-endothelial space, which was filled with electron-lucent, granular or fibrillar material in all the glomeruli examined. The mesangial area was markedly oedematous and displayed disintegration of the matrix, indicating mesangiolysis (Fig. 2). Further electron microscopical examination of the ballooned tufts demonstrated that this unusual feature was not due to cystic dilatation of the capillary lumina but was principally due to enormous expansion of the sub-endothelial space (Fig. 3a). The space was filled with electron-lucent or finely granular

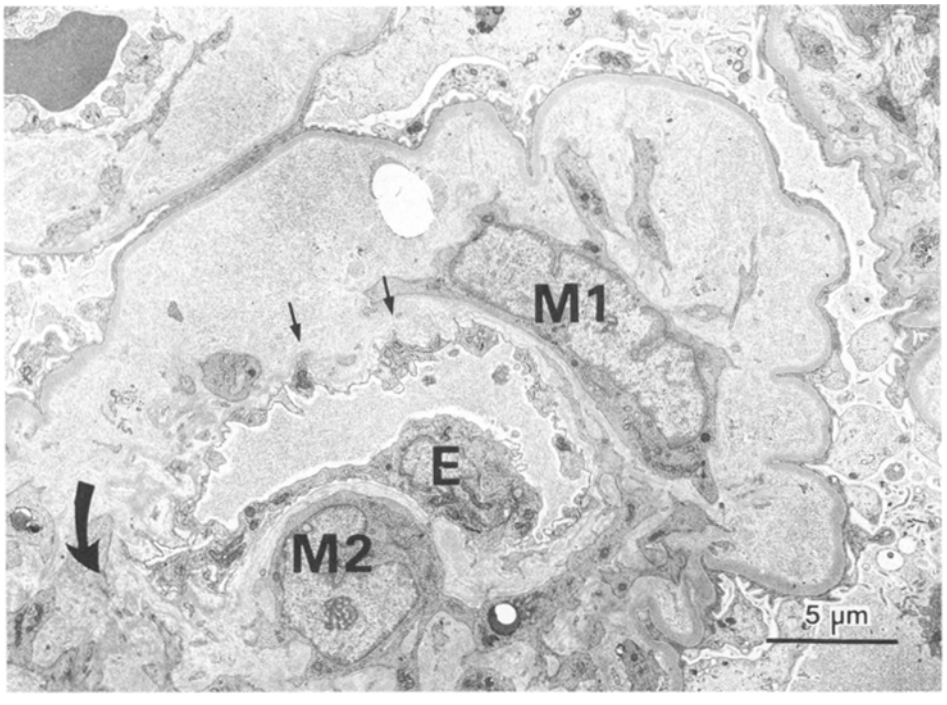

Fig. 2. Widening of the sub-endothelial space filled with granular material. Mesangial matrix is loose and disintegrated (*large arrow*). A mesangial cell (*M1*) almost devoid of matrix shows divergent cytoplasm. An endothelial cell (*E*) is delineated by irregular basement membrane-like materials (*small arrows*). Uranyl acetate and lead citrate, ×3500

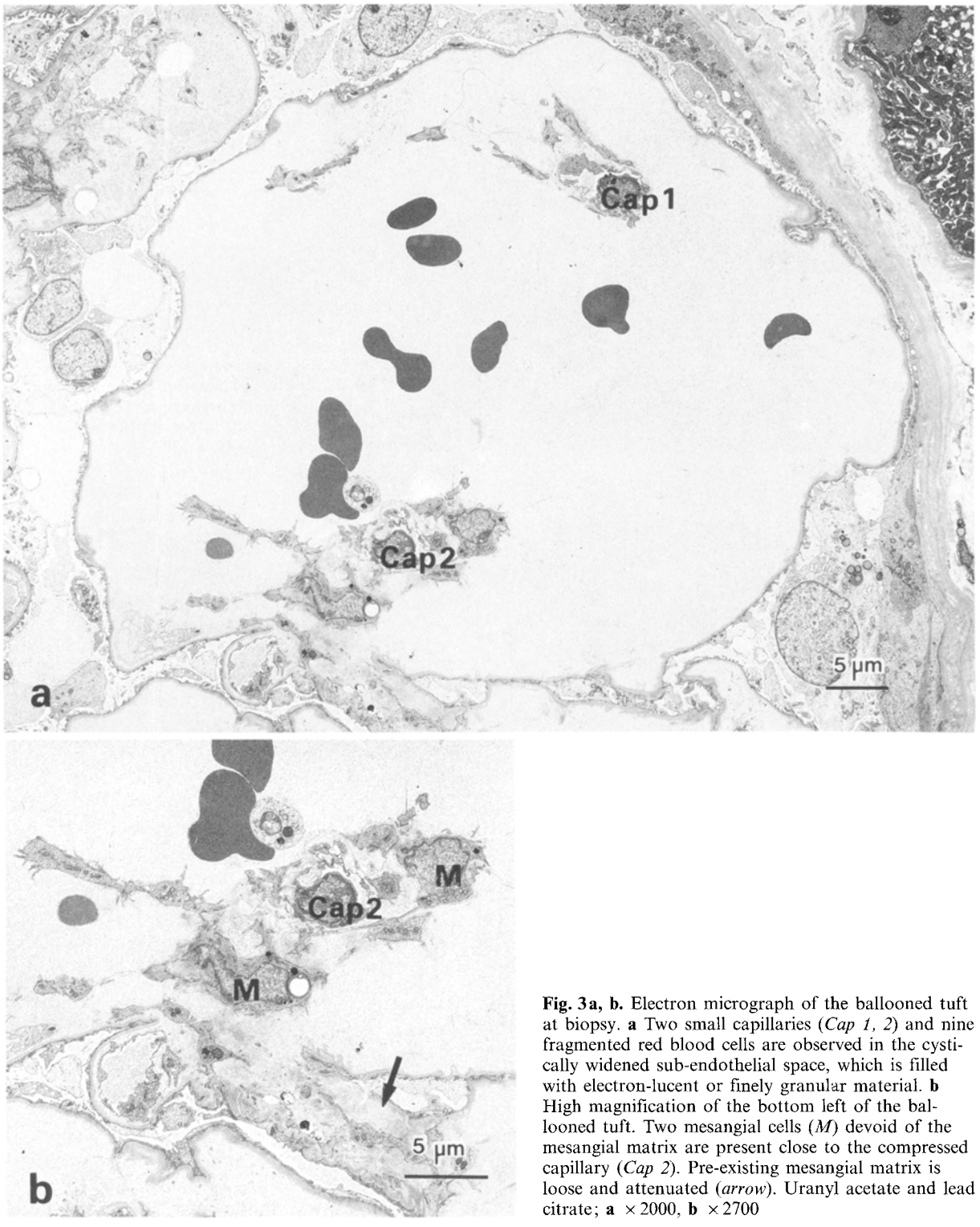

Fig. 3a, b. Electron micrograph of the ballooned tuft at biopsy. **a** Two small capillaries (*Cap 1, 2*) and nine fragmented red blood cells are observed in the cystically widened sub-endothelial space, which is filled with electron-lucent or finely granular material. **b** High magnification of the bottom left of the ballooned tuft. Two mesangial cells (*M*) devoid of the mesangial matrix are present close to the compressed capillary (*Cap 2*). Pre-existing mesangial matrix is loose and attenuated (*arrow*). Uranyl acetate and lead citrate; **a** ×2000, **b** ×2700

material, in which some fragmented RBCs were included. Isolated mesangial cells almost denuded of matrix co-existed intimately with the narrowed capillaries, which were lined by endothelial cells outlined by a newly formed basement membrane (Fig. 3b). The epithelial cells covering the ballooned tufts showed local effacement of foot processes.

At autopsy less than 10% of glomeruli were globally sclerotic. Most of those remaining revealed enlargement of the mesangial area without mesangial cell proliferation and occasionally showed nodular formation in the mesangium (Fig. 4). Nodules that resembled those of diabetic nephropathy were weakly stained by both PAS and PAM. Ballooning of the tufts and a double contour appearance still remained in about 5% of glomeruli (Fig. 4). There were foci of tubular atrophy and intersti-

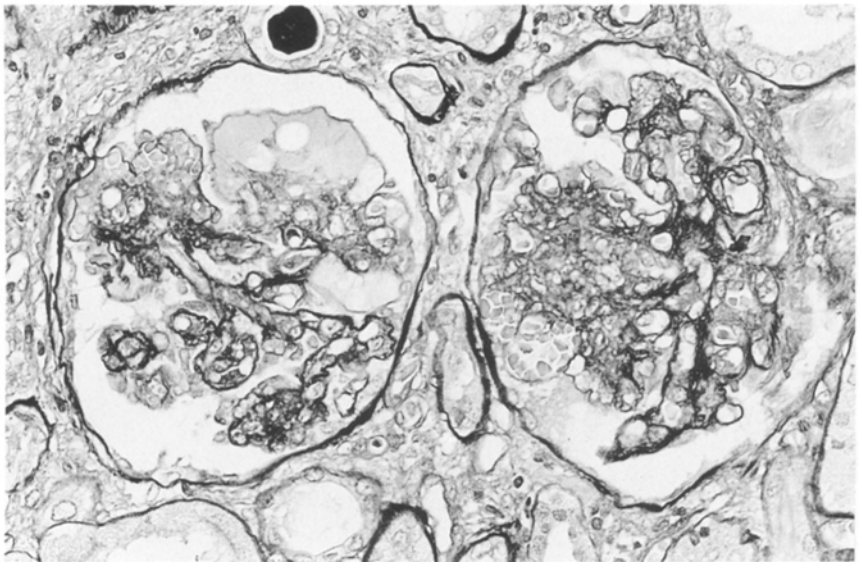

Fig. 4. Light micrograph of autopsy specimen. Nodular enlargement of the mesangial area is seen in both glomeruli. Note ballooning of the tuft in the left glomerulus. Periodic acid-Schiff, ×180

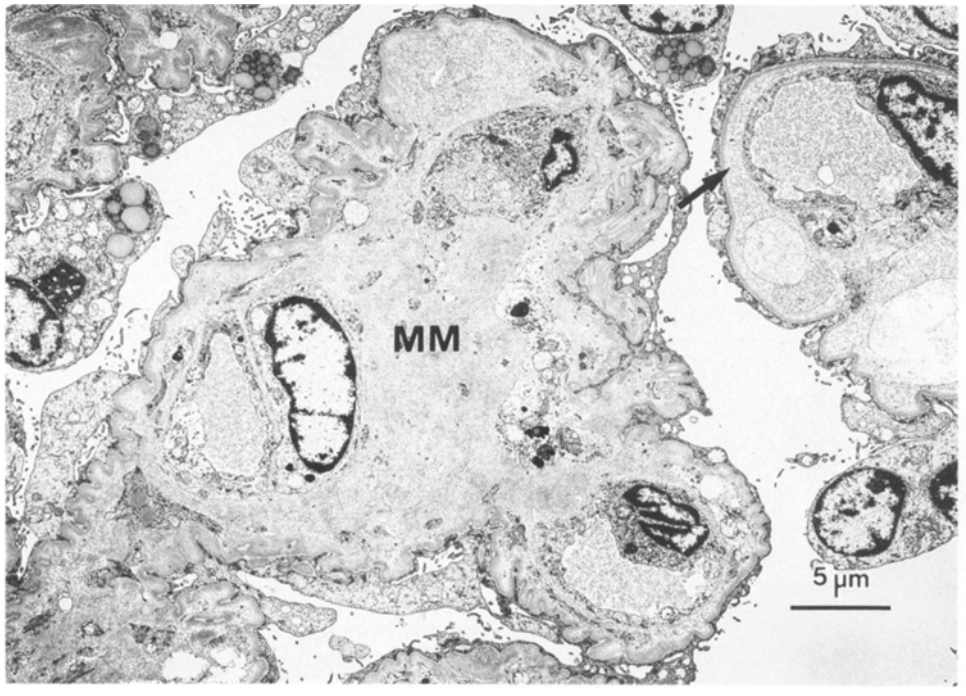

Fig. 5. Electron micrograph of autopsy specimen. The glomerular tuft including three capillaries is covered by wrinkled basement membrane. Mesangial matrix (*MM*), granular or fibrillary in appearance, is markedly increased in amount. The sub-endothelial space remains widened (*arrow*). Uranyl acetate and lead citrate, ×2800

tial fibrosis. Arteries showed mild to moderate intimal thickening. No fibrin thrombi were noted.

On electron microscopy, the mesangial area was widened due to a marked increase in the matrix which was variously oedematous and granular or fibrillary in appearance (Fig. 5). Cell debris was scattered in the increased matrix. The glomerular tufts were occasionally covered by wrinkled glomerular basement membrane (GBM). Electron microscopic examination of the ballooned tufts revealed healing or reparative features of the expanded sub-endothelial space and numerous fibrillary materials appeared in the sub-endothelial space, especially around the mesangial cells and the narrowed capillaries (Fig. 6). The sub-endothelial space, unaffected by the reparative process, was still filled with electron-lucent or finely granular material in which cell debris and some fragmented RBCs were included.

Other major autopy findings were multiple metastases of leiomyosarcoma in the liver and para-aortic lymph nodes.

Discussion

This patient was treated with MMC alone and developed renal failure 6 months after initiation of chemotherapy; this failure was associated with severe anaemia and was thus suggestive of MAHA. He showed no signs of recur-

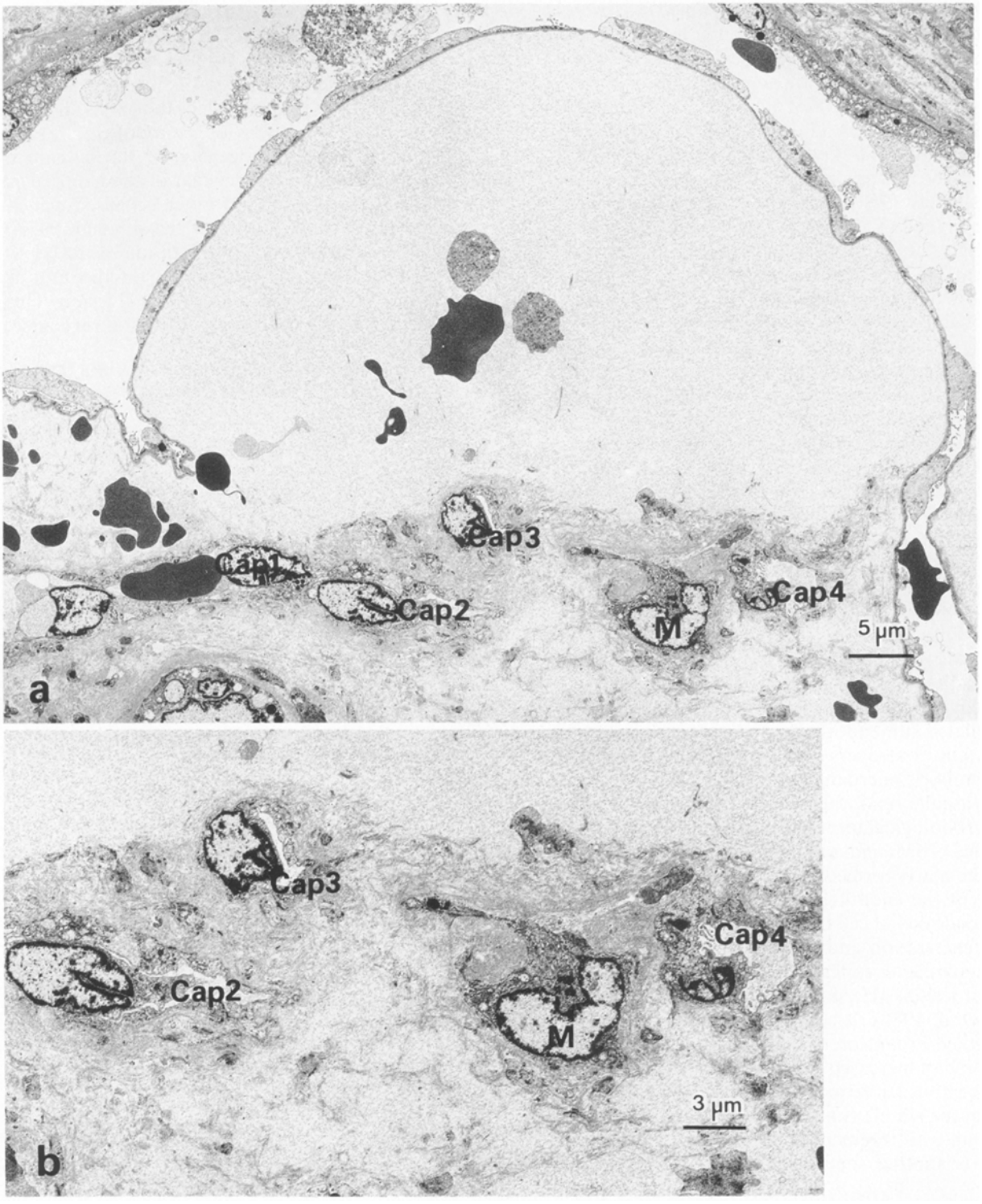

Fig. 6a, b. Electron micrograph of the ballooned tuft at autopsy. **a** Cystically dilated sub-endothelial space is seemingly composed of two parts. The upper part, as at biopsy, is filled with electron-lucent or granular material, while the lower part shows a reparative process around the narrowed capillaries (*Cap 1–4*). Many fragmented red blood cells and cell debris are included in the upper part. **b** High magnification of the reparative area. Masses of fibrillary material are observed around the slit-like capillaries (*Cap 2–4*) and the mesangial cell (*M*). Uranyl acetate and lead citrate; **a** ×2100, **b** ×3400

rent tumour on initial admission and renal dysfunction was not progressive. His clinical course was similar to that observed in patients with a milder type of MMC-induced renal impairment (Liu et al. 1971; Hayano et al. 1988) and apart from ballooning of the glomerular tuft, the patient's renal lesion was compatible with that of MMC-induced nephrotoxicity.

Electron microscopy demonstrated enormous widen-

ing of the sub-endothelial space accompanied by severe mesangiolytic changes. Thus far, mesangiolysis has been described in a variety of renal diseases such as the haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura (Shigematsu et al. 1976; Morita and Churg 1983), scleroderma (Salyer et al. 1973), pre-eclamptic nephropathy (Shiiki et al. 1990), diabetes mellitus (Yajima 1976; Nakamoto et al. 1980), and transplant rejection (Hsu et al. 1980). The ballooning of the glomerular tufts observed in the present case bears a superficial resemblance to the glomerular cyst or capillary aneurysm secondary to mesangiolysis. Typically, such a glomerular cyst is inducible experimentally by intravenous injection of habu venom. In the development of a glomerular cyst, one of the most important changes is the dissolution of the mesangial matrix with loss of the anchoring points of the capillary walls. As a result, the basement membrane is no longer held in a fixed position and thus the adjoining capillary luminae merge together (Morita and Churg 1983). The connection of contiguous capillaries results in a large cyst which includes many RBCs, fibrin and some inflammatory cells. The dilated space, therefore, is essentially the capillary lumen itself, not the sub-endothelial space. However, ballooning of the glomerular tuft in the present case apparently resulted from colossal expansion of the sub-endothelial space concurrently involving the mesangial area. Collaborative action with mesangiolysis caused a giant, balloon-shaped sub-endothelial space. Capillary luminae in the ballooned tuft were narrowed and compressed by the hugely dilated sub-endothelial space.

There is still controversy as to whether the initial insult in thrombotic microangiopathy involves the platelet or the vascular endothelial cell (Ives and Daniel 1991). In morphological terms, separation of endothelial cells from the GBM and accumulation of pale, fluffy material in the newly formed space indicate an increased permeability of the endothelial cells (Heptinstall 1983). Evidence of endothelial cell damage such as atypical nuclei, loss of fenestration and platelet adherence was observed in human and experimental models of MMC-induced renal lesions (Hanna et al. 1981; Cattell 1986; Cordonnier et al. 1986). It seems likely that, in our patient, the marked expansion of the sub-endothelial space was induced by an increased permeability of endothelial cells with enormous subsequent insudation of the serum contents from the circulation. The presence of fibrin-like materials along with fragmented RBCs in the sub-endothelial space is another supportive finding (Shigematsu et al. 1976).

The autopsy specimen revealed diffuse enlargement of the mesangium due to prolonged deposition of the mesangial matrix, while cell proliferation was unremarkable. It is surprising that ballooning of the glomerular tufts was still present at the autopsy which was performed 16 months after the onset of the disease. Deposition of fibrillary material, presumably collagen fibres, was identified in the mesangium as well as in the expanded sub-endothelial space. These features were fundamentally identical to those of healing or a reparative stage of mesangiolysis described in thrombotic microangiopathy (Shigematsu et al. 1976; Churg et al. 1989). Although disseminated malignancy may be associated with thrombotic microangiopathy (Lohrmann et al. 1973; Laffay et al. 1979) the generation of fibrillary material in the ballooned tufts implied that the ballooning of the tuft in the present case was long-standing.

In conclusion, the morphogenesis of the ballooned tufts in our patient differed from that of the glomerular cysts previously described; the former is caused principally by an enormous expansion of the sub-endothelial space, while the latter is made of dilatation of the capillary lumen. It is likely that ballooning of the tufts is an extreme type of the MMC-induced renal lesion. This change may take a long time to repair even if reversible.

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