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Severe Glomerular Mesangiolysis in a Patient with Rectal Adenocarcinoma Treated with Cytotoxic Drugs

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Summary. A 72 year old man with rectal adenocarcinoma developed chronic renal failure when treated by surgery and subsequent chemotherapy (5-fluorouracil, Mitomycin C and Cytosine arabinoside) and immunotherapy. Light microscopy provided evidence of severe glomerular changes with extensive mesangiolysis and vascular damage. Electron microscopy confirmed the mesangiolysis and showed nuclear changes in mesangial cells with nuclear pockets, chromatin loss and margination. There was further indirect evidence of endothelial cell damage.

It is suggested that the glomerular changes should be attributed to a direct cytotoxic effect on the mesangial cells.

Key words: Mesangiolysis – Renal toxicity – Mitomycin C – Nuclear damage

Mesangial disintegration with cystic glomerular capillary dilations has been observed in several types of experimental glomerulonephritis (GN) such as radiation nephritis (Madrazo et al. 1970), immune complex GNs (Shigematsu and Kobayashi 1973 and 1976; Kondo et al. 1976) and in GNs due to toxic agents (Cattel and Bradfield 1977; Bradfield et al. 1977; Morita et al. 1978). In human pathology, mesangiolysis has been frequently observed in the haemolytic-uraemic syndrome (Shigematsu et al. 1976), in diabetic glomerulosclerosis (Nakamoto et al. 1980), in transplant glomerulopathy (Hsu et al. 1980) and has occasionally been reported in Schoenlein-Henoch GN, scleroderma kidney, acute post-partum renal failure (Heptinstall 1974; Kincaid-Smith 1975) and in GN during echovirus infection (Huang and Wiegenstein 1977). Mesangial disorganization has been reported in a few patients affected by several types of neoplasia treated with cytotoxic drugs (Liu et al. 1971; Berger and Nabarra 1980; Birembaut et al. 1981).

The mechanism responsible for this process is still unclear, being either related to a markedly increased vascular permeability and local intravascular coagulation, or to a direct toxic effect on the mesangial cells. This report deals with a peculiar mesangiolytic damage in a patient affected by rectal

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adenocarcinoma treated with chemotherapy and immunotherapy who presented with chronic renal failure.

Case Report

A 72 year old non diabetic man underwent resection of rectal adenocarcinoma (T3a, NO, MO) in december 1977. At that time his blood pressure, renal function and haematological data (red and white blood cell count, platelet count and blood smear morphology) were normal. The CEA level was 33.4 ng/ml (normal value 10 ng/ml). A month later he was placed on a chemotherapy regimen consisting of 5 fluorouracil (500 mg/daily) and Mitomycin C (2 mg/daily) for 5 days and Cytosine arabinoside (100 mg) twice in the same week, at intervals of 4 weeks. Twelve cycles were performed.

During this period, urinalysis, blood pressure, renal function and haematological data remained normal. CEA level reverted to normal. In April 1978 immunotherapy with BCG (2 mg weekly in the first two months and 2 mg monthly thereafter) was also undertaken. In February 1979 (two months after the end of chemotherapy) BUN rose to 87 mg/100 ml and creatinine to 1.10 mg/100 ml. Immunotherapy was discontinued. Four months later (June 1979) blood pressure rose to 190/130 mm Hg, BUN was 99 mg/100 ml and creatinine 2.04 mg/100 ml. Red blood cells were 3,100,000/mm^3, white cells 6,400/mm^3 and platelets 200,000/mm^3. Blood smear morphology was normal. Urinalysis revealed slight proteinuria (0.52 g/l), microscopic haematuria and cylindruria. Serum C3 and immunoglobulins levels were normal. An open biopsy was then done. The patient has been followed-up for 34 months after the biopsy. He is still alive, and presents a therapy-sensitive hypertension and a stable renal failure. He has no laboratory and clinical manifestations of neoplastic extension or recurrence.

Results

Light Microscopy. More than 50 glomeruli were examined; few of them displayed ischemic changes. Most glomeruli were hypocellular and showed a diffuse thickening of the capillary walls (Fig. 1). The mesangial region was enlarged and the matrix appeared reticular (Fig. 1). Areas of mesangiolysis were present in several glomeruli, displaying either a focal or a diffuse distribution (Figs. 1 and 2). The mesangial matrix was barely discernible by PAS stain and the capillaries of the glomerulus were dilated, sometimes appearing as large cavities filled with blood (Fig. 2). Some cells, in such areas, whose nature was difficult to assess by light microscopy, showed large irregular nuclei (Fig. 2).

Several small arteries and arterioles were damaged, showing either hyalinosis or mucinous onion skin-like intimal proliferation. Mild irregularly distributed interstitial fibrosis and tubular atrophy were present (Fig. 1).

Electron Microscopy. Mesangial areas were greatly expanded and displayed clear spaces devoid of cells. The mesangial matrix was swollen, acquiring an appearance of a meshwork filled with finely granular or fibrillar material. Vesicular membranes and cellular debris were scattered throughout. Residual mesangial cells were large and showed numerous cytolysosomes and irregularly shaped nuclei with several nuclear pockets (Fig. 3). The nuclei of many mesangial cells appeared severely damaged. The chromatin was irregularly distributed or marginated, or it had completely disappeared in some

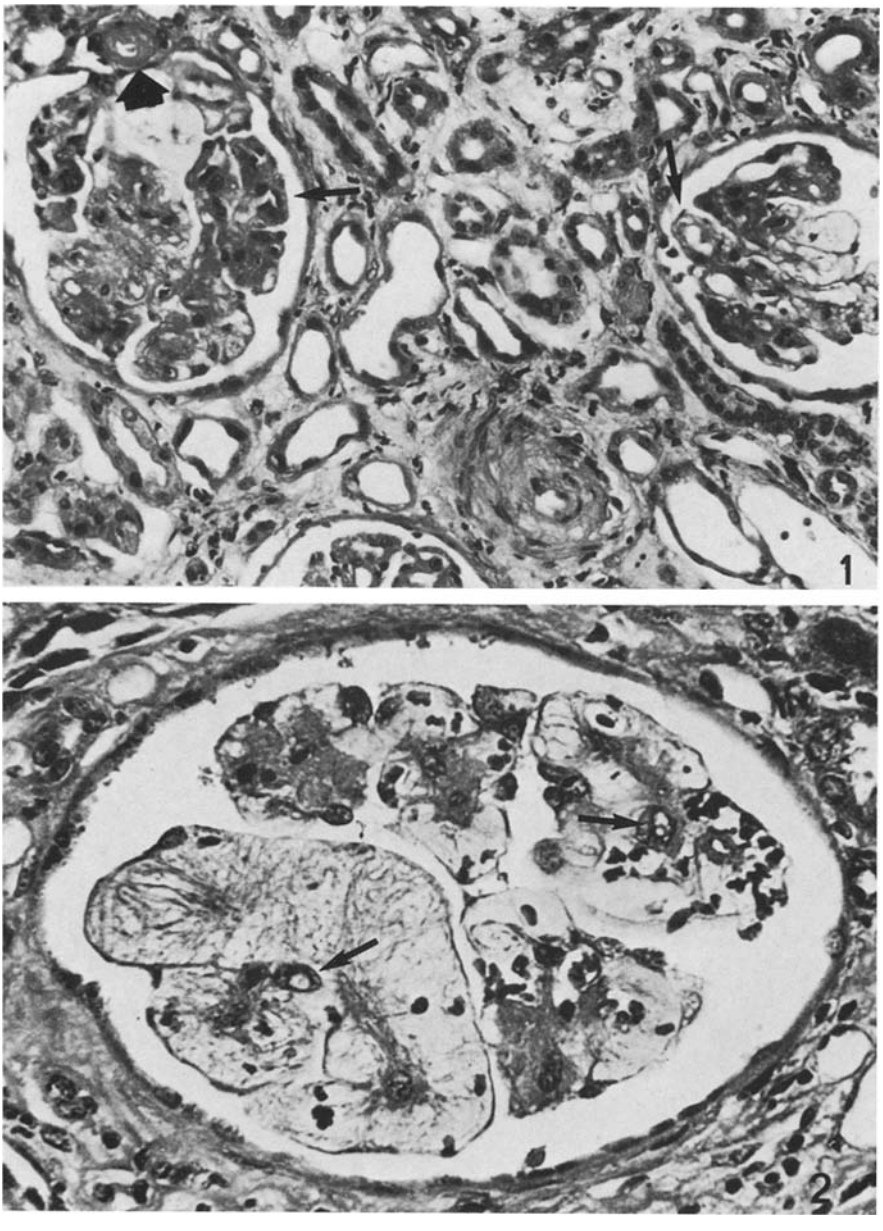

Fig. 1. Two glomeruli showing hypocellular, enlarged mesangial stalk. In some areas the mesangial matrix has a reticular appearance. Capillary walls are irregularly thickened (*small arrows*). A segmantal area of mesangiolysis is evident in the glomerulus on the right. The artery on the bottom shows onion skin-like intimal proliferation. The large arrow points out an afferent arteriole with hyalinosis of the wall. PAS × 250

Fig. 2. Glomerulus showing extensive mesangiolysis. Capillaries are dilated. *Arrows* point out cells showing large and irregular nuclei. PAS × 450

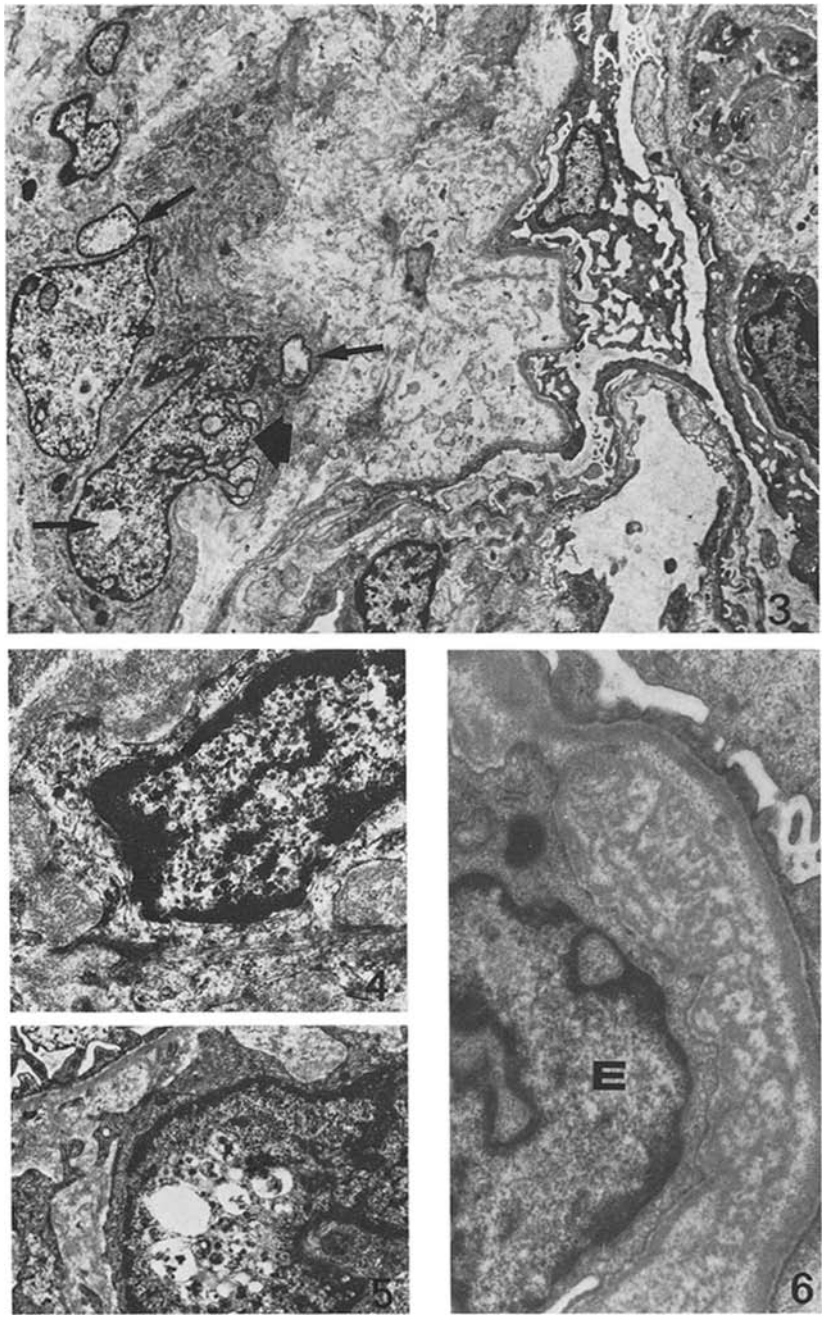

Fig. 3. Greatly expanded mesangial area with swollen matrix containing cellular debris. Mesangial cells show irregular nuclei with nuclear pockets (*large arrow*) and loss of chromatin (*small arrows*). The lamina rara interna of the capillary on the bottom is widened. The capillary lumen on the top right is filled by a platelet aggregate. × 3,200

Fig. 4. The nucleus of a mesangial cell containing free coarse granules. × 16,900

Fig. 5. Severely damaged nucleus of a mesangial cell. Intranuclear vesicles are evident either empty, or containing granular material. × 8,500

Fig. 6. Detail of a capillary wall. The lamina rara interna is widened. A reticular basal lamina-like material is interposed between endothelium (*E*) and the lamina densa. × 11,000

areas (Figs. 3, 4 and 5). Occasionally free coarse granules or intranuclear vesicles, either empty or containing granular material, were evident (Figs. 4 and 5). Glomerular basement membranes were thickened, mainly because of swelling of the lamina rara interna, filled by floccular electron lucent material. The lamina rara interna of some capillaries was enormously widened and contained blood cells and, occasionally, fibrin-like material. In several basement membranes a reticular basal lamina-like material was present in the widened lamina rara interna (Fig. 6). Capillary lumina were lined by normally appearing endothelial cells. On occasion white blood cells and platelet aggregates were evident in the lumina.

Immunofluorescence. In the glomeruli all immune antisera (anti-human IgG, IgA, IgM, C3, C_{1q}, C4) gave negative results with the exception of anti-fibrinogen antiserum which showed a faint positivity on the inner side of the capillary walls and within the lumina. C3 and IgM were focally distributed in the walls of some arterioles.

Discussion

The salient features of the glomerular pathology in this patient were severe mesangiolysis and peculiar changes in the nuclei of the mesangial cells. Arteriolar hyalinosis or arterial onion skin-like intimal proliferation were also evident.

Mesangiolysis is an highly characteristic morphological feature, the pathogenetic mechanism of which is debated. It does not seem to be connected with any specific pathological process, being observed in both experimental and human GNs where immunological, toxic and vascular processes are involved. Mesangiolysis does not seem to be related to the deposition of immune complexes in the glomeruli. Shigematsu et al. (1976) showed that in rabbit accelerated serum sickness mesangial disintegration does not always correlate with the severity and extension of immune complex deposition. In keeping with these data is the absence of granular deposits of immunoglobulins and of electron dense deposits in the glomeruli of our patient.

Mesangiolysis has been reported in some renal disorders such as haemolytic-uraemic syndrome, thrombotic-thrombocytopenic purpura, scleroderma and acute post-partum renal failure (Heptinstall 1974; Kincaid-Smith 1975; Shigematsu et al. 1976). Mitomycin C can cause an haemolytic-uraemic-like syndrome (Krauss et al. 1979; Kressel et al. 1981) which could be responsible of the mesangial changes. It does not seem to be the case in our patient since clinical features consistent with or even suggestive of the haemolytic-uraemic syndrome have not been observed during the period of chemotherapy or in the following months.

A direct mesangial cell necrotizing injury has been suggested in the experimental Habu snake venom GN (Suzuki et al. 1963) and, in human pathology, either in the mesangiolytic GN during echovirus infection (Huang and Wiegenstein 1977), or in the glomerulopathies following cytotoxic drugs

(mainly Mitomycin C) therapy (Liu et al. 1971; Fillastre et al. 1981). In previous papers dealing with glomerular damage in patients treated with cytotoxic drugs, nuclear abnormalities of endothelial (Liu et al. 1971; Hanna et al. 1981), and mesangial cells (Berger and Nabarra 1981) were reported. In particular, the former authors described eosinophilic nuclear inclusions which were shown to be cytoplasmic invaginations in to the nuclei. Similar findings were also present in the mesangial cells of our patient. However nuclear pockets are non-specific features, being present in both normal and pathological cells. In addition, mesangial cells showed more severe nuclear changes, such as loss and disintegration of the chromatin. The latter findings can therefore give morphological evidence for the nuclear damage caused by Mitomycin C and/or other drugs, which are known to interfere with "de novo" synthesis of purines (Fillastre et al. 1981).

Unlike the reported of Hanna et al. (1981), there is no direct evidence of the endothelial cell damage in our case. Nevertheless several capillaries exhibit reticular basal lamina-like material in the widened lamina rara interna. According to Vracko (1974) and Vracko and Benditt (1972) reticulation of the basal lamina indicates repeated episodes of endothelial injury, cell death and regeneration. The absence of actual endothelial cell changes does not permit us to assess the possible causes of previously occurring damage.

In conclusion, our data provide evidence that, apart from other mechanisms, direct nuclear damage of the mesangial cells may be responsible for mesangiolysis and for subsequent cystic glomerular capillary dilations.

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