A renal biopsy study in toxæmia of pregnancy

Using routine light and electron microscopy linked with immunofluorescence and immuno-electron microscopy

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SUMMARY Renal biopsy specimens from 11 women with severe pre-eclamptic toxæmia were examined by light and electron microscopy linked with immunofluorescence and immuno-electron microscopy. The part played by the mesangium in causing capillary loop thickening is stressed, and the progress of this 'strangulation' is illustrated. In contrast to the findings of most previous authors, IgM was demonstrated by direct immunofluorescence in all biopsy specimens, and its presence and site within the glomerulus were shown by immuno-electron microscopy in three cases.

The light and electron microscopic features of the renal lesion in toxæmia of pregnancy (pre-eclampsia and eclampsia) have been demonstrated by many authors, and the findings have recently been reviewed by Heptinstall (1974). Thomson *et al.* (1972) found similar lesions in both toxæmia and abruptio placentae and suggested that the glomerular lesion in these two groups of patients was the result of the response of the endothelial cells and mesangium to deposited fibrin or its derivatives. This hypothesis was supported by early workers using immunofluorescent techniques, which detected fibrin within endothelial and mesangial cells and along the capillary walls (Vassalli *et al.*, 1963; Morris *et al.*, 1964).

The possibility of immunological processes being implicated in the pathogenesis of pre-eclampsia on the basis of renal biopsy studies was raised recently by Petrucco *et al.* (1974) in Adelaide and by ourselves in Bristol (Tribe *et al.*, 1974). Both renal centres reported the presence of immunoglobulins, especially IgM, within the glomeruli. In view of this new evidence for immunoglobulin deposition and its possible implications concerning the pathogenesis of pre-eclampsia, it seemed important both to verify the presence and localise the site of IgM deposition using the recently developed technique of immuno-electron microscopy (Davies *et al.*, 1977). We now present the findings in renal biopsies

undertaken in the early puerperium in 11 patients with pre-eclampsia.

Patients and methods

PATIENTS

During a period of one year we studied 11 pregnant women who developed severe pre-eclamptic toxæmia (PET), defined as a diastolic blood pressure of 90 mmHg or greater accompanied by proteinuria of 0.5 g/24 h or more with or without oedema. Several of the cases had unusual clinical features, which are detailed in Table 1 together with the results of laboratory investigations.

RENAL BIOPSY TECHNIQUE

Percutaneous renal biopsies were performed in the early puerperium between two and 17 days after delivery, the average time being nine days postpartum. Specimens were obtained using a Tru-Cut disposable biopsy needle under local anaesthesia with the patient in the prone position. Concurrent excretory urography and image intensification allowed accurate localisation of the kidney and placing of the biopsy needle. Apart from transient mild haematuria there were no complications.

Methods

HISTOPATHOLOGY

Light microscopy

The biopsy specimens were fixed in 10% buffered

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Table 1 Clinical and laboratory details

Case	Age	Parity	Time of biopsy after delivery (days)	Gestation (weeks)	BP max	Max blood urea* (mg/100 ml)	Serum uric acid* (mg/100 ml)	Lowest creatinine clearance (ml/min)	Proteinuria (g/24 h)
1	23	0+0	8	39	175/110	29	4.5	66	1.5
2	25	1+0	9	36	200/120	36	3.5	102	1.0
3	23	0+0	12	34	170/110	23	4.1	140	4.0
4	27	0+0	3	22	170/110	32	5.9	79	10.0
5	21	0+0	7	38	200/140	32	NA	54	0.5
6	47	0+0	14	36	180/115	44	6.3	73	++ +
7	25	0+0	12	24	180/110	30	NA	26	1.0
8	28	0+0	15	27+	150/110	91	7.9	25	++ +
9	31	0+0	6	30	160/110	25	7.8	86	2.0
10	31	1+0	17	28	160/90	81	7.0	66	3.5
11	22	0+0	15	32	160/110	47	4.6	66	2.0

NA = not available; FD = forceps delivery; Ass Br = assisted breech; CS = Caesarean section; Abn = abortion; SVD = spontaneous vertex delivery
 NW = not weighed; A = alive; SB = stillborn; IUD = intrauterine death; FDP = fibrin degradation products.

*Conversion: Traditional to SI units—Blood urea: 1 mg/100 ml $\approx$ 0.17 mmol/l (normal range 2.5-7.5 mmol/l)

Serum uric acid: 1 mg/100 ml $\approx$ 0.06 mmol/l (normal range 0.2-0.45 mmol/l)

neutral formalin, and paraffin sections were cut at 3 μ m and stained routinely with haematoxylin and eosin (H and E), van Gieson elastic (VGE), periodic acid schiff (PAS), and periodic acid-silver methenamine (PASM).

Electron microscopy

Specimens were fixed in 1% osmium tetroxide, dehydrated, and embedded in epoxy resin (Durcupan). Sections were cut at 500 Å using an LKB ultramicrotome, stained with uranyl acetate and lead citrate, and examined with a Philips 201 electron microscope.

Immunohistology

The specimens were snap-frozen with liquid nitrogen. Direct immunofluorescence studies were performed on 4 μ m cryostat cut sections picked up on to previously prepared Teflon-coated slides, five sections per slide and dried for 1 hour. The sections were stained with FITC-labelled antisera to IgG, IgA, IgM, fibrin/fibrinogen, and the C3 component of complement (Wellcome Reagents and Hoechst Pharmaceuticals) using controls as described by Davies *et al.* (1973). These were examined and graded by two observers using a Wild M20 microscope with blue light fluorescence.

IMMUNO-ELECTRON MICROSCOPY

In three cases (3, 10, and 11) frozen tissue was available after immunofluorescence for immuno-electron microscopy studies.

These were carried out according to the method described by Davies *et al.* (1977): 40 μ m frozen sections were cut, fixed in 4% buffered methanol-free formalin, and after prolonged immersion in buffer

treated with peroxidase-labelled antisera (Dakopatts). HRP-labelled anti-human IgG, IgM, and IgA (heavy chain specific) were used in dilutions varying between 1/2 and 1/16. After further immersion in buffer the HRP was developed with diaminobenzidine tetrahydrochloride and hydrogen peroxide in buffer (Graham and Karnovsky, 1966). Fixation in Palade's sucrose was followed by processing to Epon. 1 μ m sections were examined by light microscopy and ultrathin sections by electron microscopy without further staining.

Controls

Sections treated with unlabelled antisera were also processed in the same way. Tissue from patients with other renal diseases were treated with the same reagents. The antisera were examined by immunoelectrophoresis.

Results (summarised in Table 2)

Renal tissue was available for light microscopy in all 11 cases. Only one glomerulus was found in case 8, but between four and 40 glomeruli were present in all the other specimens. This allowed simple grading of the changes into mild, moderate, severe, and very severe.

LIGHT MICROSCOPICAL CHANGES

The appearances were similar to those described by Sheehan and Lynch (1973) and Heptinstall (1974). The abnormalities are largely confined to the glomeruli and include:

- Involvement of all glomeruli.
- Enlargement of the glomeruli.
- An increase in the number of cells in the tuft.

Maternal FDP normal range 0-0 µ/ml)	Mode of delivery	Child		Outcome of pregnancy	Clinical details
		Sex	Weight (kg)		
	FD	F	3.33	A	Fulminating PET
	Ass Br	F	2.10	A	Severe PET
	CS	M	2.19	A	Severe PET on pre-existing essential hypertension
	Abn	F	NW	Abn	Molar placenta and co-existing fetus (both triploid)
	CS	M	NW	A	Fulminating PET
	CS	M	2.20	A	Severe PET
	Abn	M	0.53	Abn	Fulminating PET at 24 weeks. Placenta infarcted with mild hydropic changes (normal karyotype)
	Abn	M	NW	Abn	PET associated with acute on chronic pyelonephritis
	CS	M	1.29	A	Fulminating PET
	SVD	F	1.0	SB	PET from 24 weeks. APH at 28 weeks with IUD. Postpartum eclampsia.
					Micro-angiopathic haemolytic anaemia
	CS	F	1.5	A	Antepartum eclampsia. Unbooked patient

with some lobulation in the severe cases. Swelling of the cytoplasm of the endothelial cells, which reduces the capillary lumina and may obliterate them in severe cases. This makes the glomeruli characteristically bloodless and led to the term 'endotheliosis' in the early literature.

(d) A probable increase in mesangial cells and matrix.

(e) Small amounts of fibrin can usually be demonstrated.

(f) The capillary basement membranes are usually reported as of normal thickness, but in severe cases thickening occurs, which may mimic membranous or membranoproliferative glomerulonephritis.

All these changes were found in the renal biopsy specimens from our 11 patients apart from our failure to demonstrate fibrin. The changes varied in severity from case to case, four cases showing mild,

three moderate, three severe, and one very severe abnormalities. Figures 1 and 2 illustrate these findings, and we stress the abnormalities seen on PASM sections in this severe case. It showed a well-marked splitting of the capillary loops, producing a 'tramlining effect' very similar to that found in membranoproliferative glomerulonephritis but without any marked mesangial increase.

ULTRASTRUCTURAL CHANGES

Glomerular tissue was studied by electron microscopy in all 11 cases. This was usually restricted to portions of one or two glomeruli.

Our findings mirrored fairly accurately those found on light microscopy, with three cases graded mild, three cases moderate, four cases severe, and one very severe. The changes agreed broadly with those described by other authors (Heptinstall, 1974), but our interpretation of the part played by

Table 2 Histology results

Case	Age	No. of glomeruli	Microscopy		Direct immunofluorescence*				
			Light	Electron	IgG	IgA	IgM	Fibrin	Complement
1	23	15	Mild	Mild	—	±	++	+	—
2	25	12	Mild	Severe	±	+	++	+	—
3	23	16	Severe	Severe	—	—	++++	+	—
4	27	40	V. severe	V. severe	—	±	+++	+ Focal	—
5	21	4	Mild	Mild	±	+	+++	+ Focal	—
6	47	20	Moderate	Mild	—	±	++	—	+ (V)
7	25	20	Severe	Severe	—	—	+++	+	—
8	28	1	Moderate	Moderate	—	+	++	+ Mesangial	+ (V)
9	31	6	Severe	Severe	—	—	+	—	—
10	31	10	Moderate	Moderate	—	—	+	—	+ (V)
11	22	6	Mild	Moderate	—	—	++	—	++ (V)

*Graded by two observers on arbitrary scale by intensity of staining (from — (negative) to ±, +, ++, and +++).

V = vascular

Fig. 1 *Light microscopy: (a) Representative glomerulus in case 4. Note increase in endothelial and mesangial cells with compression of the capillaries ('endotheliosis') and a tendency to lobulation. The capillary loops appear thickened and these appearances mimic membranoproliferative glomerulonephritis. Haematoxylin and eosin $\times 845$.*

Fig. 2 *Light microscopy: (b) Glomerulus from case 4 stained by PASM to show the double contouring ('tramlining') of the capillary loops (arrowed) in the renal biopsies from severe cases of pre-eclamptic toxemia. $\times 1055$.*

Fig. 3 *Ultrastructure I. Electron micrograph illustrating the earliest changes found in the basement membranes of the capillaries. Note the irregular expansion of the lamina rara interna by loosely woven fibrillary material (arrowed). The foot processes are preserved. Lead citrate and uranyl acetate (LC and UA). $\times 37\,600$.*

the mesangium in the basement membrane thickening differs from that of other authors and will be described in detail.

In 10 of the biopsy specimens there was good preservation of the epithelial foot processes. In one case (4) there was extensive foot process fusion; interestingly, this patient had the largest protein leak (10.0 g/24 h).

There was variable proliferation of the endothelial cells and a less marked increase in the mesangial cells and matrix.

In the severest cases lipid droplets were found both in the epithelial cell cytoplasm and in the thickened basement membranes.

The basement membranes were variably thickened in all cases but with preservation of some loops of normal calibre in even the most severely diseased glomeruli. The mildest changes (Fig. 3) were focal,

irregular expansion of the lamina rara interna by loosely woven fibrillary material. Sometimes the expansion had translucent areas, and small islands of endothelial cytoplasm were isolated in the thickened zone (Fig. 4). In other cases this zone included probable small lipid droplets.

In cases with moderate changes, it became apparent that the widening of the lamina rara interna was greatest at the mesangial aspect of the loop. It was also evident that mesangial cell cytoplasm was extending around the capillary loops, forming a 'double contour' akin to the process seen in mesangiocapillary (membranoproliferative) glomerulonephritis (Fig. 4). This ultrastructural change explains the 'tramlining' seen on the silver-stained light microscopical sections (Fig. 2).

In nearly all cases there were areas in the thickened loops which showed subendothelial electron dense

Fig. 4 Ultrastructure II. Low-power electron micrograph illustrating progression of basement membrane changes. The expanded lamina rara interna shows translucent areas, and mesangial cytoplasm is starting to extend around the capillary loop, leaving islands of isolated endothelial cytoplasm. LC and UA $\times 10\,600$.

Fig. 5 *Ultrastructure III. A segment of duplicated thickened capillary loop showing granular subendothelial electron dense deposits (arrowed). Compare with the immuno-electron microscopic findings in Figs 8 and 9. LC and UA $\times 35\,400$.*

deposits (Fig. 5). It is of great interest that it is in these areas that IgM was found on immuno-electron microscopy (Figs 8 and 9).

In the severest cases the capillary lumina were virtually obliterated by mesangial tissue, which has extended completely round the inner walls of the loops, a process often referred to as 'mesangial strangulation'. Figure 6 illustrates our severest case, in which a squashed red blood cell fills the grossly narrowed lumen surrounded by a double contour thickened membrane at least $10\times$ normal width. No obvious fibrillary fibrin was identified in any of the specimens.

IMMUNOFLUORESCENT FINDINGS

Adequate renal tissue, including two or more

glomeruli, was available in all 11 patients for direct immunofluorescent studies, and the results are summarised in Table 2.

The heavy and extensive staining for IgM was the most striking finding in these specimens. This was basically finely granular in nature although some areas looked linear. The deposition, which was discontinuous, involved all glomeruli but was irregular and spared some segments of the glomerular tufts. It involved the peripheral loops, and there were some foci in mesangial areas. This pattern of IgM deposition is illustrated in Figure 7. In four cases this was graded $+++$, in a further five cases $++$, and in only two cases $+$.

Traces ($\pm$) of IgG were found in two cases and traces ($\pm$) of small amounts of IgA were found in

Fig. 6 Ultrastructure IV. Low-power electron micrograph from the severest case (4). There is now marked narrowing of the capillaries by grossly thickened double-contoured basement membranes. The foot processes are mainly fused. LC and UA $\times 5000$.

six cases. In all instances these were segmental and usually confined to the mesangium.

Especial attention was paid to the deposition of fibrin since earlier authors (Vassalli *et al.*, 1963; Thomson *et al.*, 1972) had reported large amounts of fibrin or fibrinogen derivatives in the glomeruli of pre-eclamptic patients. In marked contrast to the findings of these workers, only small amounts of fibrin were detected in 7 of our 11 biopsy specimens. In all cases the fluorescence was segmental and mesangial in site.

Complement (C3) was detected in the glomerular arterioles of four patients and was found only once in the glomeruli.

IMMUNO-ELECTRON MICROSCOPY

All three cases showed deposits of IgM. The deposits were widespread in one case (3) but were more

limited in distribution in the other two. The deposits were localised in the subendothelial region but did not fill the entire abnormal areas between endothelial cell and lamina densa (Figs 8 and 9). No deposits stained for IgG or IgA or with unlabelled serum. Lipid droplets (extracellular and intracellular) were electron dense in all these control sections as they all had been osmicated.

Discussion

Our findings on light microscopy broadly agree with those of previous authors, with the exception of the 'tramlining' effect seen in the silver-stained sections from the most severe cases. This striking picture, illustrated in Fig. 2, was reported by Kincaid-Smith in 1975, and she comments that it differs from mesangiocapillary glomerulonephritis only in that

Fig. 7 *Immunofluorescence. Case 3. The pattern of IgM deposition in the glomerulus is shown. This is finely granular and discontinuous and involves the capillary loops with some foci in the mesangium. FITC-labelled rabbit anti-human IgM $\times 510$.*

the glomeruli show less proliferation. She thought this double contour or apparent duplication of the basement membrane represented organisation of subendothelial deposits of fibrin and illustrates cases with masses of granular and fibrillary fibrin in the subendothelial zone. We believe that mesangial interposition and IgM deposition also play a part and were the most important features causing basement membrane duplication in our post-partum specimens.

Our ultrastructural findings are also largely in accord with those of other authors. These have been recently reviewed by Dunnill (1976), and it is only necessary to comment on certain aspects in the literature. As early as 1964 Altcheck, in a study of renal biopsies in 100 patients with toxæmia of pregnancy, thought the renal glomerular lesion was pathognomonic. The lesion, as he described it, consisted of swelling of the cytoplasm of the endothelial cell, deposits underneath the basement membrane and within the swollen endothelial cytoplasm, and an increase in intercapillary cells. These stream out of the intercapillary areas and insinuate their cytoplasm between the endothelial cells and the basement membranes. This latter finding, with the modern terminology of 'mesangial' rather than 'intercapillary' cells, is the outstanding ultrastructural feature in our series and has not been stressed by other workers. Most authors, including Pirani *et al.* (1963) and Thomson *et al.* (1972), thought that the subendothelial deposits were derived from fibrinogen and used this evidence to support

the concept that intravascular coagulation is concerned in pre-eclampsia. Further evidence for an abnormal state of intravascular coagulation was provided by Vassalli *et al.* (1963) and Fiaschi and Naccarato (1968), who demonstrated fibrin or fibrinogen by immunofluorescent techniques in the glomeruli of pre-eclamptic patients. Both these workers also found smaller amounts of gamma-globulin or IgG.

In 1974, however, Petrucco *et al.* were able to demonstrate both IgM and IgG in 11 renal biopsies from patients with pre-eclampsia and suggested that an immunological mechanism may be responsible for the renal lesions in pre-eclampsia.

The main immunological difference between our observations and those of earlier workers was plentiful IgM deposits and little fibrin in our biopsy tissue, in contrast to marked fibrin with little or no immunoglobulin in other series. It is not clear whether IgM was looked for in some of the earlier studies. If IgM really was absent, then a possible explanation may be the timing of the biopsies in relation to delivery; ours were taken in the post-partum period whereas some others were taken before delivery.

The granularity of the IgM deposits, both by direct immunofluorescence and at electron microscopy, is in itself strong evidence of immune complex deposition. The immuno-peroxidase studies show that the IgM deposits are present in the subendothelial area, which communicates with the mesangium and from which deposits may be cleared. This

Figs 8 and 9 *Immuno-electron microscopy. Case 3. Dense granular deposits can be seen lying in the subendothelial permesangial regions. Horse-radish peroxidase labelled anti-human IgM. $\times 5200$ and 11 900.*

is the zone that Germuth and Rodriguez (1973) have shown to be the site of deposition of large antigen-antibody complexes in experimental immune complex disease and is the site where one would expect to find IgM complexes.

The presence of deposits of immunoglobulin does not necessarily signify an immune complex disease. IgM has been demonstrated in advanced glomerular disease of non-immune origin (Berger *et al.*, 1971; Velosa *et al.*, 1976) and also in focal glomerular sclerosis and minimal change glomerulonephritis, where an immune complex origin has not been demonstrated (Prasad *et al.*, 1977; Sherman *et al.*, 1977). In order to establish whether the IgM is present with an antigen it would be necessary to identify its specificity, but we have not done this. It is, however, possible that the deposits represent the presence of pathological immune complexes resulting from an immunological reaction to trophoblastic antigens. Direct evidence for this does not exist, but it has been reported that circulating immune complexes are more frequent in pre-eclamptic toxæmia than in normal pregnancies (Thomson *et al.*, 1976; Stirrat *et al.*, 1978).

An alternative explanation is to postulate that the IgM occurs secondarily to the laying down of fibrin or fibrinogen products in the glomeruli which has been described frequently by other authors. The presence of IgM in this condition is irrefutable, but it does require explanation. It seems likely to prove to be a secondary phenomenon, but it may hold the key to the pathogenesis of the disease.

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