EDITORIAL COMMENT

Mesangiolysis

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Mesangiolysis is an injurious glomerular process that affects primarily the mesangium. It can be defined as a dissolution or attenuation of mesangial matrix and degeneration of mesangial cells. This type of injury can be seen in a variety of glomerular diseases arising from a multitude of pathologic conditions (Table 1).

Overall, the spectrum of renal injuries in which mesangiolysis may be a contributing element encompasses a significant portion of conventional renal biopsy practice.

Morita T et al[1], using morphologic criteria, recognizable by light microscopy, classified most of the mesagiolysis – associated conditions into three groups:
a. mesangiolysis due to primary mesangial injury
b. mesangiolysis after endothelial injury and
c. mesangiolysis due to persistent or repeated mesangial and/or endothelial damage.

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Mesangiolysis due to primary mesangial injury

The animal model used to elucidate the pathogenesis of mesangiolysis and to understand the mechanisms of glomerular repair for the first group of conditions, is the anti-thymocyte antibody induced mesangiolys is in the rat. In this model, an antibody directed against an antigen on mesangial cells, resulting in rapid mesangial cell death and concomitant disruption of the mesangial architecture[2]. The adjacent glomerular capillary walls lose their anchoring sites, and balloon outwards, resulting in the development of capillary microaneurysm. Initially, there is an influx of leukocytes, principally monocytes into the damaged region, with erythrocytes, platelets and fibrin, resembling to segmental proliferative glomerulonephritis. New mesangial progenitor cells from the extra glomerular region of the juxta-glomerular apparatus proliferate and migrate into the damage glomerular tufts to form new supporting mesangial structure[3]. During this process, the migrated cells undergo a phenotypic change expressing a smooth muscle actin, indicative of myofibroblastic differentiation. Subsequently, a provisional mesangial matrix is produced, followed by remodeling of this matrix and of the proliferating cells, ending in the restoration of normal glomerular architecture, or leaving in focal segmental increase of extracellular matrix[2].

Many, but not all, of the mediators of this process have been indentified in this model. There is an autocrine production of platelet-derived growth factor (PDGF) β-chain by the myofibroblast-like mesangial cells and by monocytes infiltrating the damaged glomeruli, who binds to PDGF receptor β, which is also expressed by progenitor and mature mesangial cells[4]. The use of PDGF aptamers will cause a diminished proliferative response of the mesangial cells[5].

The production of transforming growth factor b (TGFb) is critical for the production of the provisional matrix during the reparative response[6]. The vascular endothelial growth factor (VEGF) may be critical to the proliferation and restoration of the endothelial cell layer of the capillary wall[7]. Also, there is a component of apoprosis, currently unknown, as excess cells participating in earlier stages of proliferative response are eliminated in the process of final restoration of glomerular architecture[2].

Repeated injections of anti-Thy-1 antibody may produce progressive mesangial lesions ending in chronic glomerular sclerosis[9]. Anti-mesangial cell autoantibodies have been detected in immunoglobulin A (IgA) nephropathy and Henoch-Schönlein purpura, with glomerular aneurysms in some patients suggesting a mesagiolysis process[8].

Mesangiolysis, often subtle and easily overlooked in the earliest phase, is recognized by the presence of unusually long, often serpentine, sausageshaped capillary loops resulting from a disruption of the mesangium and coalescence of several adjoining loops. Sometimes this coalescence converted several loops into a sac-like or aneurysmal dilatation. When such areas of coalescence were filled with leukocytes, fragmented red cells, platelets and sometimes fibrin, they could be mistaken for areas of endocapillary proliferation.

Mesangiolysis after endothelial injury

In the second group of diseases (Table 2) mesangiolysis is preceded by endothelial damage.

The most frequent glomerular lesion, attributed to endothelial damage, is subendothelial widening due to accumulation of "fluffy" or finely granular material, presumably containing fibrin or cell fragments; this material is often bounded by a thin layer of new base-

Table 1. *Pathologic conditions associated with mesangiolysis*

Thrombotic microangiopathies
Toxic glomerulopathy (snake venom, anti-cancer drugs, cyclosporine)
Diabetic nephropathy
Circulatory disturbance (hypertensive nephropathy, ischemia)
Radiation nephropathy
Transplantation (transplant glomerulopathy, graft-versus-host disease, bone marrow transplantation)
Monoclonal immunoglobulin deposition disease
Glomerulonephritis (membranoproliferative, crescentic, IgA nephropathy)
Miscellaneous (amyloidosis, sickle cell hemoglobulinopathy, hypocalcemia)

ment membrane, accounting for the double contour seen by light microscopy. Endothelial cells are often swollen and occasionally detached or absent. The endothelial damage does not have to be severe; it is usually moderate or mild, so that the detached endothelial cells maintain the ability to laying down a new basement membrane. The mesangial waists, in some capillary loops show a loosening of mesangial matrix and separation from the basement membranes. Total dissolution of the mesangium result in the coalescence of several loops usually without inflammatory cells. Mesangial dissolution may lead to form one large saclike dilatation variably filled with partially fragmented red cells, platelets, occasional neutrophils and fibrin tactoids. The mesangium is sometimes expanded, with deposition of a nonhomogeneous material, similar to that seen in the widened subendothelial space. The lesions are irregular in their distribution within individual bioply specimens. Normal glomeruli are admixed with those affected by mesangiolysis.

Extensive mesangiolysis with hemolytic uremic syndrome and delayed renal failure is a known complication of bone marrow transplantation (BMT). Total body irradiation has been proposed as the main etiogenic factor because it causes injury to endothelial cells sensitized by antineoplastic agents[10]. But the precise physiopathology of BMT-associated mesangiolysis is not well understood[11].

It is generally accepted that some chemotherapeutic agents make the kidney more vulnerable to nephrotoxicity due to total body irradiation, but sometimes they cause mesangiolysis directly, without irradiation[1]. Mitomycin-C therapy has been associated with extensive lesions of mesangiolysis[10] (Fig.1). Like mitomycin-C, cyclophosphamide exerts its antineoplastic effect by DNA alkylation and is known to produce mesangiolysis in newborn mice[11]. Although mitomycin is the most commonly implicated agent causing thrombotic microangiopathy and mesangiolysis[12], therapy with a variety of antineoplastic agents, such as carboplatin, deoxycoformycin, multidrug regimens with bleomycin, cisplatin and vinca alkaloid may complicated with this lesions[1].

Widening of the subendothelial space with accumulation of finely granular material and mild signs of mesangiolysis is the most frequent glomerular lesion of transplant glomerulopathy. (Fig 2)

Mesangiolysis in cyclosporine-glomerulopathy is often associated with luminal micro-thrombi and lesion of

Table 2. *Diseases with mesangiolysis after endothelial injury.*

- **Thrombotic microangiopathies**
hemolytic uremic syndrome
antiphospholipid syndrome
malignant hypertension
pre-eclampsia
- **Toxic glomerulopathy**
anti-cancer drugs
cyclosporine
nitrosourea
snake venom
- **Conditions of transplantation**
renal allograft rejection
bone marrow transplantation
graft versus host disease

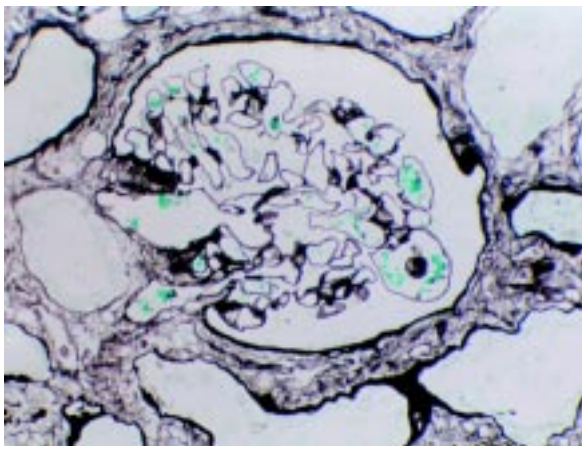

Fig. 1. *Mesangiolysis after mitomycin-C therapy. Loss of glomerular capillary anchoring sites and development of capillary microaneurysm. Silver methenamine X 400.*

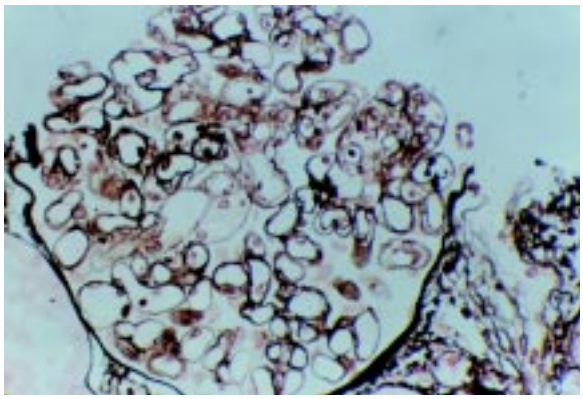

Fig. 2. *Transplant glomerulopathy. Widening of the subendothelial space and double contour of the glomerular basement membrane. Silver methenamine X 400.*

cyclosporine vasculopathy, suth us lumpy hyaline deposits within the vascular wall of the relative arterioles[13].

All the above mentioned conditions share many morphologic features, such as endothelial cell swelling, subendothelial widening with acellular fluffy material, thrombosis and mesangiolysis. They can be classified together in one category as thrombotic microangiopathy. This kind of mesangiolysis has several important consequences for renal function and prognosis. The development of large, ectatic capillary lumina can be expected to have seriously adverse effects on the normal function of mesangial cells in modulating glomerular hemodynamics and glomerular filtration. The loss of mesangium results in a loss of intraglomerular pressure regulation, even if the potentially obstructive glomerular microthrombi disappear. Glomerular collapse coexiste with glomerular mesangiolysis in biopsy specimens. The histopathologic lesion considered to be "late stage of mesangiolysis" is characterized by widened spaces confined by the glomerular basement membrane containing nodular aggregates of pale-staining matrix. This altered matrix, undefined in nature, with mild positivity in PAS and PASM stains, in sharp contrast with normal matrix and basement membrane staining. The lesion gives to the glomeruli a distinctive form of glomerular sclerosis, with very little cellular proliferation[14].

Mesangiolysis due to persistent or repeated mesangial and/or endothelial damage

Mesangiolysis is manifest differently when is associated with chronic sclerosing mesangial injury as in diabetes. Glomerular capillary microaneurysms in diabetic nephropathy, arising by detachment of the mesangial anchor points, are due to local mesangiolysis (Fig 3). Most focal mesangiolysis are located at the periphery of Kimmelstiel-Wilson (KW) nodule. The clustering of focal mesangiolysis, KW nodules and capillary microaneurysms and their strong association with each other indicates that the three lesions are pathogenically interrelated[15]. Focal mesangiolysis and KW nodules are positively associated with proteinuria and hyalinization of afferent and efferent arterioles. Afferent and efferent arteriolar hyalinization could reflect chronic intraglomerular hypertention, which might produce focal mesangiolysis through endothelial damage-induced paracrine effects on mesangial cells[16].

The presence of fragmented red blood cells within focal mesangiolysis implies endothelial damage and intraglomerular hypertension presumably results from sustained contraction of the efferent arteriole[15].

These findings suggest that KW nodules evolve from focal mesangiolyses and glomerular capillary microaneurysms[15, 17].

The findings of red blood cell fragments are associated with worse proteinuria and worse prognosis. A possible pathogenic mechanism of this lesion involve the fibrinolytic/proteolytic system and the local activation of plasminogen activator inhibitor-1 (PAI-1)[18].

Another hypothesis, supported by the relationship between serum matrix metalloproteinase-2 (MMP-2) activity and severity of glomerular lesions, suggests that excess MMP-2 proteolytic activity cause extracellular matrix degradation resulting in mesangiolysis. The serum MMP-2 activity in the diabetic patients with mesangiolysis is significantly higher than in those without mesangiolysis[19].

The early edematous stage of focal mesangiolysis evolve into proliferative one with increased mesangial cells, belived to produce increased matrix leading to KW nodule initiation and nodule growth. Recurrent mesangiolysis induce in the genesis of lamellated nodules[1, 15].

Focal mesangiolyses and glomerular capillary microaneurysms are deemed transient lesions, being absent in end-stage kidneys.

Several diseases are characterized by tissue deposition of non-organized or organized immunoglobulins. The glomerular lesions of non-organized immmunoglobylin deposition diseases (Randall-type diseases) are

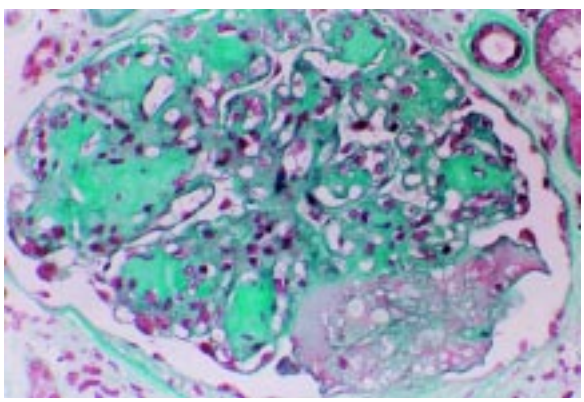

Fig. 3. *Focal mesangiolysis in diabetic glomerulosclerosis. Masson trichrome X 400.*

nodular glomerulosclerosis, glomerular capillary microaneurysms and repeated mesangiolysis, and they present the same picture like in diabetic glomerulopathy[20]. Capillary aneurysms and many mesangiolytic cystic lesions are reported to be prominent in cases with proliferative changes and conspicuous crescents formations[21,22].

A wide variety of glomerular lesions express circumferential mesangial interposition. The pathomorphogenesis of this interposition involves low-grade mesangiolysis and subsequent passive dislocation of mesangial cells towards the lateral wall of glomerular capillaries, though a high hydraulic pressure of blood, theories that advocate an active movement of mesangial cells. Circumferential mesangial interposition can disappear spontaneously or after treatment, suggesting that mesangial cells may return to the original site with their inherent contractility after the insults are removed, in order to restore handicapped filtering surfaces. But the precise mechanism of regression remains obscure[23].

Two rare cases of mesangiolysis have been reported, one in a patient under dieraty and drug therapy for weight loss[24] and one another in a patient with glomerular endocapillary proliferation of CD57 large granular lymphocytes,that caused glomerular endothelial injury by a cell-mediated cytolytic mechanism, resulting in the development of mesangiolysis and microaneurysm formation[25].

In five mentally retarded children with nephrotic syndrome due to focal segmental glomerulosclerosis, different degrees of mesangiolysis, beside segmental hyalinosis, developed into dissecting microaneurysms of the capillary loops[26].

In conclusion mesangiolysis, a type of glomerular injury that mainly affects the mesangium, can be seen in a variety of glomerular diseases, suggesting a primary mesangial injury due to anti-mesangial cell antibodies or toxins, an endothelial lesion with subsequent dissolution of the mesangium or a persistent or recurrent mesangial and/or endothelial damage.

Histopathologically the disrupted mesangium result in loss of glomerular anchoring sites, coalescence of adjacent loops and development of capillary microaneurysm. The mechanism of this injury differ from case to case and the coexistent morphologic features may indicate the underlying cause. Mesangiolysis due to primary mesangial cells injury is associated with cellular proliferation resembling segmental glomerulonephritis, while mesangiolysis secondary to endothelial injury is characterized by widening of the subendothelial space and accumulation of finely granular material containing fibrin and cell fragments. Mesangiolysis due to persistent or repeated mesangial and/or endothelial damage is often located at the periphery of sclerotic nodules due to diabetes mellitus, to immunoglobulin deposition disease or to membranoproliferative glomerulonephritis.

Περίληψη

Μ. Λεοντσίνη. **Μεσαγγειόλυση.**
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Η μεσαγγειόλυση είναι ένας τύπος σπειραματικής βλάβης, ο οποίος προσβάλλει κυρίως το μεσάγγειο. Παρατηρείται σε ποικιλία σπειραματικών νόσων και υποδηλώνει μεσαγγειακή βλάβη οφειλόμενη σε αντισώματα κατά των μεσαγγειακών κυττάρων ή σε επίδραση τοξινών, ενδοθηλιακή βλάβη με επακόλουθο την διάλυση του μεσαγγείου ή επαναλαμβανόμενη και εμμένουσα μεσαγγειακή ή/και ενδοθηλιακή βλάβη. Ιστοπαθολογικά με την λύση του μεσαγγείου προκαλείται αποκόλληση των θέσεων επαφής του σπειραματικού τριχοειδούς με το μεσάγγειο, συνένωση παρακειμένων αγκυλών και δημιουργία τριχοειδικών ανευρυσμάτων. Ο μηχανισμός γένεσης της βλάβης αυτής διαφέρει σε κάθε περίπτωση, ενώ η συνύπαρξη και άλλων μορφολογικών ευρημάτων είναι ενδεικτική της υποκείμενης αιτιοπαθογένεσης.

Στις περιπτώσεις στις οποίες η μεσαγγειόλυση οφείλεται σε πρωτοπαθή βλάβη μεσαγγειακών κυττάρων, αυτή συνοδεύεται από κυτταρική υπερπλασία και μοιάζει με τμηματική σπειραματονεφρίτιδα, ενώ όταν η μεσαγγειόλυση έπεται ενδοθηλιακής βλάβης χαρακτηρίζεται από διεύρυνση του υποενδοθηλιακού χώρου και συλλογή σε αυτόν λεπτοκοκκώδους υλικού με ινική και κυτταρικά συγκρίμματα.

Όταν η μεσαγγειόλυση είναι αποτέλεσμα εμμένουσας ή επαναλαμβανόμενης μεσαγγειακής ή/και ενδοθηλιακής βλάβης εντοπίζεται συνήθως στην περιφέρεια σκληρυντικών όζων οφειλόμενων σε σακχαρώδη διαβήτη, νόσο ανοσοεναποθέσεων ή μεμβρανοπαραγωγική σπειραματονεφρίτιδα.

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