Virchows Arch. A Path. Anat. and Histol. 381, 111–119 (1978)

Virchows Archiv A

Case Report

Granulomatous Glomerulonephritis, Without Systemic Disorder

J. Szabó*, I. Biró, T. Tóth, I. Worum, and Gy. Velok

Department of Pathology, Department of Pediatrics, I. Department of Medicine, and Department of Neurosurgery, University Medical School, Debrecen, Hungary

Summary. The case of a 12-year-old girl dying of renal insufficiency is described. At autopsy granulomatous glomerulonephritis was found without any systemic disease. The glomerular light-, immunofluorescent- and electron microscopic changes were studied. Four hundred glomeruli were analyzed by light microscopic investigation and graded (I–IV). By immunofluorescent investigation, intraglomerular and in the more severely affected glomeruli, periglomerular immunoglobulin deposition was detected. Electron microscopic investigation revealed mononuclear cells and fibroblasts in the glomerular and periglomerular cellular infiltrate, resulting in fragmentation and rupture of Bowman's capsule and loss of the glomerular structure.

Key words: Granulomatous glomerulonephritis – Light-, immunofluorescent-, electron microscopy.

Granulomatous glomerulonephritis is a rare, fatal renal disease, generally associated with Wegener's granulomatosis (Wegener, 1939; Former, 1950; Fienberg, 1953; Godman and Churg, 1954; Altmann and Schicke, 1959; Carrington and Liebow, 1966; Norton et al., 1968; Aldo et al., 1970; Heptinstall, 1974; Horn et al., 1974), polyarthritis (McManus and Hornsby, 1951) and periarteritis nodosa (Smith, 1948; Churg and Strauss, 1951; Mellors and Ortega, 1956; Patalano and Sommers, 1961; Paronetto and Strauss, 1962). Diphenylhydantoin sensibilization (Van Wyk and Hoffmann, 1948) and tuberculotoxic allergy (Simárszky, 1956) may also cause granulomatous glomerulonephritis. The histopathological picture is characterized by intra- and extracapillary cell infiltration, tuft necrosis, rupture of the glomerular basement membrane and periglomerular cell-infiltration. There are relatively few data concerning the immunofluorescent- and electron microscopic picture of the glomerular alterations. Aldo et al. (1970), Horn et al. (1974) have described glomerular ultrastructure in Wegener's granulomatosis, but in their cases no typical granulomatous glomerulonephritis was found.

* *Present address:* I. Department of Medicine, University Medical School, Debrecen, Hungary

0340-1227/78/0381/0111/$01.80

Mellors and Ortega (1956), Paronetto and Strauss (1962), Berger et al. (1971) have found gamma-globulin and fibrinogen deposition in the glomeruli by immunofluorescent investigation in cases of periarteritis nodosa with glomerular alterations. Our patient, a girl of 12 years, died of renal insufficiency. Pathological examination showed typical granulomatous glomerulonephritis, but a systemic disorder (Wegener's granulomatosis, polyarthritis, periarteritis nodosa, tuberculotoxic allergy and diphenylhydantoin sensibilization) was excluded.

Case Report

A 12-year-old girl, without any significant past history. Two months before presentation she suffered from influenza and her condition thereafter continually deteriorated. She was admitted to a county hospital with proteinuria and anaemia. During her first hospitalization extremely high BUN-(200 mg%) and serum-creatinin(16 mg%)-levels were measured. Peritoneal dialysis was carried out repeatedly resulting in diminished BUN-(85 mg%) and serum creatinin (9.2 mg%), but epileptiform convulsions and tetraparesis developed (blood pressure 190/120 mm Hg) and the girl was admitted to the Neurosurgical Department of our University Medical School. On the basis of neurological signs craniotomy and a partial temporal lobectomy was carried out for cerebral haemorrhage. The patient died 14 h after the craniotomy. Autopsy was carried out 140 min after death.

The most important autopsy findings were, as follows: heart weight 180 g, with dilated ventricles, the myocardium was flabby and yellowish-brown. Severe renal edema, catarrhal tracheobronchitis, acute peptic ulcers of the stomach and erosions of gastric mucosa were found. Light microscopy of the lung, bone marrow, spleen, liver, myocardium, paratracheal and paraaortal lymph nodes showed no changes characteristic of any systemic illness.

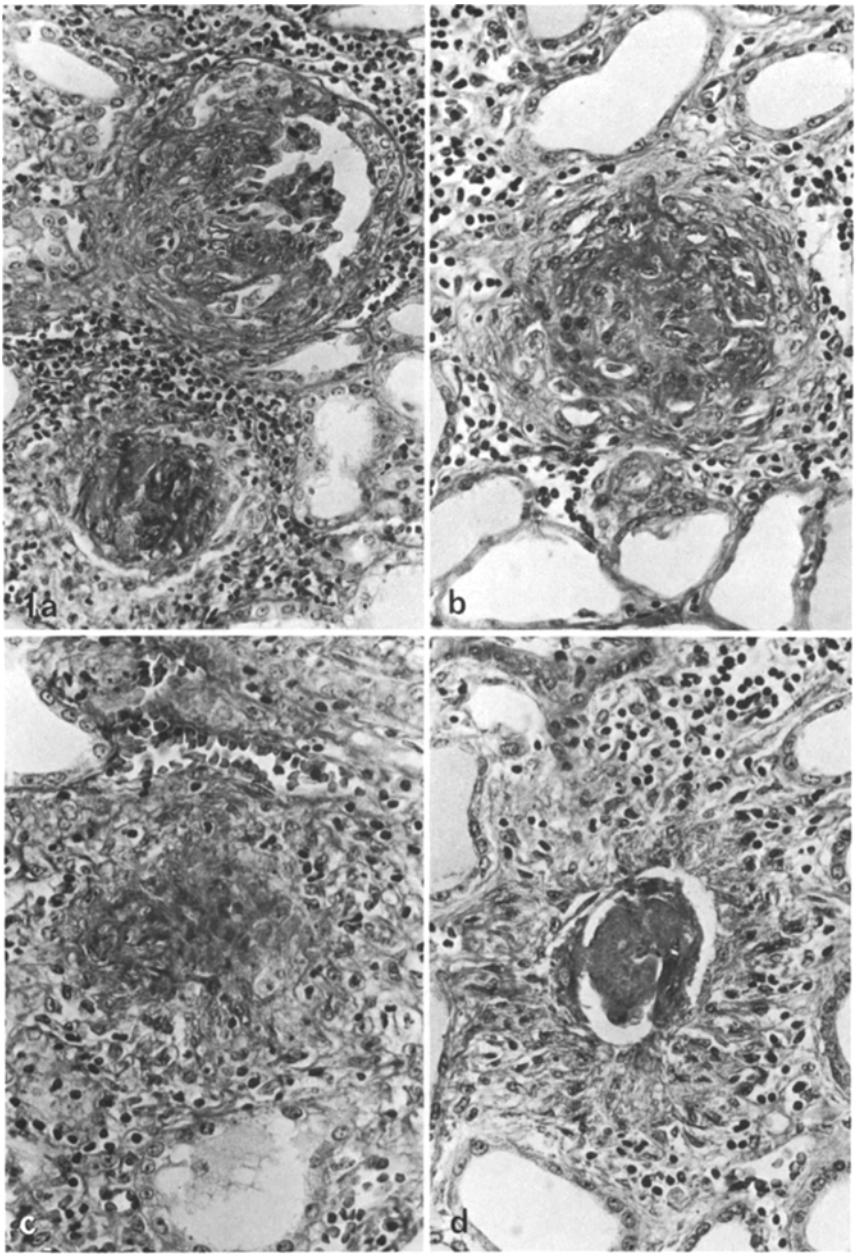
Pathology of the Kidneys

The kidneys were bigger than normal, weighing 250 g. The surface was smooth with 'flea-bitten' haemorrhagic spots. The cortex was widened (8 mm) and yellowish-red, the medulla hyperaemic.

Light microscopy was carried out after formalin fixation, H.E., van Gieson, combined trichrom, elastic van Gieson and PAS staining. For immunofluorescent investigations cryostat sections (5 μ thick) were incubated with FITC-labelled anti human IgA, IgG, IgM, fibrinogen and complement (C3).

Electron microscopic investigation was made after fixation in 3% glutaralde-

Fig 1 a–d. Light microscopic pictures. **a** Glomerular alteration, grade I.: Intensive capsular epithelial cell proliferation, Bowman's capsule is partly ruptured. The glomerular tufts are replaced by mononuclear cells. No patent capillary lumina. Elastic van Gieson, × 360. **b** Glomerular alteration, grade II.: In the place of glomerular tufts, mononuclear cells embedded in matrix-like material are seen. Bowman's capsule is completely destroyed. Note thin, periglomerular mononuclear cell infiltration. Elastic van Gieson, × 360. **c** Glomerular alteration, grade III.: In the central part of the glomerulus is hypocellular matrix-like material surrounded by dense mononuclear cell infiltration. Elastic van Gieson, × 360. **d** Glomerular alteration, grade IV: In the place of the glomerulus acellular, matrix-like material, surrounded by a thick, periglomerular, mononuclear cell infiltration is seen. Elastic van Gieson, × 360


a
b
c
d

hyd, postfixation in OsO_4, embedding in Durcupan (ACM, Fluka). The results of the various pathological examinations are detailed as follows.

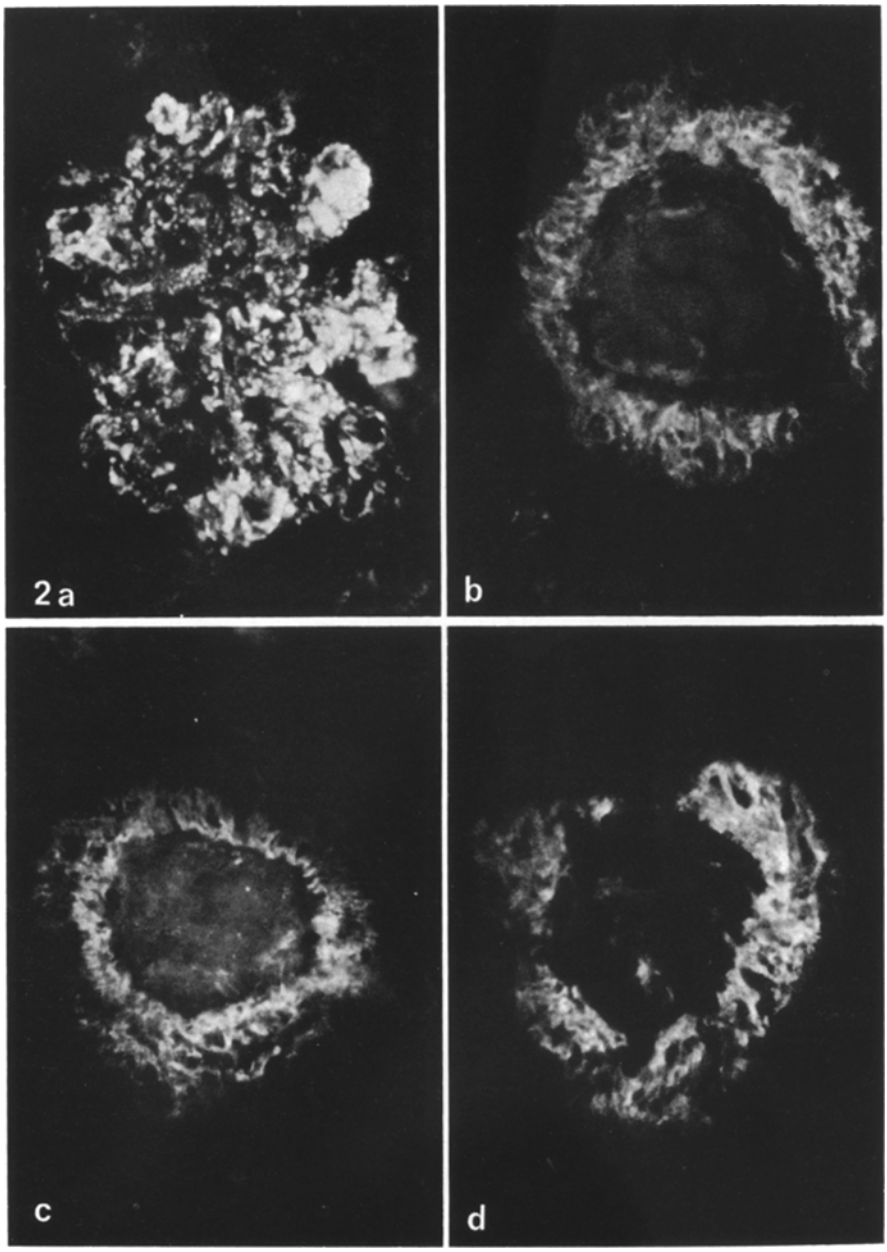
Light Microscopy

The glomerular alteration is extremely variable, and has been graded (I–IV grades). Four hundred glomeruli were examined with the following findings. Grade I changes were found in 14 of 400 glomeruli (3.5%). In these tufts the glomerular structure can be recognized. Glomerular hypercellularity, parietal epithelial cell proliferation, partial obliteration of glomerular capillaries and duplication of Bowman's capsule, are seen. Glomerular hypercellularity and capillary obliteration is due to invasion of mononuclear cells, but precise classification of the invading cells is impossible at the light microscopic level (Fig. 1a). Grade II occurred in 48 of 400 glomeruli (12%). Rupture of Bowman's capsule was seen with disorganization of glomerular structure; a narrow periglomerular mononuclear cell infiltrate is characteristic. Instead of glomerular capillaries, some mononuclear cells and PAS-positive material are seen (Fig. 1b). Grade III changes affected 106 of 400 glomeruli (26.5%). A wide, periglomerular, mononuclear cell infiltration is visible, the cells show palisade-like arrangement. In place of glomerular capillaries PAS-positive material and some cells are visible (Fig. 1c). Grade IV changes were seen in 232 glomeruli out of 400 (58%). Wide periglomerular mononuclear cell infiltration is visible. In place of glomerular tufts cell-free PAS-positive material is detectable (Fig. 1d).

Immunofluorescent Investigation

Grade I glomerular change shows a roughly granular, patchily linear IgA, IgG, C3 complement (intensity $+++$), fibrinogen and IgM deposition (intensity $+$) along the basement membrane and in the mesangial areas (Fig. 2a). Glomerular alteration grade II shows characteristic periglomerular IgA, IgG and C3 complement deposition (intensity $++$). Slight IgA, IgG and C3 complement and fibrinogen deposition in the glomeruli (intensity $+$) are also detectable (Fig. 2b). There is no IgM deposition.

Fig. 2a–d. Immunofluorescent pictures. **a** Glomerular alteration, grade I.: Granular IgA deposition in the glomerulus, intensity $+++$. ×360. **b** Glomerular alteration, grade II.: An intensive periglomerular (intensity $++$) and slight intraglomerular (intensity $+$) IgA deposition. ×360. **c** Glomerular alteration, grade III.: A very slight intraglomerular (intensity $+$) and intensive periglomerular (intensity $+++$) IgA deposition. **d** Glomerular alteration, grade IV.: Marked periglomerular (intensity $+++$) and slight (intensity $\pm$) intraglomerular IgA deposit. ×360


2a
b
c
d

Glomerular alteration, grade III shows a more intensive periglomerular immunoglobulin deposition (Fig. 2c), than seen in glomeruli of grade II change. Very slight IgA, IgG, C3 complement and fibrinogen deposition (intensity +) is present in the glomeruli. Periglomerular immunoglobulin deposition consists of IgA, IgG and C3 complement (intensity +++). There is no IgM deposition.

In severely affected glomeruli (Grade IV) an intensive periglomerular deposition of IgA, IgG and C3 complement (intensity +++) is detectable (Fig. 2d). There is no IgM deposition. The glomerular tufts have neither fibrinogen nor immunoglobulin deposits.

Electron Microscopic Investigation

In the 25 blocks embedded 42 glomeruli were found in semithin sections. Two glomeruli from each grade were selected for electron microscopic analysis.

Grade I. Many mononuclear cells are visible in the glomeruli. The cytoplasm is abundant in lysosomes and dilated endoplasmic reticular cisterns, several fibroblasts are also seen (Fig. 3). The glomerular tufts are collapsed, the basement membrane is slightly thickened. Mononuclear cells and fibroblasts are found in the capillary lumina and in the urinary space.

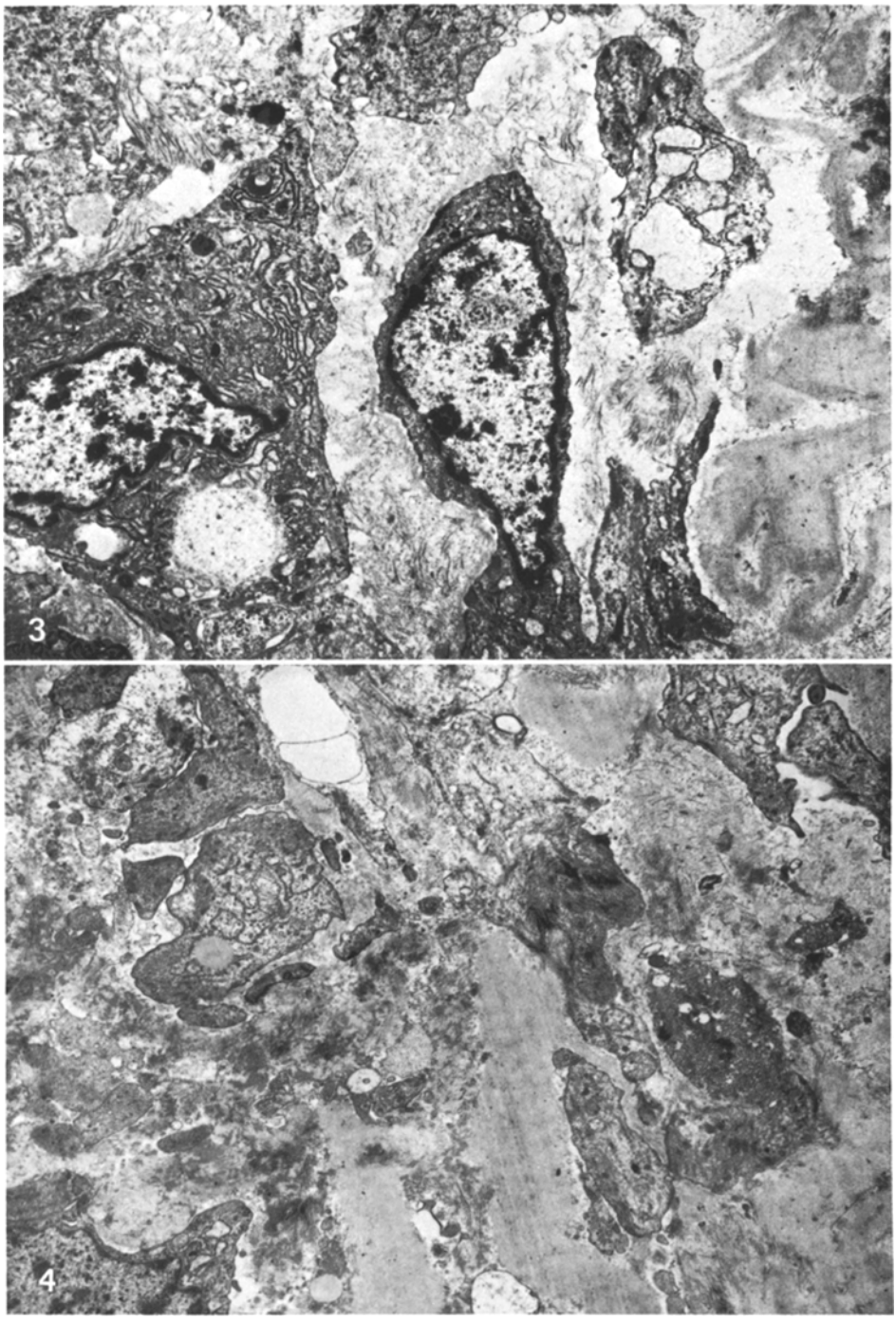
Grades II, III, and IV. Mononuclear cells and fibroblasts are found periglomerularly, and in the glomeruli in grades II and III Bowman's capsule is ruptured and fragmented. Among the infiltrating cells fibrillary material is visible as a matrix replacing the glomerular tufts (Fig. 4).

Discussion

In systemic diseases, i.e., polyarthritis, polyarteritis, the development of granulomatous glomerulonephritis can be explained by the disease itself. In cases of diphenylhydantoin sensibilization and tuberculotoxic allergy, the glomerular changes are probably the result of immunoglobulin deposition in the glomeruli. In our case, glomerular and periglomerular deposition of immunoglobulins was observed by immunofluorescent microscopy. The cells taking part in the glomer-

Fig. 3. Electron microphotograph. Glomerular alteration, grade I.: Part of a collapsed glomerulus (*right side of the picture*). Mononuclear cells with rough surface endoplasmic reticulum and lysosomes in their cytoplasm are visible in the extracapillary space. Elongated, fibroblast-like cells with fibrillary structures among them are also visible. Original magnification: ×4,800

Fig. 4. Electron photomicrograph: Glomerular alteration, grade III. Among mononuclear cells and fibroblast-like cells fibrillary structures and thick membrane fragments are seen representing remnants of the ruptured Bowman's capsule. Original magnification: ×4,800


3
4

ular and periglomerular reaction were mainly mononuclear. It is known that immunocomplexes deposited in the glomeruli can bind polymorphonuclear leukocytes and probably mononuclear macrophages (Huber et al., 1968) by their immune adherence properties (Hunsicker, 1975). These cells damage the basement membrane by discharged enzymes. It is noticable that in our case, polymorphonuclear leukocytes were not present, either intraglomerularly or extraglomerularly. In experimental acute serum sickness glomerulonephritis, the cells seen in the glomeruli are mainly mononuclear and the possibility of mesangial cell transformation into mononuclear macrophages has been raised (Kondo et al., 1972; Shigematsu et al., 1976; Szabó et al., 1977). In some forms of human glomerulonephritis also, mononuclear cells play an important role (Shigematsu et al., 1973; Beirne et al., 1977; Szabó et al., 1977). In cryoglobulinaemia glomerular alteration is due to mononuclear cell infiltration as described by Monga et al. (1976). In our case, a marked mononuclear cell infiltration was seen in the glomeruli and in the periglomerular reaction. We found immunoglobulin deposition in the affected glomeruli and periglomerularly. We suggest that the cause of this severe mononuclear infiltration is abundant immunoglobulin deposition in glomeruli. The glomerular mononuclear cell infiltration penetrates the glomerular capsule and results in a periglomerular cell collection. Systemic disease can be excluded in this case. Neither clinical data nor pathological examination could explain the cause of the fatal glomerular changes. As far as we know none of the medicines administered had toxic or allergic properties.

References

Aldo, M.A., Benson, M.D., Comerford, F.R., Cohen, A.S.: Treatment of Wegener's granulomatosis with immunosuppressive agents. Description of renal ultrastructure. Arch. Intern. Med. **126**, 298–305 (1970)

Altmann, H.W., Schiche, H.: Ein Beitrag zur Histologie und zur Einordnung der Wegenerschen Granulomatose. Beitr. Pathol. Anat. **121**, 211–241 (1959)

Beirne, G.J., Wagnild, J.P., Zimmerman, S.W., Macken, P.D., and Burkholder, P.M.: Idiopathic crescentic glomerulonephritis. Medicine **56**, 349–382 (1977)

Berger, J., Yaneva, H., Hinglais, N.: Immunohistochemistry of glomerulonephritis. In: Advances in nephrology. (Hamburger, J., Crosnier, J., and Maxwell, M.H., eds.) Vol. 1. Chicago: Year Book 1971

Carrington, C.B., Liebow, A.: Limited forms of angiitis and granulomatosis of Wegener's type. Am. J. Med. **41**, 497–527 (1966)

Churg, J., Strauss, L.: Allergic granulomatosis, allergic angiitis and periarteritis nodosa. Am. J. Pathol. **27**, 277–301 (1951)

Fienberg, R.: Necrotizing granulomatosis and angiitis of lungs with massive splenic necrosis and focal thrombotic granulomatous glomerulonephritis. Am. J. Clin. Pathol. **23**, 413–428 (1953)

Former, F.: Über die granulomatöse Periglomerulitis. Schweiz. Zschr. allg. Pathol. **13**, 42–59 (1950)

Godman, G.C., Churg, J.: Wegener's granulomatosis, pathology and review of literature. Arch. Pathol. **58**, 533–553 (1954)

Heptinstall, R.H.: Pathology of the kidney. 2nd. ed. Boston: Little, Brown 1974

Horn, R.G., Fauci, A.S., Rosenthal, A.S., Wolff, S.M.: Renal biopsy pathology in Wegener's granulomatosis. Am. J. Pathol. **74**, 423–440 (1974)

Huber, H., Polley, M.J., Linscott, W.D., Fudenberg, H.H., Müller-Eberhard, H.J.: Human monocytes: Distinct receptor sites for the third component of complement and for immunglobulin G. Science **162**, 1281–1283 (1968)

Hunsicker, L.G.: The role of complement in glomerulonephritis. Milit. Med. **140**, 614–617 (1975)
Kondo, Y., Shigematsu, H., Kobayashi, Y.: Cellular aspects of rabbit Masugi nephritis. II. Progressive glomerular injuries with crescent formation. Lab. Invest. **27**, 620–631 (1972)
McManus, J.F.A., Hornsby, A.T.: Granulomatous glomerulonephritis associated with polyarthritis, report of a case. Arch. Pathol. **52**, 84–90 (1951)
Mellors, R.C., Ortega, L.G.: Analytical pathology, new observations on pathogenesis of glomerulonephritis, lipoid nephrosis, periarteritis nodosa and secondary amyloidosis in man. Am. J. Pathol. **32**, 455–499 (1956)
Monga, G., Mazzucco, G., Coppo, R., Piccoli, G., Coda, R.: Glomerular findings in mixed IgG-IgM cryoglobulinemia. Light, electron microscopic, immunofluorescence and histochemical correlations. Virchows Arch. Cell. Pathol. **20**, 185–196 (1976)
Norton, W.L., Suki, W., Strunk, S.: Combined corticosteroid and azathioprine therapy in two patients with Wegener's granulomatosis. Arch. Intern. Med. **121**, 554–560 (1968)
Paronetto, F., Strauss, L.: Immunocytochemical observations in periarteritis nodosa. Ann. Intern. Med. **56**, 289–296 (1962)
Patalano, V.J., Sommers, S.C.: Biopsy diagnosis of periarteritis nodosa: Glomerulonephritis and renal arteriolitis as aids. Arch. Pathol. **72**, 1 (1961)
Shigematsu, H., Kobayashi, Y.: Accelerated serum sickness in the rabbit. II. Glomerular ultrastructural lesions in transient proliferative and progressive disorganizing glomerulonephritis. Virchows Arch. Pathol. Anat. **369**, 269–282 (1976)
Shigematsu, H., Shishido, H., Kuhara, K., Tsuchida, H., Suzuki, H., Hirose, K., Tojo, S.: Participation of monocytes in transient glomerular hypercellularity in poststreptococcal glomerulonephritis. Virchows Arch. Cell. Pathol. **12**, 367–370 (1973)
Simárszky, J.: Besondere tuberkulotoxische Form von granulomatöser Periglomerulitis. Zentralbl. Allg. Pathol. **95**, 177–180 (1956)
Smith, J.F.: Disseminated focal necrosis with eosinophilia and arteritis in case of asthma. J. Pathol. Bacteriol. **60**, 489–494 (1948)
Szabó, J., Szabó, T., Lustyik, Gy., Lenkey, A.: Experimental studies on factors causing acute serum sickness glomerulonephritis of immune complex origin. II. Pathomorphological analysis. Int. Urol. Nephrol. **9**, 267–281 (1977)
Szabó, J., Szabó, T., Tóth, T., Kakuk, Gy., Lustyik, Gy.: A human case of "Immune complex glomerulonephritis without depositis". Acta Med. Acad. Sci. Hung. **34**, 35–41 (1977)
Van Wyk, J.J., Hoffmann, C.R.: Periarteritis nodosa, case of fatal exfoliative dermatitis resulting from "dilantin sodium" sensitization. Arch. Intern. Med. **81**, 605–611 (1948)
Wegener, F.: Über eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arteriensystems und der Nieren. Beitr. path. Anat. Allg. Path. **102**, 36–68 (1939)

Received May 10, 1978; Final version August 21, 1978