Yonsei Medical Journal
Vol. 15, No. 2, 1974

Mesangial IgA/IgG Deposit Glomerulonephritis[1]

Suk Ho Chung[1],*, Sung Soon Kim*, Hong Do Cha*, Jung Sil Cho**
and In Joon Choi[1],**

Departments of Internal Medicine and Pathology**, Yonsei University, College of Medicine*
Seoul, Korea

ABSTRACT

Percutaneous renal biopsy was performed on a 34 year old male patient with mild proteinuria and microhematuria. Histopathologic examination showed a focal mesangiopathic glomerulonephritis, simulating a "minimal change" disease pattern by light microscope. Granular deposits of IgA, C_3, IgG, IgM, and fibrinogen were present in the glomerular mesangial area by immunofluorescent technique. A special prevalence of IgA was found. The intensity of immunofluorescent staining was correlated with the mesangial proliferative reaction by light microscopy. Electron microscopy showed electron dense granular deposits in the mesangial areas. The glomerulonephritis in this patient was related with the IgA antibody associated mesangial immune complex deposit disease mediated by the classic complement pathway. This glomerulonephritis is known to have a good prognosis. The antigenic nature, the reason of predominant immune deposits in the mesangium, and the mechanism of a special prevalence of IgA and IgM immunoglobulin classes are discussed, and special attention to the value of immunofluorescent study of renal diseases, with a review of the literature, is given.

(1) This research is supported by a part of the Faculty Research Grant, Yonsei University College of Medicine, 1974.
Presented in part at the 18th Annual Meeting of Heart Association, Seoul, Korea, November, 30, 1974.

INTRODUCTION

With light microscopy of the mesangiopathic renal lesions in renal biopsy specimens, a pathologist might classify half of adult cases as focal glomerulonephritis, a tenth as normal kidney, and the remainder as chronic glomerulonephritis. Since the introduction of the renal biopsy technic, using electron microscopic and particularly immunofluorescent examinations, considerable expansion of our understanding of human glomerular diseases has been made, not only about the etiology and pathogenesis of the diseases, but also the disease intensity and also that related to the prognosis by the treatment.

Particularly by using the fluorescent antibody technique, recently it has been able to describe a form of glomerulonephritis characterized by diffuse mesangial deposition of immunoglobulin and complement components in the glomerular mesangium in patients with recurrent or persistent hematuria, in which

either a special prevalence of IgA (Berger & Hinglais, 1968; Berger, 1969; Druet et al, 1970; Mckluskey, 1971; Hyman et al, 1973; Lowance et al, 1973) or IgM (Hyman et al, 1973; Roy et al 1973; van de Putte et al, 1974) was most frequently deposited. Therefore, a special role for IgA has been stressed by some investigators and denied by others, as above.

Quite recently, we have had experience of a case with mild proteinuria and microhematuria, showing mesangiopathy by light microscopy, and special prevalence by immunofluorescent technique of IgA deposit and very slight IgM deposit in the mesangium. This is the first case report in our country, given with special attention to the value of immunofluorescent study of renal diseases, and with review of the literature.

MATERIALS AND METHODS

A. Patient and Laboratory Data:

A 34 year old Korean male (Unit No.; 613931) was admitted to Yonsei University Severance Hospital on October 31, 1974, with the chief complaints of recurrent occipital headache, nausea and gross hematuria for three days.

Past history revealed recent hospitalization for gross hematuria at Seoul Transportation Hospital for one month around August 20, 1974, about 5 to 6 days after tonsillitis (?), under the diagnosis of acute glomerulonephritis, and later discharge with improvement.

Physical examination was unremarkable, except for slight edema in the face. Blood pressure was 110/70 mmHg. and no pitting edema was present.

Laboratory studies were recorded as follows; hemoglobin, 12.1 gm%; hematocrit, 35%; W.B.C., 9,900/mm^3 with 76% neutrophils, 23% lymphocytes, 1% eosinophils; urinary pH., 7.0; S.G., 1.008; urine protein, trace; urine RBC, 5 or 10 to many/Hpf; occasional WBC/Hpf; platelets, 172,000/mm^3; reticulocytes, 1.2%; E.S.R., 38mm/hr (corrected 20); total serum protein, 6.8 gm/100 ml with 4.4 albumin and 2.4 globulin; total cholesterol, 100 mg/100 ml; prothrombin time, 12.8 sec. (100% normal); alkaline phosphatase, 1.7 S.U.; Na, 133 mEq/l; K, 4.4; Cl, 102; CO2 content, 24; Ca, 9.8 mg/100 ml; phosphorus, 3.5; ASO titer, 1:166 reactive; total urinary protein for 24 hours, 82.5 mg; creatinine, 1023 mg; Addis count, casts 197,000/12 hrs, RBC 8,060,000/12 hrs, WBC, 1,830,000/12 hrs.

Intravenous pyelography showed a slightly enlarged left kidney (left, 14×5.5 cm.; right, 12×5.6 cm.). Renal arteriography showed no particular abnormality except findings suggestive of double renal artery.

On the 6th hospital day percutaneous renal biopsy was performed, and on the 9th hospital day, the patient was discharged, and is now on a follow-up study.

B. Renal Biopsy:

The percutaneous renal biopsy specimen was divided into two parts, and immunofluorescent, electron microscopic and histopathologic examinations were performed.

The first part of the specimen for immunofluorescent technique was immediately frozen in a dry ice-acetone mixture, cut in 3 to 4 micron thickness by cryostat, and exposed to the FITC-conjugated antihuman sera fractions. The second part of the specimen for electron microscopy was fixed in osmium

tetraoxide, stained by the usual double method, and examined with an Hitachi model HE-11 electron microscope. A third part, actually a division of the first part after it was frozen-cut for immunofluorescent examination, was fixed in 10% neutral formalin and cut in 5 to 6 micron thickness, and stained with hematoxylin-eosin, periodic acid Schiff, Masson's trichrome, and methenamine-silver-periodic acid Schiff methods, and examined with the light microscope.

The FITC-conjugated anti-human sera fractions are; anti-human immunoglobulins (IgG, IgA, IgM), and anti-human IgG, anti-human IgA, antihuman IgM, anti-human beta 1C globulin (C_3), and anti-human fibrinogen from the Hyland company. The antinuclear antibody test with patient serum was also performed.

RESULTS

Histopathologic section (S-74-4635) demonstrated a total of 6 glomeruli, one of which showed almost complete sclerosis, but the rest showed normal-appearing glomeruli. Special stainings such as periodic acid Schiff's, Masson's trichrome, and methenamine-silver-P. A. S. showed normal thickness of the basement membrane, but prominent mesangial widening with obvious P. A. S. positive materials. The tubules and interstitials including arteries were not remarkable.

Antinuclear antibody test (ANA-74-46) with the patient serum was negative. The tissue for immunofluorescent examination (RB-74-26) was the same as that of routine histology, which also demonstrated a total of 6 glomeruli. FITC-conjugated anti-human fractions such as immunoglobulins (IgG, IgA, IgM), IgG, IgA, IgM, C_3, and fibrinogen were exposed by the direct method. The intensity of fluorescence was slightly variable but granular deposits of IgA was most significantly found, particularly in the mesangium with more than two plus intensity, and slightly less intensity in C_3. IgG showed minimal and one plus intensity, and IgM and fibrinogen were trace intensity.

Electron microscopic findings were consistent with the histopathologic and immunofluorescent findings, and showed variable amounts of electron dense rather fine granular deposits mainly in the mesangium with widening of the mesangial matrix. The basement membrane appeared not particularly remarkable, sometimes with irregular foldings. The endothelium was slightly to sometimes moderately swollen, and the epithelium was also slightly swollen. Neither microtubular structures nor virus-like particles were found.

DISCUSSION

Our case showed a history of sore throat, gross hematuria and slight edema of the face. Laboratory data included microhematuria, and trace proteinuria with a total of 82.5mg. of urinary protein for 24 hours, and some casts. Antinuclear antibody test was negative. The glomerular histopathology showed mesangiopathic glomerulonephritis, with a diffuse, mainly mesangial granular deposits of immunoglobulins and complement components, specific prevalence of IgA and complement (C_3) with minimal deposits of IgG and IgM. Electron microscopy showed electron dense granular deposits in the mesangium, but the peripheral capillary loops, foot process, and epithelium were not remarkable, except for slight swelling

of endothelium. Neither subepithelial nor subendothelial deposits were particularly found. These immunofluorescent and ultrastructural findings indicated immune complex deposition, and complement-mediated immune complex deposit mesangiopathic glomerulonephritis. The histopathological, immunofluorescent, and ultrastructural findings appeared to be well correlated with the intensity or activity of the glomerular lesions.

Berger first described this lesion (Berger and Hinglais, 1968; Berger, 1969) which was once called Berger's IgA/IgG deposit disease. He (1969) reported briefly an immunofluorescent study of renal biopsies, in which a group of 55 of 300 patients aged 10 to 51 years showed microscopic hematuria and minimal proteinuria (less than 1 gm. per day) with focal glomerulitis. Twenty two of these showed intermittent gross hematuria, in all of which renal biopsies showed diffuse intercapillary deposits (mesangial) of IgA, IgG, and beta 1 C globulin, and the course of this disease was said to be "remarkably slow". Labovitz et al. (1968) reported a total of 21 cases of benign hematuria with focal glomerulitis in adults during a 4-year period, and said the short term prognosis for 2 to 10 years was excellent for adults with hematuria, minimal proteinuria, and idiopathic focal glomerulitis who had normal blood pressure and renal function, but immunofluorescent stains for IgA or IgM in their materials were not done.

The deposits of immunoglobulin and complement components in the glomerular mesangium have been reported in patients with recurrent, benign, persistent hematuria (Berger and Hinglais, 1968; Beger. 1969; Druet et al, 1970; McCluskey 1971; Hyman et al, 1973; Lowance et al, 1973; Roy et al, 1973; van de Putte et al. 1974) and the alternate (Hyman et al, 1973) and classic (Roy et al, 1973) pathways of complement activation have also been described. However a special prevalence of IgA deposit in the mesangium (Berger and Hinglais, 1968; Berger, 1969; Druet et al, 1970; McCluskey, 1971; Hyman et al, 1973; Lowance et al, 1973, was described more than of IgM (Ferris et al, 1967; Druet et al, 1970; Germuth and Rodriguez, 1973). In our case, a special prevalence of IgA and complement with alower intensity deposit of IgG, and trace deposits of IgM were found.

In most immunologically mediated glomerulonephritis in humans, the information about the antigenic nature is not known. Viruses (Smith and Aquino, 1971), however, have been suggested as a factor in recurrent hematuria. Preferential mesangial immune complex deposits have been shown in lupus glomerulitis (Koffler et al, 1969), and Germuth and Rodriguez (1973) also have shown preferential mesangial immune complex deposits in their diagram of human lupus mesangiopathy and lupus mesangiopathic glomerulonephritis which may progress to disseminated mesangiopathic glomerulonephritis. They were again shown in chronic virusinduced experimental animals (Germuth and Rodriguez, 1973), and heterologous proteininduced experimental glomerulonephritis (Germuth and Rodriguez, 1973). Germuth and Rodriguez (1973) have postulated that in the chronic B. S. A. -rabbit system, soluble small sized complexes with low level antibody producers ——Class I immune complex——deposited in the capillary loops and produce diffuse proliferative or membranous glomerulonephritis, but larger-sized complexes with intermediate level antibody producers——Class Ⅱ immune

complex——are deposited in the subendothelial and mainly mesangial (subendothelial-mesangial system) areas. Recently, Lee, et al. (1974) by immunofluorescent and electronm icroscopic examinations confirmed that larger-sized macromolecular complexes reoriented due to prednisolone and cyclophosphamide treatment, are deposited in the subendothelial zone, where they may be in contact with mesangial cells by transient or partial mesangial interposition, and are transported to the mesangial system in acute serum sickness induced rabbits. Dixon (1962-63) said in a lecture that larger sized immune aggregates may first accumulate in the mesangium. It is, thus, known that both quality and quantity of antibody determine immune complex size and tissue localization.

The quality of antibody as well as the quantity has been studied in the chronic B. S. A. -rabbit system (Germuth and Rodriguez, 1973, Kuriyama, 1973), and it has been shown that low-avidity, non-precipitating antibodies favored capillary deposition of immune complexes, but high-avidity precipitating antibodies are only deposited predominantly in the mesangium. It can be assumed, therefore, that larger-sized immune aggregates consisting of high-affinity antibody tend to deposit their immune complexes in the mesangium. Moreover, the larger-sized complexes fix complement well (Lightfoot, 1970). Van de Putte, et al. (1974) studied 47 renal biopsied patients with recurrent or persistent hematuria, and 15 of 24 immunofluorescent examined cases showed IgM, 10 IgA, and 2 showed IgG. In our case, large amounts of complement were deposited in the mesangium, and IgA was predominantly deposited in the mesangium but IgM was only a trace and IgG was lower in its intensity.

This kind of glomerular lesion with recurrent or persistent hematuria generally appears to carry a favorable prognosis. In addition to clinical follow-up studies (Ayoub and Vernier, 1965; Ferris, et al, 1967; Singer et al, 1968; Arneil et al, 1969; Berger, 1969; Johnston and Shuler, 1969; Rapoport et al, 1970; Hendler et al, 1972; Ross, 1972), also repeated renal biopsies (van de Putte et al, 1974) showed no progression. However, there are reports of mesangial immune deposits which terminated in renal insufficiency (Berger, 1969; Druet et al, 1970; Lowance et al, 1973). Therefore, though this mesangial immune complex deposit glomerulonephritis with recurrent and persistent hematuria represents the benign clincal part of glomerular disease with chronic immune deposits, study of the antigenic nature, the pathogenetic mechanism of particular mesangial localization of IgA or IgM classes and the future outcome with renal biopsy particularly using immunofluorescent technique and clinical follow-up, seem to be interesting and important.

REFERENCES

Arneil, G. C., Lam, C. N. McDonald, A. M.: *Recurrent Hematuria in 17 Children. Brit. Med. J. 2:233-235, 1969.*

Ayoub, E. M., and Vernier, R. L.: *Benign Recurrent Hematuria. Am. J. Dis. Child. 109:217-223, 1965.*

Berger, J., and Hinglais, N.: *Les dépots intercapillaires d'IgA-IgG. J. Urol., Paris 74:694, 1968.*

Berger, J.: *IgA glomerular deposits in renal disease. Transplant. Proc. 1:939-944, 1969.*

Dixon, F. J.: *The Role of Antigen-Antibody Complexes in Disease. Harvey Lect. 58:21, 1962-1963.*

Druet, P., Bariety, J., Bernard, D. et. al.: *Les*

glomerulopathies primitives a depots mesangiaux d'IgA et d'IgG; etude clinique et morphologique de 52 cas. Presse Med. 78:583-587, 1970.

Ferris, T. F., Gorden, P., Kashgarian, M. and Epstein, F. H.: *Recurrent Hematuria and Focal Nephritis. N. Engl. J. Med. 276:770-775, 1967.*

Germuth, F. G., Jr., and Rodriguez, E.: *Chronic B. S. A.-Rabbit System; Spontaneous Animal Diseases; Progression from Focal to Disseminated Mesangiopathic Glomerulonephritis. Immunopathology of the Renal Glomerulus. Boston, Little, Brown and Co. 1973, pp. 22. pp. 45. pp. 134, & 209.*

Hendler, E. D., Kahgarian, M., Hayslett, J. P.: *Clinicopathological Correlations of Primary Hematuria. Lancet 1:458-463, 1972.*

Hyman, L. R., Wagnild, J. P., Beirne, G. J., et. al.: *Immunoglobulin-A distribution in Glomerular Disease; Analysis of Immunofluorescence Localization and Pathogenetic Significance. Kidney Int. 3:397-408, 1973.*

Johnston, C., and Shuler, S.: *Recurrent Hematuria in Childhood; A Five-Year Follow-up. Arch. Dis. Child 44:483-486, 1969.*

Koffler, D., Agnello, V., Carr, R. I. and Kunkel, H. G: *Variable Patterns of Immunoglobulin and Complement Deposition in the Kidneys of Patients with Systemic Lupus Erythematosus. Am. J. Path. 56:305-316, 1959.*

Kuriyama, T.: *Chronic Glomerulonephritis induced by Prolonged Immunization in the Rabbit. Lab. Invest. 28:224-235, 1973.*

Lee, Yong B., Choi, I. J., and Lee. Yoo B.: *The Influence of Prednisolone and Cyclophosphamide on the Experimental Acute Serum Sickness Glomerulonephritis. Yonsei J. Med. Sci. 7#2;151-169 1974.*

Labovitz, E. D., Steinmuller, S. R., Henderson, L. W., McCurdy, D. K., Goldberg, M.: *"Benign" Hematuria with Focal Glomerulitis in Adults. Ann. Int. Med. 77:723-729, 1972.*

Lightfoot, R. W., Jr., Drusin, R. E., and Christian, C. L.: *Properties of Soluble Immune Complexes. J. Immunol. 105:1493-1500, 1970.*

Lowance, D. C., Mullins, J. D., and McPhaul, J. J., Jr.: *Immunoglobulin A (IgA) associated glomerulonephritis. Kidney Int. 3;167-176, 1973.*

McCluskey, R. T.: *The Value of Immunofluorescence in the Study of Human Renal Disease. J. Exp. Med. 134: Supp.;247-255, 1971.*

Rapoport, A., Davidson, D. A., Deveber, G. A., Ranking, G. N. and McLean, C. R.: *Idiopathic Focal Proliferative Nephritis associated with Persistent Hematuria and Normal Renal Function. Ann. Int. Med. 73:921-928, 1970.*

Ross, J. H.: *Recurrent Focal Nephritis. Q. J. Med. 29:391-406, 1972.*

Roy, L. P., Fish, A. J., Vernier, R. L. and Michael, A. H.: *Recurrent Macroscopic Hematuria, Focal Nephritis, and Mesangial Deposition of Immunoglobulin and Complement. J. Ped. 82:767-772, 1973.*

Singer, D. B., Hill, L. L. Rosenberg, H. S. Manshall, J. and Swenson, R.: *Recurrent Hematuria in Childhood. N. Engl. J. Med. 279:7-12, 1968.*

Smith, R. D., and Aquino, J.: *Viruses and the Kidney. Med. Clin. North. Am. 55:89-106, 1971.*

van de Putte, L. B. A., de la Riviere, G. B., and van Breda Vriesman, J. C.: *Recurrent or Persistent Hematuria; Sign of Mesangial Immune complex Deposition. N. Eng. J. Med. 290:1165-1170, 1974.*

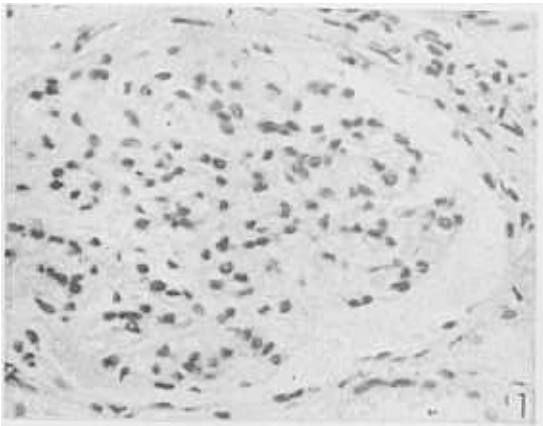
Fig. 1. A high-powered glomerulus shows mesangial proliferative change with normal thickness of basement membrane. hematoxylin-eosin stain. 430×.

Fig. 2. Immunofluorescent examination shows prominent and high intensity granular deposits of IgA particularly in the mesangium. stain for IgA. 430×.

Fig. 3. Immunofluorescent examination shows several scattered granular deposits of one plus intensity in the mesangium. stain for IgG. 430×.

Fig. 4. Immunofluorescent examination shows scattered granular deposits of two plus intensity in the mesangium. stain for C_3. 430×.

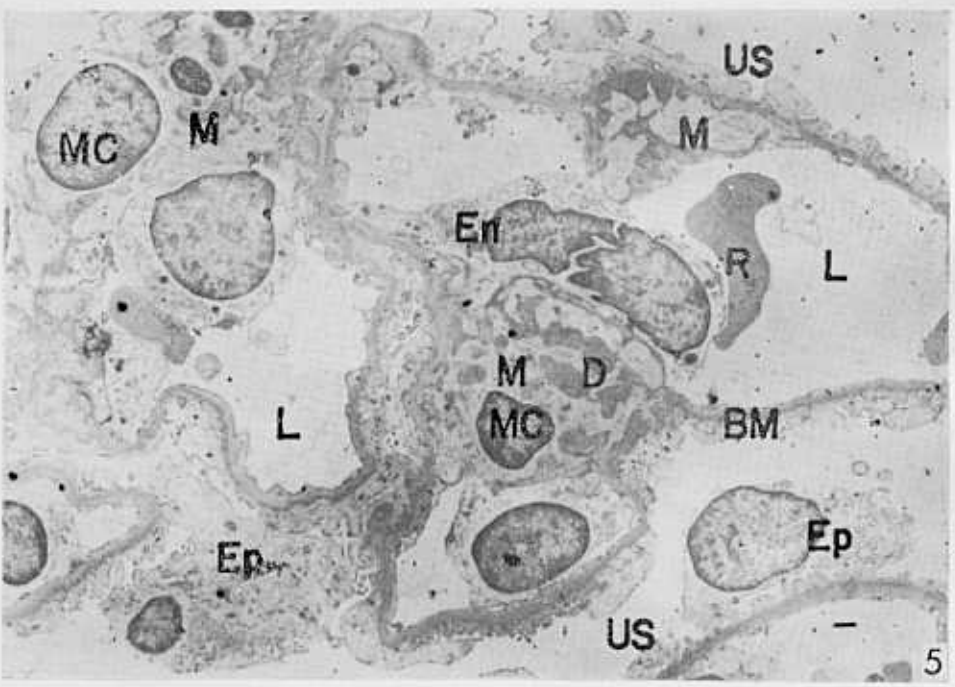
Fig. 5. Electron micrograph shows mesangial widening and accentuation with electron dense deposits within the mesangium. The lumen is patent, and the capillary wall and foot processes are not remarkable. The endothelial cells are slightly swollen. 4,500×. US, urinary space; L, lumen; R, RBC; Ep, epithelium; BM, basement membrane; En, endothelium; M, mesangium; MC, mesangial cell; D, electron dense immune deposits.


1


2


3


4



5