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NEPHROLOGY FORUM

Idiopathic IgA nephropathy

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Case presentation

A 54-year-old white man was admitted to the New England Medical Center (NEMC) for a percutaneous renal biopsy. Four years earlier mild hypertension and 3+ proteinuria had been discovered during a routine physical examination. At that time the serum creatinine was 1.2 mg/dl and the BUN was 15 mg/dl. Intravenous pyelography revealed normally functioning kidneys; the right measured 12.5 cm and the left 13.5 cm. Treatment with hydrochlorothiazide and reserpine was begun. Two and one-half years before admission, the serum creatinine was 1.8 mg/dl and the BUN was 24 mg/dl. One and one-half years before admission, urinalysis revealed 4+ protein and 15 to 25 red blood cells per high-power field; the serum creatinine was 2.1 mg/dl and the BUN 29 mg/dl. Three months prior to admission the serum creatinine was 2.6 mg/dl and the BUN 28 mg/dl; 24-hour urine protein excretion was 12 g.

Physical examination revealed a blood pressure of 200/100 mm Hg. Funduscopic examination showed only arteriovenous nicking. The lungs were clear to percussion and auscultation. Cardiac examination revealed normal S1 and S2 sounds without rubs, murmurs, or gallops. There was 1+ pretibial edema. The remainder of the examination was unrevealing.

Laboratory studies revealed the following pertinent data. Urinalysis disclosed a specific gravity of 1.017, a pH of 6, 2+ protein, and 2+ blood. Microscopic examination of the sediment revealed 50 to 80 red blood cells and 1 to 3 white blood cells per high-power field, hyaline casts, and one pigmented cast. A urine culture was sterile. The serum creatinine was 3.8 mg/dl and the BUN was 38 mg/dl. The 24-hour urine protein excretion was 5.7 g. Light microscopic study of the renal biopsy material revealed benign nephrosclerosis and acute interstitial nephritis with eosinophils predominating in the cell infiltrate. Immunofluorescence microscopy revealed 4+ mesangial deposits of IgA, trace to 2+ mesangial deposits of IgG, trace to 3+ mesangial deposits of C3, trace to 1+ mesangial deposits of C4, and no IgM; these findings were thought to be diagnostic of IgA nephropathy. A short course of prednisone, given to treat possible diuretic-induced allergic interstitial nephritis, had no demonstrable effect, and the patient's renal function continued to deteriorate. Sixteen months after the renal biopsy was performed, the serum creatinine was 10.2 mg/dl and the BUN was 111 mg/dl. Hemodialysis was instituted and plans were made for renal transplantation.

Discussion

DR. JOSÉ L. RODICIO (*Jefe del Servicio de Nefrologia, Ciudad Sanitaria de la Seguirdad Social 1° de Octubre, Madrid, Spain*): Before considering the manifestations of this interesting condition and its features in the patient presented today, let us first define IgA nephropathy and distinguish it from other renal diseases.

Definition

Berger and Hinglais first characterized IgA nephropathy in 1968 [1], although Galle and Berger had described a similar glomerular nephropathy with "intercapillary fibrinoid deposits" in 1962 [2], and Galle had observed these deposits on electron microscopy in 1964 [3]. Idiopathic IgA nephropathy is characterized pathologically by the presence of diffuse, granular mesangial IgA deposits and, by definition, by the absence of any recognizable systemic disease. All the patients originally described by Berger with IgA mesangial glomerulonephritis or idiopathic IgA nephropathy had normal renal function, macro- or microscopic hematuria, and proteinuria. Both the hematuria and proteinuria were exacerbated by upper respiratory tract infections [1, 4–6].

Because diffuse mesangial IgA deposits are observed in a variety of disorders, the diagnosis of idiopathic IgA nephropathy can be made only by exclusion. These associated disorders include alcoholic cirrhosis [7–10] and certain systemic diseases [11–17]. The systemic diseases in which mesangial deposits of IgA are regularly observed include Henoch-Schönlein purpura [11–13], systemic lupus erythematosus [14, 15], acute hepatitis [16], and ankylosing spondylitis [17]. Finally, these deposits occasionally have been found in patients with familial immunothrombocytopenia [18, 19], pulmonary hemosiderosis [20], and scleritis [21].

There is a lack of uniformity in the literature in the definition of IgA nephropathy. Some authors include every patient whose

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biopsy discloses IgA in the mesangium whether or not systemic disease coexists [7–17]. Because the clinical presentation and prognosis are related to the cause of this disorder, interpretation of studies grouping all patients with IgA mesangial deposits together is difficult. Therefore, in this analysis I have reserved the term idiopathic IgA nephropathy for only those patients in whom systemic disease has been excluded.

Clinical features

Our experience is based on 140 cases of idiopathic IgA nephropathy studied in the Jimenez Diaz Foundation and 1° de Octubre Hospital in Madrid. The 140 cases represent 24% of all the primary glomerulonephritis observed in both hospitals during the last 6 years. The incidence of idiopathic IgA nephropathy varies widely from one country to another; it is only 2% to 8% in the United States, the United Kingdom, and Canada [6, 14, 15, 22–25]; 18% to 25% in France, Italy, and Australia [1, 26–29]; and 21% to 34% in Japan [30, 31]. The explanation for this apparent variability in incidence is uncertain, but it might be related in part to differences in the indications for renal biopsy at various locations. Berger, Yaneva, and Crosnier observed that IgA nephropathy was responsible for 10% of all cases of advanced renal insufficiency in transplanted patients whose kidneys were studied histologically [27].

The patient population is 65% to 89% male [1, 14, 24, 29, 32–35], and the incidence peaks between ages 10 and 30 years [26, 36–38]. The age and sex distribution at initial presentation of IgA nephropathy in our series is listed in Table 1. Reports of familial occurrence among siblings [7, 39–41] and offspring [42, 43] suggest that this disease might have a hereditary origin.

Studies of histocompatibility antigens in idiopathic IgA nephropathy are incomplete. In some studies, a greater frequency of certain antigens was found in the patients compared to controls, but other studies have failed to verify this association. Similar confusion exists regarding the possible prognostic implications of the histocompatibility antigens: recent studies suggest, for example, that HLA-DR4 is associated with a poor prognosis [43] and others with a good prognosis [44].

Recurrent macroscopic hematuria, usually associated with a respiratory tract infection, is the most frequent clinical manifestation [14, 22, 24, 45]. In some patients the disease presents as an acute nephritic syndrome [29, 35], or acute renal failure, and rarely as nephrotic syndrome [29]. Occasionally the only manifestations are asymptomatic arterial hypertension, microhematuria, or proteinuria alone or in combination. These abnormalities are often identified during a routine medical evaluation [14, 22].

The clinical manifestations of idiopathic IgA nephropathy are exemplified by our experience with 140 patients with the disorder, of whom 76% presented with episodes of recurrent macroscopic hematuria; 80% of the cases were associated with upper respiratory tract infections, mainly acute pharyngotonsillitis. These figures conform closely to observations in other series [14, 15, 22, 24, 29, 33, 35, 46]. Typically gross hematuria appeared simultaneously or within the first 48 to 72 hours after the infection began, persisted less than 3 days, and sometimes was accompanied by lumbar pain [14]. Studies have demonstrated a bacterial cause of the infection in only a small number of cases [47], and investigators generally believe that most of these infections are viral.

Table 1. Age and sex distribution in IgA nephropathy

Age (years)	Male		Female	
	Number of patients	%	Number of patients	%
0–10	8	5.7	4	2.9
10–20	38	27.2	15	10.7
20–30	22	15.7	17	12.1
30–40	16	11.4	4	2.9
40–50	10	7.2	3	2.1
50–60	3	2.1	–	–
Total	97	69.3	43	30.7

Episodes of hematuria have been associated with a variety of other infections including lobar pneumonia, staphylococcal osteomyelitis, staphylococcal sepsis, acute gastroenteritis, influenza, infectious mononucleosis, and brucellosis. Episodes also have followed tonsillectomy, vaccination, tooth extraction, violent physical exercise, and trauma [29, 48]. Between episodes of gross hematuria, many patients have persistent microhematuria, proteinuria, or both. Proteinuria rarely reaches the "nephrotic range." In our patients we commonly observed intervals in which the urinary abnormalities completely disappeared. Microhematuria disappeared completely between attacks in 30%, proteinuria resolved in 27%, and both remitted in 15%, for periods ranging from 4 months to 4 years [35]. Patients with arterial hypertension never had spontaneous remissions.

In 15% of our patients, IgA nephropathy was first diagnosed after asymptomatic microhematuria and proteinuria were found on routine examination, and in 2.5% after detection of proteinuria alone. The frequency of IgA nephropathy among patients who first manifest asymptomatic hematuria and/or proteinuria and normal renal function is unknown because many physicians do not consider renal biopsy appropriate in such patients. Further, renal biopsies frequently are not performed in patients with hypertension and coexisting minor amounts of hematuria, or proteinuria. We believe that some of these patients, usually diagnosed as having "essential hypertension," actually suffer from idiopathic IgA nephropathy, and the finding of elevated IgA serum level in this group suggests that diagnosis. I will discuss interpretation of the serum IgA level in more detail later.

In 4% of our 140 patients and in 10% of patients in the series of Clarkson et al [29], IgA nephropathy presented as an acute nephritic syndrome similar to acute poststreptococcal glomerulonephritis: features included gross hematuria, edema, hypertension, proteinuria, and reduction of the glomerular filtration rate. In our patients, all the clinical manifestations of nephritic syndrome remitted spontaneously, but microhematuria persisted. In 2.5% of our 140 patients, idiopathic IgA nephropathy had a gradual onset, with symptoms attributable to chronic renal insufficiency and coexistent hypertension, as described by others [24, 25]. Indeed the patient presented today had a similar presentation. During a routine examination, he was found to have renal dysfunction. During the 4 years prior to the biopsy, his renal insufficiency progressed. At the time of the biopsy the serum creatinine level was 3.8 mg/dl. Instances of idiopathic IgA nephropathy first appearing with malignant hypertension and acute renal failure have been reported [7], but we have not observed any such case. Moreover, we have observed no

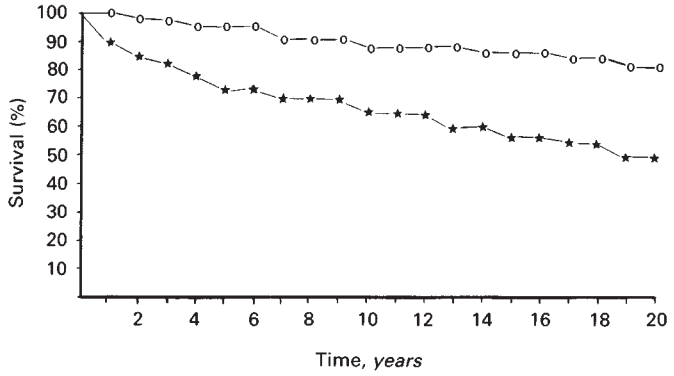


Fig. 1. *Actuarial survival curves over 20 years for 140 patients with idiopathic IgA nephropathy.* Circles denote renal actuarial survival; stars denote survival with normal GFR.

patients in whom nephrotic syndrome was the initial manifestation.

Although nephrotic syndrome is rare as a presenting manifestation, it appears during the course of idiopathic IgA nephropathy in 10% to 30% of patients [26, 29, 34, 35, 49, 50] and can either persist or spontaneously remit. Arterial hypertension also appears during the evolution of the disease, and although in some series its incidence has been as low as 10% [1, 15, 22], in others hypertension occurs in 32% to 62% [24, 26, 29]. In our patients 29% developed hypertension and 20% had the nephrotic syndrome. Both nephrotic syndrome and hypertension are poor prognostic indicators.

Figure 1 represents the survival rates for 140 patients over 20 years. The upper line indicates that 95% of patients survived 5 years after the appearance of the initial symptoms, 87% lived 10 years, and 80% were alive 20 years later. The lower line depicts the percentage of patients who survive with normal renal function over time. Normal renal function (measured by creatinine clearance) was preserved in 73% for 5 years, 65% for 10 years, and 50% for 20 years. Thus chronic renal failure develops frequently, but renal insufficiency usually progresses slowly [26, 29, 35, 50, 51]. After 10 or 20 years the survival rate is 80% or more [28, 52, 53]. In 8% of our patients, dialysis was started after a followup period ranging from 2 to 15 years after the disease appeared clinically. Five of these patients received a renal transplant from a cadaver donor. Despite a relatively high frequency of recurrence of this disease in transplanted kidneys [54, 55], I believe that transplantation is not contraindicated because of the slow progression of renal failure in this entity [53].

Fifty percent of our patients with idiopathic IgA nephropathy had high levels of serum IgA; this finding is consistent with the results of others [14, 29, 33, 36, 38, 51, 56]. The high serum IgA level is a diagnostic aid, but it is not pathognomonic of idiopathic IgA nephropathy. We have observed high levels of IgA in 12% of our patients with idiopathic membranoproliferative glomerulonephritis, 12% of patients with focal sclerosis, 33% of patients with lupus nephritis, and 54% of patients with glomerulonephritis associated with Henoch-Schönlein purpura. In systemic lupus erythematosus and in Henoch-Schönlein purpura with nephropathy, the rise in serum IgA coincides with the clinical activity of the disease; serum IgA levels return to normal during spontaneous or therapeutically induced remissions in both disorders. A high IgA serum level also has been reported in alcoholic cirrhosis [57].

Mean values for salivary IgA also rise in patients with idiopathic IgA nephropathy and correlate closely with serum IgA levels [35, 57]. Reductions in serum C3 or C4 levels were not detected in any of our patients or those of others [14, 29, 34, 47–49, 58, 59]. In the past, immune complexes in the serum of patients with idiopathic IgA nephropathy were infrequently detected [49, 60–65]. Recently, however, using more sensitive techniques, researchers have identified IgA immune complexes in as many as 40% to 60% of these patients [64, 65]. Serum cryoglobulins were detected in 15% of our patients; however, rheumatoid factor was found in only one of these individuals. Neither serum C-reactive protein, hepatitis B antigen, antinuclear antibodies, nor anti-DNA antibodies were detected.

Pathologic features

Idiopathic IgA nephropathy is a form of proliferative glomerular disease characterized by prominent mesangial deposition of IgA. The first reported series emphasized the focal and segmental character of the proliferative lesion observed on light microscopy [1, 37]. Since then most authors have indicated that the glomeruli usually are diffusely affected, showing different grades of mesangial proliferation with or without segmental proliferative changes (endothelial, mesangial and/or crescent formation) [1, 66]. Moreover, many instances have been reported in which immunofluorescent studies reveal IgA in the glomeruli, yet the glomeruli show little or no change by light microscopy. Neither necrotic capillary loops nor membranous glomerulopathy is seen in idiopathic IgA nephropathy. The widening of the mesangial areas is due to mesangial cell proliferation and increased mesangial matrix (Fig. 2); this matrix material is recognized as a moderately PAS-positive material that stains bright red with Masson's trichrome. This material corresponds to the electron-dense deposits observed on electron microscopy and to the granular IgA deposits seen by immunofluorescence. The diffuse mesangial proliferation is not accompanied by endothelial proliferation or involvement of the peripheral capillary walls. However, as many as 20% [67] of patients have extracapillary proliferation with crescent formation that can be found in a large fraction of the glomeruli [68]. Fibrous crescents and mesangial sclerosis can produce glomerular sclerosis. Nonspecific findings of vascular sclerosis, interstitial fibrosis, and tubular atrophy frequently accompany advanced glomerular abnormalities.

I prefer to think about the glomerular morphology in idiopathic IgA nephropathy as a spectrum of morphologic changes from "normal" to marked mesangioproliferative glomerulonephritis. In ascending order of severity, intermediate stages in this spectrum consist of minimal glomerular changes, widening of the mesangial area, segmental proliferation of mesangial cells, and diffuse proliferation of mesangial cells. Crescent formation usually is associated with the more severe lesions. Unfortunately the lack of uniform criteria for identifying these various lesions has led to large differences in the fraction of patients reported to have each variety (Table 2).

The immunofluorescence findings are the pathologic hallmark of this disease [1, 22, 33, 37, 68–71] and are summarized in Table 3. Characteristically, IgA is deposited in a diffuse granular pattern in the mesangium (Fig. 3), and it also appears in the peripheral capillary walls in 15% to 50% of the cases. Other

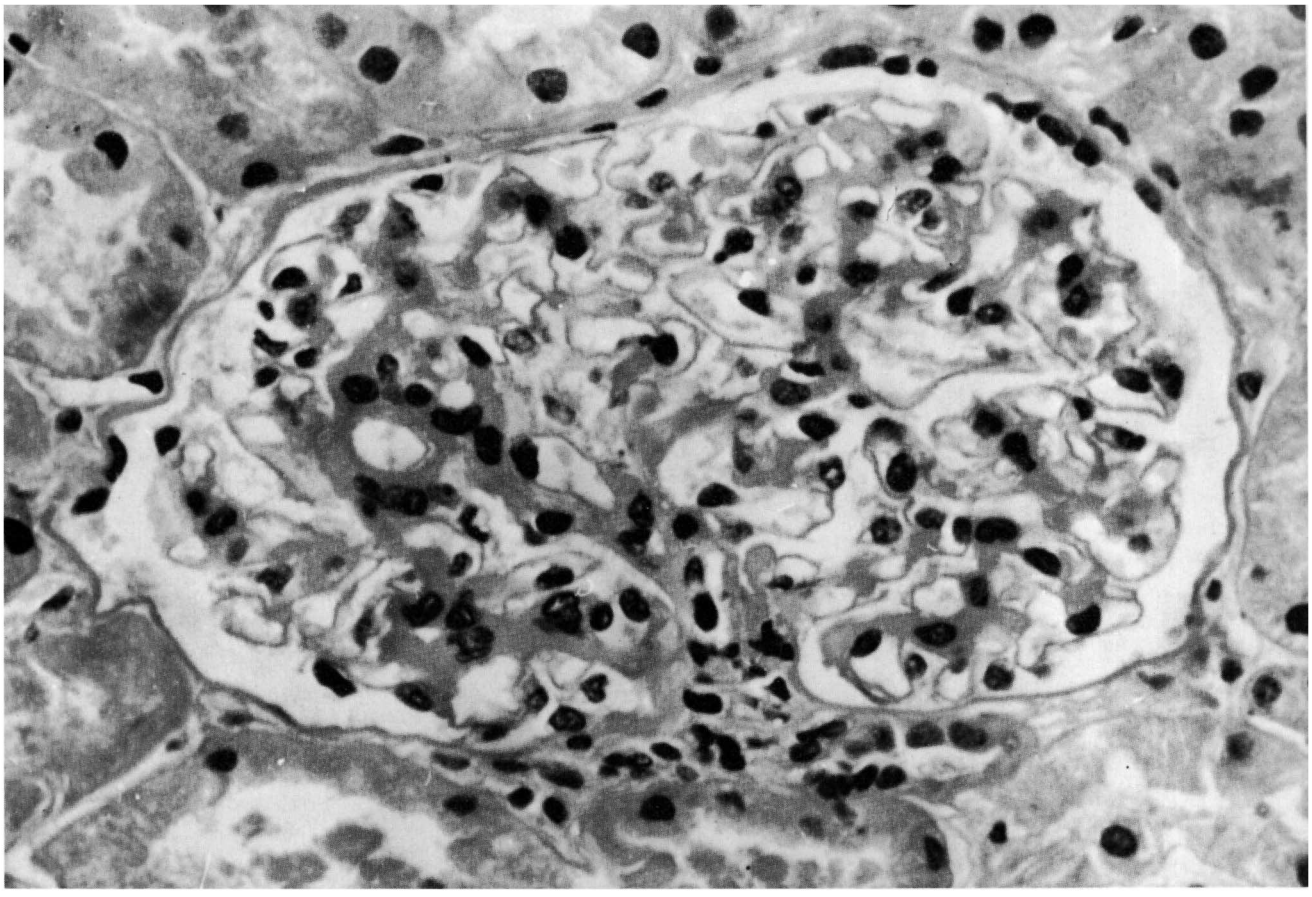


Fig. 2. *Light photomicrograph showing moderate increase of mesangial matrix and slight proliferation of mesangial cells (HE x 250).*

Table 2. Light microscopy glomerular patterns in idiopathic IgA nephropathy

	Normal (%)	Minimal changes (%)	Focal segmental changes (%)	Diffuse mesangio-proliferative changes (%)
Druet et al [26] (52 cases)	0	38.4	5.7	48
Levy et al [47] (92 cases)	0	28.2	45.6	26.2
Morel-Maroger et al [33] (98 cases)	2	0	86.6	11.4
Sakai et al [67] (130 cases)	0	19.2	19.2	61.6
Gartner et al [32] (153 cases)	2	18	5	75
Southwest Pediatric Nephrology Study Group [66] (62 cases)	25.8	0	33.8	50.4
Navas Palacios et al [70] (60 cases)	0	1.8	29.1	67.3

immunoglobulins usually accompany IgA including IgG, IgM, and IgE; C3 is almost always present, and Clq and C4 have been found in many instances. Properdin has been demonstrated in 30% to 93% of the specimens examined. Fibrinogen is found in the crescents and in the mesangial areas of 10% to 50% of the specimens. Extraglomerular immunofluorescent deposits are rarely found. Granular deposits sometimes appear in the basement membrane of Bowman's capsule [22], tubular basement membrane [26], and arterioles [15, 22]. Most of these extraglomerular deposits contain C3, although arteriolar IgA deposits are rarely seen [15]. Extrarenal deposits of IgA also have been reported in skin capillaries [72, 73] and in blood vessels of skeletal muscle [74].

The ultrastructural manifestations of IgA nephropathy are summarized in Table 4. Using electron microscopy, we found mesangial deposits in all glomeruli we studied (Fig. 4). Nevertheless, there are several reported cases without such deposits [66, 67, 71, 75]; the explanation for the absence is uncertain. Subendothelial deposits are infrequent in the peripheral capillary walls, and, when present, they are located close to the mesangial stalks; however, true peripheral subendothelial deposits do occur [26, 66, 68, 70, 71, 76, 77]. Dense intramembranous deposits also occur [66, 68, 70, 71, 75, 77] and scattered subepithelial deposits have been reported [66, 70]. Dense granular deposits also have been demonstrated in the basement membrane of Bowman's capsule and in subendothelial regions of extraglomerular arterioles [22, 70]. Structural changes of the lamina densa, such as thinning and splitting, are frequent [67, 70, 71, 75, 77].

Table 3. Immunofluorescence findings in idiopathic IgA nephropathy

	IgA									
	Mesangial (%)	Parietal (%)	IgG (%)	IgM (%)	IgE (%)	Fibr. (%)	Prop. (%)	C3 (%)	C4 (%)	C1q (%)
Zollinger and Mihatsch [71]	100	50	83.3	66.6	NM[a]	8.3	NM	100	NM	NM
Druet et al [26]	100	17.3	69.2	16.6	NM	14.9	NM	80.6	NM	NM
Southwest Pediatric Nephrology Study Group [66]	100	23	77	22	NM	45	29	77	24	15
McCoy et al [22]	100	NM	60	60	NM	50	87.5	85	0	0
Zimmerman and Burkholder [14]	100	NM	82.2	66.6	NM	68.7	83.3	100	20	0
Gartner et al [32]	100	24.2	45.8	31.3	2.4	NM	NM	95.3	NM	NM
Navas Palacios et al [70]	100	10	45.4	9	1.8	10.8	NM	43.5	0	1.8

[a] NM refers to data not mentioned.

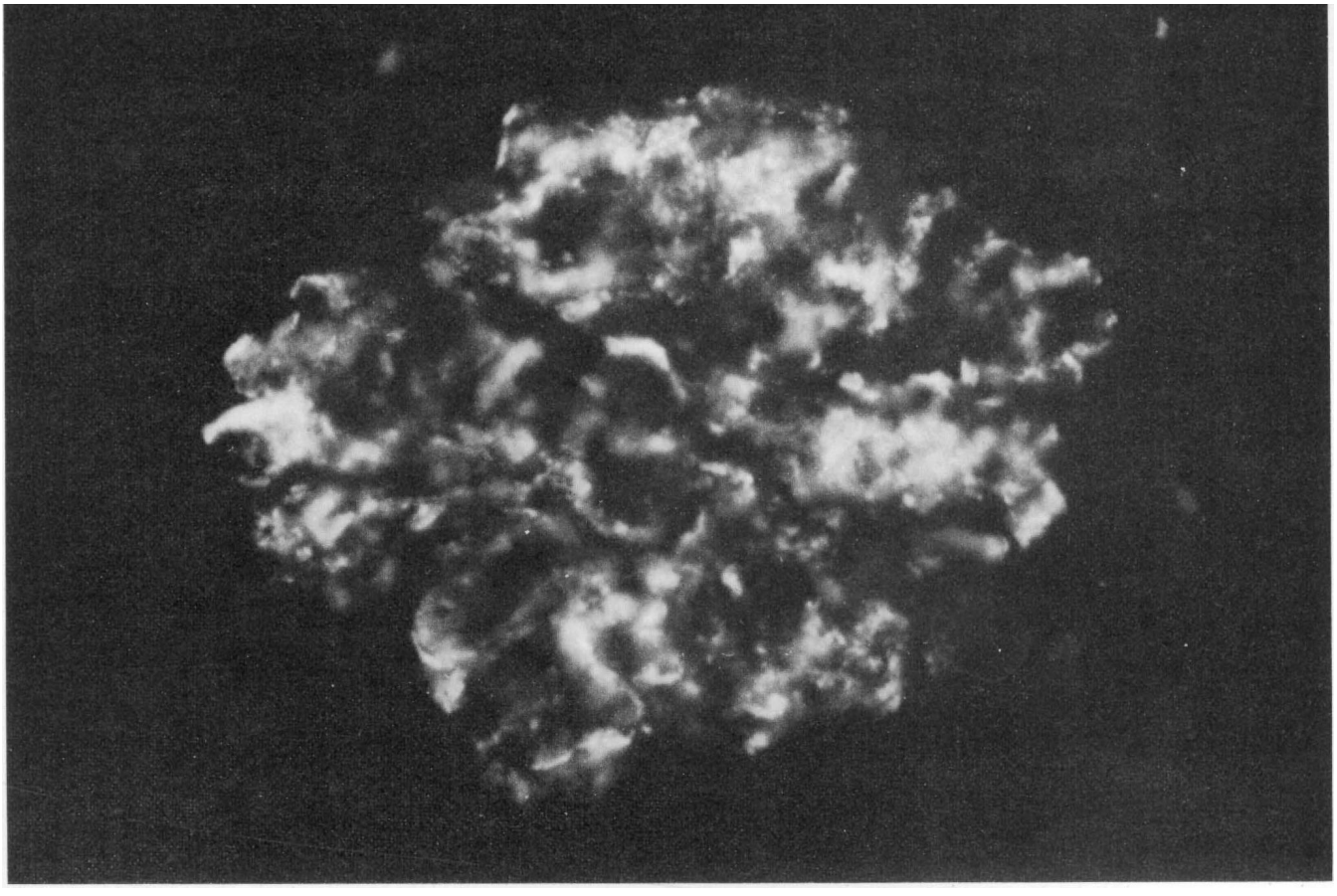


Fig. 3. *Light photomicrograph of a tissue section stained with anti-IgA labeled with isothiocyanate of fluorescein.* There are widespread mesangial deposits of IgA, with occasional parietal staining (×250).

Several investigators have tried to identify morphologic predictors of the clinical course. Marked diffuse mesangial proliferation, glomerular sclerosis, and interstitial fibrosis are associated with an unfavorable prognosis [50, 78]. Lee et al [68] applied Meadows' [79] morphologic classification of Henoch-Schönlein glomerulonephritis to idiopathic IgA nephropathy. Grades IV and V (characterized by marked diffuse mesangial proliferation and sclerosis with crescent formation) usually were followed by progressive renal failure. There have been several attempts at correlating ultrastructural findings with the light microscopic changes. Hara et al divided patients with histologic lesions into two types based on the presence or absence of subendothelial deposits and found that patients with deposits had a greater tendency to develop renal insufficiency [80]. Sakai et al [67] and Shigematsu et al [77] have suggested that alterations of the lamina densa might have prognostic significance in that this structural change correlates with segmental glomerular lesions and crescent formation.

As I mentioned earlier, deposition of IgA in the mesangium occurs in disorders other than idiopathic IgA nephropathy. The

Table 4. Ultrastructural findings in idiopathic IgA nephropathy

	Deposits						Lamina densa		
	SEp[a] (%)	IM[b] (%)	SEn[c] (%)	MES[d] (%)	BMCB[e] (%)	Arteriole (%)	Thin (%)	Split (%)	Cases (%)
Druet et al [26]	–	–	–	100	–	–	–	–	42
McCoy et al [22]	–	–	–	100	10	10	–	–	10
Zimmerman and Burkholder [14]	–	–	23	100	–	–	–	–	13
Alexander et al [15]	–	–	–	100	–	–	–	–	15
Clarkson et al [29]	56	60	48	100	–	–	33	–	50
Zollinger and Mihatsch [71]	7.1	28.5	35.7	71.4	–	–	–	21.4	14
Burkholder et al [75]	4.2	10	–	97.8	–	–	4.2	–	47
Sakai et al [67]	–	–	–	91.3	–	–	–	24.6	69
Hara et al [80]	2.1	8.4	42	100	–	–	–	–	46
Navas Palacios et al [70]	33	10	18.5	100	3.3	6.6	19.8	13.2	30
Lee et al [68]	–	5	25	80	–	–	–	–	20
Southwest Pediatric Nephrology Study Group [66]	10	9	16	96.5	–	–	40	40	58

[a] SEp refers to subepithelial.
[b] IM refers to intramembranous.
[c] SEn refers to subendothelial.
[d] MES refers to mesangial.
[e] BMCB refers to basement membrane of Bowman's capsule.

nephritis of Henoch-Schönlein purpura can be pathologically identical [64]. Light microscopy shows diffuse mesangial proliferation, segmental lesions, or both. The frequency of certain features does differ, however. In particular, epithelial crescents, glomerular loop necrosis, and vasculitis appear more frequently in Henoch-Schönlein purpura. Whereas immunofluorescence studies demonstrate similar findings [81], mesangial fibrinogen deposition occurs in a higher percentage of patients with Henoch-Schönlein purpura. Glomerular involvement in systemic lupus erythematosus has a pleomorphic character [82]; mesangial IgA deposits similar to those in idiopathic IgA nephropathy, necrosis, diffuse mesangial-endocapillary proliferation, and membranous changes can be observed. Manigand et al [83] and Callard et al [9] detected IgA mesangial deposits in most patients with alcoholic cirrhosis. Variable amounts of IgA in the glomeruli also are found in other primary glomerulonephritides [15, 50].

Diagnosis

As I have stressed, the clinical manifestations of idiopathic IgA nephropathy are extremely varied, and the disorder thus can resemble a large number of renal diseases and syndromes. When one suspects idiopathic IgA nephropathy because of the clinical manifestations in a given patient, the diagnosis can be either confirmed or excluded by the associated clinical manifestations, by measurements of IgA in the serum and, of course, by renal biopsy. Clinical suspicion should be particularly high in patients with recurrent gross hematuria that follows an upper respiratory infection by a day or two, and in such cases the diagnosis can be inferred from this history alone.

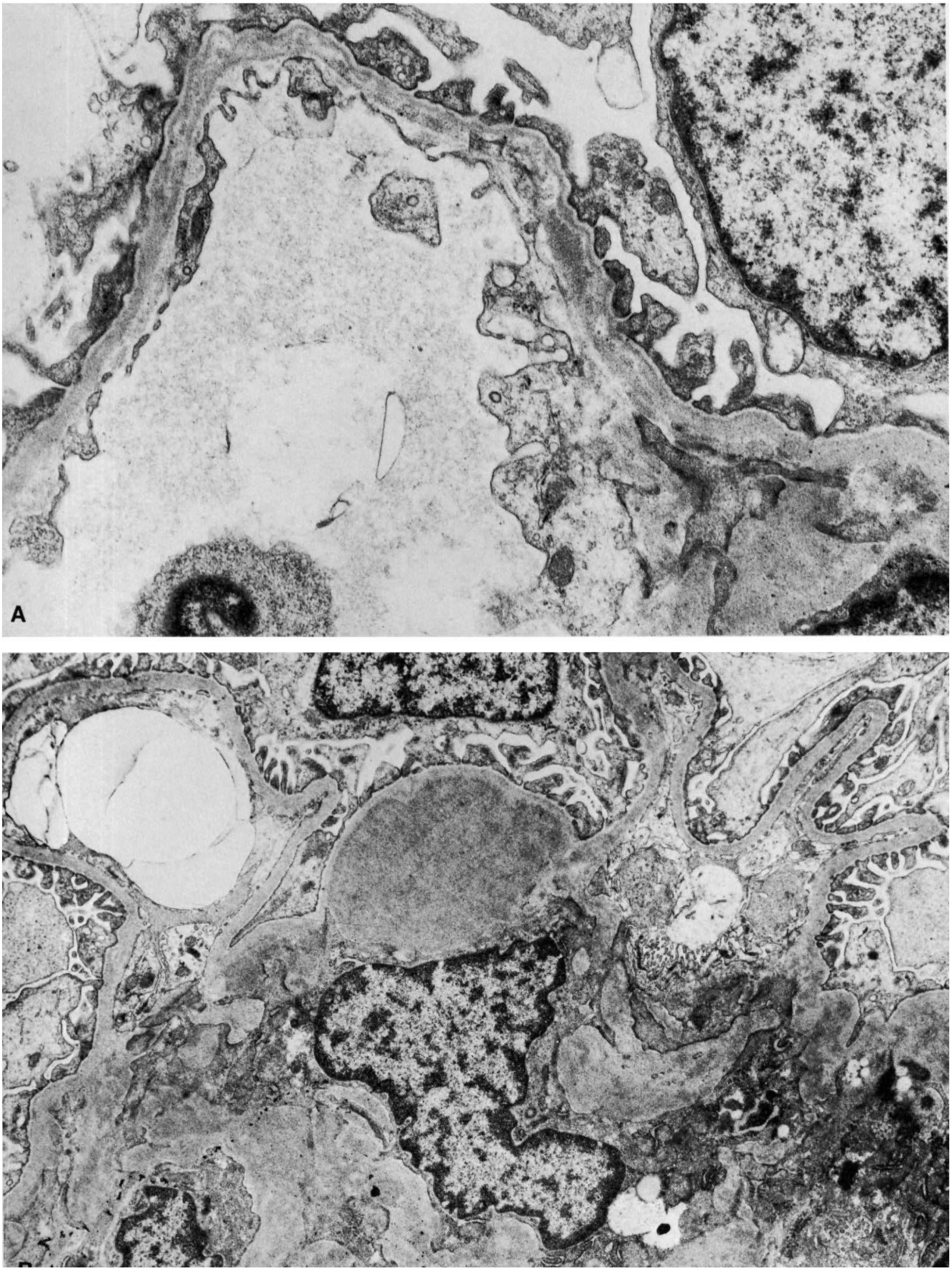
When the diagnosis is in doubt, measuring the level of IgA in the serum can be useful because IgA levels are increased in 50% to 70% of patients with idiopathic IgA nephropathy [29, 53, 56, 84], a substantially greater fraction than in other renal diseases that mimic this disorder. A definitive diagnosis depends, of course, on renal biopsy. When the biopsy demonstrates the typical findings I have described, and the patient has no manifestations of the other diseases that can produce this histologic picture (such as Henoch-Schönlein purpura, lupus, or liver disease), idiopathic IgA nephropathy can be diagnosed with confidence.

Treatment

Considering the benign course followed by most patients with this disease, treatment with steroids, immunosuppressive drugs, or anticoagulants is not warranted. However phenytoin, which reduces serum IgA levels [85–88], has been used in an attempt to improve outcome in these individuals. In a controlled trial, Clarkson et al observed no change in the clinical or pathologic evolution of the disease in 23 patients treated with 5 to 6 mg/kg/day of phenytoin for 2 years [89]. Although levels of IgA in the serum decreased in 74% of the patients treated, no significant morphologic changes were observed in the biopsies after treatment, and in all cases IgA deposits persisted in the mesangium.

Egido and coworkers reported the results of a long-term controlled trial with phenytoin [90]. The treated group comprised 41 patients; the control, 32 patients. The number of episodes of macroscopic hematuria per year decreased in both groups, but was significantly lower at each time period in the treated group than in the control one (treated group 1.92 + 0.7 episodes per first year and 0.39 + 0.20 episodes per year at the third year; control group, 1.95 + 0.8 episodes per first year and 0.97 + 0.43 episodes per year at the third year). Unfortunately, phenytoin did not influence either the pathologic lesions or the progression of the disease. Because progression to renal failure in these patients occurs over many years, however, more observations of treated and untreated patients are needed before we conclude that phenytoin is ineffective.

Fig. 4. *Representative electron micrographs from patients with IgA nephropathy.* **A** Large paramesangial deposits between the glomerular basement membrane and mesangial cell. (EM × 9600) **B** Subendothelial deposit associated with thinning and splitting of the lamina densa. (EM × 12,800)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Questions and answers

DR. JEROME P. KASSIRER: In patients with idiopathic IgA nephropathy, what is known about the mechanism of the gross hematuria that follows a respiratory tract infection by 24 to 48 hours? Is fever alone responsible? Is a previous lesion in the kidney exacerbated by the infection? Is it mediated by immune complexes?

DR. RODICIO: This phenomenon is poorly understood. Among pathogenetic mechanisms mentioned, I am not convinced that the mechanism involves immune complexes because the time between the infection and gross hematuria seems too short for such a reaction. There is some evidence, however, that an antibody mechanism is operative. Perhaps we can ask Dr. Egido, who has studied this question, to comment.

DR. JESUS EGIDO (*Servicio Nefrología, Fundación Jimenez Diaz, Madrid*): The appearance of macroscopic hematuria following upper respiratory tract infections might à priori occur by the acute deposition of immune complexes, immune complex-like substances (such as polymeric IgA) or in-situ complex formation at the mesangial level. As Dr. Rodicio pointed out, the short interval between the infection and the hematuría argue against a role for immune complexes. In a recent study we examined the hypothesis that, after viral infection or other stimuli, circulating lymphocytes from secretory tissues could produce a large amount of polymeric IgA [91]. In fact, polymeric IgA increased in most patients after polyclonal stimulation of peripheral mononuclear cells in vitro. Whether these large polymers of IgA are able to reach the mesangium in vivo and produce inflammation is not yet known.

DR. KASSIRER: In your view, are the kidneys of these patients normal before the respiratory tract infection, or do these patients have preexisting lesions?

DR. EGIDO: In a disease with a long and indolent course such as IgA nephropathy, it is not known when the pathologic changes first appear. One can only hypothesize that chronic deposition of IgA as immune complexes, in polymeric forms, or both, might occur. It is possible that the mesangium can deal with the deposited IgA initially, but that it later fails to clear the material. The gross hematuria could be produced by an acute deposition of a large amount of IgA or IgG in the forms described above. It does seem clear that IgA remains in the mesangium for long periods because repeated renal biopsies, even in terminal chronic renal failure, always show IgA.

DR. VICTOR MILLET (*Servicio Nefrología, Ciudad Sanitaria, 1° de Octubre*): If it is true that IgA is present in the kidneys during asymptomatic intervals, then a renal biopsy should be diagnostic in a patient suspected of IgA nephropathy during intervals in which hematuria is not present.

DR. RODICIO: Yes, and for this reason it is not necessary to perform a biopsy only when the disease is in its symptomatic phase.

DR. LUIS HERNANDO (*Jefe, Servicio Nefrología, Fundación Jimenez Diaz*): I would like to comment on a peculiar form of acute renal failure rarely observed in idiopathic IgA nephropathy. In one of our patients with IgA nephropathy and acute renal failure, dialysis was necessary for about one week, but the patient's renal function recovered completely. The renal histology did not differ in this patient from that observed in other patients with IgA nephropathy.

DR. SANCHEZ SICILIA (*Jefe, Servicio de Nefrología, Ciudad Sanitaria de la Paz, Madrid*): We have seen a similar patient but with two different episodes of acute renal failure. Dialysis was needed each time but each time renal function returned to normal. Gross hematuria accompanied the first episode but not the second. Renal biopsy performed during the first admission showed mesangial IgA deposits.

DR. RODICIO: One of our patients with idiopathic IgA nephropathy sustained a reduction in glomerular filtration rate in association with gross hematuria following a respiratory tract infection. He did not need dialysis, and renal function returned to normal 2 weeks later. A similar episode occurred on another occasion in the same patient.

DR. EGIDO: I suspect that acute deposition of IgA in the mesangium led to the reduction in GFR in these interesting but rare patients.

DR. KASSIRER: There has been some confusion in the literature about the definition of IgA nephropathy. In some reports all patients were included in whom IgA was found in the mesangium, whether or not the patients had systemic disease or alcoholic cirrhosis. You made a clear distinction today between idiopathic IgA nephropathy and other nephropathies in which IgA is found in the mesangium. Would you comment on the value of this distinction?

DR. RODICIO: Idiopathic IgA nephropathy is a well-defined clinicopathologic entity. It is true that the histologic findings are the same in Henoch-Schönlein purpura and in some cases of alcoholic cirrhosis and systemic lupus erythematosus. The corollary is that one should always study a patient for a systemic disease or liver disease if a renal biopsy discloses IgA deposits.

DR. EGIDO: In some cases it is very difficult to separate idiopathic IgA nephropathy from other systemic diseases on clinical grounds. We have seen some patients who had purpura coincident with one episode of gross hematuria but who never had purpura again, even though gross hematuria recurred. It seems that some patients cannot strictly be assigned to a category of idiopathic IgA nephropathy or to Henoch-Schönlein purpura, and that they belong to what might be called the spectrum of IgA nephropathy. Furthermore, since IgA is frequently observed postmortem in the kidneys of patients with alcoholic liver disease, one wonders whether patients with IgA nephropathy and a history of chronic alcohol ingestion, with or without clinical liver changes, must be considered as having idiopathic IgA nephropathy. I believe that such patients must be eliminated from series studying clinical, pathogenetic, or therapeutic aspects of idiopathic IgA nephropathy if the study is to examine a homogenous group of cases.

Commentary on the pathogenesis of IgA nephropathy

DR. MICHAEL P. MADAIO (*Division of Nephrology, New England Medical Center, and Assistant Professor of Medicine, Tufts University School of Medicine*): The events leading to IgA production, glomerular IgA localization, and glomerulonephritis in patients with idiopathic IgA nephropathy are not well understood. Recent investigation has provided some insight into the pathogenesis of this entity, however. Before reviewing these studies, it is worth noting that idiopathic IgA nephropathy might not be a single disease entity. As Dr. Rodicio has pointed out, patients with IgA in their kidneys have been grouped together even though their clinical manifestations and long-term prognoses are variable. The specific antigen as well as the precise nature of the IgA in patients with mesangial IgA

deposition may vary from individual to individual. For this reason, all-inclusive conclusions regarding the pathogenesis of IgA nephropathy must be viewed cautiously. Certain features of this entity do suggest, however, that common pathways might lead to glomerulonephritis.

Although no histocompatibility antigens are universally present in individuals with IgA nephropathy, the observation that certain HLA types are more frequent in patients with this disorder than in the general population suggests that some individuals might be genetically predisposed to this disease [43, 92–96]. Whether their increased susceptibility is related to an underlying disorder of immune responsiveness, to an impaired capacity for clearing pathogenic immune reactants from the circulation (such as a defective macrophage-phagocyte system), to local factors intrinsic to the mucosal barrier, or to the kidney itself has yet to be determined. There is some support for the hypothesis that patients with IgA nephropathy have abnormal immune responsiveness. As Dr. Egido pointed out, he and his coworkers observed that following polyclonal stimulation, peripheral lymphocytes obtained from patients with IgA nephropathy produced larger amounts of polymeric IgA than did those obtained from normal individuals [91, 97]. On further examination these investigators observed a defect in the generation of IgA-specific suppressor cells in the patients studied [98], an observation also found by others [99]. They also observed that T cells derived from patients with IgA nephropathy were more efficient in providing helper function for IgA production in response to mitogen stimulation than were T cells obtained from normal controls [98]. Furthermore, an increase in circulating helper/suppressor T-cell ratios has been detected in patients with IgA nephropathy [97, 98], and an absolute increase in circulating IgA-specific helper T cells also has been observed [100]. These findings suggest an underlying disorder of immune regulation in patients with IgA nephropathy. However, the results also could be explained by ongoing antigenic stimulation of cells involved in the IgA immune response.

The occurrence of mesangial IgA deposits in disorders other than idiopathic IgA nephropathy also may provide insights into the underlying pathophysiologic disorder. For example, the observation that IgA deposits in the mesangium are found frequently in patients with liver disease is consistent with the hypothesis that a primary abnormality in the macrophage-phagocyte system of the liver results in accumulation of immune reactants in the circulation and yields immune deposit formation within the kidney. The impaired phagocytic activity found both in vitro and in vivo in some of these patients with the idiopathic disorder adds further support to this hypothesis [101–104]. Alternatively, these findings could result from overload of a normal phagocytic system by circulating immune reactants. Indeed, following bile duct ligation, plasma IgA levels, circulating IgA-containing immune complexes, and mesangial IgA deposits increase in rats [105]. Similarly, rats with carbon tetrachloride-induced cirrhosis also develop elevated plasma IgA levels and mesangial deposits of IgA [106]. Finally, patients with alcoholic liver disease and primary biliary cirrhosis have elevated plasma polymeric IgA levels [107–109]. These clinical and experimental findings are consistent with the theory that glomerular IgA deposition results from impaired clearance of IgA or IgA-containing immune complexes from the circulation.

The recurrence of IgA nephropathy in patients who have received transplanted kidneys from related or unrelated donors suggests that the abnormality in this disorder does not lie exclusively within the kidney [53, 110]. Furthermore, the resolution of mesangial IgA deposits in patients who inadvertently received kidneys from donors with unsuspected IgA nephropathy further supports this contention [110–112].

No direct evidence has implicated or excluded a defect in the mucosal barrier in IgA nephropathy. As discussed by Dr. Rodicio, however, the close temporal relationship between respiratory and gastrointestinal infections on the one hand and episodes of nephritis on the other is striking and suggests that the mucosa is the site of immunologic stimulation. Patients with IgA nephropathy have increased IgA-bearing plasma cells in their tonsils [113]. Although the number of these cells in the small intestine in such patients is normal [114], the pathogenic IgA might have a mucosal or secretory origin. Because differences exist in human IgA found in serum and secretions, the finding of secretory IgA in the kidney would support this hypothesis. Most of the IgA in serum is monomeric (40%) and consists predominantly (80%) of the subclass IgA1 [115, 116]. Secretory IgA consists in large part of the subclass IgA2 (40%–60%) and is predominantly polymeric; the monomeric subunits are joined by the polypeptide J chain [115, 116]. At mucosal sites, polymeric IgA attaches to secretory component, a small-molecular-weight protein elaborated by epithelial cells [115, 116]. The subclass of IgA most often found in the glomerular deposits of patients with IgA nephropathy is exclusively IgA1 [65, 110, 117–121]. But several investigators have found J chain within the mesangial deposits in some patients [122–125]. Furthermore, the mesangial IgA binds to free secretory component, suggesting that polymeric IgA is deposited within glomeruli [65, 119, 125].

Studies of experimentally induced IgA nephropathy provide further evidence that the IgA deposited in the kidney is polymeric and of mucosal origin. Rifai et al have developed a mouse model of IgA nephropathy induced by IgA anti-dinitrophenol (DNP) derived from the MOPC-315 plasmacytoma and dinitrophenolated bovine serum albumin (DNP-BSA) [126]. They observed that glomerular immune deposit formation depended on the presence of both DNP-BSA and IgA anti-DNP-BSA. However, they found that only polymeric IgA antibody produced glomerular deposits; monomeric IgA failed to do so. Polymeric IgA is also found in the mesangium of rats with ligated bile ducts or carbon tetrachloride-induced cirrhosis (105, 106]. Emancipator and coworkers have developed another mouse model of IgA nephropathy [127]. Following oral administration of protein antigen in adjuvant, they showed that mice develop an increase in IgA-bearing plasma cells at mucosal sites, an increase in antigen-specific IgA antibodies in serum, and glomerular immune deposit formation consisting of protein antigen and mucosally derived polymeric IgA (J chain). These studies provide strong supportive evidence that orally administered antigens can participate in glomerular immune deposit formation, and that glomerular IgA can be derived from a mucosal source.

The precise mechanism of glomerular immune deposit formation in this disorder is unknown; whether the deposits result from the deposition of circulating immune complexes or from IgA binding to exogenous antigens located within the mesangium (or vice versa) has not been determined. Circumstantial evidence for the circulating immune complex mechanism includes the detection of complexes containing polymeric IgA in

the circulation of some of these individuals [64, 110, 121, 128]. But the lack of functional or histologic evidence of glomerulonephritis following passive administration of preformed immune complexes to normal animals makes this association questionable [129, 130]. Whatever the mechanism of immune deposit formation, these studies imply that polymeric IgA is pathogenic, whereas monomeric IgA is not. This difference could be due either to the influence of polymeric IgA on circulating immune complexes, the ability of polymeric IgA to localize within the mesangium, or the properties of deposited polymeric IgA within the mesangium. Lowance, Mullins, and McPhaul suggested that the pathogenic IgA might be an anti-mesangial antibody, based on the finding that IgA eluted from the kidney of a patient with IgA nephropathy had apparent reactivity with normal mesangium [131]. This result has not been confirmed, however [132]. Recently it was discovered that the IgA eluted from the kidneys of patients with IgA nephropathy binds to the mesangial area of autologous tissue, but not to normal glomeruli or glomeruli from patients with other glomerular disorders. Moreover, approximately one-third of the IgA antibodies eluted also cross-reacted with the mesangium of other patients with IgA nephropathy. This finding suggests that a common antigen might exist in some of these individuals [132]. To date, no specific antigens have been identified.

The factors leading to glomerulonephritis following IgA deposition are also unknown. The deposition of C3 and properdin, and the paucity of the initial components of the classical pathway suggest that activation of the alternative complement pathway is involved [22]. This hypothesis is consistent with the observation that IgA immunoglobulins are effective activators of the alternate pathway, but they cannot fix complement by the classical pathway [116]. The recent demonstration of C4 binding protein in the mesangium of some of these patients suggests that when IgG or IgM is present in glomeruli, activation of the complement system via the classical pathway also might be involved [133, 134]. Whether glomerular injury depends on complement, or whether other mediators are involved in the pathogenesis of glomerulonephritis has not yet been determined.

In summary, the available clinical and experimental evidence suggests that IgA nephropathy can occur through mucosal immunization with polymeric IgA (subclass IgA1) deposition in the kidney. This sequence of events probably is more likely to occur in individuals who have either altered helper/suppressor immune cell function or who have impaired macrophage-phagocytic activity. Many aspects of the pathogenesis await further definition, including the nature of the antigens, further identification of the pathogenic IgA, the mechanisms of immune deposit formation, and the final mediators of glomerular injury.

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