Les dépôts intercapillaires d’IgA - IgG

par MM. J. Berger et N. Hinglais (*)

with comments by
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RÉSUMÉ

Sur les biopsies rénales de 25 malades, ont été mis évidence par immunofluorescence des dépôts intercapillaires fixant le sérum anti-IgA et moins intensément les sérum anti-IgG et anti-β C-globuline. En revanche, il n’y avait aucune fixation sur ces dépôts, des sérum anti-IgM, anti-fibrinogène, anti-albumine, anti-coeruléoplasmine, anti-α, macroglobuline et anti-β-lipoprotéine. Les dépôts intercapillaires étaient présents dans tous les glomérule.

L’existence de dépôts intercapillaires n’avait été reconnue en microscopie optique que dans 3 cas. Dans la moitié des cas, le diagnostic histologique avait été celui de gloméronéphrite focale: en effet, une partie des glomérules présentaient des lésions focales hylaines ou quelquefois nécrotiques, mais les autres glomérules paraissaient normaux. Dans les autres cas, le diagnostic histologique avait été celui de gloméronéphrite inclassée, de néphrite chronique, d’altérations artériolaires isolées ou de rein normal.

La présence de dépôts denses et finement granuleux situés entre la membrane basale et les cellules intercapillaires a été vérifiée par la microscopie électronique dans les 10 cas qui ont été étudiés par cette technique.

Tous les patients avaient une protéinurie modérée et une hématurie microscopique. Dans la moitié des cas, étaient survenues une ou plusieurs hématuries macroscopiques, suivant habituellement une angine. La fonction rénale était normale dans la grande majorité des cas. Trois malades étaient hypertendus.

La durée d’évolution de la néphropathie depuis sa découverte jusqu’à la biopsie allait de quelques mois à douze ans.

Il apparaît donc que dans la plupart des cas de gloméronéphrite focale chronique, il existe en plus des lésions focales, des dépôts intercapillaires diffus. Cette constatation, outre son intérêt théorique, a une utilité pratique: l’immunofluorescence permet de faire très aisément le diagnostic de cette variété de gloméronéphrite dans les cas où la microscopie optique ferait croire à tort que le rein est normal ou atteint d’autres lésions.

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Guest Commentary

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This month, the editors have chosen to waive the usual rule that the author of the original manuscript comment on the work and its circumstances for the JASN readership. Dr. Jean Berger, who recently retired as Professor of Pathology, has chosen not to revisit the past. Because I was one of the few pathologists mentored by Dr. Berger between 1964 and 1970, I was asked to comment on a small article that appeared in French in 1968 in the Journal d’Urologie et de Néphrologie (1). This article dramatically altered the face of clinical nephrology.

Dr. Berger presented on a series of patients with recurrent hematuria who had unusual biopsy findings at the winter meeting of the French-speaking Société de Néphrologie, which was held in Paris. All of these patients had focal and segmental glomerular lesions by light microscopy. However, they had a characteristic immunofluorescence pattern that consisted of the presence of deposits of immunoglobulin IgA and that was distributed in a diffuse fashion and delineated the mesangial regions of the glomeruli while the peripheral loops were uninvolved. IgA was associated with less conspicuous deposits of IgG and C3. This presentation was received with interest but a certain degree of skepticism. Was this really a new disease as claimed by its father, or was this an immunofluorescence finding with little general significance? Many of the members of the audience knew little about IgA; furthermore, immunofluorescence microscopy was still considered an experimental research tool with little clinical application and/or significance. However, Dr. Berger was considered to be a brilliant investigator. The importance of this discovery did not escape the members of the Société de Néphrologie for long, and in the ensuing months and years, antibodies to IgA were applied to a wide variety of renal diseases.

The French Society of Nephrology was the most exciting forum. The meetings were held in the old “amphitheater” at Necker’s Hospital with antiquated wooden benches,
Intercapillary deposits of IgA-IgG

BY J. BERGER AND N. HINGLAIS

Intercapillary deposits which fixed antiserum to IgA and to a lesser extent IgG and β2G were found by immunofluorescence microscopy in the biopsies of 25 patients. In contrast, there was no staining of the deposits using antiserum to IgM, fibrinogen, albumin, ceruloplasmin, α1-macroglobulin or β-lipoprotein. The intercapillary deposits were found in all the glomeruli. The presence of intercapillary deposits was only recognizable by light microscopy in three of the cases. In half of the cases the histological diagnosis was that of focal glomerulonephritis: indeed some of the glomeruli showed segmental hyalin lesions or occasionally areas of necrosis. In the remaining cases, the histological diagnosis varied from non-classifiable nephritis, isolated arteriolar lesions or normal kidney. The presence of finely granular electron-dense deposits located between the basement membrane and the intercapillary cells was verified by electron microscopy in the 10 cases studied. All the patients had moderate proteinuria and microscopic hematuria. In half of the cases, one or several episodes of macroscopic hematuria occurred usually following an episode of acute sore throat.

The duration of the nephropathy from the first symptom to the biopsy varied from several months to twelve years. Thus, it appears that in the majority of cases of chronic focal glomerulonephritis, there are diffuse intercapillary deposits associated with the focal lesions. This observation, in addition to its theoretical interest, has some practical implications: immunofluorescence microscopy allows an easy diagnosis of this syndrome in cases in which the kidney is either normal or shows other lesions.

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These qualities, combined with the fact that there was a wealth of patients in Necker and very soon in Hôpital Tenon where Gabriel Richet had created a new department, created ideal conditions to describe and dissect glomerular pathology. The environment was without equal. Renée Habib was opening the field of pediatric renal pathology. Nicole Hinglais and Pierre Galle both were electron microscopists of great talent.

For 2 or 3 years, I had shown Berger the biopsies from Richet’s group. I spent every Wednesday afternoon in his office and was very careful to bring all of the clinical information that I could collect, as well as the slides. I also provided him with small biopsy cores before we had acquired a cryostat and some of the required technical background. I performed biopsies once a week, then I delivered the biopsy cores on wet gauze to Berger’s laboratory, a 45-minute metro ride. There was a very complex ceremony to snap-freeze the biopsies, which was observed by the late Dr. Yaneva. Transport medium was not invented, and I was using saline and wet gauze. I was young and ignorant, and Berger was usually dropping some clever diagnosis with an air of complete boredom. Nonetheless, he was a fabulous teacher and seemed to have an endless knowledge of human and experimental pathology.

In 1968, the short article first published and translated in this issue of JASN was entitled “les dépôts intercapillaires d’IgA-IgG.” The initial patients had mild proteinuria and microscopic hematuria, and most of them presented with episodes of recurrent macroscopic hematuria, often after a common cold or a gastrointestinal infection. Renal function was within normal range. The histologic findings ranged from focal and segmental lesions with occasional areas of necrosis to small intracapillary thrombosis, synechiae, and areas of hyalinosis. There was also a mild increase in the number of mesangial cells. The focal nature of the light microscopic lesions sharply contrasted with the distribution of the deposits, which involved all of the mesangial areas by immunofluorescence and electron microscopy. Within a year, Berger produced the first description of the disease in the Anglo-American literature. This seminal paper was entitled “IgA glomerular deposits in renal disease” and appeared in Transplantation Proceedings (2). This article expanded the original findings to a series of 55 patients. Of these, 22 met the clinical criteria for the so-called essential or recurrent hematuria. Thus, recurrent gross hematuria became the clinical hallmark of this new disease. Only four of the patients had significant hypertension, and one had terminal renal failure during the short follow-up period. This led to the concept that the disease was relatively benign or at least was slowly progressive (2). It is interesting that the light microscopic findings were relatively heterogeneous. Although half of the biopsies showed focal and segmental glomerulonephritis consistent with the initial description of Ross (3) in a series of patients with recurrent hematuria and focal nephritis, the others had a variety of lesions from extensive sclerosis to virtually normal glomeruli. In some instances, the glomeruli seemed normal or had minor lesions by light microscopy, whereas some biopsies showed conspicuous glomerular obsolescence usually in association with advanced tubulo-interstitial and arterial lesions. The ultrastructural findings were characteristic and consisted of electron-dense deposits in the mesangial regions often unassociated with other glomerular lesions.
Within 4 years, this immunofluorescence pattern was reported in many other centers. In France, Micheline Levy and Renée Habib reported similar findings in a series of pediatric cases (4). It rapidly became clear that this form of nephritis was common, and in 3 years, we collected 92 cases of this entity in Gabriel Richet’s department (5). The rest belongs to the history of nephrology, and in a few years similar cases were reported in multiple countries, including England, the United States, Australia, Italy, Asia, and, subsequently, in every single center (6–11). Although the name initially coined as Berger’s disease designated the idiopathic form of the disease, Berger reported that similar IgA deposits also occurred in Schonlein-Henoch purpura. The frequency of alcoholic liver cirrhosis in France led another group of investigators, led by Druet and Bariéty at Hôpital Broussais, to describe a liver-associated IgA disease (12). Those observations led to the concept of IgA nephropathy as a common syndrome reflecting disorders of IgA metabolism. This was strengthened by observations from a Dutch group, which found deposits of IgA in the skin of patients with Berger’s disease as well as with Schonlein-Henoch purpura (13).

Although the initial impression was that of a relatively benign disease, end-stage renal failure occurred in a number of patients who subsequently underwent renal transplantation. At those early times, renal biopsies were part of the routine follow-up of transplantation, and the uniform recurrence of IgA deposits in transplant recipients was reported by Berger and his Necker colleagues in 1975. It is interesting that the deposits often recurred in the absence of any renal symptomatology and did not predict early rejection (14).

The number of publications increased over the years, and today this form of nephritis is still the “commonest glomerulonephritis in the world,” to quote d’Amico’s editorial review in the *Quarterly Journal of Medicine* (15).

In summary, over the past 32 years, IgA nephropathy, alias Berger’s disease, has become recognized as a major cause of progressive glomerular disease and still represents a fascinating and unresolved area for basic and clinical research.

References