IgA nephropathy

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Abstract

Immunoglobulin A nephropathy (IgAN) was initially described in 1968 by a French pathologist, Dr. Jean Berger, and his colleague Dr. Nicole Hinglais (an electronmicroscopist) as a kidney disease having glomerular "intercapillary deposits of IgA-IgG".

Keywords

Nephropathy; IgG; Immunoglobulin

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Introduction

The entity was initially coined Berger's disease and is to date sometimes referred to as such.[1] It is the most common primary glomerular disease in many countries and remains a leading cause of chronic kidney disease and end-stage kidney disease (ESKD).[2–5] IgAN is characterized on renal biopsy by dominant IgA glomerular deposits, usually accompanied by local cellular proliferation and matrix expansion.[6] Recurrent visible hematuria concurrent with a febrile illness is the hallmark clinical feature of IgAN and is particularly common in children and young adults, whereas microscopic hematuria with or without varying degrees of proteinuria is frequently observed among adults.[7]

EPIDEMIOLOGY

The prevalence of IgAN varies widely between ethnic/racial groups, being highest in persons of East Asian descent, followed by Caucasians and is relatively rare in individuals of sub-Saharan African ancestry.[8–12] IgAN accounts for about 40% of all native-kidney biopsies in Japan, 25% in Europe, 12% in the United States, but less than 5% in central Africa.[13] Some of this variability can be explained by differences in health screening policies and biopsy practices between these regions,[14] but genetics likely contribute as well. The incidence has been estimated at 2–10 per 100,000 person-years[8–12, 15, 16] and peaks during the second and third decades of life.[17, 18] The male-to-female ratio is 2–3:1 in North America[15, 19, 20] and Europe[21] but about 1:1 in Asia.[22] Subclinical or "Ianthanic" IgAN, defined by the characteristic glomerular IgA deposits on renal biopsy without significant hypercellularity or matrix expansion and without clinical manifestation of overt kidney disease, was detected in 1.3% of autopsies of trauma victims in Finland.[23] Furthermore, a Japanese study showed that 16% of renal allografts (from living and deceased donors) had glomerular IgA deposits on biopsies taken at time of engraftment, of which 10% exhibited histological features typical of IgAN.[24] Therefore the true prevalence and incidence of IgAN may be higher than recognized because of likely undocumented subclinical cases. While most cases of IgAN appear to be sporadic, some kindreds with familial IgAN have been described.[25]

PATHOLOGY

The diagnosis of IgAN necessitates a kidney biopsy. The defining pathology feature is IgA as the dominant or co-dominant immunoglobulin in the immune deposits in the mesangial areas of the glomeruli as shown by routine immunofluorescence microscopy

(Figure 1 - Panel C).[6] IgA is the sole immunoglobulin in about 15–40% of cases; for the remaining cases, IgG, IgM, or both are present although the frequencies vary widely.[7, 26] The glomerular IgA is exclusively of the IgA1 subclass that has compositional features that play a central role in the pathogenesis of IgAN, as described later. Other immune proteins may be detected by immunofluorescence microscopy. Complement (C) component C3 is co-localized with IgA in greater than 90% of the biopsies with IgAN.[27] C3, C4, C4d,[28] properdin, terminal complement complex (C5b-C9),[29] and mannose binding lectin[30] are frequently detected whereas C1q is typically absent.[31–33] These features support the involvement of the alternative and lectin pathways of complement activation in the pathogenesis of IgAN.

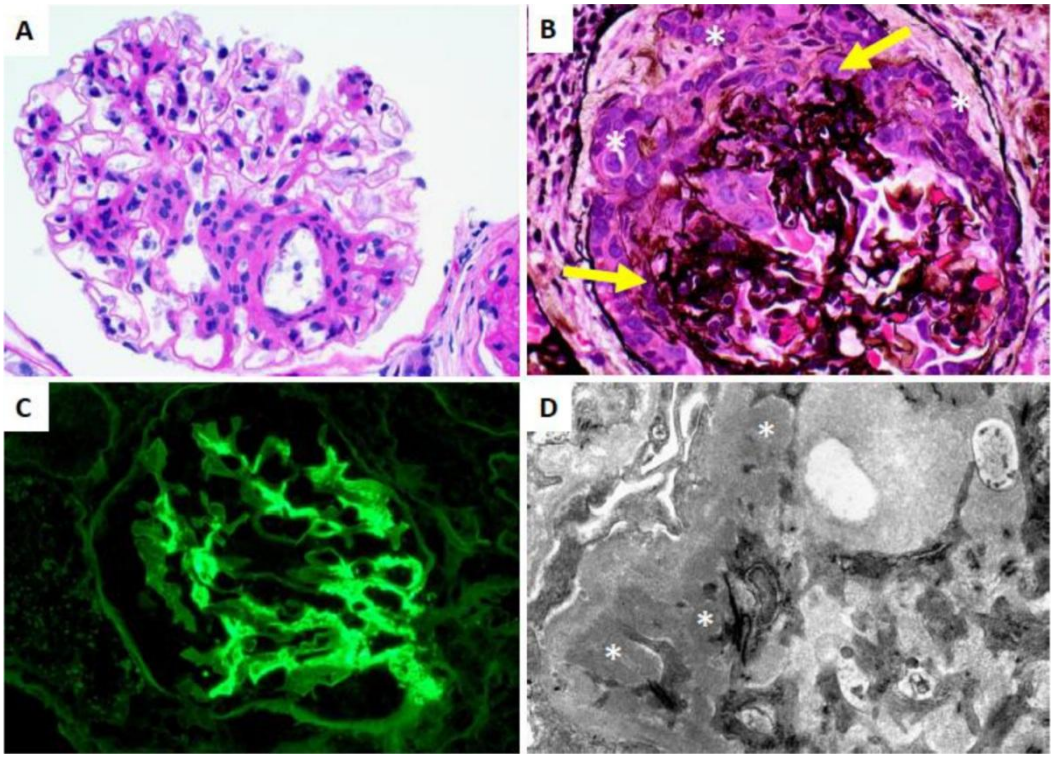

Figure (1): Pathological Characteristics of IgAN.

Panel A (Periodic acid-Schiff Hematoxylin stain x40) shows a glomerulus with increased mesangial matrix and cellularity (> 3 cells in a mesangial area), without endocapillary proliferation or crescent formation. Panel B (Jones silver stain x40) shows a glomerulus with early fibrocellular crescent (asterisks) and segmental sclerotic lesions with obliterated capillary lumina (arrows) that are entrapped within the circumferential crescent. Panel C (immunofluorescence stain with fluorescein-conjugated anti-IgA antibodies x40) shows near global, granular, staining for IgA limited to the mesangium. Panel D is an electron micrograph of a mesangial area with large electron-dense immune complex deposits in the expanded mesangium (asterisks).

Light microscopy histological features vary amongst patients and within the individual biopsy specimen. Mesangial hypercellularity and mesangial matrix expansion occur frequently (Figure 1A). Other glomerular lesions

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may include focal necrosis, segmental scarring, and crescents in Bowman's space (Figure 1B). Crescents are most commonly found in biopsies obtained during episodes of visible hematuria accompanied by acute kidney injury. Interstitial fibrosis and tubular atrophy, the culmination of renal injury via several pathways, portend a poor prognosis.[34, 35]

References

1. Chen YM, Liapis H: Focal segmental glomerulosclerosis: Molecular genetics and targeted therapies. BMC Nephrol 16: 101, 2015 [PMCID: PMC4496884] [PubMed: 26156092]

2. D'Agati VD, Kaskel FJ, Falk RJ: Focal segmental glomerulosclerosis. N Engl J Med 365: 2398–2411, 2011 [PubMed: 22187987]

3. Gbadegesin R, Lavin P, Foreman J, Winn M: Pathogenesis and therapy of focal segmental glomerulosclerosis: An update. Pediatr Nephrol 26: 1001–1015, 2011 [PMCID: PMC3624015] [PubMed: 21110043]

4. Sethi S, Glassock RJ, Fervenza FC: Focal segmental glomerulosclerosis: Towards a better understanding for the practicing nephrologist. Nephrol Dial Transplant 30: 375–384, 2015 [PubMed: 24589721]

5. D'Agati VD: Pathobiology of focal segmental glomerulosclerosis: New developments. Curr Opin Nephrol Hypertens 21: 243–250, 2012 [PubMed: 22357339]

6. Fogo AB: Causes and pathogenesis of focal segmental glomerulosclerosis. Nat Rev Nephrol 11: 76–87, 2015 [PMCID: PMC4772430] [PubMed: 25447132]

7. Mondini A, Messa P, Rastaldi MP: The sclerosing glomerulus in mice and man: Novel insights. Curr Opin Nephrol Hypertens 23: 239–244, 2014 [PubMed: 24709948]

8. Schell C, Huber TB: New players in the pathogenesis of focal segmental glomerulosclerosis. Nephrol Dial Transplant 27: 3406–3412, 2012 [PubMed: 22767631]

9. Kiffel J, Rahimzada Y, Trachtman H: Focal segmental glomerulosclerosis and chronic kidney disease in pediatric patients. Adv Chronic Kidney Dis 18: 332–338, 2011 [PMCID: PMC3709971] [PubMed: 21896374]

10. Kronbichler A, Leierer J, Oh J, Meijers B, Shin JI: Immunologic changes implicated in the pathogenesis of focal segmental glomerulosclerosis. BioMed Res Int 2016: 2150451, 2016 [PMCID: PMC4773535] [PubMed: 26989679]

11. Sethna CB, Gipson DS: Treatment of FSGS in children. Adv Chronic Kidney Dis 21: 194–199, 2014 [PubMed: 24602468]

12. Coppo R: Different targets for treating focal segmental glomerular sclerosis. Contrib Nephrol 181: 84–90, 2013 [PubMed: 23689570]

13. Korbet SM: Treatment of primary FSGS in adults. J Am Soc Nephrol 23: 1769–1776, 2012 [PubMed: 22997260]

14. Meyrier A: Focal and segmental glomerulosclerosis: Multiple pathways are involved. Semin Nephrol 31: 326–332, 2011 [PubMed: 21839365]

15. McGrogan A, Franssen CF, de Vries CS: The incidence of primary glomerulonephritis worldwide: A systematic review of the literature. Nephrol Dial Transplant 26: 414–430, 2011 [PubMed: 21068142]

16. Briganti EM, Dowling J, Finlay M, Hill PA, Jones CL, Kincaid-Smith PS, Sinclair R, McNeil JJ, Atkins RC: The incidence of biopsy-

proven glomerulonephritis in Australia. Nephrol Dial Transplant 16: 1364–1367, 2001 [PubMed: 11427626]

17. Sim JJ, Batech M, Hever A, Harrison TN, Avelar T, Kanter MH, Jacobsen SJ: Distribution of biopsy-proven presumed primary glomerulonephropathies in 2000-2011 among a racially and ethnically diverse US population. Am J Kidney Dis 68: 533–544, 2016 [PubMed: 27138468]

18. Kitiyakara C, Eggers P, Kopp JB: Twenty-one-year trend in ESRD due to focal segmental glomerulosclerosis in the United States. Am J Kidney Dis 44: 815–825, 2004 [PubMed: 15492947]

19. Asinobi AO, Ademola AD, Okolo CA, Yaria JO: Trends in the histopathology of childhood nephrotic syndrome in Ibadan Nigeria: Preponderance of idiopathic focal segmental glomerulosclerosis. BMC Nephrol 16: 213, 2015 [PMCID: PMC4681037] [PubMed: 26670137]

20. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC: Pathologic classification of focal segmental glomerulosclerosis: A working proposal. Am J Kidney Dis 43: 368–382, 2004 [PubMed: 14750104]

21. Silverstein DM, Craver R: Presenting features and short-term outcome according to pathologic variant in childhood primary focal segmental glomerulosclerosis. Clin J Am Soc Nephrol 2: 700–707, 2007 [PubMed: 17699485]

22. Thomas DB, Franceschini N, Hogan SL, Ten Holder S, Jennette CE, Falk RJ, Jennette JC: Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. Kidney Int 69: 920–926, 2006 [PubMed: 16518352]

23. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, Bowden DW, Langefeld CD, Oleksyk TK, Uscinski Knob AL, Bernhardy AJ, Hicks PJ, Nelson GW, Vanhollebeke B, Winkler CA, Kopp JB, Pays E, Pollak MR: Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science 329: 841–845, 2010 [PMCID: PMC2980843] [PubMed: 20647424]

24. Kopp JB: Focal segmental glomerulosclerosis and collapsing glomerulopathy syndromes. In: Essentials of Chronic Kidney Disease, edited by Fadem SZ, Hauppauge, Nova Science Publishers, 2015

25. Fahr T: Pathologische anatomie des morbus brightii. In: Handbuch der Speziellen Pathologischen Anatomie und Histologie, edited by Henke F, Lubarsch O, Berlin, Springer, 1925

26. Rich AR: A hitherto undescribed vulnerability of the juxtamedullary glomeruli in lipoid nephrosis. Bull Johns Hopkins Hosp 100: 173–186, 1957 [PubMed: 13426687]

27. Corwin HL, Schwartz MM, Lewis EJ: The importance of sample size in the interpretation of the renal biopsy. Am J Nephrol 8: 85–89, 1988 [PubMed: 3394725]

28. Schachter AD: Computational simulation of renal biopsy accuracy in focal segmental glomerulosclerosis. Pediatr Nephrol 21: 953–957, 2006 [PMCID: PMC1636586] [PubMed: 16773406]

29. Fogo A, Glick AD, Horn SL, Horn RG: Is focal segmental glomerulosclerosis really focal? Distribution of lesions in adults and children. Kidney Int 47: 1690–1696, 1995 [PubMed: 7643538]

30. Wagrowska-Danilewicz M, Danilewicz M: [Synaptopodin immunoexpression in steroid-responsive and steroid-resistant minimal change disease and focal segmental

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glomerulosclerosis]. Nefrologia 27: 710–715, 2007 [PubMed: 18336100]

31. Giannico G, Yang H, Neilson EG, Fogo AB: Dystroglycan in the diagnosis of FSGS. Clin J Am Soc Nephrol 4: 1747–1753, 2009 [PMCID: PMC2774958] [PubMed: 19808230]

32. Meehan SM, Chang A, Gibson IW, Kim L, Kambham N, Laszik Z: A study of interobserver reproducibility of morphologic lesions of focal segmental glomerulosclerosis. Virchows Arch 462: 229–237, 2013 [PubMed: 23262784]

33. Han MH, Kim YJ: Practical application of columbia classification for focal segmental glomerulosclerosis. BioMed Res Int 2016: 9375753, 2016 [PMCID: PMC4876206] [PubMed: 27247945]

34. Schwartz MM, Korbet SM: Primary focal segmental glomerulosclerosis: Pathology, histological variants, and pathogenesis. Am J Kidney Dis 22: 874–883, 1993 [PubMed: 8250036]

35. Stokes MB, D'Agati VD: Morphologic variants of focal segmental glomerulosclerosis and their significance. Adv Chronic Kidney Dis 21: 400–407, 2014 [PubMed: 25168828]

36. Zhong Y, Xu F, Li X, Chen H, Liang S, Zhu X, Liu Z, Zeng C: The evolution of morphological variants of focal segmental glomerulosclerosis: A repeat biopsy-based observation. Nephrol Dial Transplant 31: 87–95, 2016 [PubMed: 26160893]