An update on pathology of IgA nephropathy

Atualização em nefropatia da IgA

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Abstract

IgA Nephropathy (IgAN) is the commonest of the glomerular diseases in the world. Its progression rate of 30-40% of the cases em 20-30 years makes IgAN an important healthcare issue in Nephrology. Diagnosis of IgAN depends on biopsy findings, particularly at immunofluorescence microscopy. The frequence of IgAN diagnosis is variable in different populations and depends on screening and biopsy indication policies. IgAN pathogenesis is considered multifactorial; its primordial defect is the production of galactosis-deficient IgA molecules. This review paper discusses the most uptodate aspects of the pathogenesis, pathological classification and clinical implications of IgAN.

Keywords: glomerulonephritis; glomerulonephritis, IGA; immunoglobulin A; pathology.

Resumo

A Nefropatia da IgA (IgAN) é a mais comum das doenças glomerulares no mundo. Sua taxa de progressão de 30-40% em 20-30 anos torna a IgAN uma importante preocupação em saúde pública na area da Nefrologia. O diagnóstico da IgAN depende dos achados de biópsia, particularmente de microscopia de imunofluorescência. A frequência do diagnóstico é variável em diferentes populações e depende do rastreamento de hematúria e da indicação de biopsia. A IgAN é uma doença multifatorial: o defeito primordial é a produção de moléculas de IgA deficientes em galactose. Esta revisão discute aspectos atualizados da patogênese e classificação patológica da IgAN e suas implicações clínicas.

Palavras-chave: glomerulonefrite; glomerulonefrite por IGA; imunoglobulina A; patologia.

Introduction

IgA Nephropathy (IgAN) is a primary renal disease, or part of the syndrome of Henoch-Schoenlein Purpura, or secondary to a series of extrarrenal conditions, namely liver and gastrointestinal diseases. It was first recognised in 1968, when Berger and Hinglais reported the association of hematuria, proteinuria and upper respiratory tract infections.[1] Renal biopsy samples of affected patients showed variable light microscopy changes, apart from proliferative and exsudative glomerulonephritis.

Immunofluorescence microscopy findings were however consistent: intense mesangial IgA deposits, with less intense deposits of IgG and C3. Such observations are seemingly coincidental with previous reports by Volhard and Fahr, in 1914, and by Bates, Jennings and Earle, in 1957, who described a focal acute glomerulonephritis, coincidental with infectious conditions, but rarely followed by overt nephritic syndrome.[2]

Today IgAN is regarded as the commonest glomerular disease in the world.[2-4] Its slow but unyielding progression causes 30 - 40% of the patients to progress to end stage renal disease (ESRD) in 20 - 30 years. Thus, alongside diabetic nephropathy, IgAN emerges as an important health-care issue in Nephrology.[5] As opposed to diabetic nephropathy, however, IgAN tends to affect younger individuals, who are thus burdened by a lifelong chronically progressive disease.[6] This review intends

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to highlight the main and most recent features regarding the pathogenesis and pathology of IgAN.

Epidemiology

Diagnosis of IgAN largely depends on the screening policies and biopsy indication.[3,4,7] In Brazil, a series of 9617 renal biopsies obtained countrywide revealed that IgAN represents 9.6% of all and 20.1% of the primary glomerular diseases.[8] Its clinical presentation is variable: proteinuria - usually non-nephrotic - associated with macroscopic or microscopic haematuria and hypertension.[3]

In the USA 50% of the IGAN patients older than 30 years old has Stage 3 to Stage 5 chronic kidney disease at the diagnosis. In North American and European cohorts, the male to female ratio in affected individuals is 2:1; incidence peaks in the second and third decades of life.[3,4] A recent series of 600 Brazilian IgAN cases depicted a slight male predominance (1.24:1), with an average of 33 years old at diagnosis. Hematuria was the main presentation feature (72% of patients), followed by proteinuria (57% of patients), which was nephrotic in 28% of them.[9]

Pathogenesis

Inheritance pattern

IgAN is regarded nowadays as a slowly progressive disease, with both familial and sporadic ocurrence. IgAN may be inherited in an autosomal dominant pattern, with reduced penetrance. Exome analysis has so far detected several candidate genes involved in the pathogenesis of IgAN, which are implicated in: a) antigen processing, cytokine production and antigen presentation by class I major compatibility complex (MHC-I); b) mucosal immunity; c) alternative complement pathway regulation. Loci apparently involved in these pathways are 6q22-q23, 3p24-p23, 2q36, 4q26-q31 and 17q12-q22.[5]

Structure and production of IGA

Human IgA is mainly produced in mucous membranes; a small fraction of it is found in circulation. Human polymeric and monomeric IgA exists as IgA1 and IgA2. IgA polymers are composed of subunits aggregated by a J-chain. Transepithelial transport of IgA to luminal surface is done by polymeric immunoglobulin receptor (pIgR), which exhibits affinity to the J-chain. After luminal secretion, part of the pIgR is retained within the polymeric IgA molecule - the so called secretory component.

The J-chain is therefore essential to IgA transepithelial transport; thus, all IgA produced in mucous membranes is polymeric.[10] Five IgA receptors are known in humans: CFR (constant fraction receptor), ASGR (asialoglycoprotein receptor), pIgR, transferrin receptor and Fc α/μ receptor. Only the latter two were found in renal tissue, exclusively in mesangial cells.[11]

IgA1 shows peculiar molecular features that differentiate it from IgA2, IgM and IgG. A binding site with two to six O-glycans is located in the hinge region, between the first and second regions of the constant domain of IgA1 heavy chain. O-glycan synthesis has the following steps: 1- addition of N-acetylgalactosamine to serine or threonine residues; 2- binding of a galactosis molecule to the β1,3 conformation; 3- binding of sialic acid to galactosis or N-acetylgalactosamine - a step that prevents further conformational changes.[10,11]

IgAN is the product of a multihit process. The primordial defect lies in the production of aberrant IgA1 molecules, which are deficient in galactosis in their hinge region O-glycan residues (Gd-IgA1). Gd-IgA1 thus have their hinge region N-acetylgalactosamine residues exposed. A further necessary step into the pathogenesis of IgAN is the production of antibodies - IgA or IgG - against galactose-deficient sugar residues in Gd-IgA1.

This step is assisted by toll-like receptors (TLRs), which are involved in the response to the exposure to bacterial wall and viral envelope components, and in the polyclonal activation of B lymphocytes and immunoglobulin production, independently of preceding T cell activation.[10,11] The formation is IgG-Gd-IgA1 immune complexes is facilitated by Gd-IgA1 greater affinity to IgG. Gd-IgA1 bound to antiglycan antibodies are not amenable to linkage to asialoglycoprotein receptors on hepatocytes, which eases its escape from hepatic metabolism and its persistence in circulation.

In addition, the more sialylated the IgA1 molecule, the more negatively charged it is and the greater its affinity to mesangial cells and its resistance to hepatic removal.[3,4,11] To sum up, the determinant events in pathogenesis of IgAN are the generation of Gd-IgA1 immune complexes, their affinity to mesangia and deffective clearance from circulation and mesangia, and renal tissue responses.

In the mesangia, Gd-IgA1 immune complexes may bind to fibronectin, type IV collagen, CD71 or mesangial cell integrins.

Activated mesangial cells secrete extracellular matrix components; have the NF-κB signal transduction pathway activated and the nitric oxide synthase expression enhanced; secrete renal lesion mediators like angiotensin II (AT-II), cytokines (interleukin-6 [IL-6], transforming growth factor-β [TGF-β], macrophage chemotactic protein-1 [MCP-1], tumour necrosis factor-α [TNF-α]) and pro-fibrotic factors.

TNF-α elicits a pro-apoptotic state on visceral epithelium, since podocytic TNF-α receptors 1 and 2 (TFR1 and TNFR2) are upregulated in IgAN.[5,11] The sustained inflammatory stimulus causes mesangial hypercellularity, apoptosis, oxidative stress and mesangial matrix expansion.[4]

Pathology

From the pathologist´s viewpoint, the diagnosis of IgAN is relatively simple: it is defined by the identification by immunofluorescence (IF) or immunoperoxidase (IP) microscopy of dominant to co-dominant granular to globular IgA deposits in mesangial areas, and less frequently (24-54% of the cases), in glomerular capillary loops.[2] It is noteworthy that 3-16% of healthy individuals present glomerular IgA deposits of undetermined significance.[3]

Electron microscopy (EM) is not mandatory for the diagnosis of IgAN. Notwithstanding, it is used to confirm the presence of mesangial electrondense deposits. Capillary wall and subendothelial deposits may be present, respectively, in 50% and 55% of the cases.[12,13] Subendothelial deposits might be associated with mesangial interposition and basement membrane duplication.[12,13] Subepithelial deposits are highly atypical and should be interpreted as a superimposed immunecomplex mediated disease, not related to IgAN.[14]

At light microscopic level, however, IgAN is as highly variable as its clinical presentation and prognosis.[15] The seminal work by Berger described focal glomerulonephritis in most of the biopsies; 10% of the cases showed no changes at light microscopy. Subsequent observations led to the demonstration of a wider range of histopathological aspects, which included segmental sclerosing lesions and endocapillary and extracapillary proliferative lesions (Figure 1).[16,17]

Single grade classification schemes were proposed by Lee and Haas.[2] Lee´s and Hass´ classification schemes admit five classes, to which pertain histopathological findings of the glomerular and tubulo-interstitial compartments, with an emphasis on the formers (Table 1).

To these schemes, Alamartine added, in 1990, a semi-quantitative classification scheme, which yielded a global optical score.[18] Whilst this system relatively succeeded in establishing reasonable clinical-pathological correlation, semi-quantitative scoring systems are quite demanding and have limited reproducibility. The simplicity and similarity with the WHO classification of lupus nephritis made the single grade schemes widespread and accepted amongst pathologists.

In attempts to predict clinical course, guide treatment selection, stratify patients for clinical trials and predict the outcome, members of the Renal Pathology Society (RPS) and of the International IgA Nephropathy Network (IIGANN) assembled to propose a consensual and evidence-based histopathological classification of IgAN.

Efforts concentrated on 1- identifying and defining which lesions are characteristic of IgAN; 2- determining which were the lesions least prone to sampling and reproducibility limitations; 3- correlating lesions and clinical outcome. After the analysis of 265 renal biopsy samples of IgAN, from patients followed for 5 years, mesangial hypercellularity (M), segmental sclerosis/adhesions/synechiae (S), endocapillary hypercellularity (E) and tubular atrophy/interstitial fibrosis (T) emerged as the most reproducible parameters, with strong and independent correlation with clinical outcome.[19,20]

According to the Oxford Classification of IgAN, M, E and S are binary variables (0 - absent; 1 - present). Tubular atrophy and interstitial fibrosis are graded as T0, T1 and T2 (respectively, 0-25%, 26-50% or > 50% of affected cortical tissue). Ideally, the anatomic pathology report of an IgAN biopsy should include a detailed microscopic description, including quantitative inflammatory and scarring changes: total number of glomeruli and the number of glomeruli affected by necrosis, endocapillary proliferation, cellular and/or fibrous crescents, segmental and/or global sclerosis and the extension of tubular atrophy and interstitial fibrosis (Table 2). The diagnosis line of the report should mention the M, E, S and T scores.[19,20]

Figure 1. Protean histologic appearances of IgAN. A- Mild mesangial proliferation (M1 lesion; circle): 4-5 mesangial cell nuclei clustered within a mesangial space. PAS (Periodic Acid Schiff), 100x. B- Segmental sclerosis (S1 lesion), with segmental closure of capillary walls, mesangial matrix expansion and capsular adhesion. PAS, 400x. C- Endocapillary hypercellularity (E1 lesion), displaying closure of capillary walls by inflammatory cell infiltration and endothelial swelling. Haematoxilin and Eosin, 100x. D - Circumferential extracapillary cell proliferation characteristic of a cellular crescent. PAS, 100x.

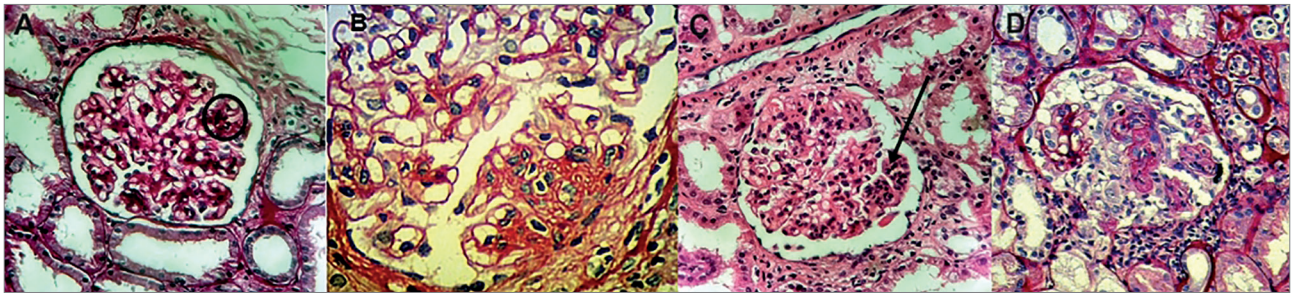

Table 1 Haas´ and Lee´s single-graded classification systems

	Haas Subclasses	Lee Grades
I	Absent to minimal mesangial hypercellularity.	Absent to minimal mesangial hypercellularity. No tubulo-interstitial inflammation or atrophy.
II	Focal segmental glomerulosclerosis-like pattern.	Focal and segmental mesangial hypercellularity. Sparse crescents. No tubulo-interstitial inflammation or atrophy.
III	Focal proliferative glomerulonephritis (< 50%) with ou without crescents.	Diffuse mesangial hypercellularity. Occasional crescents and synechiae. Focal tubulo-interstitial inflammation and oedema.
IV	Diffuse proliferative glomerulonephritis (> 50%) with ou without crescents.	Diffuse mesangial hypercellularity and matrix expansion. Frequent segmental sclerosis. Crescents in up to 45% of glomeruli. Tubulo-interstitial inflammation.
V	≥ 40% of globally sclerotic glomeruli or tubular atrophy/ interstitial fibrosis, with or without active glomerular lesions.	Similar to IV; > 45% of glomeruli with crescents. Severe tubular atrophy and interstitial fibrosis.

Table 2 Histological parameters of Oxford´s classification of IgAN

	Histological Parameter	Score
M	Mesangial proliferation	M0 (absent)/M1 (present in > 50% of glomeruli)
E	Endocapillary hypercellularity	E0 (absent)/E1 (present)
S	Segmental sclerosis/ synechiae	S0 (absent)/S1 (present)
T	Tubular atrophy/ interstitial fibrosis	T0 (0-25%*)/T1 (26-50%*)/T2 (> 50%*)

* relative to cortical extension Pathology report should ideally include: % of globally sclerotic glomeruli % of crescents % of glomeruli with necrosis % of glomeruli with endocapillary hypercellularity.

Although crescents was a highly reproducible variable, it was not originally included in the original classification. Even though 45% of the cases of the original series depicted crescents, the average percentage of glomeruli with extracapillary proliferation in affected cases was 9%; in none of the cases was this percentage higher than 55%.

In the Oxford Classification cohort the presence of crescents was not independently associated with progression to ESRD or with a decline of the estimated glomerular filtration rate greater than 50% during follow-up (combined event).[19] Further studies on crescentic IgAN point out that serum creatinine is a strong independent predictor of risk for ESRD: a value of 6,8 mg/dL is considered the upper threshold for immunosupression indication.[21,22]

However newer observations in larger cohorts emphasise the role of crescents as predictors of a higher risk of a combined event. The presence of crescents in ≥ 25% of glomeruli, seems to be independently associated with a combined event, in the presence or absence of immunosupressive treatment. These recent data support the incorporation of a crescent score to the original classification (Haas et al., personal communication).

Despite its shortcomings, the Oxford classification of IgAN was validated by several different studies pertaining to diverse ethnic groups, the most extensive of which is the VALIGA Study[15,23-28] The VALIGA study highlighted the importance of chronic tubulointerstitial lesions, segmental sclerosis and

mesangial hypercellularity as predictors of the rate of loss of renal function.[28]

Both the VALIGA Study and the Oxford Classification original cohort failed to demonstrate that endocapillary proliferation was an independent predictor of rate of renal function deterioration.[4,9] Endocapillary proliferation - capillary loop narrowing and occlusion by endothelial cell swelling, macrophage and neutrophylic infiltration and mesangial proliferation - is observed in approximately one third of the cases of IgAN and is mostly focally distributed.[15]

More recent evidences point out that the only predictors of time to ESRD are baseline estimated creatinine clearance (eGFR), baseline proteinuria, endocapillary hypercellularity (odds ratio = 3.41 for E1 compared to E0) and tubular atrophy/interstitial fibrosis.[29]

The low predictive value of E1 in previous studies might stem from interaction between the lesions and immunosuppressive therapy: in the VALIGA study cohort, 39% of the patients had received angiotensin receptor blockage and 10% had received steroids prior to the biopsy.[27,29] These data suggest that patients with endocapillary hypercellularity in IgAN might benefit from immunosupression.

At the First Oxford Conference on IgA Nephropathy, in June 2014, close scrutiny of the VALIGA Study data revealed low interobserver reproducibility for the M and E variables (interobserver correlation coeficient [ICC] = 0.49 and 0.34, respectively; Roberts, personal communication). Given the low reproducibility of prognostically valuable lesions, cell labeling studies are already underway and are expected to provide a less subjective measure of endocapillary hypercellularity.

In addition, the development of e-learning tools for continuous training and regular assessment of pathologists involved in IgAN diagnosis was proposed in 2014 and is to be launched in 2016 (Soares *et al.*, personal communication).

Conclusions

IgAN emerges as an important worldwide healthcare issue. From the pathogenetic point of view, it shares similarities both with allergic and autoimmune disorders. The lack of reliable animal models hinders experimental studies about the disease.

Nevertheless, deeper understanding of the interactions in the mucosa-kidney axis, of the role of complement and growth factors might pave the way into acknowledging which mechanisms are responsible for its clinical and pathological characteristics.

The development of the Oxford Classification of IgAN and its constant efforts for improvement are bound to amelliorate the communication of relevant findings between pathologists and clinicians and to strengthen clinico-pathologic correlations.

Conflicts of interest

None to declare.

References

1. Berger J, Hinglais N. Intercapillary deposits of IgA-IgG. J Urol Nephrol (Paris) 1968;74:694-5.
2. Haas M. IgA Nephropathy and Henoch-Schönlein Purpura Nephritis. In: Jennette JC, Olson JL, Schwartz MM, Silva FG, eds. Heptinstall´s Pathology of the Kidney. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 423-486.
3. Clinical presentation and diagnosis of IgA nephropathy. [Cited 2014 Mar 20]. Available from: www.uptodate.com
4. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med 2013;368:2402-14. PMID: 23782179 DOI: http://dx.doi.org/10.1056/NEJMra1206793
5. Lai KN, Leung JC, Tang SC. Recent advances in the understanding and management of IgA nephropathy. F1000Res 2016;5. pii: F1000 Faculty Rev-161. DOI: http://dx.doi.org/10.12688/f1000research.7352.1
6. Floege J, Amann K. Primary glomerulonephritides. Lancet 2016;387:2036-48. DOI: http://dx.doi.org/10.1016/S0140-6736(16)00272-5
7. Geddes CC, Rauta V, Gronhagen-Riska C, Bartosik LP, Jardine AG, Ibels LS, et al. A tricontinental view of IgA nephropathy. Nephrol Dial Transplant 2003;18:1541-8. DOI: http://dx.doi.org/10.1093/ndt/gfg207
8. Polito MG, de Moura LA, Kirsztajn GM. An overview on frequency of renal biopsy diagnosis in Brazil: clinical and pathological patterns based on 9,617 native kidney biopsies. Nephrol Dial Transplant 2010;25:490-6. DOI: http://dx.doi.org/10.1093/ndt/gfp355
9. Soares MF, Caldas ML, Dos-Santos WL, Sementilli A, Furtado P, Araújo S, et al. IgA Nephropathy in Brazil: apropos of 600 cases. Springerplus 2015;4:547. DOI: http://dx.doi.org/10.1186/s40064-015-1323-x
10. Barratt J, Feehally J. Primary IgA nephropathy: new insights into pathogenesis. Semin Nephrol 2011;31:349-60. DOI:http://dx.doi.org/10.1016/j.semnephrol.2011.06.006
11. Lai KN. Pathogenesis of IgA nephropathy. Nat Rev Nephrol 2012;8:275-83. DOI: http://dx.doi.org/10.1038/nrneph.2012.58
12. Haas M. A reevaluation of routine electron microscopy in the examination of native renal biopsies. J Am Soc Nephrol 1997;8:70-6.
13. Lee HS, Choi Y, Lee JS, Yu BH, Koh HI. Ultrastructural changes in IgA nephropathy in relation to histologic and clinical data. Kidney Int 1989;35:880-6. PMID: 2651762 DOI: http://dx.doi.org/10.1038/ki.1989.68
14. Hennigar RA, Tumlin JA. Glomerular diseases associated primarily with asymptomatic or gross hematuria. In: Zhou XJ, Laszik Z, Nadasdy T, D´Agati VD, Silva FG, eds. Silva´s Diagnostic Renal Pathology. 1st ed. New York: Cambridge University Press; 2009, p. 127-77.
15. Roberts IS. Pathology of IgA nephropathy. Nat Rev Nephrol 2014;10:445-54. DOI: http://dx.doi.org/10.1038/nrneph.2014.92

16. Haas M. IgA nephropathy histologically resembling focal-segmental glomerulosclerosis: a clinicopathologic study of 18 cases. Am J Kidney Dis 1996;28:365-71. PMID: 8804234 DOI: http://dx.doi.org/10.1016/S0272-6386(96)90493-X
17. Sinniah R. Idiopathic IgA mesangial nephropathy: histological features. Contrib Nephrol 1984;40:156-66.
18. Alamartine E, Sabatier JC, Berthoux FC. Comparison of pathological lesions on repeated renal biopsies in 73 patients with primary IgA glomerulonephritis: value of quantitative scoring and approach to final prognosis. Clin Nephrol 1990;34:45-51. PMID: 2225552
19. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int 2009;76:534-45. PMID: 19571791
20. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int 2009;76:546-56. PMID: 19571790
21. Lv J, Yang Y, Zhang H, Chen W, Pan X, Guo Z, et al. Prediction of outcomes in crescentic IgA nephropathy in a multicenter cohort study. J Am Soc Nephrol 2013;24:2118-25. DOI: http://dx.doi.org/10.1681/ASN.2012101017
22. Walsh M, Sar A, Lee D, Yilmaz S, Benediktsson H, Manns B, et al. Histopathologic features aid in predicting risk for progression of IgA nephropathy. Clin J Am Soc Nephrol 2010;5:425-30. DOI: http://dx.doi.org/10.2215/CJN.06530909
23. Kang SH, Choi SR, Park HS, Lee JY, Sun IO, Hwang HS, et al. The Oxford classification as a predictor of prognosis in patients with IgA nephropathy. Nephrol. Nephrol Dial Transplant 2012;27:252-8. DOI: http://dx.doi.org/10.1093/ndt/gfr295
24. Shima Y, Nakanishi K, Hama T, Mukaiyama H, Togawa H, Hashimura Y, et al. Validity of the Oxford classification of IgA nephropathy in children. Pediatr Nephrol 2012;27:783-92. DOI: http://dx.doi.org/10.1007/s00467-011-2061-0
25. Herzenberg AM, Fogo AB, Reich HN, Troyanov S, Bavbek N, Massat AE, et al. Validation of the Oxford classification of IgA nephropathy. Kidney Int 2011;80:310-7. PMID: 21544062 DOI: http://dx.doi.org/10.1038/ki.2011.126
26. Zeng CH, Le W, Ni Z, Zhang M, Miao L, Luo P, et al. A multicenter application and evaluation of the Oxford classification of IgA nephropathy in adult chinese patients. Am J Kidney Dis 2012;60:812-20. DOI: http://dx.doi.org/10.1053/j.ajkd.2012.06.011
27. Coppo R, Troyanov S, Bellur S, Cattran D, Cook HT, Feehally J, et al.; VALIGA study of the ERA-EDTA Immunonephrology Working Group. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. Kidney Int 2014;86:828-36. PMID: 24694989 DOI: http://dx.doi.org/10.1038/ki.2014.63
28. Zeng CH, Le W, Ni Z, Zhang M, Miao L, Luo P, et al. A multicenter application and evaluation of the oxford classification of IgA nephropathy in adult chinese patients. Am J Kidney Dis 2012;60:812-20. DOI: http://dx.doi.org/10.1053/j.ajkd.2012.06.011
29. Chakera A, MacEwen C, Bellur SS, Chompuk LO, Lunn D, Roberts IS. Prognostic value of endocapillary hypercellularity in IgA patients with no immunosupression. J Nephrol 2016;29:367-75. DOI: http://dx.doi.org/10.1007/s40620-015-0227-8