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IgA vasculitis; from definition to classification of morphologic variables; an updated mini-review

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Abstract

All inflammatory modifications in the vessel wall are described as vasculitis. Pediatric vasculitis may existing with various clinical presentations. Immunoglobulin A vasculitis, is an immune complex vasculitis affecting small vessels with dominant IgA deposits. It is a small vessel vasculitis which can engage kidneys, gut, joints and skin, to varying degrees. Immunoglobulin A vasculitis, is the most common pediatric vasculitis usually recovers spontaneously, however, it is necessary to closely follow up of this disease because of the risk of kidney involvement, particularly in late-onset adult form of the disease. Both IgA nephropathy and IgA vasculitis are the same diseases, while IgA vasculitis is the systemic form of IgA nephropathy with presence of small vessel vasculitis. We suggest application of Oxford classification for IgA vasculitis and including of crescent as an additional morphologic variable in addition to MEST variables, which may have prognostic implication.

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Introduction

All inflammatory modifications in the vessel wall are described as vasculitis. Pediatric vasculitis may existing with various clinical presentations. Immunoglobulin A vasculitis, is an immune complex vasculitis affecting small vessels with dominant IgA deposits. It is a small vessel vasculitis which can engage kidneys, gut, joints and skin, to varying degrees (1). Immunoglobulin A vasculitis, is the most common pediatric vasculitis usually recovers spontaneously, however, it is necessary to closely follow up of this disease because of the risk of kidney involvement, particularly in late-onset adult form of the disease (1,2). In contrast, immunoglobulin A nephropathy is detected as a renal-limited, non-systemic disease. However, immunoglobulin A nephropathy and immunoglobulin A vasculitis has many resemble histological, immunological, and clinical characteristic. Immunoglobulin A nephropathy is the most common glomerulonephritis in the world comprising 30%–40% in Caucasians and 30%–45% of all primary glomerular diseases (1-3).

Both of diseases are supposed to be related closely. For example, immune complexes containing IgA have been detected in the glomeruli of both disease. IgA vasculitis, is the most prevalent vasculitis in children and commonly has a benign prognosis. It appears mainly in the childhood and is detected rarely in adults. It appears most commonly between the ages of 3 and 15 years and more often in boys compared to girls. In fact, IgA nephropathy and IgA vasculitis are twice as frequent in males as females (1-4).

Key point

Both IgA nephropathy and IgA vasculitis are the same diseases, while IgA vasculitis is the systemic form of IgA nephropathy with presence of small vessel vasculitis. We suggest application of Oxford classification for IgA vasculitis and including of crescent as an additional morphologic variable in addition to MEST variables, which may have prognostic implication.

Materials and Methods

For this mini-review, we used a variety of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents such as IgA nephropathy, Oxford classification, extracapillary proliferation, IgA vasculitis, chronic kidney disease, crescent, and end-stage renal disease, immunoglobulin A nephropathy, immunostaining data, and endocapillary proliferation.

Clinical presentations of IgA vasculitis

IgA vasculitis has no defined cause. It happens most often in the spring. It habitually follows an infection of the respiratory tract or throat. It appears to represent an infrequent reaction of the immune system of the body to a bacterial or viral infection. Apart from infectious disease, various medications can also provoke the situation (2-4). IgA vasculitis arises most commonly in children, however individuals of any age groups can be involved. Microscopic hematuria is the most sensitive and an initial symptom representative of glomerulopathy during IgA vasculitis, in accompanying with urine protein excretion of varying range which sometimes becomes nephrotic. Hypertension is reported in one-third of patients. In adults, kidney insufficiency at the time of diagnosis is found in nearly 30% while incidence of renal insufficiency is infrequent in children. Interestingly macroscopic hematuria is extraordinary (1,2,5-8). The other classical features of the disease comprises arthritis or arthralgia, non-thrombocytopenic palpable purpura, which does not lead to sequela, gastrointestinal involvement indicated with typically abdominal pain and finally involvement of the kidney (2-6).

In contrast to IgA vasculitis, the clinical features of individuals with immunoglobulin A nephropathy are variable, from asymptomatic microscopic hematuria with/without proteinuria to episodes of gross hematuria. Similarly, a small number of cases present with clinical signs of nephrotic syndrome or symptoms and signs of acute glomerulonephritis. Currently that up to 20%–40% of cases have a slow progressive disease, resulting to end-stage kidney failure around ten years after the initial diagnostic kidney biopsy (5-7).

Thus, the diagnosis of IgA vasculitis is best established by the presence of purpura or petechiae -as mentioned usually palpable - with a lower limb preponderance plus one or more of the following four presentations; (*a*) kidney involvement consisting of proteinuria >0.3 g in 24 hours, or presence of glomerular hematuria or presence of renal failure, (*b*) arthritis or arthralgia and (*c*) abdominal pain (diffuse and colicky) (1,7-9).

Positive histopathologic lesions as like the presence of leukocytoclastic vasculitis with principal IgA deposits on skin biopsy, or proliferative glomerulonephritis with mainly IgA deposit on in mesangial/mesangiocapillary regions (5-9). To compare between adults and children with nephropathy of IgA vasculitis, Lu et al studied 208 children and 75 adult individuals with IgA vasculitis. They found, extrarenal symptoms consisting arthritis and abdominal pain were more popular in the pediatrics than in the adult group, however, renal symptoms containing edema and hypertension were moderately rare in this group. They concluded that, the clinicopathological variations among children and adults with IgA vasculitis. Other symptoms contain fever, scrotal pain, neurologic manifestations, edema in boys, and seldom pulmonary or cardiac involvement. IgA vasculitis, is a self-limiting situation, frequently subsiding within 6 to 8 weeks, however its complications might happen then after (10). Sixty-six percent of children undergo gastrointestinal symptoms like abdominal pain, gastrointestinal hemorrhage or rarely intussusception. Involvement in all joints may be found, accompanied with soft tissue edema. Joint involvement is in the category of acute polyarthritis. Scrotal and penile edema may also be detected. While, kidney involvement appears in 37% of cases, fortunately only 1% of cases lead to end-stage kidney disease. IgA vasculitis, is believed to be self-limiting, though kidney involvement is the main cause of morbidity from this illness. Importantly, recurrence of purpura may sometimes be associated with severe kidney involvement and may be found in 25% of IgA vasculitis patients (10-14). Neurological involvement may rarely be observed in IgA vasculitis. Central nervous system injury happens with the direct impact of vasculitis or indirect consequence of systemic inflammation. Clinical features consisting convulsion and confusion in some series in children, however, significant neurological involvement is detected rarely in this disease and mild involvement has been detected more commonly. Accordingly, orchitis, alveolar hemorrhage, myocarditis, or episcleritis are very rare manifestations of immunoglobulin A vasculitis (8-11).

Renal involvement in IgA vasculitis

Glomerulonephritis happens in 30%-50% of IgA vasculitis patients, largely in a mild form. However a small proportion of patients present with renal failure or proteinuria which may reach to nephrotic range. Like, IgA nephropathy, IgA vasculitis is caused by the glomerular deposition of immunoglobulin A1 (IgA1)-containing immune complexes in the mesangial area and sometimes in the subendothelial region (1-4). Disposition of the IgA1 immune complex is assumed to be the result of aberrantly glycosylated IgA1 molecules secreted into the circulation and the following identification by IgG specific for galactose-deficient IgA1. Proliferation of mesangial cells and kidney involvement like endocapillary proliferative glomerulonephritis are triggered by the deposited immune complexes in this area, which probably necessitate activation of the complement system. Physiopathological etiologies of IgA vasculitis consisting complement activation, glomerular tufts fibrin deposits, crescent (extracapillary proliferation) in the glomeruli and vascular damage due to invasion of inflammatory cells to the vessel walls (vasculitis) appear to play a crucial role. C_3 complement deposits are presented in a many patients with IgA vasculitis (4-7). Decreased level of completest usually has not been detected in IgA vasculitis, nonetheless, excessive use and deposition of C_3 complement in the kidneys may have been the cause of decreased C_3 complement serum level in a severe IgA vasculitis cases. As mentioned earlier, as a mandatory component of this disease, is the presence of small-vessel leukocytoclastic vasculitis (granulocytes in the walls of small arterioles or venules) accompanied with the deposition of immune complexes containing immunoglobulin A (IgA) in vessel walls (5-9).

In the study by Lu et al, long-term renal outcome found to correlate with the severity of the initial clinical manifes-

tations and the proportion of morphologic lesion in kidney biopsy (10). They also detected a significant positive association between morphological lesions and clinical presentations. They found also active lesions in pathology was positively correlated to kidney failure, proteinuria, abdominal pain, microscopic hematuria, presence of hypertension. Additionally, they found, chronic morphologic lesions was positively related with age (1-4,10-14). This study was also showed that, kidney involvement, and abdominal pain usually associated with severity of morphologic lesions in pathology. As mentioned, the severity of kidney damage, defines long-term prognosis in IgA vasculitis. Renal involvement episode may start years after recovery of IgA vasculitis clinical presentations. The most common finding in nephritis of IgA vasculitis is hematuria. It generally extends in the first four weeks. Additionally varying proportion of proteinuria may happen. Massive proteinuria consisting nephrotic range proteinuria may also be detected. Hypertension may be found in the initiation period or in the recovery phase. Kidney function tests are may be normal, however, occasionally severe kidney damage and proliferative glomerulonephritis may be noticed (1-5).

IgA vasculitis versus IgA nephropathy in nephrology viewpoint

The common clinical pattern of immunoglobulin A nephropathy is an sluggish and chronically progressive glomerulopathy with gradually increasing the proportion of proteinuria and irreversible decrease of renal function and structure over time with some flair-ups of macroscopic hematuria (1,2,8,13-15). This presentation for IgA nephropathy is in contrast to IgA vasculitis, which presents usually with an initial acute occurrence, which leads to complete healing in the majority of individuals (1,2,10,11,13-15) and sequels as persistent proteinuria and even developing chronic renal failure occur in a minority of patients.

IgA vasculitis versus IgA nephropathy in pathology viewpoint

In 2009, International IgA Nephropathy Network (IINN) the Renal Pathology Society (RPS) suggested an international consensus classification for IgA nephropathy, named as Oxford classification. In this classification, six pathological lesions were considered. They are, mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T), which also maned as MEST classification. This classification has been validated in numerous studies (1,2,10,11,13-15). The detail of four established morphologic features associated with the development of kidney disease and had prognostic implication are mesangial hypercellularity score (M0 ≤0.5, M1 >0.5), the intensity of tubular atrophy/interstitial fibrosis (T0 ≤25%, T1: 26%–50%, T2 >50%), the presence of endocapillary hypercellularity (E; E0: absent, E1: present) and finally presence of segmental glomerulosclerosis/adhesion (synechiae) (S0: absent, S1: present) (1,2,10,11,13-16). In pathology point of view, both disease are identical by the presence of mesangial IgA deposits, suggesting that both disease have a same origin and a common pathogenic mechanism are responsible for two features of these diseases. It seems that, IgA vasculitis be a systemic variant of IgA nephropathy. Glomerular fibrin deposits and crescent formation and also endocapillary proliferation also are more frequent in IgA vasculitis than in IgA nephropathy (1,2,10,11,13-16) . Importantly, the quantity of extracapillary proliferation is associated with the intensity of clinical signs and to the prognosis of IgA vasculitis in most studies. Crescents are frequently detected in association with capillary wall destruction, capillary fibrin deposits and endocapillary hypercellularity. The presence and extension of crescent (extracapillary proliferation) are accompanied with finding of mesangial and subendothelial IgA, C_3 and fibrin deposits. The pathologic classification of kidney disease in childhood IgA vasculitis is consisted of five categories (I, II, III, IV, and V) corresponding to the presence and proportion of crescents. However, having of prognostic implication for crescents as a long-term predictor was always a concern in several studies. It should remember that, the presence of crescent is a prominent morphologic variable of IgA vasculitis that imply it as a crucial prognostic element. Various investigations have detected that a high proportion of extracapillary proliferation predicts adverse renal outcome in IgA vasculitis, however other studies could not show, crescents having prognostic implication(1,4,5,10,11,12-17) Hence a morphologic classification which support clinicians to find an appropriate remedial modality, seems to be mandatory. In a single-center retrospective investigation to evaluate whether the MEST classification of IgA nephropathy can be used to predict long-standing outcome in individuals with IgA vasculitis, Ho Kim conducted a study on 61 biopsy-proven patients with IgA vasculitis. They found, endocapillary proliferation and interstitial fibrosis/tubular atrophy had lower kidney survival rates than those without endocapillary proliferation and interstitial fibrosis/tubular atrophy. They found endocapillary proliferation and interstitial fibrosis/tubular atrophy were independently correlated with reaching a primary outcome (17,18).

Conclusion

Both IgA nephropathy and IgA vasculitis are the same diseases, while IgA vasculitis is the systemic form of IgA nephropathy with presence of small vessel vasculitis. We suggest application of Oxford classification for IgA vasculitis and including of crescent as an additional morphologic variable in addition to MEST variables, which may have prognostic implication.

Author's contribution

HN is the single author of the paper.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publi-

cation) have been completely observed by the author.

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References

1. Trnka P. Henoch-Schönlein purpura in children. J Paediatr Child Health. 2013;49:995-1003.
2. Davin JC, Coppo R. Pitfalls in recommending evidence-based guidelines for a protean disease like Henoch-Schönlein purpura nephritis. Pediatr Nephrol. 2013;28:1897-903.
3. Kawasaki Y, Ono A, Ohara S, Suzuki Y, Suyama K, Suzuki J, Hosoya M. Henoch-Schönlein purpura nephritis in childhood: pathogenesis, prognostic factors and treatment. Fukushima J Med Sci. 2013;59:15-26.
4. Floege J, Feehally J. Treatment of IgA nephropathy and Henoch-Schönlein nephritis. Nat Rev Nephrol. 2013;9:320-7.
5. Guo YN, Wang Z, Lu J. The relationship between children kidney diseases and adult ESRD--an epidemiological investigation of 700 cases. Ren Fail. 2013;35:1353-7.
6. Pillebout E, Thervet E, Hill G, Alberti C, Vanhille P, Nochy D. Henoch-Schönlein purpura in adults: outcome and prognostic factors. J Am Soc Nephrol. 2002;13:1271-8.
7. iehl MP, Harrington T, Olenginski T. Elderly onset Henoch-Schönlein purpura: a case series and review of the literature. J Am Geriatr Soc. 2008;56:2157-9.
8. Calvo-Río V, Loricera J, Martín L, Ortiz-Sanjuán F, Alvarez L, González-Vela MC, et al. Henoch-Schönlein purpura nephritis and IgA nephropathy: a comparative clinical study. Clin Exp Rheumatol. 2013;31:S45-51.
9. Davin JC, Berge IJ, Weening JJ. What is the difference between IgA nephropathy and Henoch-Schönlein purpura nephritis. Kidney Int. 2001;59:823-34.
10. Lu S, Liu D, Xiao J, Yuan W, Wang X, Zhang X, et al. Comparison between adults and children with Henoch-Schönlein purpura nephritis. Pediatr Nephrol. 2015;30:791-6.
11. Lofters WS, Pineo GF, Luke KH, Yaworsky RG. Henoch-Schönlein purpura occurring in three members of a family. Can Med Assoc J. 1973;109:46-8.
12. Bollée G, Noël LH, Suarez F, Royal V, Gilardin L, de Serre NP, et al. Pauci-immune crescentic glomerulonephritis associated with ANCA of IgA class. Am J Kidney Dis. 2009;53:1063-7.
13. Davin JC. Henoch-Schönlein purpura nephritis: pathophysiology, treatment, and future strategy. Clin J Am Soc Nephrol. 2011;6:679-89.
14. Tanaka S, Ninomiya T, Katafuchi R, Masutani K, Tsuchimoto A, Noguchi H, et al. Development and validation of a prediction rule using the Oxford classification in IgA nephropathy. Clin J Am Soc Nephrol. 2013;8:2082-90.
15. Haas M. IgA nephropathy and Henoch-Schönlein purpura. In: Jennette JC, Olson JL, Schwartz MM, Silva FG, eds. Pathology of the Kidney. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 423-86.
16. Pillebout E, Alberti C, Guillevin L, Ouslimani A, Thervet E. Addition of cyclophosphamide to steroids provides no benefit compared with steroids alone in treating adult patients with severe Henoch Schönlein Purpura. Kidney Int. 2010;78:495-502.
17. Yang YH, Chuang YH, Wang LC, Huang HY, Gershwin ME, Chiang BL. The immunobiology of Henoch-Schönlein purpura. Autoimmun Rev. 2008;7:179–184.
18. Ho Kim C, Jin Lim B, Sung Bae Y, Eun Kwon Y, Ly Kim Y, Heon Nam K, et al. Using the Oxford classification of IgA nephropathy to predict long-term outcomes of Henoch-Schönlein purpura nephritis in adults. Mod Pathol. 2014;27:972-82.