Vasculite IgA e glomerulonefrite C3: Um Doente...Várias Doenças Autoimunes

IgA Vasculitis and C3 Glomerulonephritis: One Patient... Various Autoimmune Diseases

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RESUMO

A vasculite leucocitoclástica caracteriza-se por atingir pequenos vasos e ser provocada por complexos imunes, infeções e fármacos. Complexos imunes IgA ou IgM/IgG podem ser encontrados em imunofluorescência direta, sugerindo formas específicas desta vasculite. Alguns autores sugerem que a vasculite IgA e a nefropatia IgA são duas manifestações clínicas da mesma doença. Do ponto de vista histológico, não é possível distinguir ambas as entidades.

Os autores apresentam o caso de uma mulher, 50 anos, com diagnóstico de vitiligo e púrpura trombocitopénica idiopática. Este diagnóstico foi realizado dois anos antes do presente caso. A doente apresentou-se na consulta de doenças autoimunes com história de exantema pruriginoso dos membros inferiores e edema com 3 meses de evolução. A biópsia cutânea foi sugestiva de vasculite leucocitoclástica, com depósitos de C3, IgG (menor quantidade) e IgA. Foi assumido o diagnóstico de vasculite IgA. Após algumas semanas, a doente mantinha edema periférico, mas com agravamento da função renal. Pelo que, foi realizada uma biópsia renal, que revelou a presença de glomerulonefrite proliferativa endocapilar, com predomínio de depósitos C3 mesangiais, mas igualmente, depósitos IgA e IgM vestigial. Estes resultados são compatíveis com uma glomerulonefrite C3. A doente iniciou corticoterapia sistémica com prednisolona 1 mg/kg/dia e ramipril 2,5 mg/dia, com normalização da função renal.

Com este caso, os autores enfatizam a possibilidade de todas estas manifestações poderem fazer parte do mesmo espectro de doença, bem como, a importância da ativação do complemento na fisiopatologia da doença. Este caso constitui uma evidência adicional da importância da ativação do complemento na patogénese da vasculite IgA. No entanto, é necessária maior evidência e investigação, particularmente para compreender a glomerulonefrite C3, uma doença renal rara.

PALAVRAS-CHAVE: Complemento C3; Doenças do Rim; Glomerulonefrite IgA; Vasculite IgA

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ABSTRACT

Leucocytoclastic vasculitis refers to a small vessel vasculitis caused by immune complexes, infections and medications. IgA or IgM/IgG immune complexes can be found in direct immunofluorescence studies suggesting specific forms of leucocytoclastic vasculitis. Some authors suggested that IgA vasculitis and IgA nephropathy were two clinical manifestations of the same disease. From a histological point of view, it is not possible to distinguish a glomerulonephritis as part of an IgA vasculitis from an IgA nephropathy.

The authors present a case of a 50-year-old woman diagnosed with vitiligo ad immune thrombocytopenic purpura (ITP). ITP was diagnosed 2 years before the present case. She presented to the autoimmune diseases' appointment with a pruriginous rash of the lower extremities over the last 3 months. Skin biopsy was suggestive of leukocytoclastic vasculitis, revealing deposits of C3, IgG (less intensity) and IgA. IgA vasculitis was then assumed. After a few weeks, she kept peripheral edema, but an increasing decline in renal function was detected. Therefore, a renal biopsy was performed, which revealed endocapilar proliferative glomerulonephritis and predominantly C3 mesangial deposits, with IgA and vestigial IgM. These results were compatible with a C3 glomerulonephritis. The patient was started on systemic steroid treatment with prednisolone 1 mg/kg/day and ramipril 2.5 mg/day with progressive normalization of renal function.

With this case, the authors emphasize the possibility that all these manifestations could be part of the same disease spectrum, but also, the importance of complement activation. So, this case may constitute additional evidence of the complement activation in pathogenesis of this vasculitis, however, further investigation is need, particularly to understand C3 glomerulonephritis, a rare kidney disease.

KEYWORDS: Complement C3; Glomerulonephritis, IgA; IgA Vasculitis; Kidney Diseases; Kidney Glomerulus

INTRODUCTION

Leucocytoclastic vasculitis refers to a histopathologic description of common form of small vessel vasculitis, involving arterioles, capillaries and venues, caused by immune complexes, infections and medications.[1,2]

Leucocytoclastic vasculitis is characterized by evidence of neutrophilic infiltration within and around the vessel wall with signs of leukocytoclasia (disintegration of neutrophil nuclei into fragments or nuclear dust); fibrinoid necrosis (fibrin deposition within and around the vessel walls) and signs of damage of the vessel wall and surrounding tissue (e.g., extravasated red blood cells, damaged endothelial cells).[3]

This type of vasculitis may be confined to the skin or exhibit systematic manifestations involving other organs as the kidney.[1]

IgA or IgM/IgG immune complexes can be found in direct immunofluorescence studies suggesting specific forms of leucocytoclastic vasculitis.[3]

The authors describe a case of leukocytoclastic vasculitis with evidence of IgA complexes deposition and glomerulonephritis with C3 and IgA deposition.

CASE REPORT

A 50-year-old woman diagnosed with vitiligo ad immune thrombocytopenic purpura (ITP). ITP was diagnosed 2 years before the present case. Clinical presentation included menorrhagia and thrombocytopenia (< 10.000 platelets/uL), which resolved within 1 month after treatment with intravenous immunoglobulin and a long course of oral corticosteroids. The etiology of ITP was undetermined, including pharmacological, infectious and immunological workup. Initial immunological study was compatible with analytical systemic lupus erythematosus (SLE) [positive anti-nuclear antibody (ANA) 1/160 and anti-SSA 41 U/mL (N < 10.0 U/mL) and complement consumption (C3 60.5 mg/dL, N 81.0 - 167.0 mg/dL; C4 8.4 mg/dL, N 11,0 - 42,0 mg/dL), but with no clinical symptoms and negative anti-SSB, anti-dsDNA, extractablenuclearantibodies,lupicanticoagulant,beta-2 glicoprotein], but after 3 months all the positive immunological parameters normalized.

She presented to the autoimmune diseases' appointment with a pruriginous rash of the lower extremities over the last 3 months. They appeared and disappeared spontaneously lasting up to 3 days. She also developed edema of the lower limbs and dark urine one month before the appointment. Associated symptoms included epigastric pain and inflammatory joint pain of the right elbow and left hip. The month before, she had been diagnosed with low urinary tract infection and was treated with amoxicilin-clavulanate. She denied fevers, chills, chest pain, respiratory, gastrointestinal or urinary symptoms since then.

On examination, the patient was apyretic, normotensive, without pain or tenderness on the abdominal examination. She presented bilateral and symmetric edema of the lower limbs until the knees. Cutaneous examination revealed a purpuric macular rash of the lower extremities, mainly over the upper half of thighs and legs. She had no inflammatory signs or symptoms of the joints.

Laboratory testing revealed normocytic normochromic anemia (hemoglobin 9.5 g/dL), normal platelet count, with normal differential cell count and blood smear. Blood clot factors and coagulation studies were normal. Erythrocyte sedimentation rate was 18 mm/h and C reactive protein was 0.53 mg/L (N < 5.0 mg/L). Urine analysis revealed hematuria (> 50 U/field) with dysmorphic erythrocytes, and proteinuria (0.5 g/g creatinine), with normal renal function (creatinine 0.61 mg/dL). Hepatic parameters, triglycerides and protein electrophoresis were normal. The immunological profile was negative, including ANAs, antineutrophil cytoplasmic antibodies (ANCAs), anti-dsDNA, anti-SSA, anti-SSB and anti-C1q. Fractions C3 and C4 of complement levels were normal. Immunoglobulin (Ig) G levels were low (652.0 mg/dL, N: 793-1590 mg/dL) with normal IgM and IgA. There was no evidence of HIV, hepatitis B or C infection, CMV or EBV or syphilis.

Skin biopsy was suggestive of leukocytoclastic vasculitis, revealing deposits of C3, IgG (less intensity) and IgA. IgA vasculitis was then assumed.

Within a few days, a regression in purpuric lesions was noted, without recurrence on the following months. After a few weeks, she kept peripheral edema, but an increasing decline in renal function was detected, with serum creatinine reaching up to 1.1 mg/dL, with persistence of proteinuria (0.5 g/g creatinine). Therefore, a renal biopsy was performed, which revealed endocapilar proliferative glomerulonephritis and predominantly C3 mesangial deposits, with IgA and vestigial IgM. These results were compatible with a C3 glomerulonephritis, however, the hypothesis of a membranoproliferative glomerulonephritis by immunocomplex (including IgA variant) could not be totally excluded.

The patient was started on systemic steroid treatment with prednisolone 1 mg/kg/day, ramipril 2.5 mg/day and epoietine 5000 mg/week. There was progressive normalization of renal function, allowing steroid tapering, and after 6 months, total remission of proteinuria (0.119 g/g creatinine) and erythrocyturia (5-10/field without dysmorphicerythrocytes) was almost achieved.

DISCUSSION AND CONCLUSION

C3 glomerulopathy was adopted by expert consensus in 2013 to define a group of rare kidney diseases driven by dysregulation of the complement cascade.[4] It is characterized histopathologically by accumulation of the C3 component of complement in renal tissue.[4] The rarity of C3 glomerulopathy makes it difficult to derive precise incidence and prevalence figures.[4] However, a number of small cohort studies have generated estimates of limited reliability.[1] An optimal treatment for C3 glomerulopathy has not yet been established. However, some patients with C3 glomerulopathy seem to respond to mycophenolate mofetil and/or eculizumab. For the majority of patients, however, new therapies will be required.[4]

IgA vasculitis is a systemic disease that affects small blood vessels and is characterized by the IgA deposits in the kidneys, skin, and other organs.[5] IgA nephropathy, initially described by Jean Berger in 1968, is the most frequent primary glomerular disease worldwide.[6] The diagnosis is on the basis of finding IgA dominant or co-dominant immune deposits in the glomeruli.[6]

Since the first descriptions of IgA nephropathy (Berger's disease) and IgA vasculitis (Henoch-Schönlein purpura), the authors suggested that they were two clinical manifestations of the same disease. Recent advances in understanding pathophysiological mechanisms of these two entities have only reinforced this idea.[7]

Indeed, IgA vasculitis is characterized by the combination of cutaneous (palpable purpura), gastrointestinal (colicky pain, bloody stools) and articular (arthralgia) involvement.[8] Rarely, this vasculitis could have a neurological, pulmonary or urological involvement.[8] It is most common in childhood but may occur at any age.[8] Renal involvement occurs in IgA vasculitis with a prevalence ranging from 20% to 54% in children and 45% to 85% in adults.[7]

From a histological point of view, it is not possible to distinguish a glomerulonephritis as part of an IgA vasculitis from an IgA nephropathy.[8] Renal biopsy shows, in the two cases: on immunofluorescence, predominant IgA1 deposits in the mesangium of all glomeruli, with glomerular deposits of IgG, IgM, C3 and fibrin in variable proportions; on light microscopy, mesangial hypercellularity with increased mesangial matrix, endocapillary hypercellularity, segmental glomerular sclerosis, cellular crescents and tubular atrophy and interstitial fibrosis.[6,8] Complement component C3 is usually present in the same distribution as IgA, and the immunodeposits may contain IgG, IgM, or both.[9]

The Kidney Disease Improving Global Outcome (KDIGO) working group on glomerulonephritis compiled the first evidence-based guidelines for the treatment of IgA nephropathy and IgA vasculitis in 2012.[10] Children and adults were treated in the same way.[10] These guidelines recommend early treatment with renin-angiotensin

inhibitor or angiotensin-receptor blocker and subsequent initiation of steroids if proteinuria > 1 g/day persists after 3-6 months of conservative management.[10]

Complement activation is considered to play an important role in the pathogenesis of IgA nephropathy, and various complement proteins have been correlated with disease progression in IgA nephropathy.[11]

IgA or IgM/IgG immune complexes can be found in direct immunofluorescence studies suggesting specific forms of leucocytoclastic vasculitis.[3]

The authors have described a very complex and unusual case of a patient that developed a leukocytoclastic vasculitis with deposits of IgA, but also, C3 in skin. A few weeks, after she showed renal manifestations compatible with a glomerulonephritis with C3 and IgA mesangial deposits. Although the biopsy was suggestive of C3 glomerulonephritis, the hypothesis of IgA nephropathy can not be totally excluded. In this type of case, the proportion of C3 deposits was slightly higher. Due to the uncertainty of the diagnosis and possible association between both diseases, corticotherapy was chosen. After this therapy, there was a sustained regression of renal and skin manifestations.

Analyzing the whole case, for the authors, the most likely hypothesis of diagnosis is an IgA vasculitis with cutaneous leucocytoclastic vasculitis and renal C3 glomerulonephritis. However, there are few similar cases in literature. The good response to therapy with corticosteroids is another fact in favor of this diagnosis.

In conclusion, with this case, the authors emphasize the possibility that all these manifestations could be part of the same disease spectrum, but also, the importance of complement activation. So, this case may constitute additional evidence of the complement activation in pathogenesis of this vasculitis, however, further investigation is needed, particularly to understand C3 glomerulonephritis, a rare kidney disease.

CONTRIBUIÇÃO AUTORAL/ AUTHORS CONTRIBUTION

MG e AL: Recolha de dados, escrita e revisão
TM: Revisão

MG and AL: Data collection, writing and review
TM: Review

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