Case Report

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Rapidly progressive glomerulonephritis associated to afebrile endocarditis and anti-proteinasa 3 anca

Glomerulonefritis rápidamente progresiva asociada a endocarditis afebril y anca anti-proteinasa 3

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Abscrat

Endocarditis associated with antiPR3 ANCA and acute kidney injure generates a challenge in its diagnosis and treatment. In order to make a review about that combination, we presented a patient with necrotizing glomerulonephritis produced by a Enterococcus faecalis´s subacute endocarditis and antiPR3 ANCA positive.

Differential diagnosis is made between an acute kidney failure produced by ANCA´s vasculitis vs necrotizing glomerulonephritis by endocarditis. Frequently it is necessary to make a biopsy to get a diagnosis. Negative immunofluorescence will guide to vasculitis associated ANCA, while positive immune complexes will guide to poststreptococcal glomerulonephritis.

Other challenge that generates the association of acute kidney disease, endocarditis and antiPR3 ANCA is the treatment. ANCA positive can prompt to start immunosuppressant treatments. However, in the context of endocarditis, it could be inadvisable and even dangerous to use it. For this reason, it is controversial the use of immunosuppressant in combination with antibiotics in the acute process, in contrast with the use of only antibiotics. In the current paper we collect the 19 reports in the literature about endocarditis associated with antiPR3 ANCA, the treatment and the renal evolution of each patient. We concluded, generally, a better improvement of kidney function in patients treated with only antibiotics than those patients treated with the combination of antibiotics and corticoids. However, there are so few reports that we can´t consider significant the different between both treatment groups.

Key words: ANCA antiPR3, postinfectious/poststreptococcal glomerulonephritis, endocarditis, necrotizing glomerulonephritis.

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Resumen

La endocarditis asociada a ANCA anti-PR3 e insuficiencia renal plantea un dilema tanto en su diagnóstico como tratamiento. Para abordar una revisión de dicho tema, se presenta el caso de un paciente con glomerulonefritis rápidamente progresiva secundaria a endocarditis subaguda por Enterococcus faecalis y positividad para ANCA anti-PR3.

El diagnóstico diferencial principal se establecería entre una afectación renal de una vasculitis asociada a ANCA no diagnosticada previamente vs una glomerulonefritis postinfecciosa secundaria a la endocarditis. En muchos casos es necesario disponer de una biopsia renal que esclarezca el diagnóstico, ya que una inmunofluorescencia negativa orientará hacia una vasculitis, mientras que una positividad para inmunocomplejos iría a favor de una glomerulonefritis postestreptocócica.

El tratamiento a seguir es otro reto que se plantea en la coexistencia de insuficiencia renal aguda, endocarditis y ANCA anti-PR3 positivo. La positividad de ANCAs induce a valorar iniciar tratamiento con inmunosupresores, no obstante, en el lecho de una endocarditis puede resultar desaconsejado e incluso poner en riesgo la vida del paciente someterlo a un estado de inmunosupresión. Es, por tanto, controvertido el uso de inmunosupresión en combinación con antibioterapia en el proceso agudo en contraposición al uso de antibioterapia exclusivamente. En el actual artículo se recogen los 19 casos publicados en la literatura de endocarditis asociados a ANCA anti-PR3, así como el tratamiento que se realizó en cada uno de los casos y la evolución en la función renal de cada paciente, concluyendo, en general, una mejor recuperación de la función renal en los pacientes tratados con antibioterapia en exclusiva que en aquellos tratados con la combinación antibiótico-corticoides. Sin embargo, dado el pequeño tamaño muestral, no se puede considerar significativa la diferencia entre ambos tratamientos.

Palabras claves: ANCA antiPR3, glomerulonefritis postinfeciosa/posestreptocócica, endocarditis, glomerulonefritis necrotizante.

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Introduction

Endocarditis may have various renal manifestations, from microhematuria and/or proteinuria, to renal embolisms with arterial hypertension, macrohematuria or renal failure in up to 30% of cases. Renal failure is a significant predictor of mortality[1].

The case of a patient with necrotizing crescentic glomerulonephritis due to endocarditis associated with positive anti-proteinase 3 ANCA is presented. At the same time, the literature on the subject is reviewed.

Case report

A 72-year-old man was referred to Nephrology from the General Surgery service for elevated creatinine and edema. He reported weight loss from a cholecystectomy due to acute cholecystitis four months earlier. In the bile culture, Enterococcus faecalis was isolated and treated with piperacillin-tazobactam and with amoxicillin-clavulanate upon discharge. Three months after cholecystectomy serum creatinine increased from 1.4 to 2.4 mg/dl, accompanied by edema in the lower limbs. No fever, macrohematuria or other symptoms were associated. His medical history included hypertension on treatment with losartan, type 2 diabetes mellitus on treatment with metformin, and mild-moderate mitral regurgitation.

Physical examination revealed blood pressure of 140/70 mmHg, heart rate of 112 beats per minute, temperature of 35.7 °C, a III/VI pansystolic murmur in the mitral area and edema to the level of the knees.

Analytically, normocytic normochromic anemia, leukocytes: 5090 cells/µl and neutrophils: 80%, hypoalbuminemia, Cr: 2.7 mg/dl, urea: 139 mg/dl and creatinine clearance: 28 ml/min, were observed. Urine showed proteinuria of 1 g/24h, microalbuminuria of 194 mg/dl, and 50-100 RBCs/HPF. The proteinogram was compatible with polyclonal hypergammaglobulinemia. Viral serologies for hepatitis B, hepatitis C and HIV were negative. In the immunological tests, there was a slight elevation of anti-proteinase 3 anti–neutrophil cytoplasmic antibodies (anti-PR3 ANCA) (3.20 U/ml, normal <2 U/ml), a decrease in C3 (58 mg/dl) and C4 in the lower limit (12 mg/dL). Other immunological results (ANA, anti-MPO ANCA, anti-MBG, anti-DNA, cryoglobulins) and tumor markers were negative.

Various imaging tests were requested. Renal ultrasound showed normal kidneys and, in thoraco-abdominal CT, homogenous splenomegaly was observed. During admission, the patient exhibited a state of confusion, so cerebral magnetic resonance imaging (MRI) was requested where small vessel ischemic lesions were observed in both cerebral hemispheres. For examination of the systolic murmur, a transesophageal echocardiogram was performed, showing an image suggestive of endocarditis in the mitral valve with very severe failure (Figure 1).

Due to the persistence and progressive deterioration of renal function, a renal biopsy was performed (Figure 2). In the histological sections, lesions corresponding to focal necrotizing crescentic glomerulonephritis, fibrinoid necrosis foci of glomerular capillaries and mesangiolysis, acute tubular necrosis and moderate myointimal hyperplasia without signs of vasculitis were visualized. Immunofluorescence showed granular mesangial positivity for C3, weaker for IgM and more focal for C1q (Figure 3).

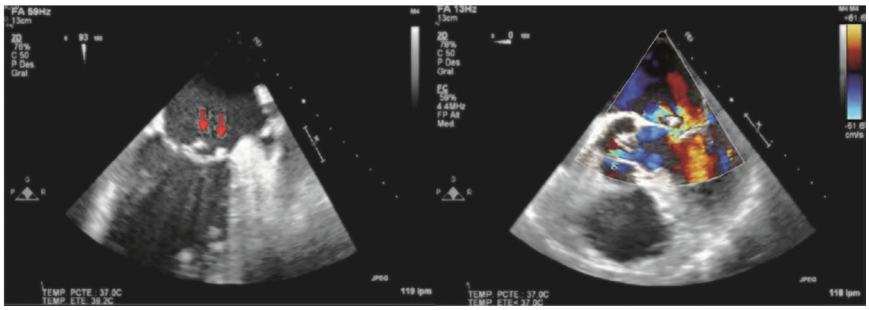

Figure 1. Transesophageal echocardiogram.
Vegetation in the auricular face of the mitral valve (left). Very severe mitral regurgitation with Color Doppler technique (right).

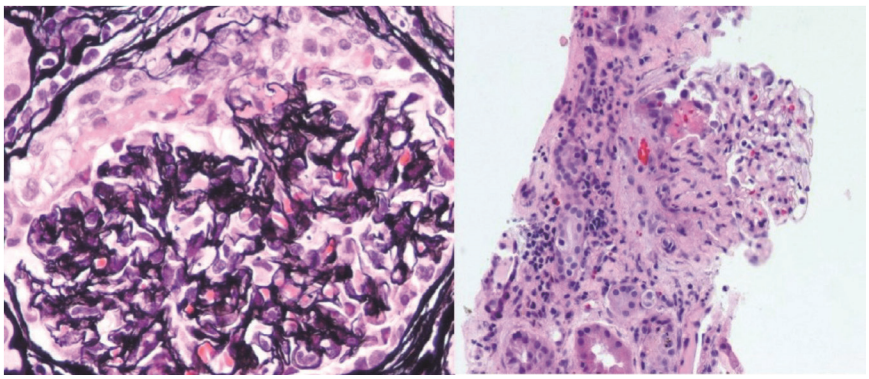

Figure 2. Histology of renal biopsy.
Jones' silver methenamine stain of renal glomerulus, capillary rupture and cellular crescents due to extracapillary proliferation (left). Hematoxylin and eosin stain of urinary cast

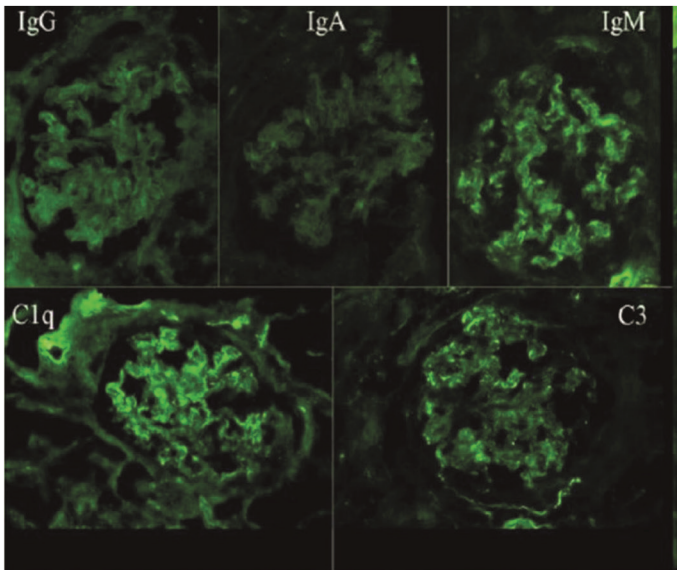

Figure 3. Direct immunofluorescence: Granular mesangial IgG, C3 and C1q deposits

Enterococcus faecalis grew in the blood cultures and was initially empirically treated with vancomycin and gentamicin, which were subsequently changed according to antibiogram results for ampicillin and ceftriaxone.

Despite the antibiotic treatment, a progressive deterioration of renal function with active urinary sediment persisted; thus, treatment with methylprednisolone boluses and, later, oral prednisone (0.5 mg/kg for 4 weeks with subsequent dose decrease) was initiated.

Finally, mitral valve replacement was performed. After surgery, renal function began to improve and levels of anti-PR3 ANCA and C3 returned to normal, but the patient died of nosocomial pneumonia.

Discussion

The patient presented rapidly progressive glomerulonephritis with mildly positive anti-proteinase 3 ANCA. This combination may lead to suspicion of ANCA glomerulonephritis. However, hypocomplementemia does not characterize ANCA glomerulonephritis and its presence together with polyclonal hypergammaglobulinemia, splenomegaly, and new onset of murmur allowed to suspect endocarditis. This diagnosis was confirmed by echocardiography and blood culture.

Absence of fever could be misleading. However, up to 16% of endocarditis may occur without fever[2] or leukocytosis, even blood cultures may be negative in some cases[3,4].

Coexistence of necrotizing glomerulonephritis, ANCA and endocarditis allows to discuss the pathogenesis of nephropathy and the therapeutic approach.

The literature collected 16 cases of positive ANCA in patients with endocarditis and acute glomerulonephritis in renal biopsy (Table 1), ten of which are positive anti-PR3 ANCA[5-13], two anti-myeloperoxidase[11,14] and five unspecified[15-19]. Anti-PR3 ANCAs can be elevated in connective tissue diseases and chronic infections such as bacterial subacute endocarditis, tuberculosis, or hepatitis B or C5 virus infection, as well as in the elderly. In this regard, endocarditis could be one of the infectious stimuli that would activate neutrophils to express antigens recognized by ANCAs15. ANCAs may be one of multiple autoantibodies whose levels increase in the context of polyclonal hypergammaglobulinemia, a characteristic of endocarditis. The debate is centered on whether ANCAs contribute decisively to the pathogenesis of tissue injury in endocarditis or are an epiphenomenon[20].

Renal histological lesions may range from focal segmental proliferative glomerulonephritis, with or without fibrinoid necrosis, and intracapillary thrombi, to diffuse exudative proliferative glomerulonephritis, with or without extracapillary proliferation[21]. There may or may not be immunoglobulin deposits21. Absence of immune deposits could support a pathogenic role of ANCAs, which characteristically produce necrotizing or pauci-immune crescentic glomerulonephritis.

Regarding the evolution of renal function, out of the 16 reported cases of endocarditis with associated glomerulonephritis, three did not recover renal function and two patients required acute hemodialysis.

One of the dilemmas that arise in the coexistence of endocarditis, positive anti-PR3 ANCA and acute glomerulonephritis is the treatment to be followed. Among the reported cases, ten patients were treated with steroids and antibiotics in combination, two of which died. Six were treated with antibiotics alone and five underwent valve replacement.

Table 1.

Cases of glomerulonephritis associated with ANCA and endocarditis

Ref	Sexo	Edad	Renal histological diagnosis (óptica/ IF)	ANCA type and initial titer	Bacteria	HD si/no	Baseline renal function basal si/no	Treatment
5	M	28	Diffuse proliferative GN mediated by immune complexes	CANCA PR3 No menciona títulos	Enterococcus faecalis	No	Sí	Antibiotics Valve replacement
6	M	62	Diffuse proliferative GN IF: C3 deposits.	CANCA 1:512 PR3 40 (RN<UI / ml)	Streptoccocus bovis Neisseria flava	No	Sí	Antibiotics Corticoids
7	M	24	FSGN with fibrocellular crescents and necrotizing lesions. IF: mesangial and subendothelial C3 deposits	CANCA PR3 14 EU (RN<10 EU)	Alfa streptococcus	No	Sí	Antibiotics Corticoids
8	M	48	GN: membranoproliferative IF: subepithelial C3 deposits	CANCA 1/320 PR3 12/Uml (RN>10)	Negative	No	Sí	Antibiotics
	M	46	FSGN with mild extracapillary proliferation. IF: C3 and C1 deposits in glomerular basement membrane and mesangium.	CANCA 1/160 PR3 25 U/ml	Negative	No	Sí	Antibiotics Valve replacement
9	M	60	Necrotizing FSGN. IF unspecified	CANCA PR 3 2,05 (RN 1.10 IA)	streptococcus viridans	No	No menciona	Antibiotics
10	M	54	Necrotizing focal GN with cellular crescents. IF: negative	CANCA PR3 3.0 (RN<0.9)	Streptococcus mutants	No	Sí	Antibiotics Corticoids Cyclophospha-mide
11	F	26	Focal segmental GN with crescents. IF: IgM and C3 deposits	CANCA 29% (RN 10%)	Streptococco viridans	Sí	Sí	Antibiotics Corticoids
12	M	24	FSGN with fibrous and fibrocellular crescents, mild mesangial proliferation. IF: Mesangial IgM and C3 deposits.	CANCA 97 EU/ml (RN<10)	Negative	No	No	Antibiotics Corticoids
13	M	54	GN with cellular crescents, interstitial nephritis. IF: negative	CANCAPR3 2.96 (RN 0,9) ANCA MPO 1,19 (RN 0,9)	Streptococcus mutants	No	Sí	Antibiotics Cyclophospha-mide Antibiotics
14	M	45	GN with fibrocellular crescents. IF: negative	CANCA positivos PANCA positivos No menciona títulos	Negative	Sí	No menciona	Antibiotics Corticoids Cyclo-phosphamide Valve replacement
15	M	40	GN with fibrocellular crescents, diffuse endocapillary hyperplasia, infiltrate and interstitial edema. IF: IgG, IgM and C3 deposits	CANCA positivo No menciona títulos	Negative	No	Sí	Antibiotics Corticoids
16	M	50	Endocapillary proliferative GN with fibrocellular crescents. IF: negative	CANCA PR3 247 U (RN<10)	Streptococcus oralis	No	No	Antibiotics Corticoids Valve replacement
17	M	64	Focal sclerosing GN, mild interstitial inflammation. IF: C3 deposits.	CANCA 60 U (RN<10)	Barthonela quintana	No	Sí	Antibiotics
18	M	59	Necrotizing extracapillary GN. IF: IgG, C3 and C1q deposits.	CANCA positivo PR3 250 AU/ml (RN<20)	Staphyloccocus aureus	No	No	Antibiotics Corticoids
19	F	56	GN with cellular crescents, segmental necrosis of capillary wall, acute interstitial nephritis. IF: IgG, C3 and endomembranous deposits.	PANCA MPO 1/2560	Negative	No	Sí	Antibiotics Corticoids Cyclophospha-mide Valve replacement

There is, therefore, no clear consensus on the treatment of endocarditis with anti-PR3 ANCA. Some authors propose as a treatment the combination of immunosuppression and antibiotics11, while others prefer antibiotic treatment alone, without immunosuppression22.

As shown in the table compiled, exclusive antibiotic treatment was associated with lower mortality, but it could also be used in patients with milder nephropathy, as there is currently no strong evidence to support immunosuppression alone5,23. In any case, it seems reasonable to delay immunosuppressive treatment until, at least, patient stabilization and infection control. At this point, C3 and anti-PR3 ANCA values tend to normalize1,5,16, as occurred in our patient.

On the other hand, it is important to propose and choose the right time to perform a valve replacement when the patient does not show rapid improvement. Without infection control, surgical intervention is too risky, and septic emboli may spread across the rest of the body. However, the risk of complications and consequences for the patient increases over time, and may lead to an unfortunate prognosis.

The KDIGO24 guidelines state that prognosis of post-endocarditis glomerulonephritis is generally favorable and is directly related to the speed with which the infection is eradicated.

Conflict of interest

The authors expressly state that there is no conflict of interest in the conduct of this article.

Ethical disclosures

Protection of human and animal subjects

The authors state that no experiments were performed on humans or animals for this study.

Data confidentiality

The authors state that no patient data appears in this article.

Right to privacy and informed consent

The authors state that no patient data appears in this article.

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