

A brief contextualization on IgG4 tubulointerstitial nephritis based on a case report in south Brazil

Uma breve contextualização sobre a nefrite tubulo-intersticial por IgG4 com base em um relato de caso no sul do Brasil

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ABSTRACT

IgG4-related disease (IgG4RD) is a recent inflammatory process of supposed autoimmune etiology, which is characterized by elevated serum IgG4 levels, dense lymphoplasmacytic infiltration rich in IgG4-positive plasma cells and storiform fibrosis. Tubulointerstitial nephritis is the most common renal manifestation, with different degrees of kidney dysfunction and variable clinical findings. Herein, the authors describe a new case of IgG4 tubulointerstitial nephritis (IgG4TN), and discuss clinic and pathologic criteria. Male patient, 72 years-old, was admitted on hospital service with clinical complaint of asthenia, loss of strength, emaciation, and anosmia. Previous history included type 2 *diabetes mellitus*. Laboratorial data included normochromic anemia, proteinuria, and creatinine elevation. Bilateral kidney ultrasonography/computed tomography revealed a heterogenous parenchyma, with diffuse irregular dense zones, areas of fibrosis on upper poles, and hydronephrosis. Kidney biopsy showed a dense interstitial lymphoplasmacytic infiltrate, with more than 50 plasma cell per high power field, irregular areas of fibroblastic and collagenous fibrosis, focal tubulitis, and normal glomeruli. Immunofluorescence revealed mild granular deposition of C3c and IgG in the tubular basement membrane. Immunohistochemistry was positive for CD138, lambda and Kappa light chains, and IgG4 (around forty five IgG4 positive plasma cells per high power field). IgG4 serum level was increased. The diagnosis of IgG4TN was then established. The patient received corticotherapy and strict control of glycemia with insulin, with marked improvement of symptoms and creatinine levels.

Keywords: diagnosis; immunity; kidney; pathology.

RESUMO

A Doença relacionada a IgG4 (IgG4RD) é um processo inflamatório recente de etiologia supostamente autoimune, que se caracteriza por níveis séricos elevados de IgG4, um denso infiltrado mononuclear rico em plasmócitos IgG4 positivos e fibrose estoriforme. A nefrite túbulo-intersticial é a manifestação renal mais comum, com diferentes graus de disfunção renal e achados clínicos variáveis. Aqui, os autores descrevem um novo caso de nefrite túbulo-intersticial associada a IgG4 (NTIgG4), e discutem critérios clínicos e patológicos. Paciente masculino, 72 anos, foi admitido no serviço hospitalar com queixa clínica de astenia, perda de força, emagrecimento e anosmia. A história prévia incluía *Diabetes mellitus* tipo 2. Os dados laboratoriais incluíam anemia normocrômica, proteinúria e elevação da creatinina. A ultrassonografia/tomografia computadorizada renal bilateral revelou um parênquima heterogêneo, com zonas densas e difusas irregulares, áreas de fibrose nos polos superiores e hidronefrose. A biópsia renal mostrou um infiltrado mononuclear intersticial denso, com mais de 50 plasmócitos por campo de grande aumento, áreas irregulares de fibrose fibroblástica e colagênica, tubulite focal e glomérulos normais. A imunofluorescência revelou deposição granular leve de IgG e C3c na membrana basal tubular. A imuno-histoquímica foi positiva para CD138, cadeias leves Kappa e lambda, e IgG4 (cerca de quarenta e cinco plasmócitos IgG4 positivos por campo de grande aumento). O nível sérico de IgG4 estava aumentado. O diagnóstico de NTIgG4 foi então estabelecido. O paciente recebeu corticoterapia e controle rigoroso da glicemia com insulina, com melhora significativa dos sintomas e dos níveis de creatinina.

Palavras-chave: diagnóstico; imunidade; patologia; rim.

INTRODUCTION

IgG4-related disease (IgG4RD) is a recently described systemic inflammatory syndrome that can involve multiple organs and/or determine elevation in serum total IgG or IgG4 levels.^{1,2} Sarles *et al.*³ firstly reported patients with sclerosing pancreatitis and hyperglobulinemia, and suggested that the process was related to an autoimmune disease. IgG4RD can compromise liver, lacrimal glands, lymph nodes, mediastinum, breast, meninges, eye, skin, urinary bladder, gastrointestinal tract, and salivary glands. IgG4 tubulointerstitial nephritis (IgG4TN) can determine kidney dysfunction and show storiform fibrosis and infiltration by high numbers of IgG4-positive plasma cells.⁴⁻⁶ Herein, the authors describe a new case of IgG4TN and describe clinic and morphologic findings and diagnostic criteria of this uncommon process.

CASE REPORT

Male patient, 72 years, was admitted on hospital service with clinical complaint of asthenia, loss of strength, emaciation, and anosmia. On physical examination, no significant alterations were identified. Previous history included type 2 *diabetes mellitus*, and was negative for hypertension, smoking, and urinary infections. Laboratorial data included normochromic anemia (hemoglobin: 10.8 d/dL), lymphocytosis (62%), glycemia of 174 mg/dL, proteinuria (2.3 g/day), creatinine elevation (2.1 mg/dL), creatinine clearance of 48 mL/min, total proteins equal to 9.3 g/dL, albumin of 3.73 g/dL, IgG of 1,080 mg/dL, and IgA of 327 mg/dL.

Liver function tests showed normal levels. Rheumatoid factor, antineutrophil cytoplasmic antibodies, antimicrobial antibody, HIV, HCV, and HBsAg were negative. Radiological chest imaging identified mediastinal lymphadenopathy and focal bilateral opacities suggesting granulomatous disease. Central nervous system computed tomography revealed no significant alterations.

Bilateral kidney ultrasonography/computed tomography revealed a heterogenous parenchyma, with irregular diffuse dense zones, areas of fibrosis on upper poles, and hydronephrosis. No signs of obstructive urinary disease or neoplasm were identified. Kidney biopsy showed a dense interstitial lymphoplasmacytic infiltrate (Figures 1 and 2), with more than 50 plasma

cell per high power field, irregular areas of fibroblastic and collagenous fibrosis (Figure 3), focal tubulitis, and normal glomeruli. Immunofluorescence revealed mild granular deposition of C3c and IgG in the tubular basement membrane. Immunohistochemistry was positive for CD138, lambda and Kappa light chains, and IgG4 (around forty five IgG4 positive plasma cells per high power field/figure 4).

Figure 1. IgG4 tubulointerstitial nephritis: Kidney biopsy showing a dense inflammatory infiltrate and fibrosis, hematoxylin-eosin, 40x.

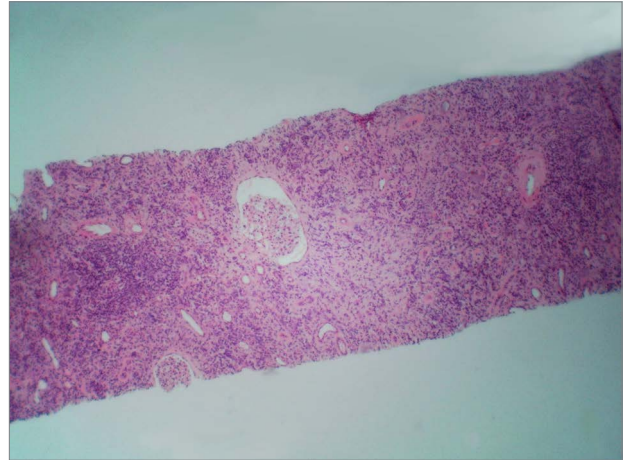
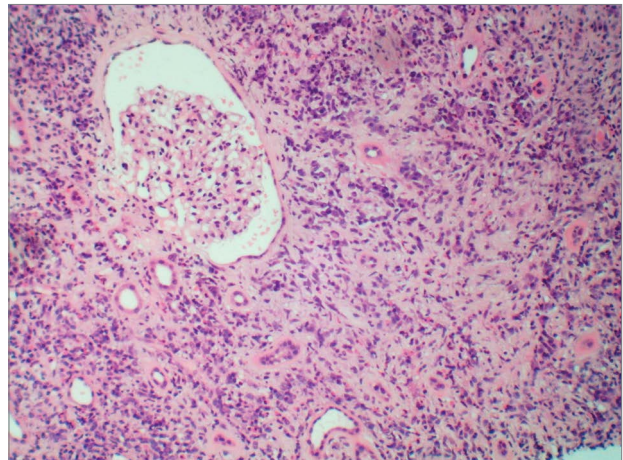


Figure 2. IgG4 tubulointerstitial nephritis: Kidney parenchyma exhibiting a dense interstitial lymphoplasmacytic infiltrate and storiform fibrosis, with normal glomeruli, hematoxylin-eosin, 100x.



IgG4 serum level was equal to 376 mg/dL (reference levels: 8-140 mg/dL). The diagnosis of IgG4 tubulointerstitial nephritis was then established. The patient received Prednisolone 54 mg/day (0.6 mg/Kg/day) and strict control of glycemia with insulin, with marked improvement of symptoms. Actual proteinuria corresponds to 420 mg/day and creatinine equal to 1,25 mg/L.

Figure 3. IgG4 tubulointerstitial nephritis: Numerous plasma cells in a high power field, hematoxylin-eosin, 400x.

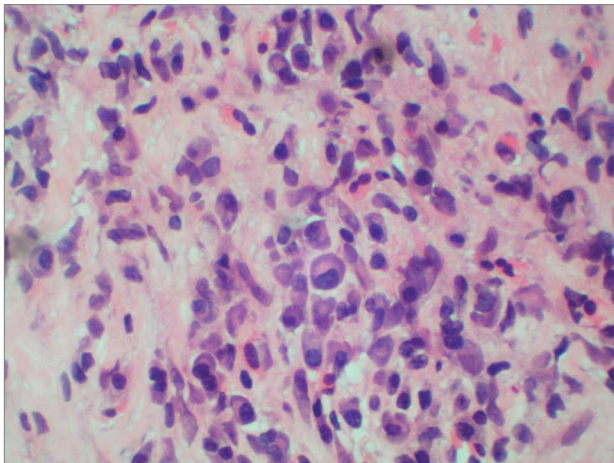
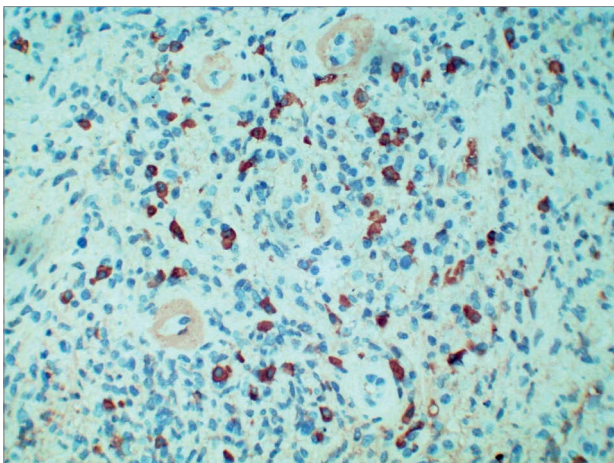


Figure 4. IgG4 tubulointerstitial nephritis: IgG4 positive plasma cells in kidney interstitium, streptavidin-peroxidase polymer, 200x.



DISCUSSION

Tubulointerstitial nephritis is characterized by inflammatory infiltration affecting tubules and interstitium of the kidney parenchyma, without compromising glomeruli and vessels.^{1,2,5,6} Tubulointerstitial nephritis has two main forms of clinical presentation: acute, which is characterized by sudden onset and rapid decline of renal function, and chronic, which is characterized by slow decline of renal function. Most common etiologic factors include drug toxicity, metabolic disorders, heavy metals, infections, and immunologic disorders.^{1,2,5,6}

IgG4TN is a recent described interstitial nephropathy that can be associated to multiple organs involvement, and some data suggests IgG4 can be related to an autoimmune disorder.^{1,2,7,8} The diagnosis of IgG4TN can be established based on clinic, radiologic, laboratorial and morphologic parameters. IgG4 production is associated with

T-helper cells type 2 activity, and IL4, IL13, IL10 and IL12 imbalance.^{1,2,7,8}

Raissian *et al.*⁹ described that the main diagnostic criteria for IgG4TN include: a) histological evidence of tubulointerstitial nephritis exhibiting numerous plasma cells, in which 10 IgG4-positive plasma cells are found in high power fields in the most exuberating zones, b) mandatory presence of immune complex deposits in a tubulointerstitial nephritis identified by immunofluorescence, immunohistochemistry or electron microscopy, c) elevated serum IgG4 or total IgG levels, d) imaging studies revealing small peripheral low-attenuation cortical nodules, diffuse patchy involvement of the kidneys, round/wedge-shaped lesions, or diffuse marked kidney enlargement, and e) evidences of other organ involvement, such as autoimmune pancreatitis, sclerosing cholangitis, sialadenitis, inflammatory aortic aneurysm, or inflammatory mass in any organ.

The majority of patients developing IgG4TN are males, with an average age of 65 years, with clinic findings of acute or progressive chronic kidney disorder.^{2,5,9,10} Clinical data includes fever, fatigue, abdominal pain, proteinuria, and anorexia.^{2,5,10} Magnetic resonance can reveal iso/hypointense kidney lesions on T1-weighted images and hypointense areas on T2-weighted images.^{8,10,11,12} Serum levels of IgG4/IgG are elevated around 85% of patients, which can be accompanied by elevated serum creatinine level and decreased C3, C4 or CH50 levels.^{8,10,11,12}

On gross examination, the involved kidney reveals white, firm, homogeneous areas. The main histologic feature of IgG4TN is the presence of more than 10 IgG4-positive plasma cells per high-power field in the compromised areas, but more than 30 IgG4-positive plasma cells per high-power field can be found too.^{2,7,9,11} Histologic findings also include lymphocytic infiltrate, some eosinophils, and variable degree of fibrosis. Inflammatory cells usually decrease in number with increasing fibrosis.^{2,7,9,11}

Interstitial fibrosis is frequently zonal, determines collagenous bundles deposition encircling mononuclear inflammatory cells, with clear demarcation between compromised and non affected areas, and is more prominent at the center than peripheral zones. It is mandatory imaging data correlation in kidney biopsy due these aspects.^{2,5,7,9,11}

Focal lymphoplasmacytic tubulitis is frequent. Occasional renal tubules are atrophic, with possible thickening of the basement membrane. Glomerular

TABLE 1 SUMMARY OF SOME PUBLISHED CASES OF IgG4 TUBULOINTERSTITIAL NEPHRITIS

Authors	Age/Gender	Clinical Findings	IgG4 serum level	Previous History	Treatment/Outcome
Fukuhara <i>et al.</i> ⁷	63/F	Incidental cystic tumor at the upper pole of the right kidney and multiple low attenuation areas in the left kidney	218 mg/dL	No previous medical history	Surgery/Prednisolone 30 mg/day/Asymptomatic
Miyata <i>et al.</i> ⁶	69/M	Anorexia, weight loss, lower abdominal pain	2,750 mg/dL	Hypertension, Early-stage colon cancer	Prednisolone 55 mg/day/Proteinuria persisted for over 2 months
Nishikawa <i>et al.</i> ¹⁵	51/F	Incompatible Renal Transplant	426 mg/dL	Bronchial asthma, Renal transplant	Methylprednisolone 16mg/day/Follow-up kidney biopsy revealed a markedly decrease in plasma cell infiltration
Wu <i>et al.</i> ⁸	71/M	Diabetic nephropathy, polyarthralgia, high gammaglobulinemia, palpable lymph nodes in the neck and axillary region	532 mg/dL	<i>Diabetes mellitus</i>	Prednisolone 30 mg/day, Cyclophosphamide 50 mg/day/Laboratory parameters returned to reference range
Stylianou <i>et al.</i> ¹³	63/M	Weakness, anorexia, weight loss, cervical lymphadenopathy, sialadenitis	1,210 mg/dL	Hypertension, vitiligo, alithiasic cholecystitis	Methylprednisolone 36mg/day/Rapid improvement of symptoms and renal function
Wada <i>et al.</i> ¹⁴	59/M	Edema of lower extremities, jaundice, upper abdominal tenderness	1,920 mg/dL	No previous medical history	Prednisolone 40 mg/day/Rapid improvement of symptoms
Otani <i>et al.</i> ¹²	58/M	Rectal cancer, lymphadenopathy	2,990 mg/dL	Sinusitis, allergic rhinitis	Prednisolone 20 mg/day/Improvement of symptoms
Present Report	72/M	Asthenia, loss of strength, emaciation, and anosmia	376 mg/dL	<i>Diabetes mellitus</i>	Prednisolone 54 mg/day/Improvement of symptoms

changes are inespecific, except in cases related to membranous glomerulonephritis.^{7,6,9,11,13} No specific vascular changes are associated with IgG4TN. IgG/IgG4 deposits in the tubular basement membrane in a granular pattern are commonly identified in IgG4TN. Kappa and lambda light chains can be found too, with focal C1q and IgM staining, and the deposits in tubular basement membrane are restricted to the affected areas.^{1,2,5,8,11}

The extension of fibrotic areas is accompanied with more IgG4 deposition in tubular basement membrane. Immunohistochemistry technique on paraffin sections is fundamental to quantify the infiltrating IgG4-positive plasma cells.^{2,8,9,11,14}

Raissan *et al.*⁹ proposed three patterns to classify the pattern of inflammation and fibrosis. The pattern A is characterized by less than 10% of interstitial fibrosis without expansive process. Pattern B exhibits expansive interstitial fibrosis and a more severe interstitial lymphoplasmacytic infiltrate. Pattern C shows a collagen-rich fibrosis with occasional inflammatory cells. Electron microscopy can be employed to evaluate the collagen deposition between fibroblasts. Table 1 shows some cases of IgG4TN found in the international literature and comparable to the reported case.

Differential diagnosis includes lupus nephritis, diabetic nephropathy, anti-neutrophil cytoplasmic

antibody associated glomerulonephritis, Sjögren Syndrome, chronic pyelonephritis, membranous glomerulonephritis, drug-induced interstitial fibrosis, granulomatous lesions, and idiopathic tubulointerstitial nephritis.^{5,9,11,12,13,15} The patients compromised with IgG4TN can response to steroid/immunotherapy around 90% of cases. Rebiopsy can shows evidences of attenuating fibrosis areas and decrease in lymphoplasmacytic infiltrate.^{5,8,10,13,14,15}

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