Is the association between Immunoglobulin A Nephropathy and Spondyloarthritis real? A case-based review

Silva SP[1,2*], Rodrigues M[3], Ochôa Matos C[4,5], Nicolau R[6], Bernardes M[7,8], Santos Faria M[9], Eugénio G[1,2], Barcelos A[1,2,10]

[1] Rheumatology Department, Unidade Local de Saúde Região de Aveiro, Aveiro, Portugal;
[2] Centro Académico Clínico Egas Moniz Health Alliance, Aveiro, Portugal;
[3] Rheumatology Department, Unidade Local de Saúde da Região de Leiria, Leiria, Portugal;
[4] Rheumatology Department, Unidade Local de Saúde de Santa Maria, Lisboa, Portugal;
[5] Clínica Universitária de Reumatologia, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Lisboa, Portugal;
[6] Rheumatology Department, Unidade Local de Saúde de Viseu Dão-Lafões, Viseu, Portugal.
[7] Department of Medicine, Faculty of Medicine, University of Porto, Porto, Portugal.
[8] Rheumatology Department, Unidade Local de Saúde São João, Porto, Portugal.
[9] Rheumatology Department, SESARAM, E.P.E, Portugal.
[10] NOVA National School of Public Health, Public Health Research Centre, Comprehensive Health Research Center (CHRC), Universidade NOVA de Lisboa, Lisboa, Portugal.

* ORCID: 0000-0003-4797-047X

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Correspondence to

Susana P Silva

E-mail: susanna_ps@hotmail.com

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Abstract

Spondyloarthritis is a group of inflammatory rheumatic diseases characterized by inflammation of the spine and sacroiliac joints. Extra-musculoskeletal manifestations may also occur, although kidney involvement is rarely reported. Immunoglobulin A nephropathy is one of the most common types of glomerulonephritis, and it can be primary or associated with various diseases, such as spondyloarthritis. Several cases have been reported, mostly through case reports and small case series, pointing to a possible common pathophysiology between these two diseases. However, there is scarce information on the prevalence of renal involvement, particularly Immunoglobulin A nephropathy, among Spondyloarthritis Portuguese patients. We present 5 cases of Immunoglobulin A nephropathy in patients with Spondyloarthritis, resulting from a multicentre Portuguese collaboration, accompanied by a systematic literature review to understand this possible association.

Introduction

Spondyloarthritis (SpA) is a group of inflammatory rheumatic diseases characterized by inflammation of the spine and sacroiliac joints. It typically affects males and causes inflammatory chronic axial pain before age 45. It may be associated with peripheral arthritis, enthesitis, and dactylitis. Extra-musculoskeletal manifestations, such as psoriasis, uveitis, and inflammatory bowel disease (IBD), may also occur[1]. Although less common, some patients may develop kidney involvement[2]. According to several studies, it can present as secondary renal amyloidosis, nonsteroidal anti-inflammatory drug (NSAID) nephropathy, glomerulonephritis, and nephrolithiasis, with an estimated prevalence of 5.2%[3]. However, there is a discrepancy in prevalence in the literature, which derives from different study outcomes. A recent study showed that renal complications were two-fold more common in SpA patients compared with the general population[4].

Immunoglobulin A nephropathy (IgAN) is a type of immune-mediated glomerulonephritis that occurs when IgA complexes deposit in the mesangium. It is characterized by haematuria and proteinuria, occasionally in the context of progressive renal failure. Diagnosis is often incidental and delayed due to the lack of symptoms experienced by the patient[2]. It can be primary or associated with various diseases, such as SpA[4,5]. Several cases have been reported, pointing to a possible common pathophysiology between these two diseases[3,6,7].

However, there is scarce information on the prevalence of renal involvement, particularly IgAN, among SpA Portuguese patients. Recently, Rodrigues et al. reported a Portuguese case series of 15 Caucasian patients with Ankylosing Spondylitis (AS) who underwent kidney biopsies, but only one of them had IgAN[8]. This study aimed to present a case-based review with a detailed revision of 5 cases of IgAN in patients with SpA, resulting from a multicentre Portuguese collaboration.

Methods

A multicentre cross-sectional study was performed, including patients meeting Assessment of SpondyloArthritis International Society (ASAS) criteria for axial SpA and peripheral SpA[9] or Classification Criteria for Psoriatic Arthritis (CASPAR) criteria for Psoriatic Arthritis (PsA)[10], diagnosed with IgAN by biopsy. Data were collected between May and December of 2022. Clinical, analytical, and treatment features were identified from the patient's clinical charts. Patients' characteristics are represented in Table I. Then, a systematic review of the literature according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was performed for literature published up to 13 December 2023. MEDLINE/PubMed and EMBASE were systematically searched using the combination of MeSH terms "IgA nephropathy", "ankylosing spondyloarthritis", "reactive arthritis", and "psoriatic arthritis". We identified 60 publications, out of which we excluded after reading the abstract, 5 reviews, 4 clinical studies, 2 pediatric cases, 6 cases non-related with IgAN and 2 related to primary IgAN, 1 paper in Chinese, and 20 non-available papers. After reading the full texts, we excluded 6 articles for insufficient case information. We included 14 papers that reported 24 cases of IgAN associated with SpA, which are presented in Table II.

Case reports

Patient 1 was a 54-year-old man with a medical history of controlled hypertension (HT) and nephrolithiasis with AS, HLA-B27 positive, treated with adalimumab (ADA). On a routine follow-up, microscopic haematuria and proteinuria (610mg/24h) were observed, with a rapid renal function decline (serum creatinine 1.3mg/dL). A renal biopsy revealed mesangial proliferative glomerulonephritis (MPG) with IgA deposits. The patient discontinued ADA and was treated with glucocorticosteroids, with renal function recovery and proteinuria improvement. He returned to inflammatory back pain and was restarted with ADA. No renal deterioration nor articular complaints were observed after 7 years of follow-up.

Patient 2 was a 62-year-old man with a medical history of dyslipidemia who presented with new onset HT, acute kidney injury (AKI) (serum creatinine 1.79mg/dL), microscopic haematuria and proteinuria (868mg/24h). A renal biopsy revealed MPG with IgA deposits, and he was promptly treated with glucocorticosteroids, which resolved the findings at the urinalysis, but he was left with chronic kidney disease (CKD). He also complained of inflammatory back pain with 12 years of evolution and was referred to a rheumatology clinic where he was diagnosed with AS. No renal deterioration was observed in 4 years of follow-up.

Patient 3 was a 72-year-old man with PsA with peripheral involvement, treated with golimumab (GOL), with a medical history of controlled HT and hyperuricemia. Proteinuria was observed in a routine urinalysis (900mg/24h), with a worsening of renal function (serum creatinine 1.30mg/dL). Renal biopsy revealed MPG with IgA deposits, which was treated with glucocorticosteroids, with partial recovery of renal function. He continued GOL without any further renal complications and remains symptom-free after 5 years of follow-up.

Patient 4 was a 20-year-old man with psoriasis who presented to the emergency department with a new onset HT and macroscopic haematuria. Analytical investigation revealed an AKI and proteinuria of 900mg. Renal biopsy revealed MPG with IgA deposits. He had a history of inflammatory back pain and was diagnosed with PsA with axial involvement, HLA-B27 positive, and treated with ADA with complete recovery of renal function. He remained clinically stable during 20 years of follow-up.

Patient 5 was a 30-year-old woman with AS, with peripheral involvement, HLA-B27 positive, treated with ADA. She also had controlled HT and dyslipidemia. She was diagnosed with IgAN after developing an AKI, which was treated with glucocorticosteroids, having remained, however, with CKD as a sequelae. She continued treatment with ADA without any renal complications after 28 years of follow-up.

Discussion

Renal impairment is considered relatively rare in SpA. Previous studies have demonstrated that the prevalence of renal complications varies considerably[3]. More recent literature describes that SpA patients have a two-fold increased risk of renal complications, including haematuria, proteinuria, renal insufficiency, and nephrolithiasis[4]. IgAN is one of the most common types of glomerulonephritis. The absence of extrarenal manifestations characterizes primary IgAN. However, this glomerulopathy has been linked to several illnesses, comprising the so-called secondary IgAN[2]. SpA-associated IgAN is uncommon, and the high prevalence of IgAN suggests that these relationships might be coincidental. Our study reports the first Portuguese case series

of patients with SpA and IgAN, followed by a systematic review of similar cases described in the literature.

IgAN associated with SpA has been described in the literature mostly through case reports and small case series (Table II). Risk factors related to IgAN include young age, male gender, and HLA-B27 positivity[4, 5]. In our case series, there was a clear predominance of male gender with AS HLA-B27 positive, but only one patient was under the age of 45. The literature also describes this association with all types of SpA, such as PsA, IBD-associated arthritis, and reactive arthritis[3, 4]. In most of our patients, kidney disease was asymptomatic, with the fortuitous discovery of proteinuria and haematuria, which is consistent with previously reported cases. Two patients had new-onset HT, and one reported macroscopic haematuria.

IgAN is a glomerular disease caused by the deposition of IgA immune complexes in the mesangium. Although the exact mechanism is not fully understood, immune system dysregulation is implicated. A glycosylation defect reduces IgA clearance, leading to its accumulation in the capillaries. Furthermore, this abnormal glycosylation removes galactose residues from IgA, making it more susceptible to immune recognition and the formation of immune complexes. These complexes become trapped in the mesangium, triggering the activation and proliferation of mesangial cells and the extracellular matrix through a cascade of growth factors, complement activation, and inflammatory mediators, including Tumour Necrosis Factor (TNF) alpha and Interleukine 17 (IL-17). Despite the numerous cases reported in the literature, the link between SpA and IgAN remains incompletely understood, although several mechanisms could explain the association between these two conditions. The pathophysiology of SpA is complex, involving genetic predisposition, immune dysregulation, and environmental factors. Patients with SpA often exhibit elevated serum IgA levels. Thus, there is a growing recognition of the association between the gut and inflammation in SpA. Dysbiosis has been suggested as a potential pathogenic factor, leading to chronic bowel inflammation and increased IgA production by the mucosa. Pro-inflammatory cytokines such as TNF alpha and IL-17, which play central roles in SpA pathophysiology, may contribute to glomerular inflammation in IgAN[11,12]. Besides IgAN, IgA-vasculitis and IgA skin deposits have also been reported in SpA patients[13, 14]. Several studies have been conducted to comprehend the relationship between mesangial cells and IgA complexes. It has been demonstrated that the addition of an anti-TNF in vitro could halt the proliferation of mesangial cells usually induced by IgA immune complexes, indicating the potential beneficial role of anti-TNF[15]. However, there are conflicting results regarding the efficacy of anti-TNF in IgAN treatment. The management of IgAN is complex and must be individualized. Supportive measures, such as blood pressure control with renin-angiotensin blockers are crucial. These drugs, along with sodium-glucose cotransporter 2

inhibitors have been shown to reduce proteinuria and slow the decline in renal function. Immunosuppression is typically reserved for patients at a high risk of disease progression. Therapies targeting the underlying disease pathogenesis are becoming increasingly available. However, most studies focus on patients with primary IgAN, rather than those with IgAN associated with SpA. In our study, all patients were treated with renin-angiotensin-blockers, four with glucocorticosteroids, one patient-initiated, and two patients kept treatment with anti-TNF agents, with no adverse outcomes. In the literature, we found 3 cases treated with different anti-TNF agents, with control of SpA but no influence over IgAN. Saint-Marcoux *et al.* reported, in a cohort of 39 AS patients treated with anti-TNF, 3 cases of IgA-associated vasculitis with renal involvement, suggesting that anti-TNF may promote autoimmunity and favor the development of antibody-mediated injury[16]. Alternatively, although Champtiaux *et al.* failed to demonstrate any improvement during IgAN with anti-TNF, they found no association between this therapy and renal adverse events[5].

Some authors have proposed that since IgAN is one of the most common primary glomerular diseases worldwide, there is a possibility that SpA and IgAN have separate but related pathogenesis and that they affect similar populations, suggesting a hereditary or environmental predisposition to both disorders[17, 18]. For instance, TNF gene polymorphisms have been associated with an increasing risk of developing IgAN[19]. On the other hand, a recent study showed that IgAN was more commonly observed in males and displayed a milder progression in patients with AS[20]. There is no definitive way to differentiate primary IgAN from its secondary forms, including those associated with systemic autoimmune diseases such as SpA. As a result, a presumptive diagnosis of secondary IgAN is typically made when both conditions are present simultaneously, as there are no reliable clinical, analytical, or histological features that can accurately distinguish one from the other. More studies are necessary to prove that IgAN associated with SpA differs from primary IgAN in its presentation, renal pathology, and prognosis.

One limitation of our case-based review is the small number of patients, probably because the diagnosis is underestimated. One possible explanation is that the most common renal presentation of IgAN is asymptomatic microscopic haematuria and proteinuria. Since renal failure is rare and renal biopsy is not frequently indicated, this might explain the relatively low incidence of IgAN reports in SpA. Many case reports are outdated, with limited information, and do not allow for a straight comparison with more recent cases.

Nevertheless, this is the first Portuguese case series of IgAN associated with SpA, and the literature does not establish if IgAN is truly secondary to SpA or its therapy. This case-based review highlights the need for continued monitoring of renal disease in these patients through

routine urinary analysis and clinical follow-up. Additionally, larger population studies are required to understand and validate the association between these pathologies.

Tables and Figures

Table I – Description of the patients and IgA nephropathy characteristics.

Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/Sex	54/M	62/M	72/M	20/M	30/F
Diagnosis	AS	AS	PsA	PsA	AS
Axial involvement	Yes	Yes	No	Yes	Yes
Peripheral involvement	No	No	Yes	No	Yes
Dactylitis	No	No	Yes	No	No
Enthesitis	Yes	Yes	No	Yes	No
Psoriasis	No	No	Yes	Yes	No
Uveitis	Yes	No	No	Yes	No
HLA-B27 status	Positive	Negative	NA	Positive	Positive
Previous treatment	ADA	None	GOL	None	ADA
CRP before IgAN (mg/dL)	0,11	4,20	2,00	0,62	NA
BASDAI before IgAN	1,2	NA	NAp	2,6	NA
BASFI before IgAN	1	NA	NAp	0,5	NA
ASDAS-CPR before IgAN	1,1	NA	NAp	1,4	NA
Initial creatinine (mg/dL) [Normal range 0.60-0.90]	0,90	1,79	1,30	3,03	NA
Initial CKD stage	Stage 1	Stage 2	Stage 1	Stage 3A	Stage 1
Initial CRP (mg/dL)	0,11	2,00	0,62	4,20	NA
Initial 24h proteinuria (mg)	610	868	900	2062	NA
Initial Haematuria	Yes	No	Yes	Yes	NA
IgAN Presentation	Microscopic haematuria Nephrotic proteinuria	Acute kidney injury Microscopic haematuria Nephrotic proteinuria	Nephrotic syndrome	Hypertension Acute kidney injury Macroscopic haematuria Proteinuria	Acute kidney injury
IgAN treatment	GCS	GCS	GCS GOL	ADA	GCS ADA
Late CKD stage	Stage 2	Stage 2	Stage 1	Stage 2	Stage 3A

ADA – Adalimumab; AS – Ankylosing Spondylitis; ASDAS-CRP - Axial Spondyloarthritis Disease Activity Score – C-Reactive Protein; BASDAI - Bath Ankylosing Spondylitis Disease Activity Index; BASFI - Bath Ankylosing Spondylitis Functional Index; CKD – Chronic Kidney Disease; CRP – C-Reactive Protein; F – Female; GCS - Glucocorticosteroids; GOL – Golimumab; HLA-B27 - Human Leukocyte Antigen B27; IgAN – IgA Nephropathy; M – Male; NA – Not available; NAp – Not applicable; PsA – Psoriatic Arthritis.

Table II – Systematic revision of IgA nephropathy cases.

Author, year	Age/Sex	Diagnosis	HLA-B27 status	Previous treatment	IgAN presentation	IgAN treatment
J C Jennette, 1982 [4]	44/M	PsA	Positive	NSAIDs	Macroscopic hematuria Acute kidney lesion	Unknown
	36/M	ReA	Positive	None	Microscopic hematuria Nephrotic proteinuria	Unknown
	55/M	AS	Positive	NSAIDs	Microscopic hematuria Proteinuria Acute kidney lesion Henoch-Schoenlein purpura	Unknown
Chen, 1988 [19]	18/M	AS	Unknown	NSAIDs	Macroscopic hematuria Proteinuria	NSAIDs
	22/M	AS	Positive	Unknown	Microscopic hematuria	Unknown
Peeters AJ, 1990 [11]	35/M	AS UC	Negative	SLZ Rectal steroids NSAIDs	Microscopic hematuria Proteinuria	NSAIDs
	50/M	AS UC	Negative	SLZ GCS	Microscopic hematuria Proteinuria Leukocytoclastic vasculitis	None
C Beauvais, 1995 [10]	50/M	AS	Negative	NSAIDs	Microscopic hematuria Henoch-Schoenlein purpura	NSAIDs
	45/M	AS	Positive	NSAIDs	Microscopic hematuria Proteinuria Henoch-Schoenlein purpura	NSAIDs
Satko GS, 2000 [21]	31/M	ReA	Positive	NSAIDs	Microscopic hematuria Microscopic proteinuria	NSAIDs

	61/M	AS	Unknown	SLZ GCS	Hypertension Acute kidney lesion Microscopic hematuria Proteinuria	Eicosapentaenoic acid
Sakellariou GT, 2007 [5]	52/M	PsA	Unknown	csDMARDs (not specified)	Microscopic hematuria Proteinuria	IFX
	46/M	PsA	Unknown	csDMARDs (not specified)	Microscopic hematuria Proteinuria	IFX (Posterior deterioration and treatment with MTX 15mg/w and CsA 150mg/day)
Jacquet A, 2009 [22]	37/M	AS	Positive	IFX	Microscopic hematuria Proteinuria	ARB
Chen, 2010 [23]	28/F	ReA	Positive	Unknown	Microscopic hematuria Proteinuria	LEF GCS
Marocchi E, 2010 [24]	46/M	AS Previous IgAN and renal insufficiency	Unknown	IFX	Worsening of proteinuria Kidney failure	IFX (continued) Hemodialysis
Özçakar L, 2013 [25]	35/M	AS	Unknown	IFX	Acute kidney lesion Proteinuria	ADA Anti-hypertensive treatment (non-specified)
Kaneko, 2015 [26]	65/M	PsA	Unknown	NSAIDs	Microscopic hematuria Proteinuria	Bilateral tonsillectomy GCS Mizoribine
Baert CH, 2021 [6]	43/M	AS	Unknown	IFX	Acute kidney lesion Microscopic hematuria Low proteinuria	IFX (continued) ACEI CCB

ACEI - Angiotensin-converting-enzyme inhibitors; ADA – Adalimumab; ARB - angiotensin 2 receptor blockers; AS – ankylosing spondylitis; CCB - calcium channel blockers; csDMARDs - Conventional synthetic disease-modifying antirheumatic drugs; F – Female; GCS – Glucocorticosteroids; IFX – Infliximab; LEF – Leflunomide; M – Male; MTX – Methotrexate; NSAIDs – non-steroidal anti-inflammatory drugs; PsA – Psoriatic Arthritis; ReA – Reactive Arthritis; SLZ – Sulfasalazine.

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