

## Case report

# Focal Segmental Glomerulosclerosis in a Patient with Ankylosing Spondylitis: A Rare Association

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### Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the sacroiliac joints and spine. Renal involvement, apart from amyloidosis, is rare in AS. Focal segmental glomerulosclerosis (FSGS) occurs extremely rarely in patients with AS. We report here a case of biopsy proven FSGS associated with AS. The exact relationship between AS and FSGS needs to be elucidated. TNF alpha may be a possible mediator involved in the development of AS-associated FSGS.

**Key words:** focal segmental glomerulosclerosis, ankylosing spondylitis, renal failure

### Introduction

Ankylosing spondylitis (AS) can present with back pain and morning stiffness due to inflammation of the sacroiliac joints and spine. The majority of AS patients possess the HLA-B27 antigen (> 95%). Patients with AS might suffer from anterior uveitis, enthesitis, cardiac, pulmonary and renal problems.

The incidence of renal abnormalities among patients with AS varies between 10-18%. Secondary renal amyloidosis is the most common cause of renal involvement in AS (62%), followed by IgA-nephropathy (30%), mesangioproliferative glomerulonephritis (5%), membranous nephropathy (1%), focal segmental glomerulosclerosis (1%) and focal proliferative glomerulonephritis (1%).

Primary focal segmental glomerulosclerosis (FSGS) is a glomerular disease causing proteinuria and nephrotic syndrome in children and adults. It is a common cause of end stage renal disease (ESRD), accounting for up to 20% of dialysis patients. The cardinal feature of FSGS is progressive glomerular scarring. We report here a case of focal segmental glomerulosclerosis associated with ankylosing spondylitis.

### Case report

A 47-year-old man had a 20-year history of ankylosing spondylitis, with a chronic use of daily indomethacin 50-150 mg for years. On admission to the Department of physical medicine and rehabilitation, he had pain in his lumbar spine, pelvis, knees, and heels. He had been treated only with NSAIDs. His spine was stiff and painful. Morning stiffness lasted for about 1 hour. The patient was able to move using a couple of walking sticks. He had a history of multiple lumbar disc hernia operation. Family history of the patient was not contributory. He had typical stooped posture, with increased thoracic kyphosis and cervical forward



**Fig. 1.** Anterior-posterior pelvic X-ray film. Bilateral Grade 4 sacroiliitis and severe diffuse narrowing hip joints

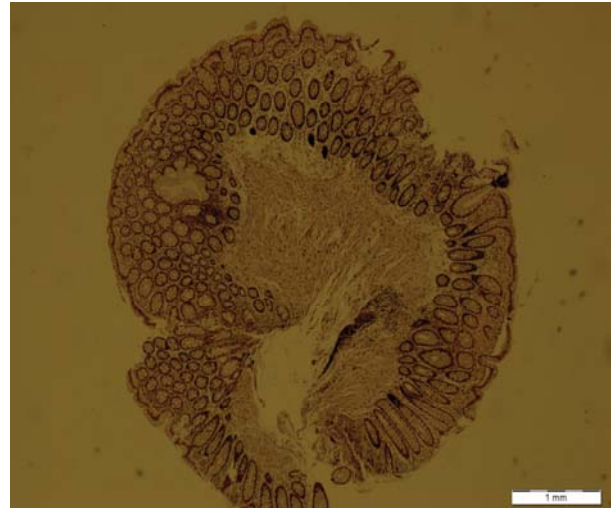
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flexion. His blood pressure was 170/80 mm/Hg and heart rate 90/min and apart from kyphosis his physical examination was normal. His waist and neck movement was markedly restricted in all directions whereas his bilateral hip flexion contractures were about 60°. The flexion of left knee was limited to 90°. All other joints were normal. Anterior-posterior pelvic X-ray film showed sacroiliitis and narrowing hip joints (Figure 1).

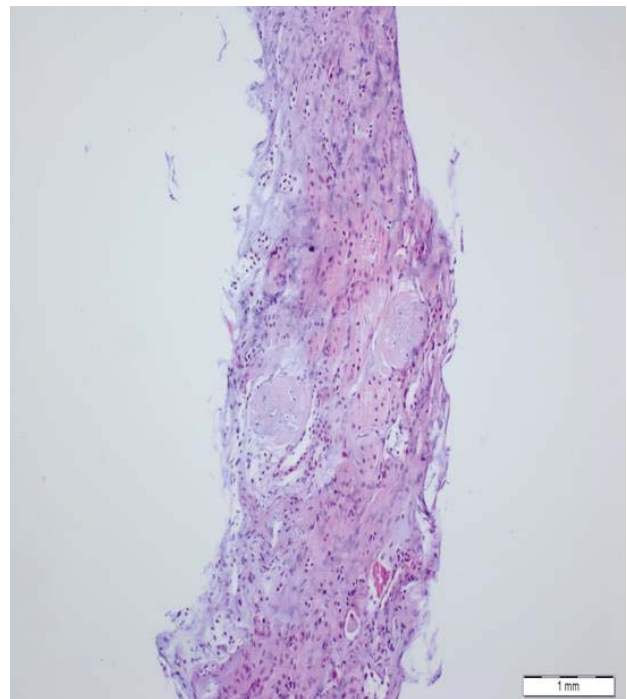
Laboratory investigations showed elevated ESR: 97 mm/first hour, hematocrit: 30%, hemoglobin: 9.5 g/dl, WBC 7920, platelets: 295000, fasting blood sugar: 87 mg/dl, urea: 133 mg/dl, serum creatinine: 3,98 mg/dl, uric acid: 8,3 mg/dl, calcium: 8,6 mg/dl, potassium: 5,3 mmol/l, phosphorus: 4,6 mg/dl, albumin: 2,5 gr/dl, CRP: 12,37 mg/dl and PTH: 391,7 pg/ml. Urinalysis revealed density 1008, pH 6,0, protein ++, leukocytes (-), erythrocytes 6/each field. Arterial blood gas showed metabolic acidosis: pH 7,35, pCO<sub>2</sub> 33,4, HCO<sub>3</sub> 18,2, lac 0,78. As the patient had increased serum urea and creatinine levels, nephrology consultation was requested. Amlodipine 10 mg tb 1\*1, sodium hydrogen carbonate 500 mg tb 3\*1 and IV iron (ferric hydroxide sucrose complex) therapy had been added to the medication. Daily urinary protein excretion was 1595 mg/day and creatinine excretion was 805 mg/day, in the twenty-four hour urine collection. Glomerular filtration rate was calculated using the short MDRD formula and found to be 17,29 ml/min/1,73m<sup>2</sup>. Renal ultrasonography of the right kidney was 101\*47 mm and parenchymal thickness of 16 mm with a Grade 2 echogenicity. Ultrasonographic size, parenchymal thickness and echogenicity of the left kidney were 100\*45 mm, 12 mm, and Grade 2, respectively. There was no sign of stone or ectasia. Serum immunoglobulins and complement components were within normal limits. Antinuclear antibodies, AMA, ANCA, ASMA and hepatitis B surface antigen were also negative. The rest of the biochemical tests revealed Fe: 27 µgr/dl, total iron binding capacity: 211 µgr/dl, transferrin saturation of Fe%: 13%, ferritin 35,94 ng/ml, vitamin B12: 540,9 pg/ml, folate: 3,2 ng/ml, RF: 0,5 U/ml; 12-lead ECG was in sinus rhythm, without pathological findings. Transthoracic echocardiogram revealed left ventricular ejection fraction 65%, LA diameter 3,9 cm, LV diastolic dysfunction grade 1, mitral regurgitation 1° and aortic regurgitation 1°. Rectal biopsy, which was performed at first step because of the high incidence of secondary amyloidosis in this group of patients, showed chronic inflammation. Histochemically samples were stained with crystal violet and Congo red. Amyloid deposition was not detected (Figure 2).

Eventually, ultrasound-guided renal biopsy was performed. Light microscopy revealed 12 glomeruli, of which 9 were globally sclerotic, and 3 with segmental glomerular sclerosis. Moderate interstitial fibrosis, tubular atrophy and medial thickening of blood vessels were apparent (Figure 3). Histochemically periodic acid-Schiff, M. Silver, Masson's Trichrome staining were used. Congo red staining was negative. No deposition of IgA, IgG, IgM, C3, C4, C1q, fibrinogen, kappa and lambda chains was identified with direct immunofluorescence method. The biopsy revealed



**Fig. 2.** Rectal biopsy.CONGO REDx10. Amyloid deposition was not detected

focal segmental glomerulosclerosis. Oral prednisolone therapy (0,5 mg/kg/day) was given along with prophylaxis of pneumocystis jirovecii. After nearly two months (fifty six days) from his first admission, the patient was readmitted to the hospital with signs of pulmonary infection, temperature of 39°C, high C-reactive protein levels



**Fig. 3.** Renal biopsy.H&Ex10.Glomerulosclerosis

(284,4 mg/dl), cough and a chest radiograph indicating left-side opacity consistent with bronchopneumonia. Serum creatinine and creatinine clearance were 6,43 mg/dl and 9,94 ml/min/1,73m<sup>2</sup>, respectively. Arterial blood gas analysis showed metabolic acidosis. A central catheter was placed and he was started on intermittent hemodialysis. Steroid dose was gradually reduced and ceased eventually. Appropriate treatment with antibiotics was used and du-

ring the follow-up period pneumonia showed regression. However, chronic hemodialysis was necessary for the patient.

## Discussion

Ankylosing spondylitis (AS) can present with a back pain and morning stiffness due to inflammation of the sacroiliac joints and spine [1]. It tends to be more severe in men and begins in early adulthood, the average age of onset being at 28 years [2]. It may also lead to anterior uveitis, enthesitis, cardiac, pulmonary and renal problems [3].

The incidence of renal abnormalities among patients with AS varies between 10-18%. Secondary renal amyloidosis is the most common cause of renal involvement in AS followed by IgA-nephropathy, mesangioproliferative glomerulonephritis, as well as membranous nephropathy, focal segmental glomerulosclerosis and focal proliferative glomerulonephritis. Possible mechanisms of renal involvement in AS generally include toxic effects of nonsteroidal anti-inflammatory drugs (NSAIDs), increased incidence of glomerulonephritis and renal deposition of amyloid. Although renal amyloidosis is a considerably rare complication of AS (1-3% in European patients), it should be considered in case of proteinuria and/or renal failure in AS. In 7% of unselected AS patients, amyloid can be found in abdominal fat or rectal biopsies, but most patients do not develop clinically severe disease [4]. Proteinuria or impaired renal function can indicate IgA-nephropathy, which is interesting because of the increased serum IgA levels in AS patients during the active inflammatory phases of spondylitis [5]. In a recent study, secondary renal amyloidosis and nephrolithiasis were the most common causes of renal involvement in ankylosing spondylitis followed by IgA nephropathy [6].

Renal involvement, apart from amyloidosis, is rare in AS. FSGS occurs "extremely" rarely in association with ankylosing spondylitis [7,8]. FSGS is diagnosed when the glomerular lesion involves only a portion of some of the glomeruli with others remaining relatively uninvolved. Before a diagnosis of primary FSGS is reached, secondary forms of the disease should be carefully excluded.

We report here a case of a 47-year-old man with ankylosing spondylitis who presented with increased serum urea and creatinine values and had a percutaneous renal biopsy showing features of FSGS. No other secondary cause of FSGS was found in our investigations. The exact relationship between AS and FSGS (etiological and coincidental) still needs to be elucidated [9]. The underlying immune disorder leading to FSGS is not known, but is probably multifactorial. The spectrum of FSGS includes primary forms mediated by a putative circulating or permeability factor and a few secondary forms caused by heritable mutations in podocyte genes, drugs, viral infections and adaptive responses to reduced renal mass/other hemodynamic stress [10]. This theory of a circulating permeability factor and the reversibility of the podocyte injury before occurrence of scar formation was well shown in a recently published case report [11].

Several mechanisms for TNF-alpha-induced proteinuria in FSGS have been proposed. A high level of TNF-alpha

mRNA was detected in mononuclear cells from patients with FSGS [12]. Podocytes are the main cells involved in the development of FSGS. It has been shown that podocytes express TNF-alpha R2 receptors and respond to cytokine stimulation by producing TNF-alpha themselves [13]. TNF-alpha induces the production of several inflammatory mediators and enzymes by mesangial cells and glomerular epithelial cells, including reactive oxygen species (ROS), eicosanoids, and other cytokines [14]. Some of these mediators are known to alter the glomerular capillary permeability barrier. A circulating, soluble form of the urokinase receptor (suPAR) can activate podocyte  $\beta_3$  integrin, leading to FSGS whereas TNF- $\alpha$  has been shown to be important for the expression of suPAR on platelets [15,16].

On the other hand, TNF-alpha is a proinflammatory cytokine involved in many chronic inflammatory diseases such as AS. Infliximab decreases proteinuria during secondary renal amyloidosis among patients treated for AS or other forms of inflammatory arthritis [17,18]. The effect of anti-TNF alpha therapy may be explained by a blockade of the TNF-alpha renal actions, as TNF-alpha is known to induce glomerular inflammation and to increase glomerular permeability [19]. Anti-TNF-alpha therapy has been recently tested in a child with resistant FSGS recurrence [20] and induced transient complete remission. Furthermore, anti-TNF-alpha infusion was effective in any relapse the patient showed.

Anti-TNF-alpha agents have been demonstrated to reduce renal symptoms associated with chronic inflammatory rheumatological diseases such as secondary amyloidosis, but few data are available on their efficacy in controlling IgA nephropathy associated with AS [21]. Belimumab (effective on TNF- alpha pathway) has improved activity scores in SLE patients [22]. In a recent animal study it has been shown that the kidney is protected from damage by TNF- $\alpha$  blockade [23].

The anti-TNF-alpha agent infliximab may be effective in treating rheumatological symptoms of AS and control associated FSGS, suggesting that the mechanisms involved in AS and the development of AS-associated FSGS might be alike. Unfortunately, we did not have the chance for our patient to analyze TNF-alpha levels and this is a limitation of our case report.

Renal side effects and possible pre-existing renal involvement should be taken into consideration while choosing an appropriate treatment for AS. The occurrence of a rare association needs to be recognised and differentiated from other more common causes of renal dysfunction in AS. For this reason, renal biopsy may be very helpful. In conclusion, this is a rare case report of a patient with AS combined with biopsy proved FSGS.

*Conflict of interest statement.* None declared.

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