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Case Report

# ANCA-Associated Vasculitis in Patient with CREST-Syndrome - Case Report

**Abstract**

**Background:** ANCA-associated vasculitis is a small vessel necrotizing vasculitis with few or no immune deposits, necrotizing glomerulonephritis is very common in the microscopic poliangiitis subset. Systemic scleroderma renal involvement is included neither in the current classification criteria, nor in the definition of CREST-syndrome. The presence of ANCA in patients with SS was first described in 1996, and since that has been reported to be rare and not presenting clinical significance. However during next decade about 50 cases with association of SS and AAV were described, and more recently, additional cases were reported and the clinical features of such association were recognized.

**Results:** We present here a case, illustrating association of systemic sclerosis and ANCA-associated vasculitis, proven by kidney biopsy findings of sclerosing and necrotizing glomerulonephritis with11% of crescents.

**Conclusions:** Patients with systemic sclerosis in general, and CREST-syndrome in particular, demonstrating unexplained deterioration of kidney function, should be tested for ANCA and undergo kidney biopsy in search for association with AAV. Immunosuppressive treatment, especially in cases with advanced sclerotic changes by kidney pathology evaluation, should be performed with caution to ensure patient's survival even in cases of progression to ESRD.

## Abbreviations

AAV, ANCA: Associated Vasculitis; AH: Arterial Hypertension; ANCA: Antineutrophil Cytoplasmic Antibody; CAPD: Continuous Ambulatory Peritoneal Dialysis; CKD: Chronic Kidney Disease; CREST: Calcinosis, Raynaud Phenomenon, Esophageal Dysmotility, Sclerodactyly, and Telangiectasias; EGPA: Eosinophilic Granulomatosis With Polyangiitis; ESRD: End Stage of Renal Disease; GPA: Granulomatosis with Polyangiitis; MPA: Microscopic Polyangiitis; MPO-ANCA: Anti-Myeloperoxidase ANCA; RNA: Ribonucleic Acid; PR3-ANCA: Anti-Proteinase3 ANCA; RRT: Renal Replacement Therapy; SS: Systemic Sclerosis; SVV: Small Vessel Vasculitis; UTI: Urinary Tract Infection

## Background

According to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small vessel vasculitis (SVV), distinguished from immune complex SVV. AAV is necrotizing vasculitis with few or no immune deposits, predominantly affecting small vessels, associated with MPO-ANCA or PR3-ANCA. AAV is subdivided into microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA/Wegener's), and eosinophilic granulomatosis with polyangiitis (EGPA/Churg-Strauss). MPA in particular is SVV necrotizing vasculitis with few or no immune deposits; necrotizing arteritis involving small and medium arteries may be present, necrotizing glomerulonephritis is very common [1].

Revised classification of systemic sclerosis (SS) published by the joint committee of the American College of Rheumatology and the European League Against Rheumatism in 2013, defined the following classification criteria: skin thickening of the fingers of both hands extending proximally to the metacarpophalangeal joints; skin thickening of the fingers; fingertip lesions; telangiectasia; abnormal nailfold capillaries; pulmonary arterial hypertension and/or interstitial lung disease; Raynaud phenomenon; and systemic sclerosis–related autoantibodies (anticentromere, anti–topoisomerase I and anti–RNA polymerase III). Renal involvement, though it is not rare and might be life-threatening, was not included into the list of classification criteria [2]. CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias), although not all are needed for the disorder to be called CREST, is an older term used to describe this subset of limited systemic sclerosis, formerly named scleroderma [3].

The presence of ANCA in patients with SS was first described in 1996 [4] and since that has been reported to be rare and not presenting clinical significance. However since 1996 to 2006 about 50 cases with association of SS and AAV were described, and more recently additional cases were reported, and the clinical features of such association were recognized [5-10].

We present here a case, illustrating association of SS and AAV, diagnosed on the basis of kidney involvement characteristics.

## Case Presentation

Caucasian female 65 years old, admitted to our clinic December 17 2015.

Main complains: weakness, muscle cramps.

## Previous medical history

Infiltrative tuberculosis diagnosed in 1988, successfully treated with specific therapy and followed for 10 years without recurrences, uterine fibroid, autoimmune thyroiditis, and mild arterial hypertension.

## History of present illness

In 2009 she developed joint pain and weakness, outpatient work-up found sideropenic anemia, mild proteinuria, microhematuria and serum creatinine 150 μmol/L. Chest X-ray showed diffuse pneumosclerosis, kidney ultrasound was unremarkable, gasrtoscopy found erosive gastritis, urine culture revealed E. Coli contamination. She was seen by local nephrologist, diagnosed with arterial hypertension, gastroduodenitis, UTI and CKD stage 3, treated with anti-ulcer and antihypertensive medications, antibiotics, oral iron preparations and NSAIDS and improved.

In 2012 she developed skin thickening and hyperpigmentation of her left abdomen and backside area, seen by dermatologist, diagnosed with limited scleroderma and treated with penicillin and antiplatelet agents. She had positive anticentromere and anti-hystone H antibodies, her serum creatinine was the same as in 2009 (147 μmol/L), her anemia was compensated, and urinary symptoms were very mild.

July 2015 she had an episode of eye redness, successfully treated with eye drops. However, she developed progressive weakness, in November 2015 her creatinine rose to 206μmol/L, and she was referred to our clinic.

**At admission**: conscious, alert, oriented. Body temperature 36.8°C, RR 18 per minute, pulse regular 78 per minute, BP 140/90 mm Hg. Slightly obese (BMI 29). Skin dry, pale, pronounced thickening and hyperpigmentation of left abdomen and buttocks area, upper extremities Raynaud phenomenon, and telangiectasia's on her chest. No edema. Eyes clear. HEENT and neck otherwise normal. Peripheral lymph nodes not felt. Joints non-painful, no swelling, movements unrestricted. No breast nodularity. Lungs clear. Heart rhythm regular, no murmur. Tongue dry, clean. Abdomen soft, non-tender, non-painful, bowel sounds normal. Liver, spleen and kidneys not felt. Urination and stools normal.

## Work-up

**Routine labs:** moderate proteinuria (1.0 g\day), microhematuria (15-20 RBC hpf), mild anemia (Hb 9.6 g/L), creatinine 226-375 μmol/L, urea 16.4-20.3 mmol/L, uric acid 492 mmol/L, CRP 12.3 mg/L (normal range <6). Other blood count and blood chemistry parameters, as well as coagulation tests, thyroid hormones, immunoglobulin's levels, infectious screening, Diaskin test and urine culture were unremarkable.

**Autoimmune screening:** positive anticentromere (13.9 U/L, normal range 0-10) and antinuclear (1/640) antibodies, and MPO-ANCA >100 U\mL (normal range 0-5), other tests within normal range. Tests for anti-plasminogen and anti-tissue plasminogen activator antibodies were not available.

**Electrocardiogram:** Sinus rhythm, cardiac rate 65 bites per minute, left ventricular myocardial underperfusion.

**Chest X-ray:** no focuses or infiltration, pulmonary vascular markings.

**Kidney ultrasound:** lower normal kidney size, few small parenchymal cysts, no stones or urinary tract obstruction.

**Echo-cardiogram:** heart chambers not dilated, mild left ventricular myocardial hypertrophy. Aortic walls, aortic and mitral annulus moderate sclerosis, cusps excursion not limited. Left ventricular ejection fraction 68%. Mild mitral and tricuspid regurgitation. Left ventriclular diastolic dysfunction type 1.

**Esophagogastroduodenoscopy** - atrophic gastritis and esophageal dysmotility.

**Kidney biopsy:** Sections of formalin fixed paraffin-embedded tissue were stained with H&E, Masson's trichrome and periodic acid-Shiff. Light microscopy found 18 glomeruli, 12 of them totally sclerosed. In 2 out of 12 sclerosed glomeruli fragments of fibrous crescents are seen. Other 2 glomeruli contain segmental cellular crescents. The rest glomeruli look enlarged and not changed. Diffuse-focal interstitial fibrosis and tubular atrophy up to 50% of parenchyma. Hypertrophy of the preserved tubules. Diffuse-focal mononuclear infiltration in the areas of sclerosis (Figures 1-4). Arteries and arterioles otherwise normal. Immunofluorescence on unfixed cryo-sections with fluorescein conjugated anti IgA, IgG, IgM, C1q, C3, fibrinogen, λ and κ light chains antibodies was negative for all immune stains.

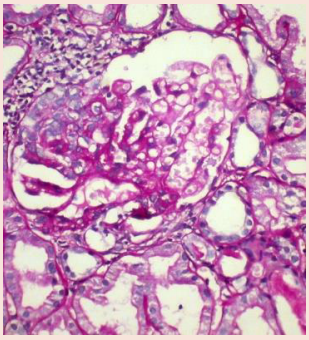

**Figure 1:** light microscopy, PAS x200. Glomerulus with segmental cellular crescent.

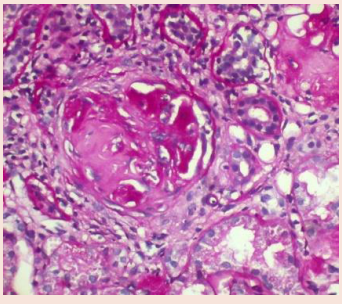

**Figure 2:** light microscopy, PAS x200.Totally sclerosed glomerulus with fibrous crescent.

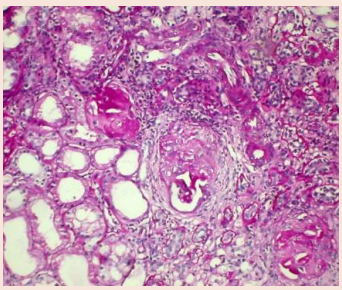

**Figure 3:** light microscopy, PAS x100. Advanced interstitial fibrosis.

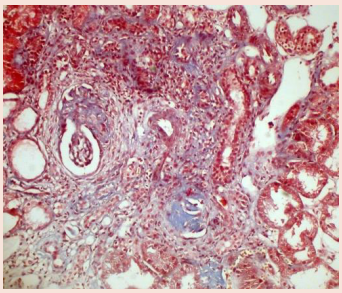

**Figure 4:** light microscopy, Masson x100. Glomerulosclerosis and interstitial fibrosis.

**Biopsy reading:** diffuse pauci-immune sclerosing and necrotizing glomerulonephritis with 11% of cellular crescents.

**Chest and paranasal sinuses CT:** irregular infiltrates in lung fields, anterior ethmoiditis, hyperplastic sphenoiditis.

**ENT specialist consult:** Chronic hypertrophic rhinitis, right tubotympanitis.

**Test T-SPOT.TB:** negative

**Phthisiatrician consult:** no data for tuberculosis recurrence, clinical and radiographic finding are compatible with vasculitis and/or pneumonia. Immunosuppressive treatment, if needed, should be combined with isoniazid and vitamin B6.

## Diagnosis, treatment and follow-up

Patient was diagnosed with overlaping CREST-syndrome and microscopic polyangiitis, and started with 3 methylprednisone pulses 500 mg each, followed by oral prednisone 30 mg/day, and cyclophosphamide boluses 200 mg i.v. every 2 weeks, accompanied by isoniazid and vitamin B6. In 6 weeks, despite of treatment, her serum creatinine doubled (696 μmol/L) and urine output decreased to 500 mL/day, whereas her blood pressure remained stable. Cyclophosphamide was discontinued and oral predinisone tapered to 20 mg/day. Patient was referred to the dialysis unit and started on CAPD. At the latest follow-up visit September 7 2016 she is doing well, treated appropriately with CAPD without any complications, prednisone is discontinued; her chest CT shows only diffuse pneumosclerosis.

## Discussion

At the primary evaluation patient with the history of infiltrative tuberculosis almost 30 years ago, mild arterial hypertension, joint pain, UTI, CKD diagnosed 7 years ago, and limited scleroderma, diagnosed 4 years before admission, was considered to have slow progression of her CKD. Even though, neither AH nor inactive UTI without obstructive uropathy were compatible with progressive impairment of kidney function, observed during her hospital stay. She met the criteria for SS, and was diagnosed CREST-syndrome, as she had 3 out of 5 features of CREST-syndrome (Raynaud phenomenon, esophageal dysmotility and telangiectasias), plus skin thickening and positive anticentromere antibodies, but scleroderma renal crisis was not the case, because her blood pressure was well controlled on her standard antihypertensive medications.

Kidney biopsy, performed to determine the cause of progressive loss of renal function revealed diffuse pauci-immune sclerosing and necrotizing glomerulonephritis with 11% of cellular crescents, characteristic for AAV. ANCA test found very high MPO ANCA, confirmative for the diagnosis of AAV. Absence of granulomatous inflammation in her kidneys, lungs and ENT, and the ANCA pattern lead us to the diagnosis of MPA. Taking into consideration prominent sclerotic changes, confirmed by kidney biopsy, the history of joint pain since 2009, and urinary abnormalities with renal dysfunction found the same time, she probably suffered AAV since 2009.

Given prominent glomerular sclerosis and interstitial fibrosis, and the history of tuberculosis, we doubt if immunosuppression is indicated. However, CT findings, along with T-SPOT.TB test results, ruled out active tuberculosis and demonstrated ENT and lung changes also compatible with MPA. That forced us to start immunosuppression with low-dose steroids and low-dose cytotoxic agents; immunosuppression was limited by proportion of nephrosclerosis, patients age and comorbid conditions; we were mostly concerned about negative influence of steroids on SS course. Under the treatment pulmonary symptoms resolved, but she progressed to ESRD. We did not consider progression of renal insufficiency as scleroderma renal crisis because patient's blood pressure remained stable. At the same time further immunosuppression seemed to be useless, and in order to avoid life-threatening treatment complications immunosuppressive drugs were discontinued and renal replacement therapy started. On RRT patient is maintaining good condition and quality of life during the follow-up period.

In our unit database for 1994-2015 years we found 87 patient with AAV and 7 patients with SS, the only one with AAV and SS association is presented here. Our case data are in agreement with recent observations [7,9], suggesting that presence of ANCA-associated vasculitis with MPO-ANCA is a rarely reported complication of scleroderma, occurring most commonly in women with limited or CREST variant of scleroderma, and constituting a differential diagnostic challenge with a scleroderma renal crisis, especially in unusual normotensive presentations. Same authors indicate that immunosuppressive therapy is effective, but with significant mortality or progression to ESRD.

## Conclusions

Patients with systemic sclerosis in general, and CREST-syndrome in particular, demonstrating unexplained deterioration of kidney function, should be tested for ANCA and undergo kidney biopsy in search for association with AAV. Immunosuppressive treatment, especially in cases with advanced sclerotic changes by kidney pathology evaluation, should be performed with caution to ensure patient's survival even in cases of progression to ESRD.

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