# Microscopic polyangiitis presented with polyneuropathy of lower extremities and ANCA-associated glomerulonephritis: Case Report

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## Abstract

We present the case of a 67-year-old female patient with microscopic polyangiitis presented with polyneuropathy of lower extremities and rapidly progressive glomerulonephritis. Disease had started as a pain and weakening of muscular strength first in the left and than in the right leg. Electromiography has shown that a mainly dominant neurological affection was paresis of peroneal nerve in both lower extremities. In laboratory examination the titer of anti-myeloperoxidase anti-neutrophilic cytoplasmic antibodies (p-ANCA) was elevated. Due to renal involvement presented as a microscopic haematuria and decreasing of renal function, patient undergone kidney biopsy. It confirmed the immune vasculitis microscopic polyangiitis type with ANCA-associated glomerulonephritis. This is one of rare case of microscopic polyangiitis without lung simptomatology, first presented with asymmetrical polineuropathy of lower extremities. The patient was treated with methylprednisolone and cyclophosphamide in dosis adjusted to the level of disease severity and the renal function (methylprednisolone 1 mg/kg of body weight for two months with gradually tapering to the minimum effective dose and cyclophosphamide 1 mg/kg of body weight). This treatment lead to the partial remission of disease. In maintenance therapy azathioprin was introduced instead of cyclophosphamide.



KEY WORDS: glomerulonephritis, polyneuropathia, ANCA-antibodies, microscopic polyangiitis

## INTRODUCTION

ANCA- associated glomerulonephritis is rapidly progressive glomerulonephritis characterised by the absence of immune deposits in biopsied kidney tissue (pauci-immune glomerulonephritis) and rapidly progressive deterioration of renal function [1]. The elevated titer of anti-myeloperoxidase ANCA is very important immunological indicator. Disease can be limited only on kidney affecting a small vessels of kidney (idiopatic necroticans glomerulonephritis with crescents) or associated with systemic ANCA-positive vasculitis which affects a small vessels of kidney and more organ systems [2]. According to The Chapel Hill Consensus Conference from 1993, in ANCA vasculitis were included Wegener granulomatosus, microscopic polyangiitis and Churg-Strauss syndrome [3]. ANCA vasculitis is the most common cause of rapidoprogressive necroticant glomerulonephritis with crescents infiltration. In this article we present a patient with ANCA vasculitis microscopic polyangiitis type who started with polyneuropathy of lower extremities six months before symptoms of kidney injury appeared.

*Case Report*

A 65-year-old female was admitted to the Clinic of Nephrology in Clinical Center University of Sarajevo on 11th March 2011 due to increased serum creatinine. She was previously hospitalised at the Clinic of Neurology from 7th February 2011 to 11th March 2011 due to polyneuropathy of lower extremities with unclear etiology. Neurological symptoms started in July 2010 as paresthesio followed by pain in the left heel, which then spread, to the whole foot and subsequently to the lower leg. In November 2010 the same symptoms appeared in the right leg, with the same pattern like the left one. Walking became problematic with symptoms worsening. Patient did not have raised temperature, sweating, headache, nor loss of consciousness. All other organic systems functioned normally. Over the previous two months blood pressure was raised. Patient has been smoking two large packs of cigarettes a day for the last 25 years. She has no previous kidney disease. Patient's medical documentation confirmed that blood urea nitrogen (BUN) and serum creatinine levels in the last three months were within normal physiological limits.

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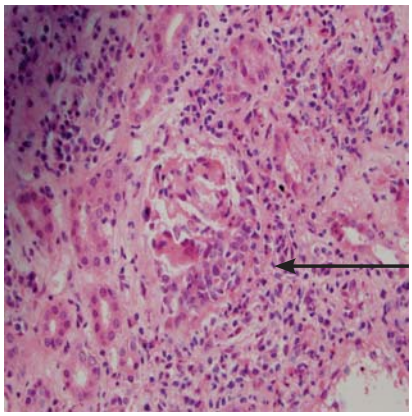

FIGURE 1. HE staining, magnified 40x. Cellular extracapillary proliferation is seen within glomerul (arrow).

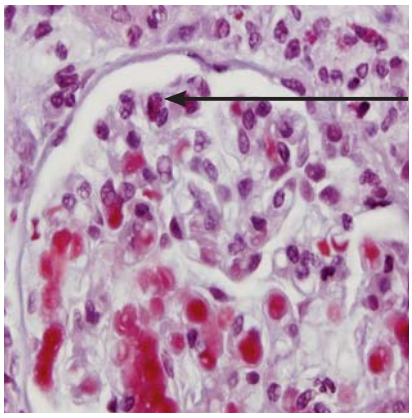

FIGURE 2. Trichrom-Masson staining, magnification 100x. Capillary lumen of some glomerules was overflowing with erythrocytes, with small thromb in one capillary lumen with a very fine focus of fibrinoid necrosis of one capillary wall (arrow).

Neurological examination and electromyogram (EMG) at Clinic of Neurology severe polyneuropathy and pronounced paresis of left peroneal nerve were found. Lumbo-sacral spine X-ray revealed a small disc herniation on L4/L5. Head MRI revealed an aftermath of cerebro-vascular damage due to lacunar thrombosis. On admission to the Clinic of Nephrology, physical examination revealed that patient was fully conscious, afebrile, eupnoic, without a skin rash and peripheral limphodenopathy or organomegaly. Auscultatory heart sounds were rhythmic, without murmurs. Blood pressure was increased (160/80 mmHg). Breath sounds were also normal. The patient didn't have back pain nor peripheral oedema. Neurological examination revealed weak gross motor function, especially of lower extremities, and pronounced paresis of the left peroneal nerve. Pulsations of the arteries on the feet bilateraly were a bit less palpable. Blood test results showed anaemia (haemoglobin 85.2 g/L) and accelerated eritrocyte sedimentation rate (130 mm/h). Concentrations of serum creatinine (461 μmol/L) and BUN (30.1 mmol/L) were increased while creatinine clearance was decreased to 10.9 ml/min. Kidney ultrasound revealed increased echo of kidney parenhima, with significant reduction of arterial branches on cortex periphery, especially on the left. These pointed to a chronic kidney disease of unknown etiology with laesioned kidney function. Lung examination was normal by X-ray and spirometric test. Repeated EMG again confirmed severe polyneuropathy of lower extremities. Color Doppler analysis on large arteries of lower extremities showed atherosclerotic changes without a hemodynamic meaning. Immunological blood tests were revealed negative results for antinuclear factor, anti-ds DNA antibodies and crioglobuline. Titers of p-ANCA (antineutrofilic) antibodies and circulated immune complexes were elevated with increased C-reactive protein (Table 1). Tumour markers were negative and imunophenotipisation of peripheral blood did not show any change in the number of T lymphocytes, their subpopularisation and B lymphocytes. Elevated serum creatinine and BUN, proteinuria of 0.9 g/d, microscopic hematury, granulated urinary cylinders and very elevated titer p-ANCA antibodies indicated to the affection of kidneys within systemic inflammation most likely of vasculitis type. Kidney biopsy was performed and proved that more than 50% of glomerules in the tissue sample were globally sclerotic. In two non-sclerotic glomerules extracapillary proliferation was found (Figure 1). Capillary lumen thromb and microscopic focus of fibrinoid necrosis of capillary wall were found in one glomerule (Figure 2). In one interlobar and a couple of arteries of small calibre there was interruption in the continuity of elastic lamina (Figure 3).

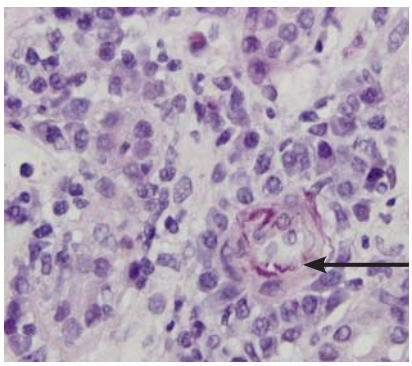

FIGURE 3. Trichrom staining, 100x. Interruption in the continuity of elastic lamina in one small artery.

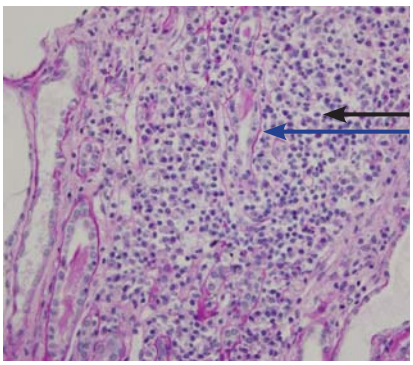

FIGURE 4. PAS staining, magnified 40x. Cellular infiltrate in interstitium (black arow) and atrophy of tubular epithelium (blue arrow)

**TABLE 1.** Laboratory data of the patient with microscopic polyangiitis and ANCA-associated glomerulonephritis

| Laboratory parameter (normal values) | Examination (month/year) | | |
|---|---|---|---|
| | 3/2011 | 5/2011 | 8/2011 |
| BUN | 30.1 mmol/L | 20.7 mmol/L | 16.1 mmol/L |
| Serum creatinine | 461 μmol/L | 252 μmol/L | 244 μmol/L |
| Creatinine clearance | 10.9 ml/min | 23.3 ml/min | 24.3 ml/min |
| Erythrocyte sedimentation rate (0-12 mm/h) | 130 mm/h | 56 mm/h | 23 mm/h |
| Hemoglobin | 85.2 g/L | 103 g/L | 104 g/L |
| C-reactive protein (0-5 g/L) | CRP 45 mg/L | 18 mg/L | 11 mg/L |
| p-ANCA antibodies (>5) | >100 | 20.78 | 0.55 |
| Circulated immune complexes (<40 μg/mL) | 54.85 μg/mL | 25.8 μg/mL | 20.5 μg/mL |

Diffuse cellular infiltration of interstitium was made of CD3 positive lymphocytes, with some B lymphocytes as well as plasma cells and eosinofilic leukocytes. In tubules was atrophy of epithelium, focaly and in part diffuse (Figure 4). Immune deposits were not found by immunofluorescency. Distinct tubulointersticial and periglomerular inflammation, focal fibrinoid necrosis of capillary wall and chronic diffused sclerotic glomerulonephritis with crescent cellular proliferation in 15% of glomerules were morphological confirmation of weakened immune vasculitis most likely of microscopic polyangiitis type. The patient treatment was started with methylprednisolone in dose of 1 mg/kg of body weight with gradually tapering to the dose of maintenance and cyclophosphamide in dose of 1 mg/kg of body weight, as the patient had very low creatinine clearance (10.9 ml/min). Two months after the start of therapy kidney function improved with creatinine clearance 23.3 ml/min and significant reduction in titer of p-ANCA antibodies to 20.78. Neurological problems in legs became less pronounced. Five months after the start of the treatment blood test results showed persistence of partial remission of disease (Table 1). EMG revealed significant improvement of neurophysiological parameters so kinesitherapy was recommended. The patients was converted to the maintenance therapy: oral prednisolone 0.25 mg/kg of body weight and azathioprin 2 mg/kg of body weight.

## DISCUSSION

Microscopic polyangiitis (MPA) is a very rare disease characterized by the lesions of arteriolae, venulae and capillaries, as well as medium arteries mainly of the kidneys and lungs, but also of other systems and organs [4]. The reported incidence of MPA in Europe is from 2.7 per million in Norway [5] to 11.6 per million in Spain [6]. Peak incidence of microscopic polyangiitis is between 65-74 years of life. Small vessels vasculitis connected with ANCA are idiopathic diseases of unknown etiology. In our 65 years old female patient this type of vasculitis was related to the polyneuropathy of lower extremities and rapidly progressive glomerulonephritis with development of renal failure. ANCA glomerulonephritis is the most common complication of the disease. It is presented in half of patients on the start of the disease progressing to 85% of patients during course of illness. Microscopic polyangiitis mainly affects small-calibre vessels of the kidneys and lungs [7]. Systemic small vessels vasculitis often begins with high temperature, loss of weight, arthralgias, usually with symptoms of upper and lower respiratory system, skin changes and problems related with musculoskeletal system [4]. These symptoms had not been found in our patient except mialgias and weakened of lower extremities. Compared the clinical aspects of peripheral neuropathy associated with Wegener's granulomatosis (26 patients), Churg-Strauss syndrome (26 patients) and microscopic polyangiitis (12 patients) in a single center cohort study conducted between 1999 and 2006, Cattaneo et al. were confirmed peripheral neuropathy in 27/64 patients [8]. Neuropathy occured earlier and presented with severe form of mononeuritis multiplex in patients with MPA compared to patients with Wegener's granulomatosis. Electrophysiologic findings and sural nerve biopsy confirmed acute axonal changes in MPA [9]. Zhang et al. were observed nervous system involvement in 36.6 % of MPA patients [10]. Microscopic polyangiitis includes mainly mononeuritis multiplex or distal symmetrical polyneuropathy [10, 11]. Presentation of asymmetrical polyneuropathy of lower extremities for six months before kidney symptoms in our patient could be independent of kidney as idiopathic polyneuropathy or as a first manifestation of an atypical presentation of MPA. Kaaroud et al. described a woman with rapidly progressive glomerulonephritis, who was presented with partial loss of motor and sensory function in both lower limbs with sphincter dysfunction seven years later [12]. Kidney disease in most of patients with ANCA-vasculitis gives only few signs and symptoms. Microhematuria, granulated urinary cylinders, proteinuria, worsening of renal function and hypertension were signs of kidney damage. Findings of p-ANCA (MPO-ANCA) antibodies in serum of a patient is connected with necrotising small-vessels vasculitis (idiopathic necrotising glomerulonephritis with crescents as vasculitis limited on kidney, microscopic poliangiits, Churg-Strauss syndrome) but it could be found with necrotising vasculitis of small and medium blood vessels like periarteritis nodosa. In our patient we considered possibility of overlapping these different types of vasculitis. Treatment of small vessels vasculitis caused by ANCA antybodies includes immunosupresive therapy leading to the remission in most of cases. Intensity of therapy must be ad-

justed to the severity of the disease [13]. The most common subdivision based on the diagnosis includes two subgroups: without or with minimal involvement of kidneys, with moderate kidney involvement (creatinine <500 μmol/L) or with severe kidney damage (creatinine > 500 μmol/L). Using standard treatment approach with combination of cyclophosphamide and corticosteroides lead to remission in more than 85% patients and one-year survival rate is more than 90%. During maintenance phase azathioprin is used instead of cyclophosphamide [14]. For group of patients with severe kidney disease, where prognosis is the worst, it is recommending additional treatment with plasma exchange (7x3 liters) or with pulse doses of metilprednisolone (3x1 gram per day intravenously). Immunosupresive maintenance therapy could be used as long as two years. Main causes of early mortality are infections and late mortality is mainly caused with progressive cicatrisation after repeated flares of vasculitis and toxic effects of drugs [15].

## CONCLUSIONS

Results from clinical and laboratory tests can support an immune ANCA vasculitis, but kidney biopsy and histopathology examination is necessary for early and exact diagnosis of ANCA vasculitis microscopic polyangiitis type with ANCA-associated glomerulonephritis, as well as early starting of therapy, which determined outcome of disease. Polyneuropathy of lower extremities presented much more before kidney symptomatology could be a first manifestation of an atypical presentation of MPA.

## DECLARATION OF INTEREST

The authors have declared that no Conflict of interest exists.

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