

PATIENT WITH RHEUMATOID ARTHRITIS AND ACUTE RENAL FAILURE: A CASE REPORT AND REVIEW OF LITERATURE

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Rheumatoid arthritis (RA) is an autoimmune disease also known as an example of connective tissue disease. There are no case-controlled studies to determine the frequency of renal disease in RA. Most of patients present slow progression of chronic kidney disease while acute renal failure is uncommon in rheumatoid arthritis. We report a case of a 40-year-old woman with established medical history of RA who presented with abrupt onset of severe hypertension with rapidly growing serum creatinine concentration and oliguria. Renal biopsy revealed oedematous intimal thickening of vessels and ischemic changes in glomeruli, and nonspecific lesions in tubules and interstitium. These pathological findings were consistent with the scleroderma nephropathy. Additionally, we provided a brief literature overview on coincidence of hypertension and different types of connective tissue diseases.

Key words: overlap syndrome, “onion skin” lesion, scleroderma renal crisis.

Introduction

Connective tissue diseases also known as autoimmune diseases usually develop with clinical presentation that in conjunction with laboratory data enables a direct diagnosis. However, in rare cases an overlap of clinical presentation may occur. The overlap between systemic sclerosis (SSc) and rheumatoid arthritis (RA) is rather uncommon. To date the largest cohort of patients with RA-SSc was reported by Szucs. In his study 5 of the 22 patients had clinical manifestation of renal involvement [1]. Especially at an early stage of disease the differential diagnosis between RA and SSc may be difficult. Both RA and SSc begins at any age, but it most often starts at the age of 40 and is more common in women than in men. Stiffness of joints, which is characteristic of RA, may also appear in SSc patients. Rheumatoid factor is detected in 70-90% of patients with RA, but it is

also present in about 30% of patients with SSc. The main clinical problem in RA is chronic joints disease with rare emergency states. In early scleroderma there is a possibility of development of scleroderma renal crisis (SRC), which is connected with high mortality. The most probable renal finding in RA patients is amyloidosis or mesangioproliferative glomerulonephritis and it correlates with quite slow progression of chronic kidney disease. Just the opposite, the scleroderma more likely develops with abrupt clinical presentation of severe hypertension and acute renal failure. Scleroderma renal crisis is the most dangerous manifestation of scleroderma nephropathy with the most characteristic pathological lesion which is intimal thickening of smaller arcuate and interlobular arteries and arterioles. The difficulty in histological diagnosis may occur in cases of severe or malignant hypertension with unclear medical history of SSc.

Case report

A 40-year-old woman was admitted to University Hospital No. 1 in Bydgoszcz, the Chair and Department of Nephrology, Hypertension and Internal Diseases because of acute renal failure with serum creatinine concentration up to 6.8 mg/dl and severe hypertension.

The patient has been treated for rheumatoid arthritis since 2005 with methotrexate administered orally. After a year the treatment was changed into monthly intravenous infusions of interleukin 6 receptor antagonist (tocilizumab). The serum creatinine, urine sediment and blood pressure remained within the normal ranges when the patient appeared for regular check-ups in the out-patient clinic.

In the previous year the systemic sclerosis was suspected due to Raynaud's phenomenon, skin fibrosis affecting upper extremities and face, as well as characteristic megacapillaries in nail fold capillaroscopy, without serological confirmation (ANA and Scl-70 antibodies were negative).

The medical history revealed that two weeks before the incidence of renal dysfunction the patient was taking non-steroidal anti-inflammatory agents because of brachialgia. Two months earlier patient received amoxicillin with clavulanic acid (Augmentin) due to symptoms of the upper airway infection.

The critical moment was the occurrence of rapidly growing hypertension with values exceeding 220 mmHg and 140 mmHg for systolic and diastolic blood pressure, respectively, and concomitant headaches, dizziness, nausea and vomiting. Head computed tomography, chest X-ray and echocardiography remained normal. Abdominal ultrasound and duplex-scan examination demonstrated normal kidneys size and structure and excluded renal arteries restriction. In ophthalmoscopy, vascular retinopa-

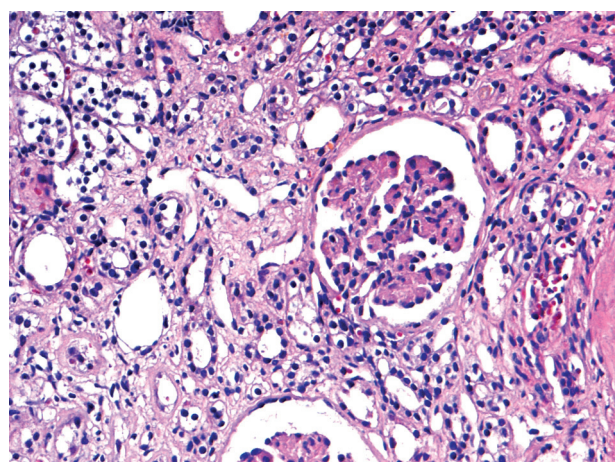


Fig. 1. Ischemic glomeruli with thickened, wrinkled basement membranes and collapsed capillaries. HE, objective magnification 20×

thy grade III according to Keith-Wegener's classification was diagnosed. The laboratory tests revealed non-nephrotic proteinuria, erythrocyturia and leukocyturia with a high number of eosinophiles in urine sediment. Serological screening was negative including complement, dsDNA, pANCA, cANCA, ANA, Scl-70, CENP, ACA, U1RNP. Even though the normalization of blood pressure was gradually achieved the patient required renal replacement therapy due to oliguria and constantly increasing serum creatinine. Because of acute renal failure of unknown origin and clinical suspicion of acute tubulo-interstitial nephritis the decision for kidney biopsy was made.

The renal tissue samples were taken and sent to the Chair and Department of Clinical Pathology *Collegium Medicum* in Bydgoszcz, Nicolaus Copernicus University in Toruń. The clinical data on the referral included: rheumatoid arthritis, acute renal failure, suspicion of acute interstitial renal alterations. Histopathological examination was based on two tissue samples taken from the left kidney. One of the cores was fixed in formalin. After a routine procedure, a paraffin block was prepared. Haematoxylin-eosin, trichrome Masson, Congo red staining and paS reaction were made on deparaffinized and rehydrated paraffin tissue of 4- μ m sections. Another specimen we have got unfixed for immunofluorescence examination. The tissue sample was frozen at -30°C . In 4 μ m tissue sections the IgG, IgM, IgA, C3, fibrinogen were determined with fluorescein-labelled anti-human serum.

The light microscopy examination demonstrated twenty six glomeruli. Most of them showed ischemic changes with wrinkled, thickened basement membranes and collapsed capillaries (Fig. 1). Slight mesangial proliferation was observed. In part of glomeruli cuboidal, high podocytes were present. Tubules focally exhibited nonspecific degenerative changes. Focal interstitial oedema was noted. Luminal narrowing of interlobular and arcuate arteries due to mucoid intimal thickening with concentrically arranged cells was the most specific lesion found in the specimen (Fig. 2). Changes of this type were observed within all vessels larger than the diameter of glomeruli, but also in some smaller ones. A Congo red stained section was negative ruling out amyloidosis. We have seen paS positive thickening of tubules basement membranes and paS positive pole around Bowman's capsule in half-circulated shape (crescent) (Fig. 3). In immunofluorescence microscopy, focal positive staining for fibrin in vessels' walls of medium calibre was present. The pathological diagnosis was consistent with morphological lesions characteristic of systemic sclerosis. Finally, after dermatological and rheumatologic examination, rheumatoid arthritis – diffuse systemic sclerosis overlap syndrome and scleroderma renal crisis was diagnosed.

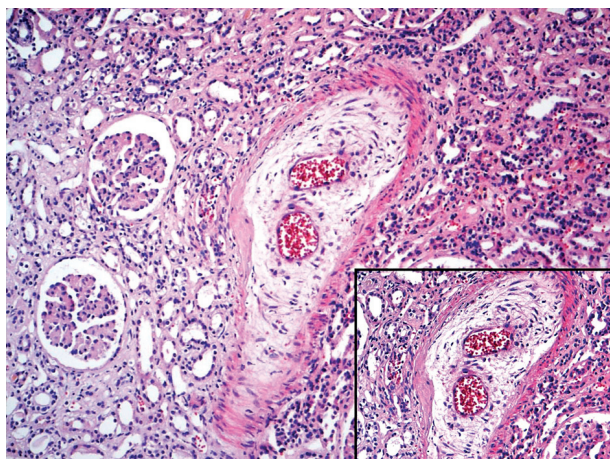


Fig. 2. Vascular "onion skin" lesion (the most typical of SSc nephropathy) with thickened intimae and concentrically arranged myointimal cells. HE, objective magnification 10 \times . Inset: highlighted the same vessel

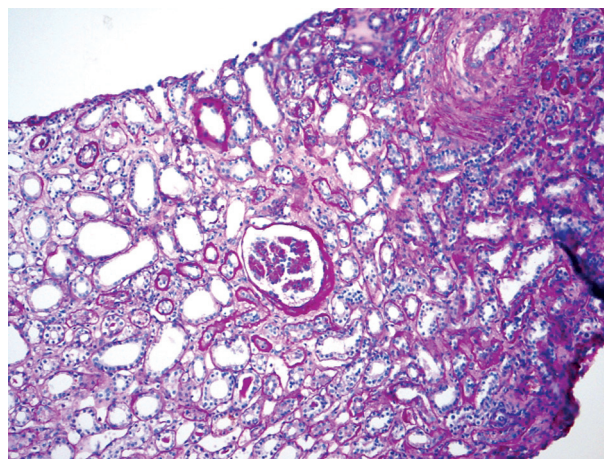


Fig. 3. paS positive crescent around Bowman's capsule. paS reaction, objective magnification 4 \times

Discussion

Systemic sclerosis is a rare multisystem connective tissue disease mainly affecting women in the third to fifth decade of life. It is characterized by widespread blood vessels damage and usually by fibrosis of the skin and internal organs. Renal involvement is a common component of systemic sclerosis. The kidneys affected in the course of systemic sclerosis were reported for the first time in the 1863 [2, 3]. Kidneys are affected in 60% to 80% of patients with SSc as evidenced by autopsy studies [4]. Systemic sclerosis occurs in two main forms. The first one is diffuse form with symmetric skin involvement of proximal and distal parts of extremities and often the trunk and face. In the limited form of more confined symmetric involvement of the skin it affects the distal parts of the extremities. Visceral manifestations take much longer to become manifest in this form [5]. It was thought that the risk of severe organ system involvement in patients with diffuse scleroderma increased linearly with disease duration [6]. However, gradual intensity of organ dysfunction during the course of illness does not always take place. Usually patients show some evidence of renal dysfunction e.g. mild proteinuria or increased serum creatinine. A quite rare complication is scleroderma renal crisis that occurs in up to 10% of patients, mainly with diffuse form of scleroderma. Scleroderma renal crisis is the term used to describe the most severe form of renal involvement in systemic sclerosis [5]. It is defined as the new onset of severe hypertension (although about 10% patients with SRC remain normotensive) and/or rapidly progressing renal failure with oliguria in patients with systemic sclerosis. The evidence of microangiopathic anaemia or thrombo-

cytopenia may also be present [2, 6, 7, 8]. The laboratory findings useful in diagnosis are non-nephrotic proteinuria, erythrocyturia, growing creatinine concentration in blood serum (0.5–1.0 mg/dl/24 hours). SRC episode in 75% occurs in the first four years after the diagnosis of SSc [2]. The long-term outcomes in SRC used to be extremely poor. Although the availability of angiotensin-converting enzyme inhibitors decreased the need of dialysis, the survival of patients with SRC is 70% at two years [9] and 40% after 9 years [5, 6].

Pathologic renal biopsy findings in the course of systemic sclerosis in light microscopy include non-specific glomerular changes which may vary considerably. In some cases, thickening of basement membranes is present. The glomeruli in scleroderma may show ischemic collapse, congestion, sclerosis. In renal crisis they may have fibrillar appearance identical to the changes seen in haemolytic uremic syndrome. The larger eosinophilic areas in the capillary wall with fragmented red blood cells in glomeruli reflect the microangiopathic haemolytic anaemia that may be present.

The most typical and almost diagnostic lesion, that one should pay attention to, is the mucoid intimal thickening. Characteristic SSc changes in arteries of interlobular size, smaller arcuate arteries, and arterioles are pathologic hallmarks of progressive systemic sclerosis. Larger arteries may be normal or reveal nonspecific changes only. The most significant finding is "onion skin" lesion and it relates to changes in intimae. The arterial lumen is considerably narrowed as a consequence of mucoid intimal thickening with concentrically arranged myointimal cells. The mucinous intimal change mostly consists of mucopolysaccharides of the hyaluronic acid type.

This change is similar to that seen in malignant nephrosclerosis (MN), haemolytic uremic syndrome, thrombotic thrombocytopenic purpura, antiphospholipid syndrome and pre-eclampsia [4]. It stains with Alcian blue and metachromatically with toluidine blue. Clear reaction or only a weakly blue staining indicates no or little deposition of mature collagen [5]. Another vascular lesion which may also be seen in SSc and malignant nephrosclerosis is fibrinoid necrosis of the afferent arterioles. However, this case did not reveal any of such features. The endothelial cells may be swollen. But even endothelial proliferation was described [10]. The media may be thinned by around the extended intima. Some authors noted slightly adventitial fibrosis [11, 12]. The internal elastic lamina is usually intact, but in chronic injury arterioles show its reduplication [5, 10]. The changes in tubules and interstitium are nonspecific and secondary to vascular ones. In immunofluorescence microscopy, the positive staining for fibrinoid, IgM and C3 in the glomeruli may be seen. The same focal positive result in the walls of interlobular arteries and arterioles may be present.

Clinical data suggested that in differential diagnosis we should distinguish between nephropathy due to rheumatoid arthritis and also interstitial nephritis. The clinical diagnosis of systemic sclerosis is based on ACR (American College of Rheumatology) standards (characteristic skin changes and/or interstitial pulmonary fibrosis) and might be confirmed by the presence of specific antibodies (ANA, Scl-70). The unique composition of clinical, serological and genetic findings in SSc-RA overlap syndrome patients was reported by Szucs [1]. Contrary to our patient, most of them developed RA after long-term SSc and had a limited form of SSc. The renal involvement occurred in 23% of these patients. Unfortunately, there are no case-controlled studies to determine the renal disease patients with rheumatoid arthritis [13]. Clinical manifestation of renal involvement in RA in most of the patients is the slow progression of chronic kidney disease. It correlates with the most common lesions found in biopsy examinations, which are mainly amyloidosis and mesangial proliferative glomerulonephritis [5, 13]. The acute renal failure may occur in interstitial nephritis due to NSAIDs' as well as other drugs' intake. We should also take into consideration acute interstitial nephritis because of the large amount of eosinophiles in urine sediment. But among biopsy findings of our patient, there were diagnostic features characteristic of neither RA nor interstitial alterations. Malignant nephrosclerosis with fibrinoid necrosis and "onion skin" lesion in smaller interlobular arteries could also be found, considering severe hypertension episode. Nevertheless, degenerative changes of tubules and interstitial oedema of low

intensity seen in our tissue sample could not reflect such symptoms.

Taking into account the pathological picture of small renal vessels, it was necessary to consider malignant nephrosclerosis in the course of malignant hypertension (MH). Although similar intimal thickening but rich in collagen is seen in MN and our knowledge about the composition contents in intimal lesion of our patient was unclear (lack of histochemical examination with Alcian and toluidine blue), we could quite easily say that this type of intimal lesion indicates rather SSc than accelerated hypertension. Lack of arteriolosclerosis hyperplastica with concentrically arranged cells in thickened media, fibrinoid necrosis of the vessel wall and features of acute glomeruli injury, have made us make such decision. Considering the fact that in the intimal lesion in early phases of MN there is only intimal thickening by myxoid connective tissue [14] it would be interesting to know more about the order of occurrence the vascular lesions in MN – can onion skin lesion without fibrinoid necrosis exist among patients with MN? It is quite difficult to understand the way of histopathological examination of hypertensive patients in Caetano's study, where the myointimal proliferation defined the diagnosis of malignant nephrosclerosis. In this study in a group of 35 patients with clinically diagnosed malignant hypertension, there was only one with fibrinoid necrosis of the vessel wall. A similar discrepancy between clinical and histopathological diagnosis was shown by Zucchelli and Fogo [15].

After the literature review, differential diagnosis should also include haemolytic uremic syndrome, thrombotic thrombocytopenic purpura, antiphospholipid syndrome and pre-eclampsia. Considering the lack of symptoms of the above-mentioned diseases in the medical history of our patient, there was no need to take them into account in pathological differentiation.

Conclusions

Although the SSc is not the only disease in which intimal thickening occurs, the mucoid character of this lesion confirms the diagnosis. The ACR criteria for the diagnosis of SSc doesn't include histopathological examination of neither the skin nor other organs. Although the diagnosis of SSc is based on clinical symptoms, there are many early SSc HIV-seropositive patients with Raynaud's phenomenon and abnormalities in nail fold capillary microscopy. These patients are in a group with the most probable SRC. That is why the renal biopsy may occur especially important and useful in cases with symptoms of scleroderma renal crisis with unclear SSc medical history.

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