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DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF THE IMMUNOLOGICAL PROFILE IN RENAL INVOLVEMENT OF IMMUNE INDUCED CONNECTIVE TISSUE DISEASES

-ABSTRACT-

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Immune mediated connective diseases; renal involvement, antibodies; renal biopsy.

BACKGROUND
Renal disease is often the most important and severe involvement of immune mediated connective diseases with a high mortality and morbidity, and the pathogenic mechanisms are different.

The pattern of glomerular injury is primarily related to the site of formation of the immune deposits (in glomeruli, subendothelial space, mesangium and subepithelial space).

**SYSTEMIC LUPUS ERYTHEMATOSUS**

Systemic lupus erythematosus is the prototype of autoimmune disease, related to the site of formation of the immune deposit and to the production of autoantibodies. The histopathological changes show the variety of autoimmune mechanisms related to the disease.

Strong evidence exists that most human glomerulonephritides are forms of autoimmune disease. The nephritogenic immune response exhibits both humoral and cellular components.

The criteria for diagnosis of renal disease are:

- proteinuria > 0.5g/24 h or a dipstick score>3+ or
- Granular, mixed, waxy or tubular casts

Other:

- hematuria> 5erytrocites
- leucocituria> 5 leucocites
- high values of plasma creatinine

*Class I: Minimal mesangial lupus nephritiis- mesangial immune deposits by immunofluorescence*
**Class II**: Mesangial proliferative- Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits

**Class III**: Focal lupus nephritis- Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli

**Class IV**: Diffuse lupus nephritis-Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli.

**Class V**: Membranous lupus nephritis-Global or segmental subepithelial immune deposits or their morphological sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations

**Class VI**: Advanced sclerotic lupus nephritis- ≥90% of the glomeruli globally sclerosed without residual activity.

In several studies of lupus nephritis, type IV nephritis is the most common (approximately 40%), while type III and V follow with an approximate frequency of 25% and 15%.

Urinalysis is the most important and effective method to detect and monitor disease activity in lupus nephritis.

Hematuria (usually microscopic, rarely macroscopic) indicates inflammatory glomerular or tubulointerstitial disease. Granular and fatty casts reflect proteinuric states (the former also possibly reflecting degenerated cellular casts), while red blood cell, white blood cell and mixed cellular casts reflect nephritic states. Broad and waxy casts reflect chronic renal failure. In severe proliferative disease, urine sediment containing the full range of cells and casts can be found (‘telescopic urine sediment’) as a
result of severe glomerular and tubular ongoing disease superimposed on chronic renal damage.

SYSTEMIC SCLEROSIS

Scleroderma renal crisis develops in approximately 10 to 20 percent of patients with the diffuse cutaneous form of systemic sclerosis and much less frequently in limited cutaneous systemic sclerosis.

Despite the widespread use of angiotensin converting enzyme inhibitors for the treatment of scleroderma renal crisis, morbidity and mortality remain high.

Scleroderma renal crisis is characterized by abrupt onset of moderate to severe hypertension

- Urine sediment that is normal or reveals only mild proteinuria with few cells or casts
- Progressive renal failure
- Microangiopathic hemolytic anemia
- Thrombocytopenia <100,000/mmc

A number of risk factors for SRC have been identified. These include diffuse skin involvement, advancing skin involvement, glucocorticoid use, and presence or absence of certain autoantibodies.

The diagnosis of SRC is based upon the characteristic findings in high-risk patients with systemic sclerosis.

- New onset of blood pressure >150/85 mmHg, measured at least twice over the preceding 24 hours
• Progressive decline in renal function with rising serum creatinine.

MIXXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease (MCTD) is defined as a generalized connective tissue disorder characterized by the presence of high titer anti-U1 ribonucleoprotein (RNP) antibodies and clinical features commonly seen in systemic lupus erythematosus (SLE), scleroderma (Scl), and polymyositis (PM). The early clinical features of MCTD are nonspecific and may consist of general malaise, arthralgias, myalgias, and low-grade fever. A specific clue that these symptoms are caused by a connective tissue disease is the discovery of a positive antinuclear antibody (ANA) in association with the Raynaud phenomenon.

The absence of severe renal disease is a hallmark of MCTD. It is possible that high titers of anti-U1 RNP antibodies, which are characteristic of MCTD, may protect against the development of diffuse proliferative glomerulonephritis, independent of whether these antibodies occur in MCTD or classic SLE. However, some degree of renal involvement occurs in about 25 percent of patients. Membranous nephropathy is the most common finding and nephrotic range proteinuria may occur. Hypertensive crises similar to Scl kidney have also been reported.
SJÖGREN'S SYNDROME

Sjögren's syndrome is typically associated with a lymphocytic and plasmocytic infiltrate in the salivary, parotid, and lacrimal glands, leading to a sicca syndrome. This immune process can also affect nonexocrine organs, including the kidneys, producing an interstitial nephritis and defects in tubular function.

The reported prevalence of renal involvement has varied widely, ranging from 2 to 67 percent. This variability is in part due to different definitions of kidney involvement.

The interstitial nephritis in Sjögren's syndrome is characterized histologically by an interstitial infiltrate that can invade and damage the tubules. The clinical manifestations of the interstitial nephritis include a variable, but generally mild elevation in the plasma creatinine concentration, a relatively benign urinalysis, and abnormalities in tubular function, including the Fanconi syndrome, distal (type 1) renal tubular acidosis (RTA), nephrogenic diabetes insipidus (tubular resistance to antidiuretic hormone), and hypokalemia.

Distal renal tubular acidosis: A defect in distal acidification occurs in up to 25 percent of patients with Sjögren's syndrome. The associated metabolic acidosis is usually mild, but some patients present with a plasma bicarbonate concentration below 10 meq/L and a plasma potassium concentration below 1.5 to 2.0 meq/L due to concurrent urinary potassium wasting.
PATIENTS AND METHODS

We designed a prospective study including 60 patients with systemic lupus erythematosus, 50 patients with systemic sclerosis, 10 patients with mixed connective tissue disease and 10 patients with Sjögren syndrome, hospitalized in Rheumatology department, Emergency County Hospital, Craiova.

The aim of the study was to determine the importance of the immunological profile for the renal disease in the immune mediated diseases.

The objectives of the study were to diagnose the immune mediated diseases, to evaluate the immunological profile, to determine the types or renal disease and to find the possible correlations between the immunological profile and the renal disease.

RESULTS AND DISCUSSIONS

SYSTEMIC LUPUS ERYTHEMATOSUS

An interesting finding is that patients with lupus nephritis were significantly younger at the time of SLE diagnosis. The age at onset was 34.43±9.51 years, 34.4±10 years in women and 33.8±4.44 years in men.

At the first evaluation, the mean value of the anti DNA ds antibodies was 117.51±69 EU/ml, with a maximum of 290EU/ml, fact that shows that the presence of anti-dsDNA antibodies was a factor associated with the presence of nephritis, the highest titres being associated with the flares of
the disease. The anti DNA ds antibodies maintained at a high value at 12 months and 24 months.

Directly correlated with anti-DNA ds antibodies, C3 and C4 had a mean value of 38.11±19.47mg/dl/9.52±1.25mg/dl. The lowest values were registered in patients with high values of anti DNA ds antibodies. We observed a decrease of their values after 12 and 24 months, probably due to their consumption in the immune processes.

The mean ESR ratio was 42±20.11mm at baseline and 45.53±23mm after 24 months, with no significant correlation between ESR and anti-dsDNA antibodies.

The mean proteinuria, after 24 months was 0.52±0.37g/dl, with a lower value compared with baseline. The decrease of proteinuria is justified by the initiation of specific therapy.

As proven by several lupus nephritis trials, our study found that the presence of anti-dsDNA antibodies was a factor associated with the presence of nephritis, suggesting a prevalent role in the disease profile regarding the renal involvement.

**SYSTEMIC SCLEROSIS**

Rodnan modified score is the only validated tool to assess the skin involvement in systemic sclerosis. Our study included 50 patients with systemic sclerosis, divided in 2 groups: one with limited cutaneous disease and one with diffuse cutaneous disease.
Regarding the renal disease, both groups, limited and diffuse cutaneous disease, had a similar percentage of patients with this involvement. The difficulty of this study was the insufficient number of patients, the assessment of renal disease and the retrospective data collection. The only correlation was the modified Rodnan score, with a higher value in patients with scleroderma renal crisis. This patients had a mean Rodnan score of 41.28 (SD 3.42), compared with the ones without this involvement (16.24).

**MIXED CONNECTIVE TISSUE DISEASE**

Mixed connective tissue disease (MCTD) is defined as a generalized connective tissue disorder characterized by the presence of high titer anti-U1 ribonucleoprotein (RNP) antibodies.

The absence of severe renal disease is a hallmark of MCTD. It is possible that high titers of anti-U1 RNP antibodies, which are characteristic of MCTD, may protect against the development of diffuse proliferative glomerulonephritis.

Our study revealed the presence of proteinuria (of subnephrotic value) in 1 patient at baseline and in 2 patients at 12 and 24 months. These patients had a significant lower titre of anti U1-RNP antibodies.

**SJÖGREN SYNDROME**
The assessment of renal disease in patients with Sjögren syndrome was a real challenge. The reported prevalence of renal involvement has varied widely, ranging from 2 to 67 percent.

We found glomerular or tubular involvement in 70% of the patients (7), confirming the affect of nonexocrine organs, including the kidneys. Distal (type 1) renal tubular acidosis was found in one patient, defect in urine concentration in 4 patients, with or without a modified glomerular filtration rate.

CONCLUSIONS

• Our study reveals the immunological changes and their significance in the long term outcome of renal disease.
• Renal disease is frequent in systemic lupus erythematosus and develops in up to 75 percent of cases
• The most important factor in renal disease development are the immune deposits in the mesangium and subendothelial space
• The pattern of glomerular injury seen in systemic lupus erythematosus (and in other immune complex-mediated glomerular diseases) is primarily related to the site of formation of the immune deposits, which are primarily due to anti-DNA.
• Most of the patients with lupus nephritis have high titres of anti-dsDNA antibodies and low titres of C3 and C4, due to their consumption in the immune processes
• Titers of anti-dsDNA antibodies often fluctuate with disease activity.
• When anti-dsDNA antibody levels are integrated with other measures of disease activity they are useful in many patients for following the course
The most frequently observed abnormality in patients with lupus nephritis is proteinuria.

Renal involvement is rather limited in systemic sclerosis patients, mostly in patients with the diffuse cutaneous form.

Scleroderma renal crisis, develops in approximately 10 to 20 percent of patients with the diffuse cutaneous form of systemic sclerosis and much less frequently in limited cutaneous systemic sclerosis.

Although the number of patients and the frequency of scleroderma renal crisis were rather low, all patients had, as risk factors, the glucocorticoid use and in one patient cyclosporine use.

Rodnan modified score is the only validated tool to assess the skin involvement in systemic sclerosis.

The modified Rodnan score had a higher value in patients with scleroderma renal crisis.

The absence of severe renal disease is a hallmark of MCTD.

High titers of anti-U1 RNP antibodies protected against the development of diffuse proliferative glomerulonephritis.

We found glomerular or tubular involvement in 70% of the patients (7), confirming the affect of nonexocrine organs, including the kidneys.

Distal (type 1) renal tubular acidosis was found in one patient, defect in urine concentration in 4 patients, with or without a modified glomerular filtration rate.

The most frequently renal abnormality in patients with immune disease was proteinuria.

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