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Kidney Damage during Sharp's Syndrome: About Two Cases

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Abstract

Context: The coexistence in the same patient of a mixed connectivitis or Sharp's syndrome is a rare eventuality. **Objective:** To underline the presence of this mixed connectivitis in our practice, whose prevalence remains unknown, particularly in Africa and more precisely in Mali. **Case Presentations:** We report two cases of Sharp's syndrome in a 48-year-old man and a 40-year-old woman with impaired renal function. The picture achieved associated massive proteinuria, hypoalbuminemia, moderate renal failure and edematous syndrome in men. In women, the picture was associated with accelerated to malignant hypertension and severe renal failure. There were no osteoarticular manifestations and the diagnosis of Sharp's syndrome was based on the presence of high levels of antibodies to U1RNP. Therapeutic management has been that of predominantly associated connective tissue disease (systemic lupus erythematosus). **Conclusion:** Mixed connectivitis or Sharp's syndrome is increasingly recognized as a separate entity thanks to advances in molecular biology. Its prevalence is low in sub-Saharan African countries with renal disease that manifests itself as proteinuria or nephrotic syndrome associated with microscopic hematuria, renal failure, and hypertension. This renal impairment is more likely to occur in severe forms of the disease.

Keywords

Sharp Syndrome/Mixed Connectivitis, Renal Failure, Mali

1. Introduction

Beside the typical forms of connectivity, Sharp reported 25 cases of patients with signs common to systemic lupus erythematosus, rheumatoid arthritis, scleroderma and polymyositis [1]. Immunologically, anti-RNP antibodies and much less frequently double-stranded DNA Ac are consistently found. Serum complement is normal or elevated. This syndrome has been called Sharp's syndrome or mixed connectivitis. Renal damage is reported to be common during Sharp syndrome, ranging from 5% to 40% in adult series and 50% in children [1]. On the other hand, the list of anti-RNP antibodies or the complement is not different between patients who will develop kidney disease and those who will not [2]. This description has given rise to many controversies that are still relevant today, as the evolution of most patients rarely evolves towards a mixed picture, but rather towards a deterministic connectivity. Anglo-Saxon authors use the term UCTD (undifferentiated connective tissue disease) to designate this syndrome [3]. For M.F. Kahn, the term "Sharp syndrome" refers to the initial syndrome, while suggesting that the subsequent picture will be an entanglement of the present syndrome and a specific connectivitis [4].

We report two observations with the presence of complicated Sharp's syndrome in a 48-year-old man and a 40-year-old woman with impaired renal function.

The objective of these observations is to highlight the presence of this mixed connectivitis in our practice, the prevalence of which remains unknown, particularly in Africa and more specifically in Mali.

2. Observation N˚1

Mr. C.M., 48 years old Malian, Bambara, uninsured trader, consulted during 2019 for edematous syndrome. When questioned, the patient complained of facial puffiness, oedema of the lower limbs, bilateral lumbar pain and dyspnea of effort. High blood pressure was diagnosed about a year ago.

On admission, he was apyretic with a blood pressure of 160/80 mmHg. On examination, localized oedemas on the lower limbs, painlessly keeping the cup, were noted, as well as conjunctival pallor. Pulmonary and cardiac examination was normal. Elsewhere the examination was without particularity. The search for proteinuria, haematuria, glycosuria, nitrites with the urinary strip was not carried out for lack of means.

The biological examinations had objectified massive proteinuria at 4.94 g/24 h, normal urinary sediment, hypochromic normocytic anemia at 9.4 g/dl, discrete impairment of renal function (urea = 7.10 mmol/l, creatinine = 150 umol/l) a protidemia at 86 g/l, albuminemia at 26.7 g/l aslo = 263 ui/l, natremia = 136 mmol/l, kalaemia = 2.9 mmol/l, glycaemia at 5 mmol/l, calcemia = 2.07 mmol/l, phosphoremia = 1.19 mmol/l. Hepatitis B and HIV serologies were negative. Hepatitis C serology was positive but viral load was undetectable. Liver function tests were normal (total bilirubin = 3.19 Umol/l, prothrombin level = 95.5%, AST = 35 ui/l, ALT = 18 ui/l). Anti-treponemapallidum antibody test was posi-

tive at 96.41. Anti-nuclear antibody (NAA) was positive at 11.1 I/O (I/O positive >1.2) associated with the presence of anti-Sm Ac and anti-U1RNP Ac, while anti-SSB, SSA, anti-Scl70 Ac were negative. The kidneys were normal size, alithiasic, undilated, well differentiated on ultrasound. A minimal pericardial effusion with conservation of the left ventricular ejection fraction was noted on cardiac ultrasound.

The diagnosis of massive non-nephrotic proteinuria with positive hepatitis C serology, the presence of Ac anti-treponemapallidum and Ac anti-U1RNP was retained. Thus the patient was treated with penicillin retard 2.4 million + Prednisone 30 mg, Cyclophosphamide 50 mg/d, hydroxychloroquine 200 mg/d, Perindopril 5 mg/d. Development was favourable under treatment.

3. Observation N˚2

Mrs. D.R., 40 years old, Malian, housewife, Peulh, not insured with the compulsory health insurance (AMO) was hospitalized on 23/12/2019 for alteration of renal function at 1429 Umol/l of creatinine.

The onset of symptomatology was about 2 months ago, marked by the appearance of vomiting, anorexia, dizziness, headache, asthenia, facial puffiness, edema of the lower limbs and dyspnea and then orthopnea. She was on antihypertensive medication including amlodipine 10 mg/d, methyldopa 1 g/d and furosemide 40 mg/d.

On admission, she was apyretic (T˚ = 36.6), weighed 108 kg, height at 1m70 with BMI = 35.76. Blood pressure was 200/110 mmHg, heart rate 112 beats per minute. On physical examination, there was an edematous infiltration with soft, symmetrical, painless edemas guarding the well, localized to the lower limbs. Cardiopulmonary examination was normal. The urinary slide-strip examination for proteinuria, hematuria, glycosuria and nitrites was not performed due to the lack of a urinary slide-strip in the ward.

Biological tests showed renal insufficiency (creatinine = 1427 Umol/l, urea = 36 mmol/l, uric acid = 744.06 Umol/l), fasting blood glucose 5.44 mmol/l, severe anemia 6 g/dl, leukopenia 2720/mm^3, thrombocytopenia 82,000/mm^3. The ionogram showed hyponatremia at 133 mmol/l, kalemia at 4.1 mmol/l. Hypocalcemia (calcium = 1.82 mmol/l) and hyperphosphatemia (phosphoremia = 2.13 mmol/l) were present. Proteinuria was 720 mg/24 h and associated hypoalbuminemia and protidemia in 27.4 g/l and 75 g/l respectively. Thick drop was positive (3400 plasmodium falciparum trophozoites) with a negative stool culture. Biology found LDH at 1106 ui/l, haptoglobin at 2.25 g/l, reticulocytosis at 155,350/mm^3, hyperbilirubinemia at 18.50 Umol/l, direct and indirect Coombs test negative. Schizocyte count was positive.

Urine analysis showed hematuria (1,500,000/ml) and leukocyturia (150,000/ml) and the culture was sterile. D-Dimers (5.68 ng/ml), troponin (282 µg/ml) were increased. Hepatitis C, hepatitis B and HIV serology were negative. Anti-nuclear antibodies (NAA = 0.9E/S), anti-U1RNP antibodies (Ac anti-U1RNP = 61.7

AU/ml N < 12) and anti-SSA antibodies (Ac anti-SSA = 54.8 AU/ml N < 12) were positive, but anti-SSB and anti-Scl70 antibodies were negative. The kidneys were not very echogenic, not very differentiated and measured 93X51X48 mm on the right and 100 × 61 × 50 mm on the left and the Doppler was without particularity.

Isolated, moderate dilatation of the left atrium with good left ventricular function was present on cardiac ultrasound and cardiomegaly (TIA = 0.64) with bilateral hilar overload on frontal chest X-ray. Stage III hypertensive retinopathy (exudates + microhemorrhages and papilledema) was found in the fundus. In view of this malignant arterial hypertension (stage III hypertensive retinopathy and visceral damage) with no particular history and an immunological assessment including the presence of anti-nuclear Ac, anti-U1RNP Ac and anti-SSA Ac, the diagnosis of Sharp's syndrome was made in perfect agreement with the rheumatology department. The insufficiency of the technical platform did not allow the performance of a renal biopsy, the diagnostic and therapeutic contribution of which is beyond doubt. Our patient's care consisted of

- Haemodialysis 2 times × 4 h/week.
- Bolus of methylprednisolone (200 mg/day for 3 days) followed by oral prednisone at 0.5 mg/kg/day or 60 mg/day followed by a tapering of the dose.
- Perindopril/amlodipine 5/10 mg 1 comp/d.
- Cyclophosphamide 50 mg /d.
- Acetylsalicylic acid 100 mg/d.

The evolution is variable from one individual to another and can fluctuate over time in the same person. Some individuals will present only a very limited mild form of the disease, while in others the evolution can be very disabling or even fatal. In our first observation, the evolution was favorable after eleven (11 months) of follow-up with normalization of blood pressure (120/80 mmHg) with an improvement of hemoglobin level to 12g/dl, proteinuria of 24H at 0.6g, creatinine level at 115 µmol/l without any complaints. However, due to financial difficulties, adherence to treatment is not totally assured. As for the second observation (hypertensive retinopathy stage III and visceral damage) the evolution was less favorable despite treatment. Currently, she is in an iterative dialysis program with stabilization of the clinical state.

4. Discussion

Sharp [5] described in 1972 a syndrome with clinical signs of systemic lupus erythematosus, systemic scleroderma, polymyositis and/or rheumatoid arthritis. This syndrome is associated with the presence of high levels of anti-U1RNP antibodies. Epidemiologically, the largest series of this connective tissue disease in the literature to date are European, with 280, 161, 147 and 103 cases in Hungary, Italy, Norway and Poland respectively [6] [7] [8] [9]. The American registry counts 122 cases collected in Minnesota (50 cases), Missouri (51 cases) and Miami (21 cases) [10] [11]. In Black Africa, a few cases of Sharp syndrome or

mixed connectivitis have been reported in Senegal, Togo and Burkina Fasso, with the highest number of cases in Senegal (6 cases in 22 years) [12] [13] [14] [15]. In 2019, two cases of mixed connective tissue disease or Sharp syndrome were diagnosed in a man and a woman aged 48 and 40 years respectively in the Nephrology Department of the CHU du Point G (Mali) in the context of a kidney disease assessment. Deboiko reported 2 cases of mixed connectivitis among 18 cases of connectivitis dominated by systemic lupus erythematosus (10 cases) between 1998 and 2000 in Côte d'Ivoire [16]. Lutalo also reported 2 cases in Zimbawe in 1985 with more of an overlap syndrome profile [17]. All these works suggest that mixed connectivitis is a rare entity in black people in general and in black Africans in particular. In the 1980-1990's, one could blame the inadequacy of the technical facilities and especially the lack of specialists (rheumatologists, internists and nephrologists) capable of searching for autoantibodies for the diagnosis of connectivitis in sub-Saharan African countries. Nowadays, many cases of connective diseases such as lupus, Gougerot Sjogren syndrome, scleroderma, polymyositis or dermatomyositis are increasingly reported in sub-Saharan Africa [14] [15] [18] [19]. The rarity of mixed connectivitis cannot therefore be attributed to a diagnostic difficulty, since in practice the detection of a high serum level of anti-U1RNP antibodies, which is essential for diagnosis, is not made in isolation. The anti-U1RNP antibody is in fact one of the nucleus soluble antigen antibodies (ENA or ECT) whose screening and titration allow the diagnosis of different connectivitis (anti-Sm for lupus, anti-Scl70 for scleroderma, anti-SSA/SSB for Sjogren's syndrome) without technicality and without additional costs specific to each entity [18] [19].

At the clinical level, the Raynaud's phenomenon appears to be rare in mixed connectivitis in black African subjects. In Gabon, there was only one case of Raynaud's among the seven cases of mixed connectivitis reported [20] and in Senegal [12] [13]. Arthralgia is a constant sign in mixed connectivitis, hence the rheumatological interest of the condition. It is often non-erosive arthritis, and its association with Raynaud's phenomenon and puckered fingers is the most frequent clinical triad of connectivitis in the literature. Our two patients did not present extra-renal manifestations of arthralgia, Raynaud's syndrome or curly fingers, classic symptoms of connective tissue disease. In our context, the discovery was fortuitous by the demonstration of anti-U1RNP antibodies to the biology for etiological assessment of massive proteinuria at 4.94 g/24h and malignant hypertension complicated by renal failure. Mixed connectivitis or Sharp's syndrome combines clinical manifestations observed in scleroderma, lupus, idiopathic inflammatory myopathies and rheumatoid arthritis. The diagnostic criteria that seem to be most appropriate in clinical practice are those described by Alarcon Segovia [21].

One serological criterion = presence of high titer anti-ribonucleoprotein (RNP) antibodies.

Clinical criteria= swelling of the hands, synovitis, myositis, Raynaud's phe-

nomenon, acrosclerosis with or proximal cutaneous sclerosis.

Our patients were diagnosed solely on the basis of serological criteria, *i.e.*, the presence of high titer anti-ribonucleoprotein (RNP) antibodies associated with renal manifestations.

Renal impairment is reported to be frequent in Sharp syndrome: 5% - 40% in adult series and 50% in children [22]. However, in a recent series of 32 patients followed for 65 months, no patient developed renal impairment. The difference in the prevalence of renal impairment between series is due to the vagueness in the definition of the disease itself and in the definition of renal impairment [23]. For example, forms similar to systemic lupus erythematosus or systemic scleroderma may have corresponding nephrological damage, including scleroderma kidney attacks [22]. In addition to the presence of high levels of anti-U1RNP Ac in both our patients, there was the presence of anti-Sm Ac in the male patient and anti-SSA Ac in the female patient, which could explain the renal impairment. In the literature renal manifestations were associated with proteinuria with or without nephrotic syndrome associated with microscopic hematuria. Renal failure and hypertension are rare [23]. Our male patient presents massive proteinuria with hypoalbuminemia. This nephrotic syndrome is multifactorial, characterized by the presence of high levels of antibodies to U1RNP and Ac anti Sm, positive hepatitis C serology, and the presence of Ac anti-treponemapallidum, which can be complicated by renal impairment, hence the interest of renal puncture biopsy for precision histological elements. As for our patient, she presented a malignant arterial hypertension (exudates, microhemorrhages, papilloedema) complicated by renal and cardiac damage. She also showed some signs of hemolysis (thrombocytopenia, increased LDH, presence of schizocytes). Although all types of glomerular involvement have been described, extramembranous glomerulonephritis seems to be the most common type of glomerulonephritis in Sharp syndrome/mixed connectivitis [2] [24]. The absence of renal puncture biopsy in our patients did not allow us to make the histological diagnosis.

5. Conclusion

Mixed connectivitis or Sharp's syndrome is increasingly recognized as a separate entity thanks to advances in molecular biology. Its prevalence is low in sub-Saharan African countries with renal disease that presents with proteinuria or nephrotic syndrome associated with microscopic hematuria, renal failure, and hypertension. This kidney damage is more likely to occur in severe forms of the disease.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Consent

Informed consent was obtained from the patients.

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