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Severe Thromboembolic Complication Revealing a Nephrotic Syndrome Due to Segmental and Focal Hyalinosis: A Case Report

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Abstract

Adult Nephrotic Syndrome (NS) is defined by proteinuria > 3 g/24h or 50 mg/kg/day, hypoprotidemia < 60 g/24h, hypoalbuminemia < 30 g/L. It is a disease with high thromboembolic risk. Peripheral vein thrombosis is common, while its association with pulmonary localizations has been more rarely reported. We report a case of nephrotic syndrome revealed by an association of pulmonary embolism, renal vein and inferior vena cava thrombosis. The diagnosis was confirmed by thoracic angioscan. Renal biopsy revealed Focal Segmental Hyalinosis (FSH). An anti-coagulant treatment and an anti-proteinuric treatment were instituted based on a calcium channel blocker (amlodipine) associated with the conversion enzyme inhibitor (perindopril).

Keywords

Thromboembolic Complication, Nephrotic Syndrome, Segmental and Focal

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Hyalinosis, Bamako/Mali

1. Introduction

Adult Nephrotic Syndrome (NS) is defined by proteinuria > 3 g/24h or 50 mg/kg/day, hypoprotidemia < 60 g/24h, hypoalbuminemia < 30 g/L [1]. It is a disease with high thromboembolic risk. Peripheral vein thrombosis is common, while its association with pulmonary localizations has been more rarely reported. Several factors are incriminated in the genesis of these thromboses. They raise the problem of their diagnosis and especially their management. Adult nephrotic syndrome is a rare entity, and its consequences can be multiple: hypercoagulability, arterial hypertension, undernutrition, and infections [2]. In current practice, it should be systematically investigated in all patients with NS and respiratory discomfort.

We report a case of nephrotic syndrome revealed by an association of pulmonary embolism, renal vein and inferior vena cava thrombosis.

2. Observation

This was a 53-year-old female patient, housewife, black race, Malian, admitted to our nephrology department of the G point University Hospital of Bamako, on September 18, 2017, for a symptomatology of progressive installation made of fever, right thoracic pain of side point type, dyspnea stage II of NYHA on a ground of oedematous syndrome (facial puffiness and oedema of the lower limbs) and oligoanuria. She had recent, unbalanced and irregularly monitored hypertension and obesity (Body Mass Index 32 kg/m^2). She had no particular family history.

On examination, Blood Pressure was 160/100 mm Hg, axillary temperature was 37.8˚C, heart rate 98 beats per minute. There were bulky edemas of the lower limbs, soft, bilateral, painless, guarding the bucket with presence of facial puffiness and diuresis was estimated at 350 ml per 24 hours.

At the pulmonary level, there was a right pulmonary condensation syndrome. The abdominal examination revealed the presence of a large amount of ascites. The rest of the physical examination was borderline normal.

Biologically, creatinine was 318 µmol/l, urea 14.95 mmol/l; the blood count showed a hemoglobin level of 11.3 g/dl; hyperleukocytosis of 24,400/mm^3 with a predominantly neutrophilic polynuclear count of 19,410/mm^3 and platelets of 458,000/mm^3. The PT was 100% and the activated partial thromboplastin rate (APTT) was 30 s/30s. The lipid profile showed a slight hypercholestolemia. Proteinuria at 4.56 g/24h without hematuria prompted plasma protein electrophoresis, which revealed hypo-albuminemia at 10.8 g/l and hypo-proteinemia at 40 g/l. Hepatic enzymology was normal.

Protein C, protein S and antithrombin III assays were not performed. The immunological workup (anti-nuclear factor and anti-DNA antibodies) was normal.

The infectious workup showed positive hepatitis B serology with a detectable viral load of 17 IU/ml, F1 cirrhometer with negative Alpha-Feto-Protein (AFP)

at 2.09 IU/ml and normal transaminases.

A frontal chest X-ray showed a right pneumopathy (see Figure 1). An angioscanner was performed, which confirmed a pulmonary embolism associated with a thrombosis of the right renal vein and the inferior vena cava (see Figure 2). Cardiac ultrasound did not show an acute pulmonary heart. The echodoppler of the lower limbs came back normal.

The diagnosis of Impure Nephrotic Syndrome (INS) with thromboembolic (pulmonary embolism, renal vein and inferior vena cava thrombosis) and infectious (lung disease) complications was made.

Treatment consisted of antibiotic therapy with Ceftazidime (1 g every 12 hours for 10 days) and curative anticoagulant treatment with calciparin (250 IU/k every 12 hours). Every 8 hours) and acenocoumarol (1 tablet of 4 mg per day) were instituted followed by a maintenance treatment based on acenocoumarol alone for six (06) months. For nephrotic syndrome, a salt-free diet, fresh plasma infusion (5 units) and treatment with Perindopril, an ACE inhibitor, were initiated.

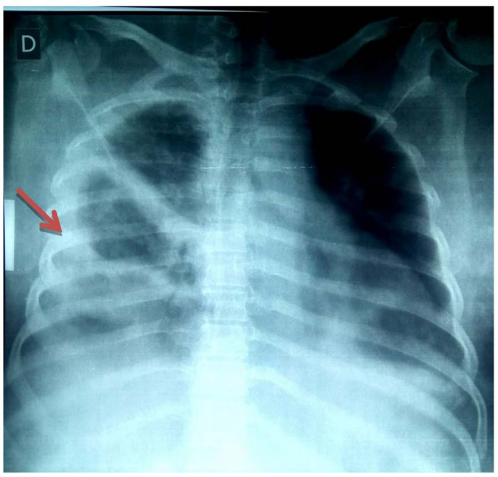

Figure 1. Chest X-ray performed at the patient's admission: Pulmonary condensation syndrome involving the right lung (right lung disease).

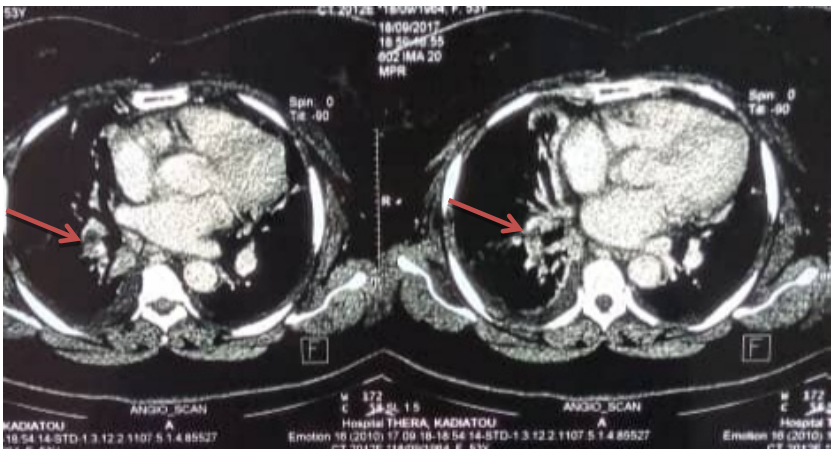

Figure 2. Angioscanner performed on admission of the patient: lobar and segmental pulmonary embolism of the right lower lobe and distal left lower lobe.

After 4 days of treatment, diuresis resumed with marked regression of the edematous syndrome and on the 10th day of his hospitalization, renal function normalized and his discharge was decided. In view of the risk of promoting HBV viral replication under immunosuppressive treatment, we opted for an antiproteinuric treatment with IEC.

We performed a renal biopsy 6 months later. It concluded to a Segmental and Focal Hyalinosis (SFH) of a glomerulus and the absence of argument in favour of an Extra Membranous Glomerulonephritis (EMG). Immunofluorescence could not be performed.

There was a significant reduction in proteinuria after six months of ACE inhibitor treatment and the last proteinuria control was 0.2 g/24h; blood pressure remained stable on amlodipine-perindopril combination at 10 mg each.

The patient was still not under antiviral treatment against hepatitis B according to the recommendations of her hepatologist (detectable viral load at 33 IU/ml, cirrhometer at F1 with negative Alpha-Feto-Protein (AFP) at 3.04 IU/ml and normal transaminases). At one year follow-up on amlodipine-perindopril 10 mg, proteinuria was absent. Blood pressure remained normal at the one-year follow-up after negativation of proteinuria and discontinuation of amlodipine and perindopril despite resumption of the normo-saline diet. In terms of hepatitis, the patient did not receive antivirals because of the low viral load and stable liver enzymes. The body mass index remained stable between 31 and 33 kg/m^2. Informed consent was obtained from the patient for case sharing after explaining the purpose of this work.

3. Discussion

Nephrotic syndrome and risk factor for thrombosis, among the recognized and classic risk factors for Venous Thromboembolic Disease (VTE), coagulation disorders are reported [3]. Nephrotic syndrome is associated with a state of hypercoagulability by several mechanisms: platelet activation by increased thromboxane A2 activity, increased von Willebrandt factor, increased red blood cell aggregation, glomerular leakage and hyperconsumption of antithrombin III, decreased protein S activity, increased hepatic synthesis of fibrinogen and procoagulant factors V and VII, increased lipoproteins preventing fibrinolysis [4]. The association between NS and VTE is frequent and sometimes underestimated in view of the array of non-specific symptoms accompanying VTE. In a cohort of 512 patients presenting with NS, a routine angioscanner scan found VTE in 180 patients, *i.e.* a prevalence of 35%. Of these, 83% (128 patients) were asymptomatic [5]. Thromboembolic events occur most often during a relapse in the first year of the nephrotic syndrome, but they can also occur after a prolonged course [6]. In our patient, the thromboembolic event occurred during the first attack of the nephrotic syndrome. The histological entity found at the renal biopsy of this patient was focal segmental hyalinosis. Contrary to some authors, the incidence of renal vein thrombosis is particularly high, especially in patients with Extra-

membranous Glomerulonephritis (EMG) or Membranoproliferative Glomerulonephritis (MPGN) [7] [8] [9] [10]. The independent risk factor for VTE was a decreased blood albumin level. This risk was increased by a factor of 2.13 (95% CI (1.32 - 3.46); p = 0.002) with each 1 g/dL reduction in albumin [7]. The etiological workup found a hepatitis B viral infection, which usually manifests as GEM and rarely as HSF [11]. Investigation of other causes, haemopathy or malignancy, was negative. In a retrospective study of a cohort of 1958 patients with NS, cancer was found in 5.2% of patients (lung, skin, hematological disease), *i.e.* a 2.5-fold increase in risk at 1 year (95% CI (1.4 - 3.84)) and a 3.5-fold increase at 2 years (95% CI (1.37 - 5.35)) compared to the general population [12]. Similarly, there is a strong association between thrombosis and active cancer, particularly in cases of atypical thrombosis sites (intra-abdominal thrombosis including renal vein thrombosis, upper limb thrombosis, and bilateral lower limb thrombosis) [13]. Thus, in the absence of a consensus, Pani *et al.* propose a 3-step workup for patients with SN, including clinical examination, biological workup, dedicated imaging (chest X-ray and abdominal ultrasound) and more invasive exploration if necessary [14]. The moderate obesity found in the patient was not considered as responsible for this glomerulopathy because of the disappearance of proteinuria and the normalization of blood pressure despite the stability of the body weight. The usual renal histological appearance described during obesity is Segmental and Focal Glomerulosclerosis (SFGS) associated with Glomerulomegaly (GM) [15] [16] [17] [18].

In the presence of VTE, anticoagulant therapy is indicated as long as the SN persists [19]. Although there is no consensus on the choice of the appropriate molecule, the risks of underdosing due to glomerular leakage of antithrombin III and decreased protein S activity must be taken into account. Warfarin has been used for the longest time, but in the case of hypoalbuminemia, the therapeutic range is narrow. Similarly, low molecular weight heparins in NS require dose adjustment in case of renal failure [19].

The advent of the new direct oral anticoagulants (DOA) could be an interesting element (oral route, no need for biological monitoring). Chaudesaygues *et al.* introduced rivaroxaban in 3 of their patients who presented with VTE associated with NS with good progression [20]. However, no study has evaluated their indication in the context of NS and they are contraindicated in case of creatinine clearance below 30 mL/min. Their use is not currently recommended as first-line therapy. There is also no consensus on the duration of treatment. In a review of the literature from 1980 to 2012, Pincus and Hynicka [19] propose curative anti-coagulant therapy for a period of 6 months after diagnosis, a period considered to be the most at risk for VTE [11]. Prophylaxis in case of GEM could be started as soon as the albumin level is below 25 g/L [19]. In France, the Haute Autorité de santé recommends primary prophylaxis in the presence of VTE risk factors, including albumin levels < 20 g/L or <25 g/L in GEM [21].

The association of pulmonary embolism, renal vein and inferior vena cava

Table 1. Renal manifestations in hepatitis B.

- Extra-membranous glomerulopathy (EMG)
- Membranoproliferative glomerulonephritis (MPG)
- Glomerulonephritis with mesangial IgA deposits
- Minimal glomerular lesions (MGL)
- Periarteritis nodosa
- Lupus nephropathy
- Extra capillary glomerulonephritis
- Segmental and focal hyalinosis

thrombosis is rare, and this is a first case in our department. The histological lesion frequently found in hepatitis B, Extramembranous Glomerulonephritis (EMG), was not found on PBR in the absence of immunofluorescence examination. However, a Segmental and Focal Hyalinosis (SFH) was found on one glomerulus.

Extramembranous Glomerulonephritis (EMG) is the most frequent histological entity among the glomerular disorders described in the context of HBV infection [22] (see **Table 1**). Hepatitis B-related GEM occurs most frequently in children in endemic areas. In Taiwan, where 17% of the population is HBsAg-positive, 96% of children with GEM are HBsAg-positive [23]. HBe antigen appears to be the main culprit in glomerular immune deposition. In the majority of cases, the disease is discovered at the time of the appearance of edema, which reveals a nephrotic syndrome. Treatment with corticosteroids is contraindicated because of the risk of increased viral replication, but antiviral treatment may be beneficial for renal damage [24].

4. Conclusion

In the presence of any pulmonary embolism or deep vein thrombosis of idiopathic appearance, a nephrotic syndrome must be systematically sought. The two modes of diagnosis are proteinuria found on BU and hypoprotidemia on standard biology. Renal abnormalities are frequently observed in patients infected with the hepatitis B virus, but the link with the virus has not been established. Thrombosis is favored by the leakage of coagulation factors (notably antithrombin III) generated by the nephrotic syndrome.

Conflicts of Interest

No conflict of interest.

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