MODERN APPLIED MEDICAL RESEARCH
1(7): 06-09
ISSN:2582-9181
Corresponding author: IBRAHIM Hamat

Severe Thromboembolic Complication Revealing Nephrotic Syndrome due to Segmental and Focal Hyalinosis

IBRAHIM Hamat[1], SAH COULIBALY[2], Yaya KANE[3], MAHAMAT Youssouf[4], Haoua YOUSSOUF SAID[5], MAHAMAT Abderraman Guillaume[6], Zeinabou Maïga Moussa Tondi[7], SABI Kossi Akomola[8], Tall Ahmed Lemrabott[5], FOFANA ABOUBACAR Sidiki[2], ALI Hissein Mahamat[6], KA Elhadj FARY[5], NIANG Abdou[5], DIOUF Boucar[5]

[1]Hemodialysis and Nephrology Department, National Reference General Hospital / 130 N'Djamena, Chad
[2]Hemodialysis and Nephrology Department, Point G Hospital, BAMAKO, Mali
[3]UFR Santé, Université Assane Seck, Ziguinchor, Sénégal
[4]Internal Medicine Department, Renaissance Hospital of N'Djamena, Chad
[5]Nephrology Department, Aristide Le Dantec Hospital of Dakar, Senegal
[6]Hemodialysis and Nephrology Department, Renaissance Hospital of N'Djamena, Chad
[7]Hemodialysis and Nephrology Department, Faculty of Health Sciences, Abdou Moumouni University, Niamey, Niger
[8]Hemodialysis and Nephrology Department of Sylvanus Olympio University Hospital, Lomé, Togo

RESEARCH ARTICLE

Received: **10-07-2021**
Accepted: **18-07-2021**
Published: **20-07-2021**

Abstract: Adult nephrotic syndrome is a rare entity and its consequences can be multiple such as infections, hypercoagulability, high blood pressure, and malnutrition. We present a case of nephrotic syndrome in a 53-year-old woman with pulmonary embolism and thrombosis of the renal vein and of the inferior vena cava.

The main complaints were fever, right chest pain, and dyspnea. Blood pressure was 160/100 mmHg, temperature 37.8°C, pitting edema, facial swelling, and urine output of 350 mL/day. The investigations showed proteinuria at 4.56 g/day, hypoalbuminemia at 10.8 g/L, serum creatinine at 318 µmol/L. Hepatitis B was positive with a viral load of 58.2 particles/mL. The chest X-ray showed right-sided pneumonia and the CT scan showed pulmonary embolism associated with thrombosis of the right renal vein and inferior vena cava. The patient received Ceftazidime, Calciparine, and warfarin. Calciparine was discontinued when the INR was in the desired range while warfarin alone was continued for six months. A salt-free diet, fresh frozen plasma infusion, followed by Perindopril were administered. A renal biopsy was performed six months later and a segmental and focal hyalinosis of a single glomerulus was found, however, there was an absence of extramembranous glomerulonephritis.

In the setting of any pulmonary embolism or deep vein thrombosis of unknown etiology, the nephrotic syndrome should be systematically sought out.

Keywords: *Thromboembolic complication, Nephrotic Syndrome, Segmental and Focal Hyalinosis, N'Djamena, Chad.*

INTRODUCTION

Nephrotic syndrome in adults is a rare condition [1] with multiple consequences such as hypercoagulability, hypertension, malnutrition, and infections [2]. The association with venous thromboembolism (VTE) is certainly underestimated. In everyday practice, it is not recommended to systematically search for nephrotic syndrome in the setting of venous thromboembolitic disease.

We present a case of nephrotic syndrome revealed by the association of pulmonary embolism with thrombosis of the renal vein and inferior vena cava.

Clinical presentation

A 53-year-old woman with hypertension and obesity has been referred for a progressive onset of fever, right-sided chest pain, dyspnea on exertion, swelling of the face, edema and oliguria. The vital signs were as follows: blood pressure- 160/100 mmHg, temperature- 37.8°C, urine output of 350 mL/day and a heart rate of 98 bpm. There was bilateral, painless pitting edema of the lower limbs. On physical examination, we noted crackles on the right side of the chest and the presence of ascites. The remaining clinical examination was insignificant.

Lab test results revealed: serum creatinine at 318 µmol/l, blood urea at 14.95 mmol/l, hemoglobin at 11.3 g/dl; leukocytosis at 24400 /mm³, predominantly polynuclear neutrophils, and mild thrombocytosis at 458 000 /mm³. The PT and PTT were normal. The lipid profile noted mild hypercholesterolemia. The proteinuria level was of 4.56 g/day without hematuria. Electrophoresis of serum proteins revealed hypoalbuminemia at 10.8 g/l and hypoproteinemia at 40 g/l. Liver enzymes were normal. Proteins C and S and

1(7): 06-09
ISSN:2582-9181

antithrombin III have not been performed. The immunological assessment was normal. Hepatitis B was positive with a detectable viral load of 58.2 particles/ml, the FibroScan found cirrhosis (F4) of mild to moderate activity with a negative α-fetoprotein.

The chest X-ray revealed pneumonia (figure 1), CT scan showed pulmonary embolism (figure 2), and thrombosis of the right renal vein and inferior vena cava. Echocardiography and Doppler ultrasonography of the lower limbs were both normal.

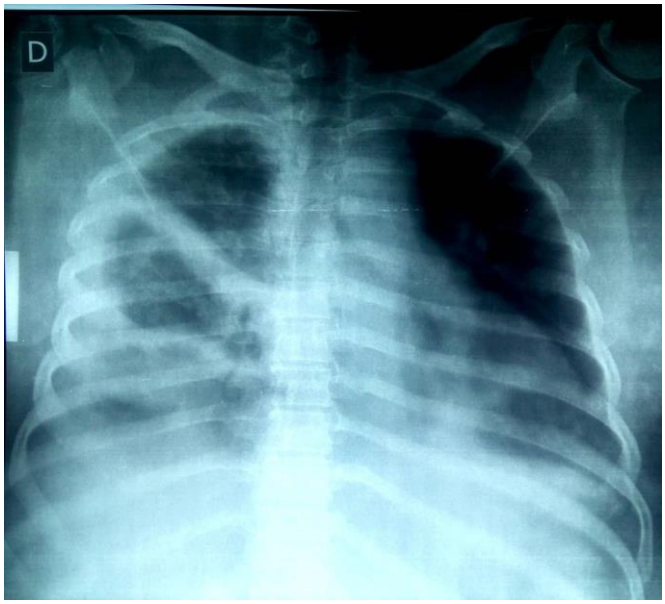

Figure 1: Chest X-ray showing consolidation of the right lung.

Extra-membranous glomerulopathy (EMG)
Membranoproliferative Glomerulonephritis (MPGN)
Glomerulonephritis with mesangial IgA deposits
Minimal Glomerular Lesions (LGM)
Polyarteritis nodosa
Lupus nephropathy
Extracapillary glomerulonephritis
Segmental and focal hyalinosis

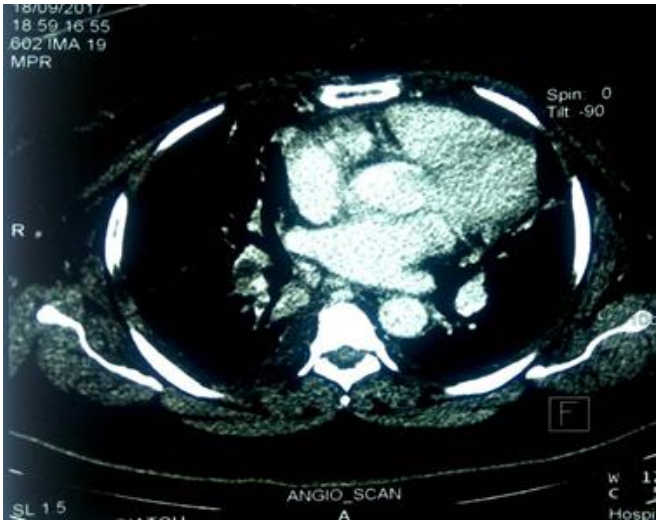

Figure 2: CT scan showing lobar and segmental pulmonary embolism of the right lower and left lower lobe.

The final diagnosis is an impure nephrotic syndrome with thromboembolic and infectious complications. Treatment consisted of Ceftazidime (1g every 12 hours for 10 days) and a curative anticoagulation treatment with Calciparin and Warfarin 4 mg daily, simultaneously. When the INR has reached the desired range (between 2 and 3) Calciparin was discontinued and warfarin was solely continued for six months. The patient received fresh frozen plasma, was put on Perindopril and a salt-free diet.

After 4 days of treatment, normal diuresis resumed, and marked regression of edematous state has been noted. The renal function became normal on day 10. We found a significant reduction in proteinuria after six months of treatment with Perindopril and proteinuria improved to 0.2 g/day. A renal biopsy was performed 6 months later and concluded to a segmental and focal hyalinosis of one glomerulus and the absence of extramembranous glomerulonephritis (EMG). Immunofluorescence could not be performed. The patient was still not on antiviral treatment for hepatitis B as recommended.

Discussion

Nephrotic syndrome and thrombosis risk factors

Coagulation disorders are among the classical risk factors for VTE [3]. Nephrotic syndrome is associated with a state of hypercoagulability by several mechanisms: platelet activation by increased thromboxane A2 activity, increase in Von Willebrand factor, platelet aggregation, hepatic synthesis of fibrinogen, factors V and VII procoagulants and lipoproteins preventing fibrinolysis [4, 5], glomerular leakage and hyperconsumption of antithrombin III and a decreased activity

1(7): 06-09
ISSN:2582-9181

of protein S. With the association of nephrotic syndrome, VTE is frequent and sometimes underestimated due to unspecific signs of VTE. In a cohort study of 512 patients with nephrotic syndrome, a systemic CT scan revealed DVT and PE in 180 patients; a prevalence of 35%. Of these, 83% (128 patients) were asymptomatic [6]. In another cohort study of 898 patients with EMG, VTE was found in 7.2% of patients. The independent risk factor of VTE was a decreased albumin. This risk was increased by a factor of 2.13 (95% CI :1.32 - 3.46), p = 0.002) at each reduction of 1 g/dl of albumin [7].

Etiological assessment of a nephrotic syndrome

If it is impossible to perform renal biopsy, the etiological assessment must be exhaustive so as to not disregard leukemia or other malignancies. Cancer is reported in 7.1% of 898 patients with EMG [8]. In another retrospective cohort study of 1958 patients with nephrotic syndrome, cancer was found in 5.2% of patients (lung, skin, blood), a risk multiplied by 2.5 to 1 year (95% CI: 1.4 - 3.84) and 3.5 to 2 years (95% CI: 1.37 - 5.35) compared to the general population [9]. Similarly, there is a strong association between thrombosis and active cancer particularly in cases of atypical thrombosis (intra-abdominal thrombosis including renal vein thrombosis, upper extremity thrombosis and bilateral thrombosis of the lower limbs) [10]. Thus, in the absence of consensus, Pani et al. proposed that in patients with nephrotic syndrome, a 3-step assessment with clinical examination, biological tests, and dedicated imaging (chest X-ray and abdominal ultrasound) should be done with a more invasive exploration if necessary [11]. There is no need for performing a CT scan or PET scan immediately [12, 13].

Nephrotic Syndrome and Venous Thromboembolic Disease

In the presence of a VTE, anticoagulant treatment is indicated as long as the nephrotic syndrome persists [14]. If there is no consensus on the choice of an appropriate anticoagulant drug, it is necessary to bear in mind the risk of reduced drug activity related to the glomerular leakage of antithrombin III and the decrease in the activity of the protein S. Warfarin has been the longest used, however, in the case of hypoalbuminemia, the therapeutic range is narrow. Similarly, low molecular weight heparin in nephrotic syndrome requires a dose adjustment in case of renal failure [14]. The advent of direct oral anticoagulants could be an alternative. Chaudesaygues et al. have successfully treated 3 of their patients suffering from nephrotic syndrome and VTE with Rivaroxaban [15]. However, no studies have evaluated their indication in the setting of nephrotic syndrome and they are contraindicated if the creatinine clearance is below 30 ml/min. Their use is not recommended for the time being as a first-line drug treatment. There is also no consensus on the duration of treatment. In a review of the literature from 1980 to 2012, Pincus and Hynicka [14] suggested a curative anticoagulant treatment for a period of 6 months after diagnosis, the most risky period for VTE [16]. Prophylaxis in the case of EMG could be started as soon as albumin drops below 25 g/l [14]. The Haute Autorité de la Santé in France, recommends primary prophylaxis in the presence of risk factors for VTE, including albumin of < 20 g/l or < 25 g/l in case of EMG [17].

The association of pulmonary embolism, thrombosis of the renal vein, and inferior vena cava is rare. It is the first case seen in our department. Extramembranous glomerulonephritis, the most common histological lesion on hepatitis B was not found in the renal biopsy, however, we cannot rule it out since immunofluorescence testing was not done.

Segmental and focal hyalinosis (SFH) was found on a single glomerulus. The patient was started on an antiproteinuric treatment by Perindopril.

Relationship between Hepatitis B and kidney lesions

Extramembranous glomerulonephritis is the most common histological entity in the case of a HBV infection [18] (see Table 1). This EMG occurs most often in children in endemic areas. In Taiwan, where 17% of the population is HBsAg-positive [19], 96% of children with EMG are HBsAg-positive [20]. HBe antigen appears to be the main cause of glomerular immune complex deposits [21]. In the majority of cases, the disease is discovered at the time of the appearance of edema that reveals nephrotic syndrome. Hypertension and renal failure are present in 1/3 of patients [22]. Corticosteroids were not introduced due to the risk of inducing viral replication. Hepatitis B antiviral therapy may be beneficial in preventing further kidney damage [23].

Conclusion

Any pulmonary embolism or deep vein thrombosis of unknown etiology should induce the search for nephrotic syndrome. The two tests for diagnosis are proteinuria and albuminemia. Renal abnormalities are frequently observed in patients infected with hepatitis B virus but the link with the virus is not yet established. Protein leakage and therefore, coagulation factors, mainly antithrombin III promote thrombosis.

References

[1] Llach F. Thromboembolic complications in the nephrotic syndrome. Coagulation abnormalities, renal vein thrombosis and other conditions. Postgrad Med 1984; 76:111—4, 116-8, 121-3.
[2] Crew RJ, Radhakrishnan J, Appel G. Complications of the nephrotic syndrome and their treatment. Clin Nephrol 2004;62:245—59.

1(7): 06-09
ISSN:2582-9181

[3] Heit JA, Michael O'Fallon W, Petterson TM. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med 2002;162:1245—8

[4] Zwaginga JJ, Koomans HA, Sixma JJ, Rabelink TJ. Thrombus formation and platelet-vessel wall interaction in the nephrotic syndrome under flow conditions. J Clin Invest 1994; 93:204—11.

[5] Mirrakhimov AE, Ali AM, Barbaryan A, Prueksaritanond S, Hussain N. Primary nephrotic syndrome in adults as a risk factor for pulmonary embolism: an up-to-date review of the literature. Int J Nephrol 2014; 9:760—916.

[6] Zhang LJ, Zhang Z, Li SJ, Meinel FG, Nance JW, Sheng Zhou C, et al. Pulmonary embolism and renal vein thrombosis in patients with nephrotic syndrome: prospective evaluation of prevalence and risk factors with CT. Radiology 2014; 273:897—906.

[7] Lionaki S, Derebail VK, Hogan SL, Barbour S, Lee T, Hladunewich M, et al. Venous thromboembolism in patients with membranous nephropathy. Clin J Am Soc Nephrol 2012; 7:43—51.

[8] LionakiS, Derebail VK, Hogan SL, Barbour S, LeeT, Hladunewich M, etal.Venous thromboembolism in patients with membranous nephropathy.ClinJAmSocNephrol2012;7:43—51.

[9] Birkeland SA, Storm HH. Glomerulonephritis and malignancy: a population-basedanalysis.Kidney Int 2003;63:716—21.

[10] Tafur AJ, Kalsi H, Wysokinski WE, Mc Bane RD, Ashrani AA, Marks R, et al. The association of active cancer with venous thromboembolism location: a population based study.Mayo Clin Proc 2011;86:25—30.

[11] Pani A, Porta C, CosmaiL, Melis P,Floris M, Piras D,et al. Glomerular diseases and cancer: evaluation of under lying malignancy. J Nephrol2015:10, 1007/s40620-015-0234-9.

[12] Carrier M, Lazo Langner A, Shivakumar S, Tagalakis V, Zarychanski R, Solymoss S, et al. Screening for occult cancer in un provoked venous thromboembolism. N Engl J Med 2015;373:697—704.

[13] Robin P,Le Roux PY, Planquette B, Accassat S, Roy PM, Couturaud F, et al. Limited screening with versus without 18 F-fluorodeoxyglucose PET/CT for occult malignancy in unprovoked venous thromboembolism: an open-label randomised controlled trial.Lancet Oncol2016;17:193—9.

[14] Pincus KJ, Hynicka LM. Prophylaxis of thromboembolic events in patients with nephrotic syndrome. Ann Pharmacother 2013 ;47:725—34.

[15] Chaudesaygues E, Grasse M, Marchand L, Villar E, Aupetit JF. Embolie pulmonaire révélant un syndrome néphrotique : à propos de quatre cas. Ann Cardiol Angeiol 2014;63: 385—8.

[16] Mahmoodi BK, Ki ten Kate M, Waanders F, Veeger NJGM, Brou- wer JLP, Vogt L, et al. High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome. Results from a large retrospective cohort study. Circulation 2008;117:224—30.

[17] Centre de référence du syndrome néphrotique de l'enfant et de l'adulte, protocole national de diagnostic et de soins; 2014.

[18] Bhimma R & Coovadia HM. Hepatitis B virus-associated nephropathy. Am J Nephrol 2004; 24(2): 198-211;

[19] Chen CH et al. J Formos Med Assoc 2007; 106(2): 148-55 ;

[20] Hsu HC et al. Kidney Int 1989; 36: 1103-1107;

[21] Mercadal L. Glomérulopathie extramembraneuse. EMC (Elsevier Masson SAS, Paris), Néphrologie, 18-036-D-10, 2004;

[22] Meyrier A et coll. Maladies rénales de l'adulte. Ellipses, 1993;

[23] Tang S et al. Kidney Int 2006; 70(4): 818;