Case Report

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Massive Pulmonary Embolism Dominating Initial Presentation of Nephrotic Syndrome- A Case Report

Internal Medicine Section

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ABSTRACT

Hypercoagulability is a well-recognised feature of Nephrotic Syndrome (NS) and may manifest clinically in the form of Renal Vein Thrombosis (RVT), Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE); these may uncommonly be among the presenting features of the syndrome. Prompt recognition and management requires that patients with NS should be followed with a high index of suspicion for thromboembolism. Here, the authors report a case of 35-year-old male patient who, while under evaluation for proteinuria, presented with massive PE. He was eventually diagnosed with primary Membranous Nephropathy (MN); a cause of NS with the highest associated risk of thromboembolism. The patient was managed with mechanical ventilation, anticoagulation and supportive care. He also received Rituximab during hospital stay. He was discharged in stable condition on apixaban and advised close follow-up.

Keywords: Hypercoagulability, Membranous nephropathy, Proteinuria

CASE REPORT

A 35-year-old male patient presented with a two weeks history of swelling of both lower limbs which was gradual in onset and more noticeable in evening hours after a day's work. There were no complaints of breathlessness, cough, chest discomfort, fever, abdominal pain and haematuria. The patient was a smoker with no history of ethanol abuse. He had no known co-morbidity, no significant medical history, family history and other than intake of Torsemide tablets for last 3 days, no significant drug history.

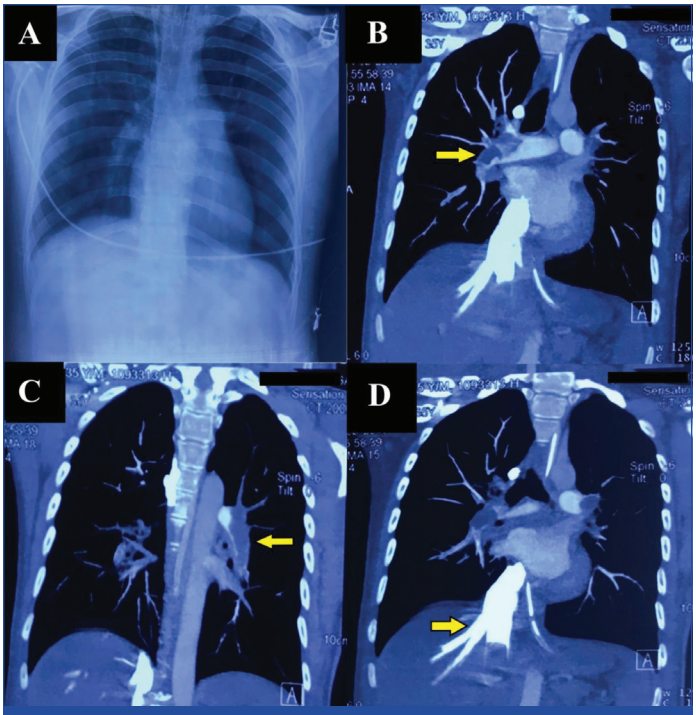
Clinical examination was unremarkable, except for presence of bilateral symmetrical below knee pitting oedema. Investigations revealed normal blood counts, normal kidney function, normal serum bilirubin, normal liver enzymes (alanine aminotransferase and aspartate aminotransferase), normal electrocardiogram and normal chest X-ray. Urine analysis showed 20-25 red blood cells per high power field and a strongly positive dipstick test for urinary protein. The patient was admitted for evaluation, with a potential possibility of a renal biopsy. However, hours after admission, he developed acute onset chest discomfort and severe breathlessness. He was very restless and nearly gasping for breath, with a respiratory rate of 32 breaths per minute, a feeble pulse with rate of 136 beats per minute, blood pressure of 80/44 mmHg and oxygen saturation of 68% on room air which increased to 84% on oxygen supplementation via face mask. On auscultation, there was bilateral air entry with normal vesicular breath sounds, normal heart sounds and increased heart rate. Bedside electrocardiogram showed sinus tachycardia, bedside chest radiograph was grossly normal and Troponin-T card test was negative.

The patient was administered intravenous fluid bolus and started on pressor support (Noradrenaline). In view of respiratory failure and worsening sensorium, patient was intubated and shifted to intensive care unit, where he received mechanical ventilation and supportive care. Meanwhile, investigation reports on day 2 of admission [Table/Fig-1] were noticeable for nephrotic range proteinuria, hypoalbuminaemia, hypercholesterolaemia, hypertriglyceridaemia and raised D-Dimer levels. So, an impression of NS complicated by PE was made. Bedside ultrasonography did not reveal any Deep Vein Thrombosis (DVT) or Renal Vein Thrombosis (RVT). The patient scored just a "moderate risk" on wells' score for PE [1]. The difficulties and risks associated with shifting a sick ventilated haemodynamically unstable patient to Computed Tomography (CT) room and acute kidney injury which resulted from shock precluded a CT pulmonary angiography. Hence, the patient was not thrombolysed but started on parenteral anticoagulation with unfractionated heparin. Over next few days, patient's condition improved. Pressor support was tapered and then eventually stopped on third day. He was gradually weaned and then taken off mechanical ventilation on fourth day of admission. Oxygen requirement decreased and acute kidney injury resolved.

Laboratory reports		Value	Reference range
24 hour urinary protein		4.5 g	<150 mg
Serum albumin (lowest reading)		1.78 g/dL	3.5-5.5 g/dL
Lipid profile	Total cholesterol	308 mg/dL	<200 mg/dL
	LDL cholesterol	253 mg/dL	<130 md/dL
	HDL cholesterol	43 mg/dL	>40 mg/dL
	Triglycerides	307 mg/dL	<150 mg/dL
D-dimer		1991.41 ng/mL	<500 ng/mL
Phospholipase A2 Receptor Antibody (Quantitative EIA*)		128.01 RU/mL	<14 RU/mL
HBsAg† (EIA*) Anti-HCV‡ Antibodies (EIA*)		Negative	----------
Anti-PR3§ Antibody (EIA*)		<0.4 U/mL (Negative)	-------
Anti-MPO‖ Antibody (EIA*)		<3.1 U/mL (Negative)	--------
ANA¶ (EIA*)		Negative	-------
Protein C		56 IU/dL	70-140 IU/dL
Protein S		38 IU/dL	74-146 IU/dL
Anti-thrombin III (activity)		49 %	83-128 %
Factor V Leiden		Negative	----------
Prothrombin gene mutation		Negative	----------
APS** profile		Unremarkable	-------
Serum creatinine	On admission	0.62 mg/dL	0.5-1.5 mg/dL
	After massive PE	2.59 mg/dL	-------
	On discharge	0.86 mg/dL	-------

[Table/Fig-1]: Details of investigation reports on second day of admission.
*EIA: enzyme immunoassay; †HBsAg: hepatitis B surface antigen; ‡HCV: hepatitis C virus; §PR3: Proteinase 3; ‖MPO: Myeloperoxidase; ¶ANA: Antinuclear antibodies; **APS: Antiphospholipid syndrome; LDL: Low density lipoprotein; HDL: High density lipoprotein

On fifth day of admission, the now-stable patient with normal kidney function underwent CT pulmonary angiography which revealed filling defects in both right and left pulmonary arteries, extending into lobar and segmental branches of bilateral upper and lower lobes, right middle lobe and lingular lobe, suggestive of pulmonary thromboembolism. No renal vein or inferior vena cava thrombosis was noticed. A note was also made of reflux of contrast into inferior vena cava and hepatic vein, suggestive of acute right heart strain [Table/Fig-2].



[Table/Fig-2]: Chest radiograph (A) and CT pulmonary angiography coronal Maximum Intensity Projection (MIP) images (B, C and D).
B: filling defect (arrow) in right pulmonary artery
C: filling defect (arrow) in left pulmonary artery extending into segmental branches
D: filling defects in both pulmonary arteries with reflux of contrast into inferior vena cava and hepatic veins (arrow)

Further investigational work-up revealed high titres of phospholipase A2 receptor antibody, and the patient was diagnosed with primary Membranous Nephropathy (MN), obviating the need for a biopsy. With investigations revealing no other apparent cause [Table/Fig-1], thromboembolism was attributed to the hypercoagulability which is associated with NS, more so in cases due to MN. The patient was shifted back to nephrology ward where he received first dose of Rituximab uneventfully and was subsequently discharged in stable condition on oral anticoagulation with apixaban. On follow-up visit for next dose of rituximab, patient was doing well, with no symptoms or signs of infection or bleeding. Kidney function was normal and proteinuria was showing decline (2.8 g per 24 hours).

DISCUSSION

The NS is known to be associated with an increased risk of thromboembolism [2]. The severity of risk is related to the underlying cause of NS, being highest in MN, and to the degree of hypoalbuminaemia [2-4]. The underlying mechanism of increased thromboembolic risk is not well understood. It is thought to be related to urinary losses and hence decreased blood levels of protein C, protein S, antithrombin-III and plasminogen. Hypoalbuminaemia secondary to urinary losses of albumin is also believed to cause an increased hepatic synthesis of fibrinogen. Albumin interacts with arachidonic acid at molecular level and hypoalbuminaemia causes increased conversion of arachidonic acid to thromboxane A2 and thus platelet hyper-reactivity. Other contributory factors include inhibition of plasminogen activation and the presence of high-molecular-weight fibrinogen moieties in the circulation [2,5,6]. Patients may also harbor predisposing factors in their genetic background that make them more prone to develop thromboembolism in NS [7].

The reasons why thromboembolic risk is higher in MN than in other causes of NS are not very clear. Huang MJ et al., conducted analysis of thrombo-elastographic records of patients with MN and minimal change disease. The study revealed that in MN, hypercoagulability involves acceleration of thrombotic processes in entirety, whereas in minimal change disease, coagulation factors preceding the initial fibrin platelet interaction are not fully activated [8].

Thromboembolic events may be asymptomatic or manifest during the course of the disease with presentations ranging from flank pain with haematuria as in RVT, swollen lower limb as in DVT and breathlessness with chest discomfort as in case of PE. Prophylactic anticoagulation in NS remains a gray zone, with few studies supporting its use in cases with MN [9,10].

Uncommonly, a thromboembolic event itself may constitute the chief complaint in the presentation of NS [11]. There have been instances where NS has primarily presented with submassive PE, however a life-threatening massive PE dominating the initial presentation of NS is exceedingly rare. Periwal P et al., reported a 36-year-old male presenting with left-sided chest discomfort who was initially diagnosed and managed as pneumonia [12]. Further evaluation, prompted by lack of improvement, revealed bilateral PE with left-sided pulmonary infarct. Work-up for any underlying prothrombotic state was unremarkable. On follow-up, the patient had noticeable clinical and laboratory features of NS, with renal biopsy consistent with a picture of MN. Jeele MOO et al., reported a 19-year-old female presenting with 3 days' history of chest pain and dyspnoea [13]. Her clinical and laboratory findings were suggestive of NS. CT angiography detected thrombi in both pulmonary arteries and inferior vena cava. Evaluation for underlying predisposing factor for thrombophilia (other than NS) was unrevealing. In both of these cases, the patients remained haemodynamically stable and PE was not massive.

CONCLUSION(S)

Patients with NS should be closely watched and followed for development of thromboembolism and patients who present with thromboembolism not otherwise explained, should be screened for proteinuria.

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