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UNPROVOKED PULMONARY EMBOLISM WITH BILATERAL DEEP VEIN THROMBOSIS REVEALING OCCULT NEPHROTIC SYNDROME DUE TO SERONEGATIVE MEMBRANOUS NEPHROPATHY

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ABSTRACT

Introduction: Nephrotic syndrome is a well-recognised risk factor for venous thromboembolism (VTE) but may present without oedema, hyperlipidaemia or impaired kidney function, delaying diagnosis.

Case description: A 73-year-old man presented with fatigue, exertional dyspnoea and weight loss over a period of three months. Computed tomography pulmonary angiography showed bilateral central pulmonary emboli. Cardiac biomarkers were elevated with preserved renal function. Therapeutic anticoagulation was initiated. To assess thrombus extent and guide management, lower limb compression ultrasonography was performed and revealed bilateral popliteal deep vein thrombosis. Urinalysis demonstrated nephrotic-range proteinuria (8 g/day) with hypoalbuminaemia and microscopic haematuria. Evaluation for other secondary causes of thrombembolism was unremarkable. Anti-phospholipase A2 receptor and thrombospondin type-1 domain-containing 7A antibodies were negative. Corticosteroid treatment was commenced. A transjugular kidney biopsy confirmed membranous nephropathy, and rituximab was administered for long-term immunosuppressive management.

Discussion: This case illustrates that nephrotic syndrome can be clinically occult and should be considered in unprovoked or extensive VTE, particularly when bilateral deep vein thrombosis is present.

Conclusion: Urine dipstick testing, and serum albumin should be considered early in the work-up of unexplained VTE, even in the absence of oedema or reduced estimated glomerular filtration rate.

KEYWORDS

Pulmonary embolism, membranous nephropathy, nephrotic syndrome, venous thrombembolism, proteinuria

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LEARNING POINTS

- Occult nephrotic syndrome can present with extensive or unprovoked venous thromboembolism despite normal estimated glomerular filtration rate and absent oedema - include urine dipstick testing and serum albumin early in the work-up.
- Lower limb compression ultrasonography can help define thrombus extent and guide management in pulmonary embolism. Bilateral deep vein thrombosis is uncommon and should prompt an expanded search for secondary causes.
- Negative anti-phospholipase A2 receptor and thrombospondin type-1 domain-containing 7A serology does not exclude membranous nephropathy. Kidney biopsy should be pursued when nephrotic-range proteinuria and hypoalbuminaemia are present.

INTRODUCTION

Pulmonary embolism (PE) is a potentially fatal condition and requires a structured assessment of thrombus burden, hemodynamic impact and underlying risk factors. Nephrotic syndrome is a well-recognised but often overlooked prothrombotic state, particularly in membranous nephropathy, driven by urinary loss of natural anticoagulants and a shift towards procoagulant proteins. Classically, nephrotic syndrome presents with oedema, weight gain and hyperlipidaemia; however, it may also manifest subtly, with preserved renal function and only nonspecific symptoms such as fatigue or exertional dyspnoea, leading to delayed recognition.

Lower limb compression ultrasonography is not routinely recommended in every patient with PE[1], but it can help define thrombus extent and guide management, including decisions regarding compression therapy, duration of anticoagulation and the need for specialist input. Bilateral deep vein thrombosis (DVT) is uncommon and should raise suspicion for secondary causes, including malignancy, thrombophilia and systemic diseases such as glomerular disorders[2].

We report a case of extensive PE with bilateral popliteal DVT in which nephrotic-range proteinuria was detected only after targeted reassessment, and seronegative membranous nephropathy was confirmed on kidney biopsy. This case highlights the value of early urinalysis and serum albumin measurement in patients with unexplained or extensive VTE, even in the absence of oedema or impaired estimated glomerular filtration rate.

CASE DESCRIPTION

A 73-year-old man was referred to the emergency department by his general practitioner because of progressive fatigue, exertional dyspnoea and an unintentional 6 kg weight loss over 3 months. His medical history included arterial hypertension, hyperlipidaemia and coronary artery disease. Regular medications were acetylsalicylic acid, lisinopril and a fixed-dose combination of ezetimibe/rosuvastatin.

On admission, vital signs were stable. Cardiac and pulmonary auscultation were unremarkable, and no peripheral oedema was present. There were no clinical signs of DVT in either leg. Electrocardiography showed left axis deviation, a discordant T-wave-inversion in V3 and notching in leads III, V1 and V2. Laboratory testing revealed an elevated D-dimer and increased cardiac troponin. Computed tomography (CT) pulmonary angiography and dual-energy CT imaging demonstrated

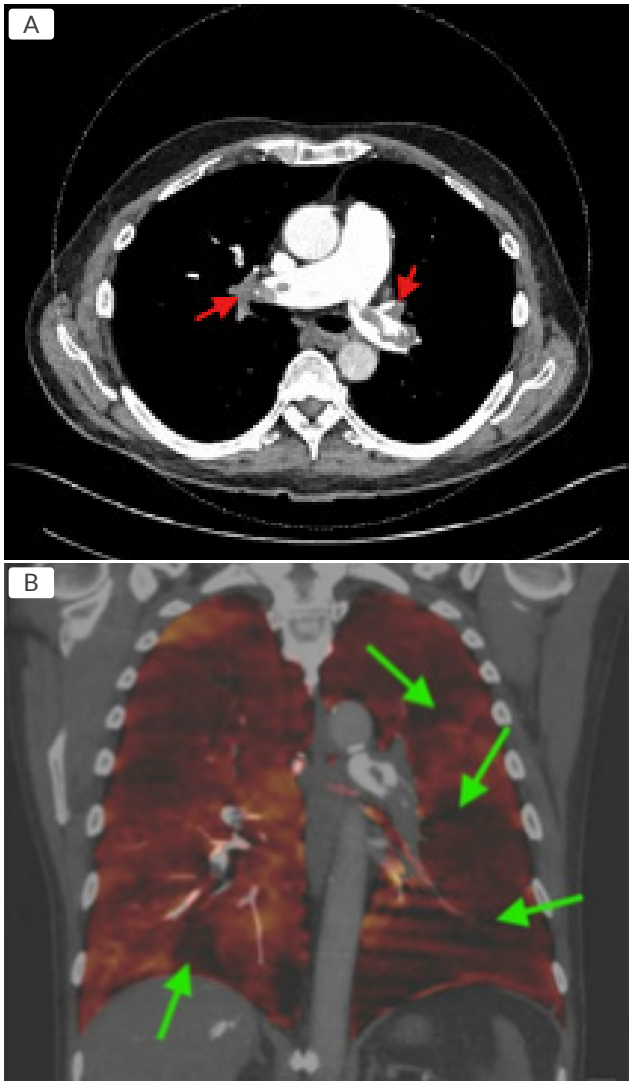


Figure 1. A) Computed tomography angiography of the chest demonstrating bilateral central pulmonary embolism, indicated by red arrows; B) Dual-energy computed tomography imaging of the chest demonstrating pulmonary perfusion defects, marked by green arrows.

central and paracentral bilateral pulmonary emboli *(Fig. 1)*. Transthoracic echocardiography showed elevated pulmonary artery pressures with preserved right ventricular function. The Pulmonary Embolism Severity Index was 83 points, consistent with intermediate-low risk according to European Society of Cardiology guidance. Therapeutic anticoagulation with heparin was initiated and the patient was admitted for monitoring. Given haemodynamic stability and a favourable early clinical course, reperfusion therapy was not pursued.

To assess thrombus extent and inform management, bilateral lower limb compression ultrasonography was performed and revealed popliteal DVT in both legs. The patient denied recent surgery, trauma, prolonged immobilisation or long-distance travel. In view of an apparently unprovoked, extensive thromboembolic presentation and the reported weight loss, an evaluation for secondary causes was initiated. The initial CT scan showed no evidence of thoracic malignancy; abdominal ultrasonography and upper and lower endoscopy were unremarkable. The patient's family physician had previously detected proteinuria during a routine check-up and had arranged a non-urgent nephrology referral. In light of bilateral DVT, a targeted reassessment was undertaken. The patient reported new-onset foamy urine concurrent with his symptoms, which he had not mentioned previously. Urinalysis confirmed nephrotic-range proteinuria (8 g/day) with albuminuria (6 g/day) and microscopic haematuria but showed no dysmorphic red blood cells. Kidney function was preserved (estimated glomerular filtration rate 80 ml/min/1.73 m^2). Serum testing showed hypoalbuminaemia and hypoproteinaemia, while lipid levels were within the normal range, likely influenced by ongoing lipid-lowering therapy. Serum and urine protein electrophoresis showed no monoclonal component.

Serological testing for anti-phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A) antibodies was negative. Further work-up for secondary causes of glomerular disease, including viral hepatitis serologies and autoimmune testing (antinuclear antibodies, antineutrophil cytoplasmic antibodies, myeloperoxidase and proteinase 3 antibodies, anti-glomerular basement membrane antibodies and anti–double-stranded deoxyribonucleic acid antibodies), revealed no abnormalities.

Therapy with intravenous methylprednisolone (500 mg/day) was started, together with supportive measures including continuation of renin–angiotensin system blockade and initiation of a sodium–glucose co-transporter 2 inhibitor; proteinuria decreased promptly. As therapeutic anticoagulation was ongoing, a transjugular kidney biopsy was performed to minimise bleeding risk and confirmed membranous nephropathy. Rituximab was commenced for longer-term immunosuppressive management. The patient was discharged in stable condition with close nephrology follow-up.

DISCUSSION

Thromboembolic events are a well-recognised complication of nephrotic syndrome and occur particularly frequently in membranous nephropathy. The prothrombotic milieu is multifactorial, involving urinary loss of endogenous anticoagulants (e.g. antithrombin), increased hepatic synthesis of procoagulant proteins (e.g. fibrinogen and factors V and VIII), platelet hyperreactivity and endothelial dysfunction[3]. The risk correlates strongly with the severity of proteinuria and, in particular, with hypoalbuminaemia. Many events occur early after onset of nephrotic syndrome[4]. The educational value of this case lies not in the association between nephrotic syndrome and VTE itself, but in the clinically subtle presentation. Despite extensive pulmonary embolism and bilateral DVT, the patient had preserved renal function and lacked typical features such as oedema and overt hyperlipidaemia. In such situations, nephrotic syndrome may be missed unless urinalysis and serum albumin are actively sought. Notably, lipid-lowering therapy may blunt hyperlipidaemia and further reduce clinical suspicion, while symptoms such as fatigue and foamy urine can be overlooked or not volunteered.

Lower limb compression ultrasonography is not mandatory in all patients with pulmonary embolism; however, it can be valuable to define thrombus extent and guide management, including compression measures, follow-up strategy and, in selected cases, consideration of specialist input. The presence of bilateral DVT is uncommon and should prompt clinicians to consider secondary causes and a broader diagnostic evaluation. In the present case, bilateral popliteal thromboses triggered a reassessment that led to detection of nephrotic-range proteinuria and hypoalbuminaemia.

Anti-PLA2R and anti-THSD7A antibodies are highly specific markers for primary membranous nephropathy, but a relevant proportion of patients remain seronegative[5]. Therefore, negative serology should not delay kidney biopsy when clinical suspicion persists[6]. Beyond PLA2R and THSD7A, additional antigens associated with membranous nephropathy have been described; these were not assessed in this case, which represents a limitation. Nevertheless, biopsy confirmed membranous nephropathy and enabled initiation of targeted immunosuppressive therapy. Current treatment options include supportive measures to reduce proteinuria and protect kidney function, alongside immunomodulatory therapy such as rituximab in appropriate risk constellations[7].

From a practical standpoint, this case supports a low threshold for performing a urine dipstick test and measuring serum albumin in patients presenting with unexplained or extensive venous thromboembolism, particularly when thrombus burden is high or bilateral DVT is present. Early recognition of nephrotic syndrome is clinically relevant because it influences both immunosuppressive management and decisions regarding intensity and duration of anticoagulation, while balancing bleeding risk.

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