CASE REPORT

Cavernous sinus thrombosis in a patient with nephrotic syndrome

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Introduction

Nephrotic syndrome (NS) is a glomerular disease characterized by altered permeability of the glomerular capillary wall to macromolecules. This results in heavy proteinuria, hypoalbuminemia, hypercholesterolemia, lipiduria, and edema.

This clinical and laboratory syndrome is a life-threatening disease, and is associated with several complications, not only related to the disease itself, but also related to its treatment.

Disease-associated complications include acute kidney injury, chronic kidney disease, cardiovascular disease, negative nitrogen balance, infections, endocrine disorders, and hypercoagulability.

Venous and arterial thromboembolism is a significant complication of NS, occurring in approximately 27% of the patients [1]. This represents an 800% increase relatively to the general population [1, 2]. The pathophysiology of thrombogenesis in NS is not fully understood, and seems to be multifactorial [3], depending on the etiology (particularly frequent in membranous nephropathy), serum albumin level (most likely when <2 g/dl), previous episodes, and genetic predisposition [1, 2, 4].

These patients are at an increased risk of deep vein thrombosis (DVT), renal vein thrombosis (RVT), and pulmonary embolism (PE). Cerebral venous thrombosis (CVT) is infrequent, being primarily reported in children [1, 2].

The authors report a case of a 45-year-old white female patient admitted with NS and multiple venous thrombosis.

Case report

A 45-year-old Caucasian Portuguese woman, with no significant medical history and under no medication, presented with face and inferior extremities swelling, and pain in her right calf. She had started amoxicillin and NSAIDs a few days before, as she was submitted to a dental treatment. She was diagnosed with DVT and admitted to the hospital, where she stopped the previous medication and initiated anticoagulation with low-molecular-weight heparin. Even so, she developed sudden shortness of breath, and after computed tomography angiography, PE was diagnosed (Fig. 1). She later on complained of persistent nausea and headache, and an MRI allowed for the diagnosis of cavernous sinus thrombosis (CST) (Fig. 2).

The laboratory tests revealed the presence of a nephrotic syndrome (total protein 4.0 g/dl, serum albumin 1.4 g/dl, 24-h proteinuria quantification 13.8 g/24 h, total cholesterol 399 mg/dl, and triglycerides 347 mg/dl), with acute kidney injury (urea 184 mg/dl and serum creatinine 4.4 mg/dl). Apart from a prolonged aPTT and a reduced anti-thrombin III, the search for thrombophilic, autoimmunity, thyroid, and hepatic disorders was unremarkable (Table 1).

Renal biopsy was initially delayed, since the patient required anticoagulation. She initiated treatment with prednisolone (oral 1 mg/kg, once daily) and cyclophosphamide (oral 1.5 mg/kg, once daily), with significant clinical and analytical response. After 15 days of therapy, 24-h proteinuria decreased from 13.8 to 0.7 g/24 h. Following renal function recovery and recanalization of the

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Fig. 1 Computed tomographic pulmonary angiography, showing segmentar and subsegmentar bilateral pulmonary embolism. *R* right, *A* anterior

cavernous sinus, anticoagulation was temporarily interrupted, and a renal biopsy was performed. Despite the relatively short period of anticoagulation suspension (72 h), the patient suffered a suprahepatic veins' thrombosis.

Renal biopsy diagnosed minimal change disease. Cyclophosphamide was suspended and prednisolone maintained in full dose for 8 weeks. After clinical resolution, the patient was discharged with oral anticoagulation (with International Normalized Ratio target of 2–3), tapered prednisolone, a statin, and a low-dose ACE inhibitor.

The patient achieved a complete remission of NS and steroids were stopped after 9 months. Anticoagulation was stopped after 20 months of therapy. After 3 years of follow-up, no relapse of the disease was observed, but a borderline positive lupus anticoagulant was discovered. The 12-week later repetition remained borderline. Five

years have passed since the initial hospitalization. During this period, the patient has been relapse-free, and no further thromboembolic events have occurred.

Discussion

This is a case of a severe form of NS diagnosed after several thrombotic events, probably triggered by NSAIDs' use. Treatment with prednisolone and cyclophosphamide was started on the grounds that it is the first line therapy for membranous nephropathy and is second line therapy in minimal change disease and in segmental focal glomerulosclerosis, in cortico-dependent patients. The renal biopsy revealed minimal change disease, and cyclophosphamide was suspended. At this time, the patient had a proteinuria of 0.7 g/24 h and serum albumin 4 g/dl. Even so, the patient experienced a new thrombotic event due to a 72 h anticoagulation suspension.

Hypercoagulation is the consequence of an imbalance between the clotting activator system and the inhibitor system. The urinary leakage of coagulation regulatory proteins, such as anti-thrombin III and plasminogen, is thought to be the main thrombophilic mechanism in the nephrotic patient, but the increased platelet activation and elevated fibrinogen and factors V and VIII also seem to have a role. These aspects are partially counterbalanced by the increased rate of liver-produced hemostatic proteins, but the balance is nonetheless shifted towards a hypercoagulability state [1, 2, 5–7].

There are other factors that increase the risk of thrombosis, specifically advanced age and the severity of hypoalbuminemia [1, 2]. Indeed, severe hypoalbuminemia appears to be the most significant biochemical risk factor for thrombosis [8].

Fig. 2 Cranial MRI, showing cavernous sinus thrombosis. *H* superior, *R* right, *L* left, *A* anterior

Table 1 Investigation blood tests at presentation

	Value	Reference range		Value	Reference range
Hemoglobin (g/dl)	14.9	12–16	Anti-cardiolipin: IgG/IgM (RU/ml)	8.3/4.2	<12/<12
Platelets ($\times 10^9/l$)	283	150–400	Anti- β_2 glycoprotein IgG/IgM (RU/ml)	2.1/3.5	<20/<20
Prothrombin time (s)	11.1	9.5–13	Lupus anticoagulant ratio	1.06	0.8–1.2
INR	0.9	0.9–1.2	ANA	Negative	
aPTT (s)	42.7	24.5–35.2	C3 (mg/dl)	135	75–140
Fibrinogen (mg/dl)	369	175–470	C4 (mg/dl)	36.9	10–34
Factor V	115%	50–150	ANCA MPO/PR3 (U/ml)	<2/<2	<20/<20
Anti-thrombin III	70%	80–120	AST (SGOT) (U/l)	29	14–36
Protein C	143%	70–140	GGT (U/l)	63	12–43
Protein S	69.3%	53–109	LDH (U/l)	558	313–618
D-dimer (ng/ml)	415	<300	VDRL test	Negative	–
Homocysteine ($\mu\text{mol/l}$)	18.03	<15	HIV	Negative	–
TSH ($\mu\text{UI/ml}$)	0.83	0.4–4	HCV	Negative	–
T4L (ng/dl)	1.3	0.8–1.9	HBV	Negative	–

The thromboembolic events are more likely to occur within the first few months of disease and during relapses. While still under debate, it is thought that the high loss of coagulation factors and acute intravascular volume depletion during these stages of the disease are responsible for that [1, 2, 8]. DVT of the extremities is the most frequent thromboembolic event in patients with nephrotic syndrome, with RVP also being notoriously frequent [1, 2]. CVT is a rare complication of nephrotic syndrome, and while uncommon, with an overall incidence of <1.5 per 100,000 annually, it has increasingly been reported, probably reflecting underdiagnosis [9]. Most cases are located in the superior sagittal sinus, while deep cerebral venous system thrombosis accounts for approximately 16% of cases [10]. Female-gender-related risk factors (pregnancy, puerperium and oral contraceptives) explain the 3:1 female-to-male ratio in CVT. Women also have a better prognosis [9]. While there have been reports of CVT in nephrotic syndrome [11, 12], cavernous sinus thrombosis is nearly always caused by an infection of the paranasal sinuses, the orbit, or the face [13]. This is the first report of a nephrotic syndrome-related cavernous sinus thrombosis, but it is difficult to exclude the possibility that the dental treatment at the beginning of the case was partly responsible for the subsequent cavernous sinus thrombosis.

Clinical presentation of CVT can be variable, subtle, and non-specific, causing delays in diagnosis. Headache is the most frequent symptom, being present in 89% of patients, and it is usually the first and sometimes only symptom of CVT [9, 10]. Nevertheless, most patients present with rapid neurological deterioration [10]. CST characteristically manifests with a variable dysfunction of cranial nerves passing through it (nerves III, IV, V, and VI). All patients with nephrotic syndrome with neurological complains

should undergo neuroimaging. The most sensitive method to diagnose CVT is MRI venography. Aside from neuroimaging, there is no specific laboratory test for CVT [9, 10].

There are no randomized trials to guide optimal prophylaxis or therapy of hypercoagulability in NS [3]. In the non-complicated NS, prophylactic anticoagulation is not recommended, unless serum albumin is below 2.0 g/dl (or below 2.8 g/dl in membranous nephropathy) [3]. For those with thromboembolic events, anticoagulation is indicated, with some authors suggesting that anti-thrombin III concentrate or fresh frozen plasma, in addition to heparin, might be needed to control the thromboembolic state [14, 15]. The duration of the therapy is still controversial, but a total of 3–6 months is recommended, and should be maintained until the provoking illness has resolved or is in remission [1, 3, 4]. Thrombolysis is reserved for those with the most severe thromboembolic disease [1].

In this case, the patient maintained warfarin during 20 months, with good result. While the initial scan was negative for thrombophilia, it was repeated, given the number and severity of thrombotic events. A twice positive borderline lupus anticoagulant test prompts us to think that there could be another hidden disease, such as antiphospholipid syndrome (APS).

It's accepted that multiple risk factors can interact to exceed the thrombotic threshold and thrombosis occurs when a transient risk factor enters the play. In the current case, the nephrotic syndrome was the triggering factor. It is known that borderline positive antiphospholipid test result confers thrombosis risk [16], so the thrombotic threshold theory seems to apply. The initial test was negative probably due to the effect of anticoagulation and urinary loss

due to the nephrotic syndrome [17]. Duration of treatment is dictated by the presence of a definite APS—whether this low titer positive result allows for that diagnosis is unclear. Furthermore, the presence of a transient precipitating factor advises for a limited duration anticoagulant therapy [18]. As stated previously, most recurrences occur within the first 6 months of cessation of anticoagulation and the recurrence risk seems to decline over time [19].

Our patient has now been without anticoagulation for over 3 years and no clinical event has occurred. In our understanding, she should only receive thromboprophylaxis in high-risk situations, such as surgery or a relapse of NS.

Conclusion

Thromboembolic disease is a severe complication of NS and a high degree of suspicion is necessary to identify some forms of the disease. Our knowledge of the thrombophilic mechanisms in the NS is still incomplete, and no clinically relevant biomarker has yet emerged. Future studies should hub on the identification of biomarkers to determine which patients benefit from prophylactic anticoagulation.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Human and animal rights statement This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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