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https://doi.org/10.1016/j.nefroe.2020.10.003

Arterial thrombosis in a patient with nephrotic syndrome and antithrombin Cambrigde II

Trombosis arteriales en un paciente con síndrome nefrótico y antitrombina Cambrigde II

Dear Editor,

Thromboembolic phenomena are a serious complication of nephrotic syndrome (NS) with a general incidence of 20%.[1] However, arterial thromboses (AT) are rare in adults.[1,2] In this document, we describe multiple AT in an adult with NS. The genetic study pointed to an antithrombin Cambridge II (ACII) mutation. To our knowledge, this is the first case of NS with AT associated with this genetic thrombophilia.

The patient is a 73-year-old male who consulted for oedemas coursing for two to three weeks and re-exacerbation of dyspnoea in the previous few hours. Four weeks before he presented a right parietal lobe stroke (albuminaemia 2.7 mg/dL). In terms of personal background, he was a smoker of 50 pack-years and had dyslipidaemia and arterial hypertension of several months' evolution. His daily treatment included enalapril 20 mg, atorvastatin 80 mg, acetylsalicylic acid 100 mg and furosemide 60 mg. The following results were obtained in the physical exploration: blood pressure 120/73 mmHg, oxygen saturation 97%, pitting oedema as far as the knee.

The analytical results were normal haemogram, fibrinogen 706 mg/dL, D-dimer 1.7 microg/mL (nv [normal value]: 0.3–0.5), rest of coagulation normal; creatinine 1.1 mg/dL, urea 39 mg/dL, albumin 2 g/dL, cholesterol 191 mg/dL, triglycerides 80 mg/dL, ions normal. IgG 389 mg/dL, the other immunoglobulins were normal with no monoclonal component; complements, autoimmunity including anti-PLA2R, thyroid hormones, prostate-specific antigen (PSA), hepatitis markers, human immunodeficiency virus (HIV) and normal or negative lues serology. Proteinuria 6.59 g/24 h without a monoclonal component; sediment with one to three red blood cells per field. The electrocardiogram (ECG) and the echocardiogram were normal. The computed tomography angiography (CTA) of the pulmonary arteries/computed tomography (CT) of the chest showed a defect in the lateral segmental artery of the right basal pyramid consistent with pulmonary thromboembolism, whereby anticoagulation was initiated (suspended transiently as necessary); a nodular opacity of 10 mm was also identified in the left upper lobe. The lower extremity (LE) Doppler ultrasound identified an aneurysm of the left femoral/popliteal arteries 2 cm in diameter, partially thrombosed but no signs of deep vein thrombosis. The renal artery abdominal ultrasound/Doppler ultrasound showed no pathological findings in the renal echostructure, nor renal artery thrombosis. The thoracic-abdominal CT scan showed a 6-mm-thick mural thrombus in the infrarenal segment of the

DOI of original article:
https://doi.org/10.1016/j.nefro.2020.10.005.

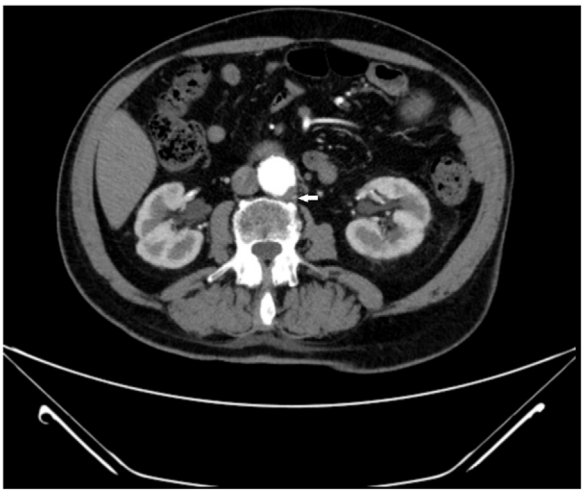

Fig. 1 – Aortic thrombosis.
Axial computed tomography of the abdomen following administration of arterial-phase intravenous contrast, showing a 32 × 27-mm dilation of the infrarenal aorta, with a small 6-mm-thick intramural thrombus on the posterior left aspect (arrow).

aorta (Fig. 1). Ten glomeruli were identified by renal biopsy; by optical microscopy and immunofluorescence lesions were compatible with membranous glomerulonephritis. The gastroscopy was normal; adenomas with low-grade dysplasia were identified in the colonoscopy and were resected. A polypectomy of several low-grade dysplasia adenomas was performed. In the thrombophilia study, the results for anticardiolipin antibodies (Ab), lupus anticoagulant, Factor V Leiden, protein C and S and the prothrombin gene were negative or normal, while antithrombin was 66% (NV 80%–100%), and the ACII (A384S) heterozygous mutation was identified by means of the allele-specific polymerase chain reaction assay followed by restriction analysis.

The pulmonary nodule was removed, and the histological study showed an *in situ* bronchogenic carcinoma. At discharge, anticoagulation with low molecular weight heparin was maintained; factor Xa levels showed adequate anticoagulation. After one year of follow-up, proteinuria of 6.5 g in 24 h persisted, with hypoalbuminaemia and preserved renal function, negative anti-PLA2R, with no tumour recurrence data, and rituximab 1 g × 2 was subsequently given.

Antithrombin is the body's most important physiological anticoagulant factor with a molecular weight similar to that of albumin and both levels are correlated in NS.[3–5] Antithrombin deficiency is present in 70% of cases of NS[6] and promotes the multifactorial hypercoagulability status of this syndrome (Table 1) which usually induces venous thrombosis.[1,7] On the other hand, in NS, AT is described in children and is usually in the lower extremities and coronary location; aortic involvement is very rare and potentially catastrophic.[8,9] Some authors point to severe hypoalbuminaemia (1.6 mg/dL) and the use of diuretics and corticosteroids as risk factors.[2,5] Membranous nephropathy is not necessarily the most frequent cause of NS associated with AT.[2,4] Our patient with popliteal vein, femoral artery and aortic thrombosis and ischaemic stroke had risk factors for AT such as dyslipidaemia, high blood pressure and smoking, and other thrombogenic diatheses involved in AT such as protein C and S deficiency or antiphospholipid syndrome were ruled out.[8]

Moreover, ACII is due to a mutation in the antithrombin gene, which is of autosomal dominant inheritance and has variable penetrance. This mutation provokes a local functional and non-circulating deficiency of antithrombin and its prevalence is probably underestimated with routine diagnostic methods since it does not affect activity on the levels of the coagulation parameters.[9] ACII is a moderate venous and arterial thrombotic risk factor[9,10]; in this latter territory, it appears to alter thrombin regulation capacity at the endothelial level. This dysfunction would be boosted in situations of hypercoagulability,[9] such as NS and it could feasibly have played some kind of a role in this patient's thromboses. From the therapeutic standpoint, in the presence of ACII, unfractionated heparin has apparently less anticoagulant efficacy than low molecular weight heparin.

The pathogenesis of arterial disease involves multiple genetic and environmental phenomena, which is why, in the presence of AT in NS, diagnostic possibilities permitting, the presence of pro-thrombotic genetic factors should be ruled out on account of their potential prognostic and therapeutic relevance.

Funding

The authors declare that they received no funding.

Table 1 – Hypercoagulability of NS.

Mechanisms: increase of factors: V, VII, von Willebrand, alpha-2 plasmin inhibitor, plasminogen activator inhibitor, fibrinogen
Urinary losses: antithrombin, possibly protein C and S
Increased platelet aggregation
Reduction in plasminogen
Nephropathies involved: membranous, membrano-proliferative, minimal changes, sclerosing and focal
Risk factors: membranous[a], diuretics, steroids, repeated venepuncture, neoplasms[a]
Venous location: renal vein (35%), pulmonary thromboembolism (8%), DVT LE (10%)
Arterial location: renal, aortic, femoral, cerebral, mesenteric, coronary
Prophylactic anticoagulation: in case of albuminuria <2 g/dL

NS: nephrotic syndrome; DVT LE: deep vein thrombosis of the lower extremities.
[a] They favour preferentially venous thromboses.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

Our thanks to Dr Jaime Corral, who performed the antithrombin genetic study, and to Dr Ricardo Enríquez for his collaboration.

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https://doi.org/10.1016/j.nefroe.2023.02.003

Variation genetics and disease: The answer is in the clinical and in the family

Variante genética y enfermedad: la respuesta está en la clínica y en la familia

Dear Editor,

We are in the midst of an upsurge in information about genetic variants associated with hereditary diseases thanks to mass sequencing and reduced costs. Being a carrier of a variant may not have pathological implications, and linking the changes found in the genome to clinical symptoms continues to be essential. We present a case that provides good proof of this.

DOI of original article:
https://doi.org/10.1016/j.nefro.2020.10.005.

The case in question involved a 47-year-old woman referred to the Nephrology Service by Primary Care physician for follow-up of autosomal dominant polycystic kidney disease (ADPKD). Her 17-year-old son was incidentally diagnosed with ADPKD according to the criteria of Pei et al.[1] in the context of abdominal pain. A genetic study was performed in the son to confirm the diagnosis due to the absence of a family background of the disease and the existence of normal ultrasound studies in all first-degree relatives. Three heterozygous variants were identified in the *PKD1* gene, hitherto undescribed and which were classified as being of uncer-