Abdominal thromboembolism associated with protein C deficiency

Ana Paula Figueiredo*, Estela Mateus*, Ana Nogueira**, Ana Caldas***, Ana Fernandes****, Barros Veloso*****

Abstract

The authors present a case report of a 58 years old female patient, previously healthy in whom extensive jejunoileal resection was made due to superior mesenteric artery thrombosis at Luanda Hospital. She was transferred to our hospital and the diagnosis of portal, superior or mesenteric and splenic axis venous thrombosis was made. The diagnostic evaluation revealed deficit of protein C and S. The concomitant study of her daughter and grand daughter also revealed a protein C deficit.

Key words: protein C Deficit, multiple abdominal thromboses, oral anticoagulant.

Introduction

Congenital protein C deficiency is described in at least 1% of patients with venous thromboembolism, and is more frequent in patients under 40 years of age.[1]

Several studies indicate autosomal dominant transmission without gender preference.[2]

There appears to be no direct link between clinical severity and the degree of protein C1 deficiency.

Protein S, another vitamin-K dependent plasma protein, acts as a cofactor to activated protein C.[3]

The authors present the clinical case of a patient with multiple abdominal thrombosis, diagnosed with congenital protein C and S deficiency, after ruling out secondary causes.

Case report

58-year-old female Euro-Caucasian patient, born and living in Vendas Novas.

Without any relevant personal background and apparently healthy up to the end of July 1994, at which point, while in Angola, she suddenly started to suffer from persistent aching abdominal pain, of a grinding kind, located in the left thigh and iliac fossa, accompanied by nausea and high fever (39.5ºC).

She was admitted to a hospital in Luanda, where complementary diagnostic exams revealed: anemia (Hb 8 g/dL) with leukogram, normal coagulation screens and tests, Plasmodium screening negative and urine culture positive for Klebsiella.

The ECG and teleradiography of the chest did not show alterations. Abdominal and renal echography evidenced only bilateral renal lithiasis without obstructive pattern.

Due to exacerbation of the clinical situation, with the onset of an acute abdomen state, the hospital performed a laparotomy, having diagnosed thrombosis of the superior mesenteric artery, followed by extensive jejunoileal resection.

The postoperative period elapsed without complications; hence the patient was discharged, asymptomatic, 14 days after surgery. About 24 hours later, she was readmitted with the initial complaints, with the coexistence of previously diagnosed anemia (Hb 7 g/dl) that had become worse in spite of the blood transfusions.

The patient was transferred to our service, at Hospital de Santo António dos Capuchos, in Lisbon.

On admission, the patient reported asthenia, adynamia, unquantified weight loss, persistent aching abdominal pain, at the same site (left flank and iliac fossa), without irradiation, accompanied by nausea with uncharacteristic sporadic vomiting and infrequent bowel movements with pasty to liquid stools, in small quantity, without blood, mucus or pus. On objective examination the skin and mucosa were slightly pale, sclerae anicteric, and she had sub-febrile temperatures (37.2ºC).

Cardiopulmonary auscultation did not reveal any alterations and deep abdominal palpation evidenced

*Internal Medicine Hospital Assistant

**Resident to the Internal Medicine Supplementary Internship

***Internal Medicine Ínterim Hospital Assistant

****Internal Medicine Hospital Assistant with a Head of Service ranking

*****Head of Service

Service 1of Santo António dos Capuchos Hospital, Lisbon

Received for publication on the 4th October 1996

pain in all the abdominal quadrants, with liver and spleen of increased volume, without signs of peritoneal irritation.

From the 3rd day of hospitalization, there was progressive exacerbation of the abovementioned symptomatology, with high fever (41ºC) of the remittent type and the appearance of dark brown urine. The physical examination showed the same results as the previous one.

Laboratorial tests showed pancytopenia: RBC 3060000, Hb 6.1 g/dL, MCV 59 FL, Hct 18.4% and MCHC 33.7 g/dL, with normal corrected reticulocytes, GB 2300 mm3 with leucocyte formula maintained and platelets 61000 mm3. ESR was normal.

Iron metabolism revealed increased ferritin levels. Coagulation screens showed TP 60% (19.3s), with INR 1.3 and PTT 40.7s. Transaminases were slightly elevated (AST 70 UI and ALT 65 UI) and the LDH was 700 UI. Urinalysis showed vestigial proteinuria.

Blood, urine and feces were cultivated with repeatedly negative results. Protein electrophoresis with immunofixation of the immunoglobulins was normal. The myelogram did not reveal any alterations, and both the Leishmania test and myeloculture were negative. The fecal occult blood test, plasmodium screening, HIV, VDRL and virus serologies were negative.

Serial chest teleradiography and ECG without alterations. Echocardiogram without evidence of any vegetation or mural thrombi and good global systolic function. Abdominal, renal and pelvic echography revealed moderate hepatomegaly with distinct splenomegaly, bilateral renal microlithiasis and probable partial splenic vein thrombosis. The abdominal study by computed tomography, echo-Doppler of the splenoportal system and angiography of the celiac trunk and of the superior mesenteric artery led to a diagnosis of vena porta thrombosis extending to the splenoportal axis, thrombosis of the superior mesenteric vein, cavernous dilation of the portal vein, ectasia of the splenic hilar vessels and hepatosplenomegaly. Carotid echo-Doppler study and the triplex scan of the lower limbs did not show any thrombi.

Other laboratory exams were carried out with negative results: serology for connectivitis, determination of complement fractions and circulating immune complexes in series were within the normal parameters; anticardiolipin antibodies and lupus anticoagulant with normal values; heat test for sucrose, and Ham's test with screening for hemoglobinuria and hemosiderinuria both negative; haptoglobin dosage, direct and indirect Coombs test negative, and viral and tumor hepatitis markers without alterations.

Of the remaining laboratory exams requested we emphasize the hemoglobin electrophoresis, which revealed the existence of β-thalassaemia minor.

The study of coagulation factors was compatible with protein C deficiency (42%), protein S deficiency (21%) and factors VII and X deficiency (respectively 51% and 33%). Factors V, VIII, IX, XII and antithrombin III were normal.

On day 23 of hospitalization with support measures, broad-spectrum antibiotic therapy (ceftriaxone, netilmicin and metronidazole) and heparin infusion, the fever curve receded, associated with rapid symptomatic improvement, and the patient was discharged on day 57 and prescribed oral anticoagulants. The patient was asked to visit the service daily for control of the anticoagulant therapy. However, she only came to the hospital 5 days later exhibiting a high fever (41ºC) and exuberant inflammatory signs on the breast. She was readmitted and, after laboratory control, the hospital verified the continued presence of pancytopenia with worsening of the coagulation test results (PT 10%, INR 4 and PTT 68 s). The chest teleradiography was normal, but it proved impossible to carry out other supplementary exams due to difficulty mobilizing the patient.

Although the treatment was reestablished with support measures and broad-spectrum antibiotic therapy, the patient died on day 13 of hospitalization with a condition of disseminated intravascular coagulation associated with sepsis.

At the same time, proteins C and S were determined in the daughter, granddaughter and brother of the patient. The first individual presented protein C deficiency of 36% and the second of 28%, both with normal protein S. The patient's brother did not present any deficiency.

Discussion

Protein C, a vitamin K-dependent plasma protein, is an important physiologic component in the anticoagulant system. Its activation occurs through thrombin.

Protein C promotes fibrinolysis, therefore its deficiency translates into a state of hypercoagulability.[1,4] The liver is probably its synthesis site.[5]

Protein S is required for the expression of antico-

agulant activity of protein C. However, protein S deficiency can also predispose to recurrent thrombosis.[3]

Patients with protein C deficiency can develop thrombosis at uncommon sites, such as the axillary, mesenteric and cerebral veins.

Superficial or deep vein thromboses, often accompanied by pulmonary embolism, are the most frequent problems. Arterial thromboses are also quite common.[1]

In the clinical case presented here, the existence of protein C and S deficiency was demonstrated in a patient with multiple abdominal thromboses.

Secondary causes that could have been related to the deficiency of these proteins were ruled out, e.g.: malignant neoplasm, liver disease, chronic kidney failure, dicumarinic agents, and the existence of lupus-like circulating proteins.[1]

After the determination of these proteins in the brother, daughter and granddaughter of the patient, the latter two also exhibited protein C deficiency, with normal protein S.

The exclusion of secondary causes and the finding of protein C deficiency in family members led us to believe that it was a congenital situation.

As regards the therapeutic approach in hypercoagulability situations, the use of heparin is recommended with the introduction of oral anticoagulants five days before suspending the heparin, given the risk of producing a paradoxical state of hypercoagulability.[1]

Prophylaxis with oral anticoagulants is not recommended in asymptomatic patients with minimum to moderate deficiency of this protein; even in cases of accentuated deficiency, prevention with the use of medications is arguable.[2]

In heterozygote patients with protein C and S deficiency, the occurrence of superficial venous infarcts, vasculitis and cutaneous necrosis is described 3 to 5 days after the start of treatment with dicumarinics. Necrosis predominantly affects the extremities, breasts and penis.[1,3,6]

The treatment of this situation includes heparin, vitamin K, plasma or protein C concentrate, but it is not clear whether the lesions can be reversed.[6]

The bilateral inflammatory profile of the patient's breasts upon her 2nd admission to hospital was considered a complication of the oral anticoagulation. Despite the established therapeutic regimen, the patient died in a condition of disseminated intravascular coagulation, in association with sepsis.. ■

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