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Dangerous thrombophilic states and internal pathologies: 3 cases of thrombosis of the abdominal veins

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Abstract. – **Thrombosis of the abdominal veins is a rare clinical condition which can be assimilated with the more frequent localization of deep venous thrombosis of the lower limbs.**

In the last few years great attention has been paid to possible risk factors for thrombosis of the abdominal veins. Two risk factors that have been identified are the presence of internal diseases and congenital and/or acquired abnormalities of haemostasis.

The authors describe 3 clinical cases (splenic and portal thrombosis due to congenital thrombophilia, Budd-Chiari syndrome, portal cavernoma consequent to ovarian neoplasia) with different etiopathogenesis to show how this apparently rare condition is today more frequently encountered and easier to recognize.

In the presence of thrombosis of major venous structures the search and the identification of intrinsic internal risk factors and of congenital and acquired thrombophilic disorders remains of great importance. Screening for thrombophilia includes blood C and S proteins, AT III, homocysteine, Leiden mutation of the factor V gene, G20210A mutation of the prothrombin gene, antiphospholipid antibodies. The presence of one or more of these risk factors allows the identification of the cases of portal thrombosis (EHPVO) responsible for about 10% of all the cases of portal hypertension, without cirrhosis or other hepatic lesions. The primary diagnostic procedure however remains color-Doppler ultrasonography which represents the most simple and the cheapest diagnostic investigation for the study of the portal and suprahepatic vein system, but it's strictly operator dependent.

Key Words:

Thrombophilia, Portal thrombosis, Thrombophilic factors.

Introduction

The extrahepatic thrombosis of the portal vein or of the suprahepatic veins is responsible for 5-10% of the cases of portal hypertension in adults[1-4]. The natural history of this condition is not well understood because of its rarity and because controlled prospective studies are lacking.

In many cases thrombosis of major abdominal veins such as that of the portal or suprahepatic veins represents a complication of hepatic cirrhosis[1]. However in spite of the most sophisticated imaging techniques and bio-humoral exams[5-13] that consent identification of possible risk factors, the percentage of cases in which etiology remains unknown is still high.

Thrombosis of major abdominal veins is a rare clinical entity if compared to the more frequent deep venous thrombosis of the lower limbs.

In this study we describe 3 recently observed clinical cases in which the recognition of hereditary and acquired thrombogenic risk factors has allowed us to identify a precise etiopathogenesis.

Clinical case n° 1

G.T, white female, 53 years of age, was admitted to the hospital in June 2000 with a low temperature, pain in the right hypochondrium and dyspepsia. She presented a past history of 6 years of diabetes type II, in therapy with oral hypoglycaemic agents; a previous diagnosis in 1987, of idiopathic splenic-portal hypertension; a history of the use of estroprogestinic combination from 3 or 4 years before the

date of the said diagnosis. In 1987 abdominal echotomography showed spleen and portal thrombosis with a liver of normal size and echogenic pattern, while the spleen seemed very oversized. An arteriography of the celiac tripod without visualization of the splenic vein showed a big collateral venous system. Esophagogastroduodenoscopy showed instead esophageal varices (T3) with red spots.

A surgical operation was suggested but the patient refused, while she accepted medical therapy and routinary check ups that showed a relatively stable clinical state, without a high risk of haemorrhage in the succeeding years (the patient has never bled and never had surgical treatment). In June 2000 the patient showed a good general state, but an ultrasonogrphy showed a 4th grade of splenomegaly, without superficial collateral venous circles and moderate ascites.

The hematochemical data showed hypersplenism with pancytopenia, slight hypertransaminasemia, non controlled diabetes type II and alteration of coagulation time (INR: 1.5 and PT: 63%). Liver biopsy showed a normal histological pattern; viral markers for hepatitis B and C were negative, so posthepatitic cirrhosis was excluded as cause of portal hypertension. Ultrasonography confirmed splenic and portal vein thrombosis, successively confirmed by computerized spiral tomography (CT).

Figure 1 shows an ultrasonographic scan of the abdomen with important splenomegaly (24 cm) and cavernomatous transformation of the portal vein, with extension of thrombus into the right and left branches. Spiral CT with contrast and quadrifasic techniques showed an increase of the gastroesophageal, coronaro-stomacic, splenic-renal, retroperitoneal, paravertebral collateral venous circulation. EGDS presented esophageal varices of IV grade (Paquet), with diffuse hypertensive gastropathy of the cardias. The functional and quantitative tests for C and S proteins, ELISA test for LAC, the amount of homocysteine and prothrombin polymorphism were normal. Anti-thrombin III (AT-III) levels were low (< 50% N.V. 80-130), but the functional test was normal. The APC resistance and the DNA analysis with PCR techniques for the research of the point mutation of factor V of Leiden were positive. Anticoagulant therapy was not started because of lack of compliance on behalf of the patient and a chronic state of stability of the clinical situation, (without bleeding and thrombotic events in other areas).

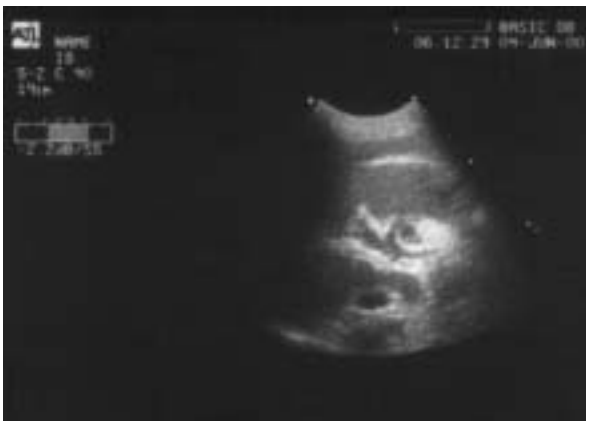

Figure 1. Portal cavernoma with an extension to the subdivision of the right branches and of the left vertical branch.

We can hypothesise for this case that the genetic condition of point mutation of factor V Leiden (that however didn't cause the thrombosis), can have acted as risk factor together with the estroprogestinic therapy and more recently the diabetic condition.

Clinical case n° 2

S.A, a 72 year old white woman was admitted to our Institute on January 2001 with abdominal tension, tiredness, oedema of the legs and signs of chronic kidney failure.

She had had an hysterectomy and right ovariectomy for presumed uterine adenofibroma about 15 years before and had a diagnosis of chronic kidney failure (of an unknown type).

We noticed a swollen abdomen, with fluid, tenderness, hepato-splenomegaly, reduction of pulmonary noises at the base of the right lung, but normal pulmonary sounds at the base of the left lung, systolic wheezing, 2/6 Levine bruit in the aortic region.

Laboratory data showed: GR 3.35; Hb 7.5; HCT 25%; MCV 70; GB 9,000, without alteration of the leukocyte formula; megakaryocityes 25,000; moderate hypertransaminasemia (GOT 40, GPT 69); FA 550; Albuminemia 2.5 g/dl; prothrombinic activity 57%; INR 1.5; fibrinogen 153; aPTT 26 sec and D-dimero 1,233 (0-250); hyperazotemia, hypercreatininemia.

Ultrasonography (Figure 2) showed an oversized liver with regular edges, irregular ecostructure because of the presence of large echi and several isoecogenic formations with anipoechogenic border. Portal vein was of irregular size with intramural thrombosis surrounded by venous dilatation (portal cavernoma). CT scan as well as confirming a cavernomatous obstruction of the portal vein also showed a neoplastic transformation of the ovaries. A diagnostic paracentesis was carried out, it showed hemorrhagic serous fluid containing lymphocytes, hyperplastic-dysplastic mesothelial cells and epithelial columnar cellular aggregates with clear atypia. Neoplastic markers Ca-125: 1028 m/ml (v.n.: 0-35), Ca 19.9: 2918.8 (v.n.: 0-17) were evidently elevated. All other common parameters of liver, renal and metabolic function were negative. The patient also underwent a screening for the primary causes of coagulopathies (AT-III, protein C-S, APC-r, prothrombinic polymorphism and homocysteine) which didn't show any abnormality of the coagulative system. Two repeated controls of D-dimer showed markedly elevate levels (1233 e 1192, n.v.: 0-250 hg/ml). The anticoagulant therapy induced a partial regression of the thrombosis with an improvement of the fluximetric parameters evident at a successive exam with echo-color-Doppler.

Clinical case n° 3

M.F, a 28 year old white male was admitted on December 2000, with abdominal pain, increased volume of the abdomen and notable tiredness.

Three years earlier, he had the first episode of deep vein thrombosis of the left lower limb, treated with medical therapy followed by rapid resolution. Six months before he was admitted for a second episode of thrombosis of the right iliac vein, partially receded after medical therapy. He was on anticoagulant therapy with warfarin. Physical exam showed a swollen abdomen, pain in the right hypochondrium and ascites.

Hematochemical blood tests showed reduction of the megakaryocytes, progressive increment of the hepatic enzymes (GOT 644-GPT 593) and the coagulation data (INR 2.3, aPTT 67.6 sec), increase of the bilirubin of both types, high D-dimer levels, with a normal hepatic synthesis profile. Abdomen ultrasonography showed hepatic steatosis and increase in volume of the caudate lobe, thrombosis of the portal vein and partial obstruction of the suprahepatic veins (Figure 3), evident signs of portal hypertension with inversion of the blood flow in the splenic vein beginning form the porta hepatis, significant abdominal ascites. CT scan confirmed the presence of ascites and showed abundant right pleural and moderate left pleural effusion. AT III, protein C-S, aPC-r, prothrombinic polymorphism, homocysteine, strip tests were normal, instead the LAC in ELISA tests (first the aCL and then after one week the LA) were positive. The reported data, together with liver biopsy demonstrated the

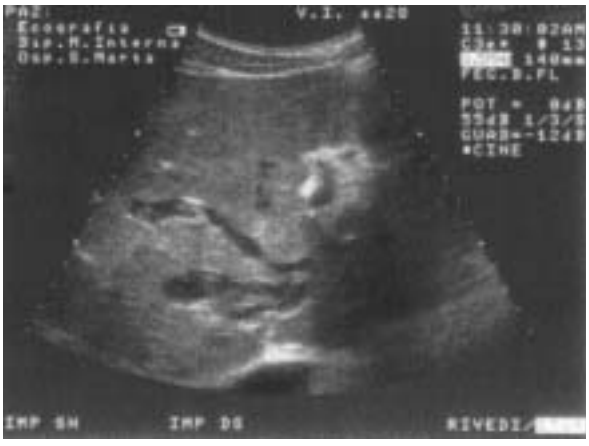

Figure 2. Irregular size of the portal vein with intramural thrombisis surrounded by venous dilation like portal cavernoma.

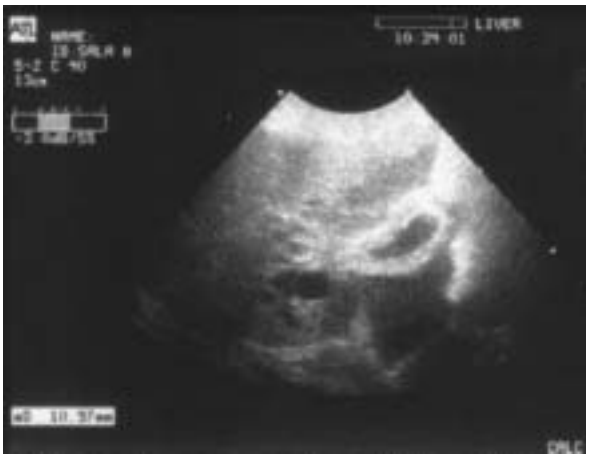

Figure 3. Thrombosis of the portal vein and obstruction of the sovrahepatic veins.

presence of centrilobular congestion and sinusoidal dilatation, that in absence of viral markers and right sided heart failure consented a diagnosis of Budd-Chiari syndrome. Anticoagulant therapy was started and patient was referred for orthotopic liver transplantation due to the acuteness of the pathology and signs of progressive liver failure.

Discussion

Thromboembolic venous disease, which has recently been the object of a renewed multidisciplinary[14,16-18] scientific interest, is considered at the moment a multifactorial disease where genetic factors act together with risk factors in the etiopathogenesis of the condition.

Among the risk factors still studied today (aside from those already well known) a great importance is attributed to the presence of internal diseases and thrombophilic states (Table I)[5,19].

The thrombophilic state represented by the internal condition which predisposes to thrombosis has been recently studied for the presence of factors which influence the coagulative/anticoagulative equilibrium. The update of the hematologic methods has allowed us to show a great prevalence in the population of prothrombotic mutations[2-3,7,11-13,16,24], but it also clear that a great part of the individual carriers of these mutations do not present thrombotic complications.

The extreme phenotypic variability of the thrombophilic state suggests that while on one hand the existence of multigenic interactions due to prothrombotic mutations surely favour thrombotic events, on the other hand, the role of acquired thrombogenic factors must not be dismissed. Patients with thrombophilia have an unusual predisposition towards thrombosis shown by atypical thromboembolic events starting at a young age, relapsing thrombosis or multiple localizations or family predisposition for TE disease. The eventual existence of thrombophilia greatly elevates the risk of the TE disease in those patients which already demonstrate one or more clinical risk factors (Table I).

In the thrombofilic condition we can consider two categories: the congenital and the acquired thrombofilic states: among the acquired risk factors the presence of antiphospholipid antibodies, is at the moment of greatly relevant practical clinical interest.

The classical early symptoms of thrombosis of the portal or suprahepatic veins are (pain in the right hypochondrium, high tempera-

Table I.

Main risk factors for tev
- Old age
- Female sex
- Blood groups
- Obesity
- Immobilization
- Pregnancy and post natal period
- Menopause (?)
- Previous thromboembolic experience
- Use of oral contraceptives
- Malign neoplasia
- Anaesthesia
- Traumas, burns
- Patients in institutions
- Internal pathologies
- Coagulation abnormalities

The most frequent internal pathological risk factors for tev
- Acute myocardial heart attack
- Cardiac failure
- Stroke
- Inflammatory bowel diseases
- Kidney transplant
- Old people in institutions
- Nephrotic syndrome
- Behçet's disease
- Hyperviscosity syndrome
- Myeloproliferative syndromes
- Polycythemia
- Sudden nocturnal haemoglobinuria
- Serious infection diseases

Haemostasis anomalies

Genetic
- Defects in AT-III
- Defects C protein
- Defects S protein
- Resistance to protein activated by Leiden factor V
- Polymorphism of the prothrombinic G20210A gene
- Dysfibrinogenemia
- ACE genetic

Acquired
- Antiphopholipid antibodies
- Heparin-induced thrombocytopenia

Other
- Hyperhomocysteinemia
- High levels of factor VIII
- Resistance to activated C protein but not caused by the presence of Leiden factor
- Abnormalities of the fibrinolysis
- Lipoprotein (a)

ture, ascites, gastro-intestinal bleeding, sometimes hepatomegalia, etc.) present in various percentages according to different series.

It's important to note that thrombosis of major abdominal veins can be asymptomatic (like the our case n° 1). This condition takes place according to the French researcher Benhamou in about 25% of the cases. In this last condition the development of efficient collateral intrahepatic and portosystemic venous bypasses together with a normally functioning liver explain the absence of clinical symptoms; in contrast there are clinical pictures (Budd-Chiari) of dramatic blood clots in the upper hepatic veins with signs of a more serious and progressive liver failure (as in case n° 3).

As to the etiopathogenetic aspect, the clinical cases shown describe the complex heterogeneity of this pathology which sometimes sees the convergence of thrombophilic conditions (primary and secondary hypercoagulability) and sometimes of internal pathologies and predisposing risk factors.

At the moment the constitutional alterations of haemostasis are better know and studied because of hematologic methods and better diagnostic tests.

For these forms the screening of hereditary coagulation deficits is usually accurate, however we must remember that the validity is sometimes undermined in these pathologies by the problem of making correct differential diagnoses between the primary and the secondary forms with eventual functional hepatocytic deficits. A practical help sometimes can come from a careful family screening.

Thrombosis of major abdominal veins has gained a great diagnostic tool with modern instrumental imaging technologies that consent a more rapid and efficient definition of these forms.

The most important imaging technique is Doppler sonography which represents the first choice exam because of the non-invasive nature of the method and the reasonable costs. The echotomography has a variable sensitivity between 85-100% and a specificity of 85%. The use of pulse-Doppler and of the color-Doppler improves the diagnostic accuracy if these exams are carried out by well experienced technicians.

We must also remember the MR that is very useful when the echo-Doppler is uncertain or when the constitution of the patient does not consent a good quality ultrasonographic exam and CT, considered by some authors less sensitive and specific than the other imaging techiniques.

The use of contrast medium, as in spiral CT with quadrifasic technique, greatly increases the diagnostic capacity of the exam.

The role of the cavography is important because it allows to study the IVC above and below the hepatic veins, the wedge pressure in the HV and the portocaval gradient; in the presence of Budd-Chiari syndrome (BCS) cavography allows us to identify the area and the morphology of the venous obstruction.

The measurement of portocaval gradient is a fundamental element for a surgical evaluation, capable of giving decisive indications for the choice of the appropriate therapeutic approach.

Liver biopsy isn't usually necessary for the diagnosis which in general is given by non-invasive exams (as above), but it gives prognostic indication as to chronic and irreversible liver damage, presence of fibrosis or of cirrhosis, which for some authors are very important for the choice of therapy and early referral for liver transplantation.

In conclusion we can say that a correct diagnosis of portal thrombosis is becoming more simple and in the presence of this pathology it is increasingly common to recognise internal risk factors represented by primary thrombophilic conditions.

The high prevalence congenital thrombophilia is probably underestimated and so an efficient screening of the congenital or acquired thrombophilic conditions, together with a monitoring of the other biohumoral and instrumental data can be useful not only for a more precise etiopathogenic diagnosis but also for future therapeutic decisions (liver transplant, anticoagulant therapy) and for a quoad vitam prognosis.

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