

Portal Cavernoma in a Patient with Crohn's Disease Associated with Factor V Leiden Mutation and Antiphospholipid Syndrome

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Abstract

Portal vein thrombosis followed by the occurrence of a portal cavernoma is a rare condition that requires convergence between systemic predisposition and local factors in order to develop. Among the complications of inflammatory bowel diseases, such eventuality is quite unusual. Ulcerative colitis accounts for the majority of these vascular complications, while in Crohn's disease the occurrence of such events is exceptional. We present the case of a young male patient aged 42, without any particular history, in whom the diagnosis of the first flare of colonic Crohn's disease was accompanied by the discovery of a portal cavernoma, followed by the demonstration of a heterozygous mutation factor V Leiden associated with the presence of an antiphospholipid syndrome with IgG anticardiolipin antibodies. This unusual association of portal vein thrombosis with antiphospholipid syndrome in Crohn's disease, observed according to our knowledge only in one other instance, raises the discussion regarding the convergent action of general thrombophilic (hereditary and acquired) and local factors in the genesis of vascular complications of inflammatory bowel diseases.

Keywords

Portal vein thrombosis – portal cavernoma – Crohn's disease – factor V Leiden mutation – antiphospholipid syndrome

Introduction

Systemic predisposition like prothrombotic state or thrombophilia, as well as local factors can generate dysfunctions leading to portal vein thrombosis (PVT) [1,

2]. Although the prothrombotic state represents an excess of coagulation activation, while thrombophilia is only a general tendency to thrombosis, most authors [2-5] treat these factors globally. It is considered that a thrombophilic state can contribute to approximately 60% of cases having PVT, while local conditions in 40% [5], even if the concept postulating that PVT occurrence is related to an interaction between several factors and is not due to an isolated event remains always valid [6].

General thrombophilic factors are hereditary or acquired. Hereditary thrombophilia can be observed in 40% of cases of PVT [7]. It is related either to changes of genes coding for certain coagulation factors (factor V Leiden, prothrombin G20210A), or to deficiencies of antithrombin or proteins C/S, and also to mutations of methyl-tetrahydrofolate reductase gene (MTHFR) such as the C677TT/C667CT variants determining hyperhomocysteinemia. Acquired thrombophilic conditions are a heterogeneous group including antiphospholipid syndrome (APS) and hematologic diseases (myeloproliferative syndrome, paroxysmal nocturnal hemoglobinuria, disseminated intravascular coagulation) alongside more frequent conditions such as cirrhosis, inflammatory state, malignancy, sepsis, pregnancy [2, 8]. Local factors can be represented either by abdominal sepsis or neoplasia or by surgical trauma [1, 2, 6, 9].

An important local factor may be inflammatory bowel disease (IBD), despite the fact that it is difficult to consider it as the one-and-only cause of PVT [2]. Hemostasis disorders seem to be definitely correlated with disease activity; however, the precise mechanism of this thrombophilic state remains unknown [10]. Intervention of multiple preexistent prothrombotic factors acting in consonance was studied, leading to the observation that the common genetic risk factors as factor V Leiden (FVL) mutation, prothrombin G20210A, C677TT/C667CT variant, type 1 inhibitor of plasminogen activation (PAI-1) and gene mutations of factor XIII (val34leu) are not found more often in patients having IBD than in others. However, when present, patients are more likely to develop thrombotic complications [11, 12]. It could be presumed that acquired factors are major actors in PVT [13], while prothrombotic conditions such as FVL

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mutation and prothrombin G20210A are rare among patients with IBD.

Case presentation

A 42 year-old male patient having no significant history was admitted for episodic colicky abdominal pain followed by diarrhea and relieved by emissions of mucus, blood, and pus-mixed “mahogany” stools. The respiratory, cardiovascular, neurological and renal evaluations were normal. Routine biological check-up showed mild iron deficiency anemia, slight neutrophilic leukocytosis and thrombopenia. There was also an inflammatory syndrome but no sign of hemolysis or hematologic malignancy. Liver enzymes and renal function were normal, as well as basic immunological investigation. Research for chronic viral hepatitis was also negative but anti-Saccharomyces cerevisiae antibodies were present. Tuberculin intradermoreaction was negative. Low-titer positivity of VDRL test was noticed, while specific tests (TPHA/FTA) were negative. Amoebiasis serology was also negative, whereas bacteriological and parasitological investigation confirmed infectious or parasitic colitis.

Colonoscopy identified deep linear fissures tiling the edema-swollen mucosa, and giving a “cobblestone” aspect (Fig. 1). The lesions, residing in the rectosigmoid and right colon and separated by healthy areas had a discontinuous, segmental, and asymmetric distribution: the ileocecal valve was also involved. Colonic biopsies (Fig. 2) showed deep mucosal ulcerations digging through submucosa, diffuse lymphocytic infiltrate tending to nodular organization along with plasma cells and few neutrophils, and some epithelioid cell granulomas confirming Crohn’s disease. Tuberculoid granulomas and giant Langhans-type cells were not observed, neither eosinophilic necrosis nor caseation. The Ziehl coloration showed no acid-fast bacilli while culture on *M. tuberculosis*-specific media and techniques of genomic amplification by PCR were negative.

Power Doppler echography showed a network of tortuous collateral vessels surrounding an enlarged portal vein partially obstructed by intraluminal echogenic material, demonstrating the portal cavernoma (Fig. 3). Contrast-

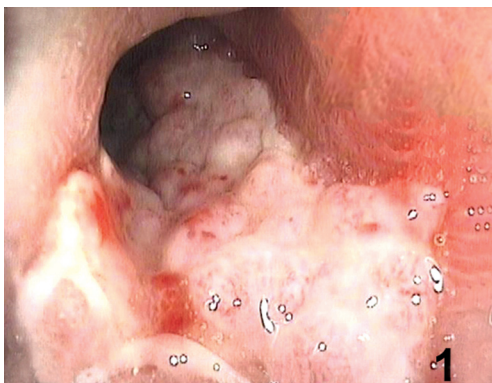


Fig 1. Longitudinal, deep serpiginous fissure, tiling an edematous mucosa, with classic “cobblestone pattern”.

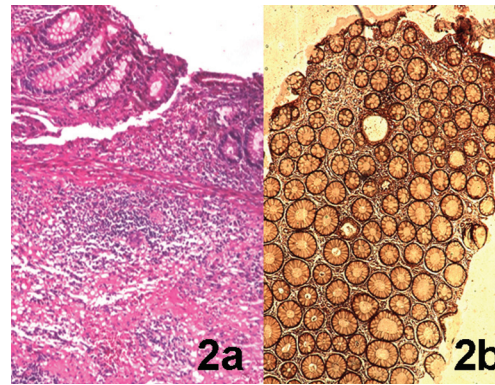


Fig 2. Colonic biopsy: **a.** H&E x 10. Diffuse lymphocytic infiltrate with tendency to nodular organization, presenting also plasmocytes and scattered neutrophils. Note deep ulceration digging the mucosa; **b.** Gömöri stain x 10. “Bipolar” morphology of the colonic mucosa consisting in alternating zones of normal architecture with areas of glandular atrophy.

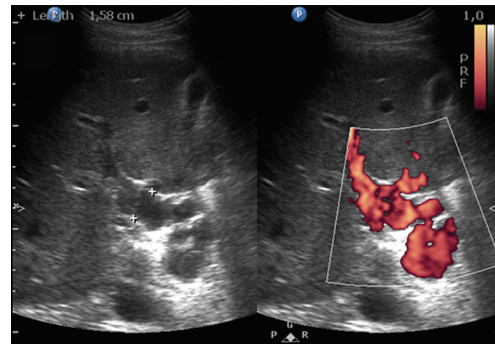


Fig 3. Power Doppler echographic view of the hepatic hilum: multiple, tortuous, canalar dilatations surrounding the portal vein.

enhanced abdominal CT scan highlighted the partial PVT and also confirmed the large cavernoma. Coronal T2-weighted MRI scan with oral ingestion of contrast also showed tortuous collaterals bypassing a dilated portal vein as well as mesenteric edema and hypervascularity, with segmental thickening of the ileal and colonic wall (Fig. 4).

Hemostasis assessment showed normal activity of plasma C and S proteins, normal antithrombin activity and antigen, and normal homocystein concentration. Resistance to activated protein C observed by phenotypic coagulation Dahlback’s test and confirmed by a second generation assay suggested the presence of a FVL mutation. Direct research for FVL by DNA analysis by real-time PCR confirmed the presence of the heterozygous arginine/glutamine mutation in position 506. Antiphospholipid syndrome was also explored. Lupus anticoagulant research was negative as well as assays for anti-beta2 glycoprotein 1, anti-phosphatidylserin and anti-prothrombin antibodies, while ELISA-anticardiolipin antibody (ACL) research was positive using both qualitative and quantitative methods.

This unusual association of PVT with APS in Crohn’s

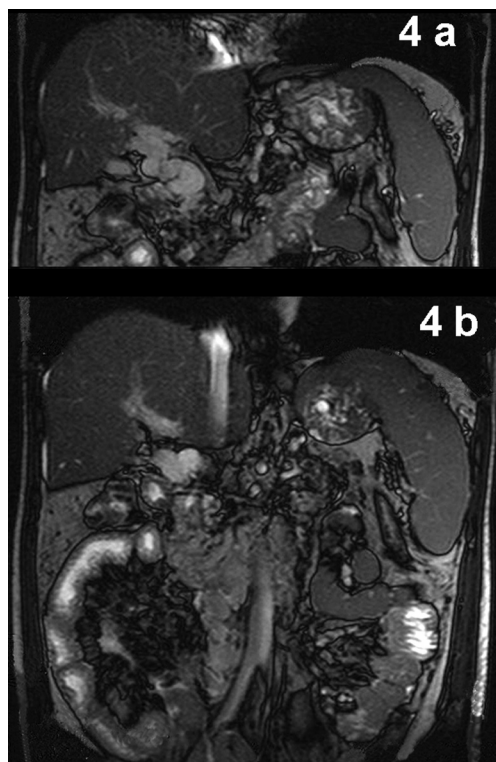


Fig 4. Coronal sequence MRI T2-trufi weighted. **a.** serpiginous dilatation of the portal vein; **b.** after oral contrast, apart the portal cavernoma, thickening of the walls of ileum and descending colon can be observed, as well as edema of the mesentery, which is hypervascularized ("combed" aspect). Note the absence of adenopathies and peritoneal effusion.

disease raises the discussion regarding the convergent action of thrombophilic and local factors in the genesis of vascular complications in IBD.

Discussion

Our patient exhibited the association of three risk factors for PVT, consisting of a mix between local factors (inflammatory process accompanying Crohn's disease) and two thrombophilic conditions (APS and FVL mutation). Although the occurrence of PVT in IBD is rare, similar cases have been already reported. Most of these cases were acute, thrombosis being triggered by sepsis or surgical trauma [14-18], but less dramatic situations can also occur [19, 20]. It seems that the connection between IBD and thrombotic events resides in the hypercoagulable state, while increased fibrinogen, factor V/VIII, platelet count, and decrease of antithrombin III have been observed during the acute flares.

In this context, presence of heterozygote FVL mutation needs discussion. According to Bernstein et al [21] it seems that this abnormality is not sufficient to explain an increased thrombotic risk among patients with IBD; the incidence of FVL allele is similar to that observed in the general population and there are even reports evidencing a low frequency of this mutation in patients with IBD and

thrombotic complications [13, 22, 23]. On the other hand, recent arguments stating a high prevalence of genotype R506Q (Leiden) among patients with IBD, apparently with no relation to more frequent thrombotic accidents, are also available [11, 12, 24].

Portal vein thrombosis, apart from positivity of anticardiolipin (ACL) IgG-antibodies (titers of 140, 100 and 120 GPL units/ml at admission and after 12 and 16 weeks, respectively) in the context of the false positivity of VDRL test, negativity of IgM-ACL antibodies, IgM/IgG-apolipoprotein H antibodies and DRVVT-tested lupus anticoagulant, confirmed the presence of the APS in this patient with Crohn's disease carrying the FVL mutation, in the absence of any other inflammatory, infectious or immune concomitant disease.

Antiphospholipid syndrome is characterized by recurrent thrombosis and immune abnormalities consisting of high levels of antibodies against membrane phospholipids such as ACL/antiphosphatidylserin antibodies, against their plasmatic proteins represented mainly by beta-2 glycoprotein I (apolipoprotein H), or by the presence of lupus anticoagulant [25, 26]. Diagnostic criteria for APS [27] require at least one clinical argument and one immune abnormality for confirmation. One of the clinical criteria is the presence of one or more confirmed clinical episodes of thrombosis, while biological arguments are based on the presence of the antiphospholipid antibodies or demonstration of phospholipid-dependent coagulation abnormalities such as lupus anticoagulant, high titers of IgG/IgM ACL antibodies or elevated levels of anti-beta-2 glycoprotein I IgG/IgM antibodies, observed at least two times in a 12 weeks interval between assessment. Other abnormalities, such as thrombocytopenia, mild hemolysis, false positive syphilis serology (VDRL), presence of ACL/anti-beta-2 glycoprotein I IgA antibodies or anti-phosphatidylserin/phosphatidyl-ethanolamin/prothrombin/phosphatidylserin-prothrombin complex antibodies [28] can also appear. The unusual association of APS to PVT in Crohn's disease has been observed to our knowledge only in a single other patient by Racine et al [2]. Even if antiphospholipid antibodies are observed in 11% from patients with Crohn's disease versus 2.5% in controls, their presence has not always been related to a history of thrombosis, nor to disease activity [29, 30]. On the other hand, there are also observations reporting thrombotic events in subjects with IBD carrying antiphospholipid antibodies [2, 31-33].

Conclusions

Beyond the spectacular aspect, our observation makes some nuance regarding the thrombophilic state in patients with Crohn's disease. Portal vein thrombosis can occur and is not always dramatic in patients carrying a high thrombophilic risk, especially when the development of collateral network and of portal cavernoma is possible. This could be one of the very rare cases [34] in which portal cavernoma occurs without being preceded by sepsis

or surgery, i.e. in the context of a combination of two or more prothrombotic conditions such as FVL mutation and antiphospholipid syndrome.

It is also important to observe that two “minor” thrombophilic elements may act within the context of the hypercoagulable state characterizing IBD, and facilitate the progressive occlusion of the portal vein and development of portal cavernoma. Accordingly, the existing evidence points to the hypothesis that at least in Crohn’s disease, prothrombotic abnormalities may be related not only to disease activity, but also to vascular complications.

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