Thromboembolism in inflammatory bowel disease

M. Schapira, J. Henrion, C. Ravoet, J.M. Maisin, J.M. Ghilain, S. De Maeght, F. Heller

Department of Internal Medicine, Clinique de Jolimont, 7100 Haine St Paul, Belgium.

Abstract

Thromboembolism represents a severe complication of inflammatory bowel disease occurring in young patient, with active disease. Deep venous thrombosis and pulmonary embolism are the most frequent thromboembolism manifestations. Arterial complications and unusual sites for thromboembolism are more rare. Overall, inflammatory bowel disease is a real prothrombotic state as almost all parameters of coagulation are enhanced. Anticoagulation during the episode of thromboembolism is mandatory, and sometimes may ameliorate the course of inflammatory bowel disease. (Acta gastroenterol. belg., **1999**, 62, **182-186**).

Key words : thrombosis, embolism, coagulation, inflammatory Bowel disease, Crohn's disease, ulcerative colitis, Heparin.

Introduction

Thromboembolism (TE), though uncommon, has been recognized as a distinct complication of inflammatory bowel disease (IBD), and is increasingly reported. Furthermore, vascular phenomenons may play a contributing role in the genesis of Crohn's disease and ulcerative colitis. When clinically apparent as vascular thrombosis, they may become a severe life threatening extraintestinal complication.

In this review, we describe the clinical setting, various possible coagulation alterations and some suggestions for treatment.

General considerations

Thromboembolism (TE) associated with inflammatory bowel disease (IBD) has been recognised for more than 60 years (1).

The incidence varies from 1,3% to 6,4% in clinical series (2,3) and as high as 40% in autopsy studies of patients with ulcerative colitis (4). However, in autopsy studies (4), only 6% of the patients with venous thrombosis were recorded as having clinical evidence of thrombosis. The low incidence (1,3%) reported in the mayo clinic series (2), probably reflects an irregular follow up as suggested by the authors. TE can occur in in-patients as well as in out-patients, the latter being predominant in at least one series (5). Thus, the incidence of thrombotic events necessitating hospitalisation is probably low, less than 1% of admissions (87 of 11402) in this recent series (1991-1995) (5).

TE was more frequent (64% vs 36%) with active disease (2) ; and could be more frequent in active Crohn's disease than in active ulcerative colitis (5).

Most cases recorded in the literature were young patients ; 60% less than 50 years in a recent clinical series (5). The risk of TE is not related to gender, to the type (Crohn's disease or ulcerative colitis) or the anatomical localisation of the IBD (2,5). Rarely, a TE event was recorded prior to the diagnosis of the IBD or the symptomatic stage of the disease (6,7,8,9). A history of recurrent TE was reported in 10% (2) to 13% (5) of patients.

Peripheral deep venous thrombosis and/or pulmonary embolism were the most common manifestations of TE in IBD representing 61 out of 92 events in the Mayo clinic series (2).

An "unusual site" (intracardiac, cerebral, peripheral artery thrombosis...) was recorded in 11% (5) to 33% (2) of cases in clinical series. Other "unusual sites" were described in case reports (Budd-Chiari Syndrome (10,11), portal vein thrombosis (12), renal vein thrombosis (13)).

Arterial TE complications have been rarely reported and were associated with either Crohn's disease or ulcerative colitis (2,14,15,16).

TE is a grave complication in IBD as the reported mortality rate was quite high (from 8% (5) to 25% (2)).

Finally, the questions of an increased risk of TE in case of IBD remains debated but may be assumed when patients are followed long enough, when we take into account the young age of patients with some unusual and sometimes multiple sites of TE and the significant proportion of TE occurring spontaneously.

Inflammatory bowel disease, a prothrombotic state ?

Multiple, sometimes hypothetical, physiopathological pathways link IBD to the microvascular system in general and to the coagulation cascade in particular (17) (fig. 1).

Typical systemic vasculitis accompanying IBD have been described, and were considered as another possible extraintestinal manifestation (2,18,19).

Histological examination of specimens of resected intestine from patients with Crohn's disease have shown that thrombosis may contribute to the pathogenesis of

Reprints : Dr M. Schapira, Clinique de Jolimont, Gastroentérologie, Rue Ferrer, 7100 Haine St Paul, Belgium.

(Genetic, environmental, unknown) factors → IBD ←→ microvascular and/or coagulation abnormalities

OR

(Genetic, environmental, unknown) factors → microvascular and/or coagulation ←→ IBD abnormalities

Fig. 1. — Possible links of IBD to thromboembolism (References : 17,18,20-24).

the disease (20). A sequence of events was proposed (vascular injury, focal arteritis, fibrin deposition, arterial occlusion, tissue infarction or neovascularisation), confined only to segments of intestine affected by Crohn's disease (20). Vascular localisation of granulomatous inflammation (granulomatous vasculitis) suggests that the microvasculature contained an early element in the pathogenesis or Crohn's disease (21). The presence of mucosal capillary thrombi in rectal biopsies of patients with ulcerative colitis raises the possibility of vascular pathogenetic mechanisms (22).

Persistent hemostatic activation could occur during phases of clinical remission of IBD (23) or in patients with active disease (24). During flare-ups of the disease acute phase reactant (as fibrinogen) are important risk factors for thrombosis (24). Sometimes, fibrinogen elevation can persist regardless of disease activity (24).

Studies have described a variety of laboratory changes that suggested a hypercoagulable state (23,24).

Figure 2 summarizes some of the abnormalities in the coagulation pathways.

Enhanced generation of thrombin (and fibrin) with inhibition of fibrinolysis was demonstrated (23,24,25, 26). Plasma elevation of factor VII coagulant activity, lipoprotein (a) and fibrinogen, were also recorded in IBD (25).

Circulating immune complexes (27,28), elevated circulating Von Willebrand factor (29) were reported, all suggesting a permanent vascular injury initiating a procoagulant state.

The presence of anti-endothelial cell antibodies in sera from patients with IBD, may also indicate a primary microvascular damage (30).

Thrombocytosis (2) but also abnormal platelet activity with hyperaggregation contributes as well to TE in IBD (31,32). However, abnormal platelet function seems not correlated with disease activity, and is present also in quiescent disease (31).

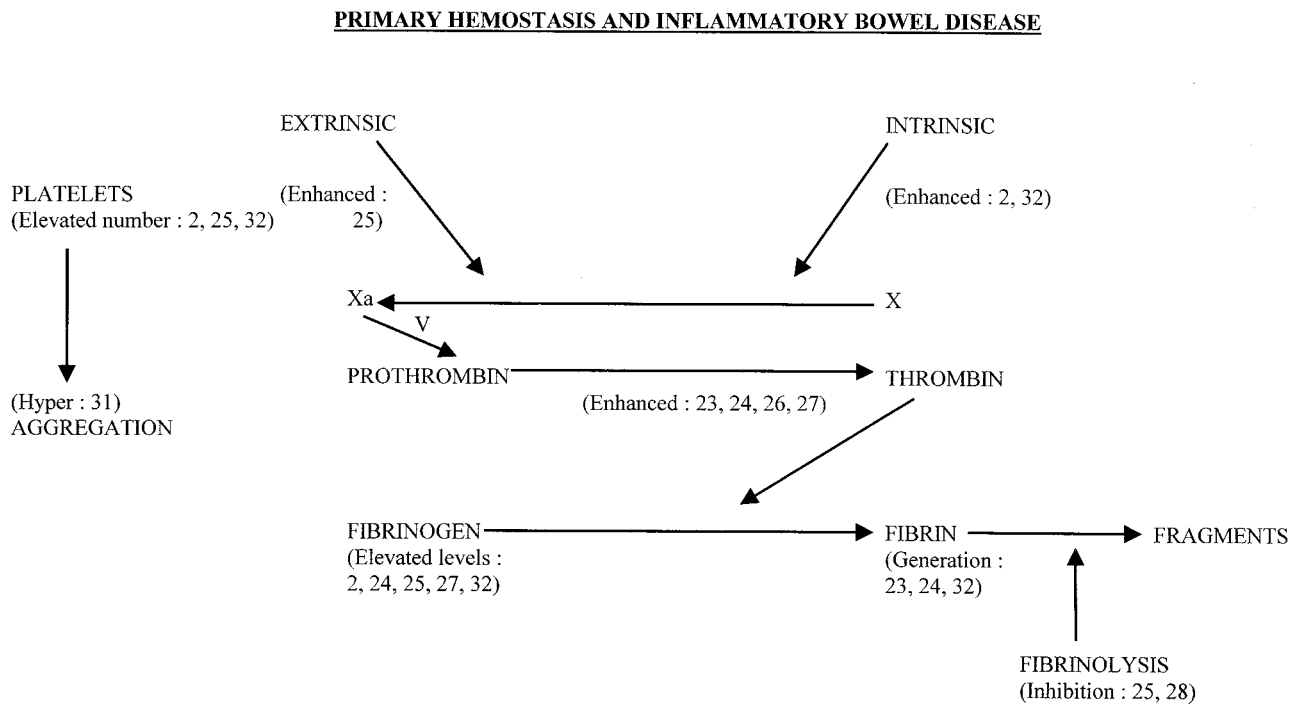

Fig. 2. — In this simplified version of blood clotting (based on ref. 24) are summarized some of the hemostastic abnormalities in IBD patients (numbers = references).

It is possible that disruption and loss of sulphated glycosaminoglycans in intestinal inflammation, may precipitate thrombosis. These negatively charged polysaccharides present also in vessel walls, regulates albumin movements and, more important, also inhibit thrombosis, are affected by inflammatory cells (33).

Hemostatic changes described in recent literature (23-33), could explain why an usual risk factor for TE as oral contraceptive, smoking, parenteral nutrition, post operative, sepsis, can be identified only in half of cases of TE in IBD (5,34). Premature atherosclerosis with IBD (Crohn's disease) was described mainly in case reports of young smoking women (35). Smoking induces morphological injury to endothelial cells with formation of microthrombi perhaps via inhibition of endothelial prostacyclin (34).

As a relationship seems to be established between IBD and a prothrombotic state, it is not surprising that a low incidence of IBD was reported in patients with inherited coagulopathies as hemophilia or Von Willebrand disease (36).

The paradoxical (favorable) response to heparin in patients with ulcerative colitis indirectly incriminates hypercoagulability as a risk factor in/for IBD (37).

Other more rare hemostatic alterations associated with a hypercoagulable state were examined (38-51).

The antiphospholipid syndrome (APS) described more than 10 years ago, associating thrombosis with the presence of lupus anticoagulant and/or anticardiolipin antibodies, is one of the strongest published risk factor for arterial and venous thrombosis (38). Although there is a significantly high prevalence of patients with anticardiolipin antibodies in Crohn's disease, 11% (39) to 20% (40) (control subjects : 2,5%), there was no correlation with TE or clinical activity of the disease (39). However, several cases of TE in IBD associated with APS have been described (41,42,43,7,44).

Other classical risk factors for thrombosis were studied in IBD (low levels of : protein S (45,28), protein C (45,28) or antithrombin III (28)) without definite conclusions.

Recently, factor V Leiden (and activated protein C resistance) (46) were studied in a limited number of IBD patients (5,47), with conflicting results.

Finally, hyperhomocysteinemia, another known risk factor for venous and/or arterial thrombosis (48) was studied in IBD, showing higher levels in IBD patients than in control (49). At least 2 case reports of TE in IBD with this metabolic condition have been reported (50,51).

When TE occurs in inactive IBD (about a third of cases) screening should be done looking for an inherited or acquired tendancy for TE (APS, protein C, protein S etc).

In conclusion, various coagulation alterations have been described as possible causes for TE in IBD. Recognized risk factors for TE are significantly higher in patients with IBD. However, since no single and clear mechanism has been described, a multifactorial mechanism is suspected.

Treatment

To our knowledge there have been no large scale controlled trials of anticoagulation therapy in patients with TE in IBD.

In the acute setting of thrombosis, venous complications should receive anticoagulant therapy (Heparin) and other supportive measures. As deep venous thrombosis and/or pulmonary embolism, the most frequent TE manifestation in IBD implies severe prognosis, they should be treated without taking into account the presence of IBD (3). Thus, active IBD is not a contraindication to anticoagulation (3,39). However, the use of anticoagulants in cerebral venous thrombosis remains a controversial issue (6). A case of portal vein thrombosis treated successfully by a combined treatment (urokinase with tissue plasminogen activator into the superior mesenteric artery and Heparin intravenously) has also been reported (52).

Arterial thrombosis in IBD sometimes may need surgical prodecures as thrombectomy or embolectomy (16), or percutaneous transluminal thrombectomy and thrombolysis (53). Anticoagulant therapy (Heparin and Warfarin) remains the main treatment in arterial thrombosis (14,15,16).

The presence of an APS with IBD is an indication for continuous Warfarin treatment as the risk of recurrence is high (54).

As the risk for TE in IBD is higher in active disease, simple prevention measures should also be taken (mobilisation, shorter I.V. perfusion periods...) (5). Stop smoking and if possible replacing the oral contraceptive pill by another contraceptive method should also diminish the TE risk (34).

The preliminary encouraging results of heparin treatment in ulcerative colitis (39), perhaps indicates that anticoagulation should be a part of the treatment of active IBD. The favorable effect of heparin in IBD, may also be due to other intrinsic properties of heparin : anti inflammatory effects, endothelial cell interaction, cytokine interaction, reduce of radical oxygen metabolites and intestinal repair (55).

References

1. BARGEN J.A., BARKER N.W. Extensive arterial and venous thrombosis complicating chronic ulcerative colitis. *Arch. Intern. Med.*, 1936, **58** : 17-31.
2. TALBOT R.W., HEPPELL J., DOZOIS R.R., BAERT R.W. Vascular complications of inflammatory Bowel disease. *Mayo. Clin. Proc.*, 1986, **61** : 140-145.
3. EDWARDS F.C., TRUELOVE S.C. The course and prognosis of ulcerative colitis, part III complications. *Gut*, 1964, **5** : 1-22.
4. GRAEF V., BAGGENSTOSS A.H., SAVER W.G., SPITELL J.A. Venous thrombosis occuring in non specific ulcerative colitis, a necropsy study. *Arch. Intern. Med.*, 1966, **117** : 377-382.
5. JACKSON L.M., O'GORMAN P.J., O'CONNELL J., CRONIN C.C.,

COTTER K.P., SHANAHAN F. Thrombosis in inflammatory Bowel disease : clinical setting, procoagulant profile and factor V Leiden. *Q.J. Med*, 1997, **90** : 183-188.
6. MOTTE S., FLAMME F., DEPIERREUX M., WAUTRECHT J-CL., VAN GOSSUM A., DEREUME J.P. Venous thromboangiitis associated with regional enteritis. *Int. Angiol.*, 1992, **11** : 237-240.
7. DUPUIS F., PETIT A., SALAUN D., DAVOUS N., SKAL M. Anticorps antiphospholipides et thrombose veineuse profonde au cours d'une rectocolite hémorragique révélée par un pyoderma gangrenosum. *Presse. Med.*, 1996, **25** : 1084.
8. JORENS P.G., DELVIGNE C.R., HERMANS C.R., HABER I., HOLVOET J., DE DEYN P.P. Cerebral arterial thrombosis preceding ulcerative colitis. *Stroke*, 1991, **22** : 1212.
9. VIANNA J.L., D'CRUZ D.P., KHAMASHTA M.A., ASHERSON R.A., HUGHES G.R. Anticardiolipin antibodies in a patient with Crohn's disease and thrombosis. *Clin. Ex. Rheumatol.*, 1992, **10** : 165-168.
10. BRINSON R.R., CURTIS W.D., SCHUMAN B.M., MILLS L.R. Recovery from hepatic vein thrombosis (Budd-Chiari syndrome) complicating ulcerative colitis. *Dig. Dis. Scl.*, 1988, **33** : 1615-1620.
11. MACCINI D.M., BERG J.C., BELL G.A. Budd-Chiari syndrome and Crohn's disease an unreported association. *Dig. Dis. Scl.*, 1989, **34** :, 1933-1936.
12. CROWE A., TAFFINDER N., LAYER G.T., IRVINE A., NICHOLLS R.J. Portal vein thrombosis in a complicated case of Crohn's disease. *Postgrad. Med. J.*, 1992, **68** : 291-293.
13. MIROUX F., ARRIVE L., MONNIER-CHOLLEY L., ISSAHAR A., MEHDI M., LEWIN M., TUBIANA J.M. Thrombose de la veine rénale et rectocolite hémorragique. *J. Radiol.*, 1996, **77** : 671-673.
14. CHAMOUARD P., DUCLOS B., WEILL-BOUDSON M., KURTZ T., BAUMANN R., WEILL J.P. Accidents thrombotiques artériels au cours de la maladie de Crohn. *Gastroenterol. Clin. Biol.*, 1990, **14** : 278-282.
15. HALLIDAY C.E.W., FARTHING M.J.G. Arterial thrombosis in Crohn's disease. *Med. J. Aust.*, 1988, **149** : 559-560.
16. NOVOTNY D.A., RUBIN R.J., SLEZAK F.A., PORTER J.A. Arterial throboembolic complications of inflammatory Bowel disease. Report of three cases. *Dis. Colon. Rectum.*, 1992, **35** :, 193-196.
17. SATSANGI J., JEWELL D.P., ROSENBERG W.M.C., BELL J.L. Genetics of inflammatory Bowel disease. *Gut*, 1994, **35** : 696-700.
18. WEIR A., TAYLOR-ROBINSON S.D., POOLE S., PIGNATELLI M., WALTERS J.F.R., CALAM J. Cytoplasmic antineutrophil cytoplasmic antibody-positive vasculitis associated with ulcerative colitis. *Am. J. Gastroenterol.*, 1997, **92** : 506-508.
19. CRESPO I., MURPHY J., WONG R.K.H. Superior mesenteric venous thrombosis masquerading as Crohn's disease. *Am. J. Gastroenterol.*, 1994, **89** : 116-118.
20. WAKEFIELD A.J., SAWYER A.M., DHILLON A.P., PITILLO R.M., ROWLESS P.M., LEWIS A.A., POUNDER R.E. Pathogenesis of Crohn's disease : multifocal gastrointestinal infarction. *Lancet*, 1989, **334** (2) : 1057-1062.
21. WAKEFIELD A.J., SANKEY E.A., DHILLON A.P., SAWYER A.M., MORE L., SIM R. Granulomatous vasculitis in Crohn's disease. *Gastroenterology*, 1991, **100** : 1279-1287.
22. DHILLON A.P., ANTHONY A., SIM R., WAKEFIELD A.J., SANKEY E.A., HUDSON M., ALLISON M.C., POUNDER R.E. Mucosal capillary thrombi in rectal biopsies. *Histopathology*, 1992, **21** : 127-133.
23. HUDSON M., HUTTON R.A., WAKEFIELD A.J., SAWYERR A.M., POUNDER R.E. Evidence for activation of coagulation in Crohn's disease. *Blood. Coagul. Fibrinolysis*, 1992, **3** : 773-778.
24. VECCHI M., CATTANEO M., DE FRANCHIS R., MANUCCI P.M. Risk of thromboembolic complications in patients with inflammatory Bowel disease, study of hemostatis measurements. *Int. J. Clin. Lab. Res.*, 1991, **21** : 165-170.
25. HUDSON M., CHITOLIE A., HUTTON R.A., SMITH M.S.H., POUNDER R.E., WAKEFIELD A.J. Thrombotic vascular risk factors in inflammatory Bowel disease. *Gut*, 1996, **38** : 733-737.
26. CHAMOURD P., GRUNEBAUM L., WIESEL M.L., FREY P.L., WITTERSHEIM C., SAPIN R., BAUMANN R., CAZENAVE J.P. Prothrombin fragment 1+2 and thrombin — antithrombin III complex as markers of activation of blood coagulation in inflammatory Bowel disease. *Eur. J. Gastroenterol. Hepatol.*, 1995, **7** : 1183-1188.
27. SOUTO J.C., MARTINEZ E., ROCA M., MATEO J., PUJOL J., GONZALEZ D., FONTCUBERTA J. Prothrombotic state and signs of endothelial lesion in plasma of patients with inflammatory Bowel disease. *Dig. Dis. Sci.*, 1995, **40** : 1883-1889.
28. CONLAN M.G., HAIRE W.D., BURNETT D.A. Prothrombotic abnormalities in inflammatory Bowel disease. *Dig. Dis. Sci.*, 1989, **34** : 1089-1093.
29. STEVENS T.R.J., JAMES J.P., SIMMONDS N.J., MC CARTHY D.A., LAURENSON I.F., MADDISON P.J., RAMPTON D.S. Circulating Von Willebrand factor in inflammatory Bowel disease. *Gut*, 1992, **33** : 502-506.
30. ALDEBERT D., NOTTEGHEM B., REUMAUX D., LASALLE P., LION G., DESREUMAUX P., DUTHILLEUL P., COLOMBEL J.F. Anti endothelial cell antibodies in sera from patients with inflammatory Bowel disease. *Gastroenterol. Clin. Biol.*, 1995, **19** : 867-870.
31. WEBBERLEY M.J., HART M.T., MELIKIAN V. Thromboembolism in inflammatory Bowel disease : role of platelets. *Gut.*, 1993, **34** : 247-251.
32. CHAMOURD P., GRUNEBAUM L., DUCLOS B., WIESEL L., CAZENAVE J.P. Manifestations biologiques d'un état prothrombotique au cours de la maladie de Crohn évolutive. *Gastroenterol. Clin. Biol.*, 1990, **14** : 203-208.
33. MURCH S.H., MACDONALD T.T., WALKER-SMITH J.A., LEVIN M., LIONETTI P., KLEIN N.J. Disruption of sulphated glycosaminoglycans in intestinal inflammation. *Lancet*, 1993, **341** : 711-714.
34. WAKEFIELD A.J., SAWYER A.M., HUDSON M., DHILLON A.P., POUNDER R.E. Smoking, the oral contraceptive pill, and Crohn's disease. *Dig. Dis. Sci.*, 1991, **36** : 1147-1150.
35. LEVY P.J., TABARES A.H., OLIN J.W. Lower extremity arterial occlusions in young patients with Crohn's colitis and premature atherosclerosis : report of six cases. *Am. J. Gastroenterol.*, 1997, **92** : 494-497.
36. THOMPSON N.P., WAKEFIELD A.J., POUNDER R.E. Inherited disorders of coagulation appear to protect against inflammatory Bowel disease. *Gastroenterology*, 1995, **108** : 1011-1015.
37. GAFFNEY P.R., DOYLE C.T., GAFFNEY A., HOGAN J., HAYES D.P., ANNIS P. Paradoxical response to heparin in 10 patients with ulcerative colitis. *Am. J. Gastroenterol.*, 1995, **90** : 220-223.
38. HUGHES G.R.V. The antiphospholipid syndrome : ten years on. *Lancet*, 1993, **342** : 341-344.
39. LONJON I., BEAUGERIE L., DESCHAMPS A., BARTHET C., CARBONNEL F., NGO Y., COSNES J., ABUAF N., GENDRE J.P. Prévalence et rôle des anticorps anticardiolipine dans la maladie de Crohn. *Gastroenterol. Clin. Biol.*, 1996, **20** : 633-637.
40. CHAMOURD P., GRUNEBAUM L., WIESEL M.L., FREYSSINET J.M., DUCLOS B., CAZENAVE J.P., BAUMANN R. Prevalence and significance of anticardiolipin antibodies in Crohn's disease. *Dig. Dis. Sci.*, 1994, **39** : 1501-1504.
41. MEVORACH D., GOLDBERG Y., GOMORI M., RACHMILEWITZ D. Antiphospholipid syndrome manifested by ischemic stroke in a patient with Crohn's disease. *J. Clin. Gastroenterol.*, 1996, **22** : 141-143.
42. GREENFIELD S.M., TEARE J.P., WHITEHEAD M.W., THOMPSON R.P.H. Case report : amaurosis fugax, Crohn's disease and the anticardiolipin antibody. *Lupus*, 1993, **2** : 271-273.
43. SILBURN P.A., SANDSTROM P.A., STAPLES C., MOWAT P., BOYLE R.S. Deep cerebral venous thrombosis presenting as an encephalitic illness. *Postgrad. Med. J.*, 1996, **72** : 355-368.
44. PAPI C., CIACO A., ALIERNO G., DI BATTISTA G., TALAMANCA L.F., LO RUSSO F., NATALI G., CAPURSO L. Severe ulcerative colitis, dural sinus thrombosis, and the lupus anticoagulant. *Am. J. Gastroenterol.*, 1995, **90** : 1514-1517.
45. AADLAND E., ODEGAARD O.R., ROSETH A., TRY K. Free protein S deficiency in patients with Crohn's disease. *Scand. J. Gastroenterol.*, 1994, **29** : 333-335.
46. KOSTER T., ROSENDAAL F.R., DERONDE H., BRIET E., VANDENBROUCKE J.P., BERTINA R.M. Venous thrombosis due to poor anticoagulant response to activated protein C : Leiden thrombophilia study. *Lancet*, 1993, **342** : 1503-1506.
47. ONKEN J.E., CIACCIA D., GARBUTT J.T., ORTEL T.L. Activated protein C resistance phenotype in patients with inflammatory Bowel disease. *Gastroenterology*, 1997, **112** : A1056 (abstract).
48. REES M.W., RODGERS G.M. Homocysteinemia : association of a metabolic disorder with vascular disease and thrombosis. *Thrombos. Res.*, 1993, **71** : 337-359.
49. CATTANEO M., VECCHI M., ZIGHETTI M.L., SAIBENI S., MARTINELI I., OMODEI P., MANUCCI P.M., DE FRANCHIS R. High prevalence of hyperhomocysteinemia in patients with inflammatory Bowel disease : a pathogenic link with thromboembolic complications ? *Thromb. Haemost.*, 1998, **80** : 542-545.
50. SLOT W.B., VAN KASTEEL V., COERKAMP E.G., SEELEN P.J., VAN DER WERF S.D.J. Severe thrombotic complications in a post partum patient with active Crohn's disease resulting in ischemic spinal cord injury. *Dig. Dis. Sci.*, 1995, **40** : 1395-1399.
51. GONERA R.K., TIMMERHUIS T.P.J, LEYTEN A.C.M., VAN DER HEUL C. Brief report : two thrombotic complications in a patient with active ulcerative colitis. *Neth. J. Med.*, 1997, **50** : 88-91.
52. TSUJIKAWA T., IHARA T., SASAKI M., INOUE H., FUJIYAMA

Y., BAMBA T. Effectiveness of combined anticoagulant therapy for extending portal vein thrombosis in Crohn's disease. *Dis. Colon. Rectum.*, 1996, **39** : 823-825.
53. ZUND G., ENZLER M.A., BRUNNER U., SCHIMMER R., SCHOPKE W., LAGIADER F. Akute ischamie der unteren extremitat bei einem jugendlichen mit morbus Crohn. *Vasa*, 1992, **21** : 216-218.
54. KHAMASHTA M.A., CUADRADO M.J., MUJIC F., TAUB N.A., HUNT B.J., HUGHES G.R.V. The management of thrombosis in the antiphospholipid antibody syndrome. *N. Eng. J. Med.*, 1995, **332** : 993-997.
55. KORZENIK J.R. IBD : a vascular disorder ? The case for heparin therapy. *Inflamm. Bowel. Dis.*, 1997, **3** : 87-94.