# Chronic lymphocytic leukemia with portal hypertension and without liver involvement : A case report underlining the roles of increased spleno-portal blood flow and "protective" sinusoidal vasoconstriction

J.Y. Wilputte[1], J.P. Martinet[2], P. Nguyen[3], P. Damoiseaux[3], J. Rahier[4], A. Geubel[1]

(1) Service de gastroentérologie ; (4) Service d'anatomopathologie, cliniques UCL St Luc, Bruxelles ; (2) Service de gastroentérologie, cliniques UCL de Mont-Godinne, Yvoir ; (3) Service de médecine interne, C.H. Dinant.

## Abstract

**We report the case of a 72-year-old woman with well-controlled chronic lymphocytic leukemia (CLL) and splenomegaly who developed portal hypertension with bleeding oesophageal varices in the absence of liver fibrosis or regenerative nodular hyperplasia at surgical wedge liver biopsy. The hepatic venous pressure gradient (HVPG) was elevated and splenectomy resulted in both its normalisation and the regression of oesophageal varices. This case shows the potential for an increased spleno-portal flow to generate severe portal hypertension likely through a "protective" sinusoidal vasoconstriction.** (Acta gastroenterol. belg., **2003**, 66, **303-306**).

**Key words** : portal hypertension, chronic lymphocytic leukemia.

## Introduction

In CLL without liver infiltration, overt portal hypertension is an extremely rare event. A single case has been reported in association with regenerative nodular hyperplasia. Three other poorly symptomatic cases with moderately elevated HVPG (8, 8 and 11 mm Hg) have also been reported. In another case in which portal hypertension was likely related to both liver infiltration and increased splenic blood flow, splenectomy resulted in the disappearance of portal hypertension. We report the case of a patient with CLL and splenomegaly in whom bleeding oesophageal varices led to the diagnosis of portal hypertension in the absence of regenerative nodular hyperplasia or significant liver lymphocytic infiltration. In this case, HVPG was unexpectedly strikingly elevated and normalized following splenectomy. This observation strongly favours the pathogenic role of an increased splenic blood flow alone in the genesis of severe portal hypertension, which was entirely reversible following splenectomy. It also raises the question of the diagnostic value of the HVPG as a reliable indicator of sinusoidal and/or post-sinusoidal portal hypertension.

## Case report

In June 1997, a 72-year old non-alcoholic woman was referred for melaena, weakness and mild pulmonary oedema. Her past history included a type II diabetes mellitus and a CLL, diagnosed 5 year before, for the treatment of which methylprednisolone and chlorambucil have been discontinued one year before admission. Liver function tests remained normal during these last five years. At admission she was pale and clinical examination disclosed splenomegaly (known since the diagnosis of LLC) but no hepatomegaly or adenopathy or ascites. Blood cell count was compatible with microcytic anemia (haemoglobin : 8.5 g/dl and MCV : 77 $\mu^3$) and iron deficiency was documented. The serum albumin, bilirubin, prothrombin time, ASAT, ALAT, $\gamma$-GT and Alkaline phosphatase were normal. Other causes of chronic liver disease were ruled out on the basis of negative HBS Ag, anti-HBC Ab, anti-HCV Ab, antinuclear Ab, antimitochondrial Ab, anti-smooth muscle Ab, anti-LKM Ab and normal serum concentrations for alpha-1-antitrypsin. The C-14 Aminopyrine breath test was normal. An upper gastro-intestinal endoscopy revealed unexpected grade 3 oesophageal varices. At computed tomography, the presence of an enlarged spleen was confirmed (18 cm) ; the liver parenchyma was unremarkable. Two Doppler-ultrasound examinations disclosed a patent portal vein with a hepatopetal flow and a normal velocity. Hepatic vein catheterisation was performed and showed an increased HVPG at 24 mm Hg (wedged pressure : 28 mm Hg ; free pressure : 4 mm Hg) suggestive of a portal hypertension of the sinusoidal and/or post-sinusoidal type. A colloidal sulfur-technetium isotopic scan further confirmed the splenomegaly with an increased uptake of the tracer in the spleen. At laparoscopy, the liver appeared normal in size and appearance ; there was no overt sign of peritoneal portal hypertension. Liver biopsy showed only a mild macrovesicular steatosis and slightly enlarged sinusoids containing a few mononuclear cells, while fibrosis and cholestasis were absent in both the lobules and the portal tracts (Fig. 1A and B). Since beta-blockers were contra-indicated because of recent pulmonary oedema and diabetes, the patient was discharged without any primary prophylaxis for variceal bleeding. Nevertheless, portal hypertension was believed partly involved in chronic microcytic anemia although no red sign was seen on varices at the time of endoscopy.

Address for reprints : A. Geubel, service de gastroentérologie, Cliniques universitaires Saint-Luc, av. Hippocrate, 10, 1200 Bruxelles.
E-mail : geubel@gaen.ucl.ac.be.

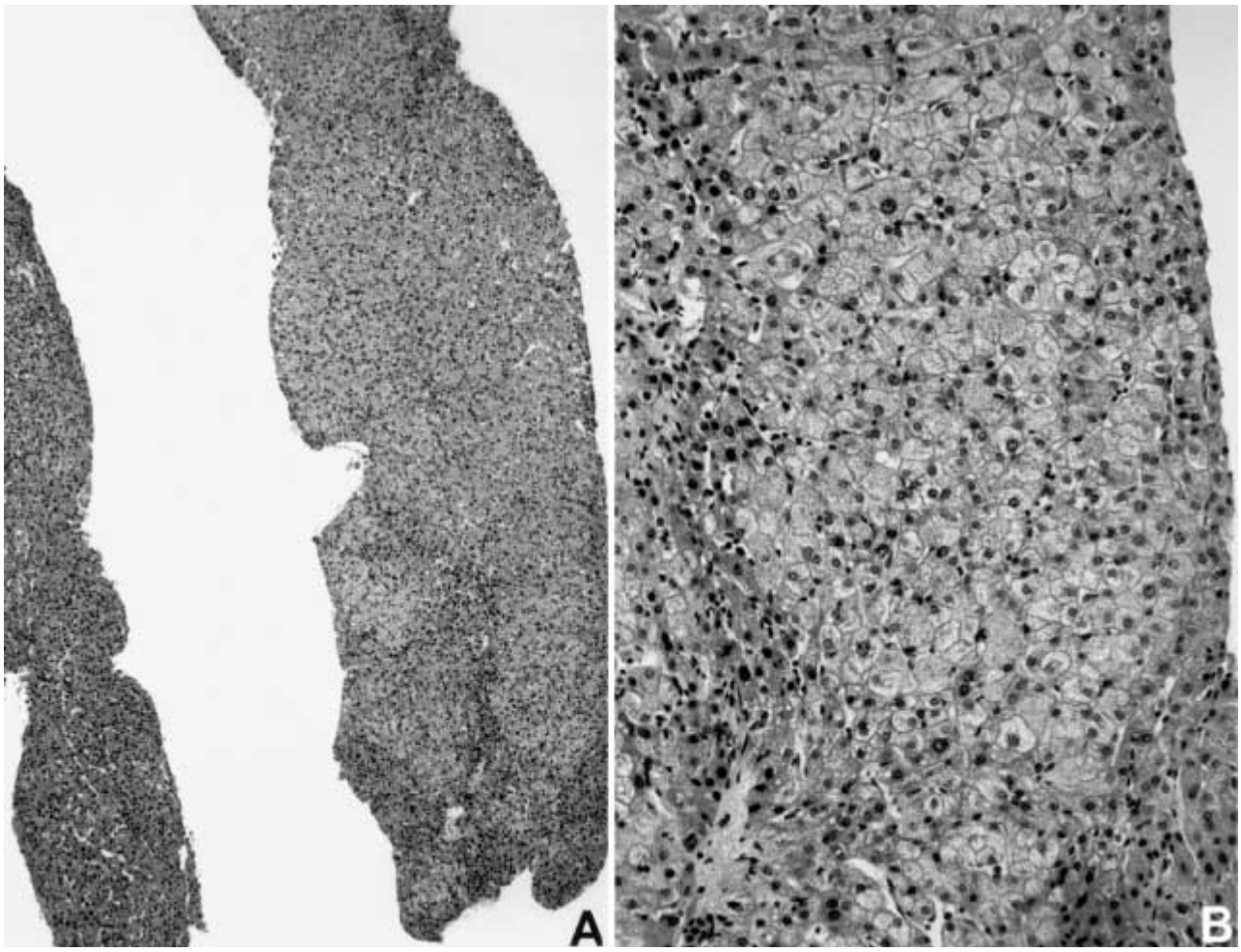


Fig. 1. — Low magnification liver biopsy shows a normal aspect with a preserved architecture without any fibrosis or nodularity (A). Higher magnification of the same biopsy showing the presence of a slight sinusoidal lymphocytic infiltration (B).

She was readmitted in October 1997 for upper GI bleeding. At that time, clinical examination disclosed ascites and splenomegaly but without hepatomegaly. Upper GI endoscopy showed grade 3 oesophageal varices with red spots, varices were treated by band ligations that allowed a rapid control of bleeding. Ascitic fluid examination showed 7 g/l of proteins and only 10 leucocytes/ml whereas there was 68 g/l of protein in the plasma with 35 g/l of albumin. Considering that portal hypertension was mainly due to an increased splenic blood flow despite the elevated HVPG, a splenectomy was performed one month later. At laparotomy, the portal vein was patent, normal in appearance, without any narrowing or compression by hilar lymph nodes. The spleen weighted 1340 grams and was infiltrated by numerous B-lymphocytes expressing CD20 and CD5. A surgical wedge liver biopsy was obtained and showed only a few B-lymphocytes positives for CD20 and MB2 in sinusoids and portal tracts, in the absence of fibrosis. The reticulin stain showed a normal reticulin network. Two weeks after surgery, the size of oesophageal varices was reduced. After seven months, the patient was doing well, without relapsing bleeding and a further endoscopy showed a reduction in the size of oesophageal varices. Two months later, a repeated hepatic vein catheterisation showed the absence of HVPG with wedge and free pressures both being at 3 mm Hg. The control liver biopsy obtained through the transjugular approach remained unchanged. The patient eventually died three years later due to a sepsis related to Streptococcus Pneumoniae despite adequate vaccination before splenectomy.

## Discussion

We have reported on variceal oesophageal haemorrhage complicating portal hypertension in a patient with stable CLL, splenomegaly, increased HVPG and repeatedly nearly normal liver histology. Splenectomy resulted both in the regression of oesophageal varices and in the normalisation of the HVPG.

Clinically important portal hypertension has been seldom reported in CLL. All cases but one were associated with liver lymphocytic infiltration seen mainly in the

portal triads (1,2,3), in sinusoids (4,5) or both (6). In the remaining case, portal hypertension was related to the presence of regenerative nodular hyperplasia (7). When lymphocytic liver infiltration was a feature, HVPG was found elevated if there was sinusoidal or combined (sinusoidal and portal) infiltration, and was absent if the infiltration was confined to the portal tracts (8).

In two cohort prospective studies (9,10) 3 cases of CLL with increased HVPG and absence of any liver infiltration were reported. In these 3 cases HVPG was slightly elevated (8, 8 and 11 mm Hg). The 3 patients were essentially asymptomatic with no oesophageal varices but slight ascites.

On the contrary, our case was characterized by both a minimal lymphocytic liver infiltration and by a strikingly increased HVPG. The presence of nodular regenerative hyperplasia as well as septal cirrhosis were considered highly unlikely on the basis of repeated liver biopsies, one of which being a wedge surgical specimen obtained at laparotomy which exhibited a normal reticulin stain**.**

In portal hypertension associated with CLL, the pathophysiology of portal hypertension remains ill defined, being related both to the presence of liver infiltration and an increased splenic blood flow due to splenomegaly (11). Argument in favour of the role of the latter includes the reports of regression of portal hypertension following splenectomy in CLL (12) or other myeloproliferative (13) and lymphoproliferative disorders (14,15,16,17,18). In our case, the absence of significant liver infiltration together with the regression of features of portal hypertension strongly suggests that the sole increase in splenic blood flow played a major role. In this hypothesis, the HVPG was elevated suggesting a sinusoidal bloc, which normalised following splenectomy. Only two cases in which moderately elevated HVPG (6 and 11 mmHg) normalized after splenectomy have been reported : one with a splenic arteriovenous fistula (19) and a liver biopsy showing minimal septal and pericentral fibrosis together with mild periportal inflammation and a second one with lymphoma (14) in which liver histology showed dilated sinusoids and a lymphoproliferative infiltrate. In addition, Dubois *et al.* (9) showed in a prospective study of poorly symptomatic lymphoproliferative and myeloproliferative disorders (with mild ascites and no oesophageal varices) that 27% patients with increased portal flow without hepatic infiltration had a moderately elevated HVPG (up to 11 mm Hg).

Our case shares similarities with the syndrome termed "non cirrhotic portal hypertension" in which perisinusoidal fibrosis has been demonstrated at electron microscopy (20). This entity, probably described for the first time by Guido Banti in the 1880's, appears to account for almost one third of portal hypertension in India or in Japan and is associated with frequent variceal haemorrhage in 25 to 35 year old patients. In this condition, splenomegaly and the consecutive increase of spleno-portal blood flow are believed a the predominant factor and the enhancer of the portal hypertension (21). Portal hypertension in our case also resembles that observed in idiopathic tropical splenomegaly (22) in which splenomegaly is also the source of an increase in spleno-portal blood flow and in which liver biopsy shows portal or sinusoidal lymphocytic infiltration. More than half of the cases with this condition exhibit an elevated wedge hepatic venous pressure, this pressure being closely correlated with the increase in liver blood flow. Moreover, HVPG was elevated in 9 out 15 cases and decreased after splenectomy in two.

In our case, no anatomical changes could account for either portal or sinusoidal fixed resistance to portal blood flow. The complete reversibility of the HVPG after splenectomy along with a normal histology strongly suggests a dynamic increase in sinusoidal resistance to portal flow. We assumed that the increase in splenic blood flow was the main contributor to portal hypertension. However, in this hypothesis, the sole increase in portal blood flow is unlikely to be associated with strikingly increased HVPG. This strongly suggests the major role for an increased intrahepatic resistance due to a "protective" sinusoidal vasoconstriction. Such a "protection" has been documented in human arterioportal fistula with muscular hypertrophy of portal vessels and minimal fibrosis (19,23,24). This protection against increased blood flow could take place in the sinusoids, where the stellate cells are the main regulators of the vascular tone (25). This hypothesis is supported by the documented transformation of the stellate cells into myofibroblastic-like cells in myeloid metaplasia (26,27).

Splenectomy in patients with haematological malignancies carries a substantial risk. This procedure is accompagnied by an increased mortality (up to 19%) and morbidity (about 50%) : infections, bleedings, portal thrombosis, hepatic enlargement due to myeloid metaplasia,… (28,29,30). Among these complications, sepsis, especially from Streptococcus pneumoniae, can reached a risk of 2.3 per 100 person-years or a relative risk up to 28 compared to the general population (31,32,33). More, the risk of portal vein thrombosis can reached about 10% (34,35,36). In haematological disorders, splenectomy must than only be considered for patients suffering from painful splenomegaly, anemia, thrombocytopenia, therapy-resistant disease, autoimmune phenomena or symptomatic portal hypertension (29,37,38).

In conclusion, we have reported a case of CLL with splenomegaly complicated by bleeding oesophageal varices due to severe portal hypertension. The absence of fibrosis or significant lymphocytic infiltration suggests that the main contributor for this portal hypertension was of presinusoidal origin, through an increased spleno-portal blood flow. This hypothesis was confirmed by the reversibility of the oesophageal varices after splenectomy. The huge HVPG (24 mm Hg),which was also completely reversible after splenectomy, rather

suggests that portal hypertension is of the sinusoidal and/or the post-sinusoidal type. It also suggests that, at least in that peculiar situation, elevated HVPG might closely reflect the extent of the protective vasoconstriction against increased spleno-portal blood flow.

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