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Haematological splenomegaly does not directly relate to portal hypertension: From a clinical study to surgical choice

Antonio Manenti[1], Fabio Forghieri[2], Maurizio Zizzo[1], Dario Colasanto[3], Mario Luppi[2]

ABSTRACT

Background: Splenomegaly induces an increased inflow into the portal venous system; however, in the absence of pathology of the liver and of a portal vein system, secondary portal hypertension is unusual. We analyzed this problem through a clinical observational method.

Methods: We selected 20 patients with splenomegaly secondary to B-cell chronic lymphocytic leukaemia; their imaging tests and clinical pathways were re-examined.

Results: In the absence of diseases of the liver or of the portal venous system, an increased portal blood flow, secondary to the splenomegaly, could not be considered the sole cause of portal hypertension.

Conclusions: The normal liver has a high venous capacity, and in the absence of other factors, the sole increase in portal venous flow cannot directly justify portal hypertension. This conclusion is still well founded, even if multiple humoral mediators, some of which are also released from the spleen in a number of pathological conditions, can differentially modulate the haemodynamics of hepatic sinusoids.

Key words: *Splenomegaly, portal hypertension, chronic lymphocytic leukaemia*

Introduction

A primitive splenomegaly increases blood inflow in the portal venous system. In the absence of comorbidities of the liver or of the portal venous system, this pathology can be hardly considered the unique cause of portal hypertension (PH). We tested this hypothesis through a retrospective observational clinical study in patients with splenomegaly secondary to B-cell chronic lymphocytic leukaemia, considering this condition a suitable model of over-inflow in the portal system [1-6]. Patients with splenomegaly that was secondary to other haematological diseases, especially myelofibrosis or myeloid leukaemia, were excluded for the more frequent secondary liver haematopoiesis or leukemic infiltration.

Patients and Methods

In Western countries, the presently rare occurrence of splenomegaly in adults obliged us to find a homogeneous historical cohort of cases among haematological patients. We identified a clinical condition suitable for our study in splenomegaly secondary to B-cell chronic lymphocytic leukaemia as a consequence of its usually long clinical course.

Author affiliations : *[1]Department of Surgery, [2]Department of Haematology, [3]Department of Radiology, University of Modena, Italy*
Correspondence : *Antonio Manenti, MD, Department of Surgery, University of Modena, Modena, Italy. e-mail: antonio.manenti@unimore.it*
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Inclusion criteria

We included only cases with a chronic course of hematologic disease for what would be an exhaustive clinical study. For their enrolment, we considered the following features as discriminating: a homogenous and solid splenomegaly with a volume > 1,000 ml secondary to a chronic B-cell lymphocytic leukaemia without secondary infiltration of the liver or of other organs, a still-normal hematocrit and platelet count, an accurate imaging study, including colour Doppler ultrasound (US), contrast-enhanced multi-slice computed tomography (CT), and a follow-up of 2 years. In each case, a condition of real splenomegaly was determined with CT software [7,8]. Upper digestive endoscopy was considered necessary only in case of indicative digestive symptoms.

Exclusion criteria

At first, the exclusion criteria were haematological: systemic disease onsets, including hepatic, gastro-intestinal or genito-urinary disorders, previous pharmacological treatments, spleen radiotherapy, evolution of the chronic haematological pathology toward a more aggressive malignant disease, or extramedullary haematopoiesis. Similarly, patients with associated portal vein thrombosis or compression from adjacent lymph nodes were not considered because of a possible condition of pre-hepatic PH.

We also excluded patients with associated focal splenic lesions (cyst, abscess, hamartoma, haematoma, arterial-venous fistula, capillary angiomatosis, infarction, etc.), perisplenic infiltration (sugar-iced spleen), and splenic vein abnormalities other than its increased diameter.

Cases with abnormal hepatic morphology, altered liver functional tests, ascites, HBV or HCV positivity, detected at first diagnosis, or observed in the follow-up were excluded.

Following these parameters, we selected a 20-patient cohort (15 males and 5 females), aged between 50 and 75 years, all with chronic B-cell lymphatic leukaemia at an intermediate risk corresponding to a Rai stage II. In all these cases, the results of clinical, laboratory and imaging tests were re-examined, as well as their follow-up up to 2 years.

Results

The calculated mean volume of the spleen was 2,971 ml, ranging from 1,400 to 4,720ml, the normal value being between 107 and 314 ml. The splenic longitudinal axis was proportionally augmented and the splenic parenchyma always showed a homogeneous contrast enhancement.

The splenic vein, with US and CT, consistently appeared enlarged throughout its entire course without

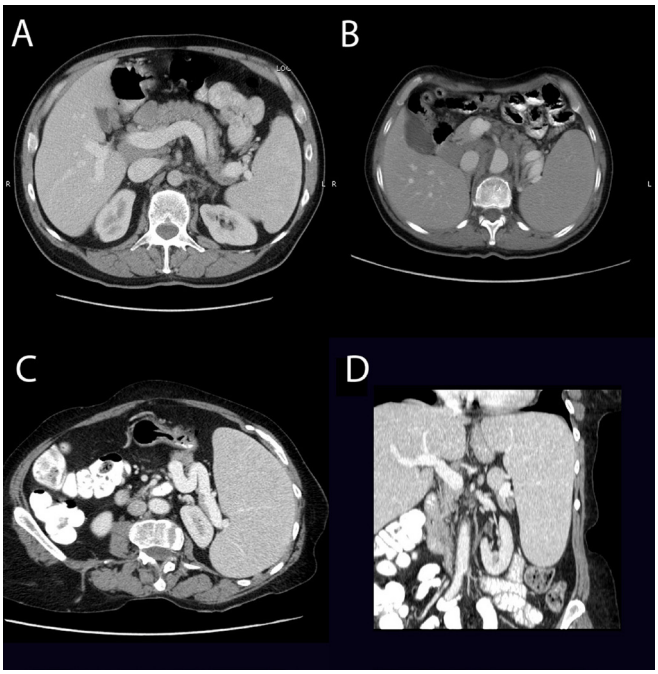

Figure 1. CT images in different cases of chronic B-cell lymphocytic leukaemia. **(A)** The splenic vein is regularly enlarged throughout its entire course while the portal vein looks normal. **(B)** The splenic vein is enlarged and follows a winding course. **(C)** The splenic vein is enlarged. **(D)** Coronal reformatted image of the same case - the portal trunk at the hepatic hilum is normal.

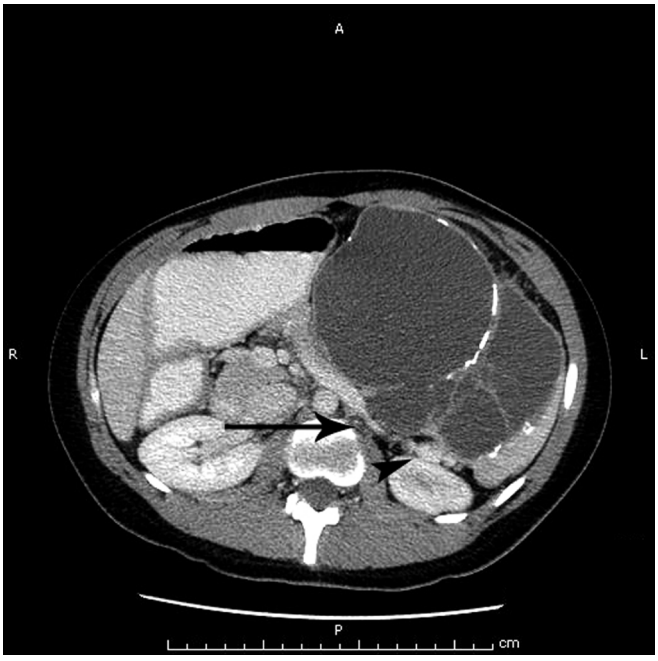

Figure 2. CT of comparison: splenomegaly from multi-cystic hydatid disease of the spleen. Extrinsic compression on the splenic vein (arrow), with secondary left-sided PH, and spleno-renal collaterals (arrow head).

any sign of compression or thrombosis (Figure 1). No sign of segmental PH was found in any district of the portal venous system, particularly in the gastro-splenic area, suggesting a left-sided PH (Figure 2) [9].

Portal blood flow, investigated by US, always demonstrated a normal direction towards the hepatic hilum with a pulsatile feature and a speed proportionally increasing with splenic volume. The cross-sectional area of the portal vein was always within normal value limits. The progressive increase of splenomegaly, often observed in the follow-up, was complicated by subcortical infarcts in 3 cases, but never by clinical or imaging signs of PH.

Discussion

In our study, we avoided invasive procedures of direct measurement of the portal venous pressure, which envisage some risks in haematological patients. Likewise, hepatic biopsies were not performed having already excluded morpho-functional liver abnormalities.

In all our cases, CT and US allowed a detailed study of the spleen and of the entire portal venous system, carefully excluding signs of PH, especially of porto-systemic shunts [10-13]. During the entire follow-up period, the splenic vein, which had always appeared enlarged, did not show other lesions, in particular thrombosis, compression, or development of secondary collaterals.

In principle, we considered a simple and direct correspondence between splenomegaly and PH as being incorrect. Splenomegaly can undoubtedly cause an increase in portal blood flow, but it is not sufficient by itself to directly determine PH. This proves the liver's high venous capacity [14]. As a consequence, the hypothesis of an exclusive and determinant "forward" factor can hardly be accepted in the absence of abnormalities of the liver or of the portal venous system.

In hepatic cirrhosis, other particular physio-pathological mechanisms contribute to PH; among them, increased intra-hepatic resistance, vasodilatation, and hyper-dynamic circulation in the splanchnic area promoted by different mediators [15-20]. In this context, a portal venous overload, secondary to splenomegaly, can be considered an adjuvant, but not the exclusive and major factor. However, it must be admitted that a PH of different origin can cause congestion and a secondary splenomegaly, thus further worsening, through a vicious circle, portal haemodynamics [14].

The condition of an arterio-portal fistula, where the portal overload at a systemic pressure causes a secondary PH through arterialization and intimal hyperplasia of the intra-hepatic fine portal branches and liver sinusoids, is completely different [21]. Other patho-physiological correlations between splenomegaly and PH are not simply hemodynamic, but bio-humoral ones, deservingof further analysis [22-25].

In the case of liver cirrhosis, it has been demonstrated that congested splanchnic organs, the spleen included, release endothelin-1 that promotes vasoconstriction of the hepatic sinusoids. However, this function cannot be considered particularly influential in the case of splenomegaly secondary to chronic lymphocytic leukaemia, where not a simple venous congestion but a massive infiltration of neoplastic cells involves the splenic parenchyma. On the contrary, a progressive massive leukaemic involvement of lymphoid organs is followed by release of different cytokines, such as a-TNF and interleukins 17 and 6, which promote vasodilatation in the systemic capillaries, either directly or through release of oxygen radicals, chiefly nitric oxide and its metabolites. A similar action can be expected to also involve the liver sinusoids. Nevertheless, this event cannot be considered relevant for our cases of chronic lymphocytic leukaemia.

These clinical observations appear impressive, especially considering that our previous experimental studies were performed with animals (dog) in order to study the effects of overflow in the portal system and the determined patho-physiological consequences could not be directly linked to human pathology. We demonstrated that an acute increase in portal flow is rapidly followed by oedema of the hepatic parenchyma, clear congestion of the entire portal venous system and the connected splanchnic organs, and opening of many porto-systemic collaterals [26].

Conclusions

Splenomegaly and PH are often two different comorbid clinical syndromes not necessarily related to each other. When splenomegaly is associated to a condition of PH, demonstrated clinically or by imaging,

a primary disease of the liver or of the portal venous system must be taken into account. On the contrary, in the case of homogeneous splenomegaly without signs of PH, other diseases must be considered - infectious, parasitic, immunological and haematological diseases, and also malignancies.

From a surgical point of view, we can infer that splenectomy, that maintains its indications in peculiar haematological diseases, must not be considered a preventive measure for PH and its complications except in particular cases, like left-sided PH [9].

In the case of liver cirrhosis, splenectomy has particular and limited indications, essentially when it is associated to other procedures such as devascularisation of the upper stomach with esophageal transection, or liver resectioning for HCC, with the primary aim of reducing portal venous overload and to obviate to hypersplenism [27,28]. As for hepatho-splenic bilharziosis, splenectomy has been confirmed to improve coagulation and liver function [29]. Nonetheless, it must be considered that this surgical procedure carries post-operative risks, such as sepsis and thrombosis of the splenic vein stump, especially if of a large calibre, with possible extension to the portal trunk. Moreover, disconnection of important spleno-retroperitoneal venous collaterals can exacerbate portal PH [30].

From a methodological point of view, we highlight that our clinical observational study, focused on a particular topic, allowed reaching patho-physiological conclusions of general interest.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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