Clinicopathologic Session

Case 1/2001 – A 54-year-old male with chronic myeloproliferative disorder and pulmonary thrombotic arteriopathy (Hospital e Maternidade Celso Pierro/Grupo de Estudo em Correlação Anatomoclínica (GECAC) - Pontifícia Universidade Católica - Campinas, SP)

A 54-year-old male was admitted to the hospital in November '97 complaining of frequent episodes of epistaxis for 1 year, and jaundice accompanied by cephalea, anorexia, nausea, and postprandial vomiting. The patient denied the use of alcohol and tobacco, and other significant morbid antecedents.

On physical examination, the patient was icteric (+/4), eupneic, with edema (+/4) in the lower limbs. Cardiac and pulmonary examinations were within the normal range. On abdominal examination, a huge ascites was detected with collateral circulation of the portal type. The liver was palpated 8cm from the right costal margin in the midclavicular line, and 6 cm from the xiphoid process, with an increased consistency (++/4), smooth surface, and it was tender on palpation. On skin examination, numerous petechiae were observed, mainly on the thorax.

The laboratory findings were as follows: hemoglobin, 19.8g/dL; hematocrit, 59.4%, 7,200,000 erythrocytes per mm^3, 40,500 leukocytes per mm^3, and 822,000 platelets per mm^3. The differential count of leukocytes revealed the following: 405 metamyelocytes per mm^3, 2,430 band neutrophils per mm^3, 33,210 segmented neutrophils per mm^3, 800 eosinophils per mm^3, 600 basophils per mm^3, 2,025 lymphocytes per mm^3, 1,030 monocytes per mm^3. Total bilirubin was 2.88mg/dL, direct bilirubin was 1.59mg/dL, and indirect bilirubin was 1.29mg/dL. Serologic reactions for the diagnosis of hepatitis showed a reactive serum for anti-HBs antibodies, for anti-HBc-IgG antibodies, and a nonreactive serum for HBsAg. Serologic investigation for the diagnosis of hepatitis C was negative. The prothrombin time was 22.8s, the prothrombin activity was 26%, and the activated partial thromboplastin time was 75.2s.

On abdominal echography, no flow in the hepatic veins was detected. The abdominal computed tomography showed occlusion of the hepatic veins and partial occlusion of the inferior vena cava (fig. 1).

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The bone marrow biopsy revealed hypercellularity due to the granulocytic series with a large number of megakaryocytes (fig. 2).

The diagnoses of chronic myeloid leukemia, Budd-Chiari syndrome, portal hypertension, and hepatocytic failure were established.

Chemotherapy with hydroxyurea was initiated, but the patient did not use it on a regular basis. During the evolution, 7 hospitalizations occurred, the 4th because of high digestive bleeding due to a gastric ulcer, and the remaining either because of hepatocytic failure with encephalopathy or worsening of the portal hypertension findings. In all hospitalizations, the patient always had a huge ascites, requiring repetitive paracentesis. During the follow-up years, no significant variation in the number of blood-formed elements existed, and no significant variation occurred in hepatic function and in bilirubinemia.

Despite the increase in abdominal volume, the patient never reported dyspnea, except in the 5th hospitalization, when the patient had dyspnea, palpitation, and cyanosis. He remained dyspneic for 7 days. Pulmonary examination was within the normal range. An increase in the intensity of the second cardiac sound in the pulmonary area was detected. No change in blood pressure or in heart rate occurred.

On chest X-ray, the pleuropulmonary fields and the cardiac silhouette were normal.

The electrocardiogram showed sinus rhythm, a heart rate of 75bpm, QRS axis +30°, with a normal duration of the QRS, and a normal duration and amplitude of the P wave.

The last hospitalization occurred 5 months later because of worsening of the hepatocytic failure with severe encephalopathy. The electrocardiogram showed a heart rate of 110bpm, QRS axis +60°, and amplitude of the P wave in DII and aVF of 0.25 mV. The patient died during this hospitalization in metabolic acidosis.

Medical student Sandrigo Mangini

Discussion

Clinical features – The diagnoses of Budd-Chiari syndrome, portal hypertension, and hepatocytic failure were based on complementary tests. Hepatopathy was attribu-

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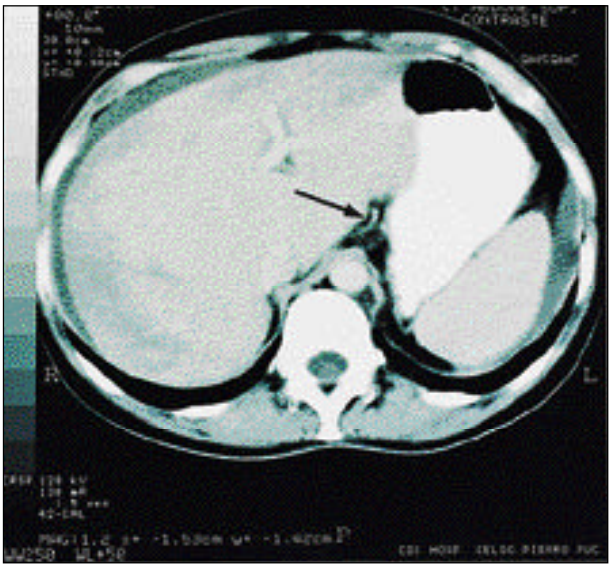

Fig. 1 - Abdominal computed tomography showing hepatomegaly with thrombosis of the inferior vena cava.

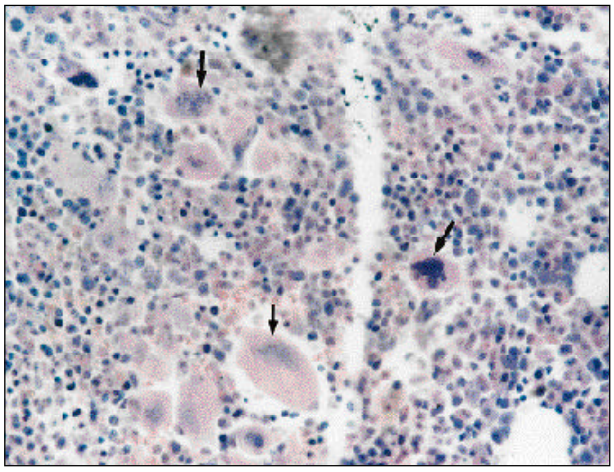

Fig. 2 - Bone marrow biopsy showing hypercellularity due to the granulocytic series and a large number of megakaryocytes (arrows). (Giemsa stain, 400 X magnification).

ted to hepatic congestion. For the diagnosis of chronic myeloid leukemia, the search for the Philadelphia chromosome, which is positive in 95% of the cases, is an important feature, but it was not performed in our case. The patient's evolution showed a progressive clinical worsening of the portal hypertension and of the hepatocytic failure, which resulted in death.

The hypothesis of pulmonary embolism by the occasion of the 5th hospitalization, 5 months prior to death, is plausible. Sudden dyspnea occurred, as did palpitation, cyanosis, and increased intensity of the second heart sound in the pulmonary area. In the presence of predisposing factors to pulmonary embolism (thrombosis of the inferior vena cava and elevation in the number of the formed elements of the blood), the electrocardiogram 10 days prior to death revealed a shift of the QRS axis from +30° to +60°, and a pulmonary P wave in DII and aVF, and may be considered suggestive of pulmonary thromboembolism close to death.

Chronic myeloproliferative disorders (polycythemia vera, essential thrombocythemia, chronic myeloid leukemia, and myelofibrosis) comprise a group of disorders that result from autonomous clonal proliferation of a totipotent primordial cell, which produces a generalized expansion of all bone marrow elements [1-5]. The clinical features of chronic myeloproliferative disorders comprise abnormalities of hemostasis, which manifest as a higher incidence of hemorrhages and thromboembolic phenomena, which are the major causes of morbidity and mortality for these patients [2]. Thromboembolic phenomena involving the pulmonary vasculature have also been reported [4-6].

Thrombotic and hemorrhagic phenomena occur in 30% to 70% of the cases of myeloproliferative disorders [2]. The risk factors for thrombotic phenomena are related to the subgroup of the disease (36% for polycythemia vera; 20% for essential thrombocythemia; 17% for myelofibrosis; and 6% for chronic myeloid leukemia), to the elevated count of erythrocytes and leukocytes, to the patient's age (older than 69 years of age), and to inadequate cytoreduction treatment. Our patient was 54 years old and always had highly elevated formed elements of the blood.

Diagnostic hypotheses – 1) Chronic myeloproliferative disorder; 2) Budd-Chiari syndrome; 3) Pulmonary thromboembolism; 4) Hepatocytic failure; 5) Portal hypertension; 6) Hepatic congestion.

Dr. Maria Aparecida Barone Teixeira

Autopsy

The analysis of a fragment of bone marrow from the costal arch was compatible with the previous biopsy.

Necropsy examination of the liver revealed partial thrombosis of inferior vena cava (fig. 3). Microscopical analysis was consistent with congestion; however, mild ductal hyperplasia in portal tracts and a mild mononuclear infiltrate were also present, favouring the hypothesis of viral aggression despite the serologic scar.

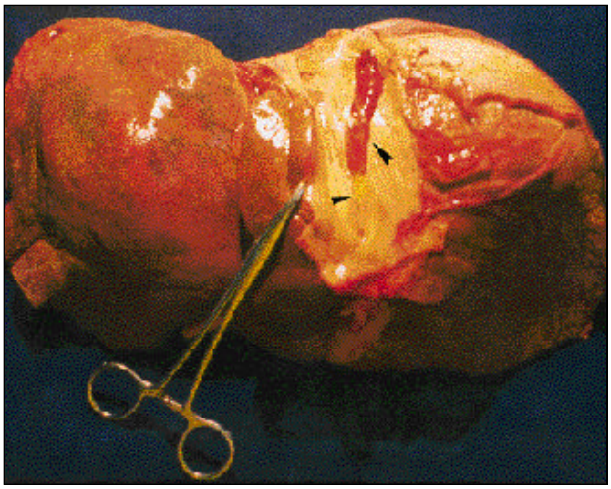

Fig. 3 - External view of the posteroinferior surface of the liver on autopsy showing the open inferior vena cava with a thrombus (arrow).

The heart weighed 250g and showed no alterations in its chambers.

Examination of the lungs revealed bilateral embolism to the major branches of the pulmonary artery in the form of a saddle embolus, in addition to infarction in the base of the right lung.

Microscopic examination revealed thrombotic arteriopathy with recent and recanalized thrombosis, the latter predominating, with irregular proliferation of the tunica intima (fig. 2A), complete obliteration of the lumen, and recanalization with colander-like lesion (fig. 2B). No thickening of the tunica media occurred (fig. 2C). The histopathologic examination also showed a large amount of megakaryocytes in the pulmonary parenchyma.

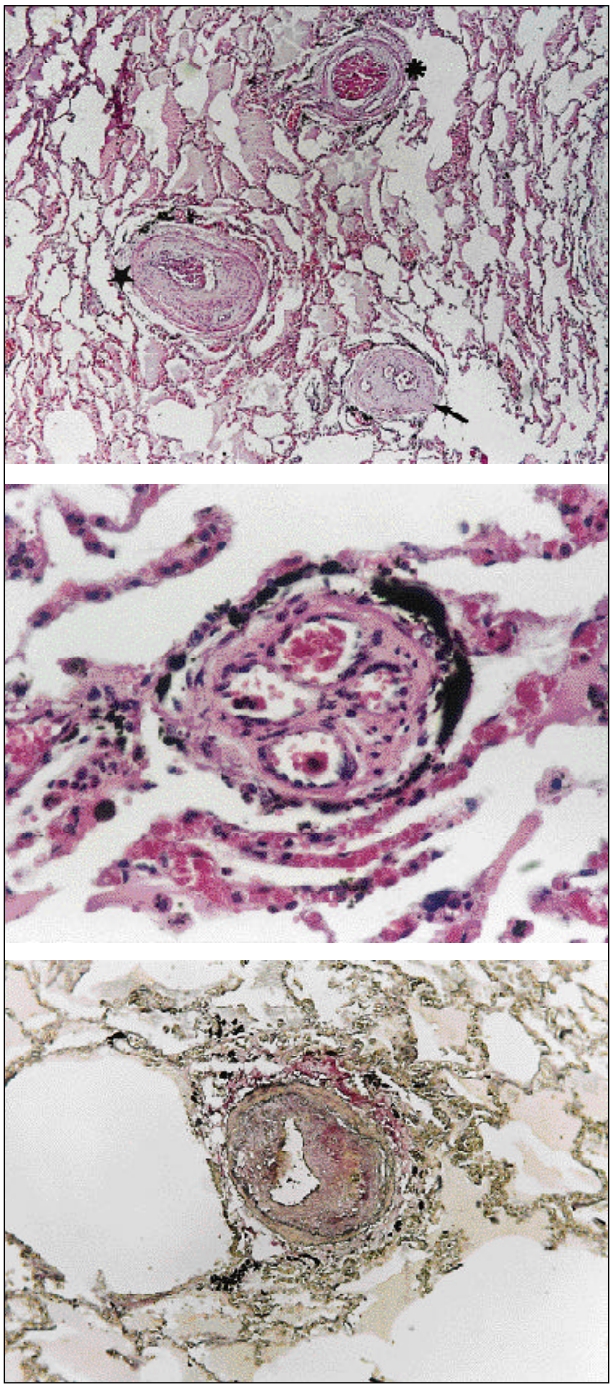

Fig. 4 - A) Microphotograph of the pulmonary parenchyma showing preacinar vessels with a recent thrombosis (asterisk), recanalized thrombosis (arrow), and irregular proliferation of the tunica intima (star). (Hematoxylin and eosin stain, magnification 40X); B) Microphotograph of the colander-like pattern. (Hematoxylin and eosin stain, magnification 400X); C) Microphotograph showing irregular thickening of the tunica intima, with no involvement of the tunica media. (Müller stain, magnification 100X).

This arteriopathy results from repetitive thrombosis or thromboembolism, or both, in pulmonary arteries and arterioles, being one of the causes of pulmonary hypertension. Histologically, this arteriopathy is characterized by recent or organized thrombosis, the latter comprising different patterns of organization (irregular proliferation of the tunica intima, complete obliteration of the lumen, and recanalization), and the tunica media is usually not impaired, unless vasoconstriction is also an associated significant factor [7].

Pulmonary hypertension may be secondary to conditions such as chronic obstructive pulmonary disease, thromboembolic disorder, portal hypertension, persistent hypoxemia, and heart diseases [8]. The pattern of pulmonary thrombotic arteriopathy may occur in primary pulmonary hypertension, and in secondary as well [9], especially in cases of thromboembolism and portal hypertension [10], in the latter being usually associated with plexiform lesions.

Repercussions of pulmonary hypertension on the heart (cor pulmonale) depend on the extension, degree, and duration of the evolution of the lesions in pulmonary vasculature [11], which are clinically well-characterized, when proper investigation is used, and also well characterized in the anatomopathological study.

Anatomopathological diagnoses – 1) Chronic myeloproliferative disorder; 2) Thrombotic arteriopathy; 3) Pulmonary embolism; 4) Chronic viral hepatitis; 5) Phase 3 hepatic congestion.

Drs. Maria Aparecida Barone Teixeira and Vera Demarchi Aiello

Comments

The pattern of hepatic congestion revealed by the microscopic study is in accordance with the hepatocytic function detected by laboratory tests and with the findings of physical examination of the liver. On the other hand, the mild jaundice that the patient constantly had resulted from the intrahepatic cholestasis out of the congestive areas. Autopsy showed a direct correlation between abdominal echography and tomography and the anatomical specimen (fig. 3 A and B), evidencing thrombosis in the inferior vena cava. The postmortem examination, however, did not show thrombosis in the hepatic veins.

For the development of thrombotic arteriopathy, we believe that several factors directly or indirectly related to myeloproliferative disorder have concomitantly contributed.

The diagnosis of thrombosis of the inferior vena cava was made 1 year before the patient's death, and it was a so-

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urce of emboli for the pulmonary vasculature. In regard to thrombocytosis, as an independent risk factor for the development of thrombotic events, Wehmeier et al [2] did not confirm such suspicion. Marvin and Spellberg [5] and Rostagno et al [6], however, correlated the development of pulmonary hypertension to thrombocytosis, this latter being associated with the endothelial lesion (an increase in vasoconstrictive substances) and a higher local platelet activation (an increase in the generation of thrombin, thromboxane B2, beta-thromboglobulin, and fibrinopeptide). An improvement in pulmonary hypertensive findings may occur after treatment with cytoreductants, platelet antiaggregating agents, and anticoagulation agents. Chyczewski et al [12] have shown a greater number of microthrombi in vessels of lungs with a large number of megakaryocytes; in our patient, we found a large number of megakaryocytes in the pulmonary parenchyma.

The relation between portal hypertension and pulmonary hypertension, even though rare, is well known, and its histological pattern is usually plexiform, associated or not with the thrombotic pattern [10]. In our case, we found only the thrombotic pattern, with no association with the plexiform pattern. Therefore, we believe that the relation between portal hypertension and pulmonary hypertension played a less important role in our case.

All factors cited may have contributed to the development of the severe thrombotic lesion, with different stages (recent thrombosis, recanalization with colander-like lesion, fibrosis with total occlusion, asymmetric enlargement of the tunica intima. However, the curious thing is that even though this situation had slowly developed, no direct correlation was found between the heart, which was normal on autopsy study, the absence of clinical signs and symptoms of pulmonary hypertension, and the presence of pulmonary arteriopathy, even though the pressure of the pulmonary artery was not measured.

Some possible hypotheses to explain the existence of a normal right ventricle with chronic pulmonary thromboembolism are as follows: 1) thrombosis of the inferior vena cava may have worked as a limiting agent to blood flow to right heart chambers; 2) a rapid and efficient recanalization of the vessels may have occurred, not allowing hemodynamic changes.

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