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CASE REPORT

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Segmental hepatic vein thrombosis associated with heparin-induced thrombocytopenia II

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Abstract We report the case of a 55-year-old man who developed heparin-induced thrombocytopenia II after a vertebral fracture. Autopsy revealed segmental hepatic vein thrombosis of the right lobe with subacute congestion and an activation of hepatic stellate cells. This case shows that heparin-induced thrombocytopenia II is a possible cause of the Budd-Chiari syndrome.

Key words Liver pathology · Heparin · Thrombocytopenia · Thrombosis · Hepatic stellate cells

Abbreviations *EMC* extracellular matrix components · *HIT* heparin-induced thrombocytopenia · *HSC* hepatic stellate cells · *PC* platelet count · *PF* platelet factor · *aPTT* activated partial thromboplastin time

Introduction

Two types of heparin-induced thrombocytopenia (HIT) have been identified. HIT I is a non-immune event with slight to moderate thrombocytopenia occurring within the first days after the onset of heparin therapy. The patients are usually asymptomatic, and thrombocytopenia resolves despite continuation of heparin administration. HIT II, also known as "white-clot syndrome", is characterized by a delayed moderate-to-severe thrombocytopenia and is frequently associated with vascular thrombosis. It is now widely accepted that HIT II is caused by an immunoglobulin, usually IgG, which is specific for complexes formed between heparin and platelet factor 4 (PF4) [1, 7]. These antibodies activate platelets via their Fc receptors [5, 10] and are also able to recognize complexes of PF4 and endothelial heparan sulfate [6, 19, 24]. These processes may lead to endothelial cell injury and promote procoagulant reactions in arterial and venous vessels [26, 27]. Among heparin-associated venous thrombotic events, deep vein thrombosis, pulmonary embolism, cerebral and adrenal vein thrombosis are most common [25, 26, 27]. A hepatic vein thrombosis associated with HIT II in a normal liver has not been previously reported.

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Clinical history

A 55-year-old man was admitted to hospital and treated with low-dose unfractionated heparin because of immobilization following traumatic vertebral fracture. Platelet count (PC) at the beginning of heparin therapy was 270×10^9/l. After 11 days, an episode of amaurosis fugax occurred, which was followed by cerebral infarction 1 day later. The PC at this time was 16×10^9/l. HIT II was diagnosed by means of an enzyme-linked immunosorbent assay (ELISA) detecting antibodies against the heparin/PF4 complex and, additionally, by means of a heparin-induced platelet-activation assay. Treatment with danaparoid was initiated. PC increased up to 71×10^9/l. Two weeks after beginning danaparoid administration, the patient suffered further ischemic cerebral infarction (PC 28×10^9/l). Anticoagulation was changed to recombinant hirudin because cross-reactivity of danaparoid with heparin-induced antibodies was demonstrated. PC nevertheless remained below 50×10^9/l ($11–47\times10^9$/l). The liver enzymes were slightly increased (aspartate aminotransferase up to 68 IU/l, alanine aminotransferase up to 77 IU/l, γ-glutamyltransferase up to 393 IU/l). No symptoms indicating hepatic vein occlusion (hepatomegaly, ascites, abdominal pain) were noted. Seven weeks after the initial presentation (5 days prior to death), the patient suffered from myocardial infarction and was transferred to the intensive care unit. Despite continuation of activated partial thromboplastin time (aPTT)-controlled anticogulation with hirudin, he died 5 days later. Massive pulmonary embolism was suspected and an autopsy was performed.

Materials and methods

Specimens obtained at autopsy were fixed in 4% buffered formalin. After paraffin-embedding, routine stainings were made and additional immunohistochemical investigation of the liver was performed using the following primary antibodies: smooth-muscle-α-actin, laminin, type-IV collagen (monoclonal mouse antibodies, Dako, Hamburg, Germany) and type-I collagen (polyclonal rabbit antibody, Quartett, Berlin, Germany). The antigen antibody binding was visualized using the avidin-biotin method with 3-amino-9-ethylcarbazol as chromogen.

Pathological findings

The autopsy confirmed massive pulmonary embolism arising from deep vein thrombosis of both legs. In addition, thrombotic stenosis of the left internal carotid artery and thrombotic occlusion of the right internal carotid artery were found. A transmural ischemic infarction in the lateral wall of the left ventricle due to thrombotic occlusion of the circumflex coronary artery was apparent on gross examination. Microscopic examination revealed widespread desintegration of myofibers and onset of marginal fibrovascular response. All occluded vessels showed no ulcerative lesions or advanced atherosclerotic changes. The thrombi were seen on histological examination to be composed of platelets and fibrin, the typical "white clots" [9]. The liver was smooth surfaced and weighed 1950 g. On cut section, the lateral half of the right lobe showed acute hyperemia similar to a Zahn infarct (Fig. 1A), but thrombotic material was visible in medium-sized hepatic veins (Fig. 1B). Ascites and pleural effusion were not found. The main hepatic veins, the vena cava inferior, the portal vein and the hepatic artery were patent without signs of obstructive abnormalities. Microscopic examination showed severe centrilobular congestion with dilatation of sinusoids and recent liver cell loss around terminal hepatic venules in the affected parenchyma of the right lobe. Multiple thrombi, in parts already well organized, were found in medium-sized hepatic veins of the right lobe without extension into terminal hepatic venules or main hepatic veins (Fig. 2). Neither the affected parenchyma nor the rest of the liver showed any signs of perivenular/sinusoidal fibrosis on routine connective tissue stains (Fig. 3A, C). The immunohistochemical staining for laminin, type-I and type-IV collagen did not reveal increased deposition of these components. In the perivenular areas with hepatocellular damage, an increase in number and size of hepatic stellate cells (HSC) was detected by immunostaining for α-actin (Fig. 3D) [18, 21].

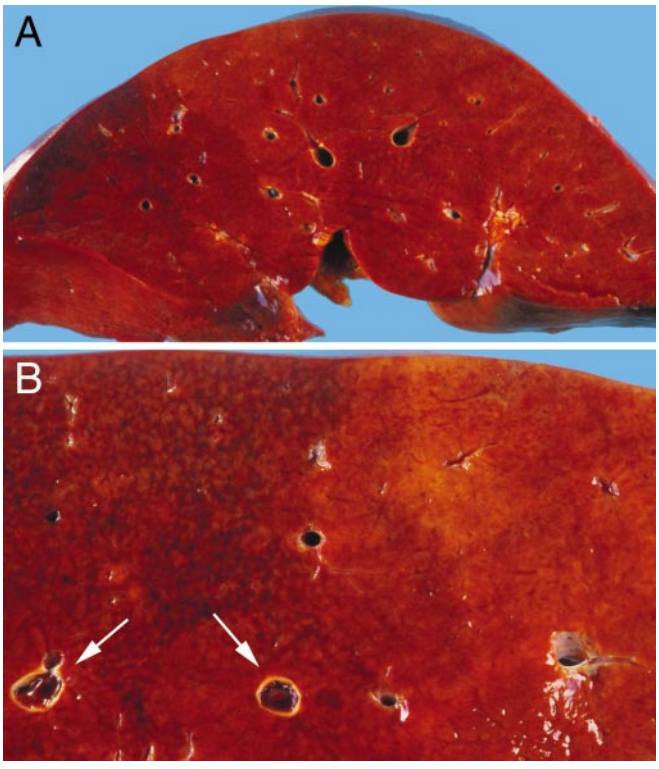

Fig. 1 Cut section of the liver. **A** Congested appearance of the lateral half of the right lobe. **B** Partially obliterating thrombi in medium-sized hepatic veins (*arrows*)

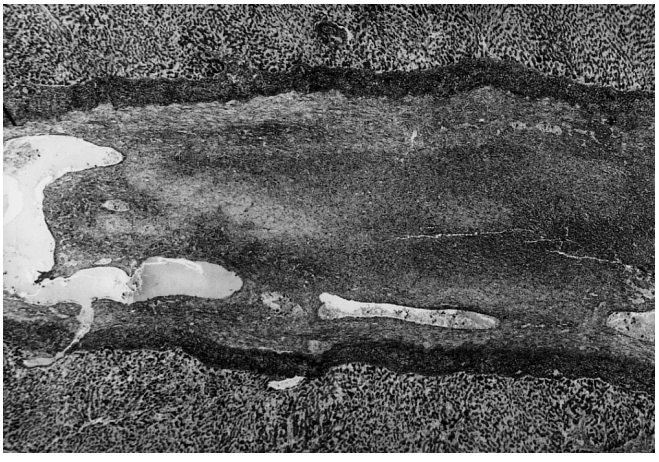

Fig. 2 Organized and partially recanalized hepatic vein thrombosis (acid fuchsin orange G-stain, original magnification 20×)

Discussion

Obstruction of the hepatic venous outflow tract is accompanied by a broad spectrum of symptoms ranging from asymptomatic occlusion to fatal Budd-Chiari syndrome [23]. The latter often occurs in patients predisposed to thrombosis, e.g., in polycythemia vera, paroxysmal nocturnal hemoglobinuria and antithrombin-III deficiency [13, 15, 17, 23]. Budd-Chiari syndrome as a result of HIT II has not been previously reported.

In cases where the obstruction of hepatic veins is limited to one lobe, a normal liver enzyme profile and only mild, transient and non-specific clinical symptoms such as abdominal pain and fever have been reported [2, 20]. The macroscopic appearance of the congested parenchy-

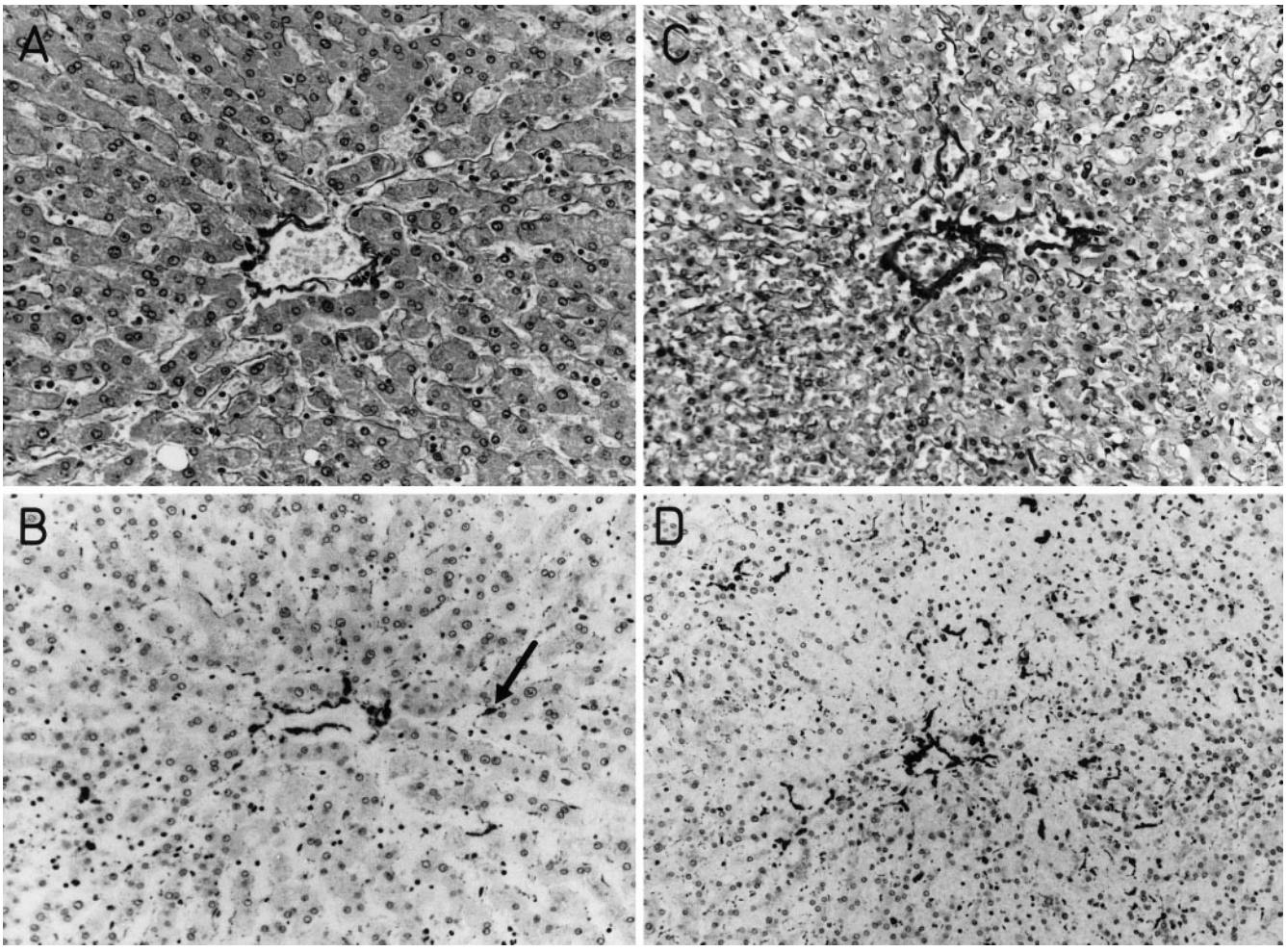

Fig. 3 Perivenous liver parenchyma in the non-congested (**A** and **B**) and in the congested zone (**C** and **D**). **B** There are only few hepatic stellate cells in the non-congested parenchyma (*arrow*). **C** The congested area shows no signs of perisinusoidal fibrosis. **D** The number and size of hepatic stellate cells are increased in the congested zone. (**A** and **C**: sirius-red, original magnification 135×; **B** and **D**: α-actin, original magnification 110×)

ma in unilobular hepatic vein obstruction shows similarity with a Zahn infarct [3]. A long-standing unilobar outflow block can be followed by a partial Budd-Chiari syndrome, which is characterized by parenchymal atrophy and widespread fibrosis in the obstructed lobe while the remnant liver becomes hypertrophied [11, 12].

It is well known that hepatic fibrosis derives from an increase in the production rate of extracellular matrix components (EMC). Fibrillar and non-fibrillar collagens, glycoproteins and proteoglycans are primarily produced by activated HSC [16, 22]. In addition, inhibition of matrix degradation is also a causative factor for excessive accumulation of EMC observed in chronic liver disease [8, 14]. Since the time of thrombus formation can be estimated by 2–4 weeks in the present case, it is possible to investigate changes of liver sinusoids in a definite short time interval after venous outflow obstruction.

Immunoreactivity for α-actin is generally accepted as an indicator of the activated state of HSC, which is characterized by synthesis and secretion of EMC [18, 21]. Despite a significant increase in the number of those activated HSC in the congested parenchyma, an accumulation of EMC could not be detected, either by conventional or by immunohistochemical staining methods. A possible explanation would be that the increased production of EMC may be counterbalanced by enhanced matrix degradation. HSC are the predominant source of major matrix-degrading enzymes [8, 14]. This would fit experimental data showing that matrix production and degradation are stimulated simultaneously in early liver damage. Inhibition of matrix degradation in repeated or continuing injury is responsible for the quantitative and qualitative changes of EMC in the process of irreversible fibrosis [8].

In HIT II, thrombotic involvement of hepatic veins is a rare event. Broughan et al. (1996) have described a case of fulminant thrombotic occlusion of hepatic arteries and veins in a human liver allograft [4]. To our knowledge, localized hepatic vein thrombosis associated with HIT II in a formerly normal liver has not been previously reported. This is in contrast to other hypercoaguable states in which thrombotic involvement of the liver is not uncommon [13, 15, 17, 23]. It has to be empha-

sized that the diagnosis of hepatic vein thrombosis in the present case was an incidental finding at necropsy. The frequency of lesions similar to those reported in our patient might therefore be underestimated because of mild or non-specific symptoms.

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