ELSEVIER

European Journal of Cancer 40 (2004) 2643–2644

European Journal of Cancer

www.ejconline.com

Editorial Comment

Hepatic veno-occlusive disease and portal vein thrombosis; closer than we think?

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Available online 23 September 2004

In the current issue of *EJC*, Brisse and colleagues report on the development of portal vein thrombosis (PVT) in 5 paediatric patients treated with aggressive chemotherapy for various malignancies [1]. Interestingly, they report that 4 out of 5 had evidence of hepatic veno-occlusive disease (HVOD), and this was associated with the use of busulfan. In addition, one of those, treated with intense chemotherapy for resistant disease, had evidence of abdominal sepsis leading to ascending pylephlebitis, which is a recognised cause of PVT and ensuing portal hypertension [2]. This patient died as a direct consequence of uncontrolled gastrointestinal bleeding, and two others from the series have succumbed to their malignancies [1].

HVOD is a clinical syndrome of tender hepatomegaly, fluid retention, hypoalbuminaemia and hyperbilirubinaemia. The histological hallmarks are small vessel endothelial injury, congestion of hepatic sinusoids with necrosis of adjacent hepatocytes and concentric narrowing and fibrosis of hepatic venules. The deranged intrahepatic microcirculation and venous stasis give rise to the clinical picture of portal hypertension. Biological changes described in HVOD include increased serum levels of hyaluronic acid, von Willebrand factor (vWF), thrombomodulin and plasminogen activator inhibitor-1 (PAI-1), depletion of glutathione in the hepatocytes, and upregulation of cytokines, such as tumour necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β) and interleukins-1β, −2, −6 and −8 [3].

PVT is diagnosed on the basis of cavernous transformation of the portal vein, unremarkable hepatic biochemical indices and clinical signs of established portal hypertension, such as splenomegaly, dilated cutaneous abdominal veins and oesophageal varices. The clinical diagnosis is typically made following an acute gastrointestinal bleeding or incidentally on the basis of abdominal distension and asymptomatic splenomegaly with hypersplenism. The aetiology is unknown, but, historically, a proportion of children have had umbilical vessel manipulation and/or neonatal sepsis. Recently, a sizeable groups of both adult and paediatric patients were identified with documented prothrombotic conditions, such as factor V Leiden deficiency and prothrombin gene 20210 G-A heterozygosity, anti-thrombin III, protein S and C deficiency, anti-cardiolipin positivity, homocystinuria and folate reductase deficiency [4].

HVOD is an acute, life-threatening complication of haematopoietic stem cell transplantation (HSCT), following irradiation, conditioning or chemotherapy with busulfan, actinomycin D, 6-thioguanine, cyclophosphamide, gemtuzmab ozogamycin and dacarbazine, or exposure to certain alkaloids, such as pyrrolizidine. In contrast, PVT is rarely diagnosed acutely, which may have contributed to its still elusive pathophysiology. The incidence of HVOD is increased with pre-existing liver disease, while intrahepatic lesions are absent or minimal in PVT.

Kikuchi and colleagues in their large series from adult HSCT recipients have described an incidence of PVT and HVOD of 0.4% [5]. They have suggested that impaired portal vein flow could be secondary to: (a) HVOD-related hepatic sinusoidal obstruction and (b) hypercoagulability induced by the low levels of antithrombin III and protein C due to the temporary failure of hepatic synthetic function [5]. Unfortunately, Brisse and celleagues retrospective series provides no data on

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2004.08.023

the levels of these proteins [1]. In the clinical setting it is often difficult to ascertain whether the low levels of antithrombin III and protein C are the cause or a consequence of liver or vascular injury.

It is tempting to consider that the co-occurrence of HVOD and PVT in both Brisse's and Kikuchi's series is more than coincidental. The simplest explanation may be that PVT could be in keeping with the severity of HVOD, as proposed by Kikuchi and colleagues [5]. It is also conceivable that the relatively well understood pathophysiological mechanisms occurring during HVOD affecting the intrahepatic sinusoidal network could have similarities with less well defined processes damaging the portal vein and leading to PVT. Could the initial trigger, which in HVOD appears to be an endothelial injury of the sinusoidal cells, be responsible for thrombosis in a large vessel such as the portal vein? Approximately one half of adult patients with mild to moderate HVOD post-HSCT have involvement of the hepatic veins [6]. Both TNF-α and IL-1β, that are upregulated in HVOD, are procoagulant and induce expression of leucocyte adhesion molecules E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), on the endothelial cell surface [7]. Furthermore, chemotherapy-induced immunosuppression after HSCT may increase the likelihood of developing abdominal sepsis and ascending pylephlebitis. Finally, individual differences may exist since specific polymorphisms of the glutathione-S-transferase and TNF-α genes have been described in adults developing HVOD [7]. To study these aforementioned above phenomena in the PVT setting, there are at least two major problems: (1) the lack of an adequate experimental model, and (2) the frequent delay in the development of clinical signs and symptoms. Clinicians normally see the patients with PVT *post festum*, when investigation into underlying aetiology and mechanisms becomes more difficult. Closer hepatic Doppler ultrasound surveillance of patients undergoing HSCT by serial assessment of the hepatic artery resistance index and portal flow and further study of coagulation homeostasis in both conditions may provide some information on this interesting concept.

The possibility of a common pathogenic link between HVOD and PVT raises attractive prospects for better management. Defibrotide is a novel agent with modulatory effects on the vascular endothelium, cytokine release and haemostasis and is increasingly used for the treatment of HVOD [8]. Should this drug be tested in the setting of acute PVT, a condition in which paediatricians are reluctant to use thrombolytic agents, such as tissue plasminogen activator (TPA), due to an increased risk of bleeding? This option will need to await a better understanding of the pathogenesis of both conditions, to which the study of Dr. Brisse and his colleagues provides important clinical clues.

Conflict of interest statement

None declared.

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