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Original Paper

Veno-occlusive Disease of the Liver in Right-sided Wilms' Tumours

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Veno-occlusive disease of the liver (VOD) is an important complication in children with Wilms' tumour. Although in most patients this complication resolves uneventfully, fatal cases have been reported. Several observations strongly suggest that actinomycin-D is the likeliest cause of VOD in Wilms' tumour, but VOD seems to be rather uncommon in other malignancies treated with chemotherapy including actinomycin-D. The present case of VOD and the review of the literature stress the pathogenetic and clinical implications of VOD in the presence of a Wilms' tumour treated with actinomycin-D, originating in the right kidney. Greater awareness of this 'predisposing factor' may alert paediatricians to the presence of minimal signs of the syndrome. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: Wilms' tumour, actinomycin-D, liver toxicity, veno-occlusive disease
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INTRODUCTION

THE GREAT success of treatment for Wilms' tumour, even with a considerable reduction in treatment intensity, focuses increasing attention on veno-occlusive disease of the liver (VOD) as one of the major complications in children with the tumour. VOD in children is most commonly observed in those undergoing allogeneic bone marrow transplantation (BMT), and is significantly associated with the intensity of the pretransplant chemotherapy conditioning regimens [1]. Standard dose chemotherapy-induced VOD (SDC-VOD) of the liver in children appears to be a clinical entity distinct from BMT-associated VOD, showing variable severity. The disease is characterised by right abdominal pain, hepatomegaly and ascites, thrombocytopenia and variable elevation of liver enzymes [2]. Although in most patients this complication resolves uneventfully, fatal cases have been described [3].

Several observations of patients undergoing treatment strongly suggest that actinomycin-D is the likeliest cause of SDC-VOD in Wilms' tumour [4–6]. SDC-VOD has also been described in paediatric patients with rhabdomyosarcoma or with other malignant tumours treated with chemotherapy combinations including actinomycin-D, although SDC-VOD seems to be rather uncommon in these latter malignancies [7–9].

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Several hypotheses have been formulated in an attempt to clarify the pathogenesis of SDC-VOD in Wilms' tumour, such as abdominal irradiation on the right side [10, 11], previous hepatitis [12], the administration of halogenated hydrocarbon anaesthetic agents during surgery [13], and the inclusion of vincristine [14] in the chemotherapy schedule. However, the large majority of patients did not receive irradiation [15]; previous hepatitis did not appear to influence the onset of SDC-VOD [16]; in many children the syndrome was observed during pre-operative chemotherapy which included actinomycin-D [4]; and administration of vincristine alone has not caused SDC-VOD in nephroblastoma [17].

It is interesting that left-sided tumours were slightly over 50% in a very large series of patients [18], but most of the reported cases of SDC-VOD were in patients with the right-sided tumours [16, 17, 19–21].

The present case of VOD and the review of the literature stress the pathogenetic and clinical implications of VOD in the presence of a Wilms' tumour treated with actinomycin-D, originating in the right kidney. Greater awareness of this 'predisposing factor' may alert paediatricians to the presence of minimal signs of the syndrome.

PATIENTS AND METHODS

The case history of a 3-year-old child with right-sided Wilms' tumour who developed SDC-VOD is presented. A literature review was undertaken. To avoid selection, sporadic

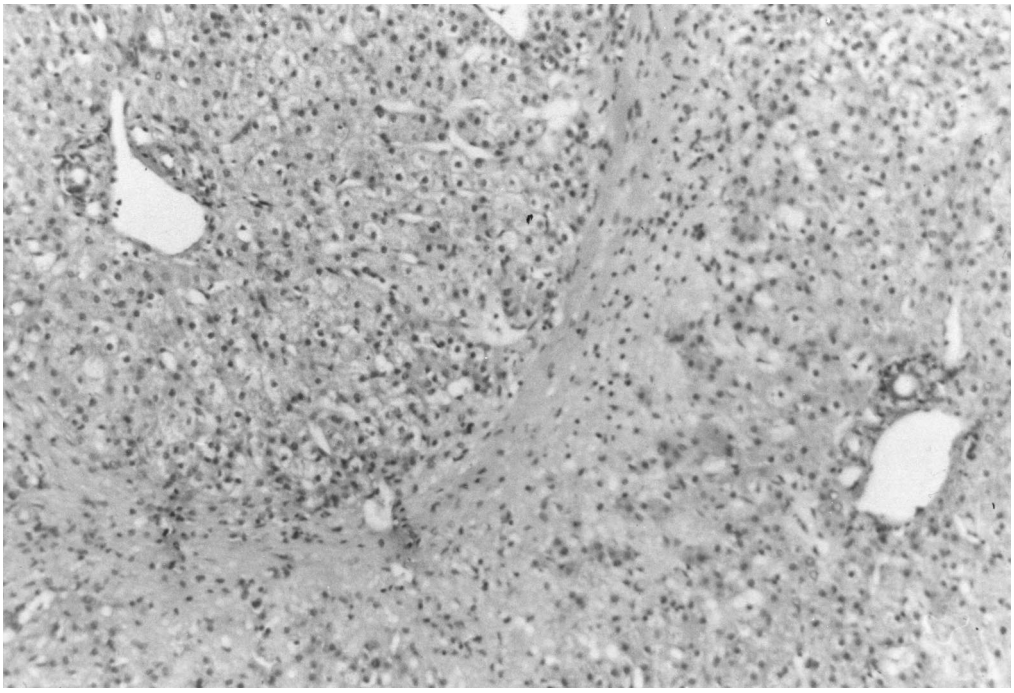

Figure 1. Liver biopsy showing fibrosis with small areas of hepatocellular necrosis; sinusoids are slightly dilated (haematoxylin and eosin×40).

cases were not included in the review evaluation. Also, because postoperative irradiation combined with chemotherapy may lead to an increased probability of hepatotoxicity, only non-irradiated patients were evaluated, except for 1 case of Byork's series who only received 1,000 rads to the tumour bed. In fact, all cases of VOD reported in patients treated with radiation therapy and actinomycin-D had been irradiated with doses > 20 Gy.

RESULTS

Case history

A male aged 3 years with a large, right-sided, stage III, Wilms' tumour and favourable histology, without distant spread, was treated according to the pre-operative SIOP-9 protocol [21]. He had received two courses of actinomycin-D, each consisting of 0.45 mg/m^2/day×3 days at 2 week intervals, as well as vincristine at 1.5 mg/m^2 on days 1 and 8. One week following the last administration of actinomycin-D, the child experienced fever, hepatomegaly, jaundice, ascites and weight gain (+12% from baseline). In addition, he developed a first degree encephalopathy, which developed to third degree during the following day. Haemoglobin was 6.8 g/dl, white blood cells 4,390/mm^3, platelets 12 000/mm^3. A liver profile revealed: serum glutamic-oxaloacetic transaminase (sGOT) 8750 U/l, serum glutamic-pyruvic transaminase (sGPT) 2723 U/l, total bilirubin 4 mg/dl (direct: 2 mg/dl) and lactate dehydrogenase (LDH) 15 790 U/l. Coagulation parameters included: activated partial thromboplastin time (aPTT) 42 sec, prothrombin time (PT) 19%, fibrinogen 223 mg%, fibrin degradation products (FDP) normal. Over the following 24 h, liver enzymes and coagulation parameters appeared slightly more abnormal. At the end of the second day, ultrasonography of the liver showed signs of VOD: generally increased echogenicity, portal vein and its branches dilated with reversed portal flow, free intraperitoneal fluid. Intravenous heparin (6,500 U/24 h) and antithrombin III concentrate infusion (1,000 U/day) were started; after infusion of fresh frozen plasma (10 ml/kg) and platelets in order to reduce the haemorrhagic risk, fibrinolytic treatment with recombinant tissue plasminogen activator (r-tPA, Actilyse, Boehringer) was started (10 mg over 5 h). Then the child underwent replacement treatment with fresh frozen plasma (10 ml/kg) and antithrombin III concentrate (1,000 U/day) together with intravenous heparin (5,000 U/24 h) and r-tPA (12 mg over 5 h for three consecutive daily administrations).

Laboratory tests and serial abdomen Doppler examinations 48 h after the last administration of r-tPA showed a

Table 1. *Side of Wilms' tumour and veno-occlusive disease (VOD): our cases and a review of the literature*

Authors [ref.]	Number of patients with VOD	VOD in right-sided Wilms' tumour	VOD in left-sided Wilms' tumour
Byork and colleagues [16]	4/100	4	0
Green (Roswell Park Cancer Institute, Buffalo, U.S.A.)	15/319	11	4
Ludwig and colleagues [20]	7/136	7	0
Raine and colleagues [17]	5/355	3	2
Our series	2/38	2	0
Total	33	27	6

Binomial test $P = 0.0002$ [21].

normalisation of the hepatic and portal flow, without signs of ascites; antithrombin III concentrate infusion was stopped, while heparin was discontinued a week later.

Within a week of therapy, the child's general condition and the haematochemical parameters rapidly improved. Three weeks later, the child underwent surgery. The liver biopsy led to a histological picture compatible with recent VOD consisting of distended central veins with thrombosis and intramural fibrosis. The adjacent parenchyma showed small areas of hepatocellular necrosis with slightly dilated sinusoids (Figure 1).

Review of the literature

Table 1 shows the side distribution of Wilms' tumour in the reported cases of VOD from the major Cooperative Group Wilms' Tumour Studies and from our series. Data from the literature on monolateral Wilms' tumour localisation showed a highly significant statistical predominance of VOD in right-sided tumour patients (binomial test $P = 0.0002$ [21]).

DISCUSSION

VOD is characterised by an obliteration of the small intrahepatic branches of the hepatic veins due to intimal proliferation and fibrosis associated with centrilobular hepatocellular necrosis. The case presented is an example of severe SDC-VOD. The pathogenesis of SDC-VOD is unknown, but actinomycin-D is the probable cause of this syndrome. However, there is no explanation for the high incidence of SDC-VOD in Wilms' tumour patients as compared with patients with other malignancies [7, 9]. Even more intriguing is the observation that most reported cases of SDC-VOD occurred in patients with a right-sided tumour (see Table 1).

Data from the literature on monolateral Wilms' tumour localisation showed a highly significant statistical predominance of VOD in right-sided tumour patients (binomial test: $P = 0.0002$ [21]). It is interesting to note that, if one considers cases of SDC-VOD after the exclusion of the excess of right-sided tumours, the incidence of this complication appears to be similar in Wilms' tumour patients and in patients with other malignancies [7–9].

Why most of the reported cases of VOD had right-sided tumours is not clear. However, it is possible that the presence of a long-standing mass of the right kidney may interfere with the vascular blood flow of the hepatic veins, blocking the drainage of the liver. The absence of valves in the suprahepatic vessels may have a contributory role in determining a chronic stasis and, consequently, some kind of damage in the sinusoid vessels of the liver. Strong support for this hypothesis is offered by the observation of Ludwig and colleagues [20] who observed that all 7 children with VOD in their large series of Wilms' tumour patients had 'r-sided tumours of huge size' (mean volume 473 cm^3). In other reviews, the weight of the tumour is not mentioned. Furthermore, most patients with Wilms' tumour who developed VOD had received only one or two courses of actinomycin-D-containing chemotherapy regimens. Therefore, VOD would seem to result from a sequential hepatic insult, and actinomycin-D would seem to represent the precipitating factor on top of a long-standing predisposing condition.

Whatever the pathogenesis of this complication may be, and whatever the mechanisms involved in producing its higher incidence in right-sided Wilms' tumour, we believe that paediatric oncologists should be aware that there is increased risk of VOD in right-sided Wilms' tumour and they should be alerted to minimal 'warning signs' of this sometimes life-threatening complication when a right-sided Wilms' tumour is present. Future reports on VOD in Wilms' tumour should specifically provide detailed information on items such as side distribution and weight of the tumour in order to clarify this problem.

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