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Review

Portal vein thrombosis during antineoplastic chemotherapy in children: Report of five cases and review of the literature

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Abstract

We report five paediatric cases of portal vein thrombosis (PVT) occurring during chemotherapy, observed in two institutions over an 8-year time period. These children aged 2.5–15 years were treated for Burkitt's lymphoma, Ewing's tumour, small cell bone tumour or medulloblastoma. PVT was diagnosed on colour Doppler ultrasonography (US). In four patients, thrombosis occurred 2–45 days after severe hepatic veno-occlusive disease (HVOD) secondary to intensive chemotherapy containing busulfan. In one case, PVT occurred in the absence of HVOD in a patient with pre-existing periportal lymphomatous infiltration. Four patients experienced persistent portal hypertension, which resulted in death in one. PVT during chemotherapy in children is a rare event and appears to be closely related to intensive chemotherapy containing busulfan and to be associated with HVOD.

Keywords: Portal vein; Liver; Child; Antineoplastic agents; Alkylating agents; Haematopoietic cell transplantation; Thromboembolism; Hepatic veno-occlusive disease; Ultrasonography

1. Introduction

Portal vein thrombosis (PVT) in children is classically observed after neonatal umbilical vein catheterisation [1]. Rarer causes of secondary obstruction of the portal vein have been reported in children: during abdominal sepsis [2], after splenectomy [3] or after liver transplantation [4]. Hepatoblastoma or hepatocellular carcinoma may also be complicated by PVT [5]. Forms associated with constitutional protein C or protein S deficiency or antiphospholipid syndrome are exceptional [6,7]. Usually, no predisposing factor is identified and PVT is classified as idiopathic, sometimes associated with congenital malformations [8]. The development of PVT during antineoplastic chemotherapy has only rarely been described and mostly in adults after intensive chemotherapy with haematopoietic stem cell transplantation [9–11]. To our knowledge, only three sporadic paediatric cases of PVT during cancer treatment have been reported to date [12,13] and the pathogenesis and the prognosis of these thromboses remain unclear.

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We report five new paediatric cases of PVT occurring during chemotherapy and analyse their possible mechanisms and outcome.

2. Patients and methods

2.1. Patients, diseases and treatment regimen

Medical records of five children with PVT treated between 1992 and 1999 in two institutions were retrospectively analysed (see Table 1). During the same time period, 378 intensive chemotherapies with autologous stem cell transplantation (ASCT) were performed in children in the Institut Gustave Roussy and 196 in the Institut Curie.

Patient No. 1 had Murphy stage III abdominal Burkitt's lymphoma and was treated according to the B-arm of the SFOP LMB (Société Française d' Oncologie Pédiatrique – Lymphome malin de phénotype B) 96 protocol [14], with a first course of COP (cycloph- osphamide, vincristine and prednisolone plus methotrexate and hydrocortisone intrathecal), followed by induction with two courses of COPAdM (cyclophosphamide, vincristine, prednisolone, doxorubicin and methotrexate high-dose plus methotrexate and hydrocortisone intrathecal), and a consolidation phase with two courses of CyM (cytarabine, methotrexate HD plus methotrexate and hydrocortisone intrathecal). Patient No. 2 had stage IV Ewing's tumour and was treated according to the SFOP EW (Société Française d' Oncologie Pédiatrique – Ewing) 93 protocol with five courses of cyclophosphamide (150 mg/m^2/day from day D1 to D7) and doxorubicin (35 mg/m^2/day on D8) [15] followed by three courses of etoposide (100 mg/m^2/day from D1 to D5) and ifosfamide (1.8 g/m^2/day from D1 to D5) [16]. High-dose chemotherapy [17] was then performed using the combination of busulfan (140 mg/m^2/day from D6 to D3) and melphalan (140 mg/m^{2}on D3) with ASCT. Patient No. 3 had stage IV small round cell bone tumour and was treated according to the Ewing's tumour protocol (ongoing Euro-Ewing 99), comprising six courses of VIDE (vincristine 1.5 mg/m^2 on D1, etoposide 150 mg/m^2 from D1 to D3, ifosfamide 3 g/m^2 from D1 to D3 for the first two courses, then cyclophosphamide for the following four courses and doxorubicin 20 mg/m^2 from D1 to D3) and two high-dose chemotherapy regimens with thiotepa (900 mg/m^2 from D6 to D4) and two months later busulfan (150 mg/m^2 for four days) and melphalan (140 mg/m^2), both with ASCT. Patient No. 4 had localised medulloblastoma and was treated with surgery and conventional chemotherapy (Baby Brain Tumour Protocol-CCSG) [18] for 15 months (cisplatin, vincristine, carboplatin, cyclophosphamide, etoposide), then high-dose chemotherapy for local recurrence using busulfan (150 mg/m^2/day for four days) and thiotepa (300 mg/m^2/day for three days) with ASCT. Patient No. 5 had metastatic medulloblastoma treated with surgery and chemotherapy according to the BB-SFOP (Baby Brain-Société Française d' Oncologie Pédiatrique) protocol [19] comprising seven cycles of three courses (cisplatin, procarbazine, vincristine, carboplatin, cyclophosphamide) over a period of 13 months, then intensification for meningeal relapse by busulfan (150 mg/m^2/day for four days) and thiotepa (300 mg/m^2/day for three days) with ASCT.

2.2. Definition of hepatic veno-occlusive disease

Diagnosis of hepatic veno-occlusive disease (HVOD) was based on the definition of McDonald and colleagues [20]: at least two of these three criteria within 30 days of transplantation without alternative explanation: (1) hepatomegaly and/or liver tenderness, (2) weight gain of more than 2% of the baseline weight, (3) elevation of serum bilirubin level of more than 34.2 μmol/l. The grade of HVOD was defined according to Bearman's classification [21]. HVOD was confirmed on liver biopsy in patients No. 3 and 4.

2.3. Diagnosis of portal hypertension

Diagnosis of portal hypertension (PHT) was based either on intrahepatic gradient measurements by transjugular catheterisation in patients No. 3 and 4, or based on clinical or radiological signs (i.e. oesophageal varices or portacaval shunts at Doppler ultrasonography (US)).

2.4. Ultrasound criteria of portal vein thrombosis

PVT was diagnosed if echogenic material and/or loss of Doppler signal were observed in the main portal vein, the main portal branches and/or in segmental portal branches.

3. Results

3.1. Frequency of portal vein thrombosis

Fives cases were observed between 1992 and 1999 in the two institutions. Four were observed after intensive chemotherapy, thus this constitutes 4/574 or a crude percent of 0.7% of all intensive chemotherapies with autologous stem cell support performed in both paediatric centres over this time period.

3.2. Clinical, biological and radiological features at the time of diagnosis of portal vein thrombosis

PVT occurred after COPAdM2 in the absence of HVOD in patient No. 1 (Fig. 1) and was not associ-

Table 1
Clinical features and outcome

Patient No.	1	2	3	4	5
Gender/age at diagnosis (in years)	M/7	M/15	M/14	M/3.5	F/2.5
Tumour/stage	Burkitt's lymphoma/St. III	Ewing's tumour/St. IV	Small cell bone tumour/St. IV	Medulloblastoma/localised	Medulloblastoma/meningeal spread
Initial location	Abdomen, Pleura	Ilium	Femur	Cerebellum	Cerebellum
Intensive chemotherapy	0	Bu–Mel	HD Thiotepa Bu–Mel	Bu–Thiotepa	Bu–Thiotepa
HVOD	0	+	+	+	+
Onset (day post-ASCT)		D18	D16	D24	D18
Grade (Bearman)		III	III	III	III
Duration (in weeks)		3	16	16	4
Portal vein thrombosis					
Time of onset	D18 > COPAdM2	D23 > ASCT	D61 > ASCT	D51 > ASCT	D20 > ASCT
Isocoagulant heparinotherapy	+	+	0	0	0
Revascularisation/delay (in days)	(cavernoma)	10	10	13	3
Outcome	CR	CR	Died	Died	Died
Follow-up/cause of death	39 m	33 m	PHT	Disease	Disease

Note – Bu: busulfan; Mel: melphalan; HD: high-dose; D: day; HVOD: hepatic veno-occlusive disease; ASCT: autologous stem cell transplantation; CR: complete remission; PHT: portal hypertension; M, male; F, female; St.: Stage; COPAdM (cyclophosphamide, vincristine, prednisolone, doxorubicin and methotrexate high-dose plus methotrexate and hydrocortisone intrathecal).

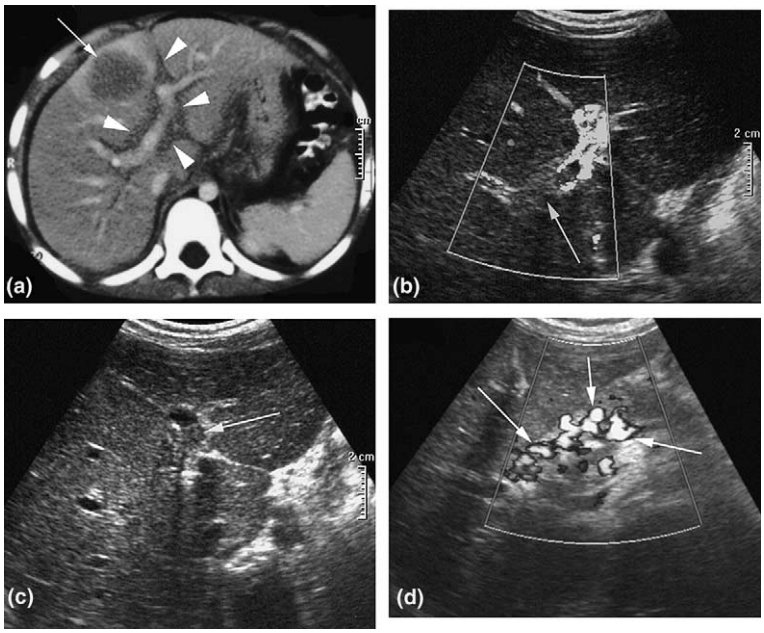

Fig. 1. 7-year-old boy with Murphy stage III abdominal Burkitt's lymphoma (patient No. 1). Initial post-contrast computerised tomographic (CT)-scan (a) shows intrahepatic location (arrow) and peritoneal lymphomatous involvement extended into the recess of ligamentum teres (arrowheads), encasing the two main portal branches, still permeable. Power Doppler US after COPAdM2 (b) shows a complete abdominal response, but a right main portal branch thrombosis (arrow) without any clinical, laboratory or ultrasound sign of HVOD. Power Doppler US after CyM1 (c–d) shows extension of the thrombosis (arrow) to the left portal branch (c) and occurrence of a hilar cavernoma (arrows) (d) hence the patient received isocoagulant heparin therapy. 39 months after the end of treatment, the child is still in first complete remission, but presents persistent cavernoma associated with signs of chronic PHT.

ated with any clinical sign or significant modification of liver function tests. In the four other patients, thrombosis occurred 2–45 days after the onset of HVOD (20–61 days after ASCT). Patient No. 3 only presented with an acute episode of clinical PHT during the PVT, associated with an increase in his serum bilirubin level. Clinical and biological features of HVOD were already present and not modified when PVT occurred in the three other patients. PVT was diagnosed by Doppler US in all patients. Thrombosis involved the portal trunk (4/5) or a segmental intrahepatic branch (1/5) (Fig. 2). Loss of Doppler signal was observed in all cases, but an echogenic thrombus was clearly demonstrated in only 3/5 patients.

3.3. Risk factors of thrombosis before the occurrence of portal vein thrombosis

Four patients received intensive chemotherapy containing busulfan. All these patients presented severe HVOD (grade III).

Patient No. 3 developed gastrointestinal sepsis occurring seven weeks after ASCT, with thickening of the intestinal wall on computerised tomography (CT) and magnetic resonance imaging (MRI), septated ascites with pseudomembranes, which was subsequently confirmed at laparotomy, nine days before the diagnosis of PVT.

In patient No. 1, initial peritoneal lymphomatous involvement extended into the recess of *ligamentum teres* and encased the main portal branches, which, nevertheless, were permeable at diagnosis.

The standard clotting tests (prothrombin time, activated partial thromboplastin time, fibrinogen, thrombin time) performed in patients No. 2–5 were normal. An auto-immune chronic thrombocytopenia was detected in patient No. 1 and the complete clotting assessment performed (prothrombin level, activated partial thromboplastin time, fibrinogen, protein C, protein S, antithrombin III, test for Leiden factor V and factor II mutations, test for variants of methylenetetrahydrofolate reductase and antiphospholipid antibodies) did not reveal any thrombogenic risk factor.

3.4. Treatment of portal vein thrombosis

All patients with HVOD received symptomatic treatment [22]. Isocoagulant heparin therapy (100 IU/kg/day) was given to patients No. 1 and 2 for 10 and 15 days, respectively. None received thrombolytic therapy.

3.5. Outcome

Revascularisation occurred after 3–13 days in 1/2 patients who received heparinotherapy and in 3/3 who did not. Despite revascularisation, PHT developed in 4/5 children with severe gastrointestinal bleeding in 2/4 patients (No. 3 and 4).

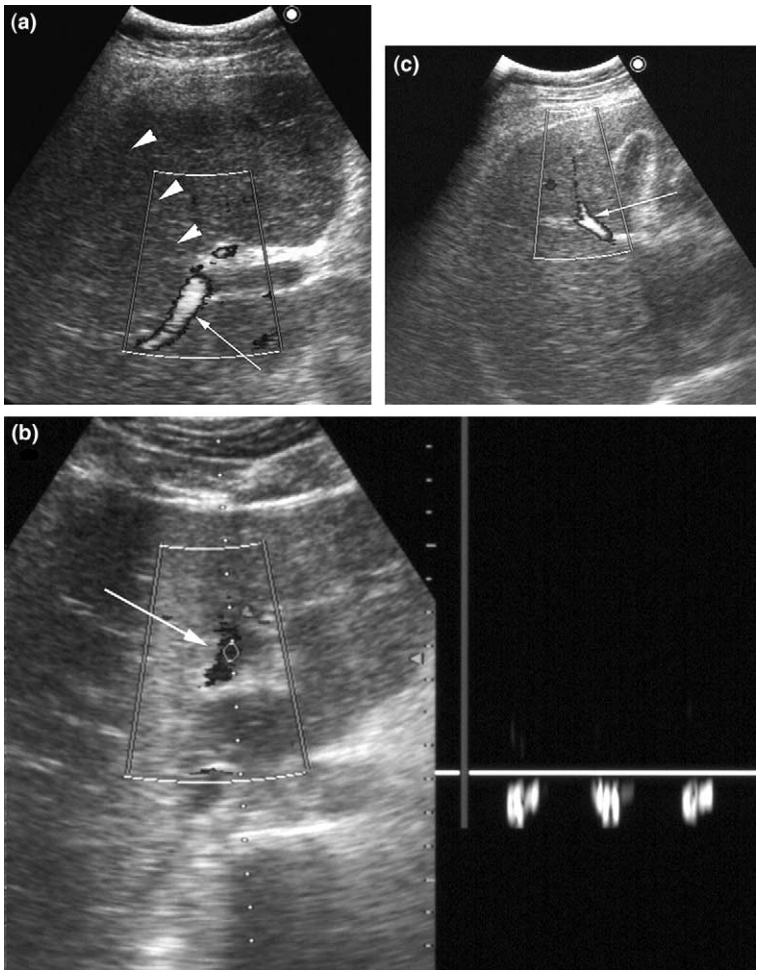

Fig. 2. 15-year-old boy with stage IV Ewing's tumour of the left ilium (patient No. 2). Power and pulsed Doppler US (a–b) performed during high-dose chemotherapy using the combination of busulfan and melphalan complicated by HVOD. US shows the lack of visualisation (a) of the anterior segmental right portal branch (arrowheads), while the posterior branch (arrow) is clearly identified, and (b) abnormal reverse flow in the left main portal branch (arrow), while flow in the portal trunk was still hepatopetal (data not shown). Power Doppler US (c) performed 3 weeks after symptomatic treatment of HVOD and isocoagulant heparin therapy shows normal permeability of the portal veins, including recovery of a normal flow within the anterior segmental right portal branch (arrow), together with resolution of the clinical, laboratory and ultrasound signs of HVOD. The child is currently in first complete remission, 33 months after completion of treatment and presents no signs of PHT.

Patient No. 3 died four months after high-dose chemotherapy due to gastrointestinal bleeding with disseminated intravascular coagulation, uncontrolled despite antiulcerant treatment, haemostatic gastrectomy and selective embolisation.

Patient No. 1 is in first complete remission, but presents persistent cavernoma associated with signs of chronic PHT (splenomegaly and oesophageal varices). The two patients with medulloblastoma died of disease progression 8 and 12 months post-intensification. Patient No. 2 is in first complete remission without any sign of PHT.

4. Discussion

PVT has only rarely been described during antineoplastic chemotherapy. Twelve cases have been reported in adults: one case following a course of L-asparaginase in a patient treated for acute lymphoblastic leukaemia [9], three cases in patients treated for lymphoma by intensive chemotherapy with ASCT [10] and, more recently, eight cases after haematopoietic cell transplantation (5 autologous and 3 allogeneic) [11]. In the largest adult series of Kikuchi and colleagues [11], the frequency of PVT has been estimated to be 0.4% among transplanted patients and 1% among patients with HVOD.

In children, only three sporadic cases have been described. Kauffman and colleagues [12] reported a case of portal cavernoma after treatment of an abdominal large cell anaplastic lymphoma. More recently, Yule and Anderson [13] reported two cases of portal cavernoma occurring in infants treated with conventional doses of chemotherapy for stage 4S neuroblastoma, one of whom died from ruptured oesophageal varices.

The rarity of this complication in children is confirmed by our experience as only five cases were observed over an 8-year time period in two reference centres. In our series, the frequency of PVT has been estimated to be 0.7% among children treated with intensive chemotherapy followed by ASCT.

Diagnosis of acute PVT is misleading. Clinically, it may present with non-specific abdominal distension or ascites. Laboratory abnormalities directly related to thrombosis are rare, non-specific, and limited to a moderate elevation of bilirubin [8]. Thrombocytopenia and a decrease in clotting factors consistent with disseminated intravascular coagulation are usually observed [8]. Only one of our patients presented with an acute episode of PHT. The other patients of our series were clinically asymptomatic or had already presented with clinical and biological features related to HVOD not distinguishable from signs of PVT. Therefore, diagnosis of PVT is based on imaging techniques. The sensitivity and specificity of colour/power Doppler US for PVT in adults are estimated to be 89% and 92%, respectively [23]. In our series, thrombosis mainly involved the portal trunk, but also only a segmental intrahepatic branch in one case. The frequency of segmental flow alterations is probably underestimated, as intrahepatic portal flow abnormalities are not systematically investigated by Doppler US. Only main portal vein flow is regularly evaluated in the presence of clinical and laboratory signs of HVOD [24].

The role of antineoplastic chemotherapy in the pathogenesis of these thromboses has been only partially elucidated. Venous thrombosis is a well known complication of treatment with L-asparaginase due to decreased levels of protein C and antithrombin III [9], but none of our patients had received this drug. The predisposing role of busulfan in adults has been proposed. Grigg and colleagues [10] observed three cases of PVT in a series of 29 patients treated with busulfan and no case of thrombosis in a series of 18 patients who did not receive this drug. These three patients did not fulfilled the criteria of HVOD. In the series of Kikuchi and colleagues [11], 7/8 patients had also received busulfan and 8/8 patients had clinical evidence of HVOD on the day that PVT was diagnosed. Four of the five patients in our series received busulfan containing intensive chemotherapy and all four presented with severe HVOD. Alkylating agents, especially busulfan, constitute the main risk factor for HVOD during intensive chemotherapy in children [25,26]. The first histological lesions observed during HVOD are alterations of hepatic venules and necrosis of centrilobular hepatocytes [27]. The currently adopted pathophysiological hypothesis for HVOD involves a primary lesion of the endothelium lining the sinusoids and terminal hepatic venules. Venular microthromboses can be identified histologically, inducing alterations of the hepatic microcirculation [27,28]. Histological findings of PVT have also been described in patients treated with a combination of chemotherapy and radiotherapy [28]. The thromboses observed in our series may have been related to these abnormalities of the microcirculation, leading to a marked decrease in the intrahepatic portal flow.

Hepatic regenerative nodular hyperplasia following cancer chemotherapy has also been described [29,30]. Decreased intrasinusoidal blood flow was also the mechanism proposed to explain the secondary development of regenerative hyperplasia. Interestingly, in one case reported by Yule and Anderson [13], the combination of PVT and regenerative nodules was observed.

Hence, all these pathological associations lead us to propose a common vascular pathogenesis. Alkylating agents could first lead to acute vascular injuries: venular obstructions, decreased intrasinusoidal blood flow, and in severe forms, upstream acute PVT. Late consequences of portal venous system injuries could explain both persistent PHT and hepatic regenerative nodular hyperplasia.

The complete clotting assessment performed in patient No. 1, who developed a portal cavernoma in the absence of HVOD, did not reveal any thrombogenic risk factor. In the other patients, standard clotting tests were also normal. A transient hypercoagulability state, due to a reduction of protein C and antithrombin III levels during haematopoietic cell transplantation, strongly associated with HVOD, has been suggested to explain the development of thrombosis [10,11,31]. Assays for protein C and antithrombin III were not performed in the patients with HVOD in this series.

The presence of abdominal sepsis is a classical predisposing factor for mesentericoportal thromboses [2]. The chronology observed in patient No. 3 suggests that HVOD and gastrointestinal sepsis occurring after high-dose chemotherapy may have predisposed to the development of PVT.

The protocol used in patient No. 1, although comprising a combination of potentially hepatotoxic drugs, does not usually induce HVOD. In a similar case reported by Kaufman and colleagues [12], the child also presented lymphomatous involvement of the porta hepatis at diagnosis. The authors suggested a local thrombogenic effect of the tumour related to the production of cytokines. The initial periportal infiltration observed in our patient is comparable to that observed in this previous case and could explain the occurrence of PVT in the absence of HVOD.

Only limited data are available regarding the treatment of recent PVT, as these lesions are only rarely diagnosed at the acute phase. The value of prompt anticoagulant therapy during the acute phase has been recently reported, as it could dramatically decrease the incidence of secondary PHT [32]. In the context of HVOD in children, the high bleeding risk related to

refractory thrombocytopenia, hepatocellular insufficiency and acute PHT limits the use of anticoagulation and thrombolytic therapy. However, in adults, various thrombolytic systemic agents are used to treat even severe HVOD (human recombinant tissue plasminogen activator, defibrotide) [33]. In the series of Kikuchi and colleagues [11], 6/8 patients received thrombolytic therapy (plus heparin in 5/6 patients) and PVT resolved in 4/6 patients who received thrombolytic agents and in 2/2 patients who did not. In our series, only isocoagulant heparinotherapy was used and revascularisation was observed both in patients who received heparinotherapy and in those who did not. Although the patient numbers in the literature and in our own experience are too small to establish definite recommendations, the benefit from specific treatment appears debatable.

The prognosis of PVT in children during antineoplastic chemotherapy is still unknown. In the adults series of Kikuchi and colleagues [11], 6/8 patients with PVT died, 2/6 from GVH or disease recurrence, and 4/6 from HVOD and multi-organ failure, but PVT did not appear to contribute to their deaths. In our series, one child developed portal cavernoma associated with chronic PHT. In the other patients who presented HVOD, despite revascularisation, PHT developed in 3/4 children and was directly responsible for death in one case. As previously suggested in adults [11], PVT occurring in a context of HVOD following intensive chemotherapy may therefore only represent a symptom that reflects the severity of the intrahepatic microcirculation disorders, and not a real additional complication.

5. Conclusions

PVT rarely occurs during antineoplastic chemotherapy in children. The direct hepatic vascular toxicity of drugs, especially alkylating agents, appears to play a predominant role and may explain the clinical association between PVT and HVOD. Nevertheless, PVT may only reflect the severity of HVOD and not be a real complication. Therefore, specific treatments such as heparin or thrombolytic therapy must be used cautiously in patients with HVOD owing to the high risk of bleeding.

Conflict of interest

None.

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