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Case Report

Use of drug-coated balloons in the management of a recalcitrant postsurgical hepatic vein stenosis in a pediatric patient ☆

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ABSTRACT

Drug-coated balloons (DCB) are a treatment alternative to conventional angioplasty in arterial, hemodialysis fistulas, and venous stenoses. This case report describes a child with the diagnosis of hepatoblastoma treated with chemotherapy and a right extended hepatectomy with venous reconstruction. The patient presented with signs and symptoms of portal hypertension due to a hepatic venous outflow obstruction secondary to stenosis of the surgical anastomosis. The response to conventional angioplasty was limited with frequent recurrence of symptoms. DCBs were used as an alternative prior to stent consideration aiming to assess if these devices could provide improvement of the symptoms and as a long-term therapy. The use of DCBs increased the time interval of reinterventions in comparison with conventional angioplasty. The patient eventually required stents due to recurrence of the primary disease.

While this report does not provide an in-depth evaluation in terms of the efficacy and safety of DCB, this case illustrates a potential novel treatment modality to be considered for children, when stenotic venous lesions not amenable for stenting are present.

Background

Angioplasty with drug-coated balloon (DCB) was originally described for the treatment of peripheral arterial occlusive disease and for coronary artery stenosis [1–3]. These balloons are covered with an antiproliferative medication which is delivered to the vessel wall during inflation, in an homogeneous and predictable fashion, without the need of a stent [1]. In adult patients, this endovascular treatment modality has shown benefits in terms of vessel patency, restenosis rates, and distal flow of the treated vascular territory. Research

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work has shown the benefits of using this technology in the management of dysfunctional arteriovenous (AV) fistulas [4,5]. DCBs have also been used in the treatment of central vein stenosis with good results [6,7]. Mechanical and biological response due to local injury during angioplasty leads to restenosis. The antineoplastic drug delivered to the vessel wall inhibits cell proliferation improving long-term results [2,4].

A case in which DCBs were used to manage a recalcitrant hepatic vein stenosis following venous surgical reconstruction after hepatoblastoma resection is described. These therapeutic devices were considered as an alternative that could provide a better outcome in comparison with conventional angioplasty and delay or prevent the use of a stent.

Case presentation

Informed consent was obtained from the patient's parents for this publication and all the documents required by our research ethics board for case report consent to publication were signed. The patient had history of hepatoblastoma with inferior vena cava (IVC) invasion diagnosed at 15 months of age (Fig. 1). He was treated with chemotherapy and a right extended hepatectomy plus hepatic vein/IVC reconstruction (Fig. 1). The patient presented with acute IVC/hepatic vein stenosis due to thrombosis 2 months after surgery, which was treated with systemic anticoagulation. Symptoms improved, however four months after the surgery, and due to recurrence of ascites, an abdominal venogram was performed demonstrating an occlusion of the retro- and infrahepatic IVC up to the level of the renal veins and stenosis of the single hepatic vein at the level of the surgical anastomosis (Fig. 2). An attempt to recanalize the IVC was unsuccessful. Hepatic vein stenosis was treated with conventional angioplasty with good immediate postprocedure result (Fig. 3). Due to symptom recurrence which correlated with restenosis, this treatment was repeated on 6 occasions (Fig. 4).

The reinterventions were planned based on clinical (abdominal distention and increased visualization of thoracic-abdominal wall superficial venous collaterals) and imaging findings (ascites and changes in the sonographic appearance of the liver [size, coarse echogenicity and worsening of the hepatic vein stenosis on color-Doppler study]). Signs of restenosis were seen on venography associated with pressure gradients above 12 mm Hg across the stenosis. Eventually the treatment was guided by clinical symptoms and pressure gradients were not measured anymore.

As the results of conventional angioplasty were not optimal, the possibility of a stent was considered. The proximity of the stenosis to the right atrium and angulation of the anastomosis made the placement of a stent technically challenging. The patient's long-life expectancy, future growth and the potential eligibility for a liver transplant, were also limitations for a stent. Based on these elements, we decided the use of Paclitaxel-coated balloons to assess if this could improve the symptoms and provide a longer-term therapeutic alternative, having the stent as the next therapeutic option.

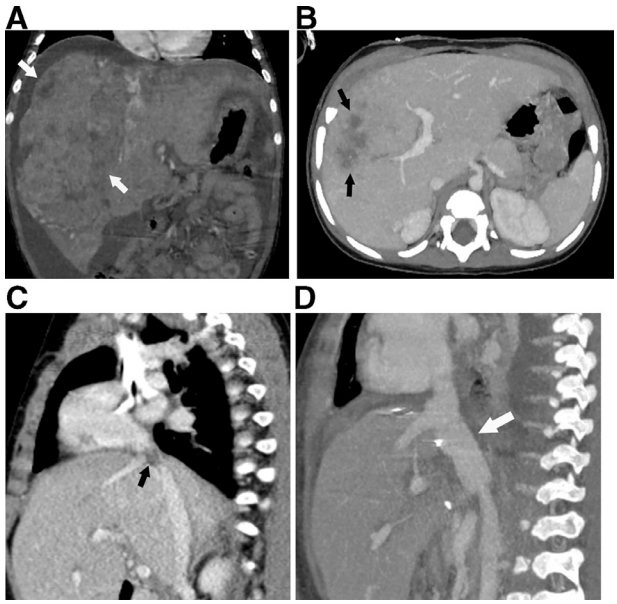

Fig. 1 – (a) Enhanced CT coronal reconstruction at presentation showed a large hepatic mass (arrows) associated with intra-abdominal free fluid. (b) The lesion showed good response to chemotherapy with decrease in size (arrows). (c) Despite the decrease in size there was still vascular invasion of the IVC (arrow). (d) Enhanced cororal CT reconstruction after an extended right hepatectomy. The upper portion of the IVC was reconstructed with a surgical conduit (arrow).

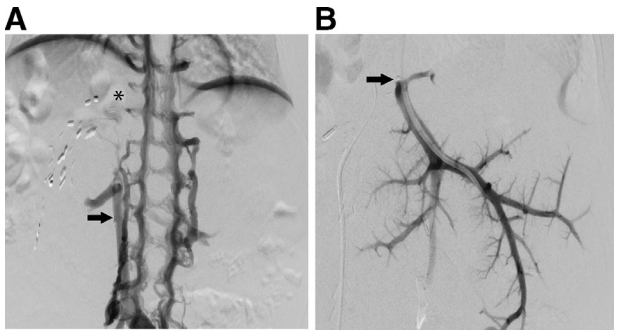

Fig. 2 – (a) Abdominal venogram demonstrated opacification of the inferior vena cava up to the approximate level of the renal veins (arrow) and occlusion of the retro- and infrahepatic IVC (*). Prominent paravertebral veins were observed. (b) Hepatic venogram showed stenosis of the surgical anastomosis (arrow) and significant dilatation of the single hepatic vein.

Informed consent was obtained from the parents for the off-label use of this device and for using it for the first time in a pediatric patient at our center. The oncology team was also consulted and agreed. The plan was internally reviewed and approved by the diagnostic imaging department as an innovative procedure.

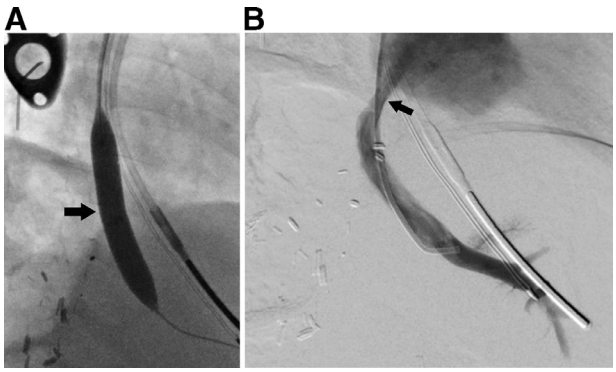

Fig. 3 – (a) The stenotic area of the hepatic vein was treated with conventional angioplasty (arrow). (b) Good results were obtained (arrow).

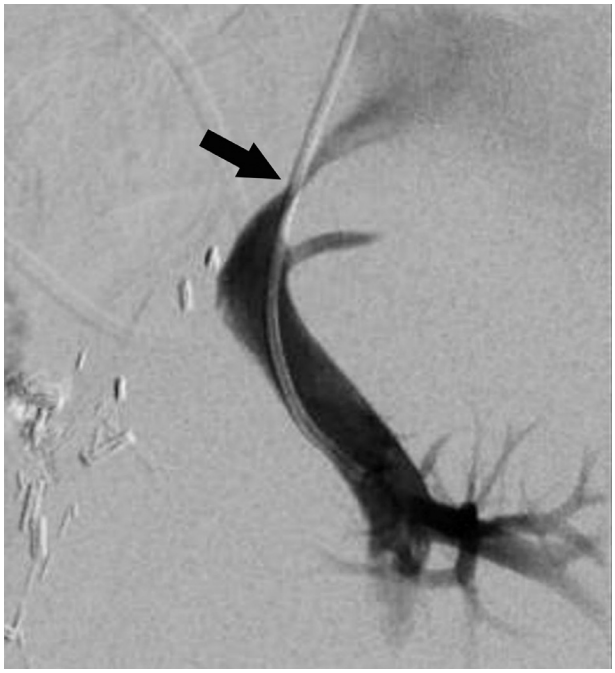

Fig. 4 – (a) Follow-up venogram when symptoms re-appeared showed significant restenosis of the treated area (arrow).

After predilatation with a 6 mm diameter-4 cm long conventional angioplasty balloon (Mustang , Boston Scientific, Galway, Ireland), a 6 mm diameter-4 cm long (largest diameter available at the time) Paclitaxel DCB was utilized (Lutonix 0.35, BARD peripheral vascular INC, Tempe, AZ). Thirty minutes postdrug delivery, standard angioplasty was performed to achieve the desired diameter of dilatation (12 mm). The effect of the device was assessed with a venography 8 weeks postprocedure showing good passage of contrast, with mild recurrence of the stenosis. A focal area of saccular dilatation was also noted. The DCB was used again followed by a conventional angioplasty. Subsequent venography was based on clinical symptoms, with repeated use of the DCB at each additional visit (Fig. 5).

With conventional angioplasty, the patient reached a maximum of 14 weeks before symptoms reappeared requiring reintervention (interval between treatments was: 14,8,8,12, and 10 weeks; mean: 10.4 weeks, SD: 2.61). After treatment with the DCBs, the patient's parents described a significant clinical improvement, including increased energy levels, improved appetite, and increased attendance at school. After the initial planned 8-week follow-up venography, the patient required reintervention after 17, 31, 22, and 19 weeks (mean 19.4 weeks, SD: 8.32). A comparison of the mean time interval required for reintervention to reestablish vessel patency between both treatment modalities was conducted (10.4 vs 22.4 weeks [t-test, $P < .05$]).

At the 31-week postprocedural mark, the stenosis was significant again, and the patient experienced an acute deterioration during the procedure. Therefore, a new conventional angioplasty with a 6-mm balloon was performed in preparation for the use of a 10 mm diameter -4 cm long DCB, which could not be used due to patient instability on that visit, but uneventfully used 4 weeks later. When this new size of DCB became available, it was no longer needed to dilate postdrug delivery (Fig. 5). A heparin bolus (100 U/Kg/dose) was given prior to all dilations and full dose anticoagulation was maintained postprocedure with low molecular weight heparin (ie, enoxaparin). The patient was transitioned to warfarin after the second use of the DCB. No complications were observed related to the use of DCBs.

Metastatic disease required a right pneumonectomy and cycles of experimental chemotherapy. The patient eventually showed local recurrence with invasion of the single hepatic vein 3 years and 8 months after the initial diagnosis, which was treated with 2 uncovered self-expandable stents that kept the patient symptom free for the last 4 months of his life.

Discussion

Hepatoblastoma is the most common liver malignancy in children with an incidence of approximately 1.2-1.5 cases per million [8,9]. It accounts for 1% of the pediatric malignancies [9] and it is usually diagnosed before the age of 3 years [8]. These type of liver tumors arise from pluripotent stem cells derived from hepatoblast which can differentiate mainly into epithelial and mesenchymal elements [10]. According to the component of the tumors, different subtypes are defined, each of them with different management and prognosis [10]. The overall survival is 70%-80%, with 30%-60% of patients having unresectable tumors at presentation and 10%-20% metastatic disease, being the lungs the most common site [8]. The best outcomes are associated with full surgical resection with negative margins, however, in extensive disease (with vascular invasion) the treatment remains controversial and patient specific [8]. Liver transplant is an alternative, however, the decision to proceed depends on the different institution's criteria of resectability, biologic aggressiveness of the tumor, metastatic disease, and response to chemotherapy [8,10]. In this case, the tumor was initially managed with chemotherapy, followed by resection. Metastatic lung disease was present and managed by focal resections and eventually

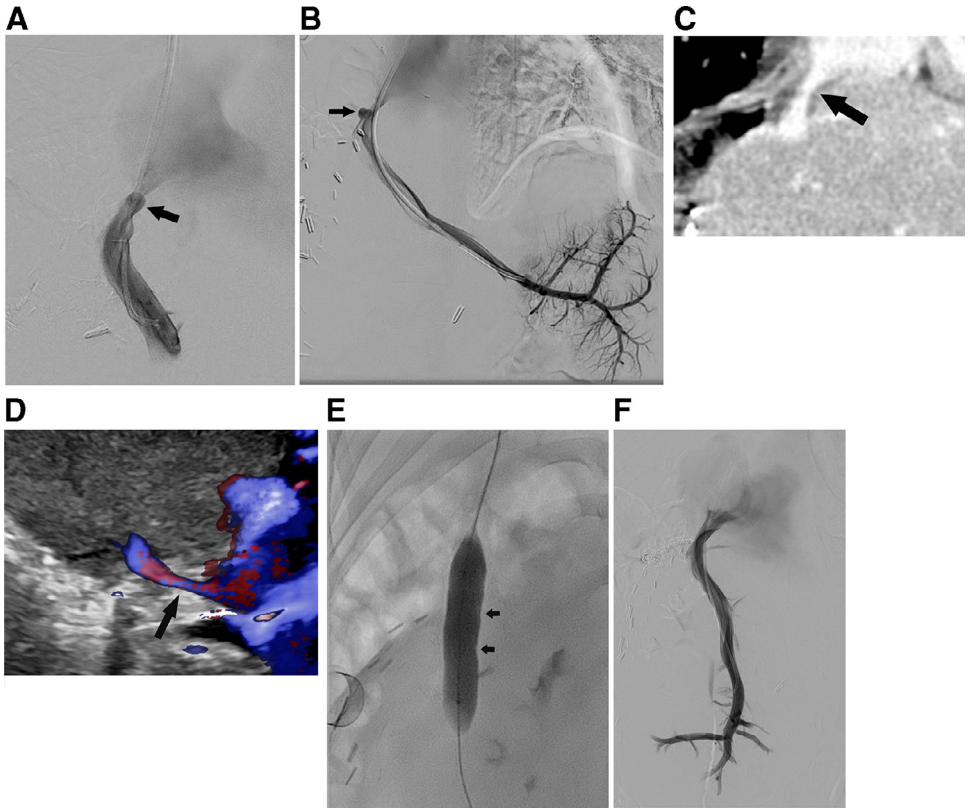

Fig. 5 – Hepatic venogram at 8 weeks (a) and 12 weeks (b) after the use of drug-coated balloons, showing recurrence of the restenosis, however, patency was preserved and the dilatation of the hepatic vein in (b) was less significant than in previous procedures. A small focal sacular dilatation was noted (arrow) which was not visible in subsequent treatments. (c) CT and (d) Ultrasound showed similar findings during the course of the treatments with patency at the area of stenosis (arrow). (e) Use of a 12 mm diameter-4 cm long drug-coated balloon in the last hepatic vein dilatation. The balloon showed mild indentations at the area of stenosis (arrows). (f) Satisfactory venographic result was obtained. The patient remained asymptomatic until there was invasion of the vein by recurrence of the primary disease.

by a right pneumonectomy. Based on the institution's protocol, the patient did not qualify to be a liver transplant candidate.

Hepatic venous outflow obstructions are categorized according to the level of obstruction [11]. Obstructions from hepatic veins up to the level of the IVC are defined as Budd-Chiari syndrome having multiple causes and usually presenting with signs of portal hypertension [11]. Hepatic vein stenosis is a known complication after liver transplantation, being described in 2%-9% of pediatric patients [12–16]. The treatment with intraluminal balloon angioplasty is the modality most commonly used in late onset stenosis showing good results with primary patency rate of 56% at 60 months and excellent primary assisted and secondary patency rates [10]. Stent placement is not recommended as an initial approach as some patients may respond well to balloon angioplasty alone; in the pediatric patients the long-term patency is unpredictable (due to intimal hyperplasia) and in a growing child a stent with fixed diameter can be a determinant of stenosis; and as many patient will require retransplantation, a metal stent may pose a high technical challenge [12–14]. Stenting is the therapeutic option in cases of failure of convention angioplasty [15,16]. It is recommended to treat when the pressure gradient between the right atrium and the hepatic vein is higher than 3 mm Hg and with a balloon 110%-130% of the diameter of the normal vein [13,16]. More than one dilatation is often required [12–16]. Hepatic vein reconstruction for resection of hepatic tumors is a technically challenging technique which has been improved based on the experience derived from liver transplant techniques, however, has associated morbidity and mortality [17]. Patency described is 46% at 3 years, with the main causes of restenosis being local recurrence and thrombosis [18]. Factors described to influence the patency are length of the reconstruction and method of resection [18]. Due to the postsurgical nature of the stenosis of the case presented, the approach utilized was the same used in post-transplant hepatic vein stenosis. A case report shows a similar scenario in an adult patient with a left hepatic vein stenosis post right-trisegmentectomy successfully treated with balloon angioplasty [19].

Paclitaxel is an antiproliferative agent with a cytostatic action which reduces neointimal hyperplasia by reducing smooth muscle proliferation and migration [20]. DCBs have been used in adult patients for applications which include peripheral arterial disease, dysfunctional AV fistulas and central vein stenoses [1–7]. The available evidence shows signifi-

cant improvement of lesion patency in AV fistulas treated with DCBs [21]. There are ongoing randomized control trials opening in the coming years which will provide evidence about the DCBs efficacy, including AV fistula's management [21] and that will also clarify the role in the central veins, which in some studies is reported as promising [6,7, 20].

The safety of Paclitaxelcoated devices was challenged after a meta-analysis by Katsanos et al [22] concluded that there seems to be a higher risk of death after the use of Paclitaxel-coated devices in the femoropopliteal arteries in the adult population. In response to this, a recent study by Dake et al [23] concluded that Paclitaxel-coated stents treatment does not result in increased long-term all-cause mortality in comparison to uncoated devices, supporting the use of these devices. Results of ongoing randomized controlled trials will provide more information about safety.

The experience of DCB in children is limited to case reports in different applications such as pulmonary and renal arteries [24–26]. There is no data about safety of DCBs in children, in whom due to their smaller volume of distribution, their systemic levels may be higher [24]. In the case of interest, as there was already exposure to chemotherapy and with the evidence available of the safety of the device in adults [27], all the teams involved considered that it was adequate to use.

In the case presented, the DCBs were used to evaluate if they could provide a better result than conventional angioplasty, potentially preventing or delaying a stent placement which could compromise a future liver transplant. DCBs increased the time interval between interventions and provided clinical improvement. No other factors changed during the management of the patient which could explain the difference. The patient eventually required stents when the disease progressed, and he was not a liver transplant candidate anymore.

There are several limitations in this report as the lack of objective criteria other than the increase of the time interval between interventions to demonstrate that the results of the DCBs were better, therefore no conclusions can be drawn. It is unclear if there will be applications of these devices in children, however, this case can help other physicians facing a similar clinical scenario and contribute in the design of future studies of DCBs in new applications, including (central) venous stenosis not amenable to stent placement. The ongoing randomized controlled trials will provide better evidence on the safety and efficacy of these devices. If used in children, measurement of systemic levels of Paclitaxel may be useful to determine if there is a difference (and potential toxicity) in comparison with the use in adults.

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