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IMAGING

CLINICAL CASE

Pulmonary Arterial Hypertension After Busulfan Administration During Conditioning Regimen in Neuroblastoma

Key Role of Rescue Treatment

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ABSTRACT

BACKGROUND Pulmonary arterial hypertension (PH) is a rare and life-threatening complication of high-dose chemotherapy with busulfan (Bu) used for hematopoietic stem cell transplantation.

CASE SUMMARY A 5-year-old male patient with retroperitoneal neuroblastoma developed PH and acute right-sided heart failure 2 months after conditioning regimen that included Bu and melphalan before autologous hematopoietic stem cell transplantation. Once pulmonary embolism and veno-occlusive disease were excluded by computed tomography, rescue treatment, including epoprostenol, bosentan, and sildenafil, was started, with complete regression of acute right-sided heart failure and normalization of pulmonary pressure.

DISCUSSION Bu can cause PH through different pathophysiological mechanisms. The prompt start of rescue treatment is a cornerstone for a good outcome. In our patient, considering the absence of signs of pulmonary veno-occlusive disease on computed tomography, a triple pulmonary vasodilator therapy was started and a rapid recovery was noted.

TAKE-HOME MESSAGE Early work-up for PH in children after Bu administration is essential to recognize a life-threatening condition requiring a rescue treatment. (JACC Case Rep. 2025;30:104050) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Neuroblastoma (NB) is the most common extracranial solid tumor of childhood, with heterogeneous behavior ranging from spontaneous regression to poor outcome according to the risk group.[1] Patients with high-risk (HR) NB require an intensive multimodal treatment, including, among the other elements, high-dose chemotherapy followed by autologous hematopoietic

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ABBREVIATIONS AND ACRONYMS

Bu = busulfan

CB/BO = constrictive bronchiolitis/bronchiolitis obliterans

CT = computed tomography

HR = high risk

NB = neuroblastoma

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PAH = pulmonary arterial hypertension

PH = pulmonary hypertension

PVOD = pulmonary veno-occlusive disease

stem cell transplantation (auto-HSCT).[1] This multimodal approach has improved the survival of children with HR NB up to 50%, but significant side effects, including pulmonary vascular complications, may affect patient outcomes.[2] The most common pulmonary vascular complications reported in HSCT recipients are pulmonary arterial hypertension (PAH) and pulmonary veno-occlusive disease (PVOD) according to the site of vascular injury.[3]

We report the case of a child with HR NB, complicated by severe pulmonary hypertension (PH) related to busulfan (Bu) administration; the pulmonary vascular toxicity was successfully resolved with early rescue treatment including prostacyclin and inotropes.

TAKE-HOME MESSAGES

- Endotheliitis causing PH related to high dose of chemotherapy, especially busulfan, can be a life-threatening condition.
- Early recognition and a prompt work-up for PH in children after Bu administration are essential to initiate a rescue treatment.

HISTORY OF PRESENTATION

A 5-year-old male patient was referred to our attention for acute respiratory distress occurring after several days of asthenia. He presented with hepatomegaly and jugular turgor.

PAST MEDICAL HISTORY

The patient was affected by a localized retroperitoneal, *MYCN*-amplified NB, treated first with 6 courses of conventional chemotherapy and surgery and then with a conditioning regimen, including Bu and melphalan, followed by auto-HSCT. Two months after bone marrow transplantation, he was hospitalized for acute dyspnea.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute respiratory distress included pneumonia, pulmonary embolism, congestive heart failure due to PH, and PVOD.

INVESTIGATIONS

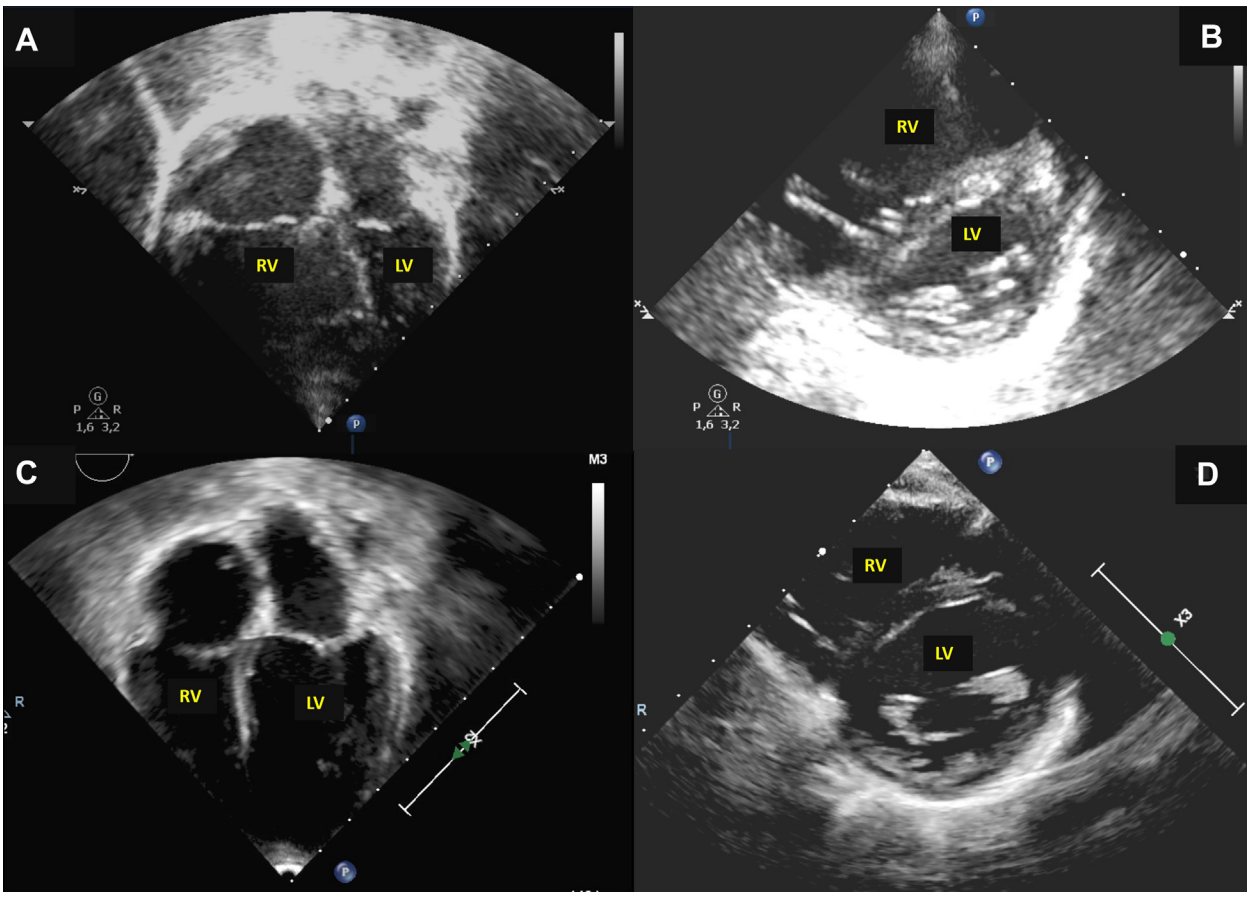
On blood tests, the N-terminal pro-B-type natriuretic peptide (NT-proBNP) level at the time of admission was 28,352 pg/mL (range values <190 pg/mL). The echocardiogram showed right-chamber dilatation with right radial ventricular dysfunction and a moderate-to-severe tricuspid regurgitation. Moreover, the right ventricular systolic pressure increased up to 75 mm Hg + right atrial pressure, while the D-shaped left ventricle, septal bounce, and preserved left ventricular ejection fraction supported a diagnosis of PH (**Figure 1**). The arterial oxygen saturation was 86%. Arterial blood gas measurements showed a pH value of 7.41, P_{CO_2} of 17 mm Hg, P_{O_2} of 65 mm Hg, lactate of 3 mmol/L, and HCO_3^- of 15.7 mEq/L.

NT-proBNP was consistent with acute heart failure. The lung computed tomography (CT) excluded both major pulmonary embolism and PVOD. In addition, CT showed pulmonary artery trunk dilatation (z-score: +3.24), septal thickening, and findings of constrictive bronchiolitis/bronchiolitis obliterans (CB/BO) with bronchiectasis and mosaic perfusion, patchy in distribution (**Figure 2**).

MANAGEMENT

The patient received treatment with sildenafil (10 mg three times a day), a phosphodiesterase-5 inhibitor, furosemide (2 mg/kg/d), inotrope (milrinone 0.5 μg/kg/min), steroid (methylprednisolone 2 mg/kg/d), and oxygen therapy. Despite this strategy, the child rapidly developed asthenia, tachycardia, oliguria, hypotension, and oxygen desaturation, and the echocardiogram showed a suprasystemic pulmonary artery pressure. The right cardiac catheterization under general anesthesia was not considered feasible given the risks associated with the procedure and was omitted at this time. The rescue therapy was intensified including dopamine (6 μg/kg/min) and epoprostenol, a prostacyclin analog. Epoprostenol was uptitrated according to the hemodynamic condition and the echocardiographic parameters, reaching a maximum dosage of 13 ng/kg/min. The patient showed hemodynamic stability, with a progressive reduction to a noninvasive normal value of pulmonary pressure, and normalization of volumes of the right ventricle and atrium within 96 hours of the start of epoprostenol. Two days later, the patient received bosentan (2 mg/kg/dose)—an endothelin receptor antagonist—while the epoprostenol was stopped after 27 days. Corticosteroid was maintained at the same dosage for 2 weeks and then tapered in 5 days. Pirfenidone was also included in the treatment regimen to avoid the progression through the fibrosis process. After 1 month, a cardiac magnetic resonance-guided right heart catheterization was conducted with the patient under general anesthesia and showed a

FIGURE 1 **Echocardiogram Before and After Pulmonary Arterial Hypertension Therapy**



(A) Four-chamber view at the time of acute right-sided heart failure revealed right ventricular (RV) dilatation with severe RV dysfunction. (B) Parasternal short-axis (PSAX) view during the end-diastolic phase, illustrating flattening of the interventricular septum (D-shape) of the left ventricle (LV) secondary to increased pulmonary pressure. (C) Four-chamber view revealed normal RV dimension and RV function 72 hours after beginning of treatment with prostacyclin and inotropes. (D) PSAX 72 hours after beginning of treatment with prostacyclin and inotropes revealed a normal position of the interventricular septum as a sign of reduced pulmonary pressure.

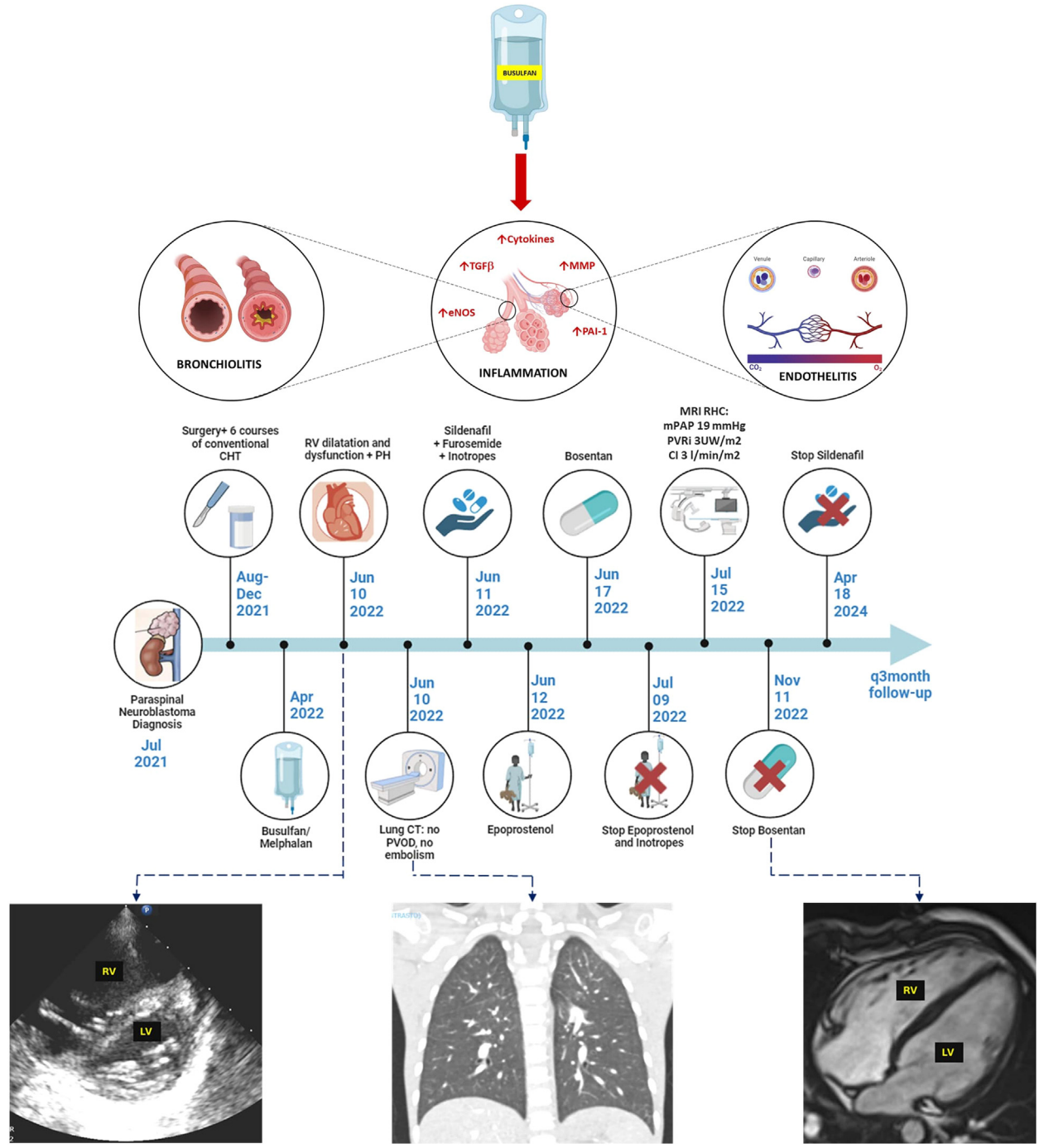
significant reduction of PH with a mean pulmonary artery pressure of 19 mm Hg, a pulmonary artery wedge pressure of 10 mm Hg, an increased pulmonary vascular resistance index of 3 WU, a cardiac index of 3.0 L/min/m^2, and good biventricular function (left ventricular ejection fraction 54%; right ventricular ejection fraction 48%). No data on echocardiographic parameters during the vasodilator test were available. After 1 month, a CT scan was repeated, which no longer showed septal thickening or signs referable to fibrotic changes. Mild enlargement of the bronchial branches with thickening of the bronchial walls was still present. Therefore, bosentan was discontinued, while sildenafil as monotherapy was administered for 18 months after bosentan discontinuation.

The patient showed a progressive improvement in clinical, laboratory, and imaging test results (Figures 1 and 2). He completed NB treatment with immunotherapy with an anti-disialoganglioside 2 monoclonal antibody. Forced vital capacity rose up to 63% of theoretical values. Genetic test results for PH-associated genetic mutations such as BMPR2, ACVRL1, ENG, TBX4, FOXF1, CAV1, KCNK3, EIF2AK4, and SMAD9 were negative.

FOLLOW-UP

After 24 months of follow-up, the patient's echocardiogram showed NYHA functional class I, normal NT-proBNP values, normal right ventricular

FIGURE 2 **Busulfan Action on Patient Journey**



(A) Busulfan administration can be associated with bronchiolitis and endotheliitis through the proinflammatory effect mediated by an increase in cytokines, matrix metalloproteinases, and epithelial growth factors. (B) Clinical course of the patient with echocardiogram, lung computed tomography (CT) scan, and magnetic resonance imaging-guided right heart catheterization (MRI RHC). CHT = chemotherapy; CI = cardiac index; eNOS = endothelial nitric oxide synthase; LV = left ventricle; MMP = matrix metallo proteinase; mPAP = mean pulmonary artery pressure; PAI-1 = plasminogen activator inhibitor-1; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PVRi = pulmonary vascular resistance index; RV = right ventricle; TGFβ = transforming growth factor-β.

dimensions and function with physiological tricuspid regurgitation, and normal right ventricular systolic pressure. Pulmonary function testing documented forced vital capacity at 75% and forced expiratory volume in 1 second at 80% of theoretical values.

DISCUSSION

The most appropriate and efficacious treatment of PH occurring after high-dose chemotherapy can be challenging because Bu can cause PH through different pathophysiological mechanisms. Considering the absence of signs suggestive of PVOD on CT, a triple pulmonary vasodilator therapy was started and a rapid recovery was noted. The hypothesis of PAH due to vascular/capillary endotheliitis is supported by the excellent response to treatment, as well as by the absence of signs suggestive of PVOD on CT scan. Finally, the absence of a genetic predisposition further supports an etiology from acute vascular damage related to treatment with the alkylating agent Bu in our patient. Also the use of corticosteroids helped to address the inflammatory component, involving both vasculature and parenchyma. The lung is a common site of complications across the spectrum of inflammatory disease and may be involved in several ways, including interstitial fibrosis, vasculature disruption, and hypoxia induced by vascular remodeling. The degree of manifestations may vary between different morbidities, ranging between PH in autoimmune diseases ("vasculature dominant") and idiopathic lung fibrosis ("lung dominant"). Corticosteroids are the mainstay of therapy, with variable response in this setting. In our case, methylprednisolone was used since the beginning for 2 weeks and tapered in 5 days, and the PH-specific drugs were continued.

In childhood, PH after both an autologous and an allogeneic HSCT for any underlying disease is rare and represents a life-threatening complication in the absence of a rapid treatment; the estimated incidence of PH after Bu conditioning is between 7% and 20%, whereas the mortality rate ranges from 32% to 50% according to a few different case series.[3,4] Bu is recognized as a major risk factor for the development of drug-induced PH.[5,6] According to Levy et al,[3] in a pediatric cohort after bone marrow transplantation, all the patients who experienced PH had been previously treated with Bu. Bu is an alkylating agent that contributes to the development of acute pulmonary endothelial injury through multiple pathophysiological mechanisms[5,6] that involve both arterioles and postcapillary venules (**Figure 2**). A hypercoagulable state mediated by transforming growth factor-β1 family members, as well as by antifibrinolytic activity due to an increase in plasminogen activator inhibitor-1 levels, has been reported[7-9] in hepatic veno-occlusive disease, and a similar action has been hypothesized in the lung. In addition, Bu has been implicated in the overexpression of endothelial nitric oxide synthase and in the increase of the circulating endothelial cells and their progenitors.[5,6] Finally, it is also known that Bu contributes to cellular aging with a proinflammatory effect mediated by an increase in cytokines, matrix metalloproteinases, and epithelial growth factors.[10] Moreover, Bu administration can be associated with CB/BO;[10] CB/BO is defined by the presence of concentric bronchiolar fibrosis, resulting in marked narrowing or obliteration of bronchioles in the absence of intraluminal granulation tissue polyps or surrounding parenchymal inflammation. Clinically, CB/BO is associated with marked airflow obstruction that is usually not responsive to steroid therapy and represents one of several pulmonary complications of HSCT, occurring less frequently in the autologous setting than in the allogeneic HSCT recipients. CB/BO is usually identified in patients after allogeneic transplants, presumably as the result of chronic graft versus host disease.[10] Obstructive lung disease is frequently associated with PH; this condition, namely PH associated with lung diseases and/or hypoxia, is considered in group 3 according to the last European Society of Cardiology/European Respiratory Society PH guidelines.[5] In this setting, standard PH therapy is not effective.

The prompt start of treatment is a cornerstone for a good outcome in patients with PH after HSCT, as shown by Levy et al.[3] It is also crucial to identify promptly the signs of venous/capillary involvement because it is usually more aggressive with a worse prognosis. Indeed, the standard PH therapy in patients with PVOD can lead to a severe and life-threatening pulmonary edema with a high mortality rate. The absence of comorbidities together with the prompt diagnosis and a timely targeted treatment seems to have played a crucial role for the favorable outcome observed in our patient.

CONCLUSIONS

A high clinical suspicion is recommended in patients who received Bu in case of respiratory symptoms suggestive for vascular complications. A screening surveillance including echocardiogram and dosage of NT-proBNP may be useful. A CT scan is crucial to exclude PVOD to set the optimal rescue treatment. Considering the favorable outcome of an aggressive treatment strategy, patients with PH should be

promptly identified and referred to specialized centers with expertise in the management of childhood PH.

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