Case Report

Pulmonary Circulation

Pulmonary arterial hypertension in pediatric patients undergoing high-dose carboplatin/thiotepa and stem cell transplant

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Patient 1 is a five-year-old girl who presented to the hospital with nausea, vomiting, and headaches. Imaging demonstrated a posterior fossa mass with associated hydrocephalus. Surgical resection was urgently performed and pathology showed medulloblastoma, WHO Grade IV, with extensive metastatic disease. The patient was enrolled on the Head Start 4 study and treated with three induction cycles of vincristine, cisplatin, cyclophosphamide, etoposide, and methotrexate followed by three tandem cycles of consolidation chemotherapy consisting of carboplatin and thiotepa followed by autologous hematopoietic stem cell transplant (HSCT). Pre-induction echocardiography was normal.

One month after her third autologous HSCT, the patient presented to the pediatric intensive care unit due to tachypnea and oxygen desaturation. Chest computed tomography (CT) ruled out pulmonary emboli but demonstrated pulmonary artery dilation and multiple patchy ground glass opacities in the lung parenchyma. Echocardiogram demonstrated an estimated systolic pulmonary artery pressure (PAP) measuring three-quarters systemic. N-terminal pro brain natriuretic peptide level (NT-pro BNP) peaked at 4454 pg/mL (normal <125 pg/mL). She was started on digoxin, furosemide, and spironolactone.

Due to limitations in gait, she was unable to complete a 6-min walk test. History was significant for prematurity completing 27 weeks gestation, but with no home oxygen requirement at time of neonatal intensive care unit discharge. Pulmonology was involved in care with no concern for chronic lung disease or interstitial lung disease, but she did have evidence of moderate obstructive sleep apnea on polysomnography. Swallow studies demonstrated no aspiration and she was treated for gastroesophageal reflux. There was no family history of pulmonary hypertension.

Cardiac catheterization confirmed pulmonary arterial hypertension (PAH) with a mean PAP of 34 mmHg and pulmonary vascular resistance index (PVRi) of 5.4 Wood Units·m^2. Sildenafil was initiated and titrated up to 10 mg TID. Supplemental oxygen was required for 10 weeks. With continued therapy, clinical symptoms improved and echocardiogram findings and NT-pro BNP levels normalized in four months. The patient was weaned off digoxin and diuretics. One year later, sildenafil was also discontinued. Unfortunately, she had tumor recurrence and suffered a severe stroke six months later. She died while in hospice care.

Patient 2 is a 6-month-old male infant who presented to the hospital with macrocephaly, vomiting, lethargy, and abnormal eye movements. Brain MRI demonstrated a large, heterogeneous mass in the right temporal-parietal region requiring emergent debulking. Pathology revealed an atypical teratoid rhabdoid tumor, WHO grade IV. Treatment as per a modified version of Children's Oncology Group (COG) protocol ACNS0333 was initiated with induction therapy consisting of three cycles of vincristine, cisplatin, cyclophosphamide, etoposide, and methotrexate followed by consolidation chemotherapy with

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carboplatin, thiotepa, and HSCT. Pre-induction echocardiography was normal.

Two weeks into the second cycle of consolidation therapy, the patient became hypoxic requiring supplemental oxygen and management in the intensive care unit. Echocardiogram demonstrated elevated systolic PAP that was two-thirds systemic, mild right ventricular dilation with fair systolic function, and a small pericardial effusion. NT-pro BNP was high at 1396 pg/mL. He was started on furosemide and chlorothiazide, as well as intravenous milrinone and dobutamine. Serial echocardiograms continued to demonstrate PAH and supplemental oxygen was unable to be weaned. Sildenafil was started and up-titrated to 10 mg TID. He eventually required intubation and mechanical ventilation. Chest CT revealed patchy ground-glass opacities, some mild thickening of interlobular septa, right ventricular enlargement, and main pulmonary artery dilation which were suspicious for pulmonary veno-occlusive disease (PVOD). Cardiac catheterization was performed while on sildenafil and IV inotropes which demonstrated mildly elevated mean PAP of 24 mmHg, PA wedge pressure of 10 mmHg and a PVRi of 3.6 Wood Units·m^2.

Within two weeks of sildenafil initiation, NT-pro BNP normalized and echocardiogram showed borderline PAP elevation. He was eventually extubated but did not tolerate weaning off high-flow nasal cannula and IV milrinone. He remained on total parenteral nutrition throughout this time. Due to the patient's tenuous cardiopulmonary status, a third cycle of high-dose chemotherapy was not offered and lung biopsy was not performed to confirm PVOD. After multidisciplinary discussion with parents, patient was transitioned to hospice care and he died at 15 months of age.

Discussion

PAH is a serious condition in pediatric patients with significant morbidity and mortality.[1] Few studies exist assessing the incidence of PAH in pediatric patients undergoing high-dose chemotherapy and/or HSCT. Among chemotherapeutic agents, the 2018 World Symposium on Pulmonary Hypertension recognized the tyrosine-kinase inhibitor (TKI) dasatanib as having a definite association with developing PAH. Alkylating agents and another TKI, bosutinib, have possible association.[2] Desai et al. reported four cases of PAH among 21 children undergoing high-dose chemotherapy with busulfan/melphalan and stem cell rescue for high-risk neuroblastoma.[3] Jodele et al. found 5 patients out of 33 with clinical and/or histological diagnosis of PAH after HSCT.[4] These studies have demonstrated alarming mortality rates for these patients with PAH.[2–4]

Our series is the second to report on the possible link between PAH and carboplatin/thiotepa therapy. Schechter et al. demonstrated 3 out of 20 pediatric patients with central nervous system (CNS) tumors who developed PAH after high-dose carboplatin/thiotepa and sequential autologous SCT.[5] Review of data at our institution demonstrated a total of 30 pediatric patients with CNS tumors who received high-dose carboplatin/thiotepa and sequential autologous SCT from 2008 to 2021. The two described cases represent the only cases of PAH in this cohort. Interestingly, an additional eight patients underwent high-dose carboplatin/thiotepa plus etoposide with autologous SCT and none of these patients developed PAH. Historically, our practice was for routine echocardiography prior to induction chemotherapy/transplant and as clinically indicated. Currently, given our experience with these two cases, serial echocardiograms and BNP levels prior to and after each transplant are performed. Patients are immediately referred to our pulmonary hypertension service if these tests are abnormal.

The pathogenesis of PAH in pediatric patients undergoing high-dose chemotherapy and HSCT is not entirely understood although multiple mechanisms have been suggested. The study by Schechter et al suggested a drug-induced pulmonary arterial vasculopathy, as well as fibrointimal hyperplasia leading to concentric luminal narrowing of small pulmonary arteries as seen on lung biopsy.[5] In addition, electron microscopy showed thickened cytoplasm of endothelial cells and hyperplasia of alveolar type 2 cells with osmiophilic lamellar bodies, suggestive of drug effects.[5] For some patients undergoing allogeneic SCT, chronic graft-versus-host-disease with resultant cytokine-mediated damage of the microvascular endothelium is a consideration.[6] Jodele et al. suggested transplant-associated thrombotic microangiopathy as a potential etiology of PAH in this patient population with microthombi formation and fibrin deposition resulting in inflammation and vasoconstriction leading to PAH.[4] Lastly, it is important to distinguish pulmonary veno-occlusive disease from PAH as the treatment strategies and approach may differ.[7]

We recommend routine PAH screening of pediatric patients undergoing chemotherapy with carboplatin/thiotepa and HSCT. It would be beneficial to institute a standardized echocardiographic protocol to serially evaluate for PAH and ventricular dysfunction.[8] In addition, serial measurements of BNP levels may alert us to deteriorating cardiopulmonary status.[9] These studies should be performed prior to each tandem cycle of carboplatin/thiotepa and autologous HSCT, after the third cycle, and at any time there is clinical concern based on dyspnea, oxygen desaturation, or increasing BNP levels. Early and prompt diagnosis of PAH in this patient population can allow for earlier initiation of PAH-targeted therapy with potential for decreased morbidity and mortality. A close working relationship between pulmonary hypertension specialists and pediatric oncologists will better serve these patients in longitudinal care. Furthermore, these cases highlight the importance of the growing field of cardio-oncology bridging the expertise of these two fields.

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Conflict of interest

The author(s) declare no potential conflicts of interest.

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Ethical approval

This research was approved by our institutional review board. As the patients in this series are deceased and institutional review board submission determined that this work did not meet the definition for human subject research, informed consent was not obtained.

Guarantor

Not applicable.

Contributorship

All authors equally contributed to the creation of this manuscript.

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