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CASE REPORT

Pulmonary edema and cardiac dysfunction after resection of a fourth ventricle tumor in a toddler: case report

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Introduction

Patients with injury to the central nervous system can develop cardiac and pulmonary symptoms in the absence of primary cardiac or pulmonary disease. In some cases pulmonary edema that responds poorly or not at all to medical therapy such as diuretics develops and is regarded as neurogenic in origin. A variety of conditions may produce neurogenic pulmonary edema (NPE) [1, 5, 11, 12].

We describe a young child who sustained fatal cardiopulmonary collapse in association with an anaplastic fourth ventricular ependymoma. This occurred after attempted resection of the tumor which had invaded the medulla along the floor of the fourth ventricle. Despite a comprehensive investigation following the collapse, it could not be attributed to a cardiac or pulmonary event.

Case report

The patient was a 3-year-old girl who was admitted for resection of a recurrent anaplastic ependymoma. The patient initially presented at 16 months of age with emesis, lethargy, weight loss, and head tilt falling to the left. On physical exam she had rightward nystagmus and a wide-based gait. A magnetic resonance (MR) scan of the brain at the time demonstrated an enhancing mass in the fourth ventricle (Fig. 1a, b). The mass was resected (Fig. 1c) and diagnosed as an anaplastic ependymoma. The patient required a ventriculoperitoneal shunt for hydrocephalus and was treated postoperatively at 4 weeks with cranial radiation.

A surveillance MR 15 months after her initial resection showed recurrence of the tumor (Fig. 1d). The patient underwent a second resection followed by chemotherapy (oral VP-16). Of note, no anthracycline or other potentially cardiotoxic agents were used. Postoperative MR scan revealed

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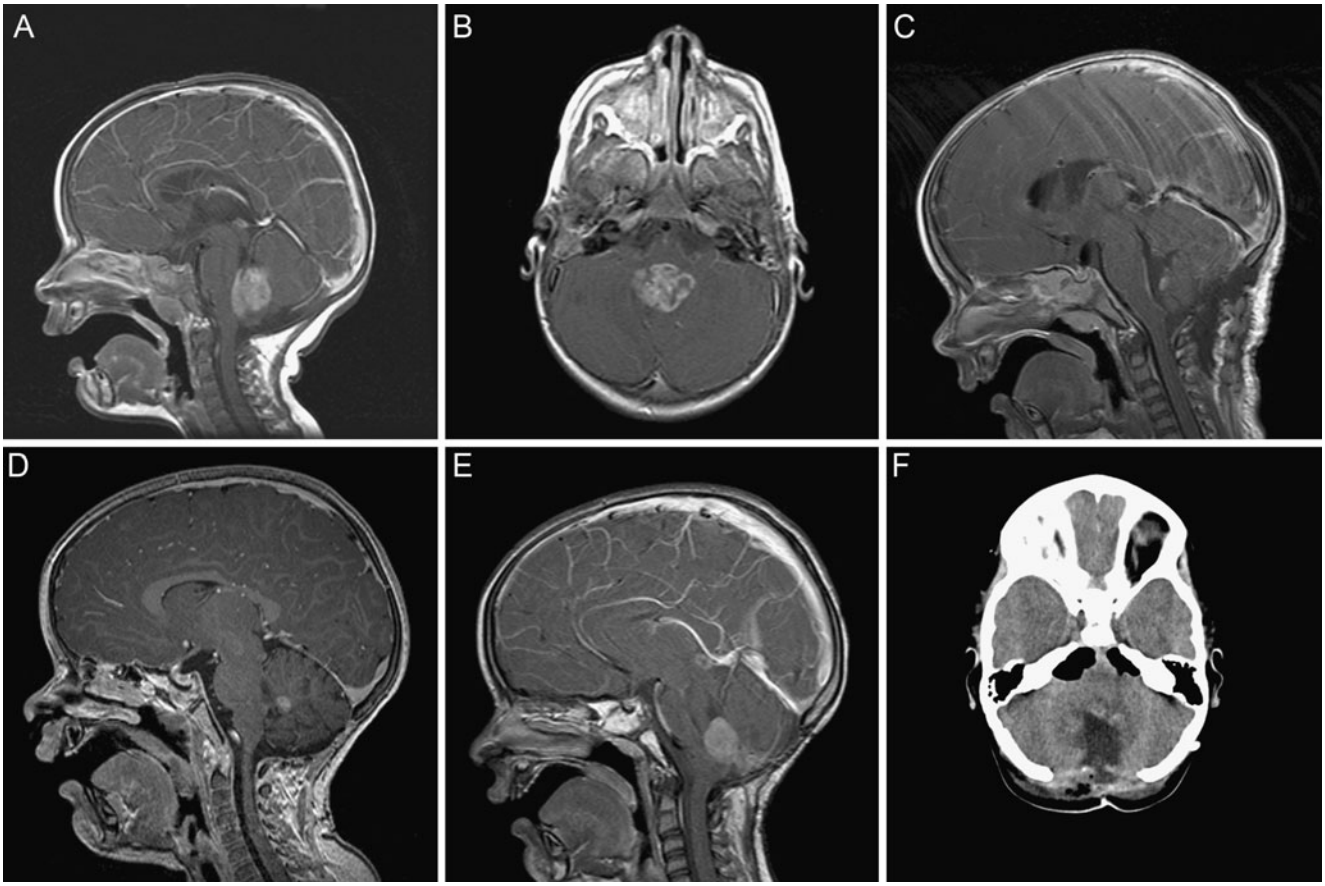

Fig. 1 Representative radiographic images. Sagittal (**a**) and axial (**b**) MR images demonstrating the large fourth ventricle tumor at the initial presentation. **c** MR image after the first resection, demonstrating a gross total resection. Follow-up preoperative MR images before the second (**d**) and third (**e**) resections, demonstrating the recurrent tumor adherent to the floor of the fourth ventricle. **f** Postoperative CT image demonstrating a gross total resection of the tumor

a left posterior inferior cerebellar artery infarct. Her postoperative course was complicated by a shunt infection.

Seven months after her second resection, a repeat MR scan demonstrated recurrence of the tumor in the fourth ventricle. She was treated with a course of avastin and irinotecan. Five months later a repeat MR scan showed no response to the chemotherapy (Fig. 1e), and a third resection was done.

Intraoperatively it was noted that the mass was adherent to the posterior medulla in the floor of the fourth ventricle. A gross total resection was thought to have been achieved. The intraoperative course was uneventful, with the exception of two brief episodes of bradycardia that occurred during manipulation of the medulla. During these episodes, the resection was temporary halted and the episodes resolved without intervention. The patient was extubated in the intensive care unit without difficulty, and her vital signs were stable; however, she was noted to have a new sixth and seventh nerve palsy. Postoperative computed tomography (CT) scan demonstrated resection of the mass (Fig. 1f).

Twelve hours postoperatively, the child exhibited progressive hypoxemia and respiratory failure. Chest X-ray demonstrated near complete opacification of the right lung (Fig. 2a), and she was intubated and mechanically ventilated. During intubation she was noted to have a large volume of fluid in the oropharynx and endotracheal tube, thought to be originating in the edematous lungs. She was therefore placed on volume control ventilation with 8 ml/kg of tidal volume and 15 cmH_2O of positive end expiratory pressure. Over the next 9 h, the child required no cardiovascular support: she was well perfused with capillary refill less than 3 s, had a lactate of 4 mmol/L, and a systemic capillary venous oxygen saturation of 65–72% (measured at the superior vena cava/right atrial junction). Subsequent chest radiographs revealed bilateral opacifications (Fig. 2b) with a declining P to F ratio of 80 and an increasing oxygenation index to 31 (FiO_2) 1.0, mean airway pressure 25, and arterial PO_2 80. As she developed acute respiratory distress syndrome (ARDS), inhaled nitric oxide therapy was initiated at 20 ppm. However, she developed cardiovascular instability as exhibited by hypotension and poor perfusion. Physical exam revealed cold

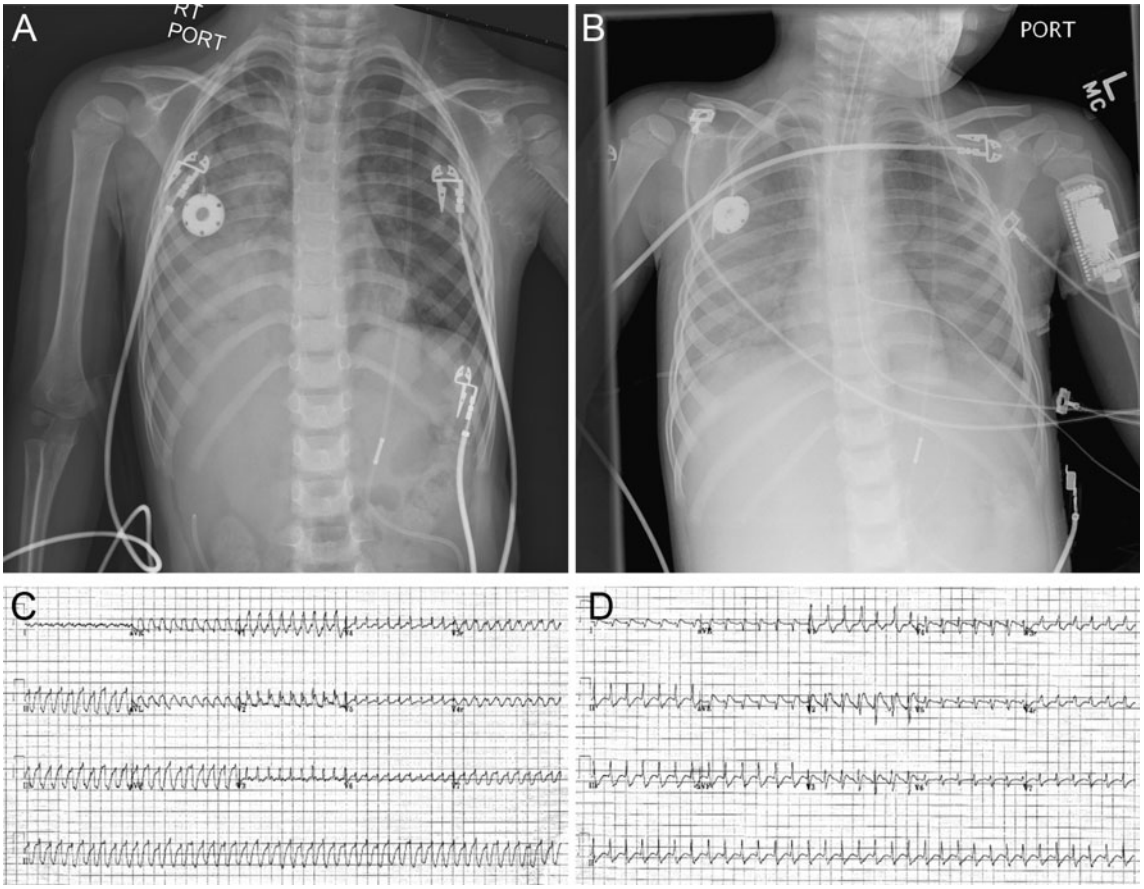

Fig. 2 Significant cardiopulmonary images from the time of the decompensation. **a** Representative chest X-ray demonstrating right chest opacification. **b** Representative chest X-ray demonstrating bilateral chest opacification. **c** Representative ECG demonstrating ventricular tachycardia. **d** Representative ECG demonstrating ST elevations in anterior lateral leads

extremities, a liver edge 3–4 cm below the costal margin, and new S3 heart sound on auscultation. Cardiac support was initiated with epinephrine and milrinone. Electrocardiogram (ECG) demonstrated sinus tachycardia with rates in the 180 s, and echocardiogram (ECHO) showed mild suboptimal contractility with no pericardial effusion.

The child's condition continued to worsen, and her chest X-ray progressed (Fig. 2b). A code was called secondary to bradycardia (heart rate of 60) and hypotension (mean arterial pressure of 30 mmHg). Chest compressions were initiated immediately with resolution of bradycardia. In addition, she received calcium gluconate to correct hypocalcemia, sodium bicarbonate to correct metabolic acidosis, and an increase in inotropic support. Later in the day, a second code was called for pulseless ventricular tachycardia (Fig. 2c). After cardioversion of the ventricular tachycardia, a lidocaine infusion was initiated for anti-arrhythmic therapy. At this time, ECG changes demonstrated ST elevations in the anterior lateral leads (Fig. 2d) with elevated levels of troponin (>22.5 ng/mL) and creatine kinase (641 IU/L). ECHO showed moderately decreased left ventricular shortening, no regional wall motion abnormalities, moderate mitral regurgitation, and no pericardial effusion. With cardiology consultation and data suggesting possible myocardial ischemia, namely ECG changes and elevated cardiac enzymes, a selective left and right coronary angiogram was performed. This demonstrated normal course and distribution of the right and left coronary systems, without evidence of embolic coronary artery disease. During diagnostic cardiac catheterization, the patient had several episodes of ventricular tachycardia that were treated with cardioversion and amiodarone. After catheterization the patient's multiple organ dysfunction (MODS) continued to worsen as she now had ARDS with pulmonary hemorrhage, congestive heart failure (CHF), and progressive end organ dysfunction including renal and liver insufficiency. The MODS progressed despite maximal support. On postoperative day 2, the decision was made by the medical team (including oncology, cardiology, critical care, and neurosurgery) and the parents to withdraw technologic support with analgesia and sedation, and the patient subsequently died.

At autopsy, the examination of the heart showed no evidence of hemorrhage or infarction. The left ventricular myocardium appeared mottled and slightly congested, and sections of coronary arteries showed no evidence of thrombo-

sis or arterial wall damage. Histological sections of the myocardium showed preserved architecture, mild congestion, and no evidence of ischemia or infarction. There were bilateral pleural effusions. The lungs were congested and edematous. Histological sections showed bilateral, diffuse hyaline membranes and proteinaceous debris within airspaces along with desquamated cells, inflammatory cells, intra-alveolar edema, and hemorrhage.

Examination of the central nervous system demonstrated cerebral edema, hypoxic–ischemic changes, and postoperative changes involving the posterior fossa and brainstem. Microscopic examination of the brainstem demonstrated residual infiltrating anaplastic ependymoma (Fig. 3a, b), most prominent in the rostral medulla. In addition to residual tumor, postoperative changes were identified in the brainstem and cerebellum. These changes included intraparenchymal hemorrhage, vascular congestion, ischemic neurons, subacute necrosis, and collections of axonal spheroids (Fig. 3c), highlighted by neurofilament protein (NFP) immunohistochemical staining (Fig. 3d).

Discussion

Cardiopulmonary complications following brain tumor resection in pediatric patients are rare and may be fatal. We describe a 3-year-old girl who developed progressive cardiopulmonary collapse after resection of a recurrent fourth ventricular tumor. Although stable after the procedure, she developed ARDS, CHF, and eventually MODS. She had been treated with chemotherapeutic agents, some of which rarely produce effects on the heart and lungs. However, the postmortem study showed no evidence of a cardiomyopathy of any kind. There was instead invasion of the floor of the fourth ventricle by the tumor and necrosis of the floor and medullary tegmentum. These lesions are the likely cause of this child's NPE. This consists of acute noncardiogenic edema, with protein-rich intra-alveolar edema, perivascular congestion, and intra-alveolar hemorrhage. Cardiopulmonary dysfunction in NPE occurs in the absence of other isolated pathologic process that may affect pulmonary or cardiac dysfunction and can be solely explained by a direct insult from neurologic disease. This entity can result from diverse CNS disorders such as viral or bacterial infections, brain tumors, head injury, subarachnoid hemorrhage, multiple sclerosis, shunt malfunction, and seizures. In addition, NPE has been described after resection of a fourth ventricular brain tumor in a 21-year-old man.

Even though not completely understood, several mechanisms have been proposed to explain how CNS lesions can trigger NPE. Based on animal models, some authors believe NPE results from a massive increase in centrally mediated sympathetic discharge. This centrally mediated

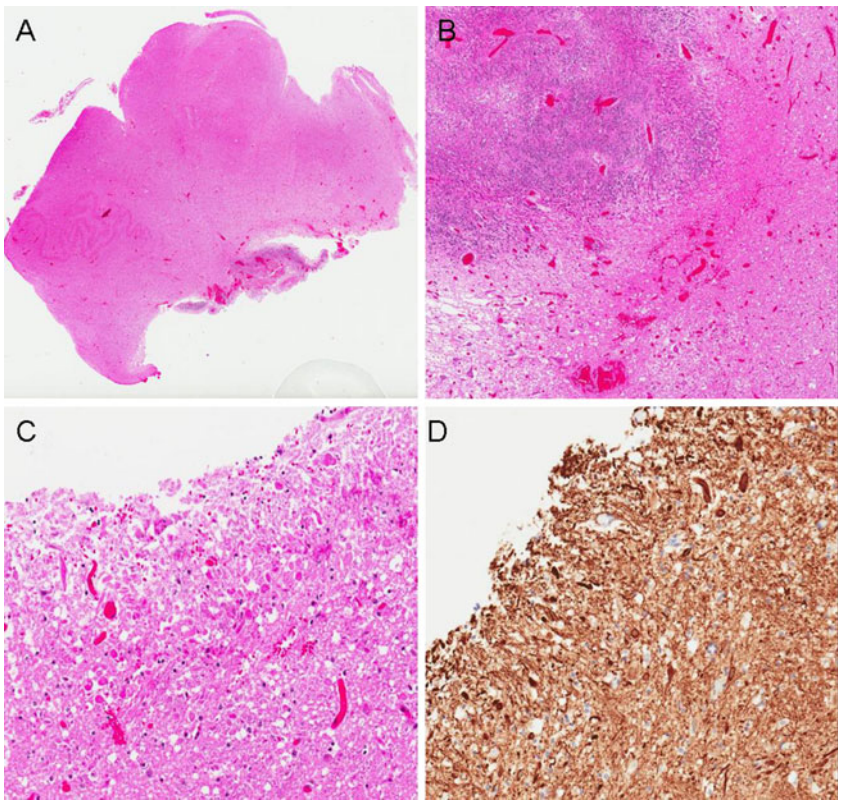

Fig. 3 Significant postmortem findings in brainstem. **a** Low-power microscopic section of the medulla showing infiltrating residual tumor, hemorrhage, and necrosis of the medullary tegmentum (floor of fourth ventricle), ×40 magnification. **b** Residual anaplastic ependymoma with surrounding hemorrhage and necrosis in medullary tegmentum (floor of fourth ventricle), ×100 magnification. **c** Axonal degeneration with spheroids in the medullary tegmentum (floor of fourth ventricle), ×200 magnification. **d** Axonal spheroids in the medullary tegmentum (floor of fourth ventricle) highlighted by NFP immunohistochemical staining, ×200 magnification

acute catecholamine surge causes direct lung injury to the endothelial cells secondary to pulmonary vascular constriction and congestion, capillary stress failure, and ultimately hemorrhage. Concomitantly, surging catecholamines may lead to cardiac stun, increased systemic vascular resistance, and an outpouring of inflammatory cytokines. Additionally, the catecholamine surge and inflammatory process are believed to result in increased vascular permeability, particularly in the pulmonary system resulting in protein-rich intra-alveolar pulmonary edema. The medulla is the common site of pathology in many cases of NPE. Keegan et al. postulated that because adrenergic areas 1 and 5 and the nucleus of the solitary tract lie in the floor of the fourth ventricle and that manipulation of this area during tumor resection may lead to some of the dysfunction seen in NPE.

This patient's tumor extensively infiltrated the floor of the fourth ventricle. Bradycardia seen intraoperatively as well as the postoperative cranial nerve deficits indicate dysfunction of structures in this region. The presence of acute and subacute necrosis in addition to residual infiltrating tumor in the brainstem is consistent with the delayed development of NPE in this case. The probable cause of fatal edema was damage to the nucleus and fasciculus of the solitary tract and the autonomic pathway connecting the brainstem with the hypothalamus. It has been suggested that the anesthetic agent during surgery may mask some of the affects of the manipulation until the postoperative period.

Diagnosis of NPE is one of exclusion, as it is necessary to eliminate other potential causes of cardiac and pulmonary dysfunction. Symptoms of NPE can be mistaken for aspiration pneumonia, myocardial infarction, heart failure, transfusion reaction, pulmonary embolus, or air embolus [9, 10]. Treatment consists of aggressive hemodynamic and ventilatory support. Even though there are no clear guidelines, use of lung protective ventilation to minimize ventilator-induced lung injury, inotropic support to overcome cardiac stun, reduction of pulmonary and systemic vascular resistance to augment forward blood flow, and implementation of all possible measures to prevent the progression of the neurologic dysfunction must be considered, including reducing intracranial pressure [2, 4, 6–9]. Despite aggressive treatment the mortality for some forms of NPE can exceed 90% [1, 3].

Conclusion

NPE is a rare clinical entity that results from many different types of neurologic disease, particularly those that involve the hypothalamus and periventricular autonomic pathways including structures in the floor of the fourth ventricle. This rare but clinically significant condition must be considered in any patient experiencing cardiopulmonary decline after resection of tumors of the floor of the fourth ventricle.

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