A 7-year-old boy with recurrent cyanosis and tachypnea: A case report

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WORD COUNT	2611	TIME SUBMITTED	12-APR-2022 01:29PM
		PAPER ID	84718281

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 72120

Manuscript Type: CASE REPORT

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Abstract

BACKGROUND

Brain tumors are the most common solid tumors in children and comprise 25% of all malignancies in children. Common presentations include headache, nausea and vomiting, gait abnormality, papilledema, and epileptic seizure; however, some symptoms can be very insidious, with atypical and misleading manifestations.

CASE SUMMARY

Here, we report a 7-year-old boy who presented with recurrent cyanosis and tachypnea after exercise for 2 years. His body mass index was 26.43 kg/m^2. Hepatosplenomegaly, blood gas analysis, biochemical parameters, chest computed tomography scan, and echocardiograph suggested type II respiratory failure, pulmonary heart disease, and mild liver injury. Non-invasive breathing support, antibiotics, and anti-heart failure therapy were given. The patient's pulse oxygen saturation increased to over 95% when he was awake but dropped to 50%-60%, accompanied by cyanosis, during sleep while receiving high-flow nasal cannula oxygen. Sleep-related breathing disorder was suspected. In the intensive care unit, however, polysomnography was unavailable. Brain magnetic resonance imaging revealed a space-occupying (cerebellum and brainstem) lesion, which was later confirmed to be pleomorphic xanthoastrocytoma by surgery and histopathology of tissue biopsy.

CONCLUSION

When treating patients with cyanosis and tachypnea, a broad differential diagnosis should be considered, including brain tumor.

Key Words: Respiratory failure; Pulmonary heart disease; Sleep-related breathing disorders; Pleomorphic xanthoastrocytoma; Children; Case report

Li S, Chen LN, Zhong L. A 7-year-old boy with recurrent cyanosis and tachypnea: A case report. *World J Clin Cases* 2022; In press

Core Tip: Brain tumors are the most common solid tumors in children. Common presentations include headache, nausea and vomiting, gait abnormality, and epileptic seizure; however, some symptoms can be insidious and misleading. Here, we report a 7-year-old boy who presented with recurrent cyanosis and tachypnea after exercise for 2 years. Type II respiratory failure, pulmonary heart disease, liver injury, and severe obesity were diagnosed. Cyanosis during sleep (peripheral oxygen saturation dropping to 50%-60%) was observed during hospitalization. Sleep-related breathing disorder was suspected. Brain magnetic resonance imaging revealed a cerebellum and brainstem space-occupying lesion. Subsequent tissue biopsy pathology confirmed brainstem pleomorphic xanthoastrocytoma.

INTRODUCTION

Central nervous system tumors are the most common solid tumor encountered in pediatric practice, reportedly accounting for approximately 25% of all childhood cancers and classified as the second most common pediatric malignancy, after leukemia[1]. Common presentations include headache (33%), nausea and vomiting (32%), gait abnormality (27%), papilledema (13%), epileptic seizures (13%), and manifestations of increased intracranial pressure (10%). Other symptoms that may be present are strabismus, altered behavior, macrocephaly, and cranial nerve palsy.

Pleomorphic xanthoastrocytoma (PXA) is a rare type of brain astrocytoma that is typically seen in children and young adolescents. While PXAs occur almost exclusively supratentorially (98% of cases, and predominantly in the temporal lobes (50%))[2], they can form in the cerebellum, brain stem, and spinal cord. In most cases, regardless of location, the initial symptom is epilepsy.

Here, we report a case of PXA that presented in a rare location and with atypical clinical manifestations, which could be misleading in clinical practice.

CASE PRESENTATION

Chief complaints

A 7-year-old boy was admitted to our hospital to address recurrent cyanosis and tachypnea on exertion that had existed for 2 years.

History of present illness

The patient had been in his usual state of health until 2 years before admission, when intermittent facial cyanosis developed that worsened on exertion, accompanied by sweating, tachypnea, and swelling of the face and bilateral legs. Systemic pain developed, which mainly affected his chest, back, and lower limbs. The episode of pain was unclear and would resolve spontaneously. The patient had occasional dry cough without fever. He had previously been treated in a local hospital, but recurrent cyanosis and tachypnea after exercise persisted for the last 2 years.

One month before admission, the patient had one suspected episode of syncope, which manifested as falling to the ground without response to voice and had lasted for 2 min to 3 min. He was subsequently sent to the Emergency Department of our hospital. His eyes did not appear in a staring state (*i.e.* no episodes of staring blankly) and he presented no limb rigidity nor urinary incontinence. History of trauma or surgery was denied. The cranial computed tomography (CT) findings were normal. The echocardiography revealed enlargement of the right ventricle (17 mm), slight broadening of the pulmonary artery (25 mm), and normal left ventricle function (estimated ejection fraction of 70%). Tricuspid regurgitation (maximum velocity of 3.8 m/s) was also found and pulmonary artery hypertension was suggested (pressure gradient = 62 mmHg). Chest CT (Figure 1A) revealed bilateral pulmonary opacities, pulmonary congestion, slight enlargement of the cardiac silhouette, broadening of the pulmonary artery, mild pericardial effusion, and localized thickening of the bilateral pleural. Cefdinir, diuretics, and nifedipine were prescribed. Cyanosis and tachypnea

were relieved. Unfortunately, although his symptoms had been relieved, they relapsed after withdrawal of the medications.

One week before admission, the tachypnea worsened, with fatigue, and the patient was again evaluated in our hospital. Upon admission, the white blood cell count was 10.5×10^9/L (reference range: 3.6-9.7 $\times 10^9$/L) and 71.2% of the cells were neutrophils (reference range: 23.6%-75%). In addition, the level of C-reactive protein was 10.9 mg/L (reference range: 0-8 mg/L) and the level of myocardial troponin I was 0.067 mg/L (reference range: 0-0.034 mg/L). A chest radiograph showed pulmonary congestion and enlarged cardiac silhouette. A diagnosis of cardiac insufficiency and pulmonary hypertension was made. Dopamine was administered intravenously (5 mg/kg/min). Therapy was started with vitamin C, hydrochlorothiazide, spironolactone, and captopril.

History of past illness

The patient had a history of recurrent respiratory infection and myoclonic jerks and snoring during sleep at night.

Personal and family history

The patient was born at full-term, with a birth weight of 2.9 kg. The family history was unremarkable.

Physical examination

On examination, the patient appeared critically ill. The temperature was 36.5 °C, pulse was 118 beats per min, blood pressure was 118/60 mmHg, respiration was 24, and oxygen saturation was 60%-70% while he was receiving oxygen through nasal cannula. His weight was 40 kg (> 97th percentile) and body mass index (BMI) was 26.43 kg/m^2. Orthopnea, nasal flaring, stretches of erythema on both cheeks, and soybean-sized cervical lymph nodes on both sides were present. Cyanosis was seen on his facial area and limbs. Coarse breath sounds with crackles were heard. The heart rhythm was

strong and regular, with an augmented second heart sound; although, no cardiac murmur was heard. The abdomen was soft and nontender. The liver extended about 2 cm below the right costal margin with a moderate texture, and the spleen was 4 cm below the left costal margin. Muscle tone was normal. Notably, he had no clubbing, edema, or jugular vein distention. Other physical examination findings were unremarkable.

Laboratory examinations

Laboratory tests indicated impaired liver function, hypoxemia, and hypercapnia (Table 1). The 1,3-beta-D glucan assay and tuberculosis T-SPOT test were negative. The culture of sputum was unremarkable. An electrocardiogram obtained on admission day showed the following: nodal tachycardia; axis leaning right (+ 130°); enlargement of the right atrium; ST-segment depression of 0.5 mv in leads II, III, arteriovenous fistula (AVF), V1-V3; and T-wave depression in leads II, III, AVF, and V4-V5. Spirometry showed mild restrictive ventilation disturbance. The ratio of measured values to predicted values of forced vital capacity (FVC) and forced expiratory volume in 1 s/FVC were 75.1% and 97.6%, respectively. Small airway obstruction was present (forced expiratory flow [FEF] at 50% [FEF50] was 64.7%, FEF at 75% [FEF75] was 36.7%, and mid maximal expiratory flow [MMEF] 75/25 was 53.2%).

Imaging examinations

Chest CT (Figure 1B) revealed improvement of opacities but the enlarged cardiac silhouette was persistent

FINAL DIAGNOSIS

PXA, hypercapnic respiratory failure, pulmonary heart disease, liver injury, and severe obesity.

TREATMENT

After hospitalization, the patient was given oxygen therapy through a mask (3 L/min). Cefoperazone tazobactam, dopamine, and reduced glutathione were infused. Diuretics and captopril were administered orally. Mild facial cyanosis was still visible, and blood gas analysis indicated an abnormally elevated partial pressure of carbon dioxide (PCO_2) of 70 mmHg (9.3 kPa). The patient was transferred to the pediatric intensive care unit (PICU).

In the PICU, high-flow nasal cannula oxygen (flow 12 L/min, fraction of inspired oxygen 50%) was administered and the pulse oxygen saturation (SaO_2) increased to over 95% when he was awake. Meanwhile, his liver function returned to normal level and pulmonary artery pressure estimated by echocardiography decreased. However, his SaO_2 decreased to 50%-60% during sleep, accompanied by cyanosis. Intracranial abnormality was considered and magnetic resonance imaging (MRI) was performed (Figure 2). A space-occupying lesion was seen at the right cerebellopontine angle, cerebellar tonsil, and medulla oblongata with partial involvement of the cervical spinal cord. The maximum cross-sectional area of the lesion was 1.7 cm × 2.3 cm with slightly hyperintense signal on T2-weighted imaging (T2WI) and slightly hypointense signal on T1-weighted imaging (T1WI). The lesion showed significantly inhomogeneous enhancement. The pituitary body and the meninges were clean.

The patient was then transferred for neurosurgery. Histopathological examination of the resected brain tissue indicated PXA with the presence of *BRAF* V600E mutation, which is the most common form of gene mutation in PXA.

OUTCOME AND FOLLOW-UP

After neurosurgery, the patient's symptoms resolved transiently but gradually relapsed. Six months later, the boy died of respiratory failure.

DISCUSSION

The common causes of cyanosis and tachypnea in children are respiratory infections and heart diseases, with liver diseases as a less frequent cause. Here, we report a rare

case of cyanosis and tachypnea that was mainly caused by a brain tumor, which was ultimately confirmed by histopathology to be PXA.

PXA generally has a favorable prognosis, with many cases being cured by surgery alone. The postoperative survival rates at 5 years and 10 years are 81% and 70%, respectively. Nevertheless, it is recognized that 15% to 20% of PXAs will undergo malignant progression. Because of the potential for malignant degeneration and the less predictable long-term prognosis, PXA has been classified as a World Health Organization grade II tumor malignancy[3], meaning that the tumor grows slowly and usually does not spread but is prone to recur postsurgery.

An underlying sleep-related breathing disorder (SRBD) was suggested by the observations of previous history of myoclonic jerks and snoring during sleep, decreased SaO_2 during sleep accompanied by cyanosis, and severe obesity. SRBDs have the potential to increase pulmonary arterial pressure during sleep but also during wakefulness in the long term[4]. Without appropriate intervention, SRBD progressively leads to pulmonary hypertension, pulmonary heart disease, and even death. In this case, several types of SRBD were considered that might have accounted for the disorder. Discriminating among these categories requires the performance of polysomnography (PSG).

Given the coexistence of elevated level of CO_2, alveolar hypoventilation syndrome was the most likely cause. It is defined as insufficient ventilation with elevated level of PCO_2 (in children PCO_2 > 50 mmHg, accounting for more than 25% of the total sleep time), either by direct determination of arterial blood gas or, more commonly, by proxy measures such as end-tidal or transcutaneous CO_2[5]. Alveolar hypoventilation syndrome is caused by some congenital or acquired conditions, including congenital central hypoventilation syndrome (CCHS), acquired alveolar hypoventilation associated with central nervous system abnormality, neuromuscular, rib cage disorders, obesity, and certain medication intake[6].

Another type of SRBD that should be considered is acquired central alveolar hypoventilation, which is very rare and can be caused by brainstem damage resulting

from tumor, ischemic damage, or infection[7]. The patient had PXA confirmed by surgery and pathological examination. The tumor was a focal glioma located at the cerebellum and brainstem, without a clear boundary. In this case, both the clinical manifestation and the location were rare. *BRAF* V600E mutation was found in the patient, which encodes an intracellular component of the mitogen-activated protein kinase pathway and has a high oncogenic potential. *BRAF* mutations can be found in 70% of typical PXA cases[8].

Except for the above two types of SRBD, obesity hypoventilation syndrome should also be taken into consideration. It is defined as a combination of obesity (BMI > 30 kg/m^2 in adults; > P_{95} in children), daytime hypercapnia (PCO_2 > 45 mmHg), and sleep-disordered breathing, after ruling out other disorders that may cause alveolar hypoventilation, such as congenital central hypoventilation syndrome, sleep-related hypoventilation due to a medication or substance, sleep-related hypoventilation due to a medical disorder. In this case, the patient's BMI was 26.43 kg/m^2, above the P_{97} level (19.4 kg/m^2 in 7-year-old Chinese boys)[9], and blood gas analysis revealed PCO_2 of 56.5 mmHg and 70.1 mmHg during wakefulness, implicating obesity in the development of alveolar hypoventilation.

We believe that brain tumor and obesity may have both been implicated in the pathogenesis of alveolar hypoventilation in this case. The coexistence of other types of SRBD, such as central apnea syndrome or obstructive sleep apnea-hypopnea syndrome, might also occur, which cannot be ruled out without PSG examination.

Other diseases presenting with dyspnea and cyanosis should be differentiated. A potential differential diagnosis is hepatopulmonary syndrome (HPS), since the patient presents with elevated liver enzymes and hypoxemia. HPS is characterized by abnormalities in blood oxygenation caused by the presence of intrapulmonary vascular dilations (IPVD) in the context of liver disease, generally at the cirrhotic stage[10]. HPS comprises the presence of advanced chronic liver disease, gas exchange abnormalities, and the presence of IPVD, without intrinsic pulmonary diseases. The patient in this case did not have a previous history of liver disease. On admission, the liver extended about

2 cm below the right costal margin with a moderate texture and the spleen 4 cm below the left costal margin. The liver enzymes were slightly elevated (alanine aminotransferase at 147 U/L; aspartate transaminase at 134 U/L) with normal bilirubin. After 3 d of treatment, the liver extended about 1 cm below the right costal margin and the spleen 2 cm below the left costal margin. The liver enzyme returned to normal; thus, the liver disorder was reversible. Additionally, the chest CT showed interstitial changes and the spirometry revealed mild restrictive ventilation disturbance, which were evidence of pulmonary diseases, thereby ruling out HPS.

Arteriovenous shunts, especially pulmonary arteriovenous fistula (PAVF), is another differential diagnosis that should be considered. PAVF is an abnormal communication between the pulmonary veins and pulmonary arteries. Most individuals may have the condition since birth[11]. The common manifestations of PAVF are shortness of breath, hemoptysis, chest pain, dizziness, and syncope. Pulmonary CT angiography is the gold standard for diagnosis, presenting opacity and AVF. Although this patient had such symptoms as tachypnea, chest pain and suspected syncope, which were similar to PAVF, he did not have hemoptysis, clubbing, or hereditary hemorrhagic telangiectasia, and the CT scans ruled out PAVF.

CCHS, previously known as Ondine's curse syndrome, is characterized by the impaired control of autonomic respiration during sleep and diminished sensitivity of CO_2 receptors. The primary cause is mutation of the *PHO2XB* gene, which is found in 90% of the cases[12]. CCHS usually starts in the neonatal period or early infancy and is accompanied by neurological abnormalities, such as autonomic and neurocognitive dysfunctions. Our patient had no such manifestations, making this diagnosis untenable.

This study had some limitations. First, PSG was not conducted because the patient was critically ill and MRI had revealed a brain tumor, which necessitated immediate surgery; thus, the information on SRBD was incomplete. Second, cardiac catheterization data were lacking, so the evaluation of pulmonary artery pressure was not accurate.

CONCLUSION

This case shows that when treating patients with cyanosis and tachypnea, a broad differential diagnosis should be contemplated, including a brain tumor.

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