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Respiratory Distress: A Great Masquerader

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Case 1 Presentation: Persistent Pulmonary Infiltrate
A 2-year-old boy has had several hospitalizations for right upper lobe (RUL) pneumonia associated with reactive airway disease. During this episode, he presents with a low-grade fever, cough, wheezing, and an oxygen saturation of 90% to 91% on room air. His temperature is 37.9°C (axillary), respiratory rate is 38 breaths/min, heart rate is 129 beats/min, and blood pressure is 92/60 mm Hg. Posteroanterior and lateral radiographic views of the chest obtained in the emergency department (ED) show a density in the RUL area (Fig. 1). On admission, he is given intravenous hydration, intravenous ceftriaxone, albuterol nebulizer treatments, oral corticosteroids, and supplemental oxygen.

Within 24 hours, the patient responds with improved work of breathing and resolution of hypoxia and fever. A follow-up radiograph shows persistence of the right upper lobe infiltrate. Initial and repeat blood cultures are negative. The patient is discharged after 6 days on a 10-day course of oral antibiotics, with a 2-week follow-up evaluation scheduled.

Two weeks later, the patient has improved further and does not have fever, tachypnea, or respiratory distress. Due to the recurrent nature of the RUL infiltrate, a chest radiograph is repeated to document radiologic resolution of the pneumonia. Surprisingly, the chest radiograph shows a persistent RUL density and mediastinal shift to the right (Fig. 2). Subsequent computed tomography (CT) scan of the chest reveals the underlying diagnosis.

Case 2 Presentation: Persistent Hypoxemia
A 5-month-old female infant is admitted for an acute episode of reactive airway disease. She presented to the ED with a low-grade fever, cough, nasal congestion, and wheezing. Her temperature is 38.0°C (axillary), respiratory rate is 48 breaths/min, heart rate is 130 beats/min,
and blood pressure is 90/58 mm Hg. In the ED, she did not have obvious cyanosis, but she did have hypoxemia, as evidenced by pulse oximetry readings between 83% and 87% oxygen saturation in room air.

Her past medical history is significant for cardiac dextroposition without situs inversus diagnosed at birth. Echocardiography (ECHO) at birth confirmed the cardiac dextroposition but showed otherwise normal cardiac structure. She was found subsequently to have trisomy 2 mosaicism. She has been hospitalized twice in the past with wheezing and hypoxemia and was diagnosed as having reactive airway disease during both hospitalizations.

During the current admission, initial therapy consists of bronchodilator medications, chest physiotherapy, oral corticosteroids, and supplemental oxygen. Over the first 48 to 72 hours, she improves clinically, with decreased work of breathing and almost complete resolution of wheezing. Despite improvement of the cough, wheezing, and nasal congestion, and her oxygen saturation remaining between 92% and 93% with supplemental oxygen, the saturation drops to the high 80s when oxygen is discontinued. She also remains mildly tachypneic.

The cause of the persistent hypoxemia is investigated further. A chest radiograph and chest CT scan do not reveal significant pulmonary or cardiac pathology to explain her symptoms. Repeat ECHO before bronchoscopy reveals her diagnosis (Fig. 3).

**Case 3 Presentation: Recurrent Croup**

A 3-month-old male infant is admitted for his third episode of croup. In his two previous episodes, he responded well to intramuscular dexamethasone and racemic epinephrine. His first episode was at 2 weeks of age. After the second episode of croup, direct laryngoscopy performed at a community hospital revealed erythema below the vocal cords. For this third episode, the patient presents to the ED with prominent stridor, significant retractions, and increased work of breathing. His temperature is 36.7°C (axillary), respiratory rate is 50 breaths/min, heart rate is 110 beats/min, and blood pressure is 97/50 mm Hg. Administration of intramuscular dexamethasone and nebulized racemic epinephrine

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**Abbreviations**

- CDH: congenital diaphragmatic hernia
- CT: computed tomography
- ECHO: echocardiography
- ED: emergency department
- RUL: right upper lobe
- SVC: superior vena cava
- 2D: two-dimensional

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Figure 3. Two-dimensional echocardiography (2 D ECHO) with color in the suprasternal view. As the video (online only) plays, the left superior vena cava (SVC) drains into the left atrium. Pulmonary veins also appear. The aorta appears with the left SVC coursing inferiorly in its usual location. Branches of the pulmonary artery appear briefly, followed by views of the left SVC entering the left atrium.

Figure 4. Preoperative view of the laryngeal inlet. Just beyond the vocal cords, a bulge is visible.
result in improvement of retractions and respiratory distress. The patient appears comfortable, with a decrease in his stridor.

The stridor, however, does not resolve fully and is biphasic, appearing in both inspiratory and expiratory phases of respiration, accompanied by a peculiar “honking” noise. Due to concerns about the persistence of stridor, he undergoes laryngoscopy and bronchoscopy that reveal his diagnosis (Fig. 4).

**Case 1 Diagnosis: Congenital Absence of the Right Lung**
The chest radiograph suggested an underlying RUL abnormality with a right mediastinal shift. Further investigation by CT scan revealed mediastinal shift to the right to replace the absent RUL and absent RUL bronchus (Fig. 5). A prominent large mass of thymic tissue on the anterior mediastinum was the “reason” for the right upper chest density on the chest radiograph series (Fig. 6).

**Discussion**
The thymus, a primary lymphoid organ, develops initially during the first trimester and matures rapidly. This anterior mediastinal structure is relatively large in infancy. It is largest relative to body size during fetal life and attains its mature weight during the first year after birth, subsequently involuting gradually before puberty. The thymus is mistaken commonly as an RUL infiltrate when it is prominent on the frontal view of a chest radiograph, but radiographically, the thymus has a sharp edge (“sail sign”). The inferior margin of the thymus is convex in configuration.

The right mainstem bronchus normally divides into the RUL bronchus and the bronchus intermedius that divides into the right middle and right lower lobe bronchi. RUL atelectasis is common in infancy because of the elliptical configuration of the opening of the RUL segment as well as the acute angle of its take-off from the right mainstem bronchus. Infants who are kept in the supine rather than upright position have a tendency to plug the RUL bronchus during aspiration or episodes of respiratory illnesses. RUL atelectasis presents as volume loss of the lung parenchyma, and in contrast with the thymic shadow, the inferior margin of the RUL infiltrate is concave.

In this patient’s case, the “RUL pneumonia” was the thymic shadow occupying the place of the congenitally absent RUL. It is uncommon to find an isolated case of congenital absence of the RUL. Review of the literature shows that lung hypoplasia usually is associated with congenital diaphragmatic hernia (CDH). Anatomic anomalies of the tracheobronchial tree and bronchial hypoplasia on the affected side have been identified in 18% and 38% of patients born with CDH, respectively.

**Patient Course**
This patient had no history of CDH. Congenital absence of the RUL eventually was diagnosed because of concern for the persistent density in the RUL region when the patient presented repeatedly with what seemed to be exacerbations of reactive airway disease with RUL pneumonia.

The patient continues to receive daily inhaled corticosteroids, which allows good control of his reactive airway disease. Because the identity of the RUL density has been determined, he has not received any further antibiotics and has not undergone repeated chest radiographs for his “recurrent RUL pneumonia.”
Case 2 Diagnosis: Bilateral Superior Vena Cava

Laryngoscopy and bronchoscopy revealed normal upper and lower airway anatomy. ECHO demonstrated a left superior vena cava (SVC) draining directly into the left atrium. Contrast ECHO with agitated saline injected through an intravenous line placed in the left antecubital area showed saline arriving in the left atrium before appearing in the right atrium, confirming a direct shunt between the left SVC and the left atrium. Magnetic resonance imaging and angiography confirmed the presence of bilateral SVC vessels, with the left SVC draining directly into the left atrium (Fig. 7).

Two-dimensional (2D) ECHO with color demonstrated an abnormal “systemic” flow pattern in the vessel draining to the left atrium (Fig. 8), in contrast to the normally expected flow pattern in a pulmonary vein draining to the left atrium (Fig. 9). Without meticulous 2D ECHO and Doppler imaging, the shunt to the left atrium lesion could have been missed.

Discussion

Hypoxia refers to inadequate oxygen supply to the body as a whole (generalized hypoxia) or to a region of the body (tissue hypoxia). Hypoxia differs from hypoxemia.

Hypoxemia refers to low oxygen content in the blood, specifically defined as a low partial pressure of oxygen within the arterial blood. It is possible to experience hypoxia (eg, due to anemia) but maintain a high partial pressure of oxygen.

Hypoxia can be classified as anoxic, anemic, stagnant, and cytochemical. Anoxic hypoxia occurs at the gas exchange level. Anoxic hypoxia (“no oxygen hypoxia”) occurs when a person breathes air with low oxygen content, as in ascending to a high altitude or diving underwater while breathing into a closed-circuit rebreather system. Increasing inspired oxygen can improve
the hypoxia. However, some cases of anoxic hypoxia are not improved by increasing the inspired oxygen, as with an intracardiac or intrapulmonary shunt.

Anemic hypoxia occurs when the oxygen-carrying capacity is affected, as with anemia (low hemoglobin) or hemoglobinopathies (e.g., sickle cell disease). Stagnant hypoxia occurs when there is decreased blood flow, as with heart failure or septic shock. Cytochemical hypoxia occurs at the cellular level, when oxygen dissociation from oxyhemoglobin is impaired, as with cyanide poisoning, blocking oxygen use at the mitochondrial level.

Persistent hypoxemia should prompt the clinician to look into different organ systems as potential causes (e.g., cardiac, pulmonary, and central nervous systems). In this case, the persistence of hypoxemia despite clinical resolution of the respiratory distress prompted investigation for extrapulmonary reasons for hypoxemia. The history of chromosomal anomaly made a cardiac or major vessel anomaly a likely consideration.

Trisomy 2 mosaicism, although very rare, is associated with cardiac defects. Despite lacking consistent phenotypic features, this genetic abnormality has been associated with craniofacial anomalies; digital anomalies; developmental delay, including language impairment; hypotonia; brain anomalies; and cardiac defects. In this case, ECHO demonstrated the left SVC draining into the left atrium, resulting in shunting of venous blood into the systemic circulation through the left side of the heart.

Bilateral SVC is the most common systemic venous anomaly, occurring at a rate of 0.3% to 0.5% in the general population, based on autopsy series. In most cases, the left SVC connects to the coronary sinus, thereby draining into the right atrium. If the coronary sinus is unroofed or absent, the left SVC connects directly into the left atrium, creating a right-to-left shunt. In this patient, this very rare cardiac anomaly was missed on the initial ECHO. More common cardiac lesions that cause right-to-left intracardiac shunting resulting in cyanosis include tetralogy of Fallot, Ebstein anomaly, and total anomalous pulmonary venous return. These cyanotic heart diseases can present later in infancy, depending on the severity of the lesion.

Intervention usually is required earlier in life for single-ventricle lesions and is dependent on multiple factors, including the presence of critical obstruction to either the systemic or the pulmonary circulation, the presence of patent ductus arteriosus-dependent circulation, and the balance between the perfusion of the systemic and the pulmonary circulations. Other cardiac lesions, such as transposition of the great vessels, involve two parallel circulations requiring intervention at birth, without which the lesion is not compatible with life. Most of these conditions are diagnosed shortly after birth and are seen readily on initial ECHO.

Pulmonary causes of hypoxemia include right-to-left intrapulmonary shunting, diffusion abnormalities, ventilation-perfusion mismatch, and structural airway abnormalities. In this patient, the unremarkable radiograph and CT scan of the chest made a variety of disorders less likely, such as pneumonia, pleural effusion, pulmonary lymphangiectasia, pulmonary sequestration, and pulmonary hypoplasia. However, other rare conditions, such as pulmonary arteriovenous malformation, are possible and require confirmation by angiography.

Other causes of hypoxemia include hemoglobinopathies that limit oxygen transport, such as methemoglobinemia. Methemoglobin has an oxidized ferric ion within its core rather than the naturally occurring reduced ferrous ion found in normal hemoglobin. This chemistry results in a molecule that does not bind oxygen. Should the concentration of methemoglobin increase in the red blood cells to a specific threshold, oxygen delivery to the tissue is impaired. A methemoglobin concentration of greater than 15% of the circulating hemoglobin leads to clinically apparent cyanosis.

Pulse oximetry typically overestimates oxygen saturation in cases of significant methemoglobinemia due to the variable light absorbance of methemoglobin at the two wavelengths used to measure oxygen saturation. However, in this patient’s case, the pulse oximetry was lower than expected, despite the absence of obvious clinical cyanosis, thereby making methemoglobinemia unlikely.

**Patient Course**
The patient was evaluated for elective surgical repair at a later date.

**Case 3 Diagnosis: Large Subglottic Hemangioma**
Laryngoscopy and bronchoscopy revealed a large subglottic hemangioma causing 80% obstruction of the subglottic airway (Fig. 10).

**Discussion**
A distinct barking, seal-like cough or prominent noisy upper airway breathing typically characterizes the presentation of viral-induced croup (laryngotracheobronchitis). In general, viral croup presents with a brief prodrome of an upper respiratory tract infection, typically with fever, nasal congestion, and cough. The usual pre-
presentation occurs at about 6 to 12 months of age. In this patient, the initial presentation of upper airway symptoms at 2 weeks of age with no prodrome was highly suggestive of external airway compression or the presence of an underlying structural anomaly within the upper airway. Recurrent episodes, each of which necessitated medical evaluation and intervention, further increased the likelihood of an underlying structural anomaly.

Neonatal stridor is abnormal and must be investigated. The differential diagnosis includes laryngomalacia, unilateral vocal cord paralysis, vascular ring, and, as in this case, subglottic hemangioma. A recent study showed that 30% of diagnoses of stridor made by non-otolaryngology physicians were incorrect. (1) Most patients diagnosed as having tracheomalacia were found to have laryngomalacia on endoscopy. Referral to an experienced pediatric airway specialist is important for specific diagnosis and surgical intervention.

The most common cause of stridor in an otherwise healthy infant is laryngomalacia, which occurs when maturation of the cartilage supporting the laryngeal inlet structures is delayed. Upper airway noise is generated during the inspiratory phase of the respiratory cycle, caused by a dynamic form of obstruction (collapsibility of the airway). Such collapsibility is generated by the pressure difference between the internal and external portions of the airway.

![Figure 10. Eighty percent obstruction caused by a hemangioma of the subglottic airway, as seen beyond the vocal cords.](image1)

The presence of the biphasic type (involving both the inspiratory and expiratory phase of respiration) of upper airway noise, as in this case, warrants further investigation because acquired subglottic stenosis is the most common cause of biphasic stridor. Commonly, biphasic stridor occurs in preterm infants who have a history of prolonged or recurrent intubation during their neonatal courses. Viewing of the upper airway is necessary to confirm the diagnosis. Of note, this patient was born at term and had no history of difficult birth or any injury during the perinatal period. Therefore, subglottic stenosis was an unlikely diagnosis.

Subglottic hemangiomas can be managed medically or surgically. Administration of corticosteroids is first-line treatment and can be used with medications such as interferon-α. In recent years, propranolol has been effective.

**Patient Course**

The patient responded transiently to administration of racemic epinephrine and systemic corticosteroids but continued to have recurrent episodes of stridor. The hemangioma was excised fully, followed by grafting of a thyroid alar cartilage wedge onto the superior portion of the subglottic area to maintain airway patency during healing (Fig. 11). This surgical intervention resulted in full recovery and no residual upper airway obstruction.

This child was treated in 2008, when propranolol, a nonselective β-antagonist, was not yet being used as a

![Figure 11. Postoperative view of the laryngeal inlet showing a patent subglottic airway after excision of the hemangioma and placement of a thyroid alar cartilage graft (white, 12 o'clock position).](image2)
therapeutic agent for airway hemangiomas. Conventional treatment at that time included corticosteroids, laser therapy, and open surgical resection. The risks and benefits of each treatment were explained to the parents of this child, and they chose surgery. More recently, numerous reports of the efficacy of propranolol in the management of such hemangiomas have appeared in the otolaryngology and pediatric literature. Proposed therapeutic effects of propranolol include decrease in size of hemangiomas through vasoconstriction, decreased expression of vascular endothelial and basic fibroblast growth factor genes, and apoptosis of capillary endothelial cells. (2) Adverse effects of propranolol reported during treatment of hemangiomas of infancy include bradycardia, hypotension, high-output cardiac compromise (in very large hemangiomas), hypoglycemia, and hyperkalemia. (3)(4)(5) Close monitoring, following a treatment protocol, and anticipatory guidance given to caretakers should minimize such adverse effects. (3)(4)

Despite these potential adverse effects, the benefits of propranolol still may greatly outweigh risks associated with surgery, which include airway stenosis, granulation, scarring, infection, and bleeding. The use of propranolol for hemangiomas currently is off-label use. Treatment options for airway hemangiomas must be determined on a case-by-case basis for each patient. Conservative medical management with propranolol may circumvent the need for surgery.

Conclusion

- Respiratory distress, cough, stridor, and wheezing are very common presenting signs and symptoms in a pediatrician’s office. Most often, they are the result of common conditions such as upper respiratory tract infection, croup, asthma, or pneumonia.
- Sometimes, these same symptoms represent rare but important and treatable conditions. The three children presented here had initial symptoms that were considered to represent routine conditions, but their subsequent evaluation revealed otherwise.
- If a patient has an unusual history (such as three episodes of croup in 3 months), an unusual clinical course (persistent hypoxemia despite improving “asthma” episodes), or persistent abnormal radiologic findings (mediastinal shift, mass), the practicing clinician should consider the rare and unusual causes of such findings and investigate further to detect any underlying disease.
- Accurate diagnosis of unsuspected and rare but treatable underlying disorders is likely to result in a permanent cure.

References

Suggested Reading
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