Case Report

Are breath-holding spells always innocuous: A case report

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ABSTRACT

The diverse clinical manifestations of Langerhans cell histiocytosis (LCH) present a dilemma to clinicians and pediatricians play an important role in its diagnosis and multidisciplinary approach. LCH, previously known as histiocytosis X, is an uncommon hematological disorder characterized by uncontrolled stimulation and proliferation of normal antigen-presenting cells, Langerhans cells. The purpose of this report is to describe the case of a 7-month-old female child with multisystem involvement who presented with breath-holding spells and to discuss the clinical, radiological, and histopathological features of LCH.

Key words: Cyanotic breath-holding spells, Langerhans cell histiocytosis, Spontaneous pneumothorax

Breath-holding spell is a benign paroxysmal non-epileptic disorder, with a reported incidence of 0.1–4.6% of otherwise healthy infants and young children from 6 months to 5 years of age [1]. They can occur either as pallid spells or cyanotic spells, the latter being more common. Pallid spells occur due to reflex vagal bradycardia and asystole, whereas cyanotic spells occur due to prolonged expiratory apnea and resulting intrapulmonary shunting. The episode is usually triggered by a provoking event where the child becomes emotionally upset or had a minor injury. While cyanotic spells are often triggered by anger or frustration, pallid spells occur following pain or fear. This is followed by crying or a silent cry with marked pallor in case of pallid spells and progress to apnea and cyanosis. Loss of consciousness, tonic posturing, and even reflex anoxic seizures may occur in more severe episodes. Following the episode, the child regains consciousness without any post-ictal phase, and episodes last anywhere between 10 and 60 s. Episodes lasting more than 1 min are unusual and suggest an alternate diagnosis [2]. The evaluation of a breath-holding spell starts with a detailed history taking of the episode. A triggering event followed by the characteristic sequence of events is usually enough to distinguish breath-holding spells from other conditions. While screening for iron deficiency anemia and arrhythmias such as long QTc syndrome is recommended for cyanotic and pallid spells, respectively, which could be the cause of the spells, the majority are self-limiting and usually do not occur after 5 years of age.

The purpose of reporting this case was its unusual presentation. Our patient presented with a history suggestive of cyanotic breath-holding spells along with neck swelling, inspiratory stridor, and the inability to maintain normal saturations on room air. In the setting of normal physical examination and characteristic history, laboratory evaluation is not required for cyanotic spells. The presence of these findings led us to further investigate the patient, and a diagnosis of Langerhans cell histiocytosis (LCH) was made. LCH is a rare clinical entity in daily clinical practice with a heterogeneous and non-specific presentation, which can easily be overlooked.

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CASE REPORT

A 7-month-old female child presented to casualty, with the chief complaint of breath-holding spells. The child had 2 episodes of cyanotic breath-holding spells, the first occurring 2 days prior and the second episode occurring on the day of the presentation. The child had been seen by a pediatrician after the first episode who counseled the parents regarding the benign nature of a breath-holding spell. The child had the third episode of a breath-holding spell in our hospital, similar to previous episodes. The child was being examined when she started crying, following which she held her breath, became limp, and developed perioral cyanosis. The episode lasted for <5 min and aborted spontaneously with the resolution of the cyanosis. There was no history of fever, limb stiffening, jerking, or incontinence associated with these episodes. Parents had noticed intermittent noisy breathing and a midline neck swelling for the last 10 days which was gradually increasing in size. There was no history of fever, irritability, feeding difficulty, or breathlessness. On enquiry, the baby was born of vaginal delivery at 37 weeks of gestation. In the immediate postnatal period, the parents had noticed a maculopapular rash leaving behind hypopigmented patches. In addition, there were

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repeated episodes of acute suppurative otitis media for 2 months of age-requiring antibiotics.

On examination, the weight was 7.5 kg (50th percentile), the length was 65 cm (15th percentile), and developmental milestones were appropriate for age. There was pallor, a midline neck swelling measuring 4 × 3 cm, which was non-tender and firm. The baby had inspiratory stridor exacerbated by crying but had no respiratory distress or cyanosis. She had seborrheic dermatitis of the scalp (Fig. 1) along with a hypopigmented rash present over the face, trunk, and back. There was no lymphadenopathy or any other swellings. On auscultation of the chest, air entry was bilaterally equal with bilateral crepitations. No organomegaly on per abdomen examination. Cardiovascular and neurological examination was normal. The SpO_2 was 88–89% (all four limbs).

An urgent chest X-ray was done (Fig. 2), which showed bilateral extensive cystic lesions, followed by computed tomography chest (Fig. 3) revealing extensive cystic changes in both the lungs, focal lytic rib lesions, and thyromegaly along with punctate thymic calcifications. Blood investigations were as follows: complete blood count-Hb 7.6 g% (10.5–14), hematocrit −27.3% (32–42), mean corpuscular volume 62.5fl (72–88), mean corpuscular hemoglobin (MCH) 17.4 pg (24–30), MCH concentration −27.8 g/dL (32–36), red blood cell (RBC)- 4370000/uL, RBC distribution width −22.6% (12–15), white blood cell – 14570 cells/uL (6000–14000) (neutrophils 46%, lymphocytes 49%, and monocytes 5%), platelets 5.18 lakh/uL (1.5–4), C-reactive protein <4 mg/dL, erythrocyte sedimentation rate 10 mm, and reticulocyte count 2.3% (0.5–1.5). Peripheral smear showed anisocytosis, hypochromia, microcytosis, and occasional target cells. Iron studies (serum iron 21 ug/dL (22–184), total iron-binding capacity – 256 ug/dL (100–400), percentage saturation – 8.2% (20–50%, and ferritin 64.9 ng/mL (10–95) were suggestive of iron deficiency anemia. Biochemical investigations showed normal renal and liver function tests. In view of thyromegaly, a thyroid profile was done showing thyroid-stimulating hormone of 719 mIU/L (0.58–5.56), FT3 0.91 pg/mL (2.7–4.95), and FT4 0.23 ng/dL (1.07–2.44).

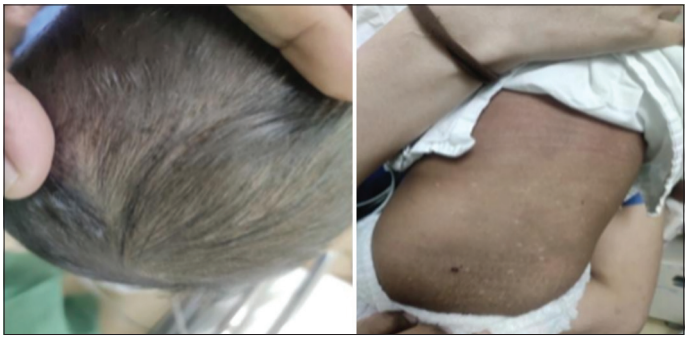

Figure 1: Seborrheic dermatitis of the scalp along with hypopigmented papules as seen on the back

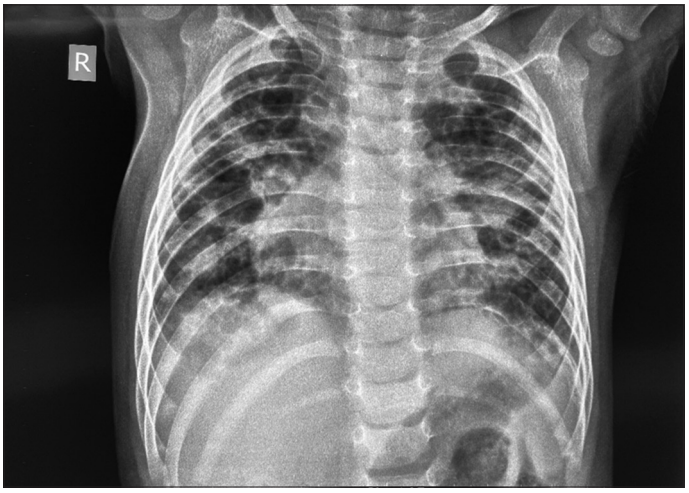

Figure 2: Chest X-ray at the time of presentation showing diffuse, bilateral cystic lesions

In view of the imaging findings, LCH was suspected, and the child was further evaluated for the same. Ultrasound-guided biopsy of the thyroid gland in view of easy accessibility was done (Fig. 4). It showed a diffuse and nodular arrangement of tumor cells having convoluted nuclei and moderate cytoplasm, eosinophilic, and neutrophilic infiltration with an absence of normal thyroid follicles. Immunohistochemistry was positive for Cd 1a, S100, and LCA (leukocyte common antigen); negative for Tdt and TTF-1, consistent with Langerhans cells. A fluorodeoxyglucose (FDG) whole-body positron emission tomography (PET) scan was done which showed metabolically active lesions throughout the body including the cervical lymph nodes, multiple lytic skeletal lesions, lung, oropharyngeal and retrosternal mass, and liver. Magnetic resonance imaging brain was done which was normal.

Based on the diagnostic criteria by the histiocyte Society LCH III, the patient was diagnosed as a multisystem LCH with a risk organ (liver) involved. BRAF V600 mutation was not detected. The baby was started on treatment as per the LCH III protocol. She was also started on levothyroxine (15 mg/kg). She required two intensive care unit admissions for bilateral spontaneous pneumothorax during her 2nd and 4th weeks of chemotherapy. Follow-up FDG PET was done at the end of 6, 12, and 24 weeks, and the child was found to be in complete remission at the end of 24 weeks. Currently, the patient is in the maintenance phase of therapy and is doing well.

DISCUSSION

LCH, initially known as histiocytosis X, requires a combination of clinical presentation, histology, and immunohistochemistry for diagnosis. The normal Langerhans cell is an antigen-presenting cells of the skin derived from the monocyte-macrophage lineage of the myeloid cell line. LCH is a disorder characterized by clonal proliferation of cells having the phenotypic markers of epidermal Langerhans cells that exhibit characteristic “coffee-bean” cleaved nuclei and eosinophilic cytoplasm. As per the diagnostic criteria by histiocyte Society LCH III - definitive diagnosis requires the demonstration of CD1a antigenic determinants on the surface of lesional cells (by immunology or immunohistology) or the finding of Birbeck granules in the lesional cells by electron microscopy. Provisional diagnosis can be made when

Figure 3: Computed tomography chest of the patient

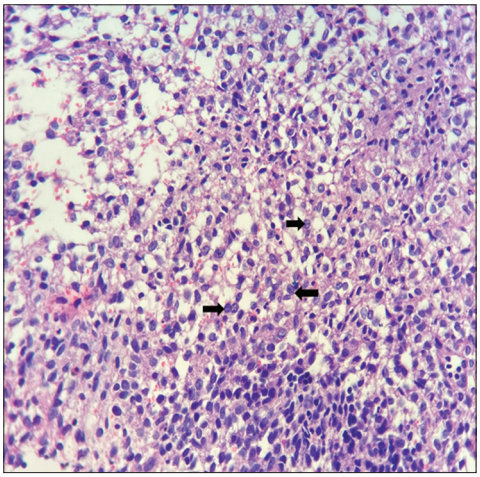

Figure 4: Histopathological picture showing diffuse infiltrate of Langerhans cell with eosinophils, arrows depicting the Langerhans cells

the lesion has characteristic morphology and phenotype and the cells express S100 and at least one of the following: ATPase, alpha-D-mannosidase, and peanut lectin [3]. The disease may present at any age, but young children are most commonly affected with a peak incidence between 1 and 4 years of age [4]. In the neonatal period, the incidence is one to two cases per million [5].

Our patient started having manifestations during the neonatal period in the form of a rash, seborrheic dermatitis, and multiple episodes of acute suppurative otitis media. A diagnosis was established at 7 months of age when she presented to our hospital with breath-holding spells, neck swelling, stridor, and inability to maintain normal oxygen saturations on room air. LCH can affect many systems/organs including the skeleton, skin, reticuloendothelial, pulmonary, central nervous system, gastrointestinal tract, and the ear, nose, and throat [6]. The

skeleton is involved in 80% of cases [7] and may be the only system involved, especially in children over 5 years of age. Thyroid involvement in LCH is rare with only around 65 cases being reported [8]. Multisystem patients with involvement of "risk" organs - liver, spleen, and hematopoietic system (bone marrow) are at higher risk of mortality as compared to risk organ-negative patients. Single-system disease (usually bone, lymph node, or skin) has a high chance of spontaneous remission with a generally benign course [9]. In contrast, multisystem disease requires treatment with systemic multiagent chemotherapy, with vinblastine and corticosteroids forming the core agents.

CONCLUSION

The clinical presentation of LCH is highly variable and heterogeneous, from being a single-system disease with a benign course to a multisystem disease with high mortality. It can present in varied ways to different specialties and hence can be misdiagnosed or diagnosed late.

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AUTHOR CONTRIBUTIONS

All of the authors have met the following criteria: (1) Made substantial contributions to the concept and design of study or acquisition of data or analysis and interpretation of data; (2) Drafted the article or revised it critically for important intellectual content; (3) Approval the final version to be published; and (4) Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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