Case Report

PHACES syndrome in association with airway hemangioma: First report from Saudi Arabia and literature review

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Abstract:

"PHACES" is a neurocutaneous syndrome that refers to the following associations: Posterior fossa malformations, Hemangiomas, Arterial malformations, Coarctation of the aorta/Cardiac defects, Eye abnormalities, and Sternal defects. Herein, we report the association of PHACES syndrome with airway hemangioma, a serious association that should not be overlooked. The findings of such an association presented here are the first to be reported from Saudi Arabia.

Key words:

Airway, hemangioma, PHACES, subglottic

PHACES syndrome described by Frieden *et al*.,[1] in 1996, is a rare neurocutaneous syndrome. The syndrome is composed of the following features: Posterior fossa malformations, Hemangiomas, Arterial anomalies, Coarctation of aorta/Cardiac abnormalities, Eye anomalies, and Sternal defects. Hemangioma is the unifying feature of PHACES syndrome. The extracutaneous manifestations of PHACES may be associated with significant morbidity. In a recent multicenter prospective study, 30 of the 33 patients with PHACES had more than one extracutaneous finding. The most common extracutaneous anomalies observed in infants with PHACES were of the arteries of the cerebrovasculature (91%) and cardiac anomalies (67%).[2]

In this article, we report an infant with cervicofacial hemangiomas and two other extracutaneous manifestations (cardiac anomalies and sternal defects), in addition to a serious association with airway hemangioma. The case presented here is the first report of PHACES syndrome with this significant association in the Saudi population. The clinical, radiologic and endoscopic features are described along with review of relevant literature.

Case Report

A 2-month-old girl with left facial hemangioma presented to the Accident and Emergency Department with 1 day history of stridor, cough and fever. The mother noticed episodes of cyanosis during crying and episodes of excessive sweating while feeding her baby. The child was a product of full-term normal spontaneous vaginal delivery with no perinatal complications. A large red lesion was noticed by the family in the first week of life on the left side of the face, which increased in size progressively but with no associated ulceration or bleeding. On examination, the baby was found to have inspiratory stridor with suprasternal and intercostal retractions. The vital signs were as follows: Temperature 37°C, respiratory rate 60 per minute, pulse rate 190 per minute, and blood pressure 109/61 mmHg. The oxygen saturation was 92% on room air. Her weight was 3.9 kg (5th percentile), head circumflex was 37 cm (25th percentile), and her length was 51 cm (5th percentile). Cutaneous examination revealed a 16 × 7 cm, well-defined, erythematous plaque consistent with hemangioma, extending from the left pre-auricular area to the left temproparietal and occipital portions of the scalp with involvement of the adjacent portion of the left ear [Figure 1]. Similar smaller hemangiomas were noted on the lower lip, floor of the mouth and soft palate. Also, a 0.8 × 0.6 cm atrophic area on sternal region [Figure 2] and a 1.2 × 1 cm atrophic area on the supraumbilical region [Figure 3] were detected representing sternal pit and supraumbilical raphe, respectively. Cardiovascular examination revealed ejection systolic murmur with no blood pressure discrepancy between upper and lower limbs. Systemic exam, otherwise, was within normal limits, including ophthalmologic evaluation.

Complete work up was performed, with plain neck X-ray demonstrating a soft tissue density in the subglottis. Head and neck magnetic resonance imaging with gadolinium revealed extension of the hemangioma to the parotid, pre- and paratracheal spaces, but with normal brain structures. Echocardiogram was normal except for a muscular ventricular septal defect, hypertrophic interventricular septum, and

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tricuspid regurgitation. Abdominal ultrasound and complete blood count were within normal range. Flexible fiberoptic laryngoscopy revealed hemangiomas on the nasal surface of the soft palate, base of the tongue, and left lateral pharyngeal wall. Direct laryngoscopy and bronchoscopy in the operating room confirmed the presence of subglottic hemangioma, which causes 70% narrowing of the airway, mainly in the left posterolateral wall of the cricoid [Figure 4]. The child was managed in the pediatric intensive care unit (PICU) with a megadose of steroids (prednisolone 5 mg/kg/day). The patient was discharged from the PICU after her condition was stabilized. Steroid therapy was continued for 3 months followed by a tapering course. Six months after the initiation of therapy, the patient was off treatment with almost complete resolution of the cutaneous and airway hemangiomas. Repeated endoscopy at that time confirmed the resolution of the airway hemangioma. The patient was evaluated at the age of 18 months, which showed no signs of recurrence.

Discussion

Hemangiomas are the most common benign tumors of infancy occurring in up to 2.6% of neonates and up to 12% of children by the first year.[3] Hemangiomas typically present with a phase of rapid proliferation in the first year of life, followed by a slow gradual involution over the next 5–7 years or more. Most hemangiomas remain asymptomatic and can be managed by close observation; however, immediate treatment is indicated for hemangiomas that might cause significant complications such as visual impairment, skeletal deformity, airway obstruction, high-output cardiac failure, bleeding or ulceration.

The association of cervicofacial hemangiomas with vascular and other intracranial malformations was first recognized by Pascual-Castroviejo[4] in 1978. In 1996, Frieden *et al*.[1] introduced the acronym PHACE to describe a neurocutaneous syndrome characterized by Posterior fossa malformations, Hemangiomas, Arterial anomalies, Coarctation of aorta/Cardiac anomalies, and Eye anomalies. The acronym has subsequently been expanded to PHACES to include Sternal clefting or Supraumbilical raphe.[9] Metry *et al*.[3] reviewed 130 cases of PHACES where this neurocutaneous syndrome was found to represent a spectrum of anomalies, and most affected children have only one extracutaneous manifestation.

Intracranial malformations are more frequent when the hemangioma involves the first branch of the trigeminal nerve.[3] Posterior cranial fossa malformations are present

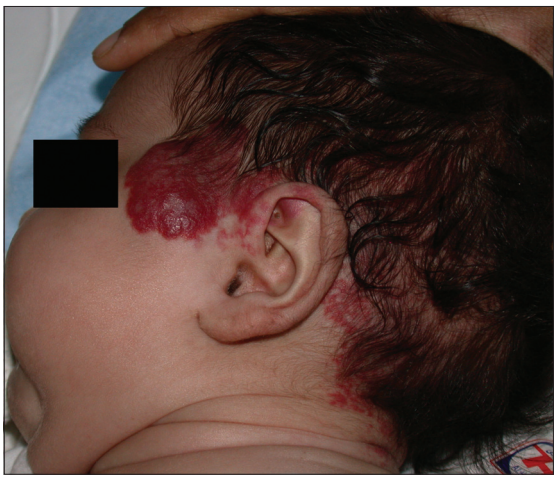

Figure 1: Cervicofacial hemangioma extending from the left preauricular region to the occipital scalp

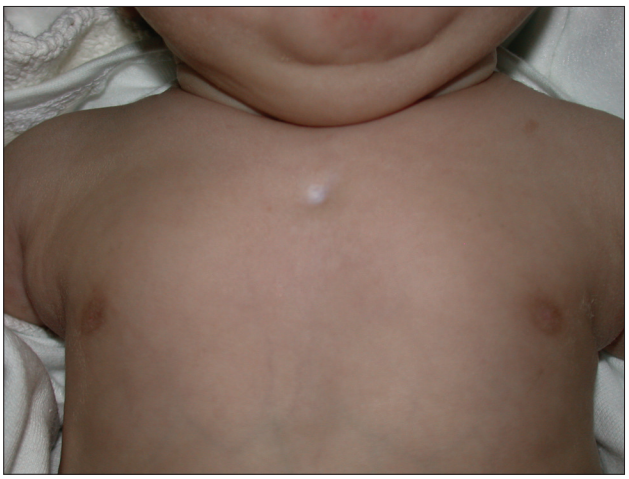

Figure 2: Sternal pit

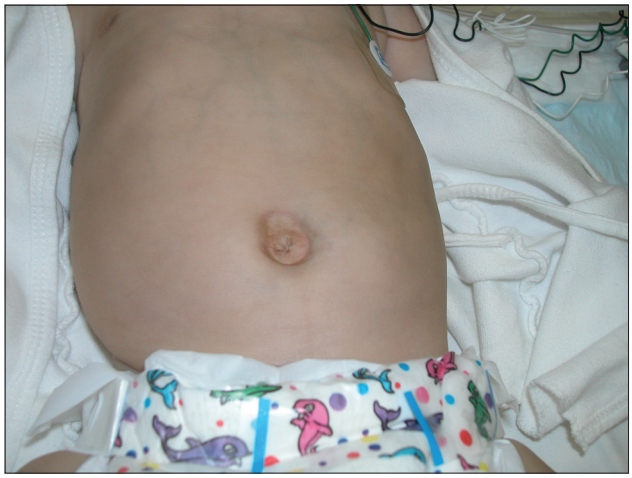

Figure 3: Supraumbilical raphe

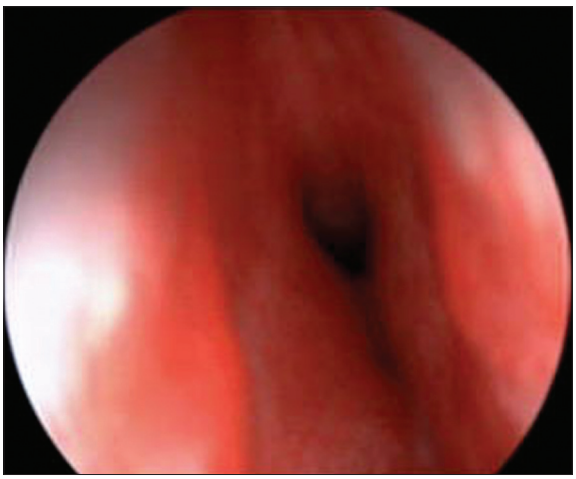

Figure 4: Intraoperative photo showing a soft tissue swelling (hemangioma) in the posterolateral wall of the cricoid (astriax)

in 74% of cases, although other series quote closer to 50%.[6] Dandy–Walker malformation is the most common associated developmental abnormality.[3] Other anomalies include hypoplasia or agenesis of the cerebellum, cerebellar vermis, corpus callosum, cerebrum, and septum pellucidum.[3] The potential for secondary neurologic sequelae among patients with underlying brain involvement exists, but the actual risk of progressive disease is not known. Burrow *et al*.[7] reported progressive neurologic disease among four patients with PHACES syndrome who were neurologically normal until symptoms of hemiparesis, acute onset of seizure, or both developed between 9 and 18 months of age. Neuroimaging revealed cerebral infarction secondary to progressive occlusive arterial changes in all patients.

Hemangiomas in PHACES syndrome are not different from sporadic lesions, but they show a 9:1 female:male ratio compared to the 3:1 ratio for the latter.[6] They are typically bulky, plaque-like lesions involving several cervicofacial segments, but without being confined by their boundaries, unlike Sturge–Weber syndrome. Left-sided facial hemangiomas predominate (43%), followed by right-sided and bilateral involvement in 29% and 27%, respectively.[3] Trigeminal division V1 is the most commonly affected dermatome. Extracutaneous hemangiomas occur in 22% of patients with PHACES syndrome, with the subglottis being the most common site.[8] Subglottic hemangiomas represent 1.5% of congenital abnormalities of the larynx. They are potentially life threatening, with varying degrees of respiratory compromise.[9] Badi *et al*.[10] confirmed that most subglottic hemangiomas are histologically and immunohistochemically infantile hemangiomas (IH) and similar to IH located in other anatomic locations.

The variety and extent of arterial anomalies associated with PHACES syndrome are wide. Arterial anomalies of the head and neck, specifically aneurismal dilatations and anomalous branches of the internal carotid artery, occurred in nearly one-third of cases in one report.[3] Pascual-Castroviejo *et al*.[4] described two patterns of arterial abnormalities: Persistent embryonic arteries (e.g., trigeminal artery) and agenesis of major arteries (e.g., internal carotid or vertebral arteries).

More than one-third of PHACES cases had cardiac and/or aortic anomalies. Coarctation of the aorta was the single most common defect. Multiple cardiac anomalies were described including patent ductus arteriosus, ventricular septal defects, arterial septal defects, pulmonary stenosis, cor triatriatum, tricuspid aortic valve, arterial enlargement, ventricular hypertrophy, tetralogy of Fallot, and patent foramen ovale.[3] Our patient had three cardiac anomalies: Ventricular septal defect, hypertrophic interventricular septum, and tricuspid regurgitation. The latter two findings were not reported previously.

Ophthalmologic findings in PHACES syndrome are seen in 30% of cases with predominance of anterior segment abnormalities.[11] The most common anomalies include choroidal hemangiomas, cryptophthalmus, exophthalmus, colobomas, posterior embryotoxon, and optic atrophy.[12]

Sternal defects and supraumbilical raphe were encountered in 43 patients with PHACES syndrome.[1] Matry *et al*.[3] reported three patients with subtle sternal pits without underlying soft-tissue or bony loss in a series of 14 patients with PHACES syndrome. Interestingly, in our case, both sternal pit and supraumbilical raphe were present. Sternal clefts in PHACES can be classified into three categories: Superior, inferior, and complete.

In the presented case, the cutaneous and airway hemangiomas responded well to the megadose of oral prednisolone. Other treatment options of airway hemangiomas might include systemic vincristine, laser therapy, tracheotomy, or surgical excision.[13] A recent meta-analysis study evaluating the effectiveness of propranolol versus steroid, CO_2 laser, or vincristine showed that propranolol is the most effective treatment for infantile airway hemangioma.[14] Prognosis of PHACES syndrome is not known for certain as presentations vary and management of extracutaneous problems is system dependent.

In conclusion, PHACES syndrome should be considered in any infant presenting with a large, segmental facial hemangioma. Children at risk should receive careful ophthalmologic, cardiac, and neurologic assessment with special attention to possible airway involvement. The necessary radiologic and endoscopic imaging studies should be carried out when indicated.

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