

CASE REPORT

Differential diagnosis difficulties related to infantile hemangioma – case report and literature review

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Abstract

Infantile hemangioma is a benign vascular tumor that is often present in the cephalic region and can grow rapidly in size, causing serious complications. The hemangioma with oro-maxillofacial sphere localization may often pose differential diagnosis problems, requiring additional investigations. We present the case of a 3-month-old baby who was brought to the Emergency Room for acute respiratory failure and dysphagia caused by the rapid increase in size of a soft palate and lateral pharyngeal wall tumor. The clinical examination revealed a "wine stain" hemangioma in the inter-eyebrow and frontal areas, a hemangioma in the right genial area, 1/1.5 cm in diameter, growing rather in depth than on the surface, and a purplish-blue tumoral mass with irregular edges, grown in the soft palate and in the right lateral wall of the pharynx, which impaired both eating and breathing. Obstructive phenomena have been aggravated by an acute respiratory infection. Due to the inconsistencies between different medical specialties about the nature of the tumor and the suspicion of malignancy, in order to establish the correct diagnosis and therapeutic management, urgent tumor biopsy was required. After starting oral treatment with Propranolol, the evolution was favorable. Infantile hemangiomas may sometimes be hard to diagnose, requiring additional imaging examinations, and sometimes-pathological examination. Since it may affect a vital function, or the patient's esthetic appearance, or if the tumor has ulcerated, bleeds or got infected, the certain diagnosis and the onset of treatment should be done as soon as possible.

Keywords: vascular tumor, vascular malformation, hemangioma, Propranolol.

✉ Introduction

Infantile hemangioma is a benign vascular tumor resulting from the proliferation of endothelial-like cells, which occurs predominantly in the female gender (3/1 ratio), in preterm infants or in newborns with low birth weight from twin pregnancies or from pregnancies resulting from *in vitro* fertilization [1]. Other incriminated risk factors are the white race and older mothers, and its incidence is approximately 5–10% among newborns and infants [2]. Hemangiomas may be present at birth or occur in the first few weeks after birth, and have a rapid growth rate in the first nine months, after which they either stagnate or they slowly regress spontaneously [3]. Hemangiomas in the cephalic region may grow at a fast pace in the first months and may cause serious complications, such as ulceration and infection, bleeding, deformity, upper airway obstruction, auditory or visual dysfunction, congestive heart failure, consumption coagulopathy, neurological conditions and rarely even death. About 12% of hemangiomas may bring about serious complications requiring treatment in specialized centers [4].

Aim

Hemangioma with oro-maxillofacial sphere localization may often pose differential diagnosis problems and

therapeutic problems, requiring additional investigation, which is why we aimed here to present a case we treated successfully in our Clinic, but not until a correct pathological examination was done.

✉ Case presentation

We report here the case of a preterm 3-month-old female infant, S.S., born of twin pregnancy and with low birth rate, who was brought on January 5, 2019, to the Emergency Room of the "St. Mary" Emergency Children Hospital Iași, Romania, for acute respiratory failure and dysphagia. The clinical examination revealed a "wine stain" hemangioma in the inter-eyebrow and frontal areas, a hemangioma in the right genial area, 1/1.5 cm in diameter, growing rather in depth than on the surface (Figure 1), and a purplish-blue tumoral mass with irregular edges, grown in the soft palate and in the right lateral wall of the pharynx, which impaired both eating and breathing (Figure 2). The patient was admitted in the Department of Pediatrics, with the File No. 452, and the antibiotic and anti-inflammatory treatment was initiated for respiratory distress. The pediatric surgeon's counsel advocated palatine and pharyngeal lateral wall hemangioma, but otorinolaryngology specialist raised the suspicion of a pharyngeal rhabdomyosarcoma and recommended biopsy.

The patient underwent a brain computed tomography (CT) scan with contrast agent, which revealed the location, form and extent of the injury: tumor formation with native densities ranging from 36–42 UH, homogeneous, relatively well defined peripherally, with important post-intravenous contrast administration contrast and with washing phenomena in the late phase of the examination. The tumor was located on the right side at the base of

the tongue, with left paramedian extension and invasion of the epiglottis, having a mass effect on the right tensor muscle of the soft palate, having dimensions of 1.99/1.58/2.2 cm [antero-posterior/transverse/cephalo-caudal (AP/T/CC)]. Tumor formation with the same structural and post-contrast kinetics, with dimensions of 2.21/1.30/1.7 cm (AP/T/CC), was situated in the soft parts of the right genial region, with deformation of the region (Figure 3).



Figure 1 – Right genial, inter-eyebrow and frontal hemangioma: first visit to hospital.



Figure 2 – Soft palate and lateral pharynx wall tumor mass.

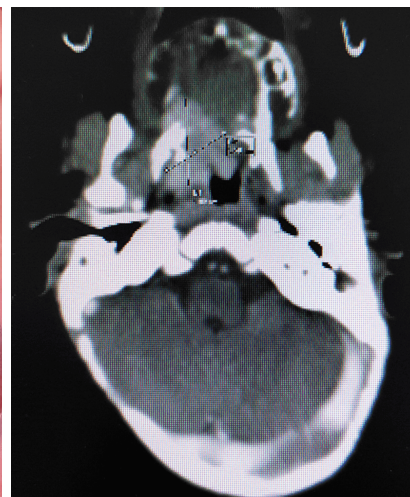


Figure 3 – CT scan appearance of the soft palate and lateral pharynx wall tumor. CT: Computed tomography.

Moreover, the clinical-paraclinical findings revealed several related conditions, namely dystrophy due to preterm birth, first-degree right hydronephrosis, apical ventricular septal defect, iron deficiency anemia, oro-pharyngeal candidiasis, and acute rhinopharyngitis. During hospitalization, the condition of the patient deteriorated due to the obstructive phenomena aggravated by the inter-current respiratory infection, which made the doctors consider tracheostomy. Antibiotic, anti-inflammatory and symptomatic treatment progressively alleviated the condition of the patient, making it possible to carry out the biopsy of the palatine velum under general anesthesia with orotracheal intubation. The anesthesiologist was informed of the existence of the cardiac malformation, as the anesthetic protocol may be different in these patients, especially in those with signs and symptoms of heart failure. There were no notable problems during the surgical procedure.

Histological assessment

Figures 4–9 illustrate the histological features of our patient lesion. The smear taken from the biopsy reveals poor cellular areas with small groups of epithelial cell lines associated with rare large, fusiform, hyperchromatic cells and cellular debris. The biopsy specimens were fixed in 10% neutral buffered formalin, embedded in paraffin and sectioned at 3–5 μ m. The microscopic examination performed after tissue staining with usual [Hematoxylin–Eosin (HE) and Szekely trichrome] and special (Alcian Blue) stainings shows very small fragments consisting of a capillary vascular proliferation, made of closely packed spindle cells with spaces containing a few red blood cells, infiltrative in salivary gland tissue with the dissociation of acini and their ducts. The stratified non-keratinized surface epithelium displays an ulcerated area covered with leukocyte exudate and necrotic tissue (Figures 4–9).

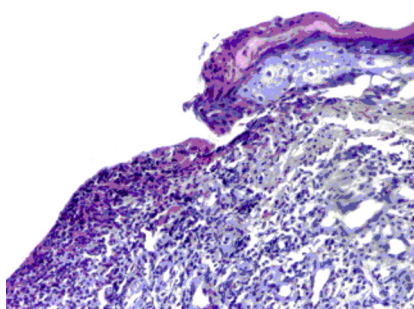


Figure 4 – Covering epithelium and capillary-like vascular proliferate in the chorion (HE staining, $\times 40$). HE: Hematoxylin–Eosin.

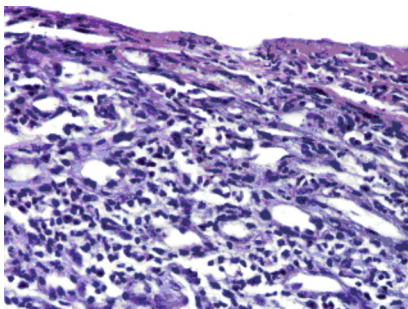


Figure 5 – Surface ulcerated epithelium and underlying vascular proliferation (HE staining, $\times 200$).

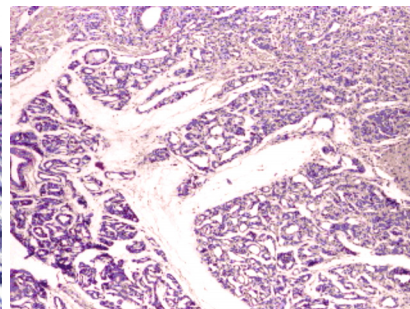


Figure 6 – Area of capillary-like vascular proliferation (HE staining, $\times 40$).

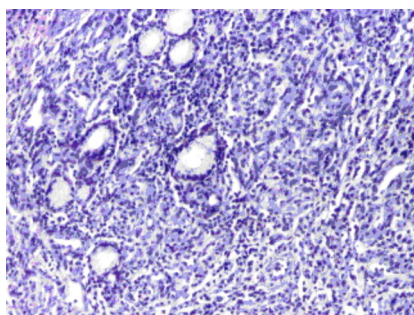


Figure 7 – Minor salivary glands dissociated from the vascular proliferation (HE staining, $\times 100$).

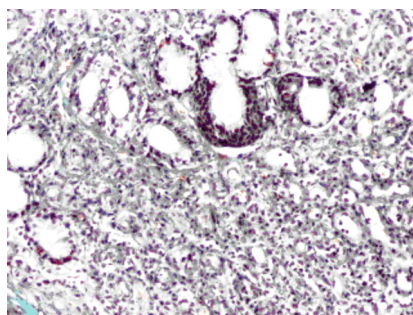


Figure 8 – Salivary glands in vascular proliferation (Szekeley trichrome staining, $\times 100$).

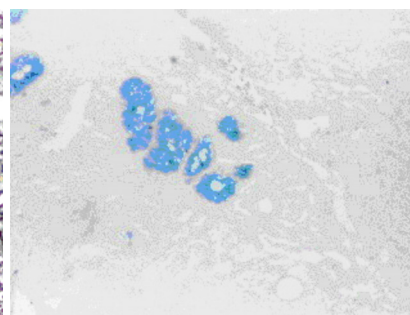


Figure 9 – Mucus-secreting salivary glands included in the vascular proliferation (AB staining, $\times 40$). AB: Alcian Blue.

The analyzed fragments do not show any surgical oncology margins in the periphery. Immunohistochemical staining was also performed using the anti-pan-cytokeratin (CK) AE1/AE3 antibody (marker confirming the epithelial cell nature). Its expression was negative in tumor proliferation and positive in the covering epithelium and in the salivary glandular epithelium (Figure 10). The pictures were taken with the Nikon E600 microscope equipped with DN100 digital camera, magnifying powers $\times 40$, $\times 100$, $\times 200$. The final pathological conclusion was capillary hemangioma infiltrative in the minor salivary gland, with ulceration in the surface.

Follow-up

After surgery, the patient started treatment with

Propranolol, orally administered at an initial dose of 1 mg/kg/day, divided into three intakes, with the monitoring of her blood pressure and pulse 30 minutes after administration. No adverse effects were observed, and after three days, the dose of Propranolol was doubled. The patient's evolution was positive, with visible diminution in the size of the genial and pharyngeal hemangiomas as early as the first week of treatment. The patient was discharged and asked to come back every month for follow-up and dose adjustment based on weight. We noted the patient's continuous positive evolution and the impressive decrease in the size of the genial and palatine velum hemangioma four months after the initiation of treatment (Figure 11).

Figure 10 – IHC staining of salivary glands epithelium for anti-pan-CK AE1/AE3 antibody ($\times 200$). Negative IHC staining of the vascular proliferation. IHC: Immunohistochemical; CK: Cytokeratin.

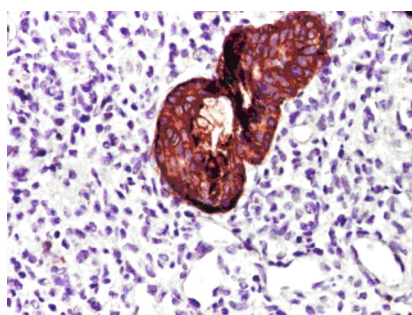


Figure 11 – Clinical appearance four months after the start of the Propranolol treatment.

Discussions

Infantile hemangioma is the most common tumor of infancy (10%) that usually appears throughout the first six months of life, showing a rapid growth phase followed by gradual involution [5]. The head and the cervical region are the areas most frequently affected by infantile hemangiomas, as up to 60% of them occur in these areas [6]. Although most hemangiomas are unique, 20% of children have two or more skin hemangiomas, which require extensive investigations to detect any visceral hemangiomas. The most common are hepatic, intestinal, splenic and intracranial hemangiomas, as well as tongue or pharynx hemangiomas, which also occurred in our case and which lead to obstructive digestive and respiratory phenomena. Children with large hemangiomas affecting an entire segment will require additional investigations for Posterior fossa brain malformations, Hemangioma, Arterial lesions, Cardiac abnormalities, and Eye abnormalities (PHACE) syndrome detection (including aortic coarctation, sternal or supraumbilical abnormalities).

Deep hemangiomas, which make up 15% of total hemangiomas, and occasionally mixed hemangiomas (25%) are sometimes difficult to differentiate from vascular malformations they resemble; therefore, differential diagnosis is important in choosing therapeutic behavior. Hemangiomas of the oral cavity are small or large superficial proliferations with variable infiltration of soft tissues. Generally, they are solitary lesions but may also be multicentric having a cobblestone appearance. The small superficial lesions are usually capillary hemangiomas, while the large superficial or deep lesions are cavernous or mixed type [7].

In our reported case, we also encountered problems of differential diagnosis of hemangioma in the genial region with a possible vascular malformation. The rapid clinical response (decrease in size) after administration of Propranolol determined us to conclude that the precise diagnosis was infantile hemangioma. In addition to vascular malformations, the differential diagnosis of visceral hemangiomas involves rhabdomyosarcomas, Kaposi form hemangioendothelioma, tuberous angiomas and angio-

sarcomas. In more than 90% cases of infantile hemangioma, the diagnosis is based on clinical characteristics, but for the rest of them additional investigations [ultrasonography, CT, magnetic resonance imaging (MRI), angiography, histopathological (HP) exam] are required in order to make a differential diagnosis with other benign or malignant tumors. A retrospective study conducted in 2009 by Hoornweg *et al.* on 423 children with infantile hemangioma confirmed the diagnosis in 89%, but the rest of the cases were in 7% vascular malformation, 2% other benign anomalies and 2% malignancies [8]. Capillary hemangioma may also easily be misdiagnosed as pyogenic granuloma but the HP assessments in such cases differentiate them [9]. Vascular anomalies can arise in any anatomical area, including oral cavity, and the management of these lesions is based on a clear diagnosis [10]. In the last years, there are situations in which the clinician confronts with malignant infantile hemangioma mimics. In such cases, the usual “wait and watch” attitude delays or ignores the optimal management [8, 11, 12]. Knight & Reiner pointed out that an onset in the neonatal period, a rapid growth, ulceration of the surface, location deep to the fascia, and a lesion greater than 3 cm in diameter are signs that are consistent in most of the cases with both infantile hemangioma and a malignancy [13]. The most frequent differential diagnosis suggested by Frieden *et al.* are dermatofibrosarcoma protuberans, giant cell fibroblastoma, infantile fibrosarcoma, rhabdomyosarcoma; Hoornweg *et al.*, in 2015, adds poorly differentiated sarcoma, malignant tumor of the nerve sheath, poorly differentiated round and spool cell malignancy and undifferentiated sarcoma [8, 11, 12]. Scorletti *et al.*, in 2018, highlights malignancies that were thought to be vascular lesions [10]. Hemangiomas, which are distinguished at birth, should be attributed to “congenital” and are not expected to grow in the postnatal period, differentiating them from infantile hemangioma, which typically develops in early infancy and appear within few months of life [14].

Given the dramatic clinical manifestations of acute respiratory failure due to the adding of a respiratory infection to the fast growth of the oro-maxillo-facial tumor, together with the digestive symptoms (dysphagia, vomiting), in our patient we could not perform the therapeutic test of orally administered Propranolol, and the CT scan could not rule out a malignant tumor. Therefore, tumor biopsy was necessary for the differential diagnosis of palatine velum and lateral pharynx wall hemangioma with a vascular malformation and especially a rhabdomyosarcoma. Thus, the certain diagnosis in this case was set by pathological examination.

Although infantile hemangiomas may regress spontaneously, it is often impossible to predict the progression of a hemangioma. Even a small initial lesion may cause a major aesthetic disability if it occurs in the oro-maxillo-facial area; it may also lead to ocular, auditory, digestive or airways obstruction (as in the case reported in this paper). The faster the growth of a hemangioma occurs, the greater the risk of complications, such as obstruction, bleeding, ulceration or infection is. This is why some physicians recommend that treatment be started as early as possible in the case of oro-maxillo-facial hemangiomas [15]. Conservative treatment for heman-

giomas includes careful monitoring and regular follow-up by specialists, pharmacotherapy (corticosteroids, Vincristine, Propranolol, Interferon alpha), cryotherapy and laser therapy. Surgical treatment includes injection of sclerosing agents and lesion excision. The therapeutic strategy may combine the two variants, taking into account the type, location and stage of hemangioma progression, the extent of the injuries or systemic involvement, the presence of local complications, the preference of the parents. Our patient received Propranolol orally, at an initial dose of 1 mg/kg/day, divided into three intakes, under close monitoring of his blood pressure, pulse, glucose level, vital signs. After three days of positive evolution, Propranolol dose was doubled and after two more days of medical supervision, the patient was discharged and he continued the treatment at home. His ventricular septal defect was not an absolute contraindication for Propranolol treatment, the association between infantile hemangioma and some structural cardiac defects being widely recognized in literature [16]. At the time of hospital discharge, the positive functional and aesthetic effects of the treatment, namely, breathing, swallowing and clinical appearance, were already visible. He returned for follow-up once a month, for dose adjustments according to weight, with a positive progression noticed four months after the beginning of the treatment. Literature shows that, generally, the therapeutic response may be noticed after the first days of administration and the duration of treatment is 4–6 months, depending on the clinical evolution of each individual patient, after which the treatment is gradually discontinued [1]. As far as our patient was concerned, we estimated a total duration of six months initial treatment with Propranolol, followed by its gradual discontinuation.

If necessary (in case of reappearance of the obstructive phenomena due to the growth of the pharyngeal hemangioma or worsening of the cosmetic appearance of the genital hemangioma, which is unlikely since the child approaches the age of natural hemangioma involution), a second cure of Propranolol may be started. Another pharmacological option is the systemic administration of corticosteroids, indicated when Propranolol is not effective, or is contraindicated. Corticosteroids and Propranolol can be used in combination in severe cases, such as large hepatic hemangiomas or in patients with airway obstruction (soft palate, pharyngeal or subglottic hemangioma). The therapeutic dose of Methylprednisolone is 2–6 mg/kg/day, orally administered in a single morning dose for a period of 3–4 months, depending on the hemangioma evolution. The therapeutic response occurs between the second and fourth weeks after the start of the treatment. The adverse effects of corticosteroid therapy are already known and they are generally more severe than those of Propranolol, therefore the treatment is shorter and the patient's monitoring is stricter [17]. Also, in case of recurrence of symptoms, systemic administration of Vincristine, intralesional injection of sclerosing agents (Ethanol, Bleomycin) or selective embolization of the tumor's nutritional artery are options that may be taken into account [18, 19].

✚ Conclusions

Infantile hemangiomas may sometimes be hard to diagnose, requiring additional imaging examinations, and sometimes-pathological examination. Since it may affect

a vital function, or the patient's esthetic appearance, or if the tumor has ulcerated, bleeds or got infected, the certain diagnosis and the onset of treatment should be done as soon as possible.

Patient consent

Written informed consent from the patient's parents for the publication of this report and accompanying images was obtained. The report was conducted in accordance with the ethical standards, being approved by the Ethics Committee of the "St. Mary" Emergency Children's Hospital, Iași, Romania.

Conflict of interest

The authors declare that they have no conflict of interests.

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