Hemangioma—Benign Tumor in Childhood

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ABSTRACT

Background: Hemangiomas are vascular tumors, i.e., neoplasms of the vascular network. These are the most common neoplasms in the age of infancy. They can be infantile and congenital. Objective: Present the case of a 7.5-year-old girl suffering from a benign vascular tumor—hemangiomatosis of the skin and liver, which is part of the autosomal recessive syndrome SDC (Spondylocostal dysostosis). Case presentation: This case shows that hemangiomas can be accompanied by other diseases as part of congenital syndromes or metabolopathies that are often genetically inherited. In the present case, it is an autosomal recessive form of SCD syndrome or spondylocostal dysostosis. Conclusion: It is important to consider SCD, i.e., spondylocostal dysostosis, as a rare autosomal recessive disease that can occur as part of hemangiomatosis. Recent studies from 2020 and 2013 have shown the efficacy of topical timolol as well as atenolol which can replace oral propranolol as the first-line agent in the treatment of hemangiomas. In randomized clinical trial (2020), when compared with propranolol, atenolol had similar efficacy and fewer adverse events in the treatment of infants with problematic infantile hemangiomas.

Keywords: Infantile Hemangioma, Propranolol; Atenolol, Spondylocostal Dysostosis.

1. BACKGROUND

Hemangiomas are the most common benign (noncancerous) tumor, the etiology of which remains unknown to the present. They are made up of proliferating, plump endothelial cells. They occur in up to 10% of the infant population. (1) More than 50% of hemangiomas occur in the head or neck area, with the growth and mass showing a true tumor character. They are usually solitary, and well-demarcated, but can also cover larger areas or be multifocal. Hemangiomas are much more common in Caucasian children and are at least four times more often in females than in males. Also, they occur more commonly in premature infants, newborns with low birth weight, and mothers with complicated pregnancies involving placental anomalies. (2) The presence of more than one skin change increases the likelihood of visceral hemangiomas. The liver is the most common site of visceral IH. Other affected organs include the brain, intestine, and lungs. If a hemangioma is located near the breathing system it can cause airway obstruction, while hemangiomas located near the eyes can lead to loss of vision. Ulceration is a common complication and can lead to secondary infection. A giant liver hemangioma or possibly hemangioendothelioma can lead to hepatomegaly, anemia, thrombocytopenia, and heart failure due to subsequent stress. (3) Therefore, the reference literature suggests that some hemangiomas are associated with certain syndromes such as expeorant thrombocytopenia (Kasabach-Merrit syndrome), and hypertrophy of the affected structures (Klippel-Trenaunay syndrome). (4)

The diagnosis is made based on the clinical picture. There is no universally accepted laboratory method to confirm a diagnosis and decide on treatment. When therapy is required, an individual assessment is made based on age, phase of hemangioma, location, size of affected vital structures, and complications. (5) Since most hemangiomas have a spontaneous regression tendency, they are treated only in complicated cases. According to guidelines for the treatment of hemangiomas in infants, the main goals are to stop uncontrolled growth and obstruction of vital structures and prevent permanent aesthetic disfigurement on the skin. (6)

Treatment is most often combined, involving conservative pharmacotherapy and surgical procedures. Drugs are used to stop proliferation and reduce tumor mass with the end result of reducing hemangioma growth, and in some
cases enabling surgery, where drug treatment is insufficient. (5) We have already mentioned that the drug of choice in the treatment of hemangiomas is Propranolol, a non-selective beta-blocker to block B1 adrenergic receptors. Published papers most often highlight the effects of Propranolol on vasocostriction (local hemodynamic effect), inhibition of angiogenesis, stimulation of apoptosis effect on capillary endothelial cells, and inhibition of vascular endothelial growth factor (VEGF) signaling pathways, basic fibroblast growth factor, and consequent angiogenesis and proliferation. Early effects are attributable to vasocostriction due to decreased release of nitric oxide (NO). Intermediate effects are due to the blocking of proangiogenic signals (vascular endothelial growth factor, basic fibroblast growth factor, matrix metalloproteinase 2/9) and result in growth arrest. Long-term effects of propranolol are characterized by induction of apoptosis in proliferating endothelial cells and result in tumor regression. (7)

2. OBJECTIVE

Present the case of a 7.5-year-old girl suffering from a benign vascular tumor—hemangiomatosis of the skin and liver, which is part of the autosomal recessive syndrome SDC (Spondylocostal dysostosis). Detailed diagnostic tests have shown bone deformities of the spine and ribs (spondylocostal dysostosis) in addition to hemangiomatosis. Genetic analysis revealed Notch signaling pathway gene mutations in the pathogenesis of multiple hemangiomas across the body, which were also found in different types of SCD, and have multiple functions during human embryogenesis that are relevant for further monitoring of the patient’s growth and development. The genetic predisposition of close family members was examined, but since no other family member was found to have similar symptoms, it was excluded by clinical examination, e.g., the results of the mother’s sister were clean.

3. CASE STUDY

The girl was born in 2014, as the second child. She was born naturally, in the 35th week of gestation, with a birth weight of 2900 g, and a birth length of 53 cm. This confirms that hemangiomas occur more commonly in premature infants, newborns with low birth weight, and mothers with complicated pregnancies involving placental anomalies. (2) Already after childbirth, several small cutaneous hemangiomas were observed. Ultimately, a total of 73 hemangiomas were identified, of which 17 were in the area of the head, 11 on the right arm, 8 on the left arm, 15 on the chest, 16 on the legs, and 6 on the back. Regarding visceral localizations, after extensive diagnostic analysis, two hemangiomas of up to 3.5 cm in size were found in the right lobe of the liver and several smaller hemangiomas of up to 6 mm in the left lobe. This case shows that hemangiomas can be accompanied by other diseases as part of congenital syndromes or metabolopathies that are often genetically inherited. In the present case, it is an autosomal recessive form of SCD syndrome or spondylocostal dysostosis. Gene mutations in the Notch signaling pathway leave developmental anomalies in various organs: liver, skeleton, heart, eyes, face, kidneys, and blood vessels. Notch signaling is a key regulator of the embryonic process of somitogenesis during which the vertebrae are formed. Gene mutations in this signaling pathway consequently leave a heterogeneous group of disorders called SCD. Our young patient was diagnosed with spinal segmentation disorders by radiological methods (multiple vertebral defects—including 10 vertebrae, mainly thoracic segment, and various rib anomalies such as hypoplasia, fusion, and spherical shape). On the other hand, multiple hemangiomas were found, benign vascular tumors whose pathogenesis involved the Notch pathway with its genes such as DLL3, MESP2, LFNG, and HESS7. Mutations of these genes have also been found in different types of SCD, and have multiple functions during embryogenesis. They are planned to be analyzed once the patient gets somewhat older and more developed, and after other congenital diseases are excluded.

4. CONCLUSION

In somatic status, the girl showed no deviations from normal values. There is no organomegaly. Following propranolol therapy, the above described cutaneous hemangiomas (all 73 of them) have completely disappeared, as well as visceral ones in the right lobe of the liver. The patient showed no dysmorphic signs. At a later stage, scoliosis developed, as can be seen in the photos below. (Figure 1.) Mutations in the genes involved in this signaling pathway consequently left a heterogeneous group of disorders called SCD. A similar study was first documented in Mexico in 2015 (8) in the case of a female newborn without a family history of multiple congenital anomalies, as in the present case. Our young patient was diagnosed with spinal segmentation disorders by radiological methods (multiple vertebral defects—including 10 vertebrae, mainly thoracic segment, and various rib anomalies such as hypoplasia, fusion, and spherical
shape). (Figure 2.) She was in physical therapy for scoliosis. Occasionally she had asthmatic attacks (bronchoconstriction), but with the growth and maturity of the respiratory tract, these problems disappeared.

In addition to cutaneous hemangiomas, one should take into account hemangiomas on the visceral organs and the brain. Hemangiomas should be closely monitored while considering diagnostically other rare diseases in children. It is important to consider SCD, i.e., spondylocostal dysostosis, as a rare autosomal recessive disease that can occur as part of hemangiomatosis. Past studies suggest it is probably due to an autosomal recessive form of SCD because other family members do not have similar symptoms. Clinically suspicious members were excluded by radiological examination. It is important to note that biochemical studies of coagulation parameters of whole blood showed increased values of D-dimer, and decreased values of proteins C and S, which occur in patients with hemangiomatosis, but is not associated with DIC. As part of the study, a karyogram and molecular analysis of the gene were performed for thrombophilia, but none was proven, and the karyogram is clear for females. A detailed hematological analysis was performed in terms of primary hemostatic capacity, thrombophilia genetic panel, fibrinogen, factor VIII, vWF factor, and all required laboratory findings were within the reference values. Propranolol was included in the therapy after birth and proved to be as effective as in the 2013 study. (9). The dose was adjusted according to the patient’s body weight. Recent studies from 2020 and 2013 have shown the efficacy of topical timolol as well as atenolol which can replace oral propranolol as the first-line agent in the treatment of hemangiomas. In randomized clinical trial (2020), when compared with propranolol, atenolol had similar efficacy and fewer adverse events in the treatment of infants with problematic infantile hemangiomas. (10,11) The results suggest that oral atenolol can be used as an alternative treatment option for patients with IH who require systemic therapy. Thanks to early diagnosis and a detailed multidisciplinary approach to congenital hemangiomatosis, the patient’s hemangiomas have fully disappeared, without causing major repercussions on her health, growth, and further development.

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