

A Case of Proteus Syndrome with Hemangioma Presentation

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ABSTRACT

Background: Proteus syndrome is a rare genetic disorder characterized by overgrowth of bones, skin, and other tissues, with vascular malformations, epidermal moles, and subcutaneous masses. We herein present a case of Proteus syndrome with extensive hemangiomas.

Case description: An 11-year-old girl with Proteus syndrome was presented with extensive hemangioma, asymmetrical growth in lower limbs, skin and bone lesions, and facial hemihypertrophy.

Conclusion: Given the severe complications of this syndrome and the risk of early death in the patients, early diagnosis is essential for reducing the risk of morbidity and mortality. These patients should be followed up for progressive skeletal deformities, hemangiomas, and malignant or benign tumors. In our case, risk of thrombosis and pulmonary embolism limited surgical intervention.

KEYWORDS: Proteus Syndrome, Hemangioma, Facial hemihypertrophy

Received:2018/09/29

Revised: 2018/11/27

Published:2018/11/27

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INTRODUCTION

Proteus Syndrome (PS) is a hamartoneoplastic disease [1], mainly characterized by overgrowth of bones, skin and other tissues which is accompanied with vascular malformation, epidermal moles and subdermal masses. Organs and affected tissues grow out of proportion compared to the unaffected ones. This growth is usually asymmetric and affects the left and right side of the body differently [2]. PS is a sporadic genetic disorder caused by a somatic mutation in the *AKT1* gene, which affects both genders equally [2-4]. This mutation is not inherited from parents and occurs accidentally in one cell during the early embryogenesis. We herein present a PS case with extensive hemangioma, asymmetrical growth in lower limbs, skin and bone lesions, and facial hemihypertrophy.

CASE PRESENTATION

An 11-year-old girl with complaints of skin hemangiomas and fever was referred to the Taleghani hospital in Gorgan, Iran. The patient's hemangiomas had been painful and swollen in the past four days, and the pain could not be controlled with medication in the past two days.

The patient was the first child, born via spontaneous vaginal delivery. Weight at birth was 3.4 Kg and the current weight was 40 Kg (50-75% percentile). The patient's height was 150 cm (75-90% percentile). The patient was of Turkmen ethnicity whose parents were not related. None of the parents had a history of illness in their first-, second- and third-degree relatives. Their two other children were healthy. According to the parents, similar lesions had been present on the right flank since birth, which sometimes bled superficially.

Macroductyly and syndactyly of the second and third toes of the left foot were also evident (figure 1A), as well as left facial hemihypertrophy, and pigmented dermal nevus in left side of the neck (figure 1B). No

diagnostic or therapeutic action had been taken by physicians despite many visits.

The patient had no learning problems and performed well at school. IQ was normal and there was no sign of a neurological or behavioral problem. Symptoms of puberty had not yet appeared in the patient.

After a seizure at age of 2 months, a dermal nevus in left side of her neck had appeared which has progressed ever since the incident. The patient had also experienced three episodes of afebrile seizure, which was treated with medication from the age of 2 months until 2 years of age. Moreover, she had a history of infantile asthma, which was not treated with medication, and a history of right inguinal hernia surgery.

The main reasons for the current visit were swollen and tender hemangioma in the right flank and fever. The parents reported history of right thigh inflammation since three days before the visit.

Physical examination

In the examination, an asymmetric growth of the lower limb was observed; the lower left limb was affected more than the right (a size difference of 4 cm). Macroductyly and syndactyly were present in the second and third toes of the left foot (Figure. 1A). Facial hemihypertrophy was present on the left side. In the posterior and anterior ear and neck region on the left, there were several brown-colored lesions (5-6 cm in diameter), which were similar to the dermal nevus first created after the seizure at age of 2 months (Figure 1B). Inflammation and swelling were observed in the right thigh area, but no mass or color variation was found (Figure 1C). There was a large hemangioma in the right flank that has been extended to the axillary. The hemangioma was warm, tender, and soft in consistency. In the upper hemangiomas, there was severe swelling and a number of pigmented nevi. This hemangioma has been present since birth, and sometimes bled

superficially and then healed on itself (Figure 1D).

Due to use of medication, the body temperature was 37.4 °C. Spine examination was normal, with no sign of kyphosis and

scoliosis. Examination of eye, teeth, and other organs was also normal. Orthopedic surgeons intended to perform a surgery on the left toe to improve the patient's functional status. Biopsy of the lesions did not confirm PS.



Figure 1. Presentations of the 11-year-old patient with suspected PS. A) Macroducty and syndactyly of the second and third toes of the left foot; B) Pigmented epidermal nevi in the left side of neck and posterior and anterior of left ear; C) Swelling in the right thigh; D) A large hemangioma in the right flank that has been extended to the axillary, containing a number of pigmented nevi and swelling in the right part of the hemangioma.

In the imaging findings, a hyperechoic soft-tissue mass (dimensions: 24 × 36 × 88 mm) was seen in the swollen part of the anterior right thigh, which required further investigations for hemangioma (Figure 2A). MRI with and without contrast was performed according to a special protocol, and no localized lesion was seen in the popliteal region and back of the right leg (Figure B). In the swollen region of the right flank, numerous cystic masses with thin septum

were evident. MRI was requested as a complementary study (Figure 2C). In sonography, diffuse and infiltrative lesions were observed in the subcutaneous soft tissue of the chest wall and lumbar site, especially in the right lateral wall of right hemithorax (Figure 2D). A distinct feeding vessel from the chest wall was moving towards the lesions. In MRI, signal of the upper lesion was diffusely high on T2. In MRI contrast, the signal was enhanced heterogeneously and

after the primary phases of injection, the dye did not enter lacunae. The largest lacunae were located in the superior portion of the lesion, under the axillary fossa with size of 3×4 cm. Areas of signal void were seen diffusely between the upper soft tumors.

In this patient, soft-tissue hemangioma was suggested based on the sonographic and MRI findings. No surgical therapy such as embolization and sclerotherapy was recommended because the lesions were high in number and spread in the soft tissue.

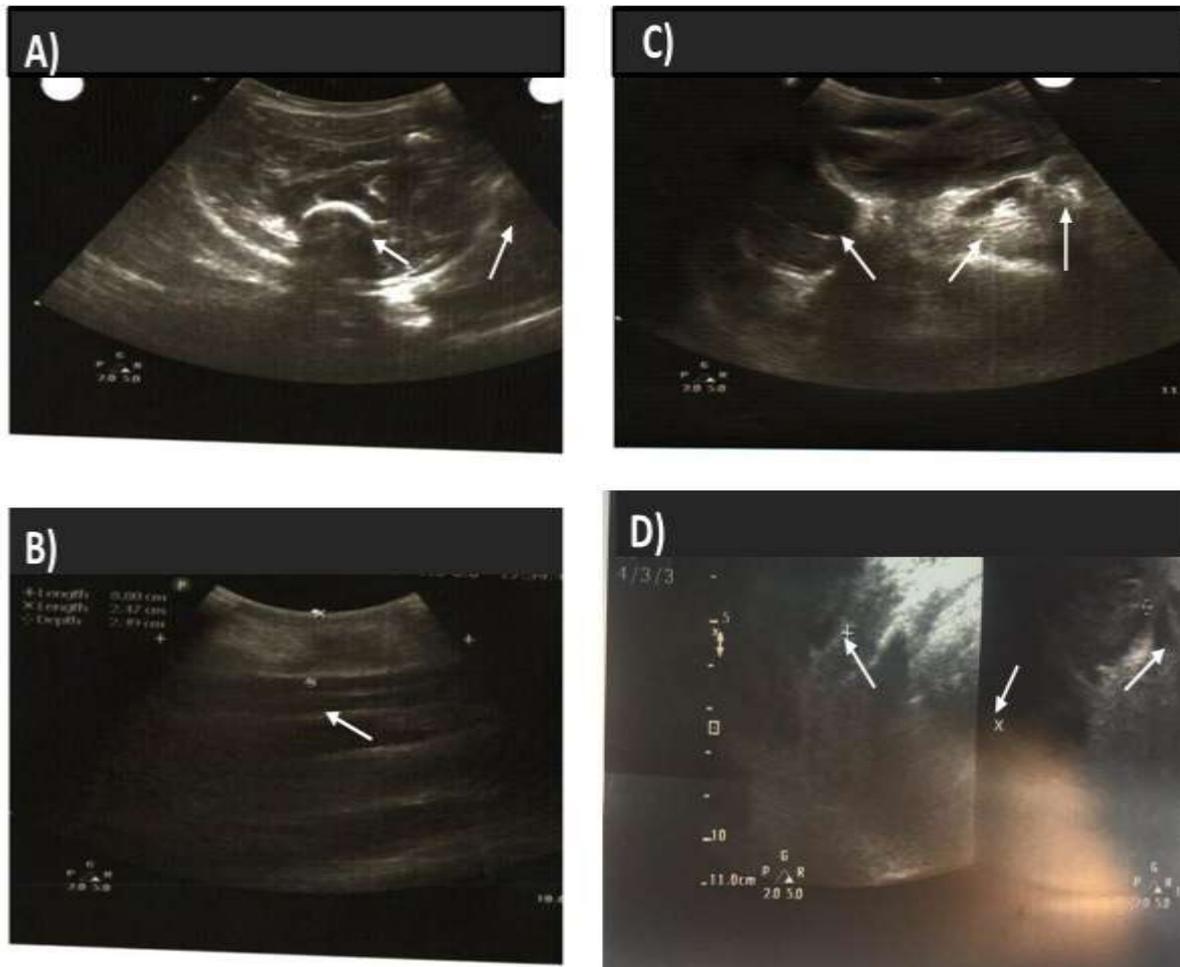


Figure 2. Ultrasound and MRI findings of the patient. Soft tissue sonography of the swollen portion of the anterior (A) right thigh, its back (B), the swollen region of the right flank (C) and color Doppler sonography of the soft-tissue lesions in the lumbar, thorax wall and the anterior thigh (D).

DISCUSSION

PS is a rare disease with a worldwide prevalence of less than one in every one million people [2]. Due to the rarity and high variability, there are no sensitive and specific diagnostic criteria. Misdiagnosis of PS had been common before the diagnostic criteria were introduced in 1999, and then completed by Turner in 2004 [5]. Unless the patient's conditions fall under both the general and specific criteria, the disorder will be classified as non-PS overgrowth [6]. Our case met all the general criteria (mosaic distribution of lesions, progressive growth and sporadic occurrence) and three specific criteria B (presence of epidermal nevi, overgrowth of toes and facial hemihypertrophy), which was also present in another case report from Romania [6]. In addition, our case met one criterion C (vascular malformation).

The syndrome had not affected other family members, and was not present in the patient's relatives, indicating its sporadic occurrence. Overgrowth in PS is asymmetric and progressive [5]. Our case also experienced progressive, asymmetrical, and inappropriate growth of the second and third toes of the left foot. This overgrowth usually occurs between age of 6-18 months, and becomes more severe with age [7, 8]. The overgrowth pattern in PS varies widely and can affect bones of arms and legs, skull, and the vertebral column. Overgrowth of the skin results in formation of a thick lesion with deep grooves, which is known as brain-like connective tissue (cerebriform) [3]. This abnormal skin overgrowth is usually found in the plantar surface of foot, which can be also accompanied with abnormal growth of blood vessels (vascular tissue) and adipose tissue. Some patients with PS also suffer from neurological disorders, such as intellectual disability, seizures, and vision loss. They also have special features including an elongated face, down-sided palpebral fissure (the outer

corner of palpebral is set downward), flat nasal bridge with wide nostrils and open mouth [3, 5]. Other potential signs of PS include presence of benign tumors and blood clot, also known as deep vein thrombosis [9], which along with pulmonary embolism and pneumonia are the most common reasons of early death in cases with PS [3]. Genetic studies demonstrated that mutation in the AKT1 gene is more frequent in the overgrown parts of the body [2]. The significant psychological implications of this syndrome in the patient and his or her family should not be neglected.

CONCLUSION

Given the severe complications of this syndrome and the risk of early death in the patients, early diagnosis is essential for reducing the risk of morbidity and mortality. These patients should be followed up for progressive skeletal deformities, hemangiomas, and malignant or benign tumors. In our case, risk of thrombosis and pulmonary embolism limited surgical intervention.

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