CASE REPORT

PEDIATRIC PROTEUS SYNDROME: A RARE CASE REPORT WITH FOCUS ON CLINICAL MANAGEMENT AND LONG-TERM OUTCOMES

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Key words: Proteus syndrome, AKT1 mutation, overgrowth disorder, vascular anomalies, multidisciplinary management.

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Abstract

Proteus syndrome (PS) is a rare mosaic genetic disorder caused by a somatic mutations in the AKT1 gene, resulting in asymmetric overgrowth of skin, skeleton, soft tissues, and internal organs. Progressive tissue expansion and vascular anomalies increase the risk of functional impairment and thromboembolic complications. Aim of the paper was to describe the clinical presentation, diagnostic evaluation, and management of a pediatric patient with PS, highlighting the role of multidisciplinary care. Case report: A 4-year-old girl presented with right upper limb overgrowth and a soft-tissue mass in the pectoral region. Diagnosis was confirmed via clinical assessment, radiologic imaging, and genetic testing for AKT1 mutation. Surgical excision of hypertrophic tissue was performed, and histopathology confirmed a benign lipomatous lesion. A two-year follow-up included monitoring of functional outcomes and disease recurrence. Postoperative recovery was uneventful, with primary wound healing. Progressive hypertrophy necessitated a second surgical intervention. Multidisciplinary follow-up facilitated timely management of emerging complications without major adverse events. Conclusion: PS requires early diagnosis and individualized, multidisciplinary management. Surgical interventions improve function, but long-term surveillance is essential due to the progressive nature of the disorder.

ПРИКАЗ НА СЛУЧАЈ

ПРОТЕУС СИНДРОМ ВО ПЕДИЈАТРИСКА ВОЗРАСТ: ПРИКАЗ НА СЛУЧАЈ СО ФОКУС НА КЛИНИЧКИ ПРИСТАП И ДОЛГОРОЧНИ ИСХОДИ

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Клучни зборови: Протеус синдром, AKT1 мутација, мозаичен раст, васкуларни аномалии, мултидисциплинарен пристап

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Печатарски права: ©2026. Розета Соколова, Лазо Јовчески, Шабан Мемети. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Протеус синдромот (ПС) е ретко, мозаично генетско заболување предизвикано од соматска мутација на генот AKT1, кое резултира со асиметричен и диспропорционален раст на различни ткива и органи. Прогресивната хипертрофија и васкуларните аномалии го зголемуваат ризикот од функционални нарушувања и тромбоемболички компликации. Цел на трудот е да се прикаже клиничкиот тек и пристапот кон третманот на пациент со ПС, со посебен акцент на мултидисциплинарната грижа. Прикажуваме случај на четиригодишно девојче со хипертрофија на десниот горен екстремитет и мекоткивна маса во пекторална регија. Дијагнозата е потврдена преку клиничка евалуација, радиолошко снимање и генетско тестирање за AKT1. Извршена е хируршка ексцизија на хипертрофичното ткиво, а хистопатологијата покажа бенигна липоматозна лезија со лимфатична малформација на пекторална регија. Двогодишното следење вклучуваше следење на функционалните исходи и рецидивот на болеста. Постоперативното закрепнување беше без компликации, со примарно заздравување на раните. Прогресивната хипертрофија бараше втора хируршка интервенција. Мултидисциплинарното следење го олесни навременото справување со новите компликации без поголеми несакани ефекти. Заклучок: ПС бара рана дијагноза и индивидуализиран мултидисциплинарен пристап, со долгорочно следење поради прогресивниот тек на болеста

Introduction

Congenital vascular and tissue malformations represent a heterogeneous group of disorders involving abnormal growth and development of blood vessels, bones, and soft tissues. The International Society for the Study of Vascular Anomalies (ISSVA) recently updated its globally accepted classification of vascular anomalies (2025), which refines the division of vascular tumors and malformations and incorporates new genetic and clinical insights into vascular anomalies[1].

Proteus syndrome (PS) is one of the rarest disorders within this group. It is a mosaic, somatic mutation-driven genetic condition caused by spontaneous, non-hereditary mutations in the AKT1 gene (10q23.3), leading to asymmetric and disproportionate overgrowth of various tissues and organs. First described by Cohen *et al*. in 1979, the syndrome is named after the Greek sea god Proteus, symbolizing its marked phenotypic variability. The estimated incidence is approximately 1 in 1,000,000 live births. Its clinical presentation is diverse and progressive, affecting multiple tissues including skeleton, skin, adipose tissue, and internal organs. Recent systematic reviews of clinical reports (Rostagni et al., 2025) have documented the spectrum of associated benign tumors, the timing of clinical onset, and characteristic features that inform early recognition and multidisciplinary management of affected children[2].

Clinically, PS is characterized by disproportionate, asymmetric overgrowth, which may affect the skin, subcutaneous tissue, skeleton, and internal organs. Cutaneous manifestations include vascular malformations, lipomas, hyperpigmentation, and various nevi, with cerebriform connective tissue nevi considered highly characteristic. Skeletal abnormalities commonly involve hyperostosis of the skull, long bones of the arms and legs, and the hands and feet, while internal organ involvement may include enlargement of the spleen, thymus, colon, or other tissues. Overgrowth is typically mosaic, presenting as patchy areas of affected and unaffected regions. A proportion of patients exhibit neurological abnormalities and progressive visual impairment.

Progressive vascular anomalies increase the risk of potentially life-threatening thromboembolic complications, including deep vein thrombosis and pulmonary embolism. The complex, multisystemic presentation underscores the need for early recognition. Its progressive and unpredictable course requires multidisciplinary management and long-term follow-up.

The differential diagnosis includes macrodystrophia lipomatosa, neurofibromatosis type 1, Parkes Weber syndrome, haemangiomatosis, Maffucci syndrome, and other rare disorders. Proteus syndrome is also known by several other names, such as partial gigantism, nevi hemihypertrophy macrocephaly syndrome, and Wiedemann syndrome. Treatment is mainly symptomatic and surgical, accompanied by genetic evaluation of affected individuals. Approximately 25% of patients with Proteus syndrome are beyond the age of 22-29 years.

Case Presentation

We present the case of a 4-year-old female patient referred to the University Clinic for Pediatric Surgery due to a soft-tissue swelling in the right pectoral and axillary region. The patient experienced pain during movement, without discomfort at rest.

The child was born from an uncomplicated first pregnancy (Apgar score 9/10) and had no family history of hereditary, degenerative, or autoimmune diseases. No abnormalities were noted at birth. On inspection, an elongated face with an open mouth and a soft tissue mass in the area of the right chest wall was noted. The mass was painless, soft on palpation, poorly demarcated, not adherent to the surrounding tissues, and no palpable lymph nodes were detected.

During the second year of life, progressive enlargement of the small finger and forearm of the right arm was observed, accompanied by the development of a soft-tissue mass in the right pectoral region.

Comprehensive clinical, radiological, and genetic assessments were performed, revealing a mutation in the AKT1 gene, consistent with the diagnosis of Proteus syndrome.

Under general anesthesia with endotracheal intubation, surgical excision of the tumorous mass was performed. A passive drain was placed intraoperatively to manage any postoperative fluid accumulation.

Histopathological examination revealed a benign lipomatous lesion with hyperplastic features. No evidence of malignancy was found.

During the postoperative period, mild wound moisture was observed due to a pre-existing lymphatic malformation. The drain initially produced a yellowish, clear, odorless fluid. After several days, the secretion stopped, and the drain was removed. The wound healed per *primam intentionem*.

During a two-year follow-up period, progressive hypertrophy of the fingers of the right hand and limited range of motion were observed, necessitating a second surgical reduction of the hypertrophic tissue.

The child underwent surgery under general anesthesia with endotracheal intubation. Fatty tissue was excised down to the fascia and musculature. Postoperatively, the wound healed well without any signs of infection. A mild asymmetry in forearm volume was observed, with the right forearm measuring 2 cm larger than the left.

The patient remains under regular follow-up with the orthopedic surgeon, geneticist, and pediatrician.

Long-term multidisciplinary monitoring is recommended due to the progressive nature of Proteus syndrome.

Clinical examination, radiographic imaging, laboratory tests, and histopathological analysis were performed. The diagnosis of Proteus syndrome was made according to the established diagnostic criteria. The patient met all general criteria, one criterion from Group B, and two criteria from Group C, including vascular malformations and a characteristic facial phenotype.



Figure 1:
Asymmetric overgrowth of the right thoracic region



Figure 2:
Macrodactyly and asymmetric enlargement of the fingers of the right hand, consistent with Proteus syndrome

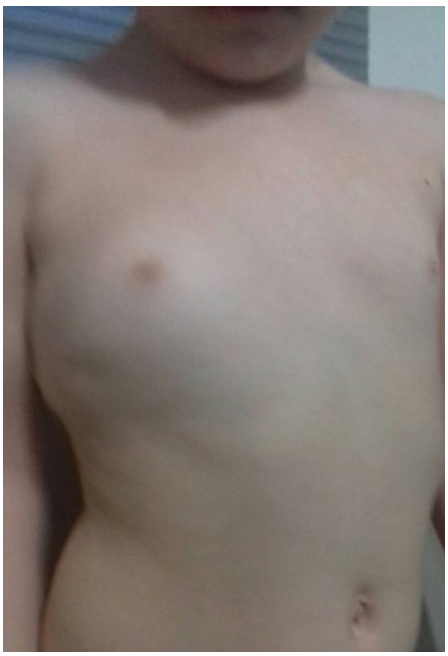


Figure 3:
Asymmetric overgrowth of the right chest wall and axillary region in a pediatric patient with Proteus syndrome

Histopathological examination of the excised tissue showed fatty tissue consistent with a benign lipomatous lesion. During follow-up, the child showed normal development and had no difficulties with the school curriculum. Abdominal ultrasound revealed no abnormalities in the urogenital system. All findings are summarized in Table 1.

General Criteria
Mosaic Distribution Progressive Course Sporadic Occurrence
Specific Criteria
Category A
Cerebriform connective tissue nevus
Category B
Linear epidermal nevus
Asymmetric, disproportionate overgrowth of two of:
Limbs, skull, external auditory canal, vertebrae, or viscera
Specific tumors in the first decade of life:
Bilateral ovarian cystadenomas
Monomorphic parotid adenomas
Category C
Dysregulated adipose tissue
Vascular Malformations
Capillary, venous, and/or lymphatic
Lung bullae
Facial phenotype:
Long face, dolichocephaly, down-slanted palpebral fissures, low nasal bridge, wide or anteverted nares, open mouth at rest
The diagnosis of Proteus syndrome requires all three general criteria, plus one criterion from category A, or two criteria from category B, or three criteria from category C. (Adapted from Biesecker, 2006)

Figure 1:
Diagnostic criteria for Proteus syndrome: general and specific (categories A–C) criteria applied in the presented case

Discussion

Proteus syndrome (PS) was initially described by Cohen and Hayden in 1979. Contemporary clinical reviews demonstrate a broad phenotypic spectrum. Skeletal overgrowth is reported in approximately 95% of patients, cerebriform connective tissue nevi in 65%, dysregulated adipose tissue in 39%, and vascular malformations in 32%[3]. These data highlight the marked clinical heterogeneity of the disorder. They also emphasize the importance of confirming a somatic *AKT1* mutation and implementing a multidisciplinary approach to long-term management.

Historical reassessment of John Carey Merrick, the "Elephant Man," revealed asymmetric overgrowth of the right arm and hand, macrodactyly affecting multiple fingers, and cerebriform connective tissue nevi involving the scalp and plantar surfaces. These findings are more consistent with Proteus syndrome than with neurofibromatosis type 1[4]. Subsequent modern clinical analyses further identified venous and lymphatic malformations, disproportionate lower limb growth, and asymmetric truncal adipose tissue distribution. All of these features align with the diagnostic spectrum of PS[5].

Clinically, Proteus syndrome manifests with a wide range of skeletal, cutaneous, soft-tissue, vascular, and internal organ abnormalities. Skeletal involvement commonly includes limb asymmetry, macrodactyly, and hyperostosis. Cutaneous features may include cerebriform connective tissue nevi, hyperpigmentation, and Blaschko's lines. Overgrowth of adipose and connective tissues is frequent. Vascular anomalies may involve venous, lymphatic, or mixed components. Internal organ involvement has also been reported. Importantly, patients with PS have a significantly increased risk of thromboembolic events, which remain a leading cause of morbidity and mortality [6].

Accurate diagnosis of Proteus syndrome requires detailed clinical assessment and radiological evaluation, including magnetic resonance imaging and ultrasonography. Molecular genetic testing is essential to identify a somatic activating mutation in the *AKT1* gene. Due to the mosaic nature of the disorder, genetic confirmation remains the definitive diagnostic criterion. Prenatal and postnatal studies have shown that pathogenic *AKT1* variants can be detected through exome sequencing of affected tissues. This underscores the importance of targeted molecular analysis in patients with segmental overgrowth[7]. The differential diagnosis includes neurofibromatosis type 1, which is characterized by café-au-lait macules and neurofibromas caused by *NF1* mutations. Clinical overlap with other overgrowth syndromes necessitates an integrated diagnostic approach combining clinical, imaging, and genetic data.

The present case illustrates the characteristic progressive and mosaic nature of Proteus syndrome. No abnormalities were observed at birth. Progressive macrodactyly of the right hand and soft-tissue overgrowth of the right thoracic and axillary regions developed during early childhood. This pattern is consistent

with previously reported segmental involvement in PS[3,6]. The identification of a benign lipomatous lesion associated with a lymphatic malformation reflects the known predisposition of patients with PS to adipose and vascular tissue dysregulation. Surgical intervention was required due to functional impairment and progressive enlargement. This mirrors the recurrent need for staged surgical procedures described in the literature. Despite adequate excision, disease progression continued and necessitated repeat surgery. This finding highlights the chronic and relapsing course of the syndrome and reinforces the importance of long-term multidisciplinary follow-up[8, 9].

Management of Proteus syndrome is primarily symptomatic and surgical. The main goals are to improve function, alleviate pain, and correct deformities. Therapeutic options include surgical excision or reduction of hypertrophic tissue, orthopedic correction, and physical therapy. Conventional medical therapies provide limited benefit. As a result, novel targeted treatments are under investigation. The AKT inhibitor miransertib (ARQ092, MK-7075) has demonstrated acceptable safety and tolerability in patients with PS and PIK3CA-related overgrowth spectrum disorders in phase 1/2 trials. Ongoing studies are evaluating its efficacy in reducing overgrowth and improving quality of life[8].

Experimental therapies such as sirolimus, an mTOR inhibitor, have shown modest reductions in pathological tissue volume in related overgrowth syndromes. However, their effects in classical Proteus syndrome are limited and variable. This is likely due to feedback activation within the PI3K/AKT signaling pathway, as suggested by case series and pilot studies.

Given the progressive and unpredictable nature of Proteus syndrome, comprehensive multidisciplinary care is essential. This approach should involve pediatrics, genetics, orthopedics, radiology, and pathology. Close follow-up is particularly important to monitor tumors across multiple organ systems. Such tumors are reported in nearly one-fifth of patients, with a median diagnosis age of about 15 years[9]. Regular imaging, thorough clinical examinations, and tailored preventive strategies, including periodic abdominal ultrasonography, are recommended. These measures facilitate early detection of neoplasms and reduce the risk of complications. Management should also prioritize optimization of quality of life and minimization of pain and functional limitations through coordinated, patient-centered care.

Conclusion

This case highlights the progressive and heterogeneous nature of Proteus syndrome in early childhood. Surgical management of benign soft-tissue overgrowth was successful, yet disease progression required repeated interventions. Early diagnosis, genetic confirmation, and long-term multidisciplinary follow-up are essential to optimize function and monitor disease evolution.

Associated vascular and adipose malformations underscore the need for regular imaging and clinical sur-

veillance. Coordinated care from pediatrics, genetics, orthopedics, and radiology is critical for timely intervention. This report reinforces the importance of individualized treatment plans and adds clinical insight to the limited pediatric Proteus syndrome literature.

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