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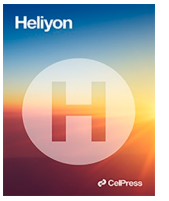

Case report

Proteus syndrome with progressive paralysis of the unilateral lower limb: A rare case report and literature review

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ABSTRACT

Objective: Proteus syndrome, a rare disorder with an incidence of one in a million, is characterized by connective tissue nevi, asymmetric limb overgrowth, and abnormal subcutaneous adipose tissue distribution. Limited awareness of this condition often hinders accurate clinical diagnosis. We report a case of Proteus syndrome with concurrent progressive paralysis in the unilateral lower limb, aiming to enhance understanding of the disease and its associated complications.
Methods: The patient, an 11-year-old male, has been conclusively diagnosed with Proteus Syndrome. This diagnosis was established by analyzing clinical manifestations, imaging studies, and laboratory tests. In addition, a literature review was conducted to systematically elucidate the etiology, diagnosis, treatment, and prognosis of this condition.
Results: According to the clinical manifestations, we confirmed a case of Proteus syndrome. This example exhibits the general characteristics of patients with severe hemihypertrophy of the bilateral lower limbs, anomalies in hypodermic and adipose distribution, and unilateral lower limb progressive paralysis. Pathological biopsy confirmed the right chest wall mass as a lipoma. Notably, the patient experiences lower limb movement disorders caused by intraspinal disease. At the same time, the gene sequencing results of this Proteus syndrome patient showed mutations in the IDUS gene and SPECC1L gene, which have not been reported before.
Conclusion: We diagnosed Proteus Syndrome with lower limb sensorimotor abnormalities, which may be caused by mutations in the IDUS gene or SPECC1L gene. This is the first report of these kinds of gene mutations in association with Proteus Syndrome.

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1. Introduction

Proteus syndrome (PS) is a rare disease characterized by a connective tissue nevus, asymmetric growth of limbs, and abnormal fat distribution. The incidence of PS is estimated to be less than 1/1,000,000 live births worldwide [1–3]. The disease was first reported in 1979, and was officially named in 1983 as Proteus syndrome, a name with ancient Greek sea-god Proteus, who could change his shape [4].

Due to the rarity of this disease, it is difficult for clinicians to make a correct diagnosis. In the present study, we report on the case of Proteus syndrome in our hospital with asymmetric growth of both lower limbs and abnormal distribution of subcutaneous fat, accompanied by progressive left lower limb paralysis as the main clinical manifestations, and briefly we described the disease.

2. Case presentation

An 11-year-old male patient was admitted to our hospital for the treatment of pressure ulcers in the buttock and sacrum. In 2016, the patient was hospitalized in Xiangya hospital due to the sudden lower limb weakness and paresthesia. After systematic treatment, the patient successfully recovered the ability to walk independently. Since 2020, the patient has exhibited a decline in muscle strength in the left lower limb, followed by a decrease in ipsilateral lower limb sensation (including touch, pain, and temperature) in 2022. While the superficial sensation in the left lower limb decreased, the muscle strength in the same limb continued to decline progressively, eventually reaching grade 0. Concurrently, there has been an accelerated development of hypertrophy in the left lower limb, subsequently leading to the development of right lower limb atrophy (Fig. 1A). The patient's parents were healthy and non-consanguineous. His brother has a history of lymphocytic leukemia, is currently still in treatment, with no other family history of hereditary disease.

The patient's physical examination revealed signs of malnutrition, a long face, and slightly downward oblique palpebral fissures (Fig. 1B). Multiple adipose-like soft tissues were observed in the right chest, back, and left lower abdomen (Fig. 1C), with the larger mass measuring about 14 × 8cm in the right chest wall (Fig. 1D). The mass exhibited characteristics of being soft, with a clear boundary, no tenderness, and good range of motion. Additionally, the patient was observed to have a thoracic scoliosis deformity, the muscle of the right lower limb was atrophic (with a muscle strength grade of 2), and the deep and superficial sensation were normal. The left hip and lower limb were significantly larger than the right. However, the muscle strength of the left lower limb was grade 0, and there was no sense of touch, pain, or temperature, and no pathological reflex was elicited.

Laboratory tests revealed the following results: hemoglobin level of 103.00g/L, hematocrit of 32.40 %, mean corpuscular volume of 79.00fL, and a platelet count of 408.00 × $10^{\hat{}}9$/L. Liver and kidney function, blood glucose, electrolytes, and coagulation function were all within normal ranges. Additionally, the serologic tests for hepatitis B, hepatitis C, HIV, and syphilis screenings were non-reactive. Subsequently, relevant imaging examinations were completed. The X-ray examination of the extremities revealed asymmetry in the lower limbs, feet, and pelvis (including soft tissue). Specifically, the pelvis was slightly tilted to the right, and the right femur, right foot, and right pelvic bones were smaller than the contralateral side, while the left side was enlarged (Fig. 2A-C). Additionally, the left acetabular joint exhibited abnormalities, with dislocation of the femoral head and accelerated development abnormality in the left proximal fibula (Fig. 2A). Anteroposterior chest X-ray indicated multiple rib enlargements and periosteum thickening on the right side. A soft tissue density shadow measuring 65 × 161mm was found under the skin of the right chest (Fig. 2D). Head CT examination

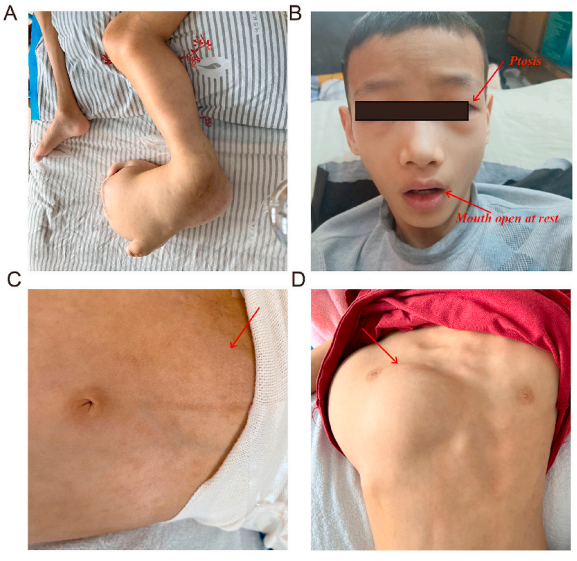

Fig. 1. A. Obvious hyperplasia and enlargement of the left lower limb; B. long face with low nasal bridge; C. Lipoma of the abdominal wall; D. Multiple lipomas on the right chest wall.

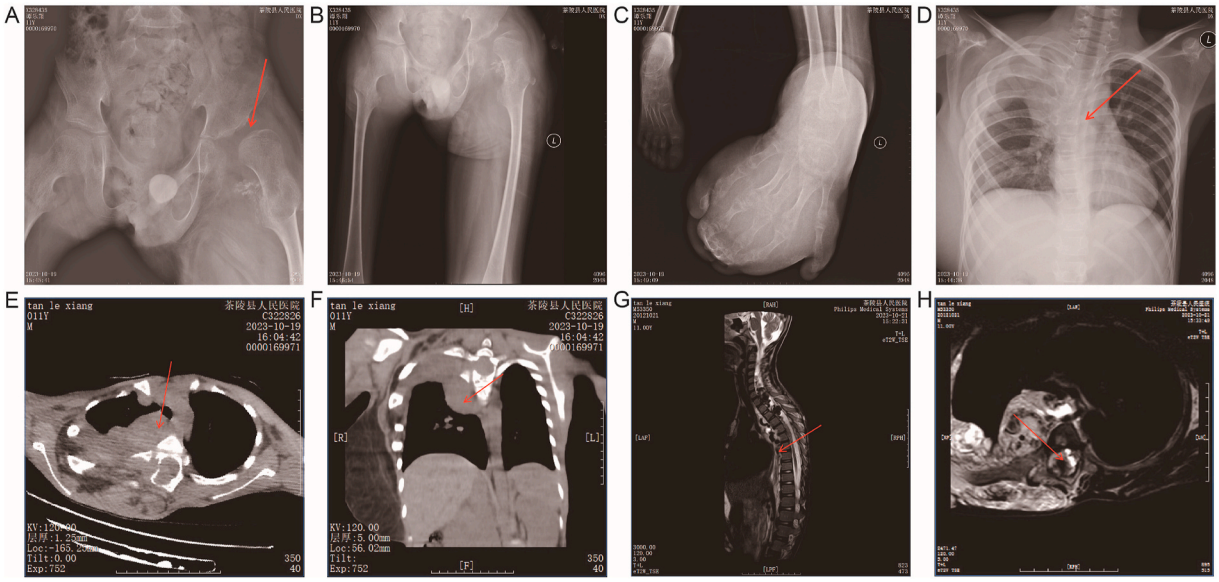

Fig. 2. A: Pelvic X-ray examination revealed left acetabular dysplasia with femoral head dislocation; B: X-ray examination of bilateral tibia and fibula demonstrated unequal size of bilateral tibia and abnormal development of the left fibula; C: Bilateral foot X-ray examination showed thickened bone development of the left foot; D: Chest X-ray examination revealed thoracic scoliosis deformity and enlargement, mass shadow on the right chest wall, and multiple thick ribs on the right side; E–F: Chest CT examination indicated a right thoracic mass; G–H: Thoracic vertebra MRI displayed vascular malformations in the right thoracic cavity, spinal canal, and spinal cord.

showed no abnormalities. Chest CT examination revealed irregular thickening of subcutaneous fat in the right chest wall, with multiple nodular soft tissue density lesions, rib bone changes, and irregular thickening of the right pleura with mass formation (Fig. 2E-F). Thoracic MRI demonstrated abnormal signals in the spinal canal at positions C3 to T6, involving the corresponding spinal cord, considered as vascular malformation. A mass was identified in the right thoracic cavity, displaying a large vascular malformation in the lesion, along with a mass under the right back chest wall and adjacent rib enlargement (Fig. 2G-H). Lumbar MRI plain scan showed no obvious abnormality. Echocardiography results showed an EF% of 71, FS% of 41, with measurements within normal limits for IVS (7mm), LV (42mm), LVPW (6mm), LA (25mm), AO (17mm), PA (14mm), RA (26mm), RV (22mm), and IVC (12mm). Mild regurgitation of the mitral, tricuspid, and aortic valves was noted. Vascular color Doppler ultrasound examination of the lower limbs showed no obvious abnormal sound images in the arteries and veins.

Pathological examination of the right chest wall mass needle biopsy confirmed the presence of right chest wall lipoma (Fig. 3). Then take patient's peripheral venous blood for clinical whole exome sequencing, which examines the DNA sequence of over 180,000 exons across 22,000 human genes plus the mitochondrial gens. The main findings from genetic testing were as follows: No pathogenic/suspected pathogenic variants associated with the clinical phenotype or variants of unknown clinical significance consistent with the genetic pattern were detected. The results of mitochondrial gene detection revealed no mitochondrial gene variations related to the

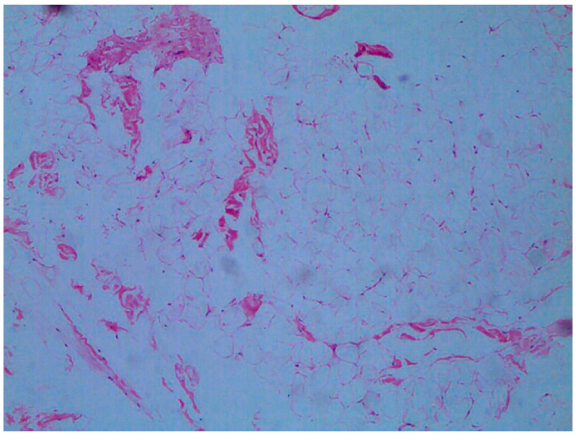

Fig. 3. A needle biopsy of a chest wall mass revealed a significant abundance of adipocytes, along with interstitial small amounts of fiber and small blood vessels, as evidenced by H&E staining (original magnification × 100).

Table 1
(Mitochondrial genetic testing results).

Primary Test Results							
Serial number	Genes	Chromosomal location	Transcript numbering & Nucleotide changes (amino acid changes)	Gene subregion	Genotype	Pathogenicity classification	Related diseases/inheritance patterns
/	/	/	/	/	/	/	/
Secondary Test Results							
Serial number	Genes	Chromosomal location	Transcript numbering & Nucleotide changes (amino acid changes)	Gene subregion	Genotype	Pathogenicity classification	Related diseases/inheritance patterns
1	IDUA	chr4:99617 7	NM_000203.3: c.1093C > G(p.Leu365Val)	EX8/CDS 8	heterozygous	unclear significance	Hurler-scheie syndrome (OMIM:607015)/AR Hurler syndrome (OMIM:607014)/AR Mucopolysaccharidosis 5 (OMIM:607016)/AR
2	*IDUA*	chr4:99790 5	NM_000203.3: c.1828+5G > A	IVS1 3/IC1 3	heterozygous	unclear significance	Hurler-scheie syndrome (OMIM:607015)/AR Hurler syndrome (OMIM:607014)/AR Mucopolysaccharidosis 5 (OMIM:607016)/AR
3	*SPECC*1L	chr22:2474 3069	NM_015330.3: c.2668G > A(p.Gly890Arg)	EX11/CDS 9	heterozygous	unclear significance	Teebi hypertelorism syndrome type 1 (OMIM: 145420)/AD Craniofacial dysostosis type 1 (OMIM: 600251)/AD

clinical phenotype. Two variants of unknown significance were identified in the IDUA gene associated with Hurler-Scheie syndrome/Hurler syndrome/mucopolysaccharidosis type 5, showing partial relevance to the patient's phenotype. Additionally, a variant of unknown significance was detected in the SPECC1L gene, which is partially related to the patient's phenotype [5–8] (Table 1).

In conclusion, the patient was diagnosed with Proteus syndrome, and the mutation gene may involve IDUA or SPECC1L. Considering the limited resources in our hospital, it is strongly advised that the patient undergo further treatment at a more specialized medical facility.

3. Discussion and conclusion

Proteus syndrome is a rare disease characterized by asymmetric and disproportionate tissue overgrowth, clinically identified by connective tissue nevus. Based on relevant case reports both domestically and internationally, there is no evidence suggesting hereditary transmission of Proteus syndrome; Instead, it is associated with gene mutations. The AKT1 gene, extensively studied in this context, features a notable mutation, c.49G→A, p.Glu17Lys, resulting in sustained activation of the AKT1 protein. This continuous activation is linked to tissue overgrowth and heightened susceptibility to tumors in individuals with Proteus syndrome [9]. Additionally, a limited number of cases have reported Proteus syndrome resulting from mutations in the PTEN tumor suppressor gene [10].

3.1. Diagnostic criteria for Proteus syndrome

Proteus syndrome has various clinical manifestations. Imaging examination can show hyperplasia and hypertrophy of the epiphysis and metaphyseal of the affected limb, and obvious thickening of the soft tissue [11]. At present, the diagnosis of Proteus syndrome is mostly based on the primary and secondary diagnostic criteria of Proteus syndrome formulated by Turner in 2004 [12]. There were three main criteria: (1) Mosaic distribution; (2) The disease course was progressive; (3) sporadic in the population; The secondary criteria included three categories: class A; Gyral connective tissue nevus; Class B: 1) epidermal warts (epidermal nevus/sebaceous nevus); 2) disproportionate overgrowth (at least one of the following lesions): ① limbs: upper/lower limbs, hands/feet, fingers/toes; ② Skull: hyperostosis; ③ External auditory canal: hyperostosis; ④ spinal dysplasia; ⑤ Visceral lesions: spleen/thymus; 3) specific tumor (bilateral ovarian cystic tumor/parotid monomorphic adenoma) before 20 years old; Class C: 1) irregular distribution of adipose tissue: lipoma/focal fat loss; 2) Vascular malformations: capillary/venous/lymphatic malformations; 3) pulmonary cysts; 4) Facial manifestations: Dolichocephaly/long face, mild ptosis/mild ptosis of palpebral fids, collapsed nasal bridge, broad or prominent nostril, open mouth at rest. Patients with Proteus syndrome had to meet all three of the "major criteria" and either category A or two of category B or three of category C abnormalities of the "minor criteria" [12].

3.2. Differential diagnosis of Proteus syndrome

Proteus syndrome usually needs to be distinguished from the following diseases: (1) Klippel-Trenaunay-Weber syndrome: it is a congenital vascular malformation, arteriovenous fistula, often manifested as local extensive vascular lesions, skin color changes and high skin temperature [13]. (2) Bannayan Riley Ruvalcaba syndrome is a rare autosomal dominant dermatosis characterized by macrosomia, genital pigmentation and intestinal polyposis [14]. (3) Maffucci syndrome is a congenital non-genetic disease caused by mesodermal dysplasia [15]. The main manifestations are multiple enchondromas and soft tissue hemangiomas, with typical X-ray findings. (4) Acromegaly: It is an endocrine disease with excessive secretion of growth hormone. Children and adolescents mainly present with gigantism and increased limb symmetry [16]. (5) Tuberous sclerosis complex (TSC): an autosomal dominant disorder characterized by facial sebaceous adenoma, seizures, and mental retardation [17]. (6) Launois-Bensaude syndrome: The etiology of Launois-Bensaude syndrome is unknown, and it is considered to be related to ectodermal abnormalities. The main manifestations are posterior neck and submandibular masses, and lipomas can occur in the trunk and limbs [18]. (7) Primary hypertrophic osteoarthropathy (PHOA): PHOA, also known as pachydermoperiostosis (PDP), is a rare congenital disease affecting the skin and bones, mostly inherited in an autosomal recessive manner. It is characterized by a peculiar bulbous deformity of the tips of the digits, conventionally described as "clubbing," periosteal proliferation of the tubular bones, and synovial effusions. The disease primarily arises from mutations in the HPGD and SLCO2A1 genes [19,20]. (8) McCune Albright's syndrome is characterized by abnormal bone development, often associated with skin pigmentation and precocious puberty [21]. (9) Neurofibromatosis type 1(NF1): an autosomal dominant genetic disease, the main clinical manifestations include cafe-au-lait spots, neurofibromas, axillary and inguinal fissuoles, Lisch nodules, and abnormal bone development. Proteus syndrome in the early stage has been misdiagnosed as neurofibromatosis [22,23].

This patient met all three of the major criteria, as well as one of the minor category B criteria (disproportionate overgrowth of the lower limbs) and three of category C criteria (lipoma, vascular malformation, and facial phenotype). Proteus syndrome was finally diagnosed on the basis of ruling out Klippel-Trenaunay-Weber syndrome, Maffucci syndrome, acromegaly syndrome, Albright syndrome, neuroma lesion and other diseases. Proteus syndrome combined with progressive lower limb paralysis is rarely reported. During the thoracolumbar MRI examination of this patient, vascular malformation lesions were found in the right thoracic cavity and cervicothoracic spinal cord, accompanied by spinal cord compression. The progressive limb paralysis was considered to be caused by vascular malformation lesions compressing the spinal cord. In addition, gene detection results of this patient detected IDUA gene and SPECC1L gene variations. IDUA has been most widely reported in association with mucopolysaccharidosis type I (MPS I), a rare disorder caused by deleterious sequence variants in the α-L-iduronidase (IDUA) gene [24]. In contrast, patients with SPECC1L mutations present with a series of structural fetal birth defects, often characterized by abnormal craniofacial development (hypertelorism,

cleft palate) and internal organ instability (diaphragmatic hernia, bicornuate uterus) [25]. Until now, there have not been any reports related to Proteus Syndrome involving the two types of mutations mentioned. There may be other types of gene variants in Proteus Syndrome, which still needs further extensive research.

As of now, there is no specific and universally effective treatment for Proteus syndrome. The majority of cases undergo corrective surgery to address the impact on daily life. However, even after surgery, there remains a risk of recurrence in the affected limb. Abroad, there have been clinical case reports suggesting the effectiveness of treatment with AKT1 gene inhibitors. Nevertheless, further extensive research is necessary to validate these findings [26]. The mortality rate associated with Proteus syndrome is notably high, reaching up to 20 %. Complications such as pulmonary infections, deep vein thrombosis, and malignant tumors are major contributors to mortality. It is crucial to acknowledge that surgical interventions may elevate the risk of death from thromboembolic diseases [27].

Given the complex nature of Proteus syndrome and its impact on various organ systems, a multidisciplinary approach is often essential in the management of affected individuals. Regular monitoring, supportive care, and exploration of novel treatment modalities through ongoing research efforts are crucial aspects of the overall care strategy for individuals with Proteus syndrome.

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Data availability statement

All data generated or analyzed during the current study are included in this published article, more detail is available from the corresponding author upon request.

Ethics approval and consent to participate

This patient provided oral and signed written consent to use his clinical materials in this study. The study was conducted in accordance with the principles contained in the Declaration of Helsinki and the ethical standards of the institutional and national research committee.

Consent for publication

The patients signed the consent for publication.

CRediT authorship contribution statement

Feng Cai: Writing – original draft, Data curation. **Zhi Liu:** Writing – original draft, Supervision, Data curation. **Jun Zou:** Resources, Project administration, Methodology. **Yunfeng Liu:** Methodology, Investigation. **Weiming Tang:** Writing – review & editing, Visualization, Conceptualization. **Liping Zhou:** Writing – review & editing, Supervision, Software, Project administration. **Xiaojian Zhu:** Resources, Methodology, Investigation, Formal analysis. **Xiaoping Huang:** Writing – review & editing, Supervision, Methodology. **Wei Long:** Supervision, Methodology. **Shushan Zhao:** Writing – review & editing, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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