

# SOLAMEN Syndrome in a Filipino Child

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## ABSTRACT

Asymmetric overgrowth syndromes are a diverse group of diseases with overlapping features including asymmetric overgrowth of a body part, vascular malformations, lipomatosis, and epidermal nevus. Three important considerations when presented with these features are Proteus syndrome, CLOVES (*Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Skeletal anomalies*) syndrome and SOLAMEN (*Segmental Overgrowth, Lipomatosis, Arteriovenous Malformation, Epidermal Nevus*) syndrome. This paper aimed to present a rare case of asymmetric overgrowth syndrome. A 3-year-old child with asymmetric overgrowth of the right upper and lower extremities was seen at the clinic. He also had epidermal nevus, lipomatosis, skeletal abnormalities, and vascular malformation. The history showed the presence of segmental proportionate overgrowth with soft tissue hypertrophy and ballooning effect based specifically on the location, timing, and progression of overgrowth. On physical examination, macrocephaly was also noted. Based on these features, the diagnosis of SOLAMEN syndrome was made. This is the first reported case of SOLAMEN syndrome in the Philippines. The importance of a careful and thorough history and physical examination cannot be overemphasized. A multidisciplinary approach in management with appropriate referral to subspecialists and early monitoring for possible malignancies are needed.

**Keywords:** SOLAMEN Syndrome, Overgrowth Syndromes, PTEN gene

## INTRODUCTION

Overgrowth syndromes are among the most diverse group of diseases characterized by excessive tissue development.<sup>1</sup> Many of these syndromes may present with similar features making the diagnosis and management challenging. Overgrowth, an excessive proliferation of an organ or tissue, can either be focal or diffuse, symmetric or asymmetric, congenital or postnatal, static or progressive and distorting or non-distorting. On the other hand, vascular anomalies can be described as either proliferative, such as hemangiomas, or static lesions, such as capillary, venous, and arterio-venous malformations.<sup>2</sup> A subgroup of these overgrowth syndromes contains overlapping features such as asymmetric overgrowth, vascular malformations (capillary, lymphatic or venous), lipomatosis, and epidermal nevus. These syndromes include Proteus Syndrome, CLOVES syndrome, and SOLAMEN Syndrome.

Proteus syndrome is described as having craniofacial features such as dolichocephaly, long face, minor down-slanting of palpebral fissures, minor ptosis or both, low nasal bridge, wide or anteverted nares, and open mouth at birth.<sup>3</sup> This unique pattern of dysmorphic features may help in distinguishing Proteus syndrome from the others. At present, this condition is caused by only a single mosaic pathogenic variant (p.Glu17Lys) in the AKT1 gene, located in chromosome 14q32.33.<sup>4</sup>

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On the other hand, CLOVES syndrome consists of congenital lipomatous overgrowth due to dysregulated adipose tissue, vascular malformations, epidermal nevi, and scoliosis, skeletal abnormalities, or both. The deformities are present at birth, often symmetrical, and increase with growth but are not rapidly progressive. In addition, central nervous system manifestations are significantly seen in this condition. This condition has been attributed to mutations in the *PIK3CA* gene located in chromosome 3q26.32.<sup>5</sup>

SOLAMEN syndrome also referred to as segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus syndrome or type 2 segmental Cowden syndrome, relates to the early loss of heterozygosity at the phosphatase and tensin homolog (PTEN) allele in the affected tissues in patients with underlying germline PTEN mutation.<sup>6</sup>

Here we presented a case of a Filipino child with asymmetric overgrowth, epidermal nevus, lipomatosis, skeletal abnormalities, and vascular malformations, which are overlapping features of Proteus syndrome, CLOVES syndrome, and SOLAMEN syndrome.

**CASE**

A 3-year-old boy was referred to the genetics clinic for consideration of epidermal nevus syndrome. He was born to non-consanguineous parents of Filipino descent (Figure 1). The mother's pregnancy and delivery were uneventful. There was no reported infection, drug use, or exposure to radiation during the pregnancy. There was no family history of a relative with similar features or a history of malignancy. At birth, the patient was noted to have multiple cotton-white colored papules linearly distributed on the right upper extremity and the right thoracoabdominal area. In the first few months of life, the lesions evolved into skin-colored non-erythematous plaques. At five months of age, a skin punch biopsy of the plaques was done,

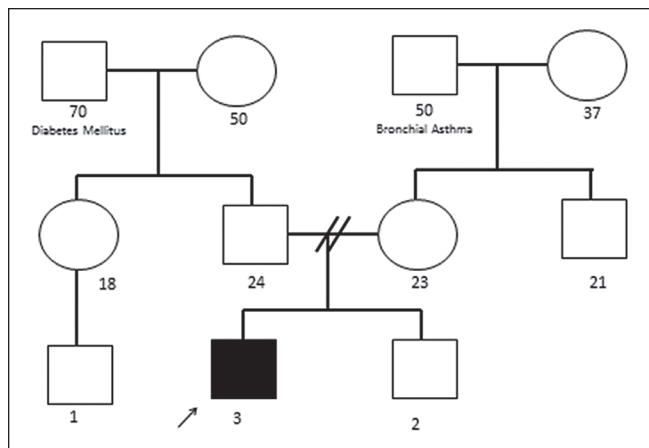
and it showed verrucous epidermal hyperplasia, consistent with an epidermal nevus. At this time, a left axillary cystic mass was palpated. Over the next few months, the asymmetry of the lower extremities, with the right more than the left, and other cystic masses were observed.

On physical examination, the patient was stunted (Z score < -2) with normal weight for age (Z score > 0). He had relative macrocephaly (Z score > +1) with dolichocephaly and bitemporal narrowing. He had hypertelorism, a prominent nasal bridge, and small ears. The skin had multiple hyperkeratotic hyperpigmented coalesced papules linearly distributed on both upper extremities and the right side of the abdomen. There were numerous cystic masses on the left neck area extending to the left axillary area and left anterior chest and on the right axillary area extending to the abdomen. The scrotal area was enlarged with palpable cystic masses, with both left and right testicles are descended. In the upper extremities, macrodactyly of the 3<sup>rd</sup> digit on the left and right upper extremities, 5<sup>th</sup> digit clinodactyly of both upper extremities, and radial deviation of the 4<sup>th</sup> digit of the right hand were observed (Figure 2). In the lower extremities, gross overgrowth of the right extremity was noted. There was also splaying of the 2<sup>nd</sup> and the 3<sup>rd</sup> digits of the left foot. There were multiple varicose veins on both extremities (Figure 3). The physical examination of the rest of the systems was unremarkable.

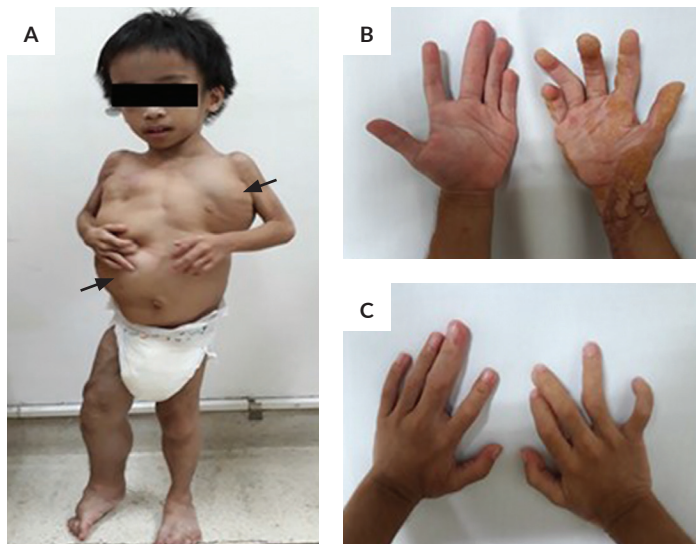
A skeletal survey (Figure 4) showed a right tibial diaphyseal diameter of approximately 150 % of the contralateral side. Likewise, the right fibular diaphysis diameter was about 260% of the diameter of the contralateral side. The soft tissues of the right lower extremity were hypertrophied relative to those on the left. There was a soft tissue swelling of the abdominal wall and soft tissue irregularity of the right lower extremity. CT scan of the thoracoabdominal area confirmed the presence of multiple lipomatosis. Scrotal ultrasound indicated normal bilateral testicles with herniated omental fat displacing the left testicle inferiorly. The lower extremity venous duplex scan showed subcutaneous venous hemangioma and a normal lower extremity arterial duplex study. Molecular studies were not sufficiently performed due to financial constraints.

**DISCUSSION**

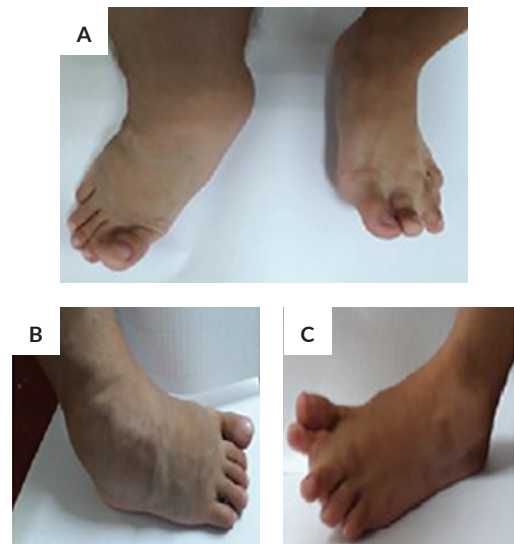
Several asymmetric overgrowth syndromes are presenting similar findings. The overlapping features of these syndromes have caused many patients to be misdiagnosed. Of these conditions, Proteus syndrome has been shown to have a high rate of misdiagnosis. Among the published reported cases of Proteus syndrome, only 47.3 % (97/255 cases) met the diagnostic criteria, 39 % (80/205) did not meet the criteria, and 13.7 % (28/205) had insufficient clinical data to make a diagnosis.<sup>7</sup> The association with vascular anomalies and other features may help limit the considerations for this case. We can further narrow down



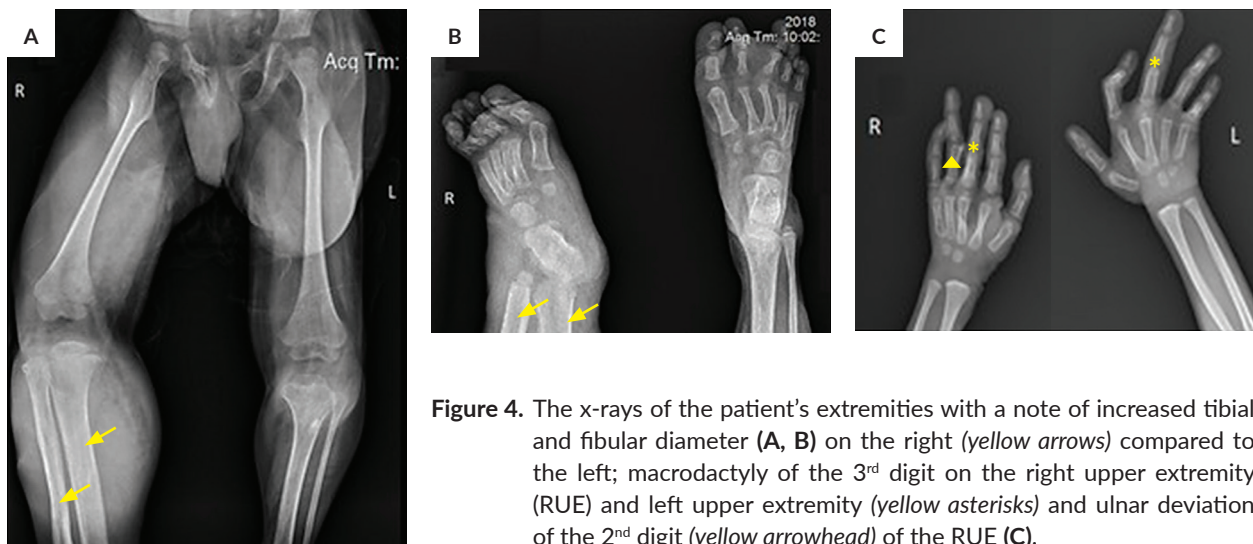
**Figure 1.** The three-generation family medical history of the patient.



**Figure 2.** (A) Whole body photo of the patient showing the cystic masses (*black arrows*), as well as the (B, C) hands with the epidermal nevus, macrodactyly on the left and right upper extremity, lateral deviation of the 4<sup>th</sup> digit on the right upper extremity and 5<sup>th</sup> digit clinodactyly on both the left and right upper extremities.



**Figure 3.** (A) The lower extremities of the patient with gross overgrowth of the right extremity (B) over the left (C), splaying of the 2<sup>nd</sup> and the 3<sup>rd</sup> digits of the left foot, and multiple varicose veins.



**Figure 4.** The x-rays of the patient's extremities with a note of increased tibial and fibular diameter (A, B) on the right (*yellow arrows*) compared to the left; macrodactyly of the 3<sup>rd</sup> digit on the right upper extremity (RUE) and left upper extremity (*yellow asterisks*) and ulnar deviation of the 2<sup>nd</sup> digit (*yellow arrowhead*) of the RUE (C).

our differential diagnoses by adding the other features, such as the epidermal nevi and lipomatosis. Proteus syndrome, SOLAMEN syndrome, and CLOVES syndrome have all these features, as shown in Table 1.

The location, timing, and progression of overgrowth can be helpful to differentiate these three syndromes. Distinguishing proportionate from disproportionate overgrowth was confusing because it incorporates two concepts: progression and distortion. The progression refers to the growth of the body parts. It is non-progressive if the enlarged body part grows at a rate similar to the patient's

development. Distortion, on the other hand, refers to the shape of enlarged structures. It is non-distorting if the enlarged structures are typical in shape but just larger than normal.<sup>8</sup> These terms used to classify the overgrowth had been a source of confusion for many physicians. The overgrowth in CLOVES syndrome is congenital, grows proportionately with the patient, and typically affects both feet. These specific features contrast with the presentation of our patient, who had these features noticeable months after birth. SOLAMEN syndrome, on the other hand, has segmental proportionate overgrowth with soft tissue hypertrophy

**Table 1.** Clinical Features of the Three Overlapping Syndromes and that of the Patient

Clinical Features	Patient's Features	CLOVE Syndrome	SOLAMEN Syndrome	Proteus Syndrome
1.Asymmetric overgrowth	(+)	(+)	(+)	(+)
a.Congenital	(-)	(+)	(-)	(-)
b.Proportionate	(+)	(+)	(+)	(-)
2.Lipoma	(+)	(+)	(+)	(+)
3.Epidermal Nevus	(+)	(+)	(+)	(+)
4.Vascular Malformation	(+)	(+)	(+)	(+)

and ballooning effect.<sup>9</sup> For Proteus syndrome, overgrowth is typically distorting, disproportionate, asymmetric, and absent at birth.<sup>10</sup> In our patient, the enlarged bony structures are normal in shape as seen on the radiographs. No bony growths are invading joint spaces or jagged edges. Having a non-progressive and non-distorted enlarged structure, our patient has proportionate overgrowth.

The subtle differences discussed may be overlooked and may lead to an over-diagnosis of Proteus syndrome. Hence, diagnostic criteria for Proteus syndrome have been developed to aid clinicians. For the diagnosis of Proteus syndrome, general criteria should be present, namely, mosaic or patchy distribution of the lesions, sporadic occurrence, and progressive course.<sup>7</sup> These were all noted in the patient. It is also important to note the presence of the specific criteria in the patient, which include disproportionate overgrowth of the right leg, epidermal nevi on both upper extremities, and the right abdominal area. A diagnosis of Proteus syndrome was initially made based on this. Conversely, the presence of macrocephaly and multiple/invasive lipomas points towards the diagnosis of SOLAMEN syndrome.<sup>9</sup>

Proteus syndrome is a rare complex disorder with an estimated prevalence of <1/1,000,000 live births. AKT1 mutations were identified as an important cause of this uncommon disease. The oncogene AKT1 (serine/threonine kinase 1), located in the long arm of chromosome 14 at position 32.33 (14q32.33), provides instructions for making the protein AKT1 kinase. This protein is essential in many signaling pathways which help regulate cell growth, division, and differentiation. Although AKT1 mutations are associated with this disorder, the molecular etiology remains to be fully elucidated.<sup>11</sup>

Another gene, PTEN (deleted on chromosome 10), is also implicated in Proteus syndrome. This gene provides instructions for making an enzyme that acts as a tumor suppressor. Germline mutations of the PTEN gene have been found in 20% of Proteus syndrome, approximately 50% of Proteus-like syndromes, and 80% of classic Cowden syndrome.<sup>12</sup> In SOLAMEN syndrome, also known as type 2 segmental Cowden syndrome, the PTEN gene is the only gene implicated. A secondary molecular event in Cowden syndrome families, which is a loss of PTEN wild-type allele, may explain the phenotype of SOLAMEN syndrome. Hence, an additional clue to the diagnosis of SOLAMEN

syndrome is the presence of autosomal dominant manifestations of Cowden syndrome in the family members.<sup>7</sup> Going back to the case, this critical family history had not been fully elucidated due to the family dynamics. The history of the paternal side of the child had not been explored.

Given that this gene is implicated in both Proteus syndrome and SOLAMEN syndrome, it is not surprising that they present with overlapping features. Because of this also, early monitoring for possible malignancy of patients with either PTEN-related Proteus syndrome or SOLAMEN syndrome is warranted. Individuals with either Cowden syndrome or SOLAMEN syndrome are at high risk for breast, thyroid, and endometrial cancers. For pediatric patients, yearly thyroid ultrasounds and yearly skin checks with physical examination are done.<sup>11</sup> Our patient has been undergoing this surveillance and monitoring.

Molecular studies have contributed significantly to the understanding of asymmetric overgrowth syndromes. Like the PTEN gene, the same genes may be implicated in conditions like Proteus syndrome and SOLAMEN syndrome.<sup>13</sup> The use of genetic testing has primarily been significant for prognosis and has limited use for diagnosis for now. Although AKT1 and PTEN mutations are implicated in Proteus syndrome, the exact cause remains unclear. In a study done by Biesecker, no mutations in the reported Proteus syndrome-associated genes were found by exome sequencing in some patients with Proteus syndrome. This implies that some mutations in unknown genes may contribute to the development of Proteus syndrome.<sup>11,14</sup> Also, for several vascular anomaly-related overgrowth syndromes shown to have post-zygotic somatic mutations, more than one tissue must be tested to assess intra-patient differences in DNA from affected (biopsy of involved area) and unaffected tissue (peripheral blood).<sup>2</sup> Germline mutations in the *PTEN* gene have shown significant variability, with detection rates ranging from 11% to 80%.<sup>15</sup> Hence, the importance of clinical evaluation cannot be overemphasized.

Given the complexity of this case, a multidisciplinary approach is needed to address the patient's needs. Mobility due to the overgrowth and the presence of kyphosis warrants the subspecialty referral to the Orthopedic and Rehabilitation Medicine services. The multiple lipomatosis was referred to the pediatric and thoracic, and cardiovascular surgery services for further management. The pediatric

hematology-oncology service is on board for malignancy surveillance and monitoring. The team is also managing him for the hemangioma with sirolimus.

## CONCLUSION

A systematic approach in evaluating patients with asymmetric overgrowth syndromes with vascular malformations, like SOLAMEN syndrome, is essential because of overlapping features with other conditions. A detailed evaluation is required in differentiating these syndromes. Early surveillance and monitoring for possible malignancies are vital in the care of patients with SOLAMEN syndrome. A multidisciplinary approach in management is also needed.

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## Statement of Authorship

All authors participated in the data collection and analysis and approved the final version submitted.

## Author Disclosure

All authors declared no conflicts of interest.

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