

Precocious puberty in a female with Proteus Syndrome

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ABSTRACT

Proteus syndrome is a complex disorder comprising malformations and overgrowth of multiple tissues and characterized by its polymorphism and mosaicism. The syndrome is rare and sporadic. Oliveira M da C et al¹ reported the first case of Proteus syndrome associated with precocious puberty in a boy. We are reporting a case of a 7-month old girl with Proteus syndrome who developed a juvenile granulosa cell tumor in one ovary causing precocious puberty. At our knowledge this is the first case of Proteus syndrome with precocious puberty in a female.

Keywords: Proteus syndrome, precocious puberty, juvenile granulosa cell tumor .

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Proteus syndrome (PS) is a disorder comprising malformations, overgrowth of multiple tissues,² associated with cutaneous abnormalities, vascular malformations and hyperostosis,^{2,3} visceral anomalies and tumors. It is considered as a congenital hamartomatous disorder that can affect multiple organ systems and it is characterized by its polymorphism and mosaicism.^{2,3} The cause of PS is unknown. It is thought to be secondary to a postzygotic mutation that survives by mosaicism.⁴

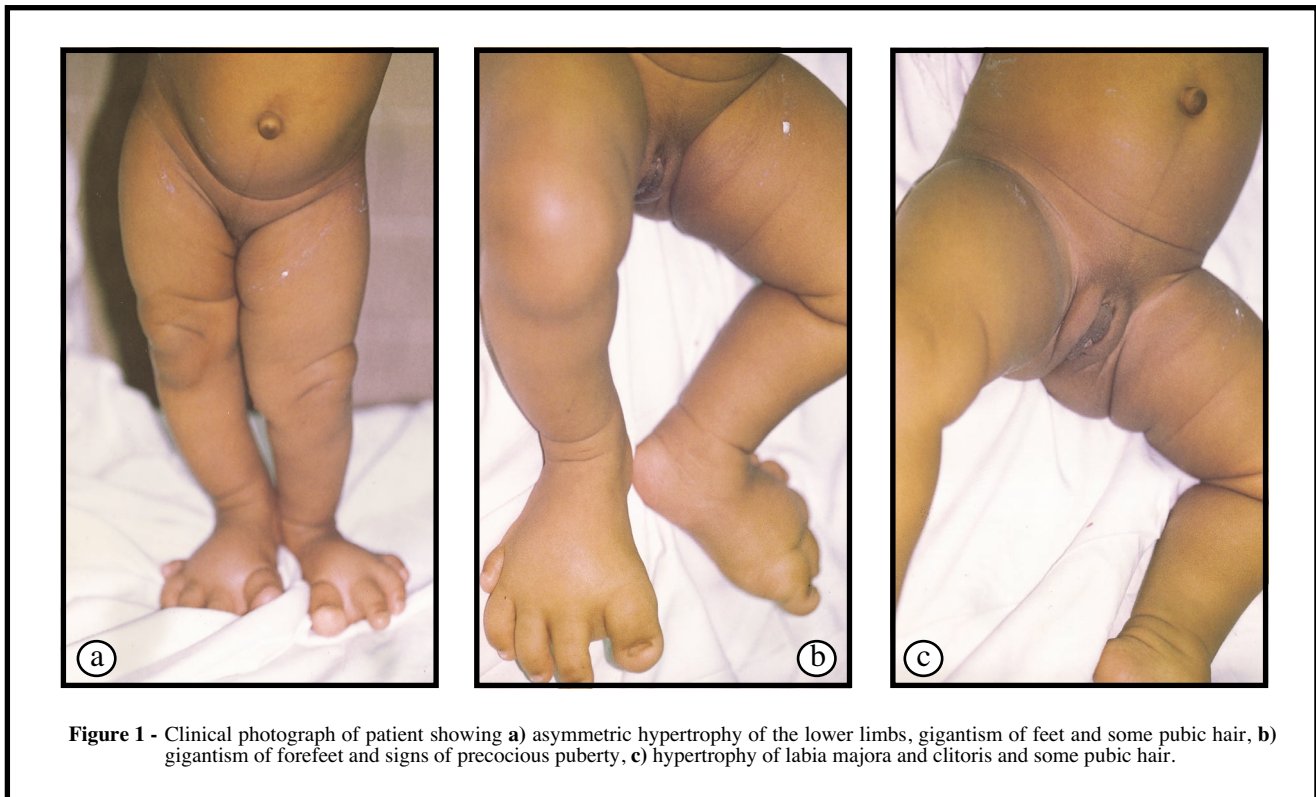
Case report. A 7-month old girl presented with bilateral asymmetrical overgrowth of the lower limbs, gigantism of forefeet with macrodactyly, mass at chest wall, abdominal distention, and signs of precocious puberty. She was born full term, by spontaneous vaginal delivery of normal unrelated parents with no family history of malformation. Her siblings were normal. At birth, she had gigantism of feet, a mass at left chest wall which increased

progressively in size. At 3-months old, she started to have abdominal distention and hyperpigmented genitalia. Examination at the age of 7 months showed weight 97 percentile, height 90 percentile, and head circumference 50 percentile. Bilateral asymmetrical overgrowth of the lower limbs, the right more than the left, gigantism of forefeet with macrodactyly (**Figure 1a & 1b**), on plain films of feet, both soft tissues and bones were hypertrophied. A 2.5x15x20 cm diameter mass at the anterior left chest wall, painless, nodular and soft with port-wine stain 2.5x3.5 cm diameter nevus was seen at the skin covering the mass. Another smaller swelling was present lateral to the right breast. Chest films and computerized tomography (CT) scan revealed the mass was cystic, loculated and containing a tiny calcification. Adjacent muscles, fat, and ribs were hypertrophied. A similar cystic mass was present at superior and middle part of posterior mediastinum (**Figure 2**). There was also a 3x1 cm diameter

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hyperpigmented skin area above the umbilicus. Abdominal examination revealed a 10 cm diameter firm, slightly mobile mass at the lower abdomen. Computerized tomography scan showed a well-defined mass with 2 components: fluid and enhancing soft tissue (**Figure 3**). There were signs of precocious puberty grade 2 including enlarged breasts, hyperpigmented hypertrophied labia majora, hypertrophied clitoris (**Figure 1c**) and vaginal

discharge. Estradiol level was 49.8 pg/ml (n = 5-11 pg/ml) Alpha feto protein of 29.8 IU/ml (6 times more than normal). Human chorionic gonatrophin (HCG), luteinizing hormone, follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH) were normal for age. Bone age was 11 months at chronological age of 7 month. Surgical biopsy from left chest wall mass was carried out and

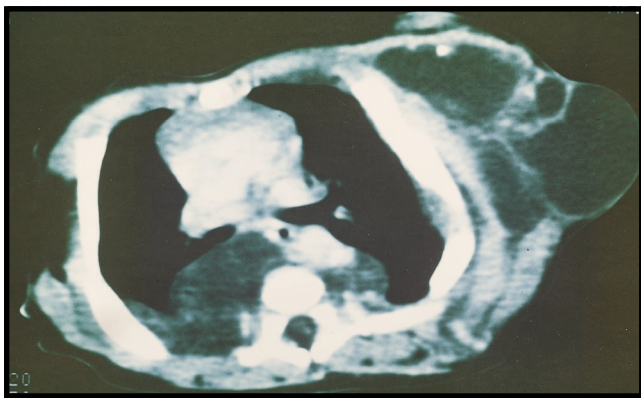


Figure 2 - Computerized tomography scan showing loculated cystic mass at left chest wall containing tiny calcification. (Histopathology: fibrous hamartoma of infancy). Hypertrophy of adjacent muscles, fat and ribs and similar mass at superior mediastinum.

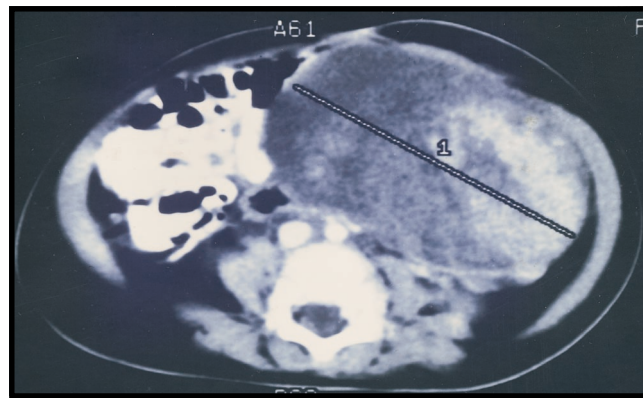


Figure 3 - Computerized tomography scan of the abdomen showing large rounded mass which is composed of 2 components: fluid and enhancing soft tissues. Histopathology: Juvenile granulosa cell tumor of right ovary.

histopathology revealed a fibrous hamartoma of infancy. Surgical exploration of the abdomen revealed that the abdominal mass was arising from the right ovary and histopathological examination revealed a juvenile granulosa cell tumor (JGCT). Postoperatively hormones were as follows: serum estradiol <20pg/ml, alpha feto-protein <1ng/ml (normal). Signs of precocious puberty regressed in 5 months.

Discussion. The presence of soft tissue masses, one in the posterior mediastinum, and 2 at chest wall (fibrous hamartoma of infancy) with hypertrophy of adjacent muscles, fat, and ribs, asymmetrical hypertrophy of lower limbs, gigantism of forefeet and macrodactyly and the skin lesions (port-wine stain and hyperpigmented areas are characteristic of PS. The principal differential diagnosis are the diseases producing hypertrophy of lower limbs, macrodactyly and skin lesions.⁵ Klippel-Trenaunay syndrome is the first differential diagnosis, it produces hemihypertrophy usually monomelic, with vascular abnormalities. However, it was ruled out due to the presence of sub-cutaneous masses, asymmetrical bilateral lower limb hypertrophy, segmental hypertrophy of feet (gigantism) and absence of varices. Neurofibromatosis which may produce, asymmetrical hypertrophy, macrodactyly and skin lesions was not considered due to lack of axillary freckling, neurofibromas and iris nodules. In Maffucci syndrome, the skin lesions (hemangioma or arteriovenous malformation) are associated with enchondromas and sometimes with malignant tumors and dwarfism. Our patient did not present any enchondroma, but with sub-cutaneous masses and hypertrophy.

In macrodystrophia lipomatosis, the gigantism is usually localized in one or more digits of a hand or foot, and rarely involves forearm or an entire limb. The skin lesions are psoriasiform and no angioma or arteriovenous fistula. The differential diagnosis included idiopathic hemihypertrophy (which involve one half of the body) and lymphangiomatosis.⁵ Juvenile granulosa cell tumor⁶ is the most common neoplasm of the ovary with estrogenic manifestations, although it composes only 10% of all ovarian tumors. These tumors have a distinctive histologic features that differ from those encountered in older women (adult granulosa cell tumor). They are usually benign, almost always unilateral. The tumor may be solid, cystic, or both. Half of the cases occur before the age of 10 years old.⁷ Approximately 80% of JGCT result in pseudoprecocious puberty

(isosexual precocity with no ovulation). The other possible presentations of JGCT are abdominal mass and acute abdomen due to rupture of the tumor. Our patient presented with both abdominal mass and precocious puberty. Surgically, the tumor was confined to the ovary and the follow-up 5 months after surgery was unremarkable. To our knowledge this is the first case of PS which developed ovarian granulosa cell tumor and precocious puberty in a female. Hagari⁸ reported a case of PS with precocious development of one breast. The hypertrophy was unilateral and not associated with other signs of precocious puberty. It could be considered as a manifestation of PS. Also Frydman⁹ reported a case of PS with ambiguous genitalia as a local manifestation of PS in the genitalia region and not related to precocious puberty. Endocrine evaluation in that case was normal.

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