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## Severe gynaecological involvement in Proteus Syndrome

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## INTRODUCTION

Proteus Syndrome (PS) is a rare sporadic overgrowth syndrome, initially described in 1979 by Cohen and Hayden as a newly recognised hamartomatous syndrome [Cohen and Hayden, 1979] and by Wiedemann *et al* in 1983 [Wiedemann, 1983]. Approximately 200 cases have been reported, with an estimated prevalence between 1:1,000,000 and 1:10,000,000 [Biesecker and Sapp, 2012]. In 2011, Lindhurst *et al* [2011] demonstrated that PS is caused by a post-zygotic activating LRG\_721t1 (AKT1) mutation (NM\_001014432.1:c.49G>A ; NP\_001014432.1:p.(Glu17Lys)), supposed to be lethal in a non-mosaic state. This gene encodes the AKT1 kinase, a key enzyme for activating the PI3K–AKT pathway involved in cell growth, proliferation, apoptosis and angiogenesis. This mutation has been identified in more than 90% of patients meeting PS diagnostic criteria. An absence of mutation in PS patients may be explained either by a mutation in another gene unknown to date, or inadequate tissue sampling for genetic testing [Lindhurst, 2011].

PS becomes apparent in early infancy (between 6 and 18 months of age) and then rapidly progresses in childhood. After adolescence, it appears to stabilise or progress less rapidly [Valéra, 2015; Marsh, 2008]. It is characterised by the excessive and asymmetric overgrowth of soft tissues, skin and bones. Clinical diagnostic criteria for PS were established in 1999 by Biesecker *et al* [Biesecker, 1999]. Plantar cerebriform connective tissue nevus is considered a pathognomonic lesion [Biesecker and Sapp, 2012]. Patients may also present with a range of tumours (most commonly ovarian cystadenomas, parotid monomorphic adenomas, and meningiomas) [Biesecker and Sapp, 2012; Cohen, 2014], pulmonary abnormalities (bullous lung disease), and a striking predisposition to deep vein thrombosis and pulmonary embolism [Biesecker and Sapp, 2012]. This latter complication, together with infections of the central nervous system, results in substantial morbidity and early mortality

[Cohen, 2001] in PS sufferers. Men and women seem to be equally affected. In women, gynaecological involvement may contribute as reported by Turner *et al* [Turner, 2004]. Here, we report on a novel case of PS with an *AKT1* mutation and with severe gynaecological involvement.

## CLINICAL REPORT

A 26-year-old female patient, born to unrelated, healthy parents, was referred to our department for evaluation of an overgrowth syndrome. At the age of 6, she had developed progressive overgrowth and deformity of the right knee, right hip, left thumb and left first toe. X-rays of the first toe showed upper and lower retrocalcaneal ossified enthesopathy. She also had debilitating scoliosis. At the age of 16, she developed a cerebriform connective tissue nevus on her left foot, associated with subcutaneous hypertrophy and bone abnormalities (X-ray images not available), resulting in an impaired gait. Debulking of this connective tissue nevus was performed at 18 years, but the lesion rapidly relapsed and was still present upon her first visit to our department (Fig 1).

Deep targeted next-generation sequencing of the *AKT1* gene on an Illumina MiSeq® was performed on peripheral blood leukocytes and connective tissue skin from the left foot. The missense heterozygous post-zygotic mutation p.(Glu17Lys) was identified on skin DNA in 6% of alleles, with a mean coverage of 4228X. In contrast, the mutation was not detected from blood leukocytes.

She had suffered from severe and recurrent metrorrhagia since the age of 25, which had never been investigated. Blood analysis (CBC and chemistry including prothrombin, APTT and fibrinogen) was unremarkable except for microcytic anaemia. Pelvic magnetic resonance imaging showed a massive microcystic tumour of the uterine cervix, extending into the uterus. She also had 2 extensive cysts (5 and 10cm in diameter) on the left ovary (Fig. 2 a-

b). A diagnostic hysteroscopy showed a very irregular mass of approximately 10cm. The biopsies performed during the diagnosis were reassuring.

Vascular Doppler ultrasonography of the leg revealed deep vein thrombosis in the left calf. Enoxaparin sodium was initiated, but resulted in increased metrorrhagia, requiring iterative blood transfusions. Low dose oral rapamycin (1mg/d) was initiated, but it was discontinued 45 days later, due to life-threatening metrorrhagia. A complete hysterectomy with left adnexectomy was performed. A histological examination of the surgical specimens revealed an ovarian serous cystadenoma, atypical endocervical hyperplastic glandular polyps, and endometrial hyperplastic polyps without atypia (Fig. 2 c-d). Deep targeted NGS of *AKT1* on DNA from FFPE gynaecological tissue was performed, but no mutation was detected due to poor DNA quality.

## DISCUSSION

Our patient demonstrated 3 specific diagnostic criteria for PS - cerebriform connective tissue nevus, asymmetric and disproportionate overgrowth – specific tumours with ovarian cystadenoma –, and carried the p.(Glu17Lys) *AKT1* mutation in the affected skin.

Although PS was clinically diagnosed, its link with metrorrhagia and the pelvic tumour was not recognised for several months. This may be due to the fact that gynaecological involvement in PS is not well known. However, life-threatening gynaecological involvement in our patient was the principal symptom of Proteus Syndrome, requiring a hysterectomy although she was young and had never had children.

Among 13 reported cases of gynaecological involvement in PS, all were diagnosed at a young age, with 11 patients under 20 years of age (range: 7 months to 30 years). Various clinical symptoms have been reported, including metrorrhagia, and premature puberty. The

nature of gynaecological lesions and their size have rarely been precisely reported. They include ovarian serous cystadenomas (4 cases) [Cohen, 1993; Skovby, 1993; Cohen, 2002; Gordon, 1995], ovarian cysts (3 cases) [Koussef, 1986; Maassen and Voigtlander, 1991; Bouzas, 1993], uterine leiomyomas [Maassen and Voigtlander, 1991], endometrial carcinoma (1 case) [Cohen, 1999], bilateral paraovarian villoglandular endometrioid cystadenomatous tumours of borderline malignancy with neoplastic perineal implant (1 case) [Raju, 2002], juvenile granulosa cell tumours (1 case) [Ezzeldin, 2002], ovarian dermoid cysts and paratubal cysts (1 case) [Hong, 2010], endometrioid paraovarian borderline cystic tumours (1 case) [Vasquez, 2015] and Müllerian papilloma associated with ovarian serous cystadenoma (1 case) [Smrkolj, 2012]. The most common and specific gynaecological lesion reported in PS is ovarian serous cystadenoma. It has therefore been included among specific diagnostic criteria for PS. To our knowledge, the atypical endocervical hyperplastic glandular polyps and endometrial hyperplastic polyps without atypia reported in our patient have not previously been reported. In contrast, such lesions are common in otherwise healthy women, and are a risk factor for endometrial carcinoma.

The p.(Glu17Lys) *AKT1* mutation could not be detected from the gynaecological surgical specimen due to poor DNA quality. The absence of mutation in the samples studied can also result from low mutation levels in tumour specimens, as suggested by Lindhurst *et al* [2014], or non-uniform distribution of mutant cells throughout the lesion, with studied samples from an area with low-level mosaicism. Overgrowth has also been found to be poorly correlated with bulk tissue mutation levels [Doucet, 2016].

Gynaecological lesions often require surgery (ranging from tumour excision to radical surgery depending on their severity). As an alternative to surgery, our decision to treat with rapamycin was based on its inhibition of the PI3KA-AKT1-mTOR pathway. It had previously been reported as effective on pelvic masses in a 9-month-old male with PTEN hamartoma

tumour syndrome, harbouring a germline *PTEN* (c.507delC; p.(Ser170Valfs\*13)) [Marsh, 2008]. In our case, efficacy could not be assessed because of early withdrawal. Other drugs targeting the PI3KA-AKT1-mTOR pathway in overgrowth syndromes are currently under evaluation.

In conclusion, clinicians must be aware that female patients suffering from PS necessitate a thorough evaluation in case of gynaecological symptoms. By reporting on a novel case of PS with gynaecological involvement, we wish to raise awareness on rare yet potentially severe manifestations of this rare and severe genetic mosaic syndrome.

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subcutaneous tumors, macrocephaly or other skull anomalies and possible accelerated growth and visceral affection. Eur. J. Pediatr. 140,5-12.

Keys:

Fig. 1: Cerebriform connective tissue nevus on the left foot, causing an increase in the size of the foot.

Fig. 2: a and b: Pelvis magnetic resonance imaging (T2). a: Voluminous mixed formation (6 x 9.5 x 7cm) of tissue and microcysts, located in the uterine cervix, with endoductal extension (indicated by an arrow). b: Two voluminous cysts (5 and 10cm, respectively) on the left ovary (indicated by an arrow). c and d: Anatomopathological examination. c: Hysterectomy: Arrow: Small internal haemorrhagic cervical polyps \*\*\*: Large exophytic cervical polyps; \*\*\*\*: Left ovary. d: Endocervical polyp: Arrow: Atypical endocervical hyperplasia.



