



# A rare gynecologic presentation of proteus syndrome: A case report

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## ABSTRACT

Proteus syndrome is a genetic condition with an estimated incidence of less than one in a million. This condition is sporadic and presents as progressive, mosaic overgrowth of different tissues. Clinical manifestations are diverse, with the reported involvement of lungs, skin, blood cells, the nervous system and bones. Gynecologic manifestations have rarely been reported in the literature. This case is the first to be reported in the literature of a woman with Proteus syndrome diagnosed in her prepubertal years and presenting at 34 years old with a cervical mass protruding from the vagina. The patient sought medical intervention only after the prolapse was advanced and symptomatic. Management of this case was surgical and consisted of vaginal hysterectomy, with vaginal suspension.

## 1. Introduction

Proteus syndrome is a very rare genetic disorder that presents with progressive overgrowth of different types of tissue, including connective, endothelial and epithelial tissue [1]. The incidence of this syndrome is less than 1 in 1 million people [2]. Internal organs are also affected: overgrowth can affect the spleen, thymus and other organs [3]. Overgrowth often leads to functional disability and physical disfigurement [1]. This condition is also associated with neurological malfunction, including seizures and hearing loss, as well as distinctive facial features that increase the burden of this condition [4]. Manifestations are not evident until late infancy, when symptoms appear. Patients with Proteus syndrome are managed symptomatically and prophylactically by a multidisciplinary team to avoid the complications of tissue overgrowth [1].

The condition is caused by a somatic activating mutation in a gene called AKT1, located on chromosome 14q, associated with mosaicism, and has a sporadic occurrence and progressive course [2,5]. Different allelic mutations can lead to the phenotypic presentation of Proteus syndrome [1]. Systemic associations include pulmonary, dermatologic, hematologic, gynecologic, neurologic and osseous [4]. The mutation involves a kinase specific to serine threonine that signals an activation of AKT/mTOR [5]. This mutation activates growth and slows down apoptosis. The mutation affects selective tissues and is pleiotropic. One of the hallmark features of Proteus syndrome is asymmetric and uneven growth of tissue, which is due to the presence of the Pglu17lys AKT1 mutation involving connective tissue [1]. In the literature, there are only

13 cases with gynecologic involvement in Proteus syndrome [6]. Most of these patients were diagnosed before the age of 11 years [6]. Among gynecologic manifestations of Proteus syndrome, ovarian serous cystadenoma is the most often reported (in 4 of the 13 cases) [6,7]. In most of the reported cases, the gynecologic manifestations of Proteus syndrome ultimately required surgical intervention [6].

## 2. Case presentation

A 34-year-old patient with a known history of Proteus syndrome, diagnosed in infancy secondary to multiple soft-tissue growths requiring surgical intervention on her hands and forehead, presented to the outpatient clinic due to concerns about a prolapse of several years' duration and worsening vaginal discharge of one-year duration. Due to embarrassment, the patient had not sought gynecologic care until the prolapse had resulted in bothering symptoms and discharge. Associated symptoms included back pain, dysuria, frequency, and urgency.

On the first gynecologic evaluation in the clinic, a speculum exam showed there was vaginal discharge and polypoid tissue prolapsing into the field, but it was not possible to fully visualize the cervix secondary to redundant vaginal tissue (Fig. 1).

The tissue was suspected to be consistent with a vaginal wall polyp, endocervical polyp, or even endometrial polyp. A biopsy was not obtained in office, in order to mitigate bleeding risks for the patient as she was concurrently on anticoagulation therapy for a history of DVT. The patient was scheduled for an exam under anesthesia, hysteroscopy, and biopsy of the prolapsing mass.

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Fig. 1. Vaginal prolapse on presentation.

Prior to the procedure, transvaginal ultrasound demonstrated a defined area of multi-lobulated complex echogenicity in the vaginal wall, not well visualized due to body habitus, with a markedly thickened and heterogeneous endometrium measuring up to 3.3 cm in double thickness. These findings were said to be suggestive of endometrial neoplasia or large polyp. Exam under anesthesia, vaginoscopy, hysteroscopy, and biopsies were performed. The findings included a large exophytic polypoid mass. The clinical findings were consistent with cervical ectropion and copious mucous. A pedunculated polyp on the mass was excised and sent to pathology. Analysis showed benign non-dysplastic cervical polyp, with chronic reactive and vasocongestive changes. Due to the patient's BMI of 64 and history of abdominal hernia, consultation with a minimally invasive gynecologic surgeon was requested for definitive surgical management.

A week later the patient presented to the emergency department with worsening dyspnea and was admitted for COPD exacerbation with recurrent DVT and UTI secondary to urinary retention. She was started on empiric broad-spectrum antibiotics for her UTI and gynecologic consultation was requested due to worsening lower abdominal pain and malodorous vaginal discharge. A CT scan of the abdomen and pelvis was obtained to rule out infection in the context of the recent gynecologic procedure, and this did not show any acute abnormality. The initial plan was for outpatient follow-up and discussion of a definitive surgical management with the appropriate surgeon; however, the patient reported worsening pain, so a second EUA was performed with hysteroscopy, cystoscopy, and biopsies with an attempt at reduction of the prolapsing mass. During this procedure, the previous findings were noted in addition to multiple polypoid growths emanating from the endocervical canal into the cervical os, polypoid ectocervix, and multiple endometrial polypoid growths inside the endometrial cavity with small calcifications along the endometrial lining.

Cervical and endometrial biopsies were taken. Pathology showed a large endocervical polyp with prominent squamous metaplasia and microglandular hyperplasia, and cervical biopsy showed a chronically inflamed cervical epithelium with prominent squamous metaplasia and reactive-type nuclear change.

The patient was discharged home and after her UTI resolved she returned for scheduled vaginal hysterectomy, with vaginal suspension and cystoscopy. Surgical pathology of the cervix showed focal cervical

intraepithelial neoplasia 2–3 (CIN 2–3) with microglandular hyperplasia and her uterus showed a benign endometrial polyp. Immunostains showed the squamous epithelium with diffuse positive staining for Ki-67.

The cervical polypoid mass measured approximately  $12 \times 7.5 \times 4.3$  cm with the attached uterus,  $11 \times 6 \times 4.8$  cm (Fig. 2). The entire specimen weighed 292 g (Fig. 3). She tolerated the procedure well and was discharged on post-operative day 3.

### 3. Discussion

The patient reported a diagnosis of Proteus syndrome given in her prepubertal years, at an outside institution. She met the clinical criteria of progressive and sporadic occurrence of lesions in her limbs, and growth of joints that are asymmetric, disproportionate with linear epidermal nevus in addition to hyperostosis of the auditory canal causing deafness in left ear; additionally she had overgrowth of viscera noted by splenomegaly on imaging, along with the gynecologic tumor that she presented with. These criteria were described by Biesecker [8].

This case highlights a unique gynecologic presentation of Proteus syndrome which could be mistaken for other gynecologic neoplasms. Although Proteus syndrome was already diagnosed and the patient had been frequently evaluated in the inpatient setting for pulmonary complications, she had never had a gynecologic evaluation due to the rare association of the syndrome with gynecologic manifestations. No typical gynecologic involvement in Proteus syndrome is well known; cases in the literature have reported associated ovarian serous cystadenomas [6], ovarian cysts [9], and uterine leiomyomas [10]. In the case of a patient with a prolapsing uterus with an irregular contour and multiple



Fig. 2. Specimen showing uterus and cervix in a coronal plane.



Fig. 3. Specimen after hysterectomy showing uterus and cervix.

tissue-like growths, differential diagnosis typically includes fibroids, neoplasm, and polyps. Typical evaluation consists of transvaginal ultrasound, pelvic exam, and surgical management, including hysteroscopy with dilation and curettage to aid in diagnosis. Initial evaluation was completed with the intention of ruling out malignancy.

Management options for the gynecologic presentation of Proteus syndrome often include surgical intervention, including hysterectomy, tumor excision, or oophorectomy, as well as medical intervention, depending on the extent of the disease. Genetic testing was not repeated in this case, as the patient already had the diagnosis, and she met the clinical criteria described by Biesecker; in addition, testing for the suspected mutation would not change management. To our knowledge and as pathology suggested, this is the first reported case of microglandular hyperplasia of the cervix with CIN 2,3 and endometrial polyp resulting in vaginal prolapse in a female patient with Proteus syndrome. Surgery was uneventful. The patient was discharged home on postoperative day 3. As this is a rare condition, additional reports would be helpful to aid in more efficient diagnosis as well as to explore additional treatment options.

#### 4. Conclusion

Proteus syndrome has a diverse spectrum of presentation. Thorough clinical examination is crucial to identify multiple organ involvement. Gynecologic assessment is essential in evaluation and referral to a specialist is of great importance to manage gynecologic overgrowth at early stage, thereby avoiding prolapse, mass symptoms and their complications as urinary tract infections. Raising awareness of the rare but severe manifestations of this rare mosaic syndrome is beneficial.

#### Contributors

Bassel Abouzeid contributed to the concept of the case report, drafting, and final revision, and was involved in patient care.

Amanda Buck contributed to the concept of the case report, drafting, and final revision, and was involved in patient care.

Samantha Haikal contributed to the concept of the case report, drafting, and final revision.

Rayan Elkattah contributed to the concept of the case report, drafting, and final revision, and was involved in patient care.

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#### Patient consent

The patient provided consent for images and clinical information to be reported in a medical publication. The patient also understood that the material may be published in a journal and may be seen by the general public.

#### Provenance and peer review

This article was not commissioned and was peer reviewed.

#### Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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