Müllerian papilloma in a patient with Proteus syndrome: case report and review of the literature

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Summary

Background: Müllerian papilloma is a rare benign tumor of the female genital tract. It mostly affects girls less than five years old. After the treatment long-term follow-up is needed as there is a chance of recurrence, but even then the prognosis is excellent. *Case:* A 19-year-old girl with Proteus syndrome presented with vaginal bleeding. The histological examination revealed Müllerian papilloma of the uterine cervix and large bilateral ovarian cystadenomas. The patient was treated with a radical operation, because there were signs of more aggressive behavior in the tumor. The patient is alive and free of disease five years after the operation. *Conclusion:* The medical care of patients affected by rare disorders depends heavily on experiences gained from cases published in the medical literature. Since there is not much experience with tumors in Proteus syndrome we believe that this case can aid in shedding light on this subject.

Key words: Müllerian papilloma; Proteus syndrome.

Introduction

Müllerian papilloma is a rare benign tumor of the female genital tract. Its precise incidence is not known as there are only case reports in the literature [1-5]. It was first described in 1951 by James who observed a benign polypoid tumor of the uterine cervix in a three-year-old girl [6]. For a long time there has been disagreement about the histogenesis of this tumor. The first descriptions named it benign mesonephric papilloma as it was thought to arise from remnants of an involuted mesonephric duct [7-9]. Ulbright in 1981 was the first to propose that the tumor was of Müllerian origin [8]. Later on there were several reports on immunohistochemical and ultrastructural findings that confirmed this hypothesis and thus the term benign Müllerian papilloma was applid [1, 2, 4].

It mainly occurs in prepubertal girls less than five years of age, and the major symptom is intermittent and noncyclical vaginal bleeding. It is less common in postmenarchal girls where the main symptom is intermenstrual or contact bleeding [1, 2, 10]. It is important that in prepubertal groups, the tumor can clinically and histologically mimic malignant embryonal rhabdomyosarcoma (sarcoma botryoides), a more common and aggressive tumor in this age group. Moreover, the differential diagnosis includes papilloma, condyloma, papillary carcinoma (villoglandular and pure papillary), verrucous carcinoma, clear cell adenocarcinoma and endodermal sinus tumor [11]. Treatment of Müllerian papilloma is usually by local excision, avulsion of the tumor with forceps, and ligation, and also laser surgery or fulguration is an option. Nevertheless long-term follow-up is needed as there is a chance of recurrence but even then the prognosis is excellent [2].

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Proteus syndrome is a rare disorder of progressive, asymmetric and disproportionate overgrowth of tissue [12]. Commonly involved tissues include connective tissue, bone, fat and skin but it appears that it can affect any tissue. It is assumed that progressive tissue overgrowth usually plateaus after adolescence [12]. As a discrete clinical entity it was first described in the literature in 1979 by Cohen and Hayden [13] and assigned its name in 1983 by Wiedemann *et al*. to denote its variability in clinical expression [14]. There are less than 100 cases published in the literature [15]. The cause is still not known but it is thought to arise from a postzygotic somatic mutation as the condition would be lethal in the nonmosaic state [16]. There is a great variability in clinical presentation of Proteus syndrome thus diagnosis can sometimes be difficult to make as there are no diagnostic tests available at this time. Table 1 lists the revised diagnostic criteria for Proteus syndrome currently used [17]. It appears that this syndrome has for a long time had a suspected but not proven predisposition to various tumors [17]. Most apparent is the association with bilateral ovarian cystadenomas and monomorphic adenomas of the parotid gland [18]. These two types of tumors are so specific for Proteus syndrome that they are included in the diagnostic criteria [17].

We present a case of Müllerian papilloma in a patient with Proteus syndrome. The case is unique in that it was a rare benign tumor occurring in a rare clinical syndrome. Herein, the clinical findings of the patient are discussed and the current clinical diagnostic criteria for Müllerian papilloma reviewed.

Case Report

A 19-year-old girl was referred to our gynecological department because of irregular menstrual and contact bleeding for the previous three months. In her past medical history it was notice-

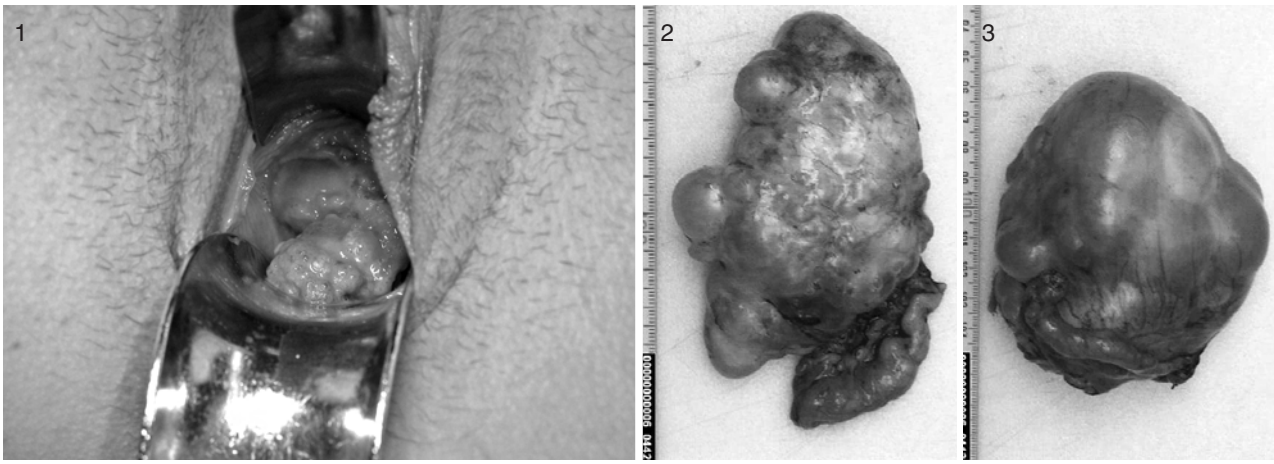

Figure 1. — The Müllerian papilloma of the uterine cervix in our patient.
Figure 2 and 3. — The removed bilateral cystadenomas of the ovaries in our patient.

able that at the age of one she had undergone a vaginoscopy because of vaginal bleeding, the cause of which was vaginitis. She was born with a congenital anomaly of her left hand. For the correction of macrodactily, she had had ten reconstructive operations of her left hand and at the age of seven she was diagnosed with Proteus syndrome. As a child she had asthma, but at the beginning of puberty the condition ceased. Her sexual development was normal, periods started at the age of 13 and until three months before they had been regular. She reported stronger vaginal discharge over the last two years but it was never bloody.

A gynecological examination under general anesthesia revealed the presence of a 2 x 2 cm papillary mass on the anterior portion of the uterine cervix. There were numerous submucousal papillary formations up to 5 mm on the anterior vaginal wall that spread to the left vaginal fornix. There was a normal sized uterus and two intraabdominal tumors palpated and no signs of parametrial infiltration. On magnetic resonance imaging a tumor in the uterine cervix and large ovarian masses on both sides were seen. The mass on the left side was 8 x 7 cm and on the right side 10 x 12 cm. The biopsy of the cervical tumor at first revealed a well differentiated villoglandular mucinous adenocarcinoma, but in the differential diagnosis there was also a Müllerian papilloma. After the revision of histology by three different pathologists, including one abroad, the diagnosis was confirmed as Müllerian papilloma with intense squamous meta-

Table 1. — *Revised Proteus syndrome diagnostic criteria* [17].

General criteria
All of the following:
- Mosaic distribution of lesions
- Sporadic occurrence
- Progressive course

Specific criteria categories
- A. 1. Cerebriform connective tissue nevus[a]
- B. 1. Linear epidermal nevus
- 2. Asymemtric disproportionate overgrowth[b]
  - One or more:
  - a. Limbs:
    - Arms/legs
    - Hands/feet/digits
    - Extremities
  - b. Hyperostoses of the skull
  - c. External auditory meatus
  - d. Megaspondylodysplasia
  - e. Viscera:
    - Spleen/thymus
- 3. Specific tumors before 2nd decade
  - One of the following:
  - a. Ovarian cystadenoma
  - b. Parotid monomorphic adenoma

Specific criteria
Either
- Category A or,
- Two from category B or,
- Three from category C

- C.1. Dysregulated adipose tissue
  - Either one:
  - a. Lipomas
  - b. Regional absence of fat
- 2. Vascular malformations
  - One or more:
  - a. Capillary malformation
  - b. Venous malformation
  - c. Lymphatic malformation
- 3. Lung cyst
- 4. Facial phenotype[c]
  - All:
  - a. Dolichocephaly
  - b. Long face
  - c. Down slanting palpebral fissures and/or minor ptosis
  - d. Low nasal bridge
  - e. Wide or anteverted nares
  - f. Open mouth at rest

To make a diagnosis of PS all the general criteria need to be available and also various specific criteria.
[a] Cerebriform connective tissue nevi are skin lesions characterized by deep grooves and gyrations as seen on the surface of the brain.
[b] Asymmetric, disproportionate overgrowth should be carefully distinguished from asymmetric, proportionate overgrowth.
[c] The facial phenotype has been found, to date, only in PS patients who have mental deficiency and, in some cases, seizures and/or brain malformations.

Table 2. — *Müllerian papilloma (cases reported in the English literature).*

Author	Patient age	Symptome	Location	Macroscopic apperance	Treatment	Outcome	Remarks
James [6]	3 years	Bleeding	Cervix	Small papilloma like tumor, friable, bleed easily	Local excision	NSR, 6 months/10 years*(selzer)	
Novak et al. [9]	14 months	Bleeding, vaginal mass	Vagina	Liverlike protrusion from the vagina	Local excision	NSR, 6 months	
Selzer and Nelson [10]	3 years	Bleeding	Cervix	Papillomatous growth	Local excision	NSR, 8,5 years	
Selzer and Nelson [10]	3 years	Bleeding	Cervix	Polypoid structure, friable, bleed on manipulation	Local excision	NSR 1,5 year after second excision/2 years	6 months from first treatment small polypoid mass on the cervix seen, the base of the polyp was excised
Janovski and Kasdon [7]	5 years	Bleeding	Cervix	1 cm polypoid mass on the posterior cervical lip and smaller on the anterior cervical lip growing into the anterior vaginal fornix	Local excision of both lesions	NSR, 4 months	The first diagnose was sarcoma botryoides, 5 months later 1 cm papillomatous mass in the vaginal roof was seen, due to disagreement regarding nature of the lesion exploratory laparotomy was done, at operation no tumor was found
Norris and Taylor [25]	1 day	Vaginal mass	Vagina	Grapelike mass protruding from introitus	Biopsy	Mass regressed, NSR, 8 years	
Norris and Taylor[25]	1 day	Vaginal mass	Vagina	0, 5 cm soft nodule	Local excision	NSR, 8 months	
Ulbright et al. [8]	5 years	Vaginal mass	Vagina	5 x 3 cm mass located in the vaginal wall, vaginal mucosa was intact and uninvolved	Resection of the tumor through abdominal approach	NSR, 1 year	
Andrews et al. [21]	3 years	Bleeding	Cervix	2 x 1.5 x 0.5 cm red, soft polyp	Local excision	NSR, 10 months	
Lüttges and Lübke [4]	5 years	Bleeding	Vagina	0.8 cm polypoid tumor, bleeding on contact	Avulsion with forceps	Not stated	2 years later recurrent 1,8 cm papillary tumor at the site of former excision
Schmedding et al. [1]	2 years	Bleeding	Cervix	Soft, red polyp, bleed easily	Local excision	NSR, 6 months	
Smith et al. [22]	4 years	Bleeding, pain	Cervix	Papillary lesion	Biopsy, 1 year later rebiopsy and fulguration	No bleeding or pain, 11 months	1 year after treatment recurrence, biopsy without complete excision (concern of significant cervical destruction)
Dobbs et al. [23], Abu et al.	52 years	Bleeding	Vagina	Polypoid mass	Ligation, local excision, biopsy	Over the period of 40 years more than 10 recurrences	At the age of 49 borderline malignant changes in the papilloma noted, due to severe cerebral palsy radical treatment not possible, at biopsy 3 years later areas of clear cell carcinoma
McCluggage et al. [19]	24 years	Pain	Vaginal	4 cm intramural nodule with overlying mucosa	Local excision	Not stated	Primigravida in 16th week of pregnancy
Cohen et al. [20]	13 years	Vaginal mass	Vagina	13 x 10 mm polypoid lesion with a cauliflower-like dark red surface	Not stated	Not stated	Acetaminophen-related Lyell's syndrome a year before with numerous pigmented scars all over the body, melanin in epithelial cells and melanocytes present in the tumor
Arbo et al. [26]	2 years	Bleeding	Vagina	Polypoid glandular epithelium	Local excision	Not stated	
Mierau et al. [2]	4 years	Bleeding	Vagina	4.8 x 0.9 x 0.9 cm grapelike mass	Local excision	NSR, 4 years	
Mierau et al. [2]	9 days	Bleeding	Vagina	'minute' erosion on the vaginal wall	Local excision	NSR, 4 years	Tumor extended to the margins of the specimen, no additional therapy
Lane et al. [5]	18 months	Bleeding	Cervix	1 cm frond-like papillary lesion	Fulguration	NSR, 8 months	On CT multiple simple cyst in left kidney, 11 months later radical nephrectomy for Wilms tumor.
Hollowell et al. [11]	15 months	Bleeding	Cervix	Villous lesion	Local excision	NSR, 6 weeks	
Reck-Burneo et al. [27]	2 years	Bleeding	Vagina	4 cm mildly lobulated, pedunculated mass	Local excision	NSR, 3 years	
Tumini et al. [28]	9 years	Bleeding	Vagina	Papillary mass	Local excision	Not stated	

Note: NSR no signs of recurrence

plasia, high proliferative index and focally atypical cells, which could have indicated severe inflammation or the beginning of malignant progression. The tumor was strongly positive for CA 125 and negative for CD 10, while estrogen and progesterone receptors were uniform and strongly positive.

Due to large bilateral ovarian tumors and Müllerian papilloma with high mitotic activity and focus of atypical cells, we performed abdominal hysterectomy with bilateral salpingo-oophorectomy. Both ovarian tumors were sent for frozen section biopsy. The definite histology was Müllerian papilloma of the uterine cervix and bilateral cystadenomas of the ovaries with a focus of high epithelial cell atypia in the right one. Figures 1-3 show the Müllerian papilloma of the uterine cervix and the removed bilateral cystadenomas of the ovaries in our patient. The operation and postoperative period were without complications. Six months later we performed another procedure to eliminate the small papillomas on the anterior vaginal wall. We biopsied one and performed laser destruction of the others. Histology of the biopsied tissue was only squamous epithelium. A similar procedure was also performed 4.5 years after the first operation, and histology of the biopsied tissue was vaginal adenosis.

The patient is alive and well with no signs of recurrence of the disease five years after the surgery.

Discussion

Müllerian papilloma is a rare lesion of the uterine cervix and vagina [1, 2]. To date only 22 cases have been published in the English literature (Table 2). It occurs almost exclusively in children usually between two and five years of age; occasionally in adults. The main symptom is vaginal bleeding [3], sometimes pain [19] or a painless vaginal mass [20] could be the leading symptom. Macroscopically tumor usually appears as a grape-like cluster or papillary mass present on the cervix or vagina but it could also represent as a small erosion [2] or intramural nodule [8, 19]. Tumor could be located on the cervix or vagina and of all published cases 13 were vaginal tumors and nine were cervical. Histologically it is most often described as papillary structures composed of branching fronds with fibrovascular cores lined by cuboidal to columnar epithelium [1, 2, 4]. There have only been three published articles [2, 8, 21] on ultrastructural findings in Müllerian papilloma, the most recent and detailed being one from Mierau *et al*. They were the first who demonstrated the presence of mucin and glycogen granules in neoplastic cells, which further supported the Müllerian origin of this tumor. The second important thing they stated – that the histological description of this tumor was composed of a fibrovascular core is misleading, since the spindle cells within the supporting stalk did not display the features of fibroblasts and virtually no collagen was found within the extracellular matrix. Immunohistochemical studies showed the surface epithelial cells to be reactive to cytokeratin, epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA). The subepithelial spindle cells were reactive for vimentin, but not for muscle specific actin, desmin or myoglobin [2].

There are few cases of recurrences of Müllerian papilloma published in the literature [22-24] and in all cases simple excision was a suitable mode of treatment. Even incomplete excision has been reported to be curative for tumors presenting during the newborn period [2]. It is thought that maternal hormones induce the intrauterine development of tumors seen in infants and since only those who represent with bleeding come to our attention it is possible that some of these tumors spontaneously regress [2]. Only one case of malignant transformation of Müllerian papilloma was observed following a series of recurrences over a period of 40 years [2].

It has been strongly suspected, but not a proven predisposition to tumors in Proteus syndrome [18]. Knudson's two-hit hypothesis for neoplasms developing in Proteus syndrome was proposed [18]. Regarding this hypothesis one allele for the postulated 'proteus gene' might mutate in a somatic cell, resulting in the somatic mosaicism of Proteus syndrome. The first hit would be cellular overgrowth, producing generally known manifestations of Proteus syndrome-like hamartomas. In some patients, a second hit on the other 'Proteus allele' might result in the uninhibited growth of neoplasms [18]. To our knowledge Proteus syndrome has never been associated with Müllerian papilloma.

In our case the proliferative index was high and there were focally atypical cells in the tumor, which could have indicated severe inflammation or the beginning of malignant progression so the future behavior of the tumor was difficult to predict; there were also large bilateral ovarian masses present and we had to carry out a more radical procedure. Also the patient was diagnosed with Proteus syndrome and since we do not know the behavior of tumors in this syndrome this added to our decision to perform a more radical operation.

Conclusions

The medical care of patients affected by rare disorders depends heavily on experiences gained from cases published in the medical literature. We believe that this is the first case of a Müllerian papilloma described in a patient with Proteus syndrome. The case is unique as there was the occurrence of a rare benign tumor in a rare syndrome. Since there is litle information on tumors in Proteus syndrome we believe that this case can aid in shedding light on the subject.

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