



Ectopic Prostate in the Uterine Cervix / Female Genital Tract Including Vagina and Vulva: A Review of the Literature

Anthony Kodzo-Grey Venyo^{1*}

¹Department of Urology, North Manchester General Hospital, Manchester, United Kingdom.

Author's contribution

This work was carried out by the sole author, who designed the review article, did the literature search, obtained copy right permission to use the figures from Professor Dilek Ertoy Baydar to reproduce the figures used in this paper, wrote as well as revised the manuscript for publication. Professor Dilek Ertoy Baydar kindly provided and personally reported on the characteristic features of all the figures.

Article Information

DOI: 10.9734/BJMMR/2015/18101

Editor(s):

(1) Andrea Tinelli, Lab. of Experimental Endoscopic Surgery, Imaging, Minimally Invasive Therapy & Technology, Department of Gynecology and Obstetric, Vito Fazzi Hospital, Lecce, Italy.

Reviewers:

- (1) Anonymous, Egypt.
(2) Sahar Mohamed Nour El-Din, Ain Shams University, Egypt.
(3) Kulvinder Kaur, Department of Obst and Gynae, Centre for Human Reproduction, India.
(4) Anonymous, Portugal.

Complete Peer review History: <http://sciencedomain.org/review-history/10273>

Review Article

Received 3rd April 2015
Accepted 10th June 2015
Published 23rd July 2015

ABSTRACT

Background: Men are known to have prostate glands but not women. The thought of prostate gland occurring in the female genital tract in women would be petrifying to all clinicians and people who are not aware of its biological behavior. Ectopic prostate in the uterine cervix (EPIUC) and the female genital tract (FGT) is very rare.

Aim: To review the literature on EPIUC/FGT and to document its biological behavior.

Methods: Information obtained from 17 references, was used for the literature review on EPIUC/FGT.

Results: Few cases of EPIUC/FGT have been reported at ages ranging between 21 and 82 years EPIUCs/FGTs may be diagnosed incidentally in biopsies of the cervix/vagina/vulva, or in hysterectomy specimens or they may mimic leiomyomas. Histological examination of cervical biopsies or of the cervix in hysterectomy specimens reveals ducts and acini some papillary or cribriform, with prominent squamous metaplasia EPIUCs/FGTs show positive Immunohisto-

*Corresponding author: Email: akodzogrey@yahoo.co.uk, akvenyo@outlook.com;

chemical staining for prostate specific antigen (PSA), prostatic-specific acid phosphatase (PSAP [PAP]), high molecular weight keratin (for basal cells). EPIUCs reported so far have exhibited benign behavior.

Conclusions: Information obtained from the literature would indicate that EPIUCs / FGTs are rare and so far have exhibited benign behavior. Clinicians should report cases of EPIUC/FGT in order to establish whether or not EPIUCs/FGTs may or may not develop into carcinomas in the future.

Keywords: Ectopic prostate in uterine cervix; cone biopsy of cervix; hysterectomy; leiomyoma; Immunohistochemistry; PSA; PSAP; 34 β E12.

1. INTRODUCTION

A female staff whilst looking after a male patient (in the recovery ward) who developed clot retention of urine following trans-urethral resection of prostate once remarked that she was reassured that as a female she would never in her life develop any problem relating to the prostate gland. The author replied are you sure that a lady can never have a prostate gland? The staff responded yes. The ensuing paper which is divided into two parts: (A) General overview, and (B) Discussions and narrations from reported cases which contains a review of the literature on ectopic prostate in the uterine cervix.

2. METHODS

Various internet search engines were used including PUBMED, Google and google scholar to identify reported cases and case series related to ectopic prostate in the uterine cervix. In total 17 references were identified related to ectopic prostate in the uterine cervix and these were used for the literature review.

2.1 General Overview

- Ectopic prostate occurring in the uterine cervix is rare and less than 70 cases have been reported [1].
- Ectopic prostate gland is most often located in the urinary bladder of males [1].
- Ectopic prostate in the cervix may be similar to multi-locular cystadenoma of the prostate, even though distinct from the prostate [1].
- Prostatic differentiation has also been reported in ovarian mesonephric remnants [1].

2.1.1 Aetiology

Some of the postulates regarding the aetiology of ectopic prostate in the cervix include:

- The suggestion that most ectopic prostates most likely represent the persistence of embryonic structures [1,2]
- The suggestion that they represent a developmental anomaly [3]
- The suggestion that they emanate from metaplasia of preexisting endocervical glands [3] or metaplastic induction of prostatic tissue by mesonephric remnants [4].
- The suggestion that they are derivatives of mesonephric remnants [3].

2.1.2 Presentation

Ectopic prostate in the uterine cervix have been incidental findings from cone biopsy or loop biopsy specimens taken for high grade dysplasia [1,5]. Ectopic prostate had also been reported in a hysterectomy specimen as an incidental finding [3]. Ectopic prostate in uterine cervix may mimic uterine fibroids [5].

2.1.3 Age

EPIUC have been reported in women aged between 21 and 82 years.

Histopathology findings (see Figs. 1 and 2 for haematoxylin and eosin staining features, Fig. 3 for mucicarmine and Fig. 4 for immunohistochemistry for PSA).

2.1.3.1 Microscopic characteristics

Microscopic examination of ectopic prostate reveals:

- Ducts and acini [1] some papillary or cribriform, with prominent squamous metaplasia [1] (see Figs. 1 and 2).

2.1.3.2 Stains for mucin

- Mucicarmine stains would usually demonstrate absence of intracytoplasmic mucin in the atypical prostatic glands (see Fig. 3).

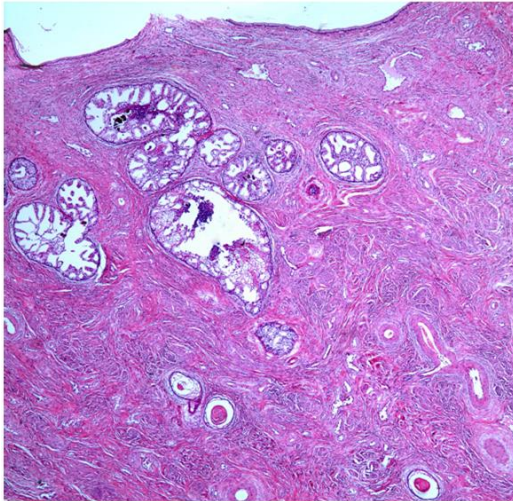


Fig. 1. Ectopic prostate in uterine cervix: haematoxylin and eosin stain x 40 magnification

Microscopic examination of the cervix, which shows the stroma containing abnormal glandular structures but the surface epithelium of the uterine-cervix, is looking unremarkable. The atypical glands are variable in size and have papillary infolding and cribriform structure. Reproduced from the archives of Professor Dilek Ertoy Baydar, Professor of Pathology, Hacettepe University Hospital, Ankara, Turkey, who had previously encountered a case of ectopic prostate in uterine cervix and jointly reported the case as illustrated in reference 11 but this figure is different from the figures in the publication. This figure was kindly provided by Professor Baydar to illustrate characteristic features of ectopic prostate in the uterine cervix to readers. Copy right to the figures is only for single use for this article and any subsequent reproduction of the figures would require copyright permission from Professor Dilek Ertoy Baydar

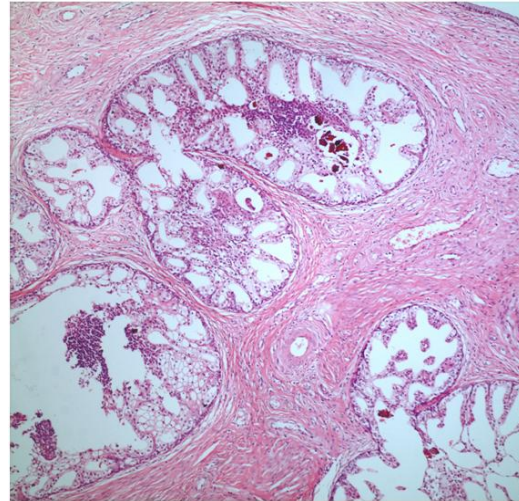


Fig. 2. Ectopic prostate in uterine cervix: haematoxylin and eosin stain (larger magnification of part of figure 1 x 100 magnification)

Microscopic examination of the cervix, which shows the stroma containing abnormal glandular structures. This higher magnification picture also more details of the atypical glands which are variable in size and have papillary infolding and cribriform structure. Reproduced from the archives of Professor Dilek Ertoy Baydar, Professor of Pathology, Hacettepe University Hospital Ankara, Turkey, who had previously encountered a case of ectopic prostate in uterine cervix and jointly reported the case as illustrated in reference 11 but this figure, is different from the figures in the publication. This figure was kindly provided by Professor Baydar to illustrate characteristic features of ectopic prostate in the uterine cervix to readers. Copy right to the figures is only for single use for this article and any subsequent reproduction of the figures would require copyright permission from Professor Dilek Ertoy Baydar

2.1.3.3 Immunohistochemical staining characteristics

Positive Immunohistochemical staining Ectopic prostate in cervix stain positively for

- PSA, [1] (see Fig. 4)
- PSAP (PAP) [1]
- High molecular weight keratin (for basal cells) [1]

2.1.3.4 Prognosis

The EPIUCs/FGTs that have been reported so far have been associated with benign behavior without recurrence; however, there is paucity of long-term follow-up information.

2.2 Discussions and Narrations from Some Reported Cases of Ectopic Prostate in the Uterine Cervix and Female Genital Tract Including the Vagina, Vulva and Animal Studies (see Table 1 for a Summary of Some of the Reported Cases)

Larraza-Hernandez et al. [6] in 1997 reported a case of EPIUC which they had diagnosed in a 38-year-old lady. They stated that histological examination showed that the cervical lesion was comprised of a cluster of benign prostatic glands with cribriform and papillary patterns and that focal squamous metaplasia occupied the superficial endocervical stroma. They also

reported that immunohistochemical staining of the specimen exhibited positive staining for prostatic-specific antigen (PSA) and prostatic-specific acid phosphatase (PSAP). It was the opinion of Larraza-Henandez et al. [6] that EPIUC could represent an embryonic rest (mesonephric rest) and that the lesion could be confused with a fibroid, microglandular hyperplasia, or adenocarcinoma in situ. They stated that their case was the first case of EPIUC to be reported in the literature.

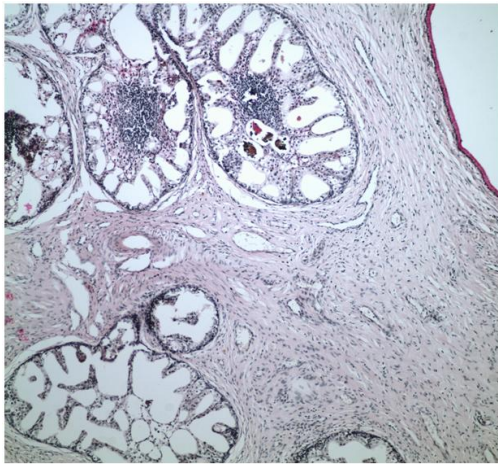


Fig. 3. Ectopic prostate in uterine cervix: Mucicarmine x 100 magnification. The illustrated prostatic glands are devoid of intra-cytoplasmic mucin

Reproduced from the archives of Professor Dilek Ertoy Baydar, Professor of Pathology, Hacettepe University Hospital, Ankara, Turkey, who had previously encountered a case of ectopic prostate in uterine cervix and jointly reported the case as illustrated in reference 11 but this figure is different from the figures in the publication. This figure was kindly provided by Professor Baydar to illustrate characteristic features of ectopic prostate in the uterine cervix to readers. Copy right to the figures is only for single use for this article and any subsequent reproduction of the figures would require copyright permission from Professor Dilek Ertoy Baydar

Nucci et al. [5] reported cases of prostatic tissue located in the uterine cervix (EPIUCs) of four patients whose ages ranged between 22 years and 77 years. They reported that three of the EPIUCs had been found incidentally in loop excisions (in two of the patients) and in cone biopsy specimen (in one patient) of the cervix for high-grade squamous dysplasia. They stated that one of the patients had presented with a mass in the cervix, which in the first instance was considered to be possibly a fibroid.

Microscopic examination of the prostatic tissue from the cervix showed acini and ducts. Some of the acini and ducts were reported to have exhibited papillary or cribriform patterns. Squamous metaplasia was noted to be prominent in all the cases. There was no Wolffian duct tissue present in any of the tissues. Immunohistochemical staining of specimens was undertaken in all the cases these showed that the glandular epithelium was positive for prostatic acid phosphatase (PAP) and prostate-specific antigen (PSA). Nucci et al. [5] further stated that:

- High-molecular weight keratin which was performed in two cases, had highlighted basal cells in a manner which mimicked normal prostate
- These cases are unusual and only one had previously been documented/ reported prior to their publication. The rarity of these types of cases would in addition contribute to the difficulty in the interpretation of benign glandular lesions of the cervix.

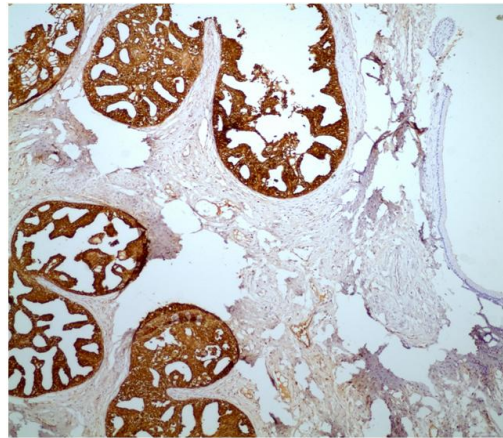


Fig. 4. Ectopic prostate in uterine cervix: Immunohistochemistry with anti-prostate specific antigen (PSA) antibody x 100 showing positive staining for PSA

Reproduced from the archives of Professor Dilek Ertoy Baydar, Professor of Pathology, Hacettepe University Hospital Ankara, Turkey, who had previously encountered a case of ectopic prostate in uterine cervix and jointly reported the case as illustrated in reference 11 but this figure, is different from the figures in the publication. This figure was kindly provided by Professor Baydar to illustrate characteristic features of ectopic prostate in the uterine cervix to readers. Copy right to the figures is only for single use for this article and any subsequent reproduction of the figures would require copyright permission from Professor Dilek Ertoy Baydar

Kim et al. [7] reported a 23-year-old woman who had adrenogenital syndrome and who was found to have extensive transitional cell metaplasia (TCM) and ectopic prostate tissue in the uterine cervix (EPIUC). They stated that:

- A case of ectopic prostatic tissue in the uterine cervix (EPIUC) had previously been reported in a patient with female pseudohermaphroditism and in their opinion their case would indicate that prolonged androgen stimulation may have a role to play in the development of prostatic tissue.
- The existence of TCM around menopausal and post-menopausal periods during which the ovaries secrete androgens, in female transsexuals who had been treated with androgens and in their patient with high endogenous androgen levels would indicate that the androgen plays a major role in the histogenesis of TCM.
- The fact that there is significant decreased Ki-67 immunopositivity in TCM in comparison with normal cervical mucosa of women in the reproductive age would allude to the possibility that TCM is a mild form of atrophy of the epithelium, which is presumed to be caused by the neutralizing effect of androgens.

Mc Cluggage et al. [8] reported 6 cases of ectopic prostatic tissue in the lower female genital tract. Five of the cases involved the uterine cervix; and one case involved the vagina. They stated that the case which involved the vagina was the first reported example of benign prostatic tissue in the vagina and the ages of the patients ranged between 21 years to 65 years. With regard to clinical detail, McCluggage et al. [8] stated that the patients were aged 21, 23, 25, 32, and 61 (cervical cases) and 65 (vagina case). They reported that all the patients had been referred to colposcopy in view of an abnormal cervical smear and that in all cases a large loop excision of the transformation zone had been performed. None of the patients had a previous history of surgery to the cervix. One of the patients aged 61 years old, had been taking hormonal preparations. The last patient was seen because of post-menopausal bleeding and had been under follow-up after endometrial curettings had shown complex hyperplasia. She had not been taking hormonal preparations. An incidental polyp was observed on the posterior wall of the vagina which was removed. With regard to follow-up, the vaginal case patient had been followed-up for 16 months with no

evidence of recurrence; 3 of the cervical cases had been followed-up for 6, 10, and 16 months and there had been no further problems and their cervical cytology had been negative. McCluggage et al. [8] summarized features of their reported cases as follows:

- The prostatic tissue was confined to the cervical or vaginal stroma and the surface was not involved in all of the cases.
- Both glandular and squamous elements were found in all of the cases and these varied in prominence.
- The squamous elements were observed to have predominated to such an extent that the underlying glandular component was easily overlooked in all the cases.
- A double cell layer of luminal and basal cells could be seen clearly focally on microscopic examination in the glandular areas.
- Only little cytological atypia or mitotic activity could be seen on microscopic examination of the specimens.
- Out of 6 cases, 3 cases on immunohistochemical staining exhibited positivity with prostate specific antigen (PSA) and all of the six cases exhibited positive staining with prostatic acid phosphatase (PSAP). In some of the cases that stained positive, the positivity was observed to be focal positivity. The positive staining with prostatic markers was observed to be confined to the glandular elements and there was no evidence of staining of the squamous areas.
- Upon immunohistochemical staining with the high molecular weight cytokeratin 34betaE12, the basal cell layer was shown and this layer often extended into the centre of the cellular islands, which mimicked basal cell hyperplasia involving the prostate gland.
- Immunohistochemical staining of all of the cases showed positive staining with CD10 (the positivity was observed to be largely restricted to the basal cell layer), positive staining with alpha-methylacyl-CoA racemase, and negative staining with p16.
- Furthermore, Oestrogen receptor (ER) and progesterone receptor (PR) were found to be negative in the glandular areas, but on the other hand, ER was positive in the squamous elements in all cases and PR was positive in one case.

- All of the cases which were tested were positive for androgen receptor and they exhibited a low MIB-1 proliferation index with only scattered positive nuclei.

Mc Cluggage et al. [8] made the ensuing concluding statements:

- The presence of ectopic prostatic tissue in the lower female genital tract may be more common than was previously thought.
- When the possibility of ectopic prostate in the female genital tract is considered, the diagnosis could be easily confirmed by using immunohistochemistry, even though staining with prostatic markers could be focal staining and PSA could be negative.
- Ectopic prostate in the lower female genital tract is almost invariably a benign condition, based upon the morphology, including the presence of a double cell layer, even though follow-up of larger numbers of cases is required to be certain.
- Some of the possible postulates regarding the histogenesis of ectopic prostate include a developmental anomaly, metaplasia of pre-existing endocervical glands, and derivation from embryonic remnants.

Güth and Singer [3] reported a prostatic tissue which involved the uterine cervix of an 82-year-old woman which was an incidental finding in a hysterectomy specimen. They stated that immunohistochemical studies confirmed the histological suspicion of ectopic prostatic tissue. Güth and Singer [3] advised that this unusual lesion should be differentiated from atypical glandular lesions of the cervix. Güth and Singer [3] also iterated that possible theories of histogenesis that had been promulgated include: a developmental abnormality, metaplasia of pre-existing endocervical glands, and derivation from mesonephric remnants [3].

Singh [9] reported a 31-year-old lady (gravida 0, para 0) who was found to have high-grade squamous intraepithelial lesion during her routine two yearly cervical smear. She had colposcopy during which three separate aceto-white areas were observed. The initial diagnosis made at colposcopy was a low-grade squamous intraepithelial lesion and chronic inflammatory change. She had a LLETZ biopsy of the cervix. Singh [9] stated that the lady had been on microgynon 50 (Levonorgestrel 0.125 mg and Ethinyloestriadiol 0.05 mg tablet), which she

had stopped taking prior to her last menstrual period and that her last menstrual period was 3 weeks preceding the colposcopy. Furthermore, Singh [9] stated that the lady did not have any significant gynaecological or medical history. Singh [9] reported that histological examination of the specimen revealed high-grade squamous intraepithelial lesion (CIN2) and associated koilocytosis which was consistent with papilloma virus. Background changes of moderate chronic cervicitis and associated squamous metaplasia were also found. Furthermore, three circumscribed foci of cribriform glandular structures lined two cell layers 2 mm deep to the overlying essentially normal appearing squamous epithelium. The glandular structures were observed to be lined by cuboidal to columnar epithelium resting upon discontinuous basal cell layer of cells which had little cytoplasm and round to oval bland nuclei. There was no evidence of cytological atypia, necrosis or apoptotic foci. One focus exhibited a central small amount of psammomatous dystrophic calcification. There was no evidence of associated fibro-muscular stromal tissue. The glandular architecture was not like the usual benign prostatic glandular hyperplasia and corpora amylacea was not found. Immunohistochemical staining of the biopsy specimen showed strong and diffuse positive staining for prostate-specific antigen (PSA) and prostatic acid phosphatase (PSAP). The results of staining for high molecular weight cytokeratin 34 β E12 and P63 confirmed the presence of basal cells [9].

Wallace et al. [10] reported a 22-year-old gravida 1, para 0 lady who had had multiple cervical smears and pathological examination of specimens had shown low-grade squamous intraepithelial lesion with evidence of human papilloma virus change. She also had cervical biopsy and histopathological examination of the specimen had shown a high-grade squamous intraepithelial lesion (CIN II). She subsequently had cone biopsy of the cervix. Histological examination of the specimen revealed mild koilocytosis (CIN I) and chronic cervicitis with a focal proliferation of acinar structures which were underlying the cervical squamous epithelium. The glandular proliferation was reported to exhibit papillary and cribriform patterns lined by two cell layers. Histological examination also revealed that the basal cell layer consisted of cuboidal cells with scant cytoplasm and bland nuclei with a super-imposed layer comprising of columnar cells with abundant vacuolated

cytoplasm. There was also evidence of squamous metaplasia which blended into transitional metaplasia in adjacent glands. Immunohistochemical examination of the specimens showed that the glands had exhibited strong diffuse positive staining with prostate-specific antigen (PSA). Furthermore, high-molecular weight cytokeratin (CYK 903) exhibited strong cytoplasmic staining of the basal cells underlying the PSA positive glandular epithelium and squamous metaplastic epithelium adjacent to the PSA positive epithelium. They stated that 3 immunohistochemical studies with PSA and cytokeratin confirmed the histological suspicion of ectopic prostate tissue.

The review data by Wallace et al. [10] would indicate the rarity of ectopic prostate in the uterine cervix. It may be argued that perhaps ectopic prostate in the uterine cervix is extremely rare. However, it may also be argued that the rarity of the condition could be explained on underreporting [10] or the diagnosis is missed because ectopic prostate in the uterine cervix is not at the fore front of the minds of pathologists when they are examining biopsies of the cervix. Wallace et al. [10] suggested that in view of the fact that few cases of ectopic prostate in the cervix had been reported the possibility of a diagnosis of ectopic prostate in the uterine cervix should be considered in the differential diagnosis of unusual glandular lesions of the cervix, including pseudo-neoplastic glandular proliferations, most notably lobular endo-cervical glandular hyperplasia.

Baydar and Himmetoglu [11] reported a 47-year-old lady who presented with urgency and menometrorrhagia. She had pelvic ultrasound scan which showed a sub-mucosal leiomyoma stretching the endometrium. Histology of her endometrial biopsy was unremarkable. Her cervical smear was negative for intraepithelial lesion or malignancy. She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Histological examination of the endometrium and adnexa revealed no abnormality. Histological examination of the cervical stroma showed abnormal glandular structures but the surface epithelium of the cervix was unremarkable. The glands were variable in size, and they had papillary infolding and cribriform structure. They were located beyond but close to the deeper tips of normal endocervical crypts without being connected with them. Some of them exhibited cellular crowding at the centre and squamous metaplasia. A few

contained dense acellular secretions in the lumen. The cells had voluminous clear cytoplasm containing vague intracytoplasmic yellowish pigment. The nuclei were basal, round with inconspicuous nucleoli. Mitosis was not observed and there was no stromal desmoplastic response or any significant inflammation. The atypical glands were found incidentally in one area. Immunohistological examination of the specimens had shown that the atypical glands had exhibited diffuse and strongly positive staining for prostate specific antigen (PSA) and prostatic-specific acid phosphatase (PSAP). P63 staining highlighted the presence of basal cells typical of normal prostate glands. Flattened or cuboidal basal cells with little cytoplasm formed the outer layer. The prostatic glands lacked intracytoplasmic mucin on special stains in contrast to normal endocervical epithelium. The aforementioned features were diagnostic of ectopic prostate in the uterine cervix. Baydar and Himmetoglu [11] stated that the differential diagnoses include: adenocarcinoma in situ, adenoid basal carcinoma of the cervix and minimal deviation adenocarcinoma of the cervix. They also stated that:

- Diagnosis of ectopic prostate in the uterine cervix can be confirmed by positive staining for PSA; however, clinicians should be aware that not all the cases are positive for PSA.
- Mc Cluggage et al. [8] reported that three cases out of six in their series were PSA negative. All six cases expressed prostatic-specific-acid phos-phatase (PSAP) and androgen receptor (AR); the PSAP positivity was found in the glandular part, on the other hand the AR were found in both the glandular and squamous areas of the ectopic prostatic tissue.
- In cases where squamous elements are extensive, the glandular component could be overlooked and this could lead to the misdiagnosis of the lesion as squamous metaplasia of the endocervical glands.
- As reported by McCluggage et al. [8] it should be noted that tubulosquamous polyp of the vagina can occur and that McCluggage et al. [8] reported 1 case of vaginal ectopic prostate in their series of 10 cases

Kelly et al. [12] reported a series of lesions in women whose ages ranged between 23 years and 81 years. The lesions were found within the

cervix in 24 patients, vagina in 10 patients, and vulva in 2 patients. Kelly et al. [12] were also of the opinion that the lesions represented part of a spectrum of lesions which had been derived from Skene's glands, and they could either have been eutopic or more commonly misplaced during embryonic development. Kelly et al. [12] reported that in all the cases that had involved the cervix, the lesion was predominantly located in the ecto-cervix and it was an incidental finding in specimens that had been obtained for a number of reasons. With regard to the cases that had involved the vagina, the lesions had usually manifested as polyps or cysts, even though rare, they had been found incidentally. The two lesions that had involved the vulva were found incidentally in punch biopsies. The main histological features of the lesions included epithelial elements of both glandular and squamous type and the glandular elements formed a double layer in some of the cases. Some of the less common findings reported included presence of sebaceous glands in two cases (one which involved the vagina, and one which involved the cervix), basaloid formations which had mimicked nephrogenic adenoma in one case which had involved the vagina. Immunohistochemical staining of the specimens revealed positive staining for prostate-specific antigen (PSA) in 13 out of 26 cases stained and positive staining for prostatic-specific acid phosphatase (PSAP) in 16 out of 26 cases examined by immunohistological studies. Six of the cases were found on immunohistochemical studies to be negative for both markers. Kelly et al. [12] suggested that these benign lesions which had been found in the cervix, vagina, and vulva had either been derived from eutopic or misplaced Skene's glands. They also stated that they had interpreted from their report that about half of the lesions from the cervix would be compatible with ectopic prostate in the uterine cervix.

Fukunaga [13] in 2013, reported a tubulo-squamous polyp which resembled a penis in the uterine cervix of a 34-year-old, gravida 0, para 0, woman. The polypoid lesion in the uterine ectocervix measured 18 mm x 8 mm x 5 mm. Fukunaga [13] stated that the polyp had a penis-like appearance in that the tip mimicked glans penis and the middle portion looked like the shaft of the penis. The surface of the lesion was covered by squamous epithelium, and tissues mimicking those of the urethra, corpus spongiosum penis, and external urethral orifice were seen. Foreskin-like tissues were apparent,

even though a penile corpus cavernosum was not apparent. Skene glands and Cowper glands were also seen. On immunohistochemical staining, the skene glands and the urethra-like epithelium were focally positive for prostate-specific antigen and / or prostatic acid proteins. Fukunaga [13] stated that the histological and immunohistochemical features of the polypoid lesion had overlapped with a tubulosquamous polyp of the vagina and ectopic prostatic tissue in the uterine cervix and had surrounded these lesions in the lower female genital tract. Fukunaga [13] concluded that the most likely theory of histogenesis of the lesion is a developmental anomaly and misplacement of Skene glands.

McCluggage and Young [14] reported 10 cases of a morphologically distinct vaginal polyp in women whose ages ranged between 39 years and 78 years with the majority being post-menopausal. Most of the polyps were found in the upper vagina and they measured between 1.0 cm and 3.0 cm. Histological examinations of the specimens showed that all the polyps were similar and they were composed of well-circumscribed expansile nest of epithelial cells embedded in a hypo-cellular fibrous stroma. The epithelial cells were described as morphologically bland and predominantly glycogenated or non-glycogenated in squamous in type but small tubules were present at the periphery of some of the nests in all cases. Some of the squamous nests were reported to have exhibited central necrosis with or without calcification, and in 3 cases, some contained keratin pearls. In 3 cases, a few tubules un-associated with squamous elements were reported to be present. McCluggage and Young [14] also reported that in 3 out of 4 cases tested, the cells lining the tubules had shown positive staining for prostatic acid phosphatase and positive staining with prostate-specific antigen was also shown in 2 out of 4 cases on immunohistochemistry. The epithelial elements were reported by McCluggage and Young [14] to have reacted with broad spectrum cytokeratins and cytokeratin 7 but the mesenchymal element was negative. They also reported that the squamous elements were oestrogen receptor positive and the mesenchymal element oestrogen receptor and progesterone receptor positive. McCluggage and Young [14] stated the following:

- The histological features of this polyp, which they had termed tubulo-squamous

polyp of the vagina, are constant and distinctive and different from other polyps and from mixed tumour of the vagina.

- In their opinion, several cases which had been reported in the literature as vaginal mixed tumour or Brenner tumour are examples of this entity.
- Possible postulates regarding the histogenesis include a mullerian origin, derivation from mesonephric remnants, or derivation from urogenital sinus-derived epithelium. The finding on immunohistochemical studies of positive staining in some cases with prostatic acid phosphatase and prostate-specific antigen raise the possibility of ectopic prostatic tissue, even though the overall appearance was different from that entity, or derivation from para-urethral Skene glands, the female equivalent of the prostate glands in the male.

Lorange et al. [15] reported a 76-year-old woman who had taken tamoxifen for carcinoma of breast and who presented with post-menopausal bleeding and a vaginal mass. Her endometrial work-up revealed a benign polyp and the polypoid tumour in the vagina was found to be myofibroblastoma harbouring ectopic prostatic glands. They concluded that:

- To their knowledge their case was the first reported case these two rare pathological entities occurring together.
- Of note the patient also had a history of tamoxifen therapy, like some of the previous patients with vaginal fibromyoblastoma.

Kazakov et al. [16] reported a series of prostatic type lesions occurring in the female lower genital tract. They stated that the cases included a 4.5 cm mass representing hyperplasia of the glandular and stromal tissue of para-urethral Skene gland, a small ectopic prostate lesion in the vulva, and 4 tubulosquamous vaginal polyps. All of the lesions were immuno-reactive for prostate-specific antigen and / or prostatic specific antigen.

Biancardi et al. [17] stated that androgenic imbalance may disrupt prostate development, leading to morphological alterations in adulthood and predisposing this gland to the development of diseases during adulthood. Nevertheless, there has been little known about the endocrine

disruption of the prostate which is caused by androgenic compounds, especially in female experimental models. Biancardi et al. [17] evaluated the prostates of aged female gerbils which had been exposed to testosterone at certain periods in intrauterine and post-natal life, in order to ascertain whether exposure at a particular age increases susceptibility to prostatic lesions in these animals. For this study, Biancardi et al. [17] employed morphological, stereological, immunohistochemical, immunofluorescence analyses. Biancardi et al. [17] found that females that had been exposed to testosterone during intra-uterine life were masculinised, showing increasing anogenital distance, absence of the vaginal opening and ectopic development of prostatic tissue. They also observed several areas of adenomatous hyperplasia which were generally associated with inflammatory foci and which were mainly located in the ectopic prostatic tissue around the vaginal wall. Biancardi et al. [17] concluded that their results showed that pre-natal exposure to testosterone severely affects the reproductive systems of female animals by disrupting normal prostate morphogenesis and increasing susceptibility to the development of prostatic diseases during ageing.

Additionally it is worth noting that PSA can react positively in carcinoid tumours and also that PSA can be positive in some urinary bladder carcinomas as well as in many rectal tumours in view of the fact that they share the same cloacal derivation of prostate and rectum. Furthermore, it may be argued that perhaps not all reported cases of ectopic prostate in the uterine cervix are genuinely ectopic prostate in that may be second opinion reviews of the cases by a number of pathologists had not been done in some of the reported cases. It would therefore be suggested that if in the future a possible case of ectopic prostate in the uterine case is encountered the specimens should be reviewed by a panel of pathologist who should confirm the diagnosis as ectopic prostate and that a panel of pathologists should cases of ectopic prostate in the uterine cervix in order to arrive at a consensus opinion on what should constitute the criteria for the diagnosis of ectopic prostate in the uterine cervix. It would also be recommended that all cases of ectopic prostate in the uterine cervix should be reported in the literature to enable clinicians and pathologists to document its biological behaviour and the diagnostic criteria.

Table 1. Showing some of the reported cases of ectopic prostate gland in the uterine cervix including a few cases involving the vagina and vulva

Authors/Reference	Number of cases	Age years	Diagnosis / Presentation	Immunohistochemistry
Lorraza-Hernandez et al. [6]	1	38	Details not available to author	Prostate-specific antigen (PSA) positive Prostatic-specific acid phosphatase (PSAP) positive
Nucci et al. [5]	4 Reported from USA	22; 25; 31; 77.	3 were found incidentally: (2 in loop excisions, 1 cone biopsy of cervix for high-grade squamous dysplasia); 1 presented with cervical mass mimicking fibroid	All cases showed strong and diffuse immunopositivity with prostate specific antigen (PSA) and prostatic acid phosphatase (PSAP) A high molecular weight keratin (34βE12) confirmed presence of basal cells in 2 cases (case numbers 1 and 3)
Kim et al. [7]	1	23	Details not available to author but the ectopic prostate was in the uterine cervix and vagina and the patient also had adrenogenital syndrome	Details not available to author
McCluggage et al. [8]	5 in cervix 1 In vagina Reported from Belfast United Kingdom	21 to 65	All patients were referred for colposcopy because of abnormal cervical smear; 1 patient aged 61 had been taking hormonal preparation; the final patient had post-menopausal bleeding and was under follow-up after endometrial curettings showed complex hyperplasia and she was not taking hormonal preparation.	3 of 6 positive for PSA 6 of 6 positive for PSAP 34βE12 +ve (all cases) CD10 +ve (all cases) Alpha-methylacyl-CoA racemase +ve (all cases) P16 negative (all cases) Androgen receptor positive (all cases)
Güth and Singer [3]	1 Case reported from Germany	82	Incidental in hysterectomy specimen	PSA positive PSAP positive
Kelly et al. [12]	24 cases in cervix; 10 cases in vagina;	23 to 81	Details of presentation of individual cases not available to	13 out of 26 cases tested were positive for PSA (the specific numbers for cervix,

	2 in vulva Reported from Belfast United Kingdom		author	vagina and vulva not differentiated in summary) Therefore the actual numbers that were ectopic prostate in cervix not clear but shows ectopic prostate can be found in the cervix, vagina and vulva Prostatic acid phosphatase was positive in 16 out of 26 cases tested Six cases were negative for both PSA and prostatic acid phosphatase Immunohistochemistry was carried out in the remaining cases
Singh [9]	1 case	31	Asymptomatic; had abnormal cervical smear showing high- grade squamous intraepithelial lesion	PSA strongly positive, PSAP strongly positive 34βE12 positive
Wallace et al. [10]	1 case (reported from USA)	22	Pregnant lady who had multiple cervical smears reported as low- grade squamous intra-epithelial lesion with human papilloma virus change, and a subsequent cervical biopsy showed a high- grade squamous intraepithelial lesion (CIN II). She next had loop conisation biopsy of cervix.	Strong positive staining of glands for prostatic specific antigen (PSA) High molecular weight cytokeratin (CYK 903) showed strong cytoplasmic staining of the basal cells underlying the PSA- positive glandular epithelium and squamous metaplastic epithelium adjacent to the PSA positive epithelium
Baydar and Himmetoglu [11]	1 case reported from Turkey	47	Urinary urgency, menometrorrhagia, ultrasound scan revealed leiomyoma of uterus and following hysterectomy histology revealed leiomyoma and ectopic prostate in uterine cervix	Diffuse and strong immunohistochemical expression of (a) PSA and (b) PSAP by atypical glands Also P63 highlighted the presence of basal cells characteristic of normal prostate gland

Mc Cluggage and Young [14]	10 cases of tubulosquamous vaginal polyp from Belfast United Kingdom	Ages ranged from 39 to 78 years	Most cases were post-menopausal with upper vaginal masses diagnosed by histological examination of the excised masses	in 3 out of 4 cases tested, the cells lining the tubules were positive for prostatic acid phosphatase and in 2 out of for cases with prostate-specific antigen staining on immunohistochemistry.
Lorange et al. [15]	1 case of vaginal mass	76 years	Post-menopausal bleeding and vaginal mass; history of being on tamoxifen for breast cancer Histological examination showed myofibroblastoma harbouring ectopic prostatic glands.	Details of immunohistochemistry not available to author.
Kazakov et al. [16]	6 cases as follows: hyperplasia of the glandular and stromal tissue of para-urethral Skene gland (1 case) , a small ectopic prostate lesion in the vulva (1 case), and 4 tubulosquamous vaginal polyps.	Details of ages not available to author	Histological examination of the excised masses showed hyperplasia of the glandular and stromal tissue of para-urethral Skene gland (1 case), a small ectopic prostate lesion in the vulva (1 case), and 4 tubulosquamous vaginal polyps.	All of the lesions were immuo-reactive for prostate-specific antigen and / or prostatic specific antigen.

3. CONCLUSIONS

Ectopic prostate in the uterine cervix and the female genital tract is very rare and pathologists and gynaecologists may not be familiar with this entity because of its rarity. The differential diagnoses include: adenocarcinoma in situ, adenoid basal carcinoma of the cervix and minimal deviation adenocarcinoma of the cervix.

It is important for pathologists, gynaecologists and all clinicians to be aware of the presence of ectopic prostate in the uterine cervix, vagina and vulva in order that an accurate diagnosis is made and in order to avoid unwarranted radical surgical treatment.

If a diagnosis of ectopic prostate in the uterine cervix, vagina or vulva is suspected

immunohistochemical staining for PSA, PSAP, AR and 34 β E12 would be required to confirm the diagnosis and special stains for example mucicarmine stains would confirm absence of mucin production by the atypical glands.

Few cases of ectopic prostate in the uterine cervix, vagina and vulva have been reported and in most of them there has not been any long follow information.

Whether any ectopic prostate in the uterine cervix, vagina or vulva would ever develop into carcinoma in the long run is not known. In view of this gynaecologists, pathologists and clinicians should be encouraged to report all cases of ectopic prostate in the uterine cervix, vagina and vulva they encounter in order to document the long-term biological behaviour.

CONSENT

Consent is not applicable in the case of a review article.

ETHICAL APPROVAL

Ethical approval is not applicable in this review article.

ACKNOWLEDGEMENT

Acknowledgement to Professor Dilek Ertoy Baydar MD, Professor of Pathology, Department of Pathology, Hacettepe University Hospital, Ankara Turkey for providing and reporting on all the figures to the author to be included in the paper to illustrate features of ectopic prostate in the uterine cervix. Copy right to the figures is only for single use for this article and any subsequent reproduction of the figures would require copyright permission from Professor Dilek Ertoy Baydar

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Arora K. PathologyOutlines.com Prostate Benign lesions / conditions Ectopic prostate revised 21 April 2012, last major update March 2012. Available:www.pathologyoutlines.com/prostate.html
2. Halat S, Eble JN, Grignon DJ, Lacy S, Montironi R, MacLennan GT, Lopez-Beltran A, Baldrige LA, Cheng L. Ectopic prostatic tissue: histogenesis and histological characteristics. *Histopathology*. 2011;58(5):750–758. DOI:10.1111/j.1365-2559.2011.03799.x. Epub 2011 Mar 25.
3. Güth U, Singer G. Ectopic prostatic tissue in the uterine cervix. *Pathologie*. 2007;28(4):291–293.
4. Smith CE, Toplis PJ, Nogales FF. Ovarian prostatic tissue originating from hilar mesonephric rests. *Am. J Surg Pathol*. 1999;23(2):232-236.
5. Nucci MRI, Ferry JA, Young RH. Ectopic prostate tissue in the uterine cervix: a report of four cases and review of ectopic prostate tissue. *Am J Surg Pathol*. 2000;24(9):1224–1230.
6. Larraza-Hernandez O, Molberg KH, Lindberg G, Albores-Saavedra J. Ectopic prostatic tissue in the uterine cervix. *Int J Gynecol Pathol*.1997;16(3): 291–293.
7. Kim KRI, Park KH, Kim JW, Cho KJ, Ro JY. Transitional cell metaplasia and ectopic prostatic tissue in the uterine cervix and vagina in a patient with adrenogenital syndrome: report of a case suggesting a possible role of androgen in the histogenesis. *Int J Gynecol Pathol*. 2004;23(2):182-187.
8. Mc Cluggage WG, Ganesan R, Hirschowitz L, Miller K, Rollason T. Ectopic Prostatic Tissue in the Uterine Cervix and Vagina: Report of a Series With a Detailed Immunohistochemical Analysis. *The American Journal of Surgical Pathology*. 2006;30(2):209– 215.
9. Singh M. Ectopic prostatic tissue in the uterine cervix: Report of a case and brief overview of basaloid cervical glandular lesions. *J Clin Pathol*. 2012;65:573–575. DOI:10.1136/clinpath-2011-200455.
10. Wallace C, Creager AJ, Cappellari JO, Bergman S. Ectopic Prostatic Tissue in the Uterine Cervix *The American Journal of Surgical Pathology*. 2001;25(9):1215–1216.
11. Baydar DE. Himmetoglu C. TEST AND TEACH Abnormal glands in the uterine cervix. *Patholgy*. 2008;40(4):407-408.
12. Kelly P, McBride HA, Kennedy K, Connolly LE, McCluggage WG. Misplaced Skene's glands: glandular elements in the lower female genital tract that are variably immunoreactive with prostate markers and that encompass vaginal tubulosquamous polyp and cervical ectopic prostatic tissue. *Int J Gynecol Pathol*. 2011;30(6): 605–612. DOI: 10.1097/PGP.Ob013e31821713b6.
13. Fukunaga M. Uterine cervical tubulosquamous polyp resembling a penis *Int J Gynecol Pathol*. 2013; 32(4):426–429. Available:www.ncbi.nlm.nih.gov/pubmed/23722517 DOI:10.1097/PGP.0b013e318263Od69.
14. Mc Cluggage WG, Young RH. Tubulo-squamous polyp: a report of ten cases of a distinctive hitherto uncharacterized vaginal polyp. *Am J Surg. Pathol*. 2007; 31(7):1013–1019.

15. Lorange E, Harmanli O, Cao QJ, Jones KA. Vaginal myofibromyoblastoma with prostate glands: Is there an association with tamoxifen use? A case report J Reprod Med. 2013;58(7-8):344–346.
16. Kozakov DV, Stewart CJ, Kacerovska D, Leake R, Kreuzberg B, Chudacek Z, Hora M, Michal M. Prostatic-type tissue in the lower female genital tract: a morphologic spectrum, including vaginal tubulosquamous polyp, adenomyomatous hyperplasia of paraurethral Skene glands (female prostate), and ectopic lesion in the vulva. Am J Surg. Pathol. 2010;34(7): 950–955.
DOI: 10.1097/PAS.0b013e3181e0f371.
17. Biancardi MF, Perez AP, Caires CR, Góes RM, Vilamaior PS, Santos FC, Taboga SR. Prenatal exposure to testosterone masculinises the female gerbil and promotes the development of lesions in the prostate (Skene; s gland). Reprod Fertil Dev; 2014.
DOI:10.1071/RD13387.

© 2015 Venyo; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

*The peer review history for this paper can be accessed here:
<http://sciencedomain.org/review-history/10273>*