FACULTY OF MEDICINE AND HEALTH SCIENCES

PROSTATIC METAPLASIA IN FEMALE-TO-MALE TRANSGENDER INDIVIDUALS:

a hitherto underrecognized androgen-induced glandular lesion in vulvar, vaginal and ectocervical tissue.

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Master's dissertation Master of Medicine in Specialist Medicine

Academic year: 2020 – 2021

GHENT UNIVERSITY

PREFACE

Over the past few years I have been able to fully explore my interests during my education as a trainee in pathology. Therefore, producing this master thesis as my final dissertation was the highlight of this training. However, writing a master dissertation is never the work of one person only. This would never have been possible without the support of many people.

In particular, I would like to thank my (co-)promotors prof. dr. Koen Van de Vijver, prof. dr. Sofie Verbeke and prof. dr. Steven Weyers for their excellent guidance and feedback.

I would also want to thank the members of my committee: prof. dr. Jo Van Dorpe, dr. Tjalina Hamerlynck and prof. dr. Griet Glorieux.

Next I want to thank my colleagues for their help anytime I had a question.

Finally, I would like to express my great gratitude to my parents, my family and friends for their infinite moral support.

TABLE OF CONTENT

1. ABSTRACT ..... - 1 -
2. INTRODUCTION ..... - 2 -
3. METHODS AND MATERIALS ..... - 5 -
4. RESULTS ..... - 7 -
   4.1. MACROSCOPIC FINDINGS ..... - 7 -
   4.2. HISTOMORPHOLOGICAL FINDINGS ..... - 8 -
      4.2.1. Atrophy and transitional cell metaplasia ..... - 8 -
      4.2.2. Prostatic metaplasia ..... - 9 -
      4.2.3. Other structures ..... - 14 -
   4.3. IMMUNOHISTOCHEMICAL FINDINGS ..... - 16 -
      4.3.1. Atrophy and transitional cell metaplasia ..... - 16 -
      4.3.2. Prostatic metaplasia ..... - 16 -
      4.3.3. Other structures ..... - 20 -
5. DISCUSSION ..... - 22 -
6. REFERENCES ..... - 25 -
7. NEDERLANDSTALIGE SAMENVATTING ..... - 29 -

1. ABSTRACT

Histological changes in the genital tract of female-to-male transgenders have been described in the past. However, not much research is done on histological changes of vaginal tissue and the amount of patients in previous studies was generally low. Anderson et al. recently described a new phenomenon in vaginal and cervical tissue which they stated as “prostatic metaplasia”. The aim of this study is to provide data on a larger scale on the description and prevalence rate of histological changes and lesions in the vagina and ectocervix of female-to-male transgenders with special attention to “prostatic metaplasia”, including an immunohistochemical profile of this lesion and its differentials. All H&E slides and immunohistochemically stained slides of 140 vulvovaginectomies with 72 accompanying uteri were reviewed. Transitional cell metaplasia was seen in vaginal (96.5%) and ectocervical (85%) tissue. Prostatic metaplasia was observed in vaginal (92%) and ectocervical (82%) tissue. Prostatic metaplasia depicts a spectrum with increasing maturation ranging from a) intracellular changes in the basal layer of the epithelium, b) prostatic type glands located within the epithelium or at the basal layer of the epithelium, c) glands with a luminal and basal layer that have invaginated into the subepithelial lamina propria and/or d) fully developed glands in the lamina propria resembling (ectopic) prostate tissue. The basal layer of the metaplastic epithelium stained with NKX3.1. The glands stained with NKX3.1, prostate-specific antigen (PSA), prostate specific acid phosphatase (PSAP), androgen receptor (AR), cytokeratine 7 CK7, cytokeratine 8-18 (CK8-18), cytokeratine 17 (CK17), cytokeratine 19 (CK19), EpCAM and also CD10 for glands in the lamina propria resembling (ectopic) prostate tissue. We believe that this metaplastic process is caused under the influence of androgens. We also believe that, since prostatic metaplasia is frequently encountered, it was often overlooked in the past. The mechanism and clinical impact of prostatic metaplasia are not yet clear. Additionally other structures such as Bartholin glands (6%), ectopic breast tissue (4%), mucous cysts (4%) and mesonephric duct remnants (4%) were encountered. Bartholin glands showed positive staining with NKX3.1, but not with PSA and PSAP. Ectopic breast tissue, mucous cysts and mesonephric duct remnants were negative with NKX3.1, PSA and PSAP. This study will raise awareness towards this metaplastic phenomenon among pathologists which will be fundamental for future research on further insights and clinical correlation of this lesion.

2. INTRODUCTION

Gender dysphoria refers to a profound distress or discomfort caused by the discrepancy between a person's assigned sex at birth and gender identity[1]. Gender affirming surgery can be part of the treatment. Different surgical procedures can be performed such as hysterectomy with bilateral salpingo-oophorectomy, vaginectomy, phalloplasty and metaidoioplasty[2,3]. These are often performed in different stages[3]. Prior to surgery most female-to-male transgenders have been treated with androgens to induce virilization[4]. The principal hormonal treatment used is testosterone. Testosterone has many effects throughout the whole body.

The effects of androgen-therapy on the histomorphology of the genital tract in female-to-male transgenders have only been scantly studied in the past. These previous studies mainly focused on the histological changes seen in the endometrium, ovaries and cervix and less on the histological changes seen in the vagina. In addition the amount of patients in these previous studies was generally low. Histological changes previously described in hysterectomy specimens are decidua-like stromal changes of the endometrium[5], with atrophic, inactive[5,7,8,9,10] to proliferative or secretory[5, 6, 7, 9, 11] endometrial glands, myometrial fibroids and hypertrophic myometrium[6]. Although the histological changes in the ovaries are more complex and sometimes incongruent, the presence of (follicular) cysts has been described in several studies[5, 6, 7, 11]. Singh et al[11] also described mesonephric duct remnants in paratubal and adnexal tissue with virilization resembling epididymis in one case.

All studies[5, 11-15] but one[7] examining the cervix of female-to-male transgenders, described similar histological changes in the ectocervix: atrophy and transitional cell metaplasia of the overlying epithelium. Although the oldest studies[14,15] don't mention the term "transitional cell metaplasia" yet, the description of these epithelial changes confirms the assumption of transitional cell differentiation. In a series of 31 cases[16] and 59 cases[17] of cervical and vaginal specimens of post- and premenopausal women transitional cell metaplasia was defined as a multilayered epithelium with crowding of nuclei and lack of apparent maturation. The epithelial cells are oriented vertically in the deeper layers and horizontally at the surface resembling umbrella cells. The nuclei are elongated with common longitudinal nuclear grooves. There is no atypia and mitosis are rare.

A distinction between transitional cell metaplasia and high grade squamous dysplasia must be made. This distinction is mainly based on morphology: the lack of cytological atypia and mitotic activity and is supported by the immunohistochemical profile: low proliferation index with Ki67 and no aberrant staining with p16.

A recent study by Anderson et al[13]. examining cervical and vaginal tissue of female-to-male transgenders described similar findings of transitional cell metaplasia and a new phenomenon which they stated as "prostatic metaplasia". Prostatic metaplasia is defined as an intra-epithelial glandular proliferation consisting of glands located at the basal aspect of the squamous epithelium, formed of cuboidal cells with uniform round nuclei and clear to pale cytoplasm. The amount of glands is variable ranging from focal to frequent, sometimes with florid proliferation or invagination into the underlying lamina propria. These glands showed positive staining with NKX3.1 (100%), androgen receptor (AR) (100%), cytokeratin 7 (CK7) (92%) and prostate-specific antigen (PSA) (69%), and were negative with PAX8, p63, GATA-3, cytokeratine 20 (CK20) and estrogen receptor (ER). When reviewing previous studies prostatic metaplasia has already been identified by Singh et al[11] in the cervix of 2 female-to-male transgender and by Kim et al[12] in the cervix of a 23 year old woman with adrenogenital syndrome, although not yet recognized as such. In the study of Singh et al the glands showed diffuse and strong positive staining with PSA.

In a letter to the editor Quddus et al[12] reported the presence of ectopic prostate tissue in the cervical stroma of a female-to-male transgender. Although this case was the first case to report the presence of nicely developed ectopic prostate tissue in the cervix of a female-to-male transgender, the presence of ectopic prostate tissue in cervical and vaginal mucosa has already been described by several authors in several case series[19-22] and case reports[12, 18, 23-29] in post- and premenopausal women with or without androgen excess. Ectopic prostate tissue presents as one or more demarcated epithelial cell nests with variable size located in the stroma at different depths. The cell nests are composed of glandular and squamous elements in varying proportions. Squamous metaplasia was frequently present and sometimes the amount was so extensive that it obscured the glandular elements which could only be found at the periphery of the cell nests. Rarely transitional cell metaplasia was identified[12, 18]. The glandular elements are lined by a double cell layer consisting of an inner layer of cuboidal to columnar luminal cells with abundant scant cytoplasm and an outer layer of flattened to cuboidal basal cells. The cell nests showed papillary infolds and sometimes a cribriform growth pattern was seen.

There was no significant nuclear atypia and mitotic figures were not identified. Some glands contained acellular eosinophilic secretions. The surrounding stroma showed no desmoplastic reaction and no significant inflammation was seen. Immunostaining was positive with NKX3.1 and PSA/PSAP (diffuse to focal) and AMACR (focal) at the glandular elements and negative with ER and progesterone receptor (PR). The squamous elements exhibit a more or less opposite immunohistochemical profile consisting of positive staining with GATA-3, keratin 34βE12, ER and rarely PR and negative staining with NKX3.1 and PSA/PSAP. AR was positive at both the glandular and squamous elements. The basal layer exhibits positivity for p63, high molecular weight cytokeratins such as 34βE12 and CYK903, CD10 and AR. These lesion is usually an incidental microscopic finding. Only in rare cases a gross lesion was apparent[20-22].

A morphologically similar lesion has also been identified in the stroma of the tubulosquamous polyp of the vagina[19, 20, 23, 25, 30, 31]. These often present as a grossly visible polypoid or cystic mass[20]. Kazakov et al[25] also reported a case of hyperplastic skene glands. These aformentioned lesions all exhibit diffuse to focal positivity for PSA, PSAP and/or NKX3.1 suggesting a prostatic differentiation. The origin of these lesions with prostatic differentiation is still unclear and several theories have been suggested in the past. At this time it is most agreed that these lesions originate from misplaced skene glands.

This current study provides data on vaginal and ectocervical tissue on a larger scale. The aim of this study is to provide a description and prevalence rate of histological changes and lesions in the vagina and ectocervix of female-to-male transgenders with special attention to the recently described phenomenon of “prostatic metaplasia”, including an immunohistochemical profile of this lesion and its differentials.

3. METHODS AND MATERIALS

Patient selection

After approval of the hospitals Ethical Committee (BC-10568), all consecutive vulvovaginectomies and their accompanying hysterectomies of female-to-male transgenders performed between January 2014 and December 2020 were reviewed. Slides were anonymously retrieved from the archives.

Macroscopic review

Macroscopic review was based upon the macroscopic details described in the pathology reports and information available on the slides.

Histopathological review

All Hematoxylin & Eosin (H&E)-stained slides and immunohistochemically stained slides were reviewed by one or two dedicated gynaecological pathologists. All cases of well differentiated (so-called ectopic) prostatic tissue were confirmed by a third pathologist subspecialized in urogenital pathology.

The following histological features were evaluated: atrophy, transitional cell metaplasia, prostatic metaplasia and well-formed prostate tissue. If prostatic metaplasia was present, the amount of glands was counted per cm mucosa and graded into low, average or high. The distribution pattern was also assessed and divided into (multi)focal or diffuse. Prostatic metaplasia was classified based upon the location of the glands: intra-epithelial, at the basal layer or invaginated into the subepithelial stroma. Futhermore the presence of other benign or dysplastic/malignant lesions was assessed. These lesions included Bartholin glands, cysts, mesonephric duct remnants, squamous dysplasia,… etc.

All available immunostained slides were reviewed. Available immunostains were: AMACR, AR, CD10, CK5, CK7, CK8-18, CK14, CK17, CK19, CK20, EpCAM, ER, GATA-3, MUC1, MUC2, MUC4, MUC5AC, MUC6, NKX3.1, p40, p63, PAX8, PR, PSA and PSAP. Based upon these available stains an immunohistochemical profile for different lesions was set. Immunohistochemistry was performed on a Ventana Benchmark Ultra platform. See Table 1 for the list of antibodies, dilutions and protocol applied.

IMMUNO-STAIN	CLONE	COMPANY	DETECTION KIT	DILUTION	ANTIGEN RETRIEVAL	TIMES (Incubation – Counterstaining – Postcounterstaining) (in minutes)	STAINING-PATTERN
AMACR	13H4	Agilent	ultraView DAB	1:50	CC1	32 - 8 - 4	Cytoplasmatic
AR	AR441	Agilent	OptiView DAB	1:50	CC1	32 - 4 - 4	Nuclear
CD10	SP67	Roche	ultraView DAB	RTU	CC1	20 - 4 - 4	Membranous/ cytoplasmatic
CK5	SP27	Roche	OptiView DAB	1:50	CC1	32 - 4 - 4	Cytoplasmatic
CK7	SP52	Roche	ultraView DAB	RTU	CC1	20 - 8 - 4	Cytoplasmatic
CK8-18	B22.7 + B23.1	Roche	ultraView DAB	RTU	CC1	16 - 8 - 4	Cytoplasmatic
CK14	LL002	Novocastra Leica	ultraView DAB	1:100	CC1	24 - 8 - 4	Cytoplasmatic
CK17	E-4	Santa Cruz	ultraView DAB	1:100	CC1	32 - 8 - 4	Cytoplasmatic
CK19	A53-B/ A.2.26	Cell Marque	OptiView DAB	1:100	CC1	32 - 4 - 4	Cytoplasmatic
CK20	Ks20.8	Agilent	ultraView DAB	1:100	CC1	40 - 8 - 4	Cytoplasmatic
EpCAM	MOC31	Agilent	OptiView DAB	1:200	CC1	32 - 8 - 4	Membranous/ cytoplasmatic
ER	SP1	Roche	ultraView DAB	RTU	CC1	16 - 4 - 4	Nuclear
GATA-3	L50-823	Biocare Medical	ultraView DAB	1:200	CC1	32 - 4 - 4	Nuclear
MUC1	Ma695	Biocare Medical	ultraView DAB	1:50	CC1	60 - 8 - 4	Membranous/ cytoplasmatic
MUC2	Ccp58	Agilent	ultraView DAB	1:25	CC1	32 - 8 - 4	Cytoplasmatic
MUC4	8G7	Santa Cruz	ultraView DAB	1:50	CC1	32 - 8 - 4	Cytoplasmatic
MUC5AC	CLH2	Agilent	ultraView DAB	1:50	CC2	32 - 8 - 4	Cytoplasmatic
MUC6	CLH5	Novo-castra Leica	ultraView DAB	1:50	CC2	32 - 8 - 4	Cytoplasmatic
NKX3.1	EP356	Roche	ultraView DAB	RTU	CC1	32 - 4 - 4	Nuclear
p40	BC28	Biocare Medical	ultraView DAB	1:50	CC1	48 - 4 - 4	Nuclear
p63	4A4	Roche	OptiView DAB	RTU	CC1	20 - 4 - 4	Nuclear
PAX8 (mono-clonaal)	SP348	Abcam	OptiView DAB	1:100	CC1	32 - 4 - 4	Nuclear
PR	1E2	Roche	ultraView DAB	RTU	CC1	16 - 4 - 4	Nuclear
PSA	ER-PR8	Agilent	ultraView DAB	1:50	CC1	32 - 8 - 4	Cytoplasmatic
PSAP	PASE/ 4Lj	Imtec	ultraView DAB	1:200	CC1	32 - 8 - 4	Cytoplasmatic

Table 1. Overview of antibodies, dilutions and protocol applied.
RTU "Ready to use"; CC1/2 "Cell Conditioning 1/2".

4. RESULTS

A total of 140 vulvovaginectomies with 72 accompanying uteri were included in this study. The patient age ranged from 18 to 73 years, with a mean age of 28.5 years. Slides were retrieved anonymously from the archives. Slides from vulvectomies that contained only keratinized squamous epithelium with skin adnexa (from the labia majora) were excluded. Slides taken from the isthmus were also included, provided that there was endocervical tissue present.

4.1. MACROSCOPIC FINDINGS

Vaginal and vulvar tissue were mostly received in the context of a vaginectomy or vulvectomy and in rare cases in the context of a phalloplasty or metaidoioplasty. Sometimes additional structures were resected such as labia (4) and lymph nodes (8). Specimens were received in one or more fragments (up to 13, mean 2 fragments). The available vaginal mucosa had an average length of 5 cm per specimen. At least 1 sample was taken of every fragment with an average of 1 to 2 fragments per specimen. The fragments were embedded in 1 or 2 tissue blocks with an average of 1 tissue block per specimen. No specimens were completely embedded.

Cervical tissue was received in the context of a hysterectomy. The average length of available ectocervical mucosa was 2 cm. In rare cases a vaginal cuff was present. Samples of the anterior and posterior part of the ectocervix which included the transformation zone were embedded in 1 to 4 tissue blocks.

In 2 cases an incidental vaginal cyst was either suspected by the gynaecologist either seen by the pathologist during gross examination, the largest being 17 mm diameter. No other gross lesions were observed.

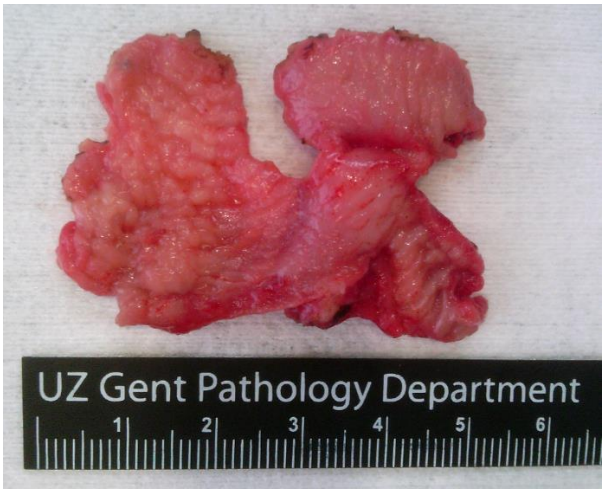


Figure 1. Vaginectomy specimen. View at the mucosal surface. No gross lesions are visible.

4.2. HISTOMORPHOLOGICAL FINDINGS

4.2.1. Atrophy and transitional cell metaplasia

Epithelial atrophy is characterized by the lack of glycogenation and some crowding of the epithelial cells. The epithelium showed concurrent transitional cell metaplasia characterized by a multi-layered epithelium consisting of epithelial cells with elongated nuclei and frequent nuclear grooves oriented perpendicular to the basal layer, thereby showing a more accentuated basal layer. At the surface the cells seemed to be vertically oriented resembling umbrella cells. Atypia and mitotic activity were not aberrant. Atrophy and transitional cell metaplasia were frequently seen in the vaginal epithelium (135/140, 96.5%). These features were less frequently observed in the cervical epithelium (61/72, 85%). When present, these features tended to be less pronounced and less diffusely spread compared to the vaginal epithelium.

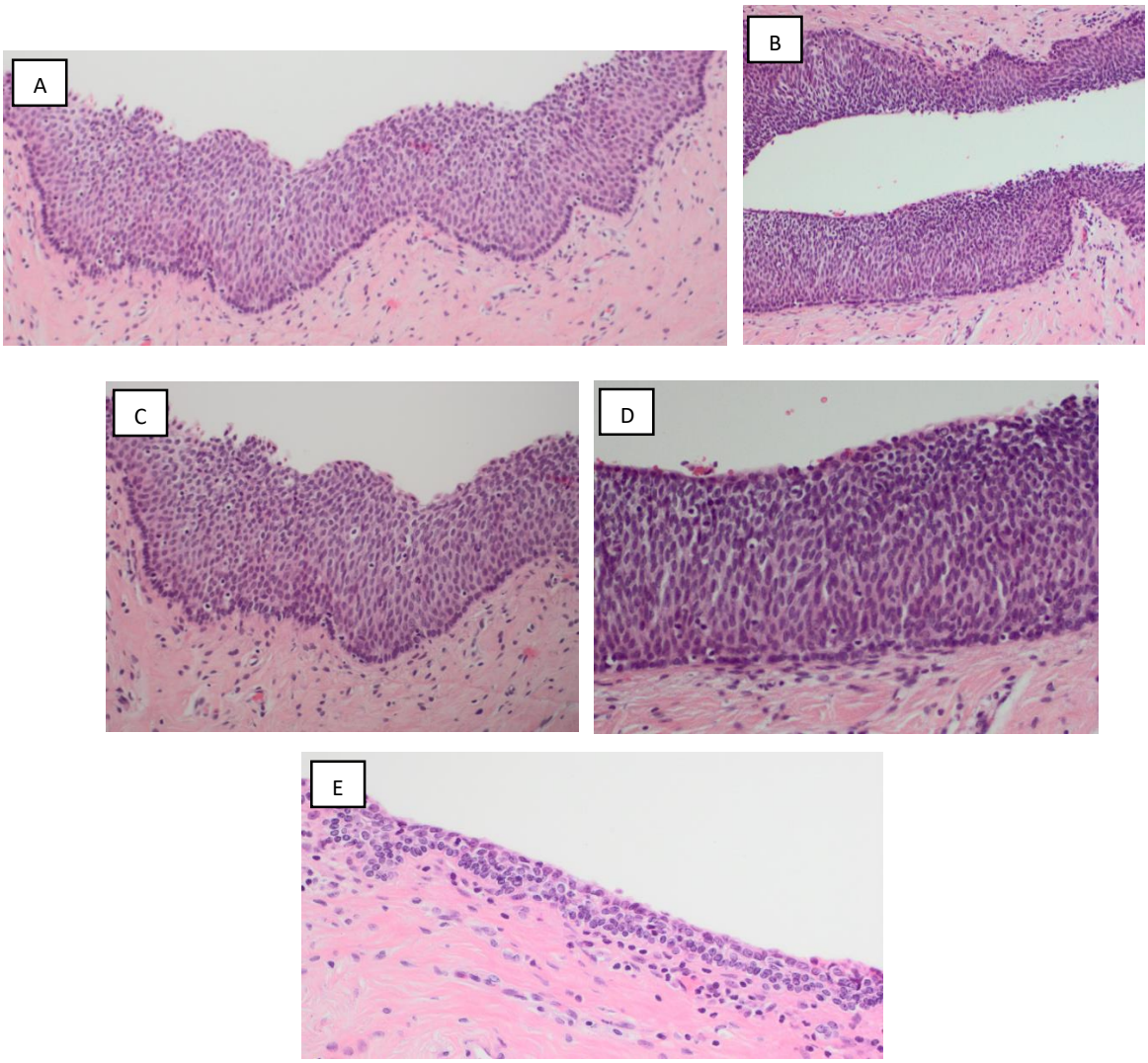


Figure 2. Epithelium with transitional cell metaplasia (A-D) and atrophy (E).
A. H&E, original magnification 100x. B. H&E, original magnification 100x. C. H&E, original magnification 200x. D. H&E, original magnification 200x. E. H&E, original magnification 200x

4.2.2. Prostatic metaplasia

Prostatic metaplasia is defined by a) intracellular changes such as vacuolization and rounding of the nuclei of the epithelial cells in the basal layer, b) prostatic type glands located within the epithelium or at the basal layer of the epithelium, c) glands that have invaginated into the subepithelial lamina propria and/or d) fully developed glands in the lamina propria resembling (ectopic) prostate tissue.

The glands within the epithelium and at the basal layer of the epithelium consisted of a single layer of cuboidal cells with pale cytoplasm and a centrally placed round nucleus. No atypia or mitotic activity was observed. Some glands contained acellular amorphous eosinophilic secretions. Glands located at the basal layer could show some invagination into the underlying lamina propria, but were mostly still attached to the epithelium. Glands that superficially invaginated into the subepithelial lamina propria seemed to display a more developed morphology characterized by papillary folding and the impression of a basal layer. Glands in the lamina propria resembling (ectopic) prostate tissue were located in the deeper stroma as well as in the superficial stroma. These glands consisted of one or more well-demarcated glandular structures with a cribriform growth pattern and/or papillary infolds. The glandular structures were lined by a two-layered epithelium consisting of an inner luminal layer and an outer basal layer. The luminal cells showed columnar cells with pale cytoplasm and a basally located round nucleus. The basal layer consisted of flattened cells. No atypia or mitotic activity was observed. In some prostatic glands transitional cell metaplasia was seen. In contrast to the previous literature on cervical ectopic prostate tissue no squamous differentiation was noticed. In rare cases there was dilatation of some glandular structures. Although some glandular structures were surrounded by a minor lymphocytic infiltrate, no desmoplastic stromal response was seen.

In almost all vaginal specimens prostatic metaplastic glands (129/140, 92%) were seen in variable amounts. Vaginectomy specimens showing a smaller amount of glands, usually had less than 4 glands per cm (24/140, 17%) in contrast to vaginectomy specimens with an abundancy of glands showing 25 or more glands per cm (24/140, 17%). Vaginectomy specimens without prostatic metaplasia tended to show less atrophy and transitional cell metaplasia. The glands were mostly spread in a (multi)focal pattern, sometimes with clustering. In fewer cases they were diffusely spread, with a greater amount of glands present.

The glands were mainly located within the lower half of the epithelium, but glands located in the upper half of the epithelium were also identified.

Prostatic metaplastic glands were also seen in the cervical mucosa albeit less frequently compared to vaginal mucosa (59/72, 82%). The glands had the same morphology and were solely seen in the ectocervix. They were usually present to a lesser extent and were more frequently located at the basal layer and less within the epithelium compared to vaginal mucosa. 14 vaginal specimens and 2 cervical specimens contained glands in the lamina propria resembling (ectopic) prostate tissue (15/140, 11%); in one case these were identified in both the vagina and the cervix of the same individual. Transitional cell metaplasia was observed in 5 cases (5/16, 30%).

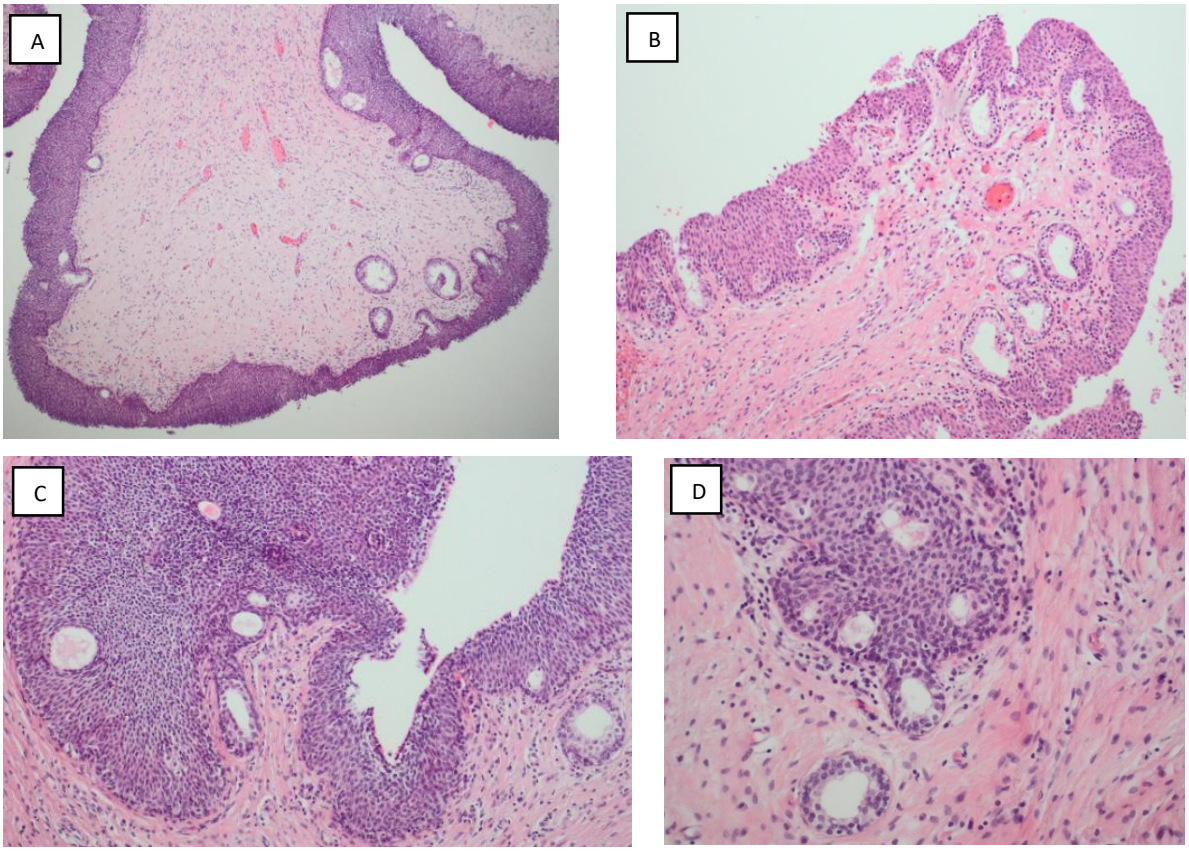


Figure 3. Overview of different glands (A-D). Intra-epithelial glands, within the epithelium and at the basal layer. Glands at the basal layer with the beginning of invagination in the lamina propria, but still attached to the epithelium. Glands in the subepithelial lamina propria.
A. H&E, original magnification 50x. B. H&E, original magnification 50x. C. H&E, original magnification 100x. D. H&E, original magnification 200x.

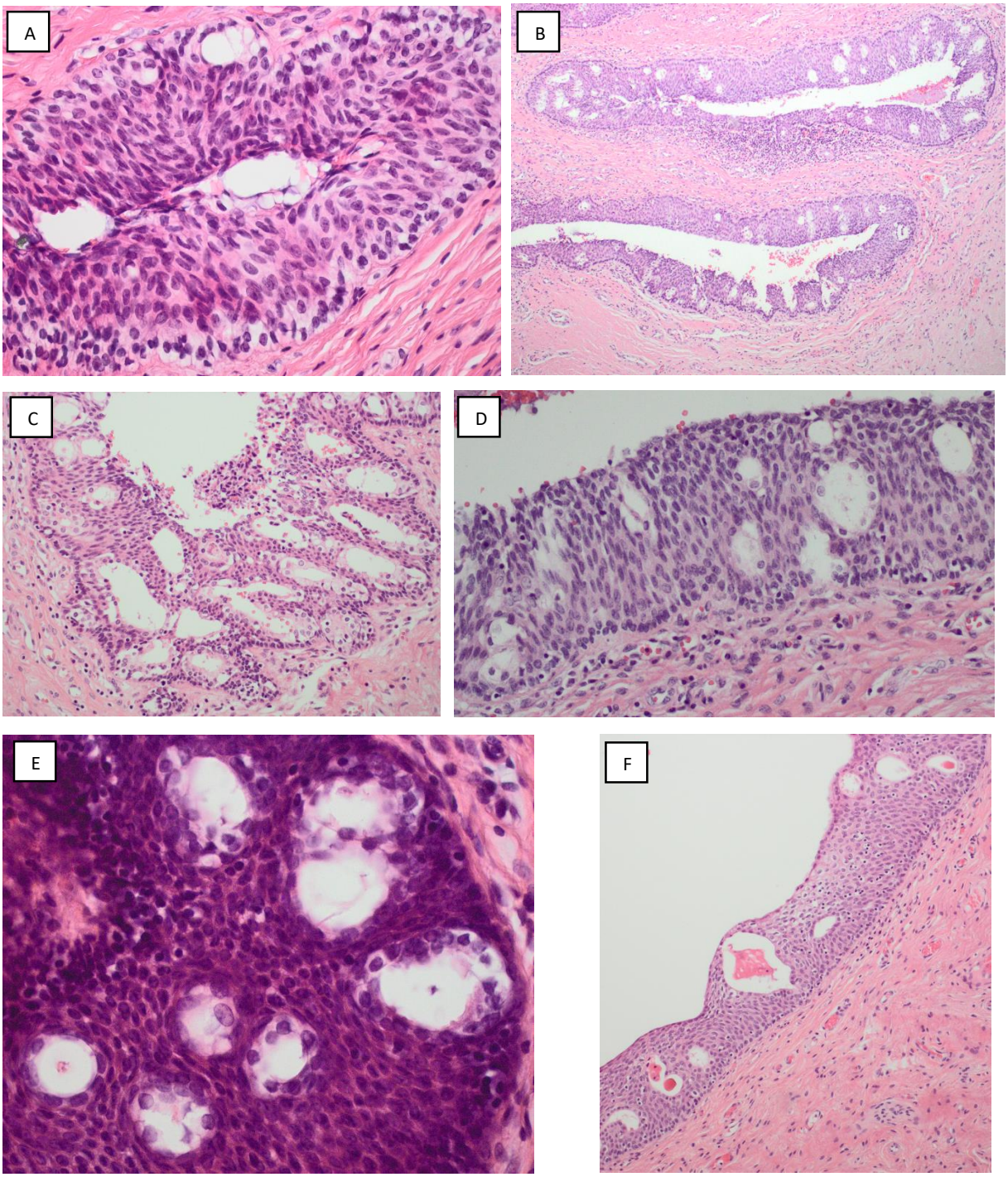


Figure 4. Basal layer and glands located within the epithelium. Intracellular changes such as vacuolization and rounding of the nuclei can be seen at the epithelial cells of the basal layer (A). Glands within the epithelium are observed across the full width of the epithelium (B-D). The glands consist of a single layer of cuboidal cells with pale cytoplasm and a centrally placed round nucleus (D-E). Some glands contain acellular amorphous eosinophilic secretions (F).
A. H&E, original magnification 400x. B. H&E, original magnification 50x. C. H&E, original magnification 200x. D. H&E, original magnification 200x. E. H&E, original magnification 400x. F. H&E, original magnification 100x.

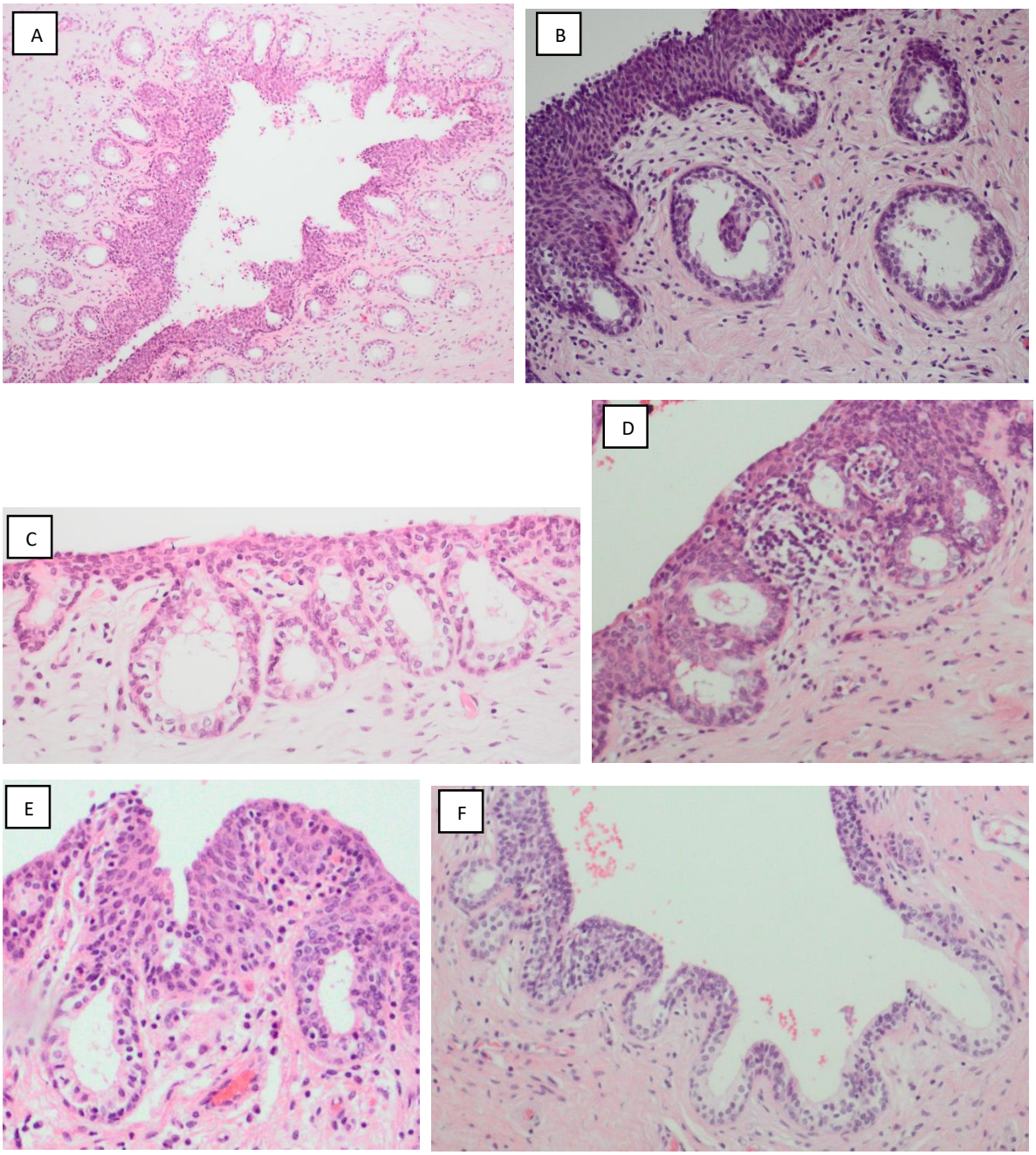


Figure 5. Glands located at the basal layer and subepithelial lamina propria. Glands located at the basal layer can show invagination into the underlying lamina propria, but are still attached to the epithelium (A-F). Glands located in the subepithelial lamina propria can show papillary infolds and seem to form a double layer (A-B).
A. H&E, original magnification 50x. B. H&E, original magnification 200x. C. H&E, original magnification 200x. D. H&E, original magnification 100x. E. H&E, original magnification 100x. F. H&E, original magnification 100x.

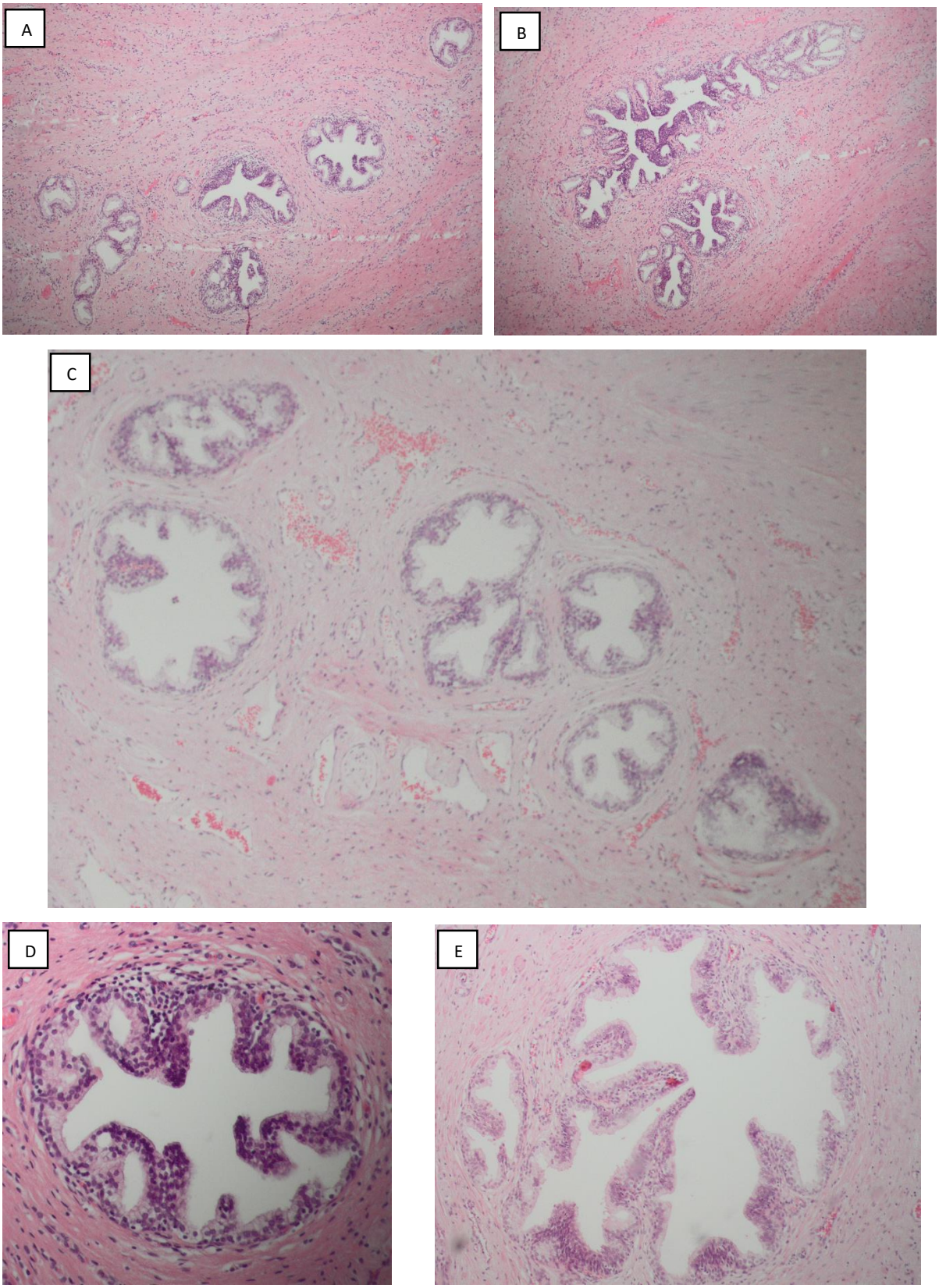


Figure 6. Glands in the lamina propria resembling (ectopic) prostate tissue. Well-demarcated glandular structures with a cribriform growth pattern and/or papillary infolds (A-E) lined by a two-layered epithelium consisting of an inner luminal layer and an outer basal layer (D). Some glands showed foci of transitional cell metaplasia (E).
A. H&E, original magnification 50x. B. H&E, original magnification 50x. C. H&E, original magnification 50x.. D. H&E, original magnification 200x. E. H&E, original magnification 100x.

4.2.3. Other structures

Bartholin glands were identified in 8 vaginectomy specimens (8/140, 6%). These commonly consisted of a single acinar-ductal structure in the deeper and sometimes more superficial vaginal stroma. The structure consisted of acini arranged in a lobular pattern draining into a centrally located ductus. The acini were lined by a single layer of columnar cells with abundant amphophilic cytoplasm and a basally located nucleus. The ductus was lined by a multi-layered epithelium of columnar cells resembling transitional epithelium. Two cases showed hyperplasia of the glands consisting of numerous acini intermixed with dilated ducti. Six cases showed ectopic breast tissue in the vaginal stroma mostly consisting of dilated ducts lined by a two-layered epithelium (6/140, 4%). In six individuals a vaginal mucous cyst was observed in the superficial or deeper vaginal stroma consisting of a cystic structure lined by a single layer of cuboidal cells (6/140, 4%). Mesonephric duct remnants were only identified in the endocervical stroma of 3 cervical specimens (3/72, 4%). Tubulosquamous polyps were not observed.

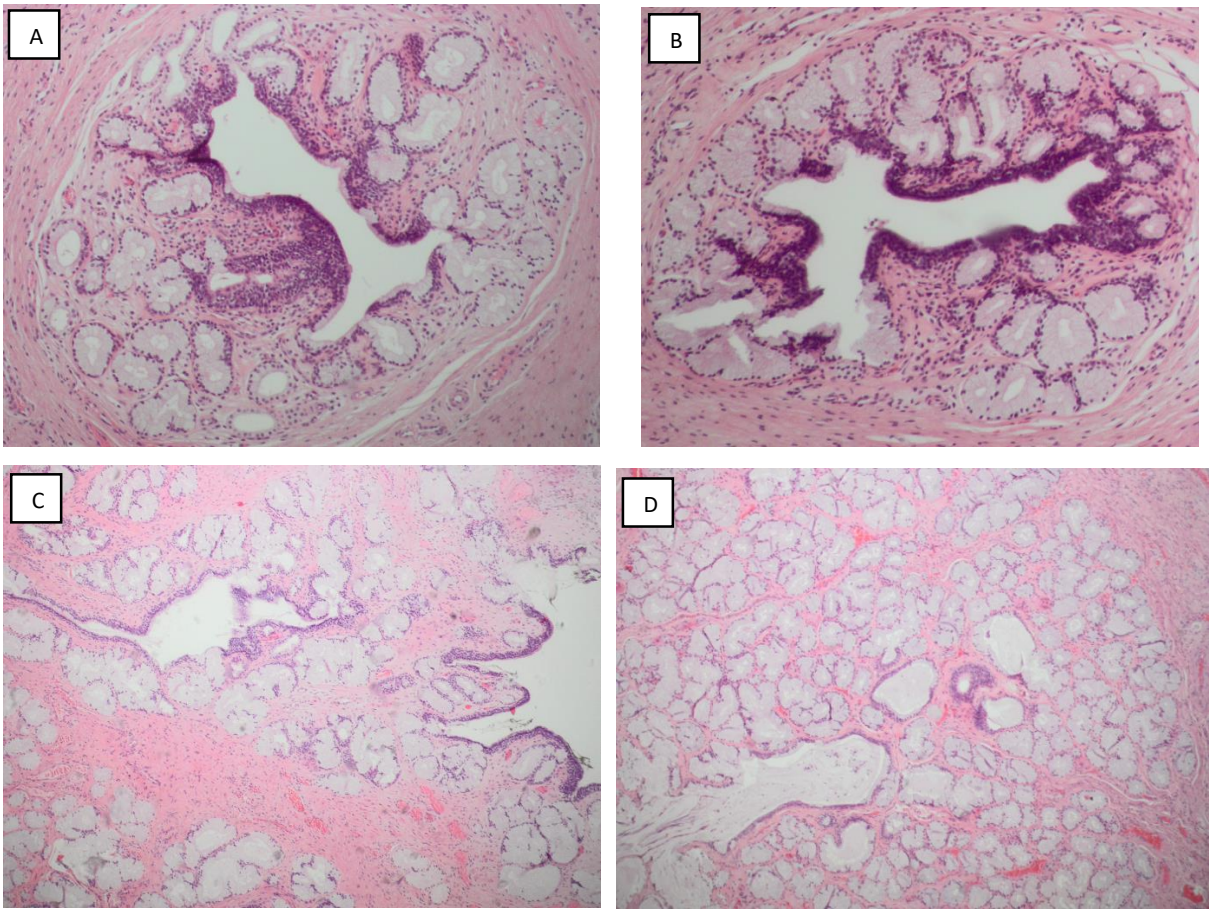


Figure 7. Bartholin glands. Bartholin glands consist of acini arranged in a lobular pattern draining into a centrally located ductus (A-B). Acini are lined by a single layer of columnar cells with abundant amphophilic cytoplasm and a basally located nucleus. The ductus is lined by a multi-layered epithelium of columnar cells resembling transitional epithelium. Bartholin gland hyperplasia can occur (C-D).
A. H&E, original magnification 100x. B. H&E, original magnification 100x. C. H&E, original magnification 50x. D. H&E, original magnification 50x.

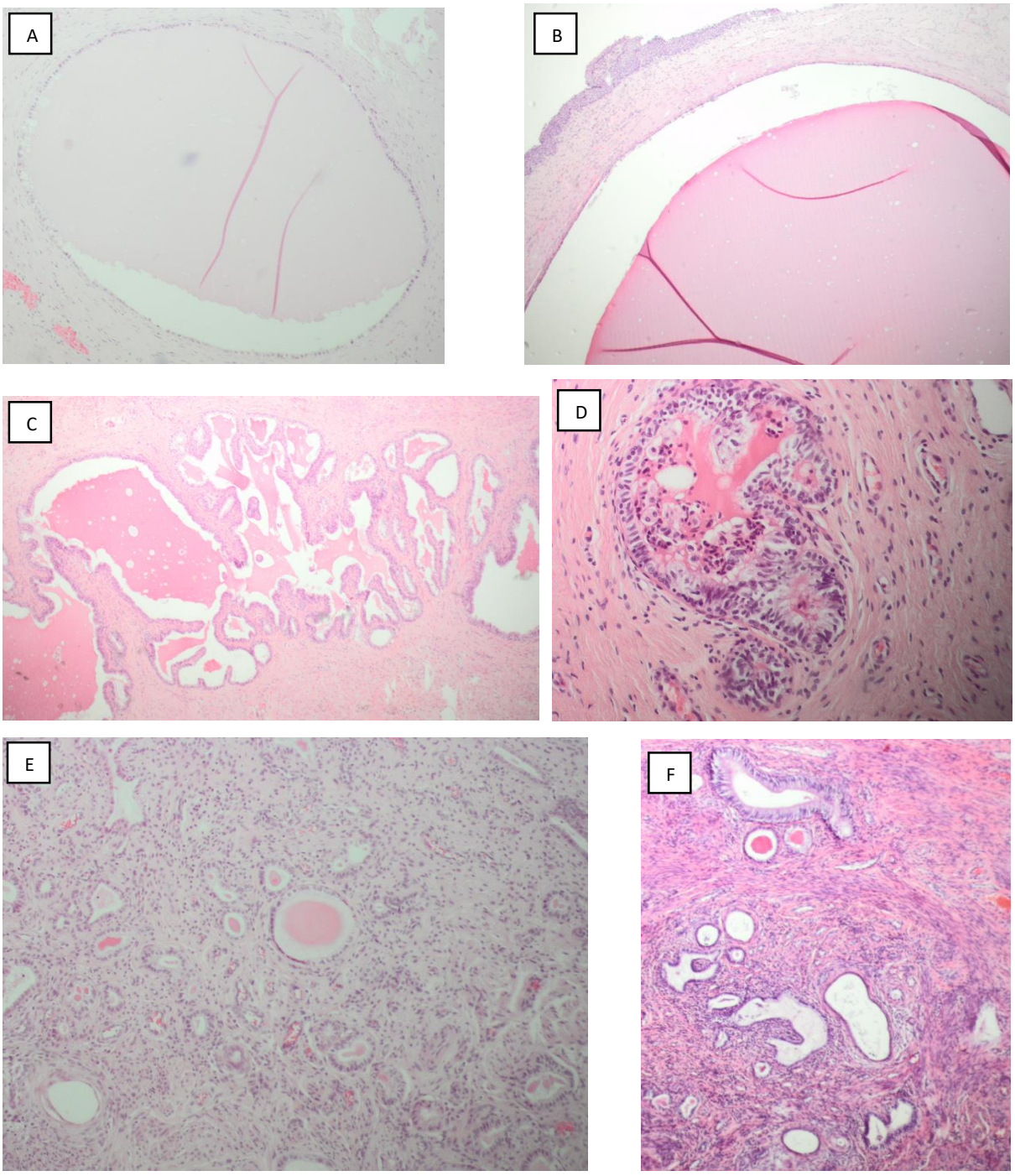


Figure 8. Other structures. Mucous cyst (A-B). Ectopic breast tissue (C-D). Mesonephric duct remnants (E-F). *A. H&E, original magnification 100x. B. H&E, original magnification 50x. C. H&E, original magnification 50x. D. H&E, original magnification 200x. E. H&E, original magnification 50x. F. H&E, original magnification 50x.*

4.3. IMMUNOHISTOCHEMICAL FINDINGS

See table 2 for an overview of immunohistochemical profiles.

4.3.1. Atrophy and transitional cell metaplasia

Atrophic squamous epithelium and transitional cell metaplasia were negative with NKX3.1, PSA or PSAP. AR showed positive staining at variable degrees. The epithelium was strongly and diffusely positive with CK5, CK8-18, CK19, p63, p40 and ER. CK7, MUC4 and CD10 showed patchy staining. GATA-3 showed focal staining and tended to have a weaker staining at the basal layer. CK14 and CK17 were positive at the basal layer. PR showed a variable weak staining at the basal layer. EpCAM showed positive staining of scattered cells. CK20, MUC1, MUC2, MUC5AC, MUC6, AMACR and PAX8 were negative.

4.3.2. Prostatic metaplasia

Although hardly visible on an H&E slide, the earliest prostatic differentiation of the basal layer of the epithelium was clearly seen with a strong and specific NKX3.1 stain.

All prostatic metaplastic glands located at different levels exhibit a similar immunohistochemically profile: they were diffusely positive with NKX3.1, PSA and PSAP. PSA tended to have a weaker and less diffuse staining than PSAP at glands located within the epithelium. NKX3.1 was positive at both the luminal layer and basal layer of glands located in the lamina propria. PSA and PSAP tended to have a weaker staining at the basal layer compared to the luminal layer of glands located in the lamina propria.

All glands were diffusely positive with CK7, CK8-18 and CK19. Glands located in the lamina propria showed positive staining at both the luminal and basal layer with a slightly weaker staining of the basal layer with CK8-18 for glands located in the subepithelial lamina propria and a patchy staining pattern with CK7 for glands resembling (ectopic) prostate tissue. CK17 showed focal positivity for glands located within the epithelium and staining at the basal layer of glands located in the lamina propria.

CK5, CK14, GATA-3, p63 and p40 were negative at glands located in the epithelium, but exhibit a strongly and diffusely positive staining at the basal layer of glands located in the lamina propria with GATA-3 showing the weakest staining.

EpCAM showed focal positivity at glands located in the epithelium and a positive staining at the luminal layer of glands located in the lamina propria.

AR showed a positive staining at the luminal layer of glands located in the lamina propria. Glands in the epithelium showed focal positivity.

ER showed a weak staining of a few scattered cells for glands located within the epithelium and staining of some scattered cells at the basal layer of glands located in the lamina propria. PR was negative at glands located in the epithelium and weakly positive at the basal layer of glands located in the lamina propria.

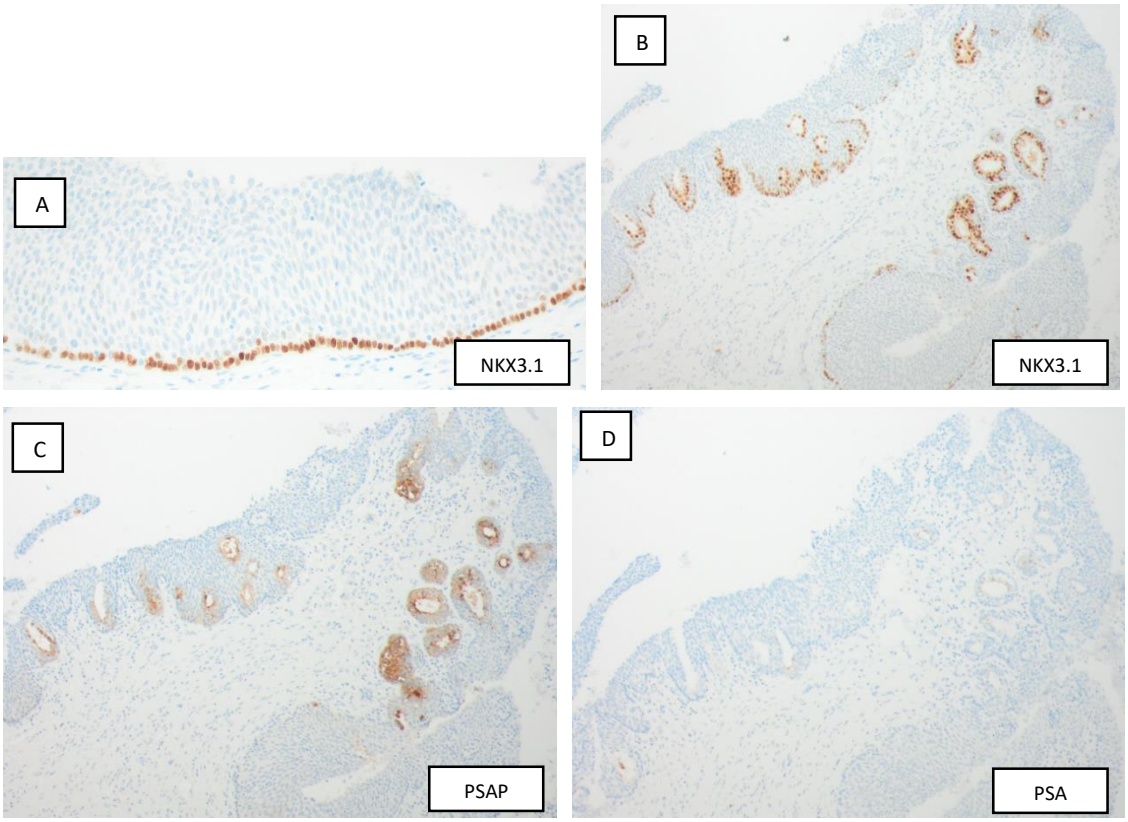
MUC4 was negative at glands located in the epithelium and glands in the lamina propria resembling (ectopic) prostate tissue. MUC4 however was focally positive for glands located in the lamina propria.

CD10 was negative at glands located in the epithelium and the subepithelial lamina propria, but was strongly and diffusely positive at the luminal and basal layer of glands in the lamina propria resembling (ectopic) prostate tissue.

All glands were negative with CK20, AMACR, PAX8, MUC1, MUC2, MUC5 and MUC6.

Areas with transitional cell metaplasia that were observed in glands resembling (ectopic) prostate tissue showed a distinct immunostaining profile. These areas were positive with CK5, GATA-3, p63, p40 and MUC4 and negative with NKX3.1, PSA and PSAP.

In addition, stromal cells showed positive staining with AR, ER, PR. All other immunohistochemical stainings were negative.



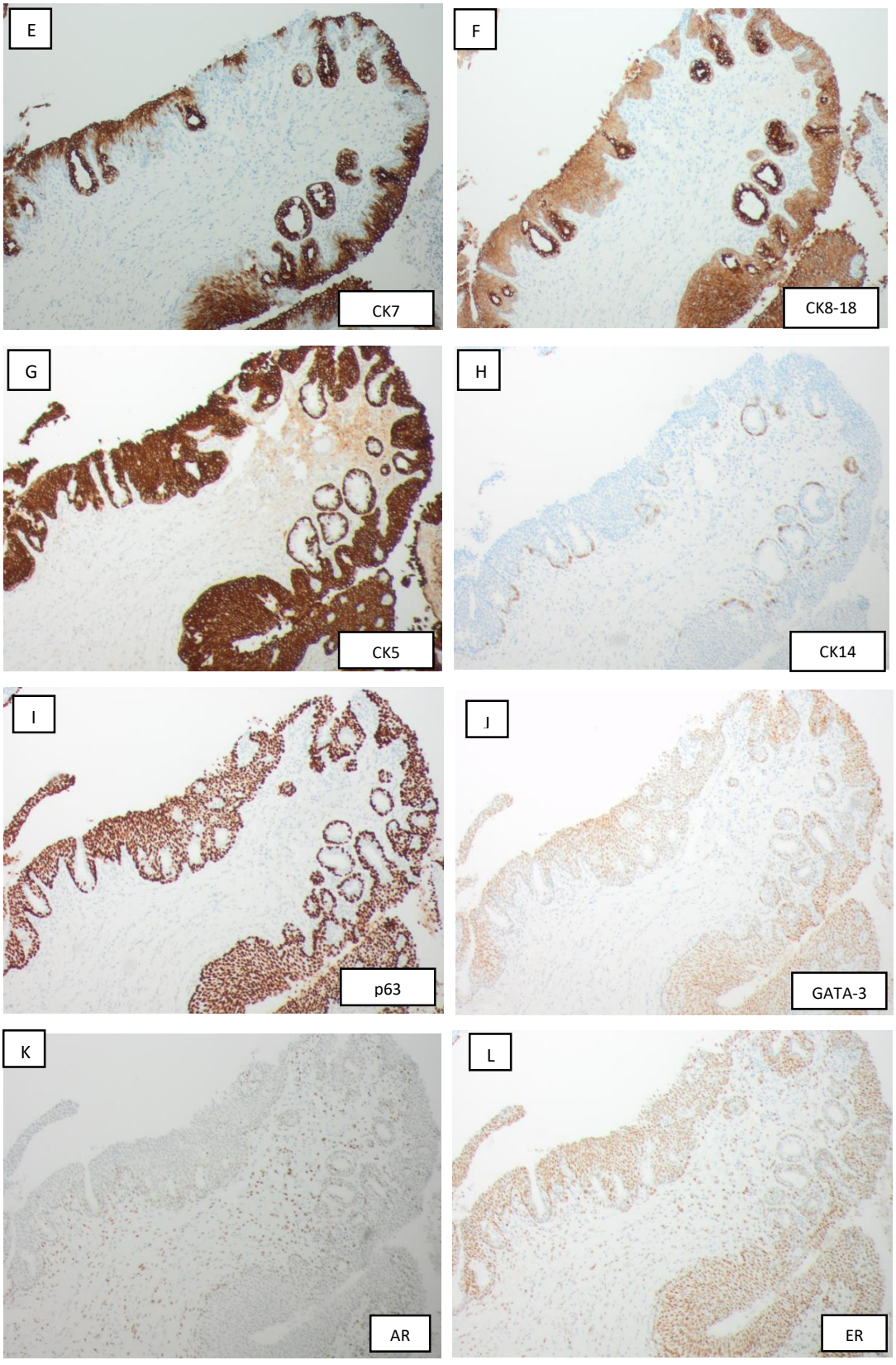


Figure 9. Immunohistochemistry: epithelium and prostatic metaplasia. The epithelium shows positive staining with NKX3.1 and CK14 at the basal layer. Strongly and diffusely staining with CK5, CK8-18, p63 and ER. AR showed a positive staining at variable degrees. CK7, GATA-3 and AR show patchy staining. Prostatic metaplastic glands showed positive staining with NKX3.1, PSA, PSAP, CK7, CK8-18 and AR. Staining at the basal layer with CK5, CK14, p63 and GATA-3. Focal staining with ER. *A. Original magnification 200x. B-L. Original magnification 100x.*

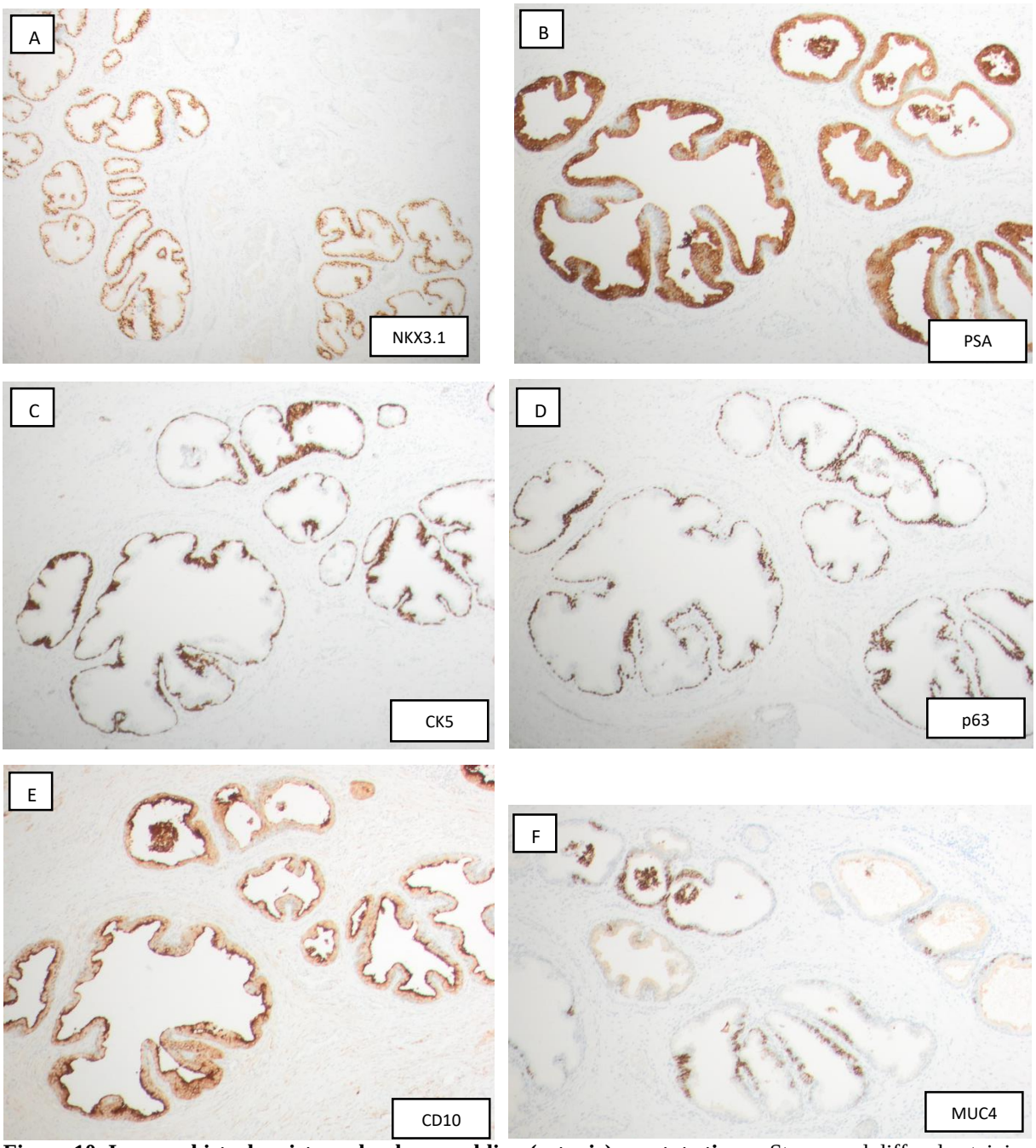


Figure 10. Immunohistochemistry: glands resembling (ectopic) prostate tissue. Strong and diffusely staining with NKX3.1 (A), PSA (B) and CD10 (E). Staining at the basal layer with CK5 (B) and p63 (D). Staining of foci with transitional cell metaplasia with MUC4 (F), CK5 (C) and p63 (D). *A-F. Original magnification 50x.*

4.3.3. Other structures

Bartholin glands were strongly and diffusely positive with NKX3.1, CK5, CK7, CK17, CK8-18, CK19 and CD10 in the acini and ducti. CK14 and AR showed a patchy positive staining, with AR having a weaker staining. p63 and p40 showed patchy positive staining at peripheral cells in both acini and ducti. GATA-3 showed a patchy positive staining in ducti and negative staining in acini. PSA and PSAP were negative. ER, PR, CK20, AMACR, PAX8, MUC1, MUC2, MUC4, MUC5AC and MUC6 were also negative.

Ectopic breast tissue and mucous cysts were negative with NKX3.1, PSA and PSAP. Ectopic breast tissue was positive with GATA-3 and mucous cysts were positive with PAX8.

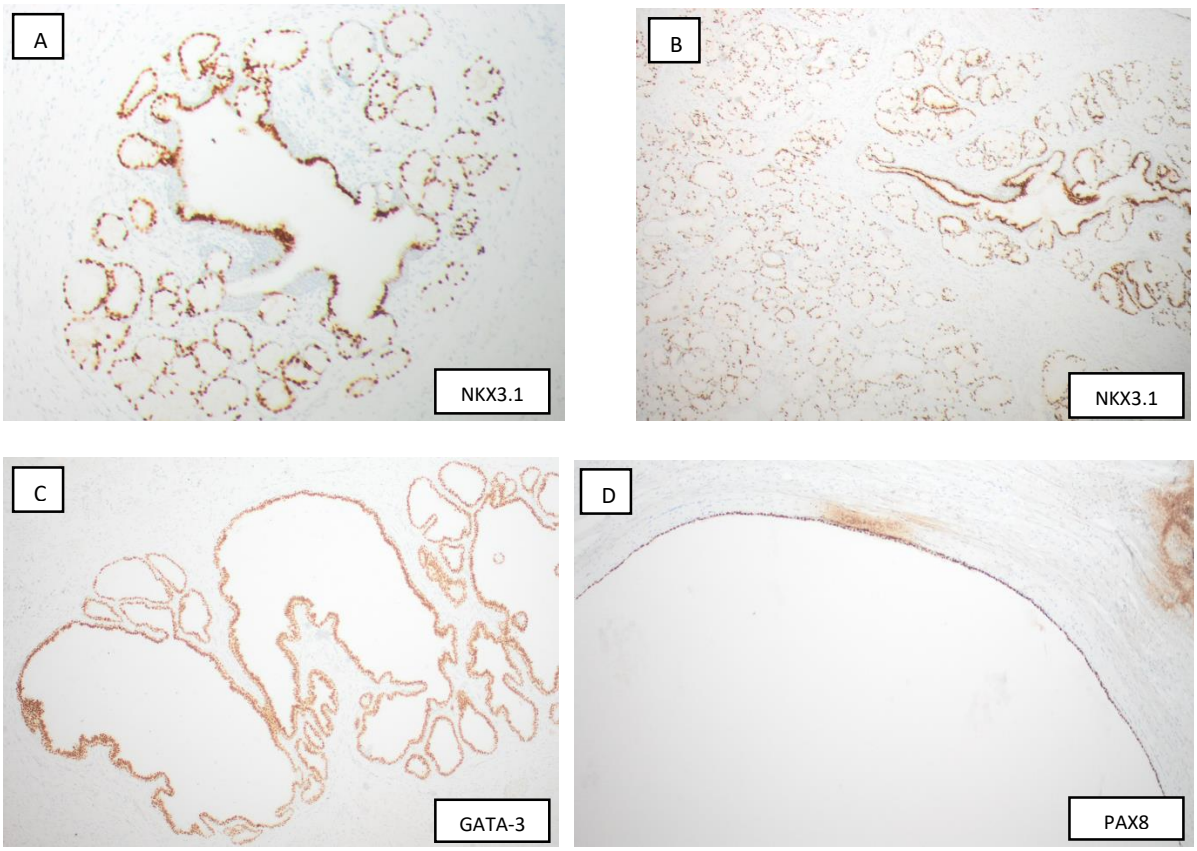


Figure 11. Immunohistochemistry: other structures. Bartholin glands show positive staining with NKX3.1 (A-B). Ectopic breast tissue stains with GATA-3 (C). Mucous cysts stain with PAX8 (D).
A. Original magnification 100x. B. Original magnification 50x. C. Original magnification 50x. D. Original magnification 50x

ANTIBODY	VAGINAL/CERVICAL EPITHELIUM	PROSTATE METAPLASIA	BARTHOLIN GLANDS
NKX 3.1	Basal layer	Positive	Positive
PSA	Negative	Positive	**Negative**
PSAP	Negative	Positive	**Negative**
CK5	Positive	Negative EP Basal layer LP/EPT + TCM	Positive
CK7	Patchy positive	Positive	Positive
CK8-18	Positive	Positive	Positive
CK14	Basal layer	Negative EP Basal layer LP/EPT	Patchy positive
CK17	Basal layer	Focally positive EP Basal layer LP/EPT	Positive
CK19	Positive	Positive	Positive
CK20	Negative	Negative	Negative
GATA-3	Patchy positive	Negative EP Basal layer LP/EPT + TCM	Patchy positive in ducti. Negative in acini.
p40	Positive	Negative EP Basal layer LP/EPT + TCM	Patchy positive in peripheral cells
p63	Positive	Negative EP Basal layer LP/EPT + TCM	Patchy positive in peripheral cells
AR	Variably positive	Focally positive EP Luminal layer LP/EPT	Weak and patchy positive
ER	Positive	Focally positive EP Focally positive basal layer LP	Negative
PR	Basal layer (weak)	Negative EP Basal layer LP (weak)	Negative
CD10	Patchy positive	Negative EP/LP Positive EPT	Positive
AMACR	Negative	Negative	Negative
PAX8	Negative	Negative	Negative
EpCAM	Scattered cells	Focally positive EP Luminal layer LP	Not performed
MUC1	Negative	Negative	Negative
MUC2	Negative	Negative	Negative
MUC4	Patchy positive	Negative EP/LP/EPT Positive TCM	Negative
MUC5AC	Negative	Negative	Negative
MUC6	Negative	Negative	Negative

Table 2. Overview of the immunohistochemical profile of different structures.
EP "glands in the epithelium"; LP "glands in the lamina propria"; EPT "glands in the lamina propria resembling (ectopic) prostate tissue"; TCM "foci of transitional cell metaplasia in glands in the lamina propria resembling (ectopic) prostate tissue". Prostatic metaplasia shows positive staining with PSA and PSAP, whereas Bartholin glands are negative with PSA and PSAP.

5. DISCUSSION

This study confirms the findings of prostatic metaplasia on a larger scale both in vaginal and cervical tissue, due to excess androgen exposition in female-to-male transgenders. We describe a spectrum ranging from changes at the basal layer of the squamous epithelium to the development of genuine prostate tissue in the vulvovaginal and ectocervical regions.

The earliest form of prostatic metaplasia depicts intracellular changes of the basal squamous epithelium, hardly visible on a routine H&E slide, but nicely accentuated by the immunohistochemical marker NKX3.1, a marker mainly used in the diagnosis of metastatic prostate cancer. The next step in this process is the development of small incomplete glands, still located in the epithelium. These intra-epithelial glands can be found at the basal layer up to the upper part of the epithelium. Better formed prostatic glandular structures located at the basal layer start to invaginate into the superficial lamina propria, either still being attached to the epithelium, either completely separated and detached from the epithelium. This process of differentiation seems very similar to the embryological development of the prostate[32], and has been suggested by Anderson et al. in 7 patients receiving androgen therapy for gender dysphoria. In our study we confirm these findings in 129 of 140 (92%) female-to-male transgenders, which is the largest series described so far. We also describe well developed prostate glands superficially and/or deeply located in the vaginal or cervical stroma in 15 of 140 (11%) female-to-male transgenders. Although not reported by Anderson et al. in their small series, we believe that this prostatic tissue constitutes the end of this spectrum and differs from the previously described ectopic prostate tissue of the cervix or tubulosquamous polyps of the vagina as seen in patients who did not receive any androgen or testosterone therapy. Therefore we suggest the term “prostatic-like glands” instead of ectopic prostate tissue to describe these glands in female-to-male transgenders treated with androgens. This hypothesis is also supported by the lack of squamous metaplasia, often described in ectopic prostate tissue[19-23, 25, 26, 28, 29] and tubulosquamous polyps[19, 25, 30] . Also no grossly visible masses were seen as often described in vaginal tubulosquamous polyps[20].

We believe that the vaginal epithelium might contain a certain precursor cell originating from the urogenital sinus that can develop into a glandular cell with prostatic features. The vagina and the prostate indeed both originate from the urogenital sinus. To prove this theory further embryological studies are necessary. Similar to Anderson et al we believe that these metaplastic changes are caused under the influence of androgens. Both Anderson et al and Kim et al. also reported these metaplastic changes in vaginal and cervical tissue of patients with endogenous androgen excess. Animal models indicate that prostatic metaplasia can be induced by androgens in vaginal tissue[33]. The positivity for AR in the epithelium, metaplastic glands and stroma is further supporting this theory. However, Anderson et al also reported the presence of prostatic metaplasia in 2 patients who had no known androgen excess.
Another hypothesis is that the prostatic metaplasia and the well differentiated prostatic-like glands as seen in our series might be derived from Skene glands. Skene glands, also known as the lesser vestibular glands, are small para-urethral glands originating from the embryological urogenital sinus and are considered as the 'female prostate'. They also show positivity for NKX3.1. However, their distinguished para-urethral location in the front part of the vagina cannot explain the wide amount of prostatic metaplasia we observe over the entire length of the vagina up to the cervix.

The amount of prostatic glands seem to correlate with the degree of atrophy and transitional cell metaplasia. Prostatic metaplasia is seen in both vaginal and cervical tissue, in the latter however to lesser extent. Also atrophy and transitional cell metaplasia occur less frequent in the cervix, which might be explained by differences in hormonal exposure.

Another finding in our series is the consistent positivity of Bartholin glands for NKX3.1. Prostatic-like glands and Bartholin glands are both glands located in the lamina propria, usually with a different morphology, but in a small biopsy the distinction might not always be clear. Whereas prostatic-like glands also show positive staining with PSA and PSAP, this was not seen in Bartholin glands.

In our study prostatic metaplasia has a very high prevalence. It is therefore notable that these glands are so little reported in previous studies. The presence of prostatic metaplasia has only been described in three previous reports: 1 case report by Singh at al. concerning cervical tissue of 2 female-to-male transgenders, a case series by Anderson et al concerning vaginal and cervical tissue of 13 patients (7 with exogenous, 4 with endogenous and 2 without androgen excess) and a case report by Kim et al concerning cervical tissue of a 23 year old woman with adrenogenital syndrome. Other studies examining cervical tissue of female-to-male transgenders did not mention these glands. Khalifa et al. even explicitly stated that "None of the specimens described in this study showed the androgen-induced virilization effects recently reported by Singh et al. in the form of paratubal epididymis-like structure and prostate-type glands involving the cervical epithelium". But as already suggested by Anderson et al., this form of metaplasia might not have been recognized in the past. Reviewing the pathology reports of our case series can confirm the theory that these lesions were often overlooked. One of the pathology reports mentioned the presence of "vaginal adenosis, embryonic type", whereas the corresponding slides showed lots of prostatic metaplastic glands including numerous glands invaginated into the lamina propria. Other glands and cysts enter the differential as well. In our series of 140 female-to-male transgenders, we also encountered a few mucous cysts and ectopic breast tissue, all of which were NKX3.1, PSA and PSAP negative.

However the clinical impact of prostatic metaplasia is not yet clear nowadays, it is of interest to gain a better understanding of the clinical impact. Female-to-male transgenders are receiving a long-term androgen treatment and not all patients choose the undergo gender affirming surgery. Additionally depending on the surgical procedure residual vaginal tissue is retained or used for reconstruction. Although we believe that the metaplastic glands are benign based on the lack of atypia and mitotic activity, it is not yet clear whether these can become malignant lesions. Although none of our patients developed a malignant lesions, further follow-up studies are required. Moreover is unknow whether these metaplastic glands possess an active secretory function. This study will raise awareness towards this metaplastic phenomenon among pathologists which will be fundamental for future research on further insights and clinical correlation of this lesion.

6. REFERENCES

1. Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfaefflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, version 7. Int J Transgenderism. 2012;13(4):165–232.

2. Monstrey SJ, Ceulemans P, Hoebeke P. Sex Reassignment Surgery in the Female-to-Male Transsexual. Semin Plast Surg. 2011 Aug;25(3):229-44.

3. Loren S Schechter, Salvatore D'Arpa, Mimis N Cohen, Ervin Kocjancic, Karel E Y Claes, Stan Monstrey. Gender Confirmation Surgery: Guiding Principles. J Sex Med. 2017 Jun;14(6):852-856.

4. T'Sjoen G, Arcelus J, Gooren L, Klink DT, Tangpricha V. Endocrinology of Transgender Medicine. Endocr Rev. 2019 Feb 1;40(1):97-117.

5. Mahmoud A Khalifa, Aimi Toyama, Molly E Klein, Victor Santiago. Histologic Features of Hysterectomy Specimens From Female-Male Transgender Individuals. Int J Gynecol Pathol. 2019 Nov;38(6):520-527.

6. Loverro G, Resta L, Dellino M, et al. Uterine and ovarian changes during testosterone administration in young female-to-male transsexuals. Taiwan J Obstet Gynecol 2016;55:686–91.

7. Michaël Grynberg, Renato Fanchin, Geneviève Dubost, Jean-Claude Colau, Catherine Brémont-Weil, René Frydman, Jean-Marc Ayoubi. Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population. Reprod Biomed Online. 2010 Apr;20(4):553-8.

8. Anna Myriam Perrone, Silvia Cerpolini, Nunzio Cosimo Maria Salfi, Claudio Ceccarelli, Lucilla Badiali De Giorgi, Guido Formelli, Paolo Casadio, Tullio Ghi, Giuseppe Pelusi, Carla Pelusi, Maria Cristina Meriggiola. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. J Sex Med. 2009 Nov;6(11):3193-200.

9. W Futterweit, L Deligdisch. Histopathological effects of exogenously administered testosterone in 19 female to male transsexuals. J Clin Endocrinol Metab. 1986 Jan;62(1):16-21.

10. N Miller, Y C Bédard, N B Cooter, D L Shaul. Histological changes in the genital tract in transsexual women following androgen therapy. Histopathology. 1986 Jul;10(7):661-9.

11. Kamaljeet Singh, C James Sung, W Dwayne Lawrence, M Ruhul Quddus. Testosterone-induced "Virilization" of Mesonephric Duct Remnants and Cervical Squamous Epithelium in Female-to-Male Transgenders: A Report of 3 Cases. Int J Gynecol Pathol. 2017 Jul;36(4):328-333.

12. M Ruhul Quddus, Renan Ribeiro E Ribeiro, Kamaljeet Singh. Androgen-induced Hyperplastic Prostatic Glands in the Uterine Cervix. Int J Gynecol Pathol. 2020 Dec 14.

13. William J Anderson, David L Kolin, Grace Neville, David A Diamond, Christopher P Crum, Michelle S Hirsch , Sara O Vargas. Prostatic Metaplasia of the Vagina and Uterine Cervix: An Androgen-associated Glandular Lesion of Surface Squamous Epithelium. Am J Surg Pathol. 2020 Aug;44(8):1040-1049.

14. T H van der Kwast, H B Dommerholt, C C van Vroonhoven, S Chadha. Androgen receptor expression in the cervix of androgen-treated female-to-male transsexuals: association with morphology and chain-specific keratin expression. Int J Gynecol Pathol. 1994 Apr;13(2):133-8.

15. N Miller, Y C Bédard, N B Cooter, D L Shaul. Histological changes in the genital tract in transsexual women following androgen therapy. Histopathology. 1986 Jul;10(7):661-9.

16. AJ Egan, P Russell. Transitional (urothelial) cell metaplasia of the uterine cervix: morphological assessment of 31 cases. Int J Gynecol Pathol. 1997 Apr;16(2):89-98.

17. MM Weir, DA Bell, RH Young. Transitional cell metaplasia of the uterine cervix and vagina: an underrecognized lesion that may be confused with high-grade dysplasia. A report of 59 cases. Am J Surg Pathol. 1997 May;21(5):510-7.

18. Kyu-Rae Kim , Kyoung-Hee Park, Jung-Won Kim, Kyoung-Ja Cho, Jae Y Ro. 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 Apr;23(2):182-7.

19. Rand Hawari, Larissa Fernandes, Kay J Park, W Glenn McCluggage. Skene's Gland Derivatives in the Female Genital Tract and Cervical Adenoid Basal Carcinoma are Consistently Positive With Prostatic Marker NKX3.1. Int J Gynecol Pathol. 2021 Jul 1;40(4):400-407.

20. Paul Kelly, Hilary A McBride, Kathryn Kennedy, Lynette E Connolly, W Glenn McCluggage. 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 Nov;30(6):605-12.

21. W Glenn McCluggage, Raji Ganesan, Lynn Hirschowitz, Keith Miller, Terence P Rollason. Ectopic prostatic tissue in the uterine cervix and vagina: report of a series with a detailed immunohistochemical analysis. Am J Surg Pathol. 2006 Feb;30(2):209-15.

22. M R Nucci, J A Ferry, R H Young. Ectopic prostatic tissue in the uterine cervix: a report of four cases and review of ectopic prostatic tissue. Am J Surg Pathol. 2000 Sep;24(9):1224-30.

23. Andres A Roma . Tubulosquamous polyps in the vagina. Immunohistochemical comparison with ectopic prostatic tissue and Skene glands. Ann Diagn Pathol. 2016 Jun;22:63-6.

24. Mahendra Singh. Ectopic prostatic tissue in the uterine cervix. Report of a case and brief overview of basaloid cervical glandular lesions. J Clin Pathol. 2012 Jun;65(6):573-5.

25. Dmitry V Kazakov, Colin J R Stewart, Denisa Kacerovska, Robyn Leake, Boris Kreuzberg, Zdenek Chudacek, Milan Hora, Michal Michal. 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 Jul;34(7):950-5.

26. Dilek Ertoy Baydar, Cigdem Himmetoglu. Test and Teach. Abnormal glands in the uterine cervix Part 1. Diagnosis: Ectopic prostate tissue in the uterine cervix. Pathology. 2008 Jun;40(4):407-8.

27. U Güth, G Singer. Ectopic prostatic tissue in the uterine cervix. Pathologe. 2007 Jul;28(4):291-3.

28. C Wallace, A J Creager, J O Cappellari, S Bergman. Ectopic prostatic tissue in the uterine cerrix. Am J Surg Pathol. 2001 Sep;25(9):1215-6.

29. O Larraza-Hernandez, K H Molberg, G Lindberg, J Albores-Saavedra. Ectopic prostatic tissue in the uterine cervix. Int J Gynecol Pathol. 1997 Jul;16(3):291-3.
30. Simon F Roy, Lise Comeau, Diane Provencher, Kurosh Rahimi. Tubulosquamous Polyp of the Vagina: Misplaced Skene's Glands Analogous to the Male Prostate. Int J Surg Pathol. 2021 Aug;29(5):510-512.

31. W Glenn McCluggage, Robert H Young. Tubulo-squamous polyp: a report of ten cases of a distinctive hitherto uncharacterized vaginal polyp. Am J Surg Pathol. 2007 Jul;31(7):1013-9.

32. Prostate organogenesis: tissue induction, hormonal regulation and cell type specification. Roxanne Toivanen, Michael M Shen. Development. 2017 Apr 15;144(8):1382-1398.

33. G R Cunha. Age-dependent loss of sensitivity of female urogenital sinus to androgenic conditions as a function of the epithelia-stromal interaction in mice.. Endocrinology. 1975 Sep;97(3):665-73.

7. NEDERLANDSTALIGE SAMENVATTING

De histologische veranderingen in de genitale tractus van transmannen werden reeds beschreven in het verleden. Er is echter nog maar weinig onderzoek gedaan naar histologische veranderingen ter hoogte van de vagina. Daarenboven was het aantal patiënten meestal laag in de eerdere studies. Anderson et al. beschreef recent een nieuw fenomeen in vaginaal en cervicaal weefsel hetgeen ze benoemden als “prostatische metaplasie”.

Het doel van deze studie is het aanleveren van data op grote schaal omtrent de beschrijving en prevalentie van histologische veranderingen in de vagina en ectocervix van transmannen met speciale aandacht voor “prostatische metaplasie”, inclusief een immuunhistochemisch profiel van deze lesie en een differentiaal diagnose.

Alle H&E-coupes en immuunhistochemische kleuringen van 140 vulvovaginectomiën en 72 geassocieerde uteri werden gereviseerd. In 96,5% van de vagina’s en 85% van de exocervixen werd er atrofie en transitionele cel metaplasie gezien. Prostatische metaplasie werd gezien in 92% van de vagina’s en 82% van de exocervixen. Prostatische metaplasie kan gezien worden als een spectrum met toenemende maturatie gaande van a) intracellulaire veranderingen ter hoogte van de basale laag van het epitheel, b) prostaatachtige klieren binnen het epitheel of ter hoogte van de basale laag van het epitheel, c) klieren met een luminale en basale laag die zijn geïnvagineerd in de subepitheliale lamina propria en/of d) volledige ontwikkelde klieren in de lamina propria die gelijkenissen vertonen met (ectopisch) prostaatweefsel. De basale laag van het metaplastisch epitheel was positief voor NKX3.1. De klieren tonen aankleuring voor NKX3.1, PSA, PSAP, AR, CK7, CK8-18, CK17, CK19 en EpCAM. De klieren in de lamina propria die gelijkenissen vertonen met (ectopisch) prostaatweefsel zijn ook diffuus positief voor CD10.

Wij zijn de mening toegedaan dat dit metaplastisch proces wordt veroorzaakt door de invloed van androgenen. We zijn eveneens van mening dat, gezien deze prostaatklieren frequent voorkomen, deze in het verleden vaak over het hoofd werden gezien. Het mechanisme en de klinische impact van prostatische metaplasie is op dit moment nog niet gekend.

Bijkomend werden eveneens andere structuren gezien zoals Bartholinklieren (6%), ectopisch borstweefsel (4%), mukeuze cysten (4%) en mesonefrische resten (4%). Bartholinklieren tonen aankleuring voor NKX3.1, maar geen aankleuring voor PSA en PSAP. Ectopisch borstweefsel, mukeuze cysten en mesonefrische resten tonen geen aankleuring voor NKX3.1, PSA of PSAP.

Dit onderzoek zal leiden tot een betere (h)erkenning van dit metaplastisch proces bij pathologen, hetgeen zal bijdragen tot verder onderzoek naar een beter begrip en klinische correlatie van deze lesie.