Prostatic Metaplasia of the Vagina and Uterine Cervix
An Androgen-associated Glandular Lesion of Surface Squamous Epithelium

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汇 报 人: 马 静

BACKGROUND

- 先天性肾上腺增生症

又称肾上腺生殖器综合征或肾上腺性变态征。主要由于肾上腺皮质激素合成过程中所必需的酶存在缺陷，致使激素合成不正常。多数病例雄性激素过多，故临床上出现不同程度的肾上腺皮质功能减退，伴有女孩男性化，而男孩则表现性早熟，此外尚可有低血钠或高血压等多种症候群。

- 治疗：激素

BACKGROUND

- 两性畸形

  是指一个个体的性器官有着男女两性的表现。可分为真两性畸形和假两性畸形。真两性畸形是指在同一个体内既有睾丸又有卵巢，其外生殖器与第二性征介于两性之间。染色体核型可为正常男性型、女性型或嵌合型；假两性畸形指性腺与外生殖器不相一致，如外生殖器类似女性而内生殖器为睾丸者称男性假两性畸形（46, XY）。

- 治疗：手术切除后，激素替代治疗

BACKGROUND

- 5α-还原酶缺陷症

  是由于5α还原酶缺陷，睾酮不能转变为双氢睾酮所致，是一种家族性常染色体隐性遗传病。患者染色体为46，XY，有正常睾丸功能，睾酮合成正常，性别及内生殖器均为正常男性。但泌尿生殖窦因DHT缺乏，除有增大的阴蒂外，均分化为女性。

- 治疗：整形手术后，激素补充治疗

BACKGROUND

- 性别焦虑症（gender dysphoria, GD）

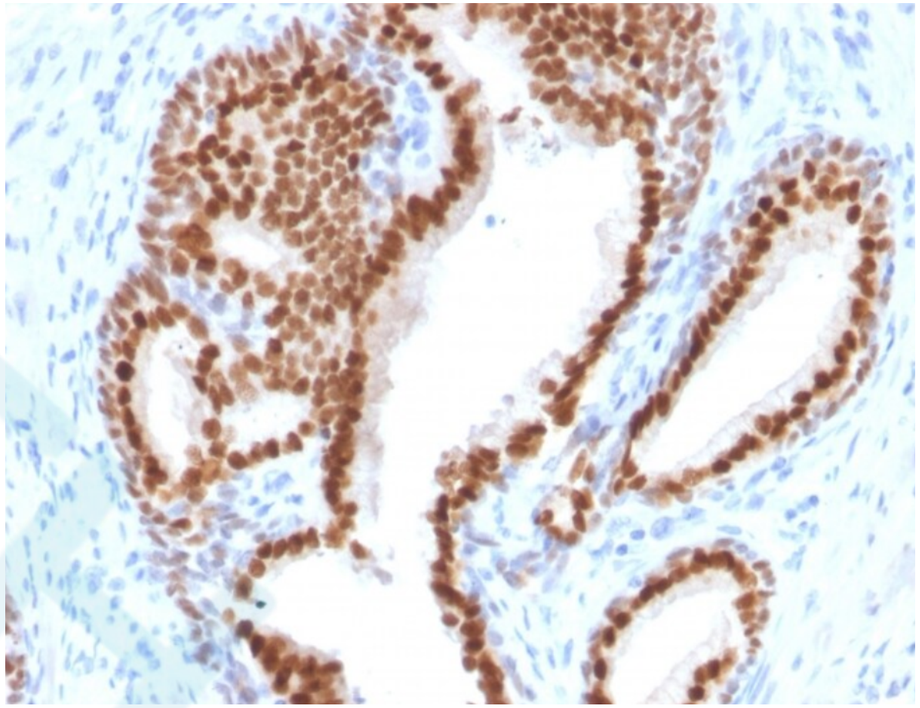
  又称性别认同障碍（Gender Identity Disorder），是焦虑症的一个小分支。这种症状主要是针对那些对自己性别不认同的人。

- 治疗：心理治疗；变性手术后激素治疗

BACKGROUND

- NKX3.1

是前列腺癌敏感和特异的组织标志物，可用于前列腺癌与尿路上皮癌的鉴别诊断(*Gurel B, et al. NKX3.1 as a marker of prostatic origin in metastatic tumors. Am J SurgPathol. 2010; 34:1097-105.*)。



Formalin-fixed, paraffin-embedded human prostate carcinoma tissue labeling Nkx3.1 using ab257308 at 2 µg/ml in immunohistochemical analysis.

BACKGROUND

- The development of prostatic-type tissue in the female genital tract is a rare anatomic phenomenon of uncertain etiology.
- These include the so called ectopic prostatic tissue of the cervix, tubulosquamous polyp (TSP) of the vagina, and adenomyomatous hyperplasia of Skene glands.
- Histologically, these are primarily lesions of the lamina propria.

BACKGROUND

- We recently encountered a vaginectomy specimen in which glands were widely distributed within the surface squamous epithelium, without involvement of the underlying lamina propria.
- Morphologically and immunohistochemically, these glands resembled prostatic glandular epithelium.
- Interestingly, the patient had received long-term androgen therapy for gender dysphoria (GD), supporting the possibility of a hormonally induced process.

BACKGROUND

- Herein, we aim to further characterize the clinical, histopathologic, and immunohistochemical features of this unusual glandular lesion.
- Transgender males receiving exogenous androgen therapy, and pediatric patients with disorders of sexual development associated with endogenous androgen excess.
- Our findings strongly support that this lesion is metaplastic in nature and likely to become more commonly encountered in surgical pathology in the context of gender-affirming surgery.

Materials and Methods

- Case Selection
- After encountering the index case, similar lesions occurring in the vagina, cervix or vulva were sought over a 26-year period (1993-2019).
- Biopsies and resections from these anatomic sites were identified from patients clinically suspected to have either exogenous or endogenous androgen excess, for example, in the setting of GD, congenital adrenal hyperplasia, and other disorders of sexual development.
- In addition, cases in which the report described “adenosis,” “glands,” or “prostatic tissue” occurring in squamous epithelium were also retrieved.

Materials and Methods

- Case Selection
- Cases were excluded if glands were absent or only present within the lamina propria.
- Positive staining for at least 1 prostatic marker (NKX3.1 or prostate-specific antigen [PSA]) was also required for inclusion.
- Control cases (n=3) of normal vaginal mucosa were retrieved from patients (aged 1, 12, and 13 y) without clinical evidence of androgen excess to compare histologic and immunohistochemical features.

Materials and Methods

- Immunohistochemistry
- In each case with available material and in controls, immunohistochemistry was performed for NKX3.1, PSA, androgen receptor (AR) and CK7.
- Additional stains performed in selected cases included p63, estrogen receptor(ER), progesterone receptor, CK20, PAX8, and GATA3.

Materials and Methods

- Immunohistochemistry
- Details of the antibody clones, dilutions, antigen retrieval methods and sources are given in Table 1. Positive control slides were stained in parallel.

TABLE 1. Antibodies Used in This Study

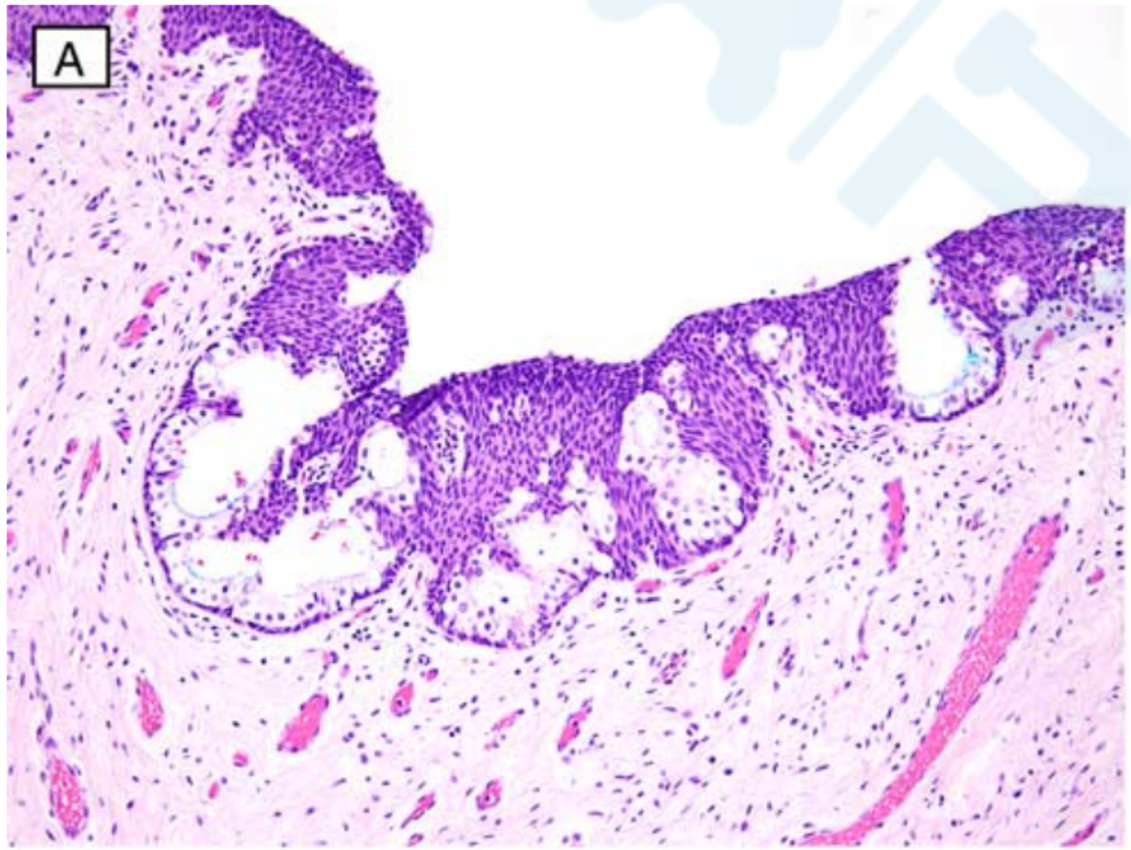
Antigen	Clone	Dilution	Antigen Retrieval	Source
PSA	Polyclonal (rabbit)	1:7500	None	DAKO, Carpinteria, CA
NKX3.1	Polyclonal (rabbit)	1:1000	Pressure cooker	Athena ES, Baltimore, MD
AR	AR441	1:200	Pressure cooker	DAKO, Carpinteria, CA
CK7	OV-TL	1:2000	10 min protease	DAKO, Carpinteria, CA
p63	4A4	1:150	Pressure cooker	Ventana, Tucson, AZ
ER	SP1	1:50	Pressure cooker	Thermoscientific, Cheshire, UK
PR	PgR636	1:50	Pressure cooker	DAKO, Carpinteria, CA
PAX8	Polyclonal (rabbit)	1:1400	Pressure cooker	ProteinTech Group, Chicago, IL
GATA3	L50-823	1:400	Pressure cooker	Biocore Medical, Concord, CA
CK20	KS208	1:50	10 min protease	DAKO, Carpinteria, CA

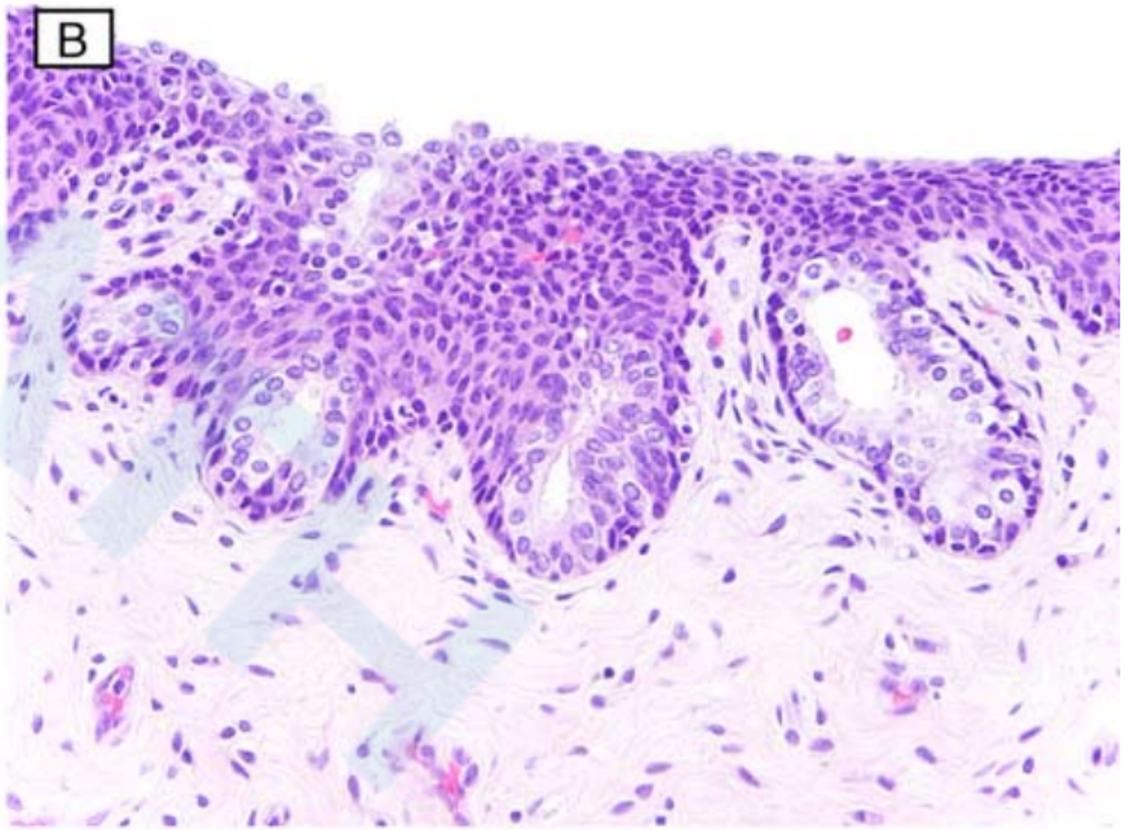
PR indicates progesterone receptor.

Results—Index Case

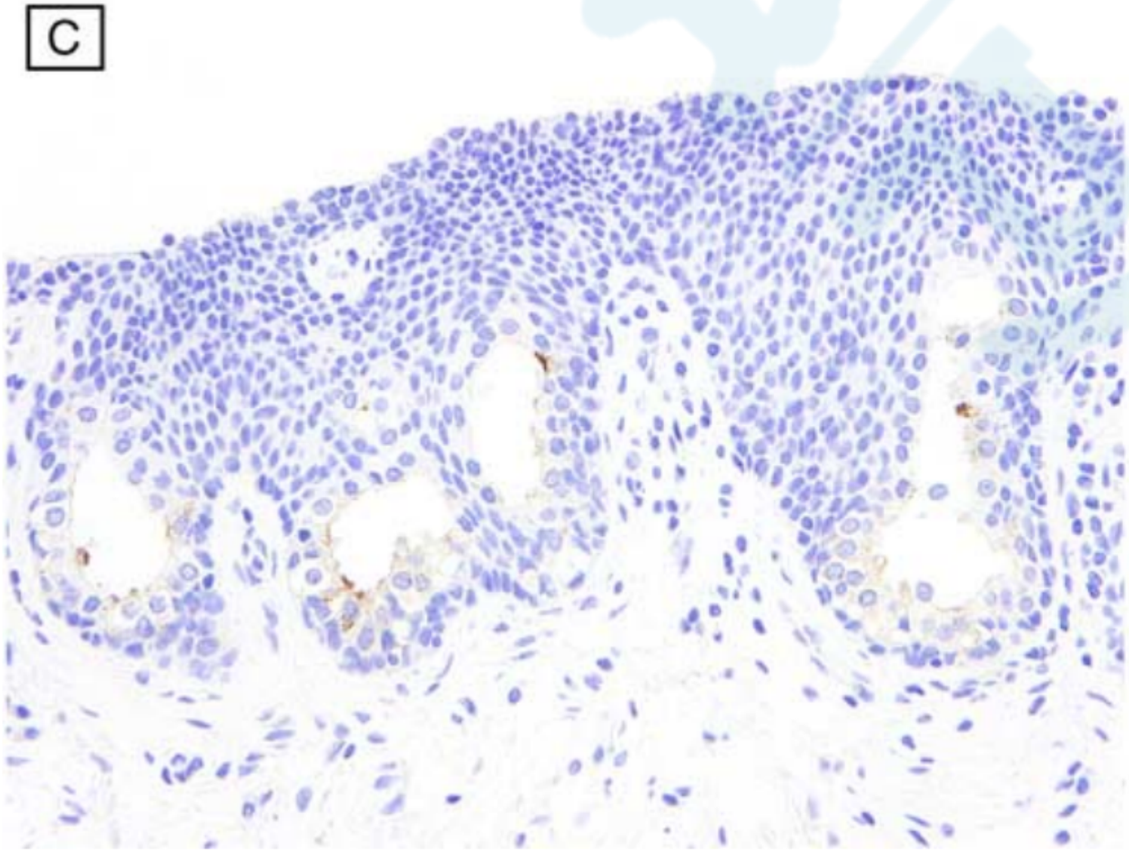
- He had received 3 years of masculinizing androgen therapy (testosterone cypionate) and had previously undergone hysterectomy and bilateral salpingo-oophorectomy as part of his transition. He presented to our institution for vaginectomy, scrotoplasty, and phalloplasty. Gross examination of the vaginal tissue was unremarkable, and sections from different areas were submitted for histologic examination.

Results—Index Case

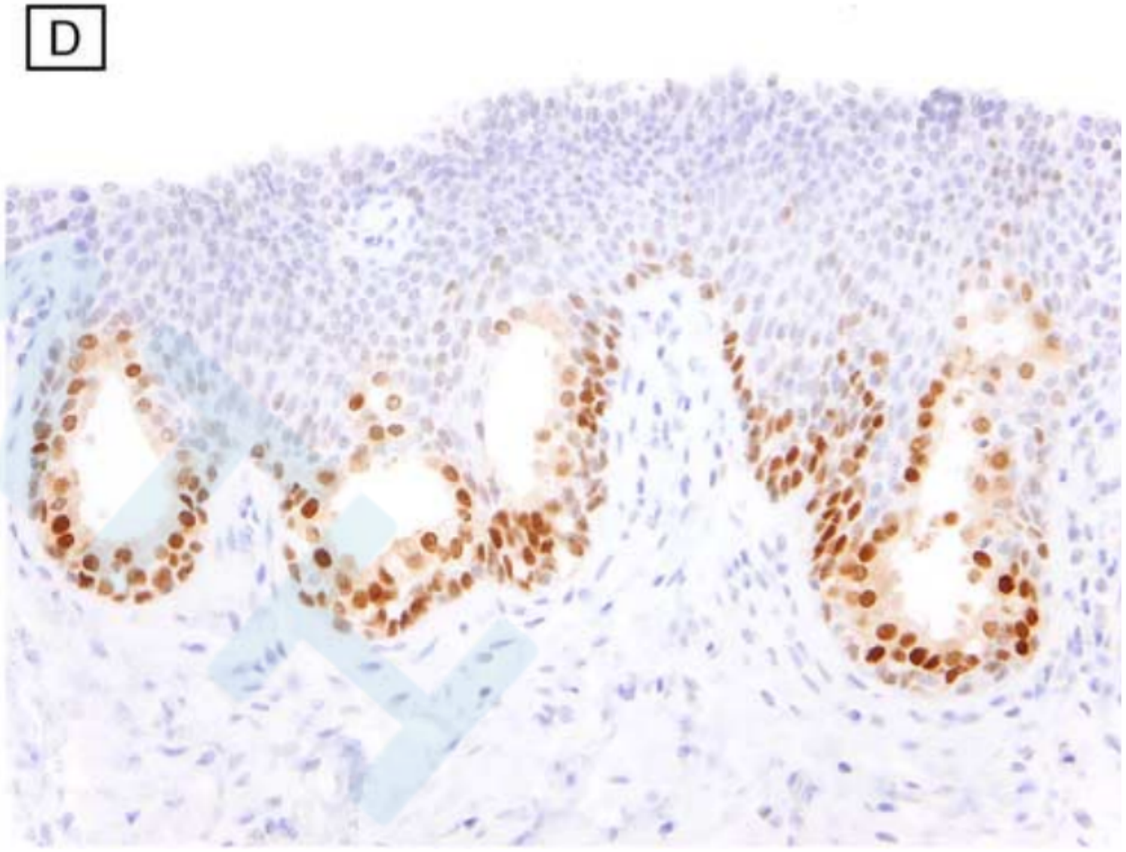




Results—Index Case



PSA



NKX 3.1

Results—Clinical Features

- Patients With GD Treated With Exogenous Androgens (n = 7)

TABLE 2. Clinicopathologic Features

Case No.	Age	Procedure	Indication	Androgen Exposure	Hormonal Therapy (Duration—Months)
1	30	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (36)
2	26	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (32)
3	23	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (60)
4	27	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (not known)
5	34	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (36)
6	25	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (72)
7	18	Hysterectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (24)
8	16	Vaginal reconstruction	Congenital adrenal hyperplasia	Endogenous	None
9	23	Perivaginal tissue resection	Congenital adrenal hyperplasia	Endogenous	None
10	17	Urethral polyp/vaginal resection	46,XY DSD	Endogenous	None
11	12	Vaginal and prostatic utricle resection	OTDSD	Endogenous	None
12	15	Vaginoplasty	Agenesis of lower vagina	None	None
13	33	Vaginal biopsy	Colposcopic lesion	Not known	Not known

DSD indicates disorder of sexual development; OTDSD, ovostesticular disorder of sexual development.

Results—Clinical Features

- Patients With Disorders Associated With Increased Endogenous Androgens (n = 4)

TABLE 2. Clinicopathologic Features

Case No.	Age	Procedure	Indication	Androgen Exposure	Hormonal Therapy (Duration—Months)
1	30	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (36)
2	26	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (32)
3	23	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (60)
4	27	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (not known)
5	34	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (36)
6	25	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (72)
7	18	Hysterectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (24)
8	16	Vaginal reconstruction	Congenital adrenal hyperplasia	Endogenous	None
9	23	Perivaginal tissue resection	Congenital adrenal hyperplasia	Endogenous	None
10	17	Urethral polyp/vaginal resection	46,XY DSD	Endogenous	None
11	12	Vaginal and prostatic utricle resection	OTDSD	Endogenous	None
12	15	Vaginoplasty	Agenesis of lower vagina	None	None
13	33	Vaginal biopsy	Colposcopic lesion	Not known	Not known

DSD indicates disorder of sexual development; OTDSD, ovostesticular disorder of sexual development.

Results—Clinical Features

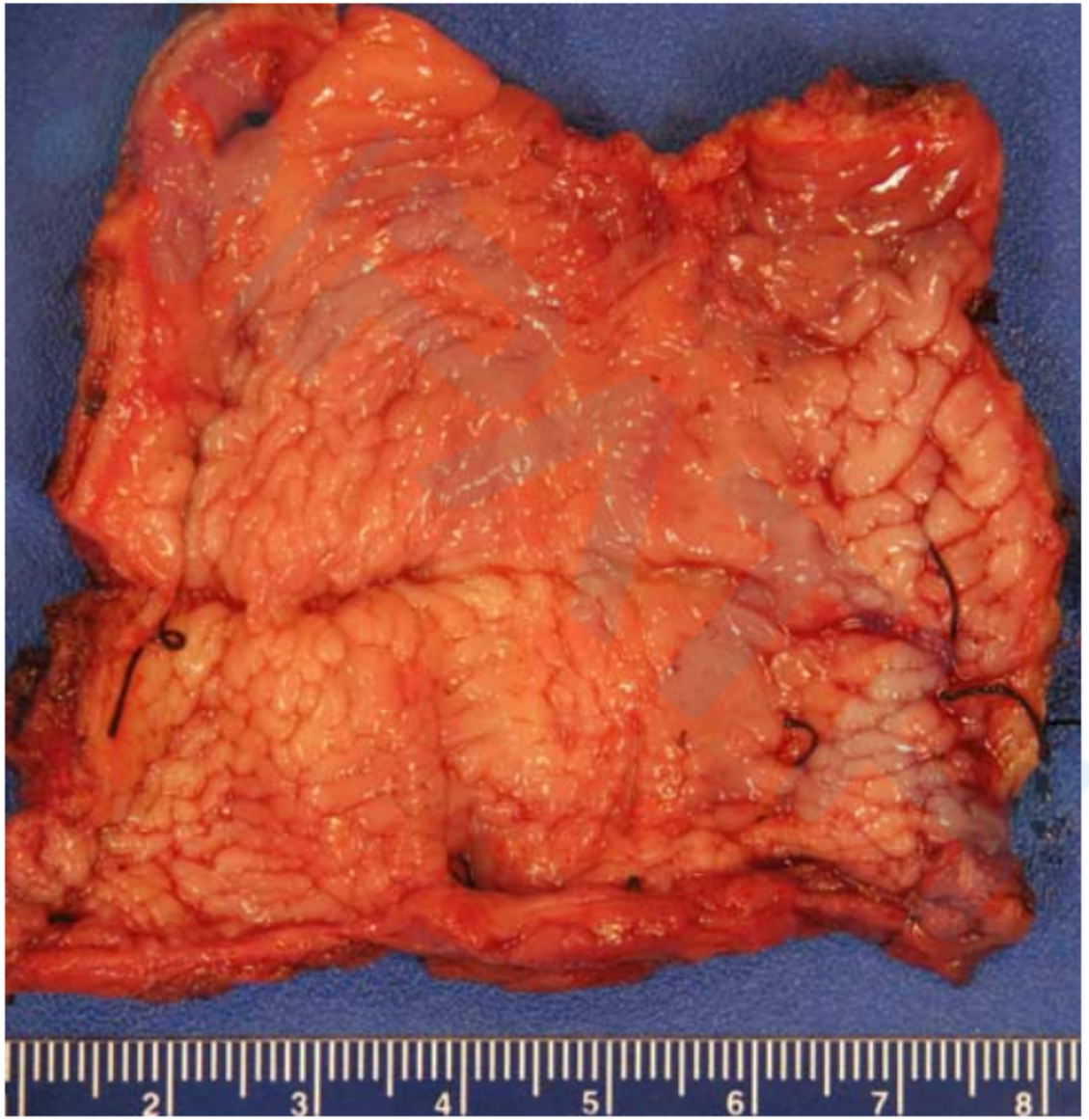
- Patients Without Evidence of Androgen Excess (n = 2)

TABLE 2. Clinicopathologic Features

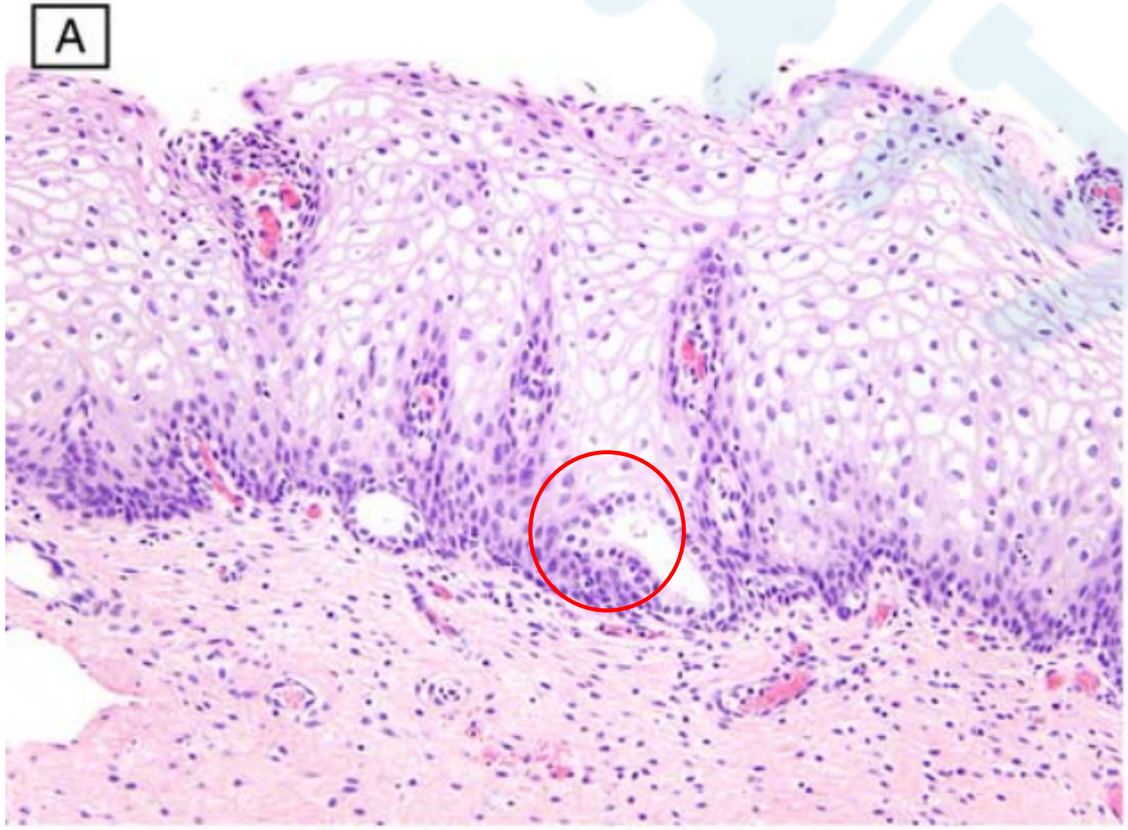
Case No.	Age	Procedure	Indication	Androgen Exposure	Hormonal Therapy (Duration—Months)
1	30	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (36)
2	26	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (32)
3	23	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (60)
4	27	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (not known)
5	34	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (36)
6	25	Vaginectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (72)
7	18	Hysterectomy	Gender-affirming surgery	Exogenous	Testosterone cypionate (24)
8	16	Vaginal reconstruction	Congenital adrenal hyperplasia	Endogenous	None
9	23	Perivaginal tissue resection	Congenital adrenal hyperplasia	Endogenous	None
10	17	Urethral polyp/vaginal resection	46,XY DSD	Endogenous	None
11	12	Vaginal and prostatic utricle resection	OTDSD	Endogenous	None
12	15	Vaginoplasty	Agenesis of lower vagina	None	None
13	33	Vaginal biopsy	Colposcopic lesion	Not known	Not known

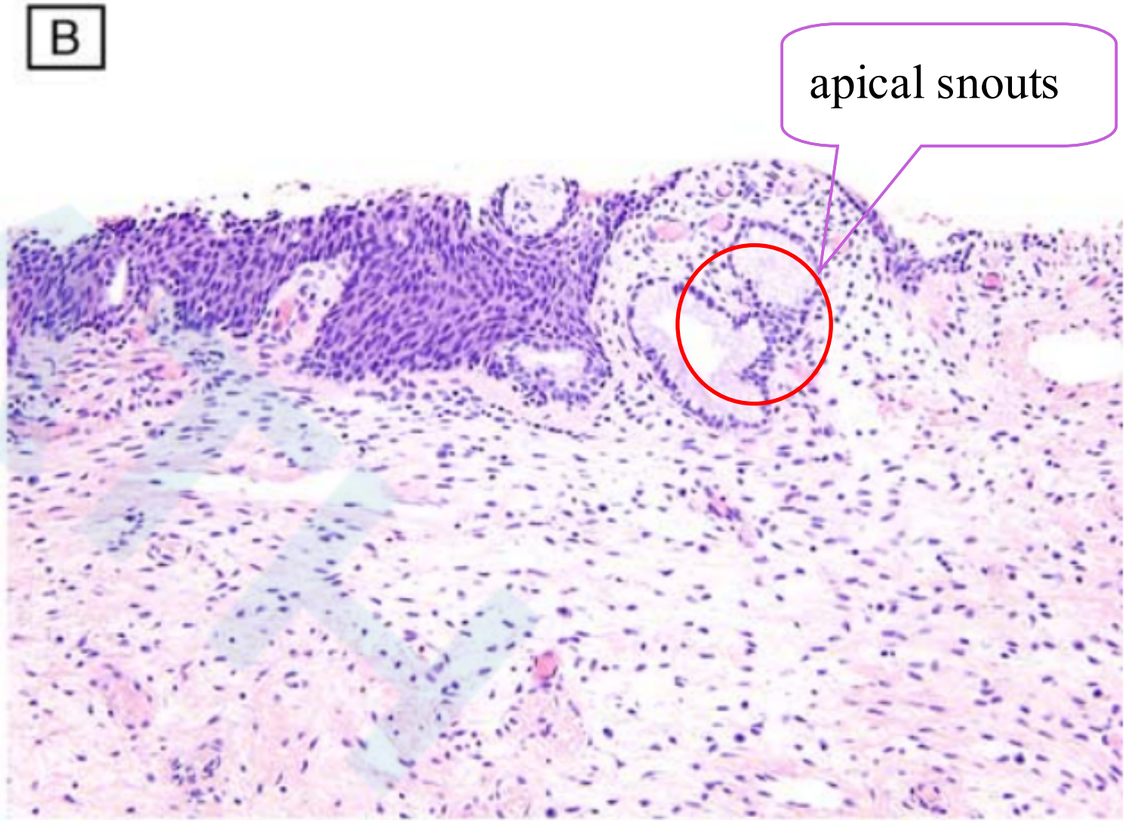
DSD indicates disorder of sexual development; OTDSD, ovostesticular disorder of sexual development.

Results—Histopathology



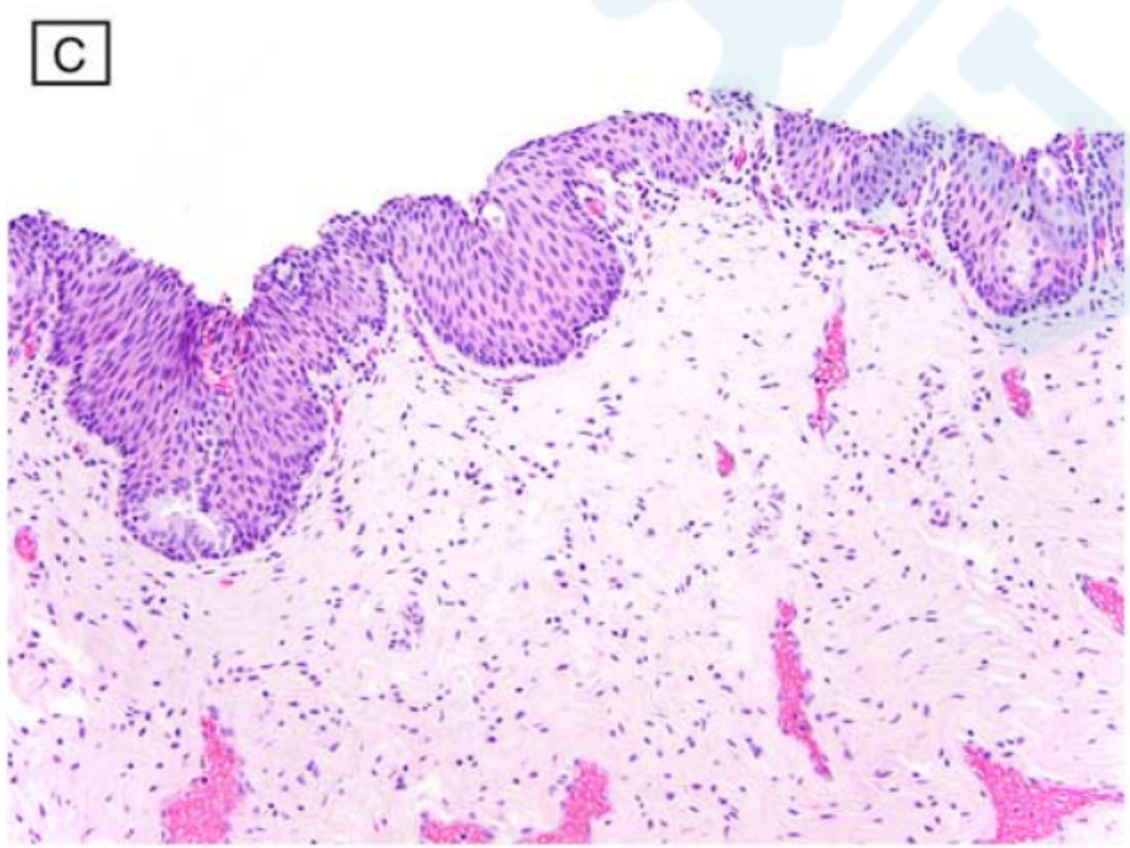
Results—Histopathology



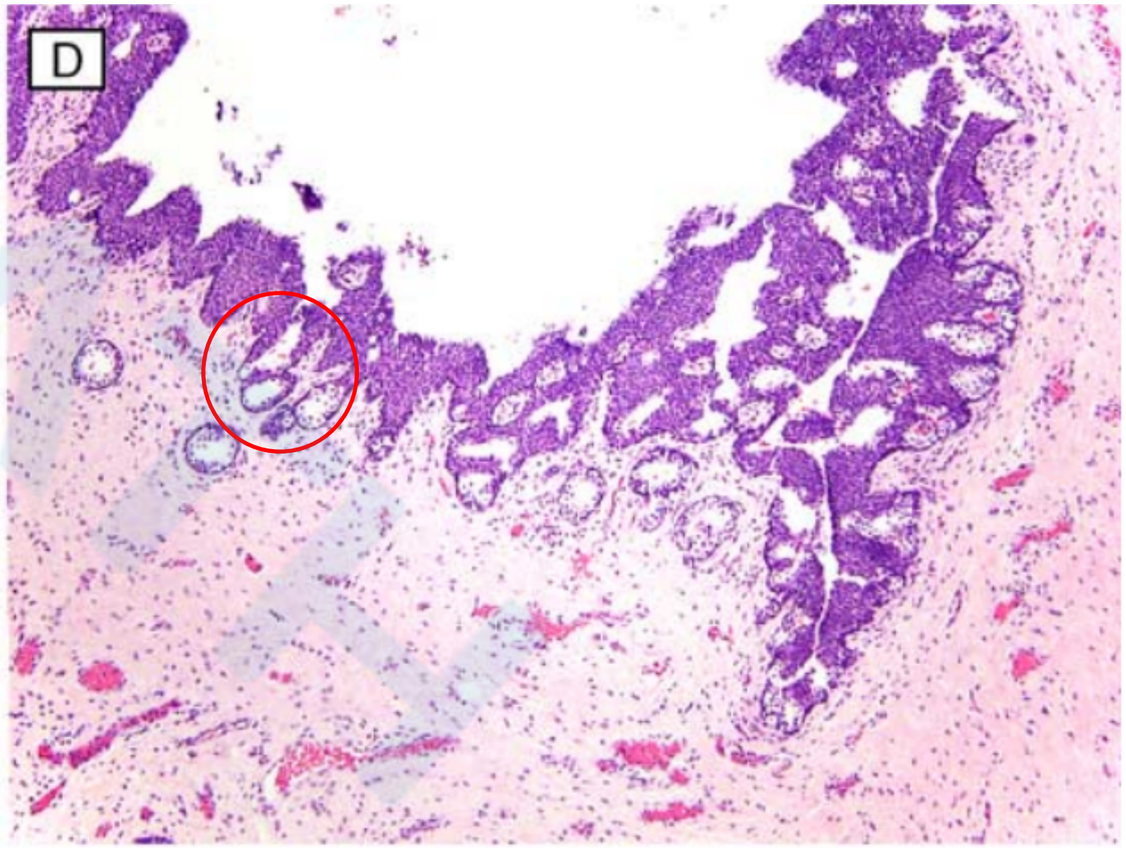


Case 7

Results—Histopathology

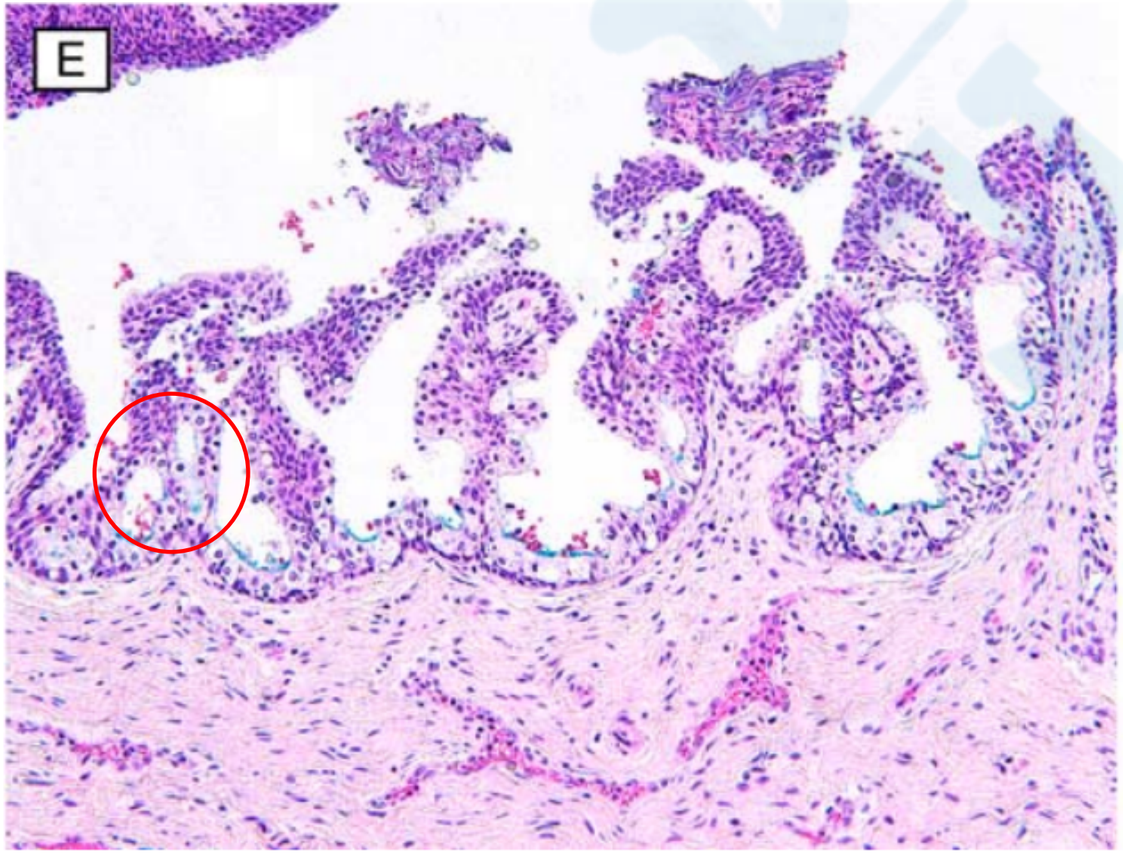


Case 2

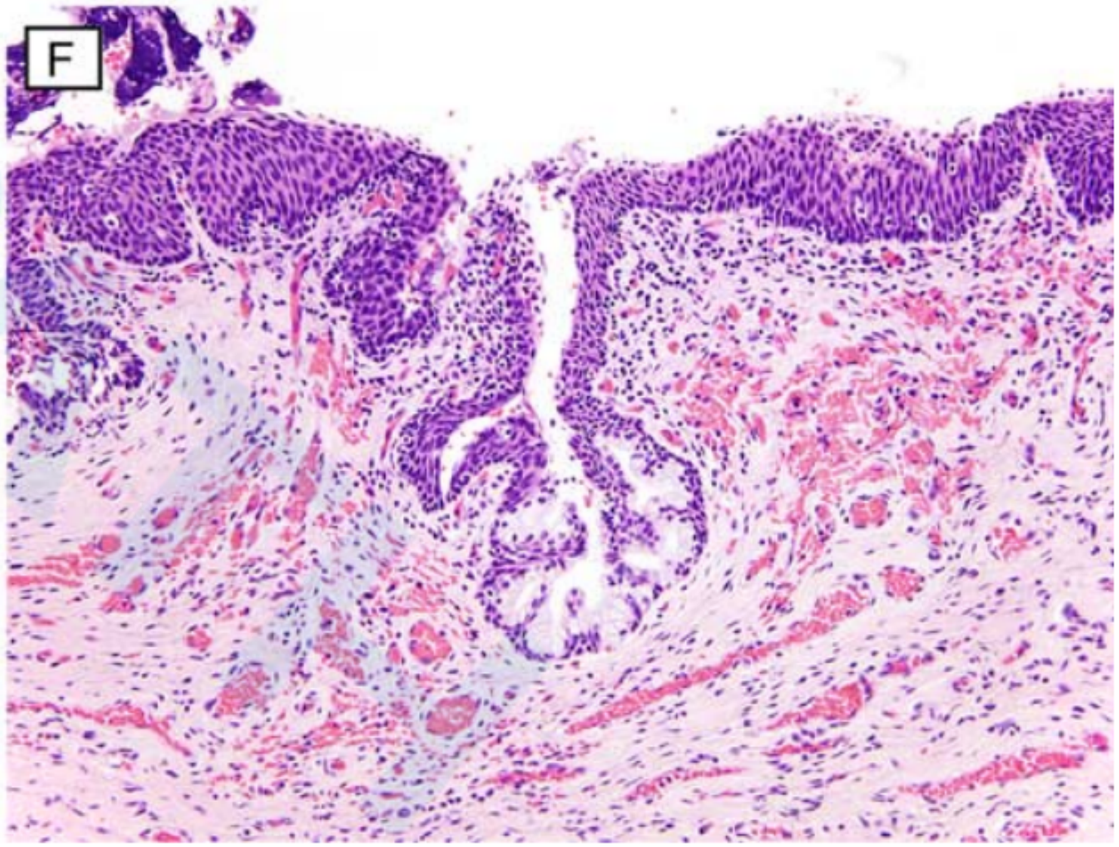


Case 4

Results—Histopathology

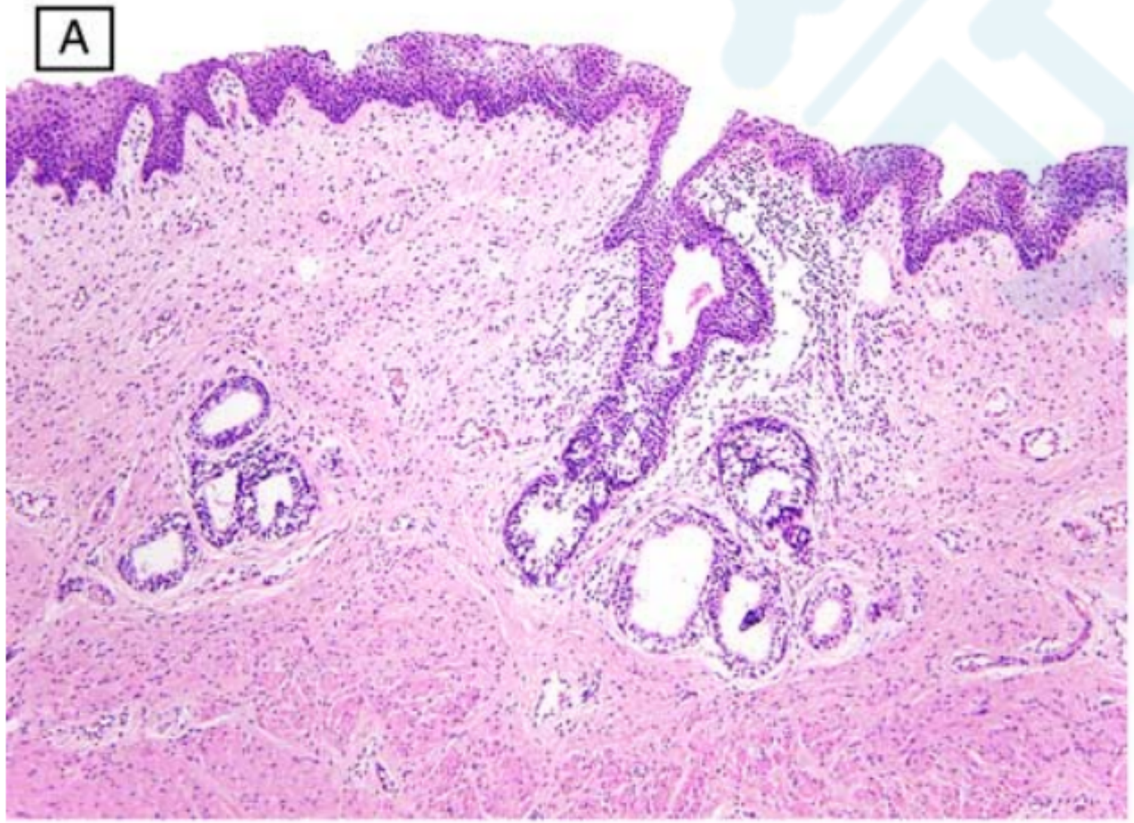


Case 4

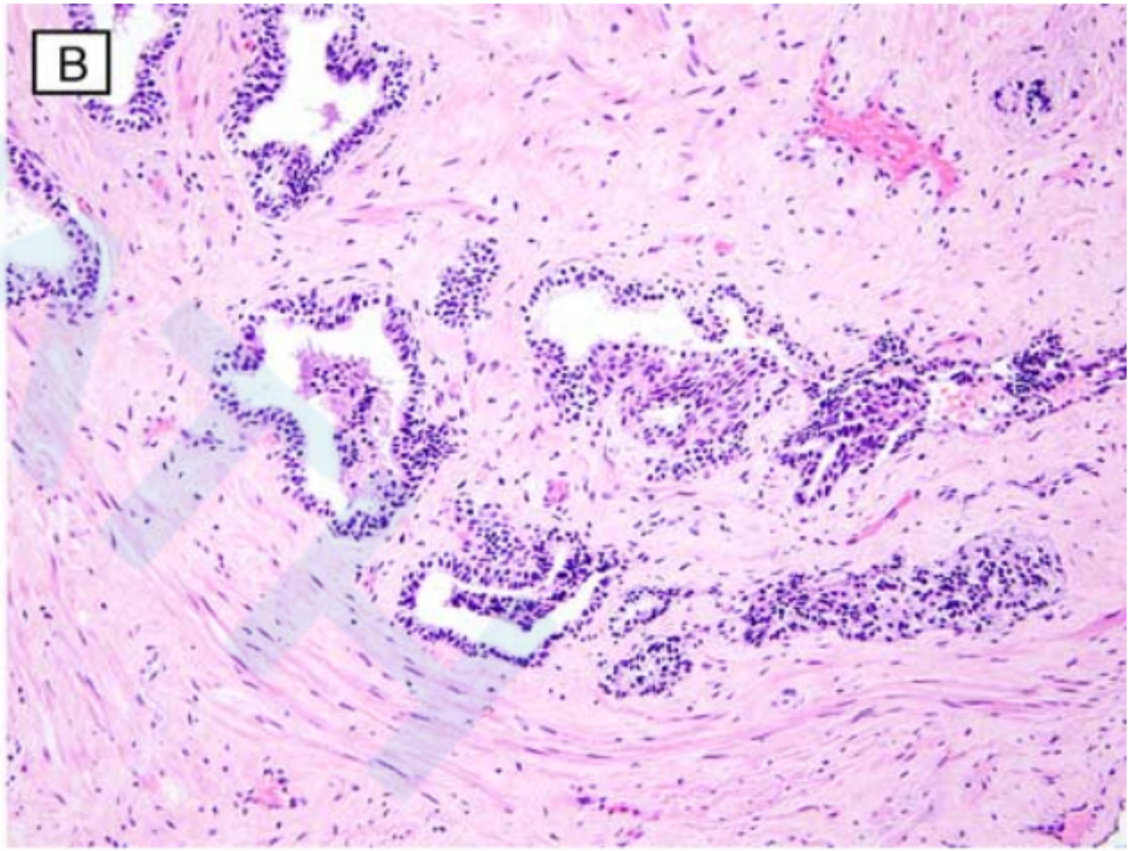


Case 6

Results—Histopathology

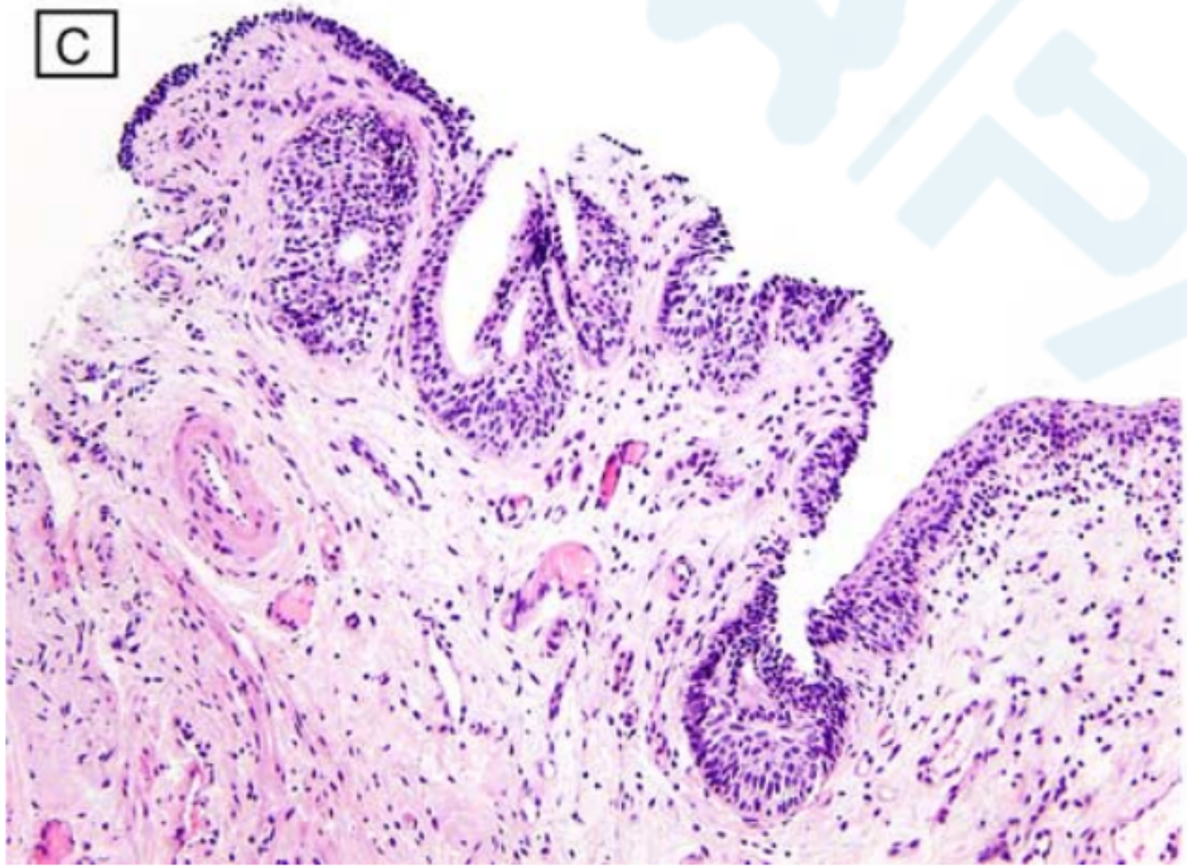


Case 11

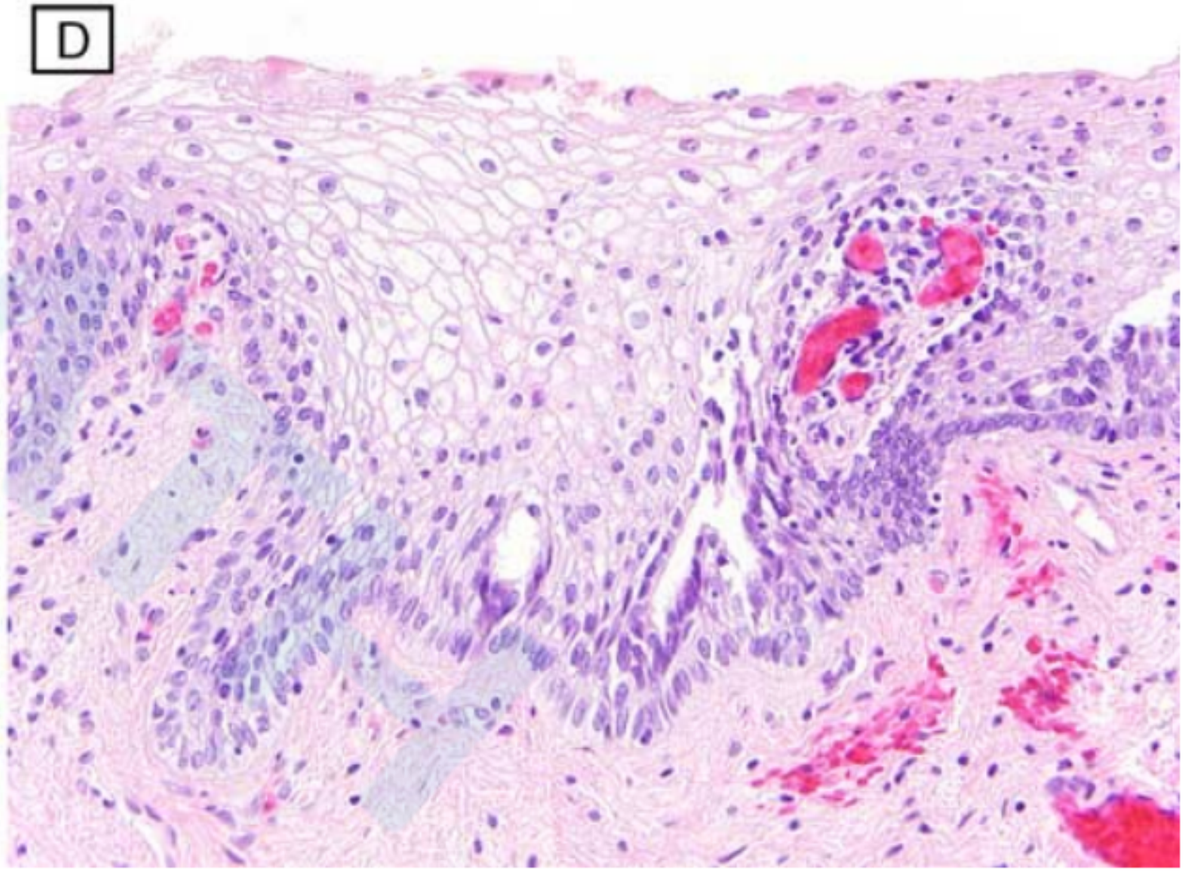


Case 9

Results—Histopathology

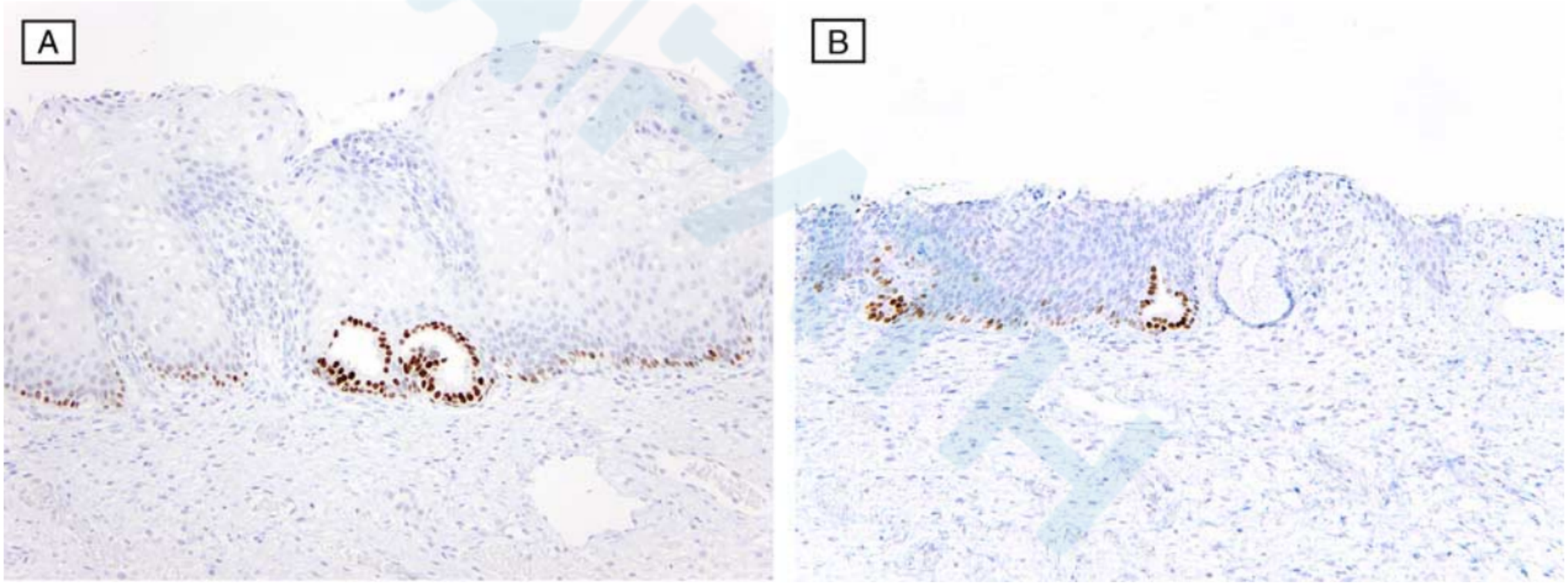


Case 8



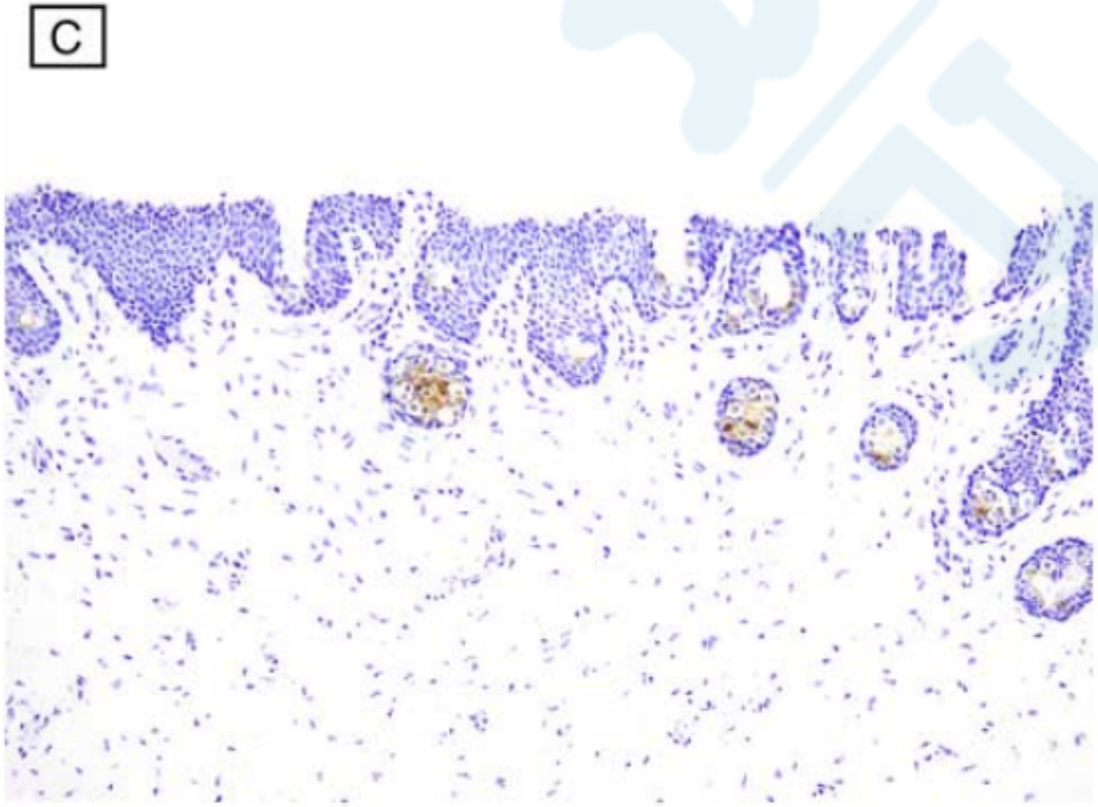
Case 13

Results—Immunohistochemical Results

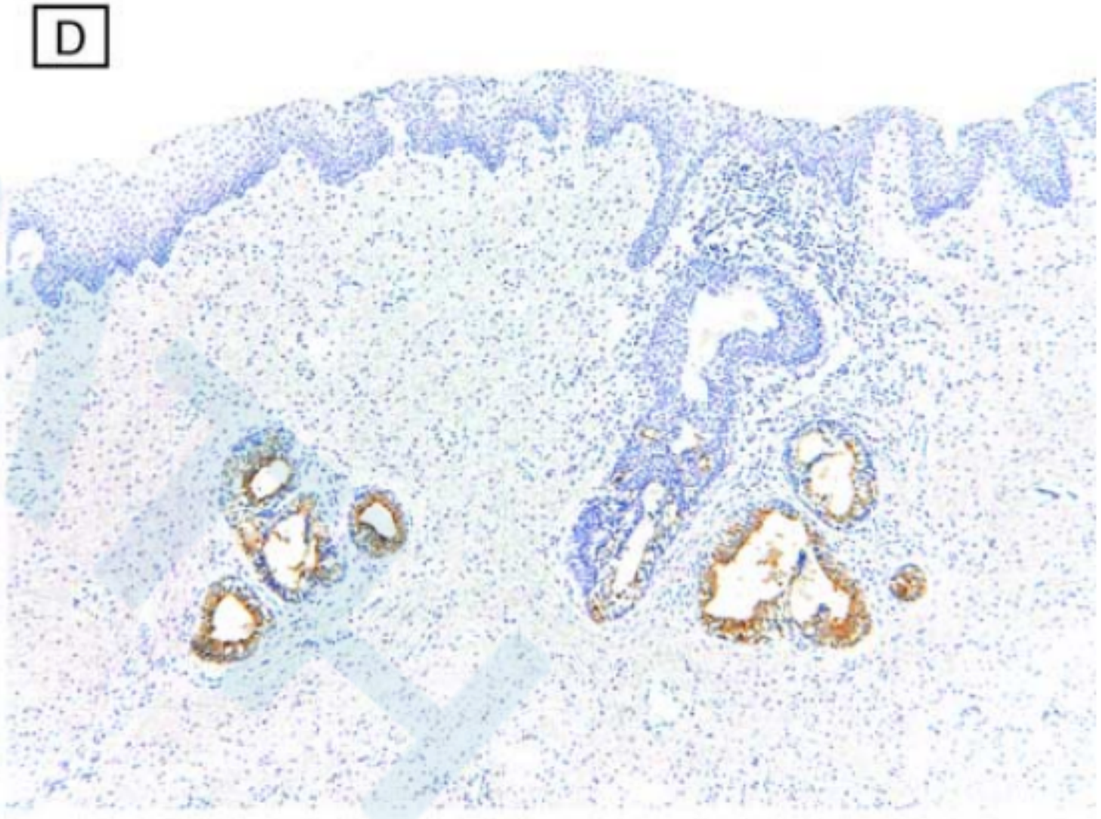


Case 7 NKX3.1

Results—Immunohistochemical Results

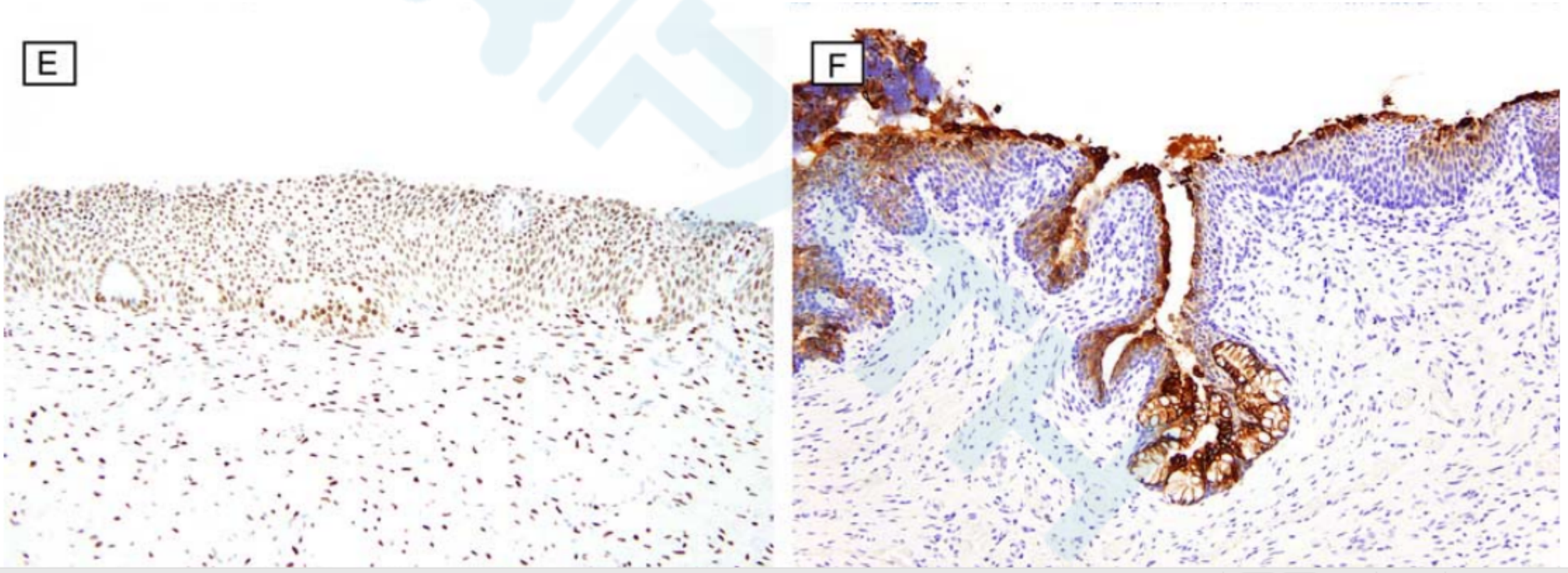


Case 4, PSA



Case 11, PSA

Results—Immunohistochemical Results



AR

CK7

Results—Immunohistochemical Results

TABLE 3. Histologic and Immunohistochemical Findings

Case No.	Gland Location	Gland Distribution	# of Blocks Involved (Submitted)	Transitional Metaplasia	NKX3.1	PSA	AR	CK7	Additional Stains
1	Vagina	SE	6 (6)	Yes	+	+	+	+	Negative: ER, GATA3, PAX8, CK20
2	Vagina	SE	4 (5)	Yes	+	−	+	+	
3	Vagina	SE	1 (4)	Yes	+	+	+	+	
4	Vagina	SE	3 (3)	Yes	+	+	+	+	
5	Vagina	SE	6 (7)	Yes	+	+	+	+	
6	Vagina	SE	19 (29)	Yes	+	+	+	+	
7	Exocervix	SE	1 (2)	Yes	+	+	+	+	Negative: p63
8	Vagina	SE+LP	1 (1)	No	+	+	+	+	
9	Vagina	SE+LP	1 (1)	No	+	+	+	+	
10	Vagina	SE+LP	1 (2)	No	+	−	+	+	
11	Vagina	SE+LP	3 (4)	No	+	+	+	+	Positive: CK20
12	Vagina	SE+LP	1 (2)	Yes	+	−	+	−	
13	Vagina	SE	1 (1)	No	+	−	ND	ND	Negative: PAX8
Total, n (%)				8/13 (62)	13/13 (100)	9/13 (69)	12/12 (100)	11/12 (92)	

− indicates negative; +, positive; LP, lamina propria; ND, not determined; SE, surface epithelium.

Results—Controls

- Control vaginal tissue (n=3) showed squamous epithelium with no specific pathologic changes.
- In all controls, the normal vaginal epithelium was negative for NKX3.1 and PSA.
- There was multifocal weak positivity for AR in stromal fibroblasts as well as squamous cells of the basal layer.

Results—Follow-up

- Clinical follow-up ranged from 1 to 156 months (median: 9 mo).
- Postoperative sequelae in the androgen-treated GD patients undergoing vaginectomy included urethral stricture (n= 3), urethrocutaneous fistula (n = 1), and urinary tract infection (n =1).
- No patients developed neoplasms or other mass lesions of the lower genital tract requiring subsequent biopsy or resection.

DISCUSSION

- This study characterizes a novel form of prostatic type tissue occurring in the surface squamous epithelium of the vagina, which appears particularly common in patients receiving androgen therapy.
- In addition, we observed similar prostatic metaplasia in patients with disorders often associated with an endogenous excess of androgens.
- Our data provide substantial evidence that androgen exposure is associated with the development of prostatic metaplasia.

DISCUSSION

- Our findings also build upon data from experimental animal models which indicate that androgens may induce prostatic metaplasia in vaginal tissue, likely reflecting the shared embryologic origin of the vagina and prostate from the urogenital sinus.
- Our study provides evidence that cervicovaginal epithelium can remain plastic into adulthood, since prostatic metaplasia was very commonly seen in transgender patients who initiated androgen therapy as adults.

DISCUSSION

- We found the glands to be consistently positive for NKX3.1 (100%), AR (100%), and CK7 (92%). Staining of cervicovaginal prostatic metaplasia for PSA (69%) was weaker and less frequent than was the staining for NKX3.1, AR, and CK7.
- Therefore, weak or negative PSA staining does not rule out the diagnosis.
- In many cases where prostatic metaplasia was limited to the surface epithelium, the glands showed weak or negative PSA staining, whereas the more exuberant foci that invaginated the lamina propria showed stronger staining.

DISCUSSION

- Understanding the clinical impact of prostatic metaplasia is important, since transgender males receiving long-term high-dose androgens may choose to permanently retain their vaginas.
- In addition, at the time of vaginectomy, residual vaginal tissue is typically left behind and sometimes utilized as a flap for urethral lengthening during concurrent phalloplasty.
- Prostatic glands have a known secretory function which may be retained in prostatic metaplasia. Prostatic secretions, could potentially alter the vaginal milieu, with an as yet undetermined impact on such factors as microbiologic flora, tissue repair, and cancer susceptibility.

DISCUSSION

- The effect of such altered physiology on non-neoplastic and neoplastic disease is not yet known.
- Its bland histologic appearance and our follow-up data to date support its classification as benign.
- Although there are rare individual case reports, such as that of a patient with congenital adrenal hyperplasia who developed prostatic adenocarcinoma, there is no strong evidence to suggest an increased risk of gynecologic malignancy in congenital adrenal hyperplasia or transgender males.

DISCUSSION

- In summary, we conclude that androgen-associated prostatic metaplasia of the vagina and cervix is a distinct clinicopathologic entity, occurring in patients exposed to increased levels of exogenous or endogenous androgens.
- Its clinical context, histologic pattern of maturation, and association with AR-positive and NKX3.1-positive basal cells in squamous epithelium all support a metaplastic process and provide evidence for the ongoing plasticity of urogenital sinus-derived tissue in adults.

DISCUSSION

- We hope that awareness of this lesion will aid in its recognition and distinction from other cervicovaginal glandular proliferations.
- Future studies will be important to identify any possible clinical sequelae through more extensive follow-up and to further understand the role of androgens in eliciting an apparently unique differentiation pathway in genital tract squamous mucosa.

THANKS