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Review article

Clinical implications of the forgotten Skene's glands: A review of current literature



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ARTICLE INFO

Article history:

Received 15 November 2015

Received in revised form

5 February 2016

Accepted 10 February 2016

Available online 4 May 2016

Keywords:

Dysuria

Female prostate

Prostate specific antigen

Skene's glands

Urethral masses

ABSTRACT

Introduction: The clinical and pathological aspects of the Skene's glands have not been addressed in the current scientific literature.

Aim: To review the current literature to focus on the clinical and pathological aspects of the Skene's glands. The historical perspective including embryology, anatomy, histology, and current role of prostatic specific antigen (PSA) as a tumor marker of lesions which develop from the Skene's glands, 'female prostate.'

Material and methods: Medline searches were performed to review the current literature regarding Skene's glands pathology, clinical manifestations, diagnosis, role of PSA, and its treatment options.

Discussion: Anatomical pathology including inflammatory, cystic, solid, benign, and malignant tumors of Skene's glands is emphasized. The unique role of PSA in these lesions is reviewed. Cognizance of periurethral, perimeatal and urethral masses is essential for anatomical pathologists, radiologists, urologists and gynecologists who encounter complex female urethral masses in their clinical practice. Imaging techniques of Skene's glands to diagnose urethral, perimeatal and periurethral masses in female are reviewed.

Conclusions: The literature of the interesting scientific concepts related to the Skene's glands are reviewed. The role of PSA in these lesions is expanded for diagnoses and treatment options of pathology of the Skene's glands. Methods of imaging are necessary for radiologist, pathologists, and clinicians alike, for the proper treatment of Skene's gland lesions.

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1. Introduction

In 1880, Alexander Skene discovered prostatic glandular tissue proximally located next to two large ducts adjacent to the

female urethra, thus proving the existence of the female prostate.¹ Before Skene's discovery, several researchers speculated the idea of the existence of a female prostate. A researcher named Galen first discussed the idea of the female prostate, but he believed the prostatic tissue was located closer

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to the fallopian tubes than the urethra. In 1672, de Graaf described ducts in close proximity to the female urethral meatus, and believed that these structures drained the female prostate.² In 1853, Virchow described stone-like masses inside the ducts surrounding the urethral meatus. He concluded these urethral glands and ducts were homologous to the male prostate. In 1889, Tourneaux similarly described glands adjacent to the urethral meatus, stating that these glands were structurally similar to the prostatic glands of a five- to six-month-old male fetus.³ Pallin, in 1901, found that the Skene's glands are not homologous to the whole male prostate, but to the cranial and ventral portions. In 1922, Johnson examined female fetuses at different developmental stages comparing female embryology with that of a male. He noted that the Skene's glands first appear in 60-mm female embryo, and that the glands were distributed along the anterior, posterior, and lateral walls of the urethra. He also stated that compared to their male counterpart, Skene's glands are 'fewer in number, less closely packed together, have fewer branches, thicker epithelial walls, smaller lumina, and less evidence of epithelia with active secretion.'⁴ In the 1940s, Huffman described Skene's glands as located primarily along the distal half of the urethra. Additionally, he stated the 'female periurethral glands are homologous with only that portion of the male prostate arising cephalad to the urogenital sinus.' Huffman also recognized the importance of the Skene's gland and diverse pathologies that can arise from them. He noticed that inflammation and irritation of the glands might result in cystic enlargement. This could lead to obstruction and abscess formation of the anterior vaginal wall and urethra while creating urethra-vaginal fistulas.^{5,6}

2. Aim

To readdress the focus to Skene's glands and recall the overlooked historical perspective, embryology, anatomy, histology, and current role of prostatic specific antigen (PSA) as a tumor marker of lesions which develop from the Skene's glands 'female prostate.'

3. Material and methods

Medline searches were performed to review the current literature regarding skene's glands, pathology, clinical manifestations, diagnosis, and treatment options.

4. Discussion

4.1. Embryology, anatomy, and histology of Skene's glands and their ducts

The Skene's glands and ducts are normally located on the distal third of the female urethra, emptying approximately of an eighth of an inch from the outer edge of the meatus.¹ According to Huffman who performed serial sections and wax model reconstructions of the paraurethral glands, no ducts were found to be larger than 4 cm. Additionally, they extend

aligned along the urethra's lateral, ventral, and to a lesser extent, the dorsal side. The glands themselves are described as 'branched tubular glands, with straight or slightly curved branches, which empty into the paraurethral ducts.' Furthermore, the glands are limited to the urethra with no evidence of vestibular or vaginal mucosa involvement.^{5,6} Johnson described that Skene's glands are structurally similar to the male prostatic glands as they are solid, round, directed toward the bladder, and extend into the surrounding mesenchyme. They differ because there are fewer of them, they are dispersed, and do not exhibit active secretions.⁴ Regarding embryological aspects, Johnson described the appearance of Skene's glands in a 60-mm female fetus, which originate from the urogenital sinus.⁴ Histologically, they are composed of columnar epithelium and contain pale staining cytoplasm. The nucleus is described as being a large rounded structure that is located centrally or basally. Furthermore, within the columnar epithelium, the mucous secreting cells are stained for mucicarmine.⁵ The lumen of a Skene's gland is composed of tall cylindrical secretory cells with short microvilli. Ample secretory granules and vacuoles are noted, in addition to numerous mitochondria and Golgi complexes. Dispersed throughout the secretory cells are basal cells, referred to as 'reserve cells,' which play a role in the regeneration of cells in the Skene's glands. The nucleoli of the basal cells contain dense chromatin.⁷ Zaviacic et al. describes expression of human protein 1 in the prostatic tissues of both males and females. Human protein 1 can be found in the secretory cells of the Skene's glands which may function to protect the urothelium from the harsh urinary environment.⁸

4.2. Presence of PSA in Skene's glands and tumors arising from Skene's glands

Like the male prostate, the female prostate Skene glands have been shown to stain for PSA. Tepper et al. examined 18 female urethras with paraurethral glands by staining tissues for antibodies to PSA and prostate-specific acid phosphatase (PSAcPH). In total, 83% were positive for PSA and 67% positive for PSAcPH. This study thus proved the homology between the female paraurethral glands and male prostate.⁹ It should be noted that the total PSA level in a female arises from the combination of female prostatic tissues such as diseased breast tissue.¹⁰ Sloboda et al. described a case of a 46-year-old female with adenocarcinoma of the paraurethral glands that stained positive for PSA and PSAcPH, therefore linking it to male prostatic carcinoma.¹¹ Further studies have produced similar results, correlating carcinoma of the Skene's gland to male prostatic carcinoma.¹² Additionally, just like males, PSA can be used as a reliable tumor marker, as levels correlate with responsiveness to treatment.^{10,13} Korytko et al. described a case of a 71-year-old female diagnosed with a Skene's gland adenocarcinoma with an initial PSA of 54.42 ng/ μ L. Treatment consisted of 73.8 Gy of intensity-modulated radiotherapy in 41 fractions, after which her PSA was 0.65 ng/ μ L (32 months after treatment). Therefore, females presenting with periurethral adenocarcinomas should be evaluated to determine if they are Skene's glands in nature, which would allow PSA levels to assess for treatment response.¹³ Dodson et al. further discuss the decline in PSA

levels in treatment for urethral adenocarcinoma. However, it is important to note that not all adenocarcinomas of the female urethra are Skene's gland in origin. Therefore, further histological testing must be done to assess for the origin of PSA negative urethral adenocarcinomas.¹⁴

4.3. Significance of female ectopic prostatic tissue in reproductive system

Normally, female prostatic tissue is located in the lower third of the urethra. However, ectopic prostatic tissue has been documented to be located primarily within the female reproductive system. Kelly et al. described what appeared to be ectopic prostatic tissue in 26 women whose ages ranged from 23 to 81. Locations of ectopic tissue included the cervix, vagina, and vulva, with the majority being found in the cervix. The majority of these cases had associated lesions, which led to the initial biopsy of the tissues. However, some were incidental findings. Lesions of the cervix were mainly located at the ectocervix, while ectopic tissue was mainly found in the form of polyps and cysts within the vagina. Immunohistochemistry was performed on the samples that depicted 13 of the 26 cases positive for PSA and 16 out of 26 positive for PSACPH. It should be noted that all lesions examined in this study were benign.¹⁵ Although female ectopic prostatic tissue is exceedingly rare, several cases have been reported of ectopic tissue in the cervix. Most were incidental findings that were positive for PSA and PSACPH.¹⁶⁻²⁰ However, McCluggage et al. described six cases of ectopic prostatic tissue, where only three out of six specimens stained positive for PSA, but all were reactive to PSACPH.²¹ Positive immunoreactivity for PSA and PSACPH has also been revealed in tubulo-squamous vaginal polyps, indicating that they probably arose from Skene's glands. These polyps are generally located in the upper portion of the vagina, most commonly seen in postmenopausal women.²²⁻²⁴ Vaginal myofibroblastomas have also exhibited ectopic prostatic tissue. Lorange et al. described vaginal bleeding within a case of a 76-year-old female on tamoxifen for breast cancer treatment. Endometrial work-up revealed a myofibroblastoma with ectopic prostatic tissue, which was the first of its kind.²⁵ Uzoaru et al. reported two cases of benign cystic teratoma arising from ectopic prostatic tissue.²⁶

4.4. Diagnosis of pathologies associated with Skene's glands

Females presenting with urogynecological symptoms should initially have a pelvic exam, urine culture, vaginal secretion culture, and sexually transmitted disease (STD) testing. During physical examination, one should look for any abnormalities adjacent to the urethral meatus, including cysts, abscess, or tumors. If no abnormalities are noted, one may perform a urethrocytostcopy and retrograde urethrocytography to search for obstruction or communications with the vagina, urethra, and bladder.²⁷ Radiologic imaging of masses at urethrovaginal space can be accomplished by using 3D ultrasonography, endovaginal ultrasound with duplex Doppler, endoluminal MRI, and CT scan for precise diagnosis. One study discussed the use of 3D ultrasonography and color/power Doppler to diagnosis a Skene's gland cyst, for clear

definition and 3D reconstruction of the cyst.²⁸ If carcinoma is suspected, MRI/CT scans may be performed for staging including the anatomical field of lymphatic drainage of the Skene's glands.

4.5. Differential diagnosis of perimeatal, urethral, and periurethral masses of urethrovaginal space

Many times pathologies of the Skene's gland tend to be overlooked due to similarities in clinical pathology and presentations of masses. Table 1 addresses the various masses that are found near the Skene's glands and Table 2 summarizes the clinical pathologies of Skene's glands.

4.6. Cysts of Skene's glands

Immunohistochemistry targets diversify pathologies that arise from Skene's glands. Rare cases of paraurethral cysts resulting from Skene's gland have been reported.^{27,111-113} Differentials for Skene's gland cyst include Bartholin's duct cyst, epidermal inclusion cyst, hidradenoma papilliferum, lipoma, urethrocele, and urethral diverticulum.¹¹⁴⁻¹¹⁷ Etiology of Skene's gland cysts includes mechanical trauma, or obstruction of the duct.^{118,119} Martin et al. described four cases of Skene's gland cyst. The majority of these patients complained of dysuria, dyspareunia, and sensation of a mass in their urethra. All women were first treated with antibiotics, hygienic treatment, and manual drainage with no improvement in symptoms. Retrograde urethrocytostcopy was performed to assess any signs of stenosis or anatomical defect, such as a fistula. STD work-up was negative. Surgical removal with local anesthesia was the only option. After removal, all four patients remained symptom free, with no noted complications.²⁷ Although Skene's glands cysts are uncommon in female adults, they are even less commonly found in children. One case involves a neonate with a pelvic mass that was noted on prenatal ultrasound. Delivery work-up diagnosed the mass as a paraurethral cyst located at the vaginal orifice that drained spontaneously with no complications.¹¹¹ Allouis et al. also reported three neonates with paraurethral cysts. In all three patients, drainage by needle puncture was curative.¹¹²

4.7. Skene's gland abscess

Skene's gland abscesses are a relatively uncommon phenomenon, with most cases appearing within the third or fourth decades of life. Differentials for Skene's gland abscess are similar to those for a Skene's gland cyst.¹¹⁴ Common clinical manifestations of a Skene's gland abscess include dysuria, urethral pain, dyspareunia, recurrent urinary tract infections, abnormal urethral draining, and problems voiding. The presence of pus and point tenderness at the distal urethra is common. When diagnosis is indefinite, further work up involving an MRI, voiding cystourethrogram, cystourethroscopy, or transvaginal ultrasound may be necessary.¹²⁰⁻¹²² Nickels et al. described a case of a 3-year-old child presenting with vulvar pain. Upon examination the patient discovered an enlarged right labium majora and erythematous patch next to the urethra. The patient was diagnosed with a Skene's gland abscess, which was drained resulting in complete resolution of

Table 1 – Differential diagnosis of periurethral masses.

Differential diagnosis	Authors
Adenosquamous cell carcinoma	García et al. ²⁹
Amelanotic melanoma	Satyanarayan et al. ³² ; Yoshii et al. ³³
Amyloidosis	Pehlivanov et al. ³⁷
Angiomas	Cook et al. ⁴⁰ ; Davis et al. ⁴¹
Bladder eversion	Kalorin et al. ⁴⁵ ; Kim et al. ⁴⁶
Carcino-sarcoma	Mosel et al. ⁴⁹
Condyloma	Kishimoto et al. ⁵¹ ; Horn et al. ⁵²
Ectopic ureter	Demir et al. ⁵⁶ ; Ohzeki et al. ⁵⁷
Ectopic ureterocele	Lopez et al. ⁵⁹
Endometriosis	Dadhwal et al. ⁶² ; Klenov et al. ⁶³
Fibroepithelial polyp	Akbarzadeh et al. ⁶⁵ ; Mullins et al. ⁶⁶ ; Wilkinson et al. ⁶⁷
Fibrosarcoma	Blanco Rabassa et al. ⁶⁹
Gartner's duct cyst	Rosenfeld et al. ⁷¹ ; Emmons et al. ⁷²
Glomus tumor	Silver et al. ⁷⁴ ; Banner et al. ⁷⁵
Hemangiomas	Davis et al. ⁴¹
Hematoma	Mosković et al. ⁸⁰ ; Frioux et al. ⁸¹
Infected granuloma	Hoge et al. ⁸³
Leiomyoma and leiomyosarcoma	Jordanov et al. ^{5,86}
Lymphoma of the urethra	Vögeli et al. ⁸⁹
Metastatic disease to the urethra	Suzuki et al. ⁹⁰
Nephrogenic adenoma	Kelly et al. ¹⁵
Papillary endothelial hyperplasia (Masson tumor)	Nevin et al. ⁹⁴
Parasitic diseases	Vilela et al. ⁹⁷ ; Kashyap et al. ⁹⁸
Paraurethral cysts	Fukata et al. ³⁰ ; Deppisch et al. ³¹
Paraurethral leiomyoma	Chong et al. ³⁴ ; Moriya et al. ³⁵ ; Di Cello et al. ³⁶
Periurethral abscess	Babalola et al. ³⁸ ; Butler et al. ³⁹
Periurethral cyst (Skene's duct cyst)	Shaririaghdas et al. ⁴² ; Moralioglu et al. ⁴³ ; Durakbasa et al. ⁴⁴
Prolapsed ureterocele	Landi et al. ⁴⁷ ; Goh et al. ⁴⁸
Retention cyst	Wollgarten et al. ⁵⁰
Reticulosarcoma	Spampinato et al. ⁵³ ; Ciulla et al. ⁵⁴ ; Marini et al. ⁵⁵
Rhabdomyosarcoma of urethra	Liu et al. ⁵⁸
Sarcoidosis	Schol et al. ⁶⁰ ; Allen et al. ⁶¹
Sarcoma of urethra	Kushelev et al. ⁶⁴
Skene's gland calculi secondary to ureaplasma urealyticum	Gellman et al. ⁶⁸
Slings	Forzini et al. ⁷⁰
Transitional carcinoma of the urethra	Kasai et al. ⁷³
Tubulo-squamous vaginal polyp	Chaturvedi et al. ⁷⁶ ; Petrová et al. ⁷⁷
Urethral adenocarcinoma	Satyanarayan et al. ⁷⁸ ; Mimura et al. ⁷⁹
Urethral caruncle	Chiba et al. ⁸²
Urethral cysts	Woo et al. ⁸⁴
Urethral diverticulum and its contents	Dong et al. ⁸⁷ ; Jadhav et al. ⁸⁸
Urethral polyp	Akbarzadeh et al. ⁶⁵
Urethral mass from injection of bulking agents for incontinence	Berger et al. ⁹¹ ; Lai et al. ⁹²
Urethral prolapse	Lai et al. ⁹² ; Horsburgh et al. ⁹³
Vaginal wall cysts	Molina Escudero et al. ⁹⁵ ; Jayaprakash et al. ⁹⁶

Table 2 – Clinical pathology of Skene's glands.

Clinical pathology	Authors
Urethral caruncle	Surabhi et al. ⁹⁹ ; Conces et al. ¹⁰⁰
Urethral prolapse	Lai et al. ⁹² ; Horsburgh et al. ⁹³ ; Bennett et al. ¹⁰²
Prolapsed ureterocele	Landi et al. ⁴⁷ ; Goh et al. ⁴⁸
Condyloma	Kishimoto et al. ⁵¹ ; Horn et al. ⁵² ; Brook et al. ¹⁰⁸
Leiomyoma	Jordanov et al. ^{85,86} ; Dasan et al. ¹¹⁰
Periurethral cysts (Skene's duct cysts, urethral diverticulum)	Shaririaghdas et al. ⁴² ; Moralioglu et al. ⁴³ ; Durakbasa et al. ⁴⁴ ; Parente Hernández et al. ¹⁰¹
Vaginal wall cysts	Kimbrough et al. ¹⁰³ ; Ali et al. ¹⁰⁴
Bartholin's gland cysts	Lee et al. ¹⁰⁵ ; Dragojević et al. ¹⁰⁶ ; Bhide et al. ¹⁰⁷
Nevus	Fitzhugh et al. ¹⁰⁹

symptoms. In general, a Skene's gland abscess is treated with incision and drainage, with minimal complications. However, one case reports a 14-year-old female who developed a suburethral diverticulum secondary to Skene's gland

abscess.¹²³ Another case describes the formation of calculi within a Skene's gland abscess. Cultures of the abscess grew *Ureaplasma urealyticum*, which contains the enzyme urease that causes formation of stones. Treatment of a Skene's gland

abscess is either conservative or surgical. Conservative treatment involves antibiotics and waiting abscess drainage. Incision and drainage, simple aspiration, or drainage with marsupialization are appropriate forms of treatment.¹²⁰⁻¹²² Shah et al. conducted a retrospective study observing surgical management of Skene's gland abscess. The study group involved 34 women who had undergone excision of the abscess. According to this study, 88.2% of women had resolution of symptoms, 30.0% eventually had recurrence of symptoms requiring further treatment, and 85.3% had complete resolution of symptoms after all treatment. Patients whose symptoms continued mainly complained of urethral pain and frequent urinary tract infections.¹²⁴

4.8. Infections of the Skene's glands

Gonorrhea, tuberculosis, and trichomoniasis are harbored in the skene's glands along with other parts of the vagina. The infection may be asymptomatic.^{125,126}

4.9. Benign and malignant tumors of Skene's glands

4.9.1. Benign tumor of Skene's glands

Tubulo-squamous vaginal polyps are immune positive for prostatic specific antigen suggestive of displaced periurethral Skene's glands.²²

4.9.2. Malignant tumors of Skene's glands

4.9.2.1. Urethral adenocarcinoma arising from Skene's glands. Urethral adenocarcinomas are rare, and some reports have described them to be of Skene's gland in origin. Common clinical presentation includes painless urethral bleeding, enlarged urethral mass, urinary frequency, urethral obstruction, focal tenderness, urinary tract infections, and urethrorrhagia, because these symptoms are not specific to urethral adenocarcinoma.¹²⁷ Furthermore, due to its rarity and vague presentation, delayed diagnosis may occur. Approximately 10-16% of all urethral cancers are adenocarcinoma.^{14,128} Urethral adenocarcinoma has been shown to originate from multiple tissues such as Skene's glands, Mullerian ducts, or urethritis glandularis.^{129,130} Chan et al. reported a case of a 72-year-old woman who presented with a urethral mass, confirmed on biopsy to be an adenocarcinoma. Immunohistochemistry testing for cytokeratin 7 (CK7) and cytokeratin 20 (CK20) was done to determine if the tumor was epithelial in origin. The tumor showed expression of both CK7 and CK20, making the tumor unlikely to be Mullerian or Skene's gland in origin. If the tumor was Skene's gland in origin, it would not express CK7.¹²⁹ However, cases of urethral adenocarcinomas that are Skene's gland in origin have been reported. Dodson et al. conducted a study looking at 13 females with urethral adenocarcinomas. One of the cases histologically appeared to be prostatic in nature. Staining of tumor by PSA is considered a histological evidence of origin from Skene's glands. The tumor was immune histochemically reactive to PSA confirming the tumor's origin from Skene's glands. Furthermore, the PSA levels declined rapidly after removal of the tumor making it a useful marker in responsiveness to treatment.¹⁴ Another case describes a 70-year-old woman presenting with a urethral mass, determined to be adenocarcinoma without mucosal

involvement. The tumor stained positive for PSA and was determined to be Skene's gland adenocarcinoma. Surgical removal of the tumor resulted in a sudden drop in PSA.¹³¹ If the urethral tumor stained negative for PSA, it may still have been Skene's gland in origin. Reis et al. described two cases of Skene's gland adenocarcinoma both of which were PSA negative. The tumors etiologies were confirmed based on gross and microscopic findings, which resembled Skene's glands. Not all cells of the Skene's gland produce PSA; therefore it is plausible to have a Skene's gland adenocarcinoma stain negative for PSA.¹³² Treatment of urethral adenocarcinoma usually involves surgical resection, and sometimes chemoradiation. Chen et al. report two cases of locally invasive urethral adenocarcinoma. One patient underwent surgical resection, dying 2 months later due to disease progression. The other patient had surgery and chemoradiation, and was disease free for approximately 6 months, which is an improvement compared to the expected median disease free period of 5.5 months. This study recommended adjuvant chemoradiation for locally advanced urethral adenocarcinomas.¹³³

4.9.2.2. Adenoid cystic carcinoma. Skene's gland has also been associated with adenoid cystic carcinoma. Ali reported a 50 year old woman with adenoid cystic carcinoma of Skene's glands, which presented as a suburethral mass, biopsy revealed adenoid cystic carcinoma arising from the Skene's gland. Along with glandular tissue the tumor also contained cystic material that stained for periodic acid-Schiff. The tumor showed extensive nerve involvement and stained positive for cytokeratins, carcinoembryonic antigen, and S-100 protein.¹⁰⁴ Ueda et al. described a rare case of adenoid cystic carcinoma that arose from Skene's glands, where the best course of action was surgery. However, in this case, the tumor had invaded more extensively and required pelvic exenteration with radical vulvectomy.¹³⁴ In order to avoid more radical treatment options, precise preoperative assessment is necessary.

5. Conclusions

Anatomy, embryology, and clinical pathology of the Skene's glands and its ducts are discussed in this paper. The role of PSA in Skene's glands, which can simulate prostate cancer, is reviewed. Differential diagnosis that simulates lesions of Skene's glands and ducts is addressed. Current imaging of these rare lesions is useful to radiologists, clinical pathologists, and clinicians.

Conflict of interest

The authors declare they have no conflict of interest.

Acknowledgements

We gratefully acknowledge literature research assistance from Mrs. Wendy Isser, Ms. Grace Garey, and Ms. Amanda Dalpiaz.

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