Mullerianosis of the urinary bladder: First case report in the Philippines

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ABSTRACT

Mullerianosis is a rare, benign, and morphologically complex, tumor-like lesion that consists of an organoid structure with normal Müllerian tissue. The diagnosis requires the presence of at least two of the three mullerian tissues: endometriosis, endosalpingiosis, and endocervicosis. There are only less than twenty (20) cases reported in literature. At present there is no published case report of mullerianosis here in the Philippines. This is a case report of a 30-year old Filipino woman who presented predominantly with lower urinary tract symptoms of severe dysuria, hematuria, and lumbar pain and was evaluated for a urologic problem secondary to a posterior bladder mass. Subsequent evaluations revealed the diagnosis of mullerianosis. This is where the interest in mullerianosis sets, its potential to mimic a neoplastic lesion of the urinary tract from clinical and diagnostic viewpoints. The clinical importance to diagnose this case correctly is of grave importance for appropriate management.

Keywords: Mullerianosis, endometriosis, endosalpingiosis, endocervicosis

INTRODUCTION

Mullerianosis is a very rare and complex tumor-like lesion, first described by Young and Clement in 1996, composed of at least two (2) out of three (3) mullerian tissues such as endometrial- endometriosis, cervical-endocervicosis, and tubaric-endosalpingiosis.[1] Up to present, this entity is very rare with fewer than 20 cases reported in English literature[1-15]. Currently there is no published case report of this rare condition here in the Philippines. Most of the published literature reports presence of mullerianosis in the urinary bladder.[1-8] It occurs in nulliparous and multiparous women under the age group, ranging from 23-53 years old in most literature.[1-8]

The rarity of this lesion may cause misdiagnosis; its correct identification is tremendously important for appropriate management, since patients may benefit from hormonal therapy and surgical management may perhaps be avoided.[2]

This paper presents the first case report of mullerianosis of the urinary bladder here in the Philippines. A 30-year old nulligravida who presented with hematuria, dysuria, and lumbar pain, she underwent computed tomographic urography which revealed a bladder mass, probably a malignant neoplasm, suggestive of a transitional carcinoma. Cystoscopy and transurethral biopsy, however, revealed a probable case of mullerianosis. Histochemical staining confirmed a case of mullerianosis. The patient underwent hormonal treatment and had clinical improvement after three (6) months of therapy. Awareness of this lesion is necessary for proper diagnosis and appropriate management.

CASE REPORT

This is a case of P.M., 30 years old, married, nulligravida, Filipino, Catholic, from Indang, Cavite, and works as an Information Technologist in Kuwait. She consulted in the Philippines on October 16, 2015 with the chief complaint of hematuria.

The patient was apparently well until one year prior to admission when the patient started having severe dysuria, and hematuria with note of passage of blood clot per urine, associated with lumbar pain. The patient sought consult with a private physician in Kuwait, a bimanual examination revealed a palpable bladder mass, which was confirmed by ultrasound. No further evaluation, follow up and medications were started.

Six months prior to present consultation, the patient sought another consult due to persistence of symptoms. She then underwent computed tomographic urography which revealed a large well-defined enhancing soft tissue intraluminal growth in the antero-superior aspect of the urinary bladder at the midline level, measuring 3.9 x 3.5 x 2.5 cm, with mild homogenous enhancement after contrast administration, suggestive of neoplastic etiology, most likely a transitional carcinoma, hence patient underwent cystoscopy and transurethral biopsy. The cystoscopy revealed that the mass forms a bridge in the middle of the urinary bladder at the base separating bladder into two

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halves. The growth at the dome of the urinary bladder extends to the right lateral wall. There were multiple blue domed cysts with different sizes. Several biopsies were taken. Histologic report revealed the following results; the lamina propria and the muscularis shows multiple tubular and glandular spaces lined by ciliated tubal like and non-ciliated columnar epithelium and a focal area lined by mucinous epithelium. A focus of hemosiderin laden macrophages surrounding a strip of surface endometrial like epithelium, some of the fragments is lined by an admixture of urothelium and mullerian epithelium. Some of the fragments also show a few cystic nests and congested vessels. Immunohistochemical staining was done revealing that the epithelial lining of these tubular spaces showed positive for CK7, vimentin, estrogen receptor and progesterone receptor and negative for CK20. The stroma surrounding some of these glands shows CD 10 positivity. Final histochemical findings of the biopsy are compatible with mullerianosis of the bladder.

The patient was advised resection of the bladder mass, however, patient opted to go home to the Philippines, hence her subsequent consultation.

On the day of consultation, the patient initially consulted with a private urologist, an ultrasound of the kidney, urinary bladder, and pelvis was requested which revealed an isoechoic mass measuring 3.3 x 3.1 x 3.4 cm seen arising from the superior wall of the urinary bladder. Initial impression was endometriosis of the bladder. The plan of the urologist was to do surgical excision of the bladder mass. The patient was then referred to an obstetrician-gynecologist for evaluation and co-management.

Her past medical history is non-contributory, she had asthma since childhood; her last attack was in 2013. She had breast cyst incision in 2005. For her menstrual history, she had her menarche at twelve years old, with regular menstrual periods occurring every twenty-eight to thirty-five days, lasting for about five days, using two moderately soaked pads per day. She started experiencing non-progressive dysmenorrhea two years ago only on her second day of menses, with no any other symptoms.

On physical examination, the external genitalia are normal looking with normal distribution of pubic hair, no masses, no lesion. Speculum exam revealed a smooth vagina, with no masses, no lesion, with prominent rugae, the cervix looks parous, pinkish, smooth, no masses, no lesions, and with no discharge coming out of the cervical os. Upon internal examination the cervix is midline closed, non-parous, corpus slightly enlarged. Bimanual examination revealed a 4 cm tender mass palpated anterior to the cervix and posterior to the bladder. There is no adnexal mass or tenderness, and no blood per examining finger. All other systemic exams were unremarkable.

On the same day of the consultation the patient was requested by the obstetrician-gynecologist to undergo a transvaginal ultrasound, which revealed a mass anterior and separated from the uterine body measuring 3.51 x 3.07 x 2.81 cm (Figure 1). It is seen within the posterior wall of the urinary bladder. The sonologic diagnosis was a bladder mass versus a parasitic subserous myoma.

The primary impression was mullerianosis of the urinary bladder based on the histopathologic report and histochemical staining done in Kuwait, subsequently; patient was given gonadotropin releasing hormone agonist 3.75 mg intramuscularevery 4 weeks for 3 doses.

After the third dose, a repeat transvaginal ultrasound was done and the previously seen bladder mass is still evident, anterior and separated from the uterine body, measuring 3.47 x 2.71 x 2.32 cm (Figure 2).

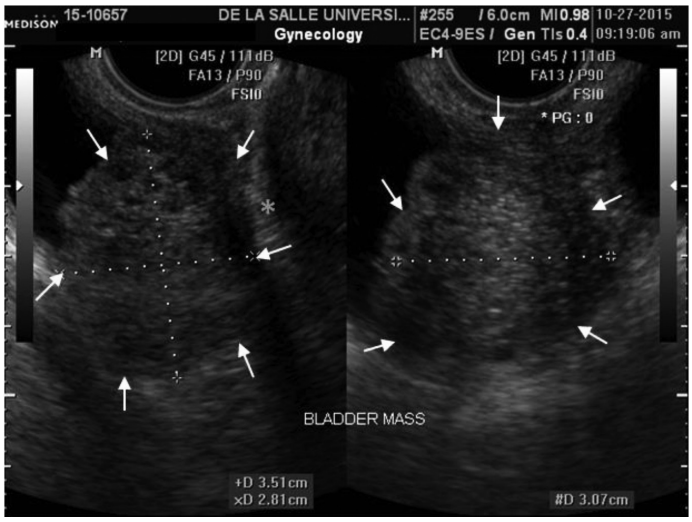

Figure 1. Bladder mass (yellow arrows) as described pre-treatment with gonadotropin releasing hormone agonist. Asterisk (*) posterior wall of the urinary bladder

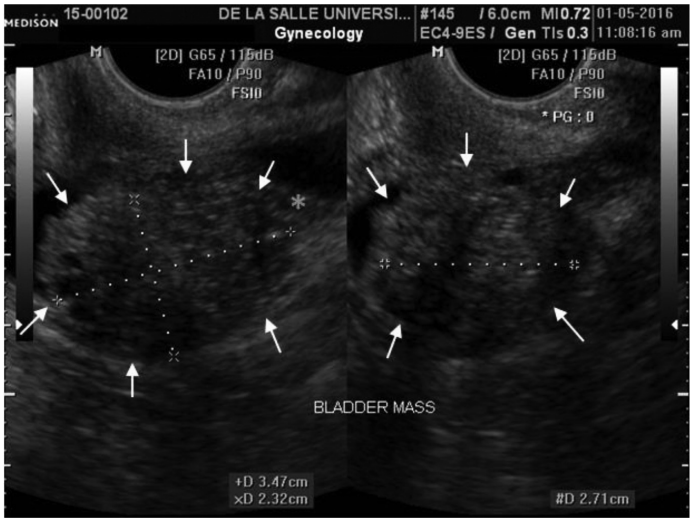

Figure 2. Bladder mass (yellow arrows) as described post-treatment with gonadotropin releasing hormone agonist. Asterisk (*) posterior wall of the urinary bladder

The patient at this time was asymptomatic and physical exam revealed that the cervix is closed, non-parous, and posterior, there is a 2 cm movable firm, non-tender mass anterior to the cervix.

The gonadotropin releasing hormone agonist was given for three more doses in Kuwait and at present the patient remains to be asymptomatic.

CASE DISCUSSION

Mullerianosis is a rare benign new growth that may present as a growing mass anywhere in the pelvic area, it consists of three histologic tissues, comprised by endometriosis, endocervicosis, and endosalpingiosis.[1-2] It was first described by Young and Clement in 1996, and is defined as the presence of at least two of the three tissues previously mentioned. They reported three cases where the patients had masses up to 4 cm in maximal size, which involved the posterior wall of the urinary bladder, treated by transurethral resection. Microscopic examination showed prominent involvement of the lamina propria and muscularis propria by tubules and cysts lined by müllerian-type epithelium.[1]

Up to present, this entity is very rare with fewer than 20 cases reported in English literature and in journals[1-15]. *Currently there is no published case report of this rare condition here in the Philippines*.

Most of the published literatures reports presence of mullerianosis in the urinary bladder, its most common location[1-8], *likewise the index patient had the lesion on the dome of the urinary bladder*, although the lesion was also reported to occur rarely in the following locations like the ureter[10-11], mesosalpinx[12], inguinal lymph nodes[13], and conus medularis of the spinal cord[14]. It occurs in nulliparous and multiparous women under the age group, ranging from 23-53 years old in most literature. However, one case of mullerianosis was reported in a 70 year-old woman presenting with persistent vaginal bleeding after polypectomy, magnetic resonance imaging done for further studies revealed bladder lesions despite absence of any urinary symptoms. Cystoscopy done revealed three polypoid masses on the bladder trigone. The polypoid lesions were biopsied and histopathology and histochemical studies revealed mullerianosis[5]. It may also be associated with previous history of pelvic surgery or cesarean delivery[3-5]. *The index patient did not have any history of pelvic surgery, and hence the etiology may be that of a different theory*.

The pathogenesis of this rare entity is still unclear, with few cases reported there were only two theories formulated. Since mullerianosis is somehow related with endometrisos, implantation theory was formulated, and is applicably limited to patients who had previous pelvic surgery or cesarean delivery. Also the presence of two or more mullerian tissues like that of the fallopian tubes and cervix seems arguable against implantation theory, and the presence of the lesion on distant sites could not be explained by this theory[2,4-8]. Hence implantative theory may only be valid for cases of mullerianosis, occurring in women with previous pelvic surgery or cesarean delivery, those with single mullerian tissue, and invalid for those presenting with lesions in distant parts. The more appropriate theory for these cases would be that of the theory of metaplastic origin, first proposed by Donne et al. In this report, the theory of metaplastic origin was based on the following observations, mostly the opposite of that of the implantative theory, in that the presence of two or more mullerian tissues rather than an isolated one is better explained by metaplasia, secondly this multiplicity reflects the lesion's capacity of differentiation; and lastly the invariable location of the lesion at the posterior wall and dome of the bladder, an area that topographically corresponds to its peritoneal covering[16]. There is also a report by Koren and colleagues where they describe the continuity between the mullerian glands and the urothelium, and that it is hormonally receptive[17], all of these observations leads to metaplastic origin theory.

Clinical features from case reports presented differently, but the most frequent clinical presentations are non-specific lower urinary tract symptoms including hematuria[4], dysuria, painful and increased frequency of micturition[6], bladder mass, right iliac fossa pain[7], pelvic cyclical pain, and other symptoms related to the extent of involvement[8]. Occasionally, it is an incidental finding during investigation for other disorders[4]. *The index patient presented with hematuria, dysuria, and lumbar pain*.

As with endometriosis and endocervicosis, mullerianosis has the potential to be misdiagnosed as invasive adenocarcinoma in the bladder wall[15]. Close resemblance to malignancy lies to the histologic appearance of the glandular structures and cell and nuclear stratification, however, mullerianosis lacks invasion of the adjacent structure compared to adenocarcinoma. Adenocarcinomas also show cellular features of malignancy, and high index of proliferation or mitoses[9]. Malignant transformation of mullerianosis in a urinary bladder is extremely rare. Only one endometriod carcinoma complicating mullerianosis was reported in the literature[8].

The differential diagnoses of mullerianosis include both benign and malignant lesions. Benign lesions like cystitis glandularis, urachal remnants, and nephrogenic adenoma, malignant lesions ranging from primary adenocarcinoma of the bladder and secondary spread from adenocarcinoma of the cervix. Thus it is important to diagnose mullerianosis correctly, since management

of these lesions differ immensely. Cystitis glandularis are polypoid focus of bladder mucosal thickenings and irregularities due to metaplasia of the urothelium. To differentiate it from mullerianosis, cystitis glandularis are superficially located on the bladder wall, with preservation of the muscularis propria, histochemically it does not have staining for estrogen and progesterone receptors. Treatment also differs, cystitits glandularis should be removed by surgical excision because of its association with adenocarcinoma and patients should be monitored. Urachal remnant is any congenital anomaly associated with the urachus. The urachus is related to the dome of the urinary bladder, failure to obliterate will cause urachus to persist in a number of configurations. To differentiate, demonstration of endometrial gland in mullerianosis, through CD10 immunostaining is significant. Management for urachal remnant is also excision. Nephrogenic adenoma is a benign mass that may involve the bladder and may appear histologically, as that of mullerianosis with the presence of small tubules lined by cuboidal and hobnail cells, the difference is that nephrogenic adenoma does not feature mucinous cells, have no immunoreactivity for hormone receptors, and is situated deep in the muscularis propria. Mullerianosis may also simulate an infiltrating primary adenocarcinoma of the urinary bladder, those of primary adenocarcinoma arising from the bladder and those that are primary malignant lesion of the urachal remnants. Both malignancies arise in older women as compared to mullerianosis which arise in fertile age. Differentiation of these malignant lesions compared to that of mullerianosis is complicated by their preferential location at the dome of the bladder, as well as the lesions' demarcation from normal bladder tissue. Diagnosis can be confirmed by histologic evidence of endometrial glands with periglandular endometriod stroma, lack of cytonuclear atypia, and absence of mitoses and desmoplasia in mullerianosis. Lastly, secondary spread from adenocarcinoma of the cervix can be easily ruled out by clinical history and physical examination, as well as other diagnostic modalities as deemed appropriate[2-9].

Initial imaging may be in the form of pelvic ultrasonographylike transvaginal ultrasound and KUB ultrasound and may reveal nodular, polypoid, mass-like lesions ranging from 2-4 cm involving the dome of the bladder.[5]

KUB ultrasound in the index patient revealed an isoechoic mass measuring 3.3 x 3.1 x 3.4 cm seen arising from the superior wall of the urinary bladder which exhibits no uptake on color flow study.

The transvaginal ultrasound of the index patient revealed a mass anterior and separated to the uterine body measuring 3.51 x 3.07 x 2.81 cm. It is seen within the posterior wall of the urinary bladder.

A case report described the lesion in magnetic resonance imaging as a 2 x 3 cm mass in the posterior wall of the bladder, extending through the full wall thickness, and there was a thin plane between it and the serosal surface of the uterus[7].

Gross description is best noted during cystoscopy, in literature reviews of gross description of mullerianosis, it is described as polypoid, mass like lesions ranging from 1.0-4.5 cm in size, predominantly involving the dome or the posterior wall of the bladder[2]. A case report of mullerianosis by Guan and colleagues described mullerianosis excised from the dome of the left lateral wall of the bladder; grossly it had internal cystic structures and an inverted growth pattern. Some of the cysts were dark blue to black in color. Some reveals a submucosal nodule or a darkly colored cyst covered by hyperemic mucosa, and there may be associated scarring and fibrosis with distortion of the bladder wall.[5] *Cystoscopy in the index patient revealed that the mass forms a bridge in the middle of the urinary bladder at the base separating bladder into two halves. The growth at the dome of the urinary bladder extends to the right lateral wall. There were multiple blue domed cysts with different sizes*.

This leads us to the importance of biopsy, subsequent histologic findings, and histochemical evaluation. The definitive diagnosis for cases of mullerianosis is confirmed by histology[4]. In histologic examination by hematoxylin-eosin stain, mullerianosis of the urinary bladder appears as a lesion consisting of an admixture of variable sized, band-appearing glands that are deeply situated within the lamina propria and the muscularis propria of the urinary bladder wall, and which resemble the tubal, endocervical, and endometrial epithelia (Figure 3)[2].

In a case reported by Maeda et.al, histopathologic study of the case revealed the presence of variably-sized dilated tubular glans in the lamina propria and muscularis propria of the bladder. The surface urothelium was without atypia, and no connection between the surface urothelial mucosa and dilated tubular glands noted. The dilated glands were covered by ciliated cuboidal cells containing small round nuclei without nucleolus which corresponds to tubal-type epithelium. Some of the tubular glands were covered by columnar cells with intracytoplasmic mucin and small round nuclei, resembling endocervical mucosa. Tiny focus of endometrial tissue and stroma was observed adjacent to the dilated tubal-type gland (Figure 3).[6]

Histologic report of the index patient revealed the following results; the lamina propria and the muscularis shows multiple tubular and glandular spaces lined by ciliated tubal like and nonciliated columnar epithelium and a focal area lined by mucinous epithelium similar to that of the endocervix. A focus of hemosiderin laden macrophages surrounding a strip of surface endometrial

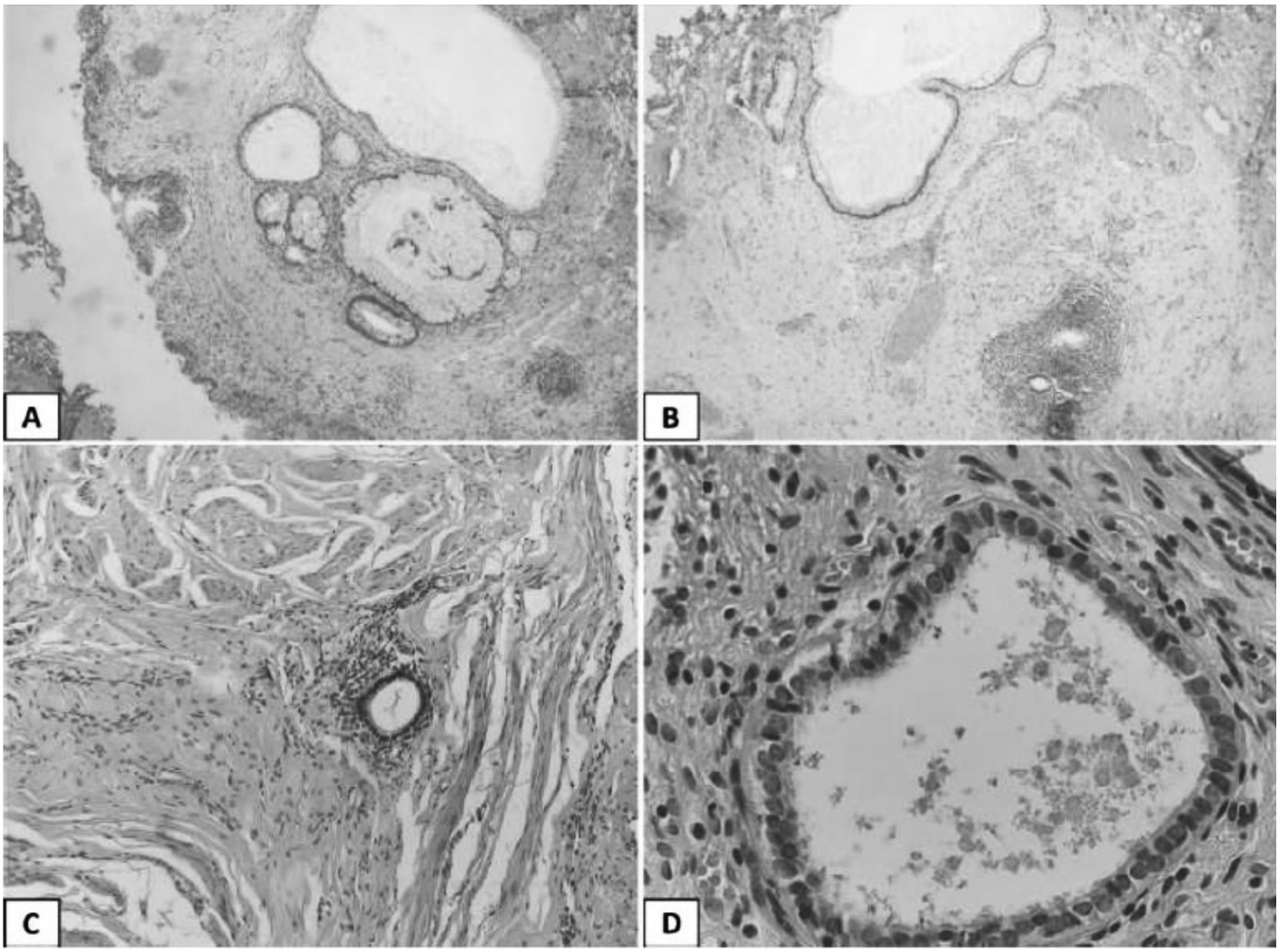

Figure 3. A, Glands lined by endocervical epithelium in the lamina propria of endoscopically resected fragments of urinary bladder wall. B, Endocervical and endometrial glands surrounded by endometrial stroma deeply located in bladder wall. C, Endometrial gland with surrounding stroma within muscularis propria of bladder fragments. D, Gland lined by ciliated tubal-type epithelium in the bladder wall (hematoxylin-eosin, original magnifications 3100 [A and B], 3200 [C], and 3400 [D]).[2]

like epithelium, some of the fragments is lined by an admixture of urothelium and mullerian epithelium. Some of the fragments also show a few cystic nests and congested vessels, consistent with the diagnosis of mullerianosis.

In line with the derivation of this tissue, immunohistochemical staining can be done to reveal the presence of estrogen receptors and progesterone receptors (Figure 4).[2] Also, similar to the orthotopic endometrium, the stroma surrounding the endometrial glands of mullerianosis is diffusely stained by anti-CD10 antibody, and the glandular epithelia stain positively for Ca-125.[2]

In the index patient, immunohistochemical staining was done revealing that the epithelial lining of these tubular spaces showed positive immunoreactivity for CK7, vimentin, estrogen receptor and progesterone receptor and negative for CK20. The stroma surrounding some of these glands shows CD 10 positivity. Immunoreactivity to CK7 with negative CK20 is immunophenotyic for tubal-type mullerian tissue, and is consistent with endosalpingiosis. Endocervicosis and endometriosis on the other hand comprise co-expression of vimentin and keratin and the presence of estrogen and progesterone receptors while CD10 is a reliable and sensitive immunohistochemical marker of normal endometrial stroma.

Diagnosis of mullerianosis imposes grave importance for its management, since correct diagnosis may benefit patients who do not want to undergo surgery since this lesion is responsive to hormone therapy[2].

Among the literatures reviewed, there was no consensus with regards to the treatment of mullerianosis, although several of the documented cases were managed primarily by resection of the bladder mass. Hormonal treatment may be started immediately with gonadotrophin releasing hormone agonist, oral contraceptives, progestogens, or danazol[18]. Many surgical

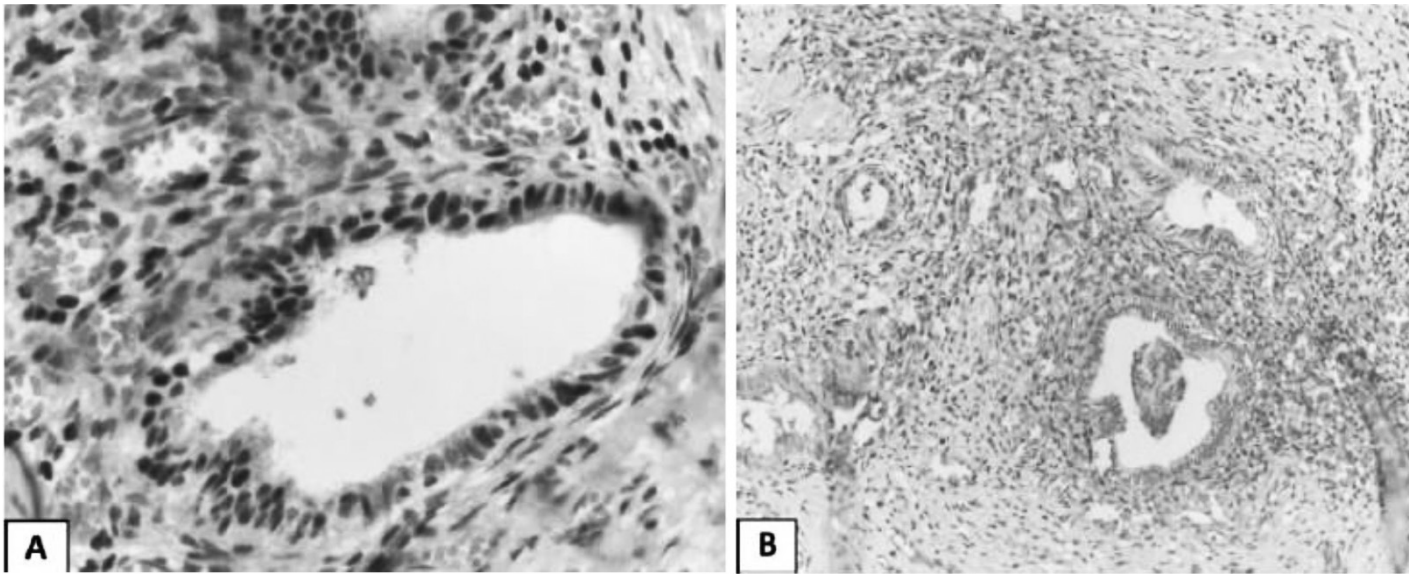

Figure 4. A, Nuclear staining for estrogen receptors in the endometrial epithelial and stromal cells found within the fragments of urinary bladder wall. B, CD10 stain in the stroma surrounding endometrial glands (estrogen receptor stain, original magnification3200 [A]; CD10 stain, original magnification3200 [B]).

modalities have been used for the treatment of these lesions: transurethral resection and both open and laparoscopic partial cystectomy[19]. Endoscopic resection of the bladder lesions is diagnostic as well as therapeutic, but the preferred treatment will depend on the age of the patient, the size, number and depthof infiltration of the bladder lesions, and their location within the bladder[5].

Hormonal therapy alone have not been widely discussed for the management of mullerianosis, this is probably primarily because a surgical approach to obtain a tissue diagnosis has usually been undertaken[20]. I*n the index patient, an initial biopsy of the tumor already gave the diagnosis of mullerianosis. The option to undergo medical therapy was the appropriate management for the index patient considering her age and fertility status (G0)*.

It is certain that the müllerian tissues are hormone responsive; thereby efforts have been made to treat symptoms with hormone therapies, reducing hormonal stimulation and assuch, reducing associated symptoms. Some available case reports have demonstrated both a reduction in symptoms and lesion size after a 3-6 month period of hormonal augmentation[20].

The index patient was given gonadotropin releasing hormone agonist 3.75 mg intramusclar every 4 weeks for 3 doses in the Philippines and was continued for 3 more doses in Kuwait.

The efficacy of gonadotropin-releasing hormone agonists in the treatment of this lesion is controversial. Indeed, though disappearance of the symptoms is observed following therapy, the lesion may remain unchanged in size and appearance. Pharmacologic treatment might be the most appropriate in the case of mullerianosis arisen in sites, such as the spinal compartment, where surgical intervention may lead to life-threatening complications[20].

Nonetheless this case report addresses a rare lesion in the index patient and it highlights the importance of identifying appropriate and effective long-term treatment. The choice of management should be pointed to the improvement of the symptoms with much less morbidity and complications.

CASE SUMMARY

We are presented with a rare case of a benign gynecologic lesion which initially presented with urologic signs and symptoms mimicking a neoplastic process probably malignant involving in most cases the urinary bladder. High index of suspicion with proper imaging modalities and extensive histologic evaluation with immunohistochemical staining will lead to the diagnosis of mullerianosis, an extremely rare, certainly benign tumor like neoplasia with histologic findings of at least two out of three lesions including endometriosis, endosalpingiosis, and endocervicosis. Correct diagnosis is of great value to patients who do not want to undergo surgical removal of this lesion primarily because this condition is responsive to hormonal therapy, as seen in this case report. ■

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