Int J Clin Exp Med 2018;11(8):8687-8692
www.ijcem.com /ISSN:1940-5901/IJCEM0067080

Case Report

Clinicopatholgic features of persistent mullerian duct syndrome complicated with seminoma: a case report and review of literatures

Xin Zeng*, Yuwan Zhao*, Yanxia Wu, Huancheng Tang, Jun Cao, Jianjun Liu

*Laboratory of Urology, Affiliated Hospital of Guangdong Medical University, Zhanjiang 524001, China. *Co-first authors.*

Received October 12, 2017; Accepted May 3, 2018; Epub August 15, 2018; Published August 30, 2018

Abstract: Persistent mullerian duct syndrome (PMDS) is a rare form of male pseudohermaphroditism characterized by the presence of a uterus and fallopian tubes owing to failure of mullerian duct regression, which was shown in a genetically and phenotypically normal male patient. PMDS can occur at any age, preoperative diagnosis of PMDS is quite difficult, as most of them were discovered incidentally during surgery before adolescence. The co-existence of PMDS with seminoma has been rarely reported in the literature. It is necessary for people to grasp knowledge to diagnose this rare case. Therefore, we report a case of PMDS complicated with seminoma. A 28-year-old-male who was made previous diagnosis of enorchia was found fallopian tubes and uterus during an exploratory laparotomy because of left abdominal pain.

Keywords: Persistent mullerian duct syndrome, AMH, seminoma

Introduction

Being a rare disorder of sexual development, PMDS was first mentioned by Nilson in 1939 [1]. Up to present, there have been only 200 cases reported in the literature worldwide. Among all reported cases, PMDS complicated with testicular cancer has been rarely reported. In this paper, in a case of PMDS complicated with seminoma, it is reported about the clinical characteristics and clinicolpathologic features and reviewed literatures to explore the clinical pathology characteristics for the pathological diagnosis and differential diagnosis.

Case report

A 28-year-old Chinese man was diagnosed postoperatively as being a PMDS with a seminoma on the basis of finding fallopian tubes and uterus without ovarian tissue during an exploratory laparotomy for left abdominal pain without palpable mass. He was considered as enorchia previously. Physical examination on the patient revealed that a phenotypically male had normal external male genitalia. The testis was absent in the scrotum since birth, nor found in the inguinal region. He had normal secondary sexual characteristics with no gynaecomastia. Although the patient had sexual life and ability to erect and ejaculate, he was childless. His brother and sister did not have similar medical history. Ultrasound revealed a substantial mass occupied in left lower abdomen (**Figure 1**). Previous diagnosis of enorchia was made. Suspecting of a malignant neoplasm invoved in the undescended testis, an exploratory laparotomy was performed. During the operation, the left abnormal testis was found and another one at the right was absent, while tubae laciniae and uterus were found in pelvic cavity, which were all excised. All the specimens were sent for histopathological examination. No obvious evidences indicated metastasis. Pathological examination of the excised specimen was reported as uterus and bilateral uterine tubes with histological findings of endometrium, cervix and left and right uterine tubes (**Figure 3A-C**). Karyotype analysis from peripheral blood resulted as 46XY (**Figure 2**).

Discussion

The pathogenesis of PMDS

The occurrence mechanism of hermaphroditism is unclear at present which is believed that

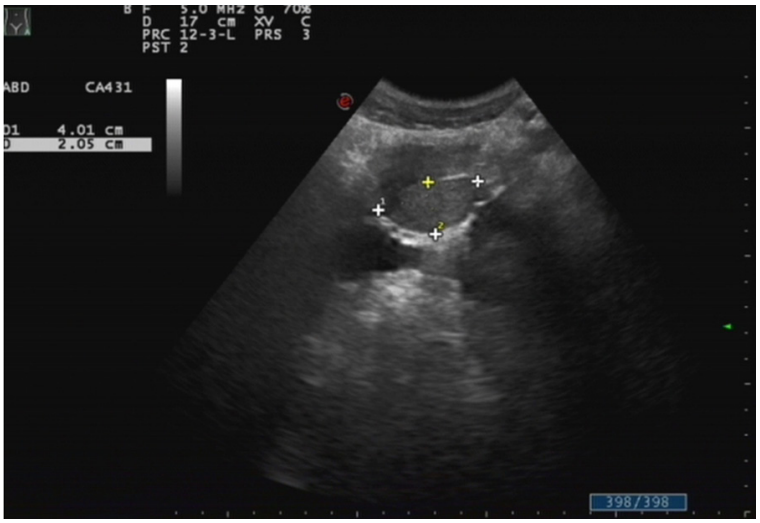

Figure 1. The abdominal ultrasound scan of the abdominal cavity showed that substantial low level echo mass occupied in left lower abdomen with the size of 4.01 cm × 2.05 cm (plus signs).

there is close correlation between chromosome, abnormal gonadal development and related endocrine disorders. In recent years, increasing investigations indicated that AMH, WT-1, SRY, SF-1, DAX-1, SOX-9 and other genes were involved in differentiation of two sexes, in the process of which any one the above gene mutation, deletion or translocation can cause the abnormal sex differentiation and lead to the occurrence of the sexual abnormality [2].

Anti mullerian hormone (AMH) also called mullerian inhibiting factor (MIF) plays an important role in differentiation of reproductive organs in male fetuses. In a human fetus, the internal genital tract of fetus is composed of mullerian duct and wolf tube before sex determination; both of them coexist within 8 weeks. In male embryos, the immature Sertoli cells of the Leydig produce AMH which is responsible for the regression of the mullerian duct by the end of the 7th week. Then, testosterone promotes wolf tube is differentiated into vas deferens, epididymis and seminal vesicle after 2 weeks. In the female embryo, the mullerian duct is differentiated into the fallopian tube and uterus, while the wolf tube is degenerated [3]. The male with normal internal and external genital appear incomplete degradation of mullerian duct when the patient lacks AMH.

The gene is responsible for AMH located in the short arm of chromosome 19, p13.3 which plays a biological role through transmembrane serine/threonine kinase receptor type II [4]. The deletion, insertion or mutation of AMH gene can affect its regulation, expression and translation, resulting in a lack of AMH. All kinds of factors that interrupt the process of the synthesis, secretion and function of AMH can lead to the occurrence of PMDS finally. The most common one is the mutation of AMH gene among these factors. A report about three brothers with PMDS in 1991 found that the mutation of the fifth exon of 2096th locus of the AMH gene resulted in the early termination of the translation [5].

PMDS has familial aggregation and genetic predisposition, which is an autosomal recessive disorder related to sex. In addition, there may be some factors that have not been noticed and confirmed, such as the failure of AMH action time, and the intrauterine environment during the embryonic period; these factors lead to the failure of mullerian duct of degeneration [6]. It was normal that AMH level and the expression of AMH gene occur in approximately half of the patients, the number of abnormal AMH receptor or insensitive AMH receptor may be another etiology of PMDS [7].

The classification of PMDS

According to the anatomical characteristics of the residual mullerian duct structure, PMDS is generally divided into 2 categories: the first kind (male form) accounts for 80% to 90% of cases, characterized by unilateral cryptorchidism with contralateral inguinal hernia. This kind can be further categorized into two hypotypes: the most common type is hernia uteri inguinalis, in which hernia content is undegraded uterus and ipsilateral fallopian tube. Another type is transverse testicular ectopia (TTE), which appears both testes in the same hernia sac with uterus and uterine tubes [4]. The second kind (female form) occupies only 10% to 20% of cases, characterized by bilateral cryptorchidism located in analogue positions of ovaries, with the uterus fixed in the pelvis bilateral,

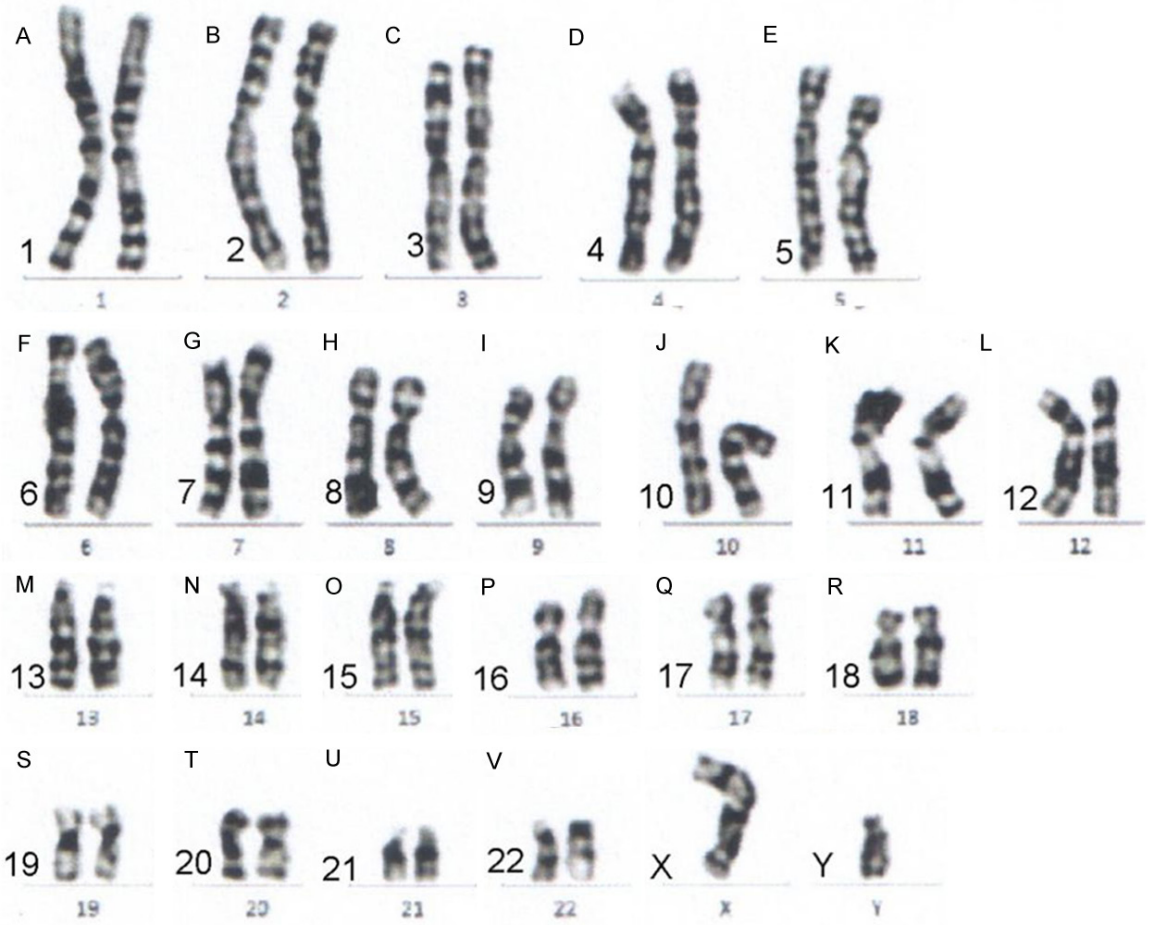

Figure 2. Chromosal analysis result was 46XY karyotype. (A to V are autosomes, X and Y are sex chromosomes).

and both testes embedded in the round ligaments [4]; as in our case.

The clinical manifestation and diagnosis of PMDS

The secondary sexual characteristics of PMDS patients are normal and perform as male sexual psychological tendency and reproductive ability. Most of PMDS patients seek treatment for inguinal hernia, bilateral cryptorchidism, oligospermia and sterility or genital system tumor. The preoperative diagnosis of PMDS is quite difficult. CT, MRI, AMH hormone levels and laparoscopy may be helpful for diagnosis [8, 9]; and it is always discovered incidentally during surgery [10].

PMDS and seminoma

The relationship between PMDS and cryptorchidism or TTE is unclear. The mechanical obstruction of the mullerian duct structure is considered to be a possible factor of preventing testis from descending into the scrotum. Increasing evidences revealed that the risk of developing a tumor of testis was greatly increased, which was 10 times higher in enorchia than the normal testis. Testicular tumours originating from an undescended testis is about 10% [11] and the relative risk of testicular neoplasm in cryptorchidism is 7.5% [12]. In patients with unrecognised intraabdominal testis, seminoma is more common than nonseminomatous germ cell tumor [13]. The incidence of testicular malignant transformation in the undescended testes of PMDS patients is estimated to be 5% to 18%, which is similar to the incidence of testicular carcinoma in abdominal testes in patients without PMDS [14]. No more than 17 cases that PMDS complicated with seminoma have been reported in the PubMed database since 1985 [15-30]. In this case,

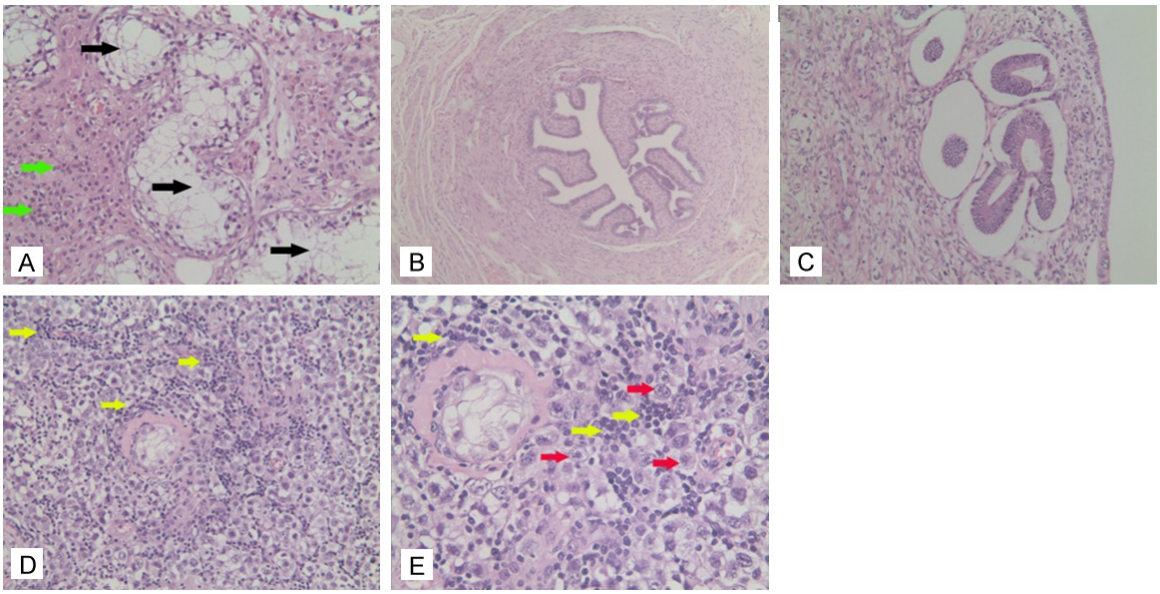

Figure 3. A. Pathological features of the left testis in patient with PMDS, which shows the dysplasia of seminiferous tubule (black arrows) and hyperplasia of Leydig's cell (green arrows) (original magnification × 200). B. Pathological features of the fallopian tube (original magnification × 100). C. Pathological features of the endometrium (original magnification × 200). D, E. Pathological features of the seminoma. The picture partially showed the diffuse single heterotypic cell (red arrows). The tumor cells were large, with abundant transparent cytoplasm, coarse granular nuclei, deeply stained chromatins, and infiltration of substantial lymphocytes (yellow arrows) (original magnification × 200, × 400).

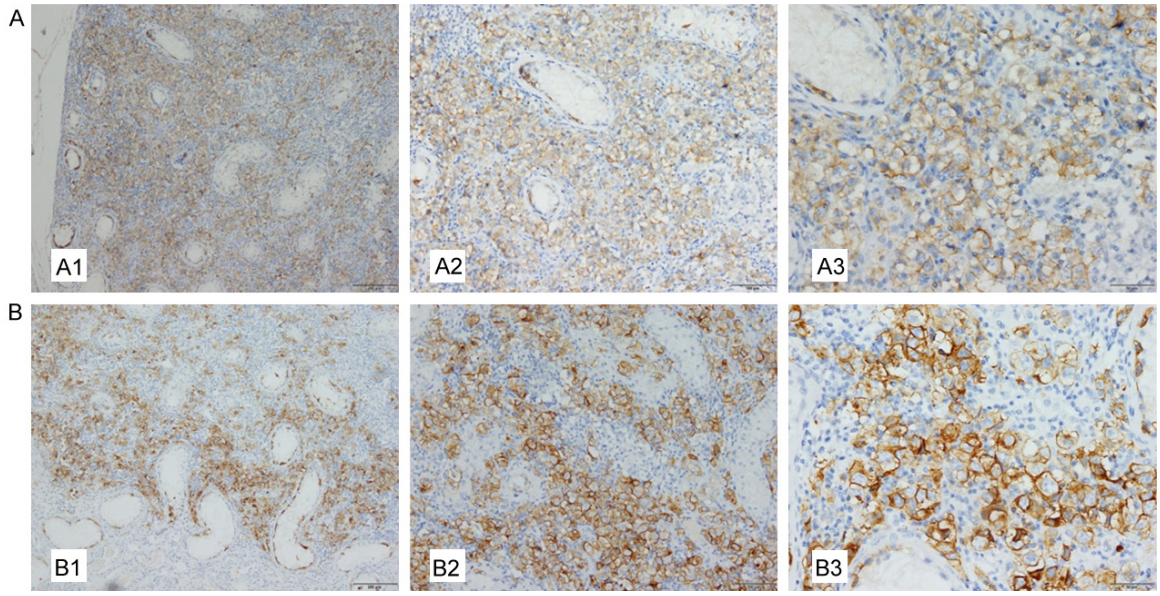

Figure 4. A1-A3. Seminoma of immunohistochemistry was positively express CD117. CD117 was highly expressed cytoplasm positive in the picture (original magnification × 100, × 200, × 400). B1-B3. Seminoma of immunohistochemistry was positively express PLAP. PLAP was highly expressed membrane positive in the picture (original magnification × 100, × 200, × 400).

besides that histology of the specimen revealed typical features of seminoma (**Figure 2D**, **2E**), the immunohistochemical detection implicated that PLAP and CD117 are positively while AFP (**Figure 4**), Vimentin, HCG, CK-LMW, Desmin, CD34 and CD30 are negative; the index of

Ki-67 is 50%; all these indicators show the clear diagnosis of seminoma. With the research development of seminoma, more and more makers, such as MAGEC2, CAG, CMTM2, are applied in the early diagnosis of seminoma [31, 32].

The differential diagnosis of PMDS

It is critical to distinguish PMDS from other intersex disorders. Mixed gonadal dysgenesis (MGD) is the most important differential diagnosis in PMDS. In MGD cases, patients have the residual mullerian duct structures and vague external genitalia. But, the karyotype of MGD is usually 45, XO/46, XY mosaic type. Therefore, a karyotype and assessment of sex hormone levels are necessary to verify both genetic sex and the existence of functional testicular tissue.

The treatment of PMDS

At present, surgical treatment is the only effective treatment for PMDS. The main goal of surgical treatment is to deal with residual mullerian duct and ectopic testis. In order to prevent any malignant transformations and place the testes into a palpable position in the scrotum, early orchidopexy with removal of mullerian duct structures is recommended by most clinicians [33]. Vas deferens should be divided from the rudimentary uterus; and the blood supply of testis should be preserved before excision of mullerian duct structures. PMDS patients with intra-abdominal cryptorchidism have higher postoperative fertility before puberty. Cryptorchidism traction should be performed early in order to correct enorchia while exairesis of hypogenetic testis is suitable for those cases of patients at over 2 years olds. The fertility rate is only about 14% for patients with intra-abdominal cryptorchidism after puberty, which have higher incidence of malignant transformations. Therefore, orchidectomy can be performed. One side of the testis should be retained in the cases of patients with bilateral cryptorchidism. PMDS patients with TTE, modified Omberdan technique is the most commonly described one that places the ectopic testis in the correct hemiscrotum through a window in the scrotal septum. Once malignant transformation had occurred, the treatment principle is the same as that of the common orchioncus. Seminoma is highly sensitive to radiotherapy and chemotherapy; and its prognosis depends on clinical stages closely; the recurrence rates are 6%, 18% and 36% separately while the tumor size are <3 cm, 3~6 cm and >6 cm. In addition, blood and lymph metastasis is also the important factor involved in the prognosis of seminoma.

Acknowledgements

The study is funded by the key department foundation of affiliated hospital of Guangdong Medical University.

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Jianjun Liu and Jun Cao, Laboratory of Urology, Affiliated Hospital of Guangdong Medical University, Zhanjiang 524001, China. Tel: +86-759-2387079; E-mail: Zj-liujj@163.com (JJL); zjcaoj@163.com (JC)

References

[1] Vandersteen DR, Chaumeton AK, Ireland K and Tank ES. Surgical management of persistent mullerian duct syndrome. Urology 1997; 49: 941-945.

[2] Federman DD. Three facets of sexual differentiation. N Engl J Med 2004; 350: 323-324.

[3] Shalaby MM, Kurkar A, Zarzour MA, Faddan AA, Khalil M and Abdelhafez MF. The management of the persistent mullerian duct syndrome. Arab J Urol 2014; 12: 239-244.

[4] Renu D, Rao BG, Ranganath K and Namitha. Persistent mullerian duct syndrome. Indian J Radiol Imaging 2010; 20: 72-74.

[5] Knebelmann B, Boussin L, Guerrier D, Legeai L, Kahn A, Josso N, Picard JY. Anti-mullerian hormone bruxelles: a nonsense mutation associated with the persistent mullerian duct syndrome. Proc Natl Acad Sci U S A 1991; 88: 3767-71.

[6] Tejeda S, Stolley MR, Vijayasiri G, Campbell RT, Estwing Ferrans C, Warnecke RB, Rauscher GH. Negative psychological consequences of breast cancer among recently diagnosed ethnically diverse women. Psychooncology 2017; 26: 2245-2252.

[7] Ju X, Li Z, Zhang C, Qin C, Shao P, Li J, Li P, Cao Q, Zhang W, Wang Z, Yin C. Clinical aspects and molecular genetics of persistent mullerian duct syndrome associated with transverse testicular ectopia: report of three cases clinical aspects and molecular genetics of the persistent mullerian duct syndrome. Urol Int 2013; 90: 83-6.

[8] Alp BF, Demirer Z, Gürağaç A, Babacan O, Sarı E, Sarı S, Yavan I. Persistent mullerian duct syndrome with transverse testicular ectopia and seminoma. Int Urol Nephrol 2014; 46: 1557-62.
[9] Manjunath BG, Shenoy VG and Raj P. Persistent mullerian duct syndrome: how to deal with the mullerian duct remnants-a review. Indian J Surg 2010; 72: 16-9.
[10] Nayak VJ, Kamath AS, Krishnappa MH and Bylappa SK. Persistent mullerian duct syndrome: A case report and review of the literature. Int J Appl Basic Med Res 2014; 4: 125-127.
[11] Abratt RP, Reddi VB and Sarembock LA. Testicular cancer and cryptorchidism. Br J Urol 1992; 70: 656-9.
[12] Swerdlow AJ, Higgins CD and Pike MC. Risk of testicular cancer in cohort of boys with cryptorchidism. BMJ 1997; 314: 1507-11.
[13] Berkmen F. Persistent mullerian duct syndrome with or without transverse testicular ectopia and testis tumours. Br J Urol 1997; 79: 122-6.
[14] Farikullah J, Ehtisham S, Nappo S, Patel L, Hennayake S. Persistent mullerian duct syndrome: lessons learned from managing a series of eight patients over a 10-year period and review of literature regarding malignant risk from the mullerian remnants. BJU International 2012; 110: E1084-E108.
[15] Tsujii T, Tari K, Yonese J, Kojima S and Takubo K. A case of persistent mullerian duct syndrome associated with seminoma. Hinyokika Kiyo 1989; 35: 905-910.
[16] Morikawa M, Wakabayashi A, Nakata Y, Tokunaka S, Takamura T and Yachiku S. Persistent Mullerian duct syndrome with seminoma: report of a case. Hinyokika Kiyo 1985; 31: 1819-1829.
[17] Nishioka T, Kadowaki T, Miki T and Hanai J. Persistent mullerian duct syndrome with seminoma: report of a case. Hinyokika Kiyo 1992; 38: 89-92.
[18] Masereel B and Michiels G. Persistent mullerian duct syndrome with torsion of an intra-abdominal seminoma. Acta Chir Belg 1999; 99: 256-259.
[19] Wu HC, Chen JH, Lu HF and Shen WC. Persistent mullerian duct syndrome wtih seminoma: CT findings. AJR Am J Roentgenol 2000; 174: 102-104.
[20] Ramanujam AS, Chandra A, Raman SG, Sagar TG and Mallikarjuna VS. Persistent mullerian duct syndrome (PMDS) with testicular seminoma. Indian J Pathol Microbiol 2001; 44: 441-443.
[21] Duenas A, Saldivar C, Castillero C, Flores G, Martinez P and Jimenez M. A case of bilateral seminoma in the setting of persistent mullerian duct syndrome. Rev Invest Clin 2001; 53: 193-196.
[22] Prakash N, Khurana A and Narula B. Persistent mullerian duct syndrome. Indian J Pathol Microbiol 2009; 52: 546-548.
[23] Chiang CY, Tsai JW, Wang HP, Sung YZ and Chang LC. Hernia uterine inguinale and seminoma in persistent mullerian duct syndrome. Int J Surg Pathol 2010; 18: 440-442.
[24] Inuganti RV, Bala GS, Kumar YK and Bharathi YK. Persistent mullerian duct syndrome with testicular seminoma: a report of two cases. Indian J Urol 2011; 27: 407-409.
[25] Chamrajan S, Vala NH, Desai JR and Bhatt NN. Persistent mullerian duct syndrome in a patient with bilateral cryptorchid testes with seminoma. J Hum Reprod Sci 2012; 5: 215-217.
[26] Kovachev SM, Nikolov SD and Mihova AP. Uterine leiomyoma in a man with persistent mullerian duct syndrome and seminoma. Isr Med Assoc J 2014; 16: 735-737.
[27] Alp BF, Demirer Z, Guragac A, Babacan O, Sari E, Sari S and Yavan I. Persistent mullerian duct syndrome with transverse testicular ectopia and seminoma. Int Urol Nephrol 2014; 46: 1557-1562.
[28] Yamada K, Takahata A, Ichijo Y, Akazawa K, Goto M, Terayama K and Yamada K. A case of testicular seminoma in persistent mullerian duct syndrome with transverse testicular ectopia. Abdom Imaging 2015; 40: 475-479.
[29] Palanisamy S, Patel ND, Sabnis SC, Palanisamy N, Vijay A and Chinnusamy P. Laparoscopic hysterectomy with bilateral orchidectomy for Persistent Mullerian duct syndrome with seminoma testes: case report. J Minim Access Surg 2015; 11: 273-275.
[30] Modi J, Modi D and Bachani L. Acute urinary retention caused by seminoma in a case of persistent Mullerian duct syndrome. Indian J Pathol Microbiol 2015; 58: 83-85.
[31] Bode PK, Barghorn A, Fritzsche FR, Riener MO, Kristiansen G, Knuth A and Moch H. MAGEC2 is a sensitive and novel marker for seminoma: a tissue microarray analysis of 325 testicular germ cell tumors. Mod Pathol 2011; 24: 829-35.
[32] Davis-Dao CA, Siegmund KD, Vandenberg DJ, Skinner EC, Coetzee GA, Thomas DC, Pike MC, Cortessis VK. Heterogenous effect of androgen receptor CAG tract length on testicular germ cell tumor risk: shorter repeats associated with seminoma but not other histologic types. Carcinogenesis 2011; 32: 1238-43.
[33] Prakash N, Khurana A and Narula B. Persistent Mullerian duct syndrome. Indian J Pathol Microbiol 2009; 52: 546-548.