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Case Report

Primary rete testis adenocarcinoma: a report of 2 cases and literature review

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Abstract: Primary rete testis adenocarcinoma (RTA) is an extremely rare extratesticular neoplasm. Due to its low occurrence and the scarcity of imaging, histopathological, and immunohistochemical features, we studied two cases of RTA by microscopic observation and immunohistochemical staining, and reviewed the correlating literature in order to investigate the clinicopathologic characteristics, diagnosis, differential diagnosis, prognosis, and therapy of RTA. The 2 patients were older men and both presented with a painless scrotal mass, back pain, hip pain, abdominal and inguinal mass, urethral fistula, lymphangitis, and hydrocele. Tumor cells presented as small tubular, papillary, sieve, and solid lamellar arrangement, with the solid lamellar being dominant. Tumor cells also showed as cubic or columnar shapes with eosinophilic or eosinophilic cytoplasm. Immunohistochemical staining showed the tumor cells were positive for EMA, CK8, AE1/AE3, and CAM5.2, but negative for PSA, calretinin, AFP, and WT-1. Ki67 index was 30%-50%. Rete testis adenocarcinoma is a rare highly malignant tumor with poor prognosis. Postoperative pathology and immunohistochemistry are the main basis for diagnosis. Total tumor resection is the chief treatment followed by radiotherapy and chemotherapy. Prognosis is related to clinical stage.

Keywords: Rete testis adenocarcinoma, histopathology, immunohistochemistry, diagnosis, differential diagnosis

Introduction

Rete testis adenocarcinoma (RTA) is a rare condition occurring preferentially in the testicular hilum. It mainly presents in older males between 40-80 years of age and is more frequent in men who are 60 years of age or older. Most patients have painful lumps, inguinal hernias, sinusitis, epididymitis, and hydrocele [1, 2]. This review included two cases of RTA diagnosed in Shanghai Pudong New Area People's Hospital in 2011 and 2013 and we reviewed the correlating literature. To investigate their imaging features, clinical manifestations, histopathological morphologies, and immunophenotypes to improve the diagnosis, differential diagnosis, and treatment options.

Materials and methods

Clinical information

Two cases of RTA diagnosed by the Department of Pathology at Shanghai Pudong New Area People's Hospital in 2011 and 2013 were included in this study. One male patient was 57 years old and admitted to the hospital due to a month of scrotal swelling on the right side [3] (we have reported it in 2013 on *Can Urol Assoc J*). Physical examination revealed an enlarged cystic right scrotum of approximately 7.0 × 6.0 cm^2, with a positive (+) transillumination test. The right testis felt firm with nodules and there was a noticeable thickening of the spermatic cord. A blood test determined that his cancer antigen 125 (CA-125) was 504.80 U/ml, alpha-fetoprotein (AFP) was 5.52 ng/ml, carcinoembryonic antigen (CEA) was 1.24 ng/ml, carbohydrate antigen 19-9 (CA19-9) was 4.93 U/ml, and human chorionic gonadotrophin (hCG) was 0.9 mIU/ml. Color Doppler ultrasonography showed that this patient had fluid surrounding his right testicle. Computed tomography (CT) showed that this patient had space-occupying lesions in the right testis (considered to be malignant), hydrocele see (**Figure 1A**), multiple metastases in the liver, retroperitoneal lymphadenopathy, ascites, and peritoneal carcinomatosis. A biopsy and further clinical work up was

recommended and it was discovered that the patient had multiple and small nodular metastatic lesions in the lower lobes of bilateral lungs and a pleural effusion on right side. Surgical exploration showed a pale yellow tinged spermatic cord hydrocele with a volume of 50 ml. One-third to one-half of the intratesticular was neoplastic, yellow-to-white colored on cross sections, and infiltrated the visceral pleura. The second RTA male patient in this study was 73-years-old and admitted to the hospital due to an enlarging mass in the right groin that developed in a month's time. Physical examination revealed that his right scrotum was empty. A 4.0 × 3.0 × 2.5 cm^3 mass was found in the right groin of the patient that was moderately firm and not movable. The right testicle had no obvious abnormality. CT showed that this patient had a nodular lesion in the right groin area of approximately 4.0 × 3.5 × 3.0 cm^3, which was considered an ectopic testis or a partial space-occupying lesion of the right groin. B-mode ultrasonography showed cystic mixed echo patterns in the right groin area, the patient's right scrotum was empty, and no normal echo signal of testis or epididymis was detected.

The two RTA patients underwent surgery and pathological examinations were performed after collecting the specimens.

Methods

Radical surgery specimens were fixed in neutral buffered formalin, dehydrated, paraffin-embedded, and sectioned into 4 μm-thick tissues, followed by hematoxylin and eosin (HE) staining and histopathology observation under light microscopy. Tissue sections from each patient underwent EnVision two-step immunohistochemical (IHC) staining. The antibodies included broad spectrum cytokeratin (CKpan), epithelial membrane antigen (EMA), AE1/AE3, cytokeratin 8/18 (CAM5.2), Vimentin (Vim), CD10, Wilms tumor protein (WT-1), prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), Mesothelial Cell HBME-1 (HBME-1), ER, PR, Melan-A, cancer antigen 125 (CA125), podoplanin (D2-40), and Syn. All antibodies and reagents used for IHC staining were purchased from Dako (Agilent Technologies, Santa Clara, CA). IHC procedures strictly followed manufacturer's instructions. Tissue sections with known each antibody positive staining was used as a positive control for the related antibody, and PBS replaced primary antibodies on corresponding tissue sections as negative controls for all the antibodies. Diaminobenzidine (DAB) coloring and hematoxylin counterstaining were performed prior to microscopic analysis.

Results

Imaging features

In the first case, the scrotum was relatively large. Testis imaging showed a space-occupying lesion with a mixture of high and low densities, approximately 6.9 × 5.0 cm^2 in size with clear margins and a tissue CT value of approximately 14 HU. In addition, an image of the testis showed a small piece of soft tissue with a CT value of approximately 40 HU. An enhanced CT scan showed mild and heterogeneous enhancement in the soft tissue with a CT value of approximately 68 HU. The density of contralateral testis had no obvious abnormality. In the second case, a regular CT scan showed in the right groin area a nodal metastasis of approximately 4.0 × 3.5 cm^2, which contained a small amount of calcification. An enhanced CT scan of the region demonstrated a mild enhancement and contained partitions in the region.

Pathological features

Gross examination: In the first case, the right testicle was 4.0 × 3.0 × 2.0 cm^3 and contained a greyish yellow mass of approximately 2.8 × 1.7 × 1.5 cm^3 that was observed in the cross-sections (**Figure 1B**). Tumors invaded the tissue sheath with the range of about 4.0 × 3.0 cm^2. Also visible epididymis and spermatic cord tissue were approximately 2.0 × 1.0 × 0.5 cm^3 and 5.0 × 2.0 × 1.5 cm^3, respectively. In the second case, one of the testicles was 5.0 × 3.0 × 2.0 cm^3 and contained greyish red and greyish yellow tissue alternates in the cross-sections and a partial rigid region of approximately 4.0 × 3.5 × 3.0 cm^3. Light microscopy: Tumor cells presented as small tubes, papillary-, sieve-like and solid lamellar structures, with the solid lamellar being dominant. The tumor cells also showed as cubic or columnar shapes with eosinophilic or amphophilic cytoplasm (**Figure 1C**). Cell nuclei presented as moderate atypia with frequent mitosis. The transitional

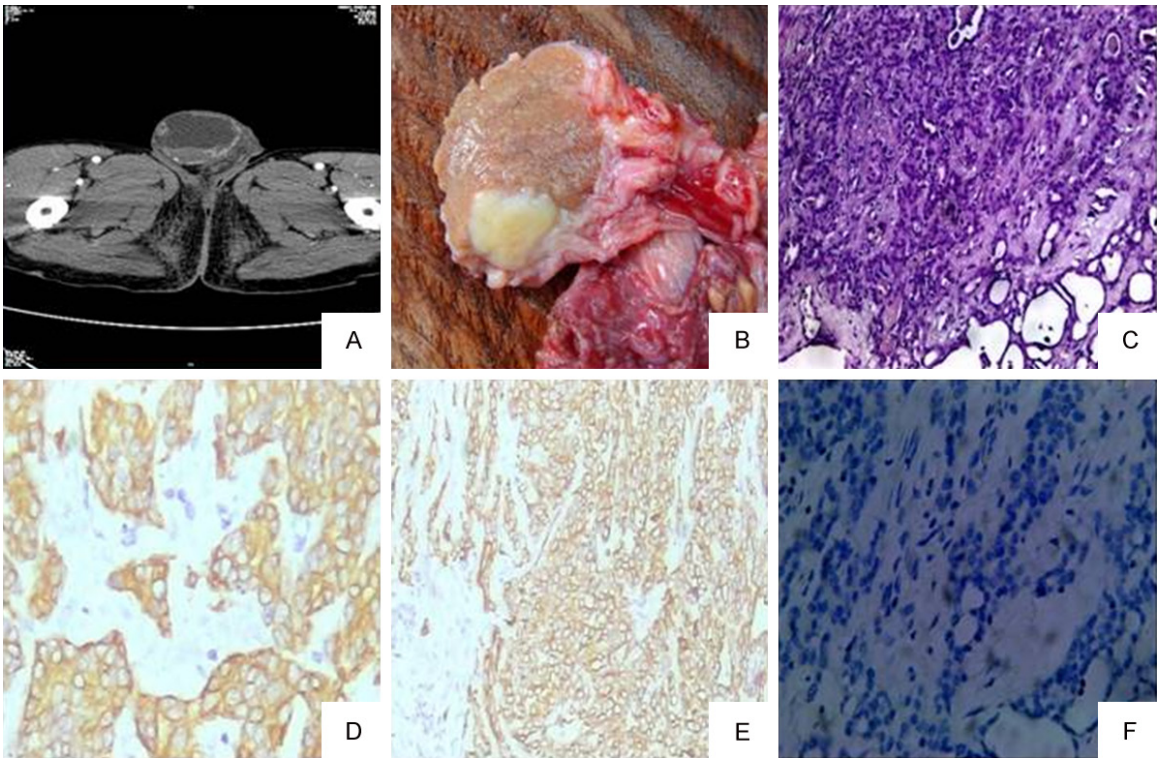

Figure 1. A. Imaging illustrates the space-occupying lesion on the right testis. B. Cross-section of testicle showing greyish white and greyish yellow alternates. C. Hematoxylin and eosin staining of tumor tissue with tubule-, papillary-, and sieve-like structures. Tumor cells presented as cubic or columnar shapes with eosinophilic or amphophilic cytoplasm (Magnification, × 100). D. Envision two-step immunohistochemical staining showing the positive results of CAM5.2 (Magnification, × 200). E. Envision two-step immunohistochemical staining showing the positive results of EMA (Magnification, × 200). F. Envision two-step immunohistochemical staining showing the negative results of HBME-1 (Magnification, × 200).

transition of normal epithelia of rete testis, epithelial hyperplasia, and tumor cells were found in this case.

Immunohistochemistry

Tumor cells positively expressed CKpan, EMA, AE1/AE3, and CAM5.2. Vim and CD10 were partially expressed in the tumor cells while WT-1, PSA, CEA, AFP, HBME-1, ER, PR, Melan-A, CA125, D2-40, and Syn were negatively expressed. **Figure 1D-F** demonstrate part of the results in IHC staining.

Pathological diagnosis

Two cases of this study were all RTA. The first RTA was confirmed by pathologists from slides conference of Shanghai, China, Osaka, Japan, and Melbourne, Australia, with tumor invasion in the testis, epididymis, and testicular sheath membrane.

Discussion

Rete testis develops from renal tubular, and the coelomic layer may play an important role in the formation of this structure. Previous reports showed that diethylstilbestrol administration in aged rats and prenatal mice induced RTA. However, no relevant evidence associated with the incidence of RTA has been reported in human. Although in most patients the tumor origin of RTA is in normal testis, some patients also have a medical history of trauma, hydrocele, inguinal hernia, and epididymitis. A causal relationship between medical history and the incidence of RTA has not been confirmed [4, 5].

Eighty percent of RTA patients have a scrotal mass. Many patients have a painless scrotal mass for over five years prior to the diagnosis. Twenty-three percent of RTA patients have metastasis-related symptoms, including lower back pain, hip pain, abdominal and groin mass-

es, urethral fistula, and lymphangitis. Thirty percent of the RTA patients also have a hydrocele. The incidence of RTA in the left testis is slightly higher than in both testicles (1:1.5). Tumor size of RTA ranges from 1-12 cm, with the average of 4.7 cm. RTA metastasizes mainly through lymphatic and circulatory systems. Metastasis via the lymphatic system mainly occurs in the iliac paraaortic lymph nodes, and metastasis via blood circulation spreads to lung, bone, liver, skin, kidneys, adrenal gland, and pleura [6]. In this study, RTA in both cases was located on the right testicle. One case had a hydrocele and multiple metastases in the liver, lung, and peritoneum, the retroperitoneal lymph nodes of this patient were swollen, and the peritoneal cave was positive for ascites.

RTA staging of this study was in accordance with Boden and Gibbs' classification of the three stages of testicular tumor. Stage A refers to RTA confined to testicle(s) with no evidence of metastasis. Stage B refers to RTA accompanied by intraabdominal metastasis only. Stage C refers to RTA accompanied by metastasis/metastases outside of the abdominal cavity. Tumor recurrence in surgical incisions or the scrotum or cancer metastases at the distal margin of the spermatic cord are classified as Stage B [7]. In this study, RTA in the first patient was classified as Stage C, and RTA in the second patient was classified as Stage A.

Diagnosis of RTA is relatively difficult. According to generally accepted RTA diagnostic criteria proposed by Feek and Hunter in 1945, patients must meet the following criteria: (1) the tumor is located in the mediastinum but not the testicle; (2) borderline lesion(s) is/are found between the normal epithelium and the tumor in rete testis; (3) there is no evidence of teratoma; (4) other primary tumors must be excluded; and (5) patient has complete parietal lamina [8]. In this study, both cases fulfilled the criteria, which confirmed the diagnosis of RTA.

Tumor cells of mesothelioma are mostly in a cubic shape with a dome-shaped top, but a few of them are in columnar forms. Tumor cells of adenocarcinoma are mainly in columnar forms. Well-differentiated epithelial mesothelioma has a brush border on the cell surface and abundant microvilli observed under electron microscopy. IHC staining of HBME-1 shows a thick layer of brush border on the tumor cell surface of mesothelioma. Adenocarcinoma cells rarely have a brush border, thus they do not show the above features under electron microscopy or in IHC staining. In addition, tumor cells in adenocarcinoma are mostly stained positive with mucicarmine while tumor cells of mesothelioma are rarely stained positive with mucicarmine. Moreover, results of IHC staining vary between mesothelioma and adenocarcinoma. For example, EMA, CEA, and CKpan are usually expressed in adenocarcinoma while calretinin, CK5/6, and D2-40 are expressed in mesothelioma [9].

A comprehensive physical examination and a detailed understanding of the patients' medical history have an important significance in the identification of primary RTA and metastatic adenocarcinoma. In addition, detailed pathological examinations of patients' specimens, including the infiltration of the normal epithelium of rete testis, epithelial hyperplasia, and adenocarcinoma support the diagnosis of primary adenocarcinoma [10].

For example, negative measurement of betahCG is used to exclude cases of germ cell tumors, negative measurement of PSA is used to exclude cases of prostate cancer, and positive measurement of CK/EMA is used to exclude cases of Sertoli cell tumors.

The basic treatment of all RTA patients is radical orchiectomy, and some patients receive postoperative radiotherapy and chemotherapy. However, because RTA is a rare and highly invasive malignant tumor of testis, [3] the value of radiotherapy is not significant and no effective chemotherapy is available; therefore orchiectomy is typically combined with retroperitoneal lymph node dissection to improve the three-year survival of patients. In this study, the first patient received radical resection of the right testis and died two months after the operation. In the second case, due to the early clinical staging, prognosis of the second patient was relatively good. This patient is still under follow-up care.

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Disclosure of conflict of interest

None.

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