Undifferentiated Primary Carcinoma of the Epididymis Treated with Sequential Chemoradiotherapy: A Case Report

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ABSTRACT

Primary epididymal adenocarcinoma is uncommon, and undifferentiated histology is exceedingly rare. Surgery is the principle treatment for primary epididymal tumors. Benign tumors are commonly managed by transscrotal epididymectomy, however, inguinal radical orchiectomy is indicated for malignant tumors of epididymis including the primary epididymal carcinomas (PEC). However, the adjuvant treatment of PEC is more complex and there exists no generally accepted consensus on this issue. Carboplatin and paclitaxel combination is the commonly preferred first-line CT regimen in metastatic epididymal tumors, however no specific chemotherapy (CT) regimen has been recommended for adjuvant management of PECs. Similarly, there are uncertainties regarding the role of adjuvant radiation therapy (RT) in this small group of patients, and to our literature knowledge only five PECs have previously been treated with adjuvant RT in a curative intent. To add to the present literature, we report a further case of undifferentiated primary epididymal carcinoma and its clinical course, in a 54-year-old male treated with adjuvant chemotherapy and radiotherapy.

Key Words: Epididymis, Undifferentiated carcinoma, Adjuvant treatment, Chemotherapy, Radiotherapy

ÖZET

Ardışık Kemoradyoterapi ile Tedavi Edilmiş Epididim İndiferansiye Primer Karsinomu: Bir Olgu Sunumu

Primer kötü differansiye epididim karsinomu oldukça nadir rapor edilen bir tümör gurubudur. Tümörün cerrahi olarak çıkarılması primer epididim tümörlerinin tedavisinde güncelyaklaşım olarak kabul edilmektedir. Benign tümörler sıklıkla transskrotal yaklaşımla çıkarılırken, primer epididim karsinomlarını da içine alan malign tümörlerin güncel tedavisi radikal orşiektomidir. Primer epididim karsinomunun adjuvan tedavisi oldukça kompleks olup genel kabul gören bir yöntem bulunmamaktadır. Karboplatin ve paklitaksel kombinasyonu metastatik epididim tedavisinde sıklıkla kullanılmakta olsa da lokalize hastalık adjuvan tedavisinde genel kabul gören bir kemoterapi protokolü bulunmamaktadır. Benzer şekilde bu nadir hastalık gurubunda adjuvan radyoterapinin rolü ile ilgili belirsizlikler de bulunmaktadır. Bildiğimiz kadarıyla literatürde küratif adjuvan radyoterapi uygulanan sadece beş vaka bildirilmiştir. Adjuvan kemoterapi ve radyoterapi uygulanan bir vaka nedeniyle kötü differansiye primer epididim adenokanserinin kombine adjuvan tedavi sonrası klinik seyrini tartışmayı amaçladık.

Anahtar Sözcükler: Adjuvan tedavi, Epididim, Kemoterapi, Kötü differansiye karsinoma, Radyoterapi

INTRODUCTION

Primary tumors of epididymis are rare and usually benign, with adenomatoid accounting for single most pathology. Sakaguchi[1] in 1916 defined the first benign epididymal tumor and the name "adenomatoid" was given later by Golden and Ash.[2] Malignant epididymal are uncommon and exist as either primary and or metastatic lesions. Primary adenocarcinomas of epididymis are exceedingly rare, with less than 30 cases reported to date. Furthermore, as suggested by Jones et al.[3] in their review, most tumors submitted as primary epididymal carcinomas (PECs) were probably metastatic, because of their inadequate description, poor illustration, and absence of immunohistologic examination.

Surgery is the principle treatment for primary epididymal tumors and suggested approach varies depending on tumor pathology. Benign tumors are commonly managed by transscrotal epididymectomy, however, inguinal radical orchiectomy is indicated for malignant tumors of epididymis including the PECs.[1,3-6] However, the adjuvant treatment of PEC is more complex and there exists no generally accepted consensus on this issue. Carboplatin and paclitaxel combination is the commonly preferred first-line chemotherapy (CT) regimen in metastatic epididymal tumors, however no specific (CT) regimen has been recommended for adjuvant management of PECs. Similarly, there are uncertainties regarding the role of adjuvant radiation therapy (RT) in this small group of patients, and to our literature knowledge only five PECs have previously been treated with adjuvant RT in a curative intent.[5,7-9] To add to the present literature, we report a further case of undifferentiated PEC and its clinical course following adjuvant CT and RT.

CASE REPORT

A 54-year-old male presented with complaints of right testicular discomfort and ipsilateral scrotal mass persisting for six months. Past history was non-significant for lymphoma, leukemia, systemic granulamatous disease, and von-Hippel Lindau disease. Physical examination revealed a healthy appearing man. On the genitourinary examination right testis was painful and a solid mass of 3 x 2 cm was palpated at right epididymal region. Remaining scrotal contents were normal. Digital rectal examination revealed a normal prostate. Laboratory investigations included a normal complete blood count, liver function tests, and electrolyte panel. On scrotal ultrasonography (USG) both testicles appeared normal in size and reflectivity, but a hypoechogenic solid mass of 2 x 2 cm was detected at the head of right epididymis.

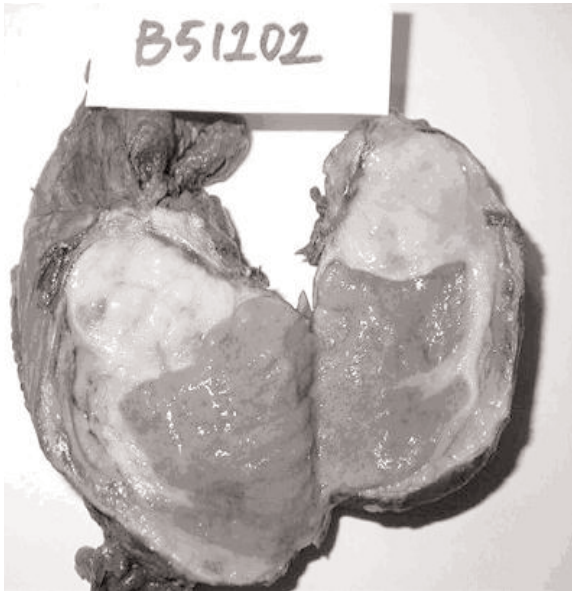

Figure 1. A solid gray-white colored tumor confined to the head of right epididymis.

Epididymal biopsy revealed an undifferentiated carcinoma. Serum PSA was normal at 0.1 mg/mL (range 0 to 4). The tumor markers (A-FP, ß-HCG, CEA, and CA-19-9) were also normal. An extensive metastatic work-up including abdominal, pelvic and thoracic computerized tomographies, bone scintigraphy, and endoscopic examination of eosophagus, stomach, duodenum and colorectum revealed no pathology. Thus the patient underwent an immediate right inguinal radical orchiectomy. Gross examination revealed a gray-white tumor mass of 3 x 2 x 2 cm confined to the head of epididymis (Figure 1), and the testicle/spermatic cord were well spared from tumor involvement. Microscopically, tumor was composed of microglandular cuboidal cells with clear cytoplasm and synsitchial epithelial cells with scattered foci of tumor necrosis. The predominant pattern was a complex tubular glands with intraluminal papillae infiltrating the epididymal muscular wall, with no in situ compo-

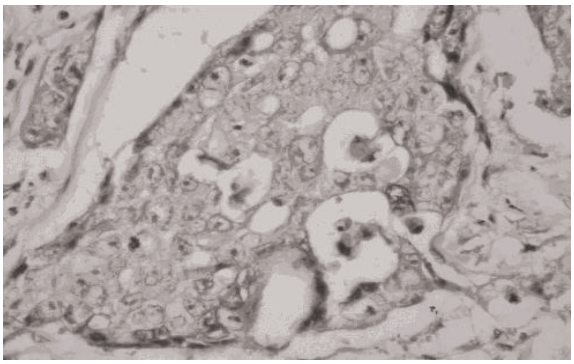

Figure 2. Microglandular and syntsichial epithelial islands composed of undifferentiated tumor cells containing large hyperchromatic nuclei and prominent nucleoli (H&E x 400).

nent. Tumor cells had hyperchromatic nuclei, prominent nucleoli, and frequent mitosis with apparent lymphovascular space invasion (Figure 2). By light microscopy, the possibility of a metastatic adenocarcinoma such as a prostatic primary could not be ruled out, because prostate carcinoma and the tumor were microglandular in appearance. However, immunostaining was negative for PSA and PAP, and strongly positive for CEA, confirming the presence of an adenocarcinoma and ruling out a metastatic prostate carcinoma. Further immunoperoxidase staining with pancytokeratin cocktail, vimentin, Leu-1, desmin, S-100, AFP, PLAP, CD30, B72.3, EMA, NSE and chromogranin were negative. Therefore, the diagnosis of an undifferentiated PCE was committed.

Based on the undifferentiated pathological tumor characteristics including the infiltrative tumor pattern with frequent mitosis and presence of lymphovascular invasion, the patient was categorized as "high-risk" for local-regional recurrences and distant metastasis. Thus, the patient underwent an adjuvant treatment protocol which included six courses of cisplatin, (75 mg/m^2, once 28 day), and etoposide (120 mg/m^2, on days 1-3, every 28 days), and a total of 50.4 Gy RT (1.8 Gy per fraction, 28 days) covering well known "dog leg field" in between third and fourth courses of chemotherapy. Treatment protocol was well tolerated with no significant toxicity. The follow-up period was ordinary and the patient was free of disease at 23rd month.

DISCUSSION

The PECs are rare with fewer than 30 documented cases, and furthermore many of those were poorly described, raising questions about their validity. Almost all reported cases of PECs are exclusively adenocarcinomas, however at least some were adenomatoid as fewer mitotic figures were defined. Jones et al.[3] have defined a narrower range of morphologies for this confusing tumor group. They reported that all PECs were almost adenocarcinomas showing tubular, tubulopapillary, or cystic growth pattern. The tumors were commonly composed by cells of cuboidal or columnar origin with frequent glycogen containing clear cytoplasms. Strong cellular reactivity for cytokeratin and EMA were seen in some tumors, but interestingly same tumors stained negatively with more specific glandular markers; CEA and Leu M1. Sheets of cells with undifferentiated anaplastic features were reported in one patient.[3] In the present case, the presence of features of poor cellular differentiation; increased mitotic figures, characteristic nuclear and nucleolar features of anaplasia, and negative staining with various markers except for CEA, were in good concordance with the current evidence which supports our diagnosis.

Metastatic tumors of epididymis commonly originate in stomach, colon, pancreas, kidney, and prostate, with the latter being commonest site. PSA and PAP staining have been used to make distinction between PECs and prostate carcinoma, but in one report, although, all well-differentiated tumors showed positive staining, 50% of tumors with a Gleason score of 10 showed no reactivity.[10] Similarly, it may be very difficult or even impossible to differentiate some renal cell carcinomas from PECs3. Thus, detection of an epididymal carcinoma mandates exclusion of all possible primaries by a thorough metastatic work-up. In our case, although handled with caution extensive metastatic work-up revealed no possible primary focus. Furthermore, we think that the absence of a tumor mass in either of both kidneys on computerized tomographic examination, a value 0.1 mg/mL PSA which lied in normal limits, and negativity of PSA and PAP staining in pathological specimen were satisfactory for exclusion of kidney and prostate primaries.

Surgery is the principle treatment for primary epididymal tumors and suggested approach varies de-

pending on tumor pathology. Benign tumors are commonly managed by transscrotal epididymectomy, however, inguinal radical orchiectomy is indicated for malignant tumors of epididymis.[5,6] In one report Becchia et al[6], suggested the transscrotal surgery as the appropriate approach for patients older than 50 years as malign pathologies were foreseen to be less likely in this age group. However, the current evidence showed that more than half of reported patients were older than 50 years, raising questions about the validity of this approach. Carrying the advantage of no risk for lymphatic violation, some authors suggest the inguinal approach as the best surgical intervention for epididymal solid masses4. In our current case, the tumor mass was solid on ultrasonographic evaluation, and pathologic examination of biopsy specimen revealed an undifferentiated carcinoma, thus being in concordance with current surgical evidence radical orchiectomy by an inguinal approach was preferred.

There are uncertainties about the adjuvant treatment of PECs, and there exists no generally accepted consensus considering this issue. Commonly, carboplatin and paclitaxel combination is the preferred first-line CT regimen in metastatic epididymal tumors, however, up to our knowledge no specific CT regimen has been recommended for adjuvant management of PECs. In the present case we planned to administer six courses of cisplatin and paclitaxel combination, but as paclitaxel had no indication for this tumor group in our country, etoposide was chosen as an alternative. Similar with CT, the role of adjuvant RT is not well-defined in the postoperative management of PECs. To our best literature knowledge, six cases including the one presented here have been treated with adjuvant RT curatively.[5,7-9] The reported follow-up period was ranged between 6 and 36 months, and there exist no report of disease recurrence at the radiation portal, in this small group of patients.[5,7-9] Our follow-up period of 23 months was modest in comparison with earlier reports, and similarly being in good concordance with them we did not experience any local-regional or distant metastasis.

In conclusion, we reported a case of extremely rare undifferentiated variant of PEC, and its clinical course following adjuvant CT and RT. We think that, although not standard, consideration of adjuvant CT and RT in treatment of patients with high risk features for local-regional and distant recurrences should be beneficial. However more experience is needed for accurate validation of this approach, and determination of the best treatment approach in this patients group.

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