Urooncology / Üroonkoloji Review / Derleme

Small cell carcinoma of the genitourinary system

Genitoüriner sistemin küçük hücreli karsinomu

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Abstract

Small cell carcinomas of the genitourinary system represent a rare entity, accounting for less than 1% of organ tumors. We aimed to review literature regarding the disease entity, organs involved, associated pathology, and treatment strategies. Medline was reviewed for all publications in English, plus within the Turkish Journal of Urology for published articles both in English and Turkish. The search criteria included "bladder", "prostate", "ureter", "urethra", "testis", "epididymes", and "penis" in combination with "small cell carcinoma" or "neuroendocrinal differentiation". Totally 60 articles were found to be of high impact; studying every organ within the genitourinary system separately. Studies in the literature showed that small cell carcinoma of the genitourinary tract is rare, and mostly associated with other pathologies. Thus, if not considered, it can be easily missed and can adversely affect the prognosis. Platinum based chemotherapy for an average duration of 8 months, together with surgical resection, represents a relative promise for treatment of such pathology.

Key words: Hormone refractory prostate cancer; neuroendocrinal tumors; non-urothelial bladder cancer; small cell carcinoma.

Özet

Genitoüriner sistemin küçük hücreli karsinomu organ tümörlerinin %1'inden sorumlu olan ender bir tanıdır. Bu derlemede hastalığın tanımı, organ tutulumu, eşlik eden patolojiler ve tedavi yaklaşımlarının açısından literatürdeki çalışmaları gözden geçirmeyi amaçladık. Medline, İngilizce yayınlar ve Türk Üroloji Dergisi'nde yayınlanmış olan İngilizce ve Türkçe yayınlar için taranmıştır. Tarama kriterleri "mesane", "prostat", "üreter", "üretra", "testis", "epididim", ve "penis" kelimelerinin "küçük hücreli karsinom" ya da "nöroendokrin farklılaşma" ile kombinasyonlarıydı. Yüksek impaktı olan ve genitoüriner sistemdeki organları ayrı olarak değerlendiren toplam 60 yayına ulaşıldı. Literatürdeki çalışmalar genitoüriner sistemin küçük hücreli karsinomunun ender olduğunu ve genellikle diğer patolojilere eşlik ettiğini göstermiştir. Bu nedenle eğer gözönüne alınmazsa kolaylıkla atlanabilir ve eğer mevcutsa prognozu kötü olabilir. Bu patolojinin tedavisinde cerrahi rezeksiyon ile beraber ortalama 8 ay süreyle platin temelli kemoterapiler umut vericidir.

Anahtar sözcükler: Hormon dirençli prostat kanseri; nöroendokrin tümörler; non-ürotelial mesane kanseri; küçük hücreli karsinom.

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Small cell carcinoma of the bladder

Small cell carcinoma (SCC) of the bladder is extremely rare and accounts for less than 0.7% of cancers arising from the bladder,[1] in contrary to small cell carcinoma of the lung where it accounts for 15% of cases.[2] The first case was described in 1981 by Cramer et al.[3] SCC of the bladder is mostly neuroendocrine epithelial tumors, associated with a more aggressive behavior and poorer prognosis than transitional cell bladder carcinomas, and mostly diagnosed at advanced stages. The overall 5-year survival rate in all stages is 19% (16-25%),[4,5] and the pure small cell histology was shown to have poorer outcome than the mixed small cell histology.[6,7]

WHO classification is the same as the small cell carcinoma of the lung, which is oat cell, intermediate, and combined.[8] SCC of the bladder, as mostly a neuroendocrine tumor, secrete antidiuretic hormone and adrenocorticotrophic hormone (ACTH). Microscopically, the tumor is composed of sheets of uniformly small round mitotically active cells with overlapping nuclei and evenly distributed chromatin, lacking prominant nuclei.[9] SCC of the bladder was highly aggressive as most of the patients (up to 95%)

were diagnosed at advanced stage (Stage II or more), from whom 25% were metastatic and two-thirds developed distant recurrence.[4,5]

SCC of the bladder has been associated with cigarette smoking, long-standing cystitis, bladder calculus, and augmented cystoplasty.[9] Contrary to the early theory of derivation from Kulchitsky cells, it is now believed that SCC of the bladder originates from the totipotent stem cells present in the submucosa of the bladder wall.[9] It can be pure or mixed, although mixed with urothelial, adenocarcinoma or squamous components represent around 60% of cases.[9]

Clinical features are similar to the conventional urothelial carcinoma with painless hematuria representing the most common presentation.[4,5,9] Demographically, the majority of patients are male, and most patients are in the sixth to seventh decade of life.[1,10]

There is no single consensus on the treatment of SCC of the bladder; although the mainstay of treatment seems to be chemotherapy followed or preceded by either radical cystectomy or radiotherapy.[1,11,12]

Small cell carcinoma of the prostate

SCC of the prostate accounts for less than 1% of de novo prostate cancer and slightly more than 1% of hormonally refractory prostate cancer.[13] The median age of presentation is 65 years.[13]

A little more than half of the clinical cases were diagnosed de novo and the remainder had a history of treatment for adenocarcinoma of the prostate,[14] with 10-20% of cases that die following treatment of prostatic adenocarcinoma, showing small cell carcinoma elements.[15]

Most cases present the oat cell type, mostly present with obstructive urinary symptoms and one third of cases present with metastatic findings. Paraneoplastic manifestations as Cushing disease and hypercalcemia are identified, but are rare to occur.[16] The tumor is aggressive and median time of survival following diagnosis is 10 months, with fewer than 5% of patients survive for 2 years.[16]

Galanis et al.[17] summarized the results of extrapulmonary small cell carcinoma treated over 20 years and reported that the disease is fatal and the use of radiotherapy for localized tumor is a failure and that the mainstay of treatment for that fatal disease is platinum based chemotherapy over a median period of 8 months.

The first primary SCC of the prostate was reported in 1977 by Wenk et al.[18] The origin of SCC of the prostate is still unknown, although there are many theories trying to explain its growth. One of these theories is that SCC of the prostate arises as a progression and terminal phase of prostatic adenocarcinoma, based on the fact that traces of neuroendocrinal differentiation is present in 10-100% of cases with prostatic adenocarcinoma.[19-22] Other theory is that SCC of the prostate arises de novo from APUD cells in the prostate[22,23] and third theory is that SCC of the prostate arises from stem cells in the prostate.[24,25]

Immunohistochemical examination is mandatory for correct diagnosis. Chromogranin A is specific and seems to be the best marker in blood and tissue, with its serum value used to show the effect of therapy resistance in prostate cancer.[26,27] Another report[28] demonstrated that, neuroendocrinal cells exhibit intense staining for vascular endothelial growth factor (VEGF). on the other hand, prostate specific antigen (PSA) usually exhibits lower levels and is not a reliable marker, apart from cases that appear mixed with prostatic adenocarcinoma.[24]

In at least half of the cases, SCC of the prostate will be diagnosed with additional histological prostatic malignancies. The proportion of SCC component may range from a small focus of the tumor burden to the predominant histology.[19]

There are no specific laboratory signs of SCC of the prostate. Elevated erythrocyte sedimentation rate and high levels of lactate dehydrogenase, alkaline phosphatase, and C-reactive protein (CRP) are not specific, but may suggest advanced disease. On the other hand, elevated serum and tissue chromogranin A and neuron-specific enolase can correlate with the progression of disease. Serum ACTH, calcitonin and parathyroid hormone levels may also be elevated. Serum tissue markers, such as carcino-embryonic antigen and CA19–9, are often elevated in SCC of the prostate but are not specific.[19,28,29]

SCC of the prostate should be considered in patients with a high disease volume, low serum PSA, poorly differentiated disease, and poor or insufficient

response to hormonal treatment.[30,31] Radiolabeled somatostatin analogs that bind to somatostatin receptors are able to visualize primary and metastatic neuroendocrine small cell carcinoma.[21]

The presence of a paraneoplastic syndrome may be a poor prognostic factor. According to the large retrospective study (83 patients) of Spiess et al.[32] high serum lactate dehydrogenase and a low albumin level at the time of diagnosis is predictive of inferior disease-related outcome.

Treatment is controversial, but as most of cases are diagnosed incidentally following radical prostatectomy as a mixed type with prostatic adenocarcinoma, adjuvant chemotherapy should be administrated.[33] Spiess et al.[32] and Asmis et al.[34] believe that surgical resection with or without radiation therapy, combined with chemotherapy should be considered as treatment strategy in local or early SCC of the prostate. This modality may provide better local control and a potential survival benefit.

In most of the cases of mixed SCC of the prostate with adenocarcinoma, the adenocarcinoma portion is of low grade.[35] Widespread dissemination and metastatic deposits in unusual locations, e.g. axillary lymph node, omentum, pericardium and soft tissue, are more often seen with SCC of the prostate than acinar adenocarcinoma.[36,37]

Small cell carcinoma of the kidney

SCC of the kidney accounts for less than 1% of all renal epithelial tumors and can arise both in the renal pelvis or the renal parenchyma.[38,39] FISH study demonstrated a high grade of chromosomal instability.[40] Revision of chromosomal abnormalities of SCC demonstrate that loss of short arm of chromosome 3 is associated with clear cell histology, less frequently present in papillary histology and not detected in small cell carcinoma. Papillary tumor type 1 shows gain of chromosome 2, 7, 12, 16 and 17. Type 2 papillary tumor shows the same chromosomal abnormalities of type 1 and also show a gain of 1q and amplification of 8q that was found to be associated with functional activation of *MYC* pathway.[41-44]

SCC demonstrates gain of chromosome 8q and *MYC* amplification, presenting overlap of cytogenetic features with type 2 papillary renal tumors.[39] Some literatures reported a mixed histology of SCC with papillary tumors, but non demonstrated mixed histology with clear cell carcinoma.[39,45]

None of cases with SCC arising from renal parenchyma showed a non-neuroendocrine component, in contrast to SCC of the renal pelvis that shows non-neuroendocrinal components.[39] The mean age of the patients with tumor is 57 years, and it occurs slightly more frequently in females.[39] Elevation of urine 5-hydroxyindoleacetic acid occurs in 10-15% of cases.[46] An association between primary renal SCC and horse-shoe kidney was found in 18-26% of cases, and with renal teratome in 15% of cases.[47,48]

The disease is very aggressive killing the patients in few months, and these patients doesn't benefit from surgery. Cases that were treated only with chemotherapy showed slightly better survival than those treated with either surgery or combined surgery and chemotherapy.[49]

Small cell carcinoma of the ureter

SCC of the ureter is extremely rare and there are only 9 cases reported in the English literature. All detected cases demonstrated mixed histology with transitional or squamous cell carcinoma.[50] No solid data regarding best treatment option was published separately due to limited number of cases.

Small cell carcinoma of the urethra

It is extremely rare with only a few cases reported in the literatures. Aggressive surgical management with adjuvant chemotherapy was suggested as a valid option for localized disease.[51]

Small cell carcinoma of the testes

It is extremely rare, accounting for 0.2% of all testicular neoplasms. It typically presents with a mass, accompanied by pain and tenderness.[52] Clinical carcinoid syndrome may be evident in up to 10% of cases.[53]

One quarter of cases was found to be associated with teratomatous component.[54,55] Intratubular germ cell neoplasia, a precursor lesion indicating germ cell origin, was recently reported, in association with testicular carcinoid.[56] Metastasis occurs in 11.6% of cases.[57] The size of the tumor (>7.3 cm), poor differentiation of the tumor, and the presence of carcinoid

syndrome are independent predictors for the development of metastases.[58]

Small cell carcinoma of the epididymes

There is only one case reported in the literature, with a small tumor that was removed surgically, together with retroperitoneal lymph node dissection and followed by adjuvant treatment. The case although managed thoroughly and the tumor burden didn't seem to be high, demonstrated recurrence, denoting the aggressive nature of the tumor.[59]

Small cell carcinoma of the penis

There are only 2 cases in the literature concerning neuroendocrine tumors of the penis. The disease was so aggressive that although managed by proper surgical methods and adjuvant chemotherapy, it showed recurrence in the inguinal and iliac lymph nodes.[60]

As a conclusion, small cell carcinoma of the genitourinary tract is rare, and mostly associated with other pathologies. Thus, if not considered, it can be easily missed and can adversely affect the prognosis.

Conflict of interest

No conflict of interest was declared by the authors.

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