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Review

Small cell carcinoma of the urinary bladder

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Summary. Small cell carcinoma of the urinary bladder (SCCUB) is a rare and aggressive cancer of the bladder. SCCUB is part of neuroendocrine family of tumors that affect several organ systems including respiratory, gastrointestinal and male and female genitourinary tract. SCCUB affect males predominantly with common risk factors include smoking, bladder calculi, bladder manipulation, and chronic cystitis. Prognosis of SCCUB remains poor due to high metastatic potential and lack of symptoms in earlier stages of the disease. Pathogenesis of the disease is linked to loss of genetic material, hypermethylation of tumor suppressors and at times amplification of the chromosomal regions carrying oncogenes. Majority of cases are treated with local resection of the tumor with neoadjuvant or adjuvant platinum-based chemotherapy regimen. Radiation therapy is used as alternative to radical cystectomy or as palliative measure. This article provides epidemiology, molecular pathogenesis, histochemistry, and current management options for SCCUB. Furthermore we reviewed all recent studies involving advancement in targeted molecular therapy for neuroendocrine tumors.

Key wods: Urinary bladder, Neoplasms Small cell carcinoma, Molecular genetics, Differential diagnosis, Prognosis 7

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Introduction

Small cell carcinoma of the urinary bladder (SCCUB) is a distinct pathologic entity grouped under extra pulmonary small cell carcinoma (Cheng et al., 2008). It is a rare cancer of the bladder affecting up to 1% of all bladder cancer cases. Other sites affected are prostate, esophagus, stomach, colon and rectum, gallbladder, larynx, salivary glands, cervix, and skin (Taxy et al., 1980; Yogore, 1980; Sarma, 1982; Porto et al., 1987; Gnepp and Wick, 1990; Abbas et al., 1995). It is a highly aggressive malignancy with most cases presented as locally advanced or metastatic disease and poor long-term survival (Fujii et al., 2001; Trias et al., 2001; Cheng et al., 2004). The aim of this review is to provide comprehensive discussion of small cell cancer of the urinary bladder including epidemiology, histology, clinical presentation, updated immunohistochemistry, treatment, and prognosis.

Epidemiology

Small cell carcinoma of the bladder is a rare malignancy with incidence reported between 0.5% and 1% of all the bladder cancers in retrospective studies (Cheng et al., 2004; Abrahams et al., 2005). Most patients are male with mean age of occurrence in sixth to seventh decade of life (Cheng et al., 2004). Small cell cancer of the bladder is linked with smoking history like all other urinary bladder cancers. Yu et al reported 79% of small cell bladder cancer patients with smoking history (Yu et al., 1990). No other environmental or personal risk factor has been identified but potential risk factors including long-standing cystitis, bladder stones, and cystoplasty were noted in several studies (Swanson et al., 1988; Barrington et al., 1997).

Pathogenesis

Small cell carcinoma of the bladder has been linked

with common chromosomal aberrations that are seen in its counterpart small cell lung cancer. Loss of genetic material is one of the many derangements linked to pathology of the disease. Loss of alleles in 3p, 4p, 4q, 5q, 8p, 10q, 13q, 17p, and 22q has been seen in many studies. In another study by Teraccciano and colleagues, loss of 4q, 5q, 10q, and 13q has been noted (Terracciano et al., 1999). These are known locations for tumor suppressor genes leading to unchecked cell division and hence neoplasia. Loss of heterozygosity or gain of part or whole chromosome at 3p25-26, 9p21, 9q32-33, 17p13 has been previously reported (Cheng et al., 2005). Tumor suppressor gene p16 is often deleted or has suppressed expression by methylation at promoter region. Leonard et al. reported homozygous deletion of p16 in patients with small cell cancer or the bladder (Leonard et al., 2002).

As in small cell lung cancer (SCLC) abnormal signaling pathways has been noted in SCCUB including expression of tyrosine kinase receptor c-kit in up to 40% of the cases (Pan et al., 2000). C-Kit is a transmembrane receptor well known for carcinogenesis and the focus of many targeted cancer drug therapies. Other pathological mechanisms for SCCUB include amplifications of chromosomal regions containing oncogenes like c-MYC leading to neoplasia. Gain or amplification at 1p22-32, 3q26.3, 8q24, 12q 14-21 has been reported in one study (Terracciano et al., 1999). Epidermal growth factor receptor (EGFR) may have a role in SCCUB as in SCLC. EGFR is the member of ErBB receptor tyrosine kinase family that promotes cell proliferation, activation, migration, and angiogenesis when activated. These growth factors also activate ras-raf-MAPK signal transduction pathway leading to cell migration and angiogenesis (Molina, 2006). Overexpression of BCL2 and mutation in TP3 are seen in SCLC leading to deregulation in apoptosis and therapeutic resistance to cytotoxic chemotherapy, radiotherapy, and tumorigenesis (Kitada et al., 1994; Jiang et al., 1995; Schmitt et al., 2000; Zakowski et al., 2006).

Abbosh et al. recognized silencing of tumor and metastasis suppressor genes as another potential mechanism contributing to carcinogenesis in the bladder (Abbosh et al., 2008). In their study they quantified the methylation status of RASSF1, MLH1, DAPK1, and MGMT in SCCUB cases. These tumor suppressor genes are commonly methylated leading to loss of function resulting in carcinogenesis, metastatic potential, angiogenesis, and aggressive nature of SCCUB.

SCCUB is part of neuroendocrine group of tumors which affect multiple organ systems including pulmonary, gastrointestinal and male and female genitourinary system. Four subgroups are included: small cell, large cell, atypical carcinoid, and typical carcinoid. These subgroups share common features like histochemical staining and morphology but differ in growth patterns and biological characteristics. Small cell and large cell are aggressive with early metastasis and poor prognosis where as typical and atypical carcinoids are fairly slow growing with good prognosis. In a single institution study Alijo et al found common histochemical pattern with NSE, CgA, synaptophysin and Leu-7 positive stains (Alijo Serrano et al., 2007).

There is also an increased association of MEN1, an autosomal dominant disorder in gene locus involving pituitary, pancreatic, and parathyroid neoplasms. These patients are in increased risk of developing carcinoids tumors including bronchopulmonary and perhaps urinary bladder cancers and therefore surveillance should be incorporated as part of management of MEN1 syndromes.

Histogenesis

Cancer stem cells have been linked in malignancies including breast, brain, prostate and lung cancers. It has been proposed that small cell cancer of the urinary bladder originates from totipotential, undifferentiated stem cells as it has been seen that small cell carcinoma frequently coexists with other histologic types of bladder cancers including urothelial carcinoma, adenocarcinoma, and squamous cell carcinoma. With laser capture microdissection, Cheng et al. identified small cell cancer of the urinary bladder coexisting with non-small cell malignant cells and had similar patterns of allelic loss leading to the hypothesis that these cells have common clonal origin (Higashiyama et al., 1995). This suggests that these malignant cells have common origin from totipotent stem cells that can differentiate into diverse cell types leading to mixed-type malignancies. It has also been proposed that almost universal tumor recurrence in neuroendocrine tumors may be due to their common origin and therefore commonality in high expressions of protective proteins like membrane transporter to efflux drugs and anti-apoptotic molecules (Choong et al., 2005). Small cell carcinoma of the urinary bladder may have originated from poorly differentiated population of submucosal cells of neural crest origin same as paragangliomas and neurofibromas of the urinary bladder (Cheng et al., 2000).

Clinical presentation

Most patients with small cell carcinoma of the urinary bladder present with hematuria which is also a common presentation for transitional cell carcinoma (TCC) of the bladder. Therefore in initial workup this is confused with TCC of the bladder. Pan et al. in their own review of 64 cases discovered that 88% of the patients presented with hematuria (Choong et al., 2005). Other symptoms include urinary urgency, frequency, nocturia, and abdominal and pelvic pain secondary to obstruction. Partanen et al. reported paraneoplastic syndromes with ectopic adrenocorticotropic hormone (ACTH) production leading to Cushing's syndrome, Hypercalcemia and hyperphosphatemia (Partanen and Asikainen, 1985). Presenting symptoms for small cell carcinoma of the bladder is indistinguishable from

transition cell carcinoma except paraneoplastic syndromes if present. Therefore clinical suspicion should be high for anyone presenting with hematuria over the age of 40 years and should include complete workup including urine analysis, urine cytology, and at times full urological evaluation of the entire urinary tract. Urine cytology by itself is not sufficient as tumor cells may not always be found in urine specimens and therefore cystoscopy and biopsy or transurethral resection of the bladder tumor is needed.

Diagnosis

Patients suspected of bladder cancer by presence of gross hematuria undergo computed tomography (CT) scanning as initial diagnostic study followed by direct visualization via cystoscopy for tissue specimen and microscopic evaluation. Use of urine cytology alone may mask the diagnosis of SCCUB due to presence of coexisting TCC of the bladder and at times urine cytology can be normal despite of large number of tumor cells in the bladder wall.

Diagnostic criteria for SCCUB are based upon WHO classification system, which is the same as for SCLC. Diagnosis of SCCUB relies on careful microscopic evaluation by a pathologist which reveals sheets or nests of small or intermediate cells separated by delicate fibrovascular stroma. Tumor cells have uniformly small, round-to-oval, overlapping nuclei with evenly distributed chromatin and inconspicuous nucleoli (Pan et al., 2000). Immunohistochemical staining of the tissue specimen is usually performed with SCCUB usually staining positive for cytokeratin and epithelial membrane antigen (Blomjous et al., 1989). Neuron specific enolase (NSE), chromogranin, and synaptophysin are among the most commonly used neural and neuroendocrine markers with other markers used are serotonin and vasoactive intestinal peptide. Cytokeratin (CK) 7 ad 20 is used to determine the cellular origin of the cancer with CK 20 being found mainly in gastrointestinal tract epithelium. CK 20 has been noted to be present in 46-73% of urothelial carcinoma (Jiang et al., 2001).

Staging

Staging workup for SCCUB includes imaging studies to rule out distant metastasis with chest, abdomen, pelvis CT with PET scanning now being used more often with increased 18-fluoro-2-deoxyglucose (FDG) to diagnose distant metastasis. On the contrary, TCC is more superficial disease in 80% of the cases and therefore may not require extensive workup. On the same note, the current TNM staging to diagnose SCCUB, similar to what used in TCC, may not be appropriate due to the more extensive nature of the disease. Therefore, a two-tiered staging system, similar to SCLC, is used in practice to diagnose SCCUB - limited-stage disease and extensive disease. Limited-stage disease is confined to an area that can be covered within a single radiation port and involves local disease with only regional lymph node involvement where as extensive disease involves disease process that cannot be covered in single radiation port and include retroperitoneal or distant lymph node involvement with metastasis to other organ systems. This two staging system helps formulate design of the treatment plan. Systemic chemotherapy is used for patients with extensive-stage disease in whom surgery is not the option.

Treatments

Surgical resection is the mainstay of the treatment for patients with limited-stage SCCUB with or without adjuvant chemotherapy. Most of these patients also receive radiation therapy. If the patient has disease limited to the bladder, cystectomy alone is considered curative. The efficacy of radical cystectomy has been questioned (Cheng et al., 2004). In one study, the investigators found no benefit in 1-year and 5-year survival rate in patients who underwent cystectomy vs. patients with chemotherapy alone in limited-stage SCCUB (Cheng et al., 2004). This may be due to the distant micrometastasis which might be present in patients with limited-stage disease. However, survival benefit has been noted with adjuvant radiation postcystectomy in other studies (Grignon et al., 1992; Holmang et al., 1995).

SCCUB is very sensitive to chemotherapy is therefore the major treatment modality for patients with this disease. Chemotherapy is commonly used as neoadjuvant modality to shrink the primary tumor prior to local resection or as adjuvant therapy after the surgical resection of the disease. In patients with extensive-stage disease this is the only treatment available.

The most commonly used regimen for SCCUB is similar to SCLC. In extensive-stage SCCUB, combinations of cisplatin and etoposide (EP) and cyclophosphamide, doxorubicin, and vincristine are standard similar to what is seen used in extensive-stage SCLC. In limited-stage SCCUB, EP became the preferred regimen because of its ease of administration with concurrent thoracic radiotherapy (TRT). Etoposide is administered at 100mg/m^2 intravenously on days 1-3 and then repeated every 3 weeks. Cisplatin is given at 70-100mg/m^2 intravenously on day 1 of the 3-week cycle. At times carboplatin is substituted for cisplatin for more favorable toxicity profile. The optimal duration of therapy is not known due to lack of studies comparing regimens and duration of the therapy. When SCCUB coexists with other types of cancer, a regimen covering both small and non-small cell carcinoma is considered. Common regimens for TCC are cisplatin, carboplatin, taxane, and ifosfamide.

Radiation therapy has a role in SCCUB for palliative purposes as well as an alternative to radical cystectomy. However, Lohrisch et al noted increased incidence of second primary TCC after bladder being exposed to

chemoradiation. (Lohrisch et al., 1999)

Combined modality is more often used due to poor long-term survival with single-modality therapy. For limited-stage SCCUB chemotherapy is given prior to cystectomy to shrink the size of tumor and facilitate resection. This leads to 78% 5-year survival in recent review study at MD Anderson Cancer Center (Siefker-Radtke et al., 2004). At other times adjuvant chemotherapy is used post surgery to target micrometastasis if present.

SCLC has been under intense investigation for molecular and targeted therapy. Since treatment options for SCCUB are extrapolated from SCLC, targeted molecular therapy may be of benefit for patients with SCCUB (Black et al., 2007). EFGR inhibitor, Gefitibnib, has been under investigation but has not shown benefits for SCLC patients in general but has case reports of successful treatments for patients with EFGR positive SCLC and may be of benefit for SCCUB patients (Okamoto et al., 2006; Zakowski et al., 2006; Fukui et al., 2007; Morinaga et al., 2007). E-cadherin expression and ratio of MMP-9 to E-cadherin are potential markers for metastatic potential of the tumor (Slaton et al., 2004). Investigations are underway to examine markers of metastasis and EGFR-targeted therapy (Black et al., 2007). Ras/Raf Inhibitor, zanestra (R115777), has shown no objective response in study with 22 patients (Heymach et al., 2004). A Phase 2 study with c-Kit inhibitor, imatinib, involving 30 patients with c-kit expressing tumor has shown no added benefit (Dy et al., 2005). Bevacizumab, a monoclonal antibody against VEGF, has shown benefit in two studies involving untreated ED-SCLC by combining bevacizumab with etoposide and cisplatin as initial treatment regimen (Ready et al., 2007; Sandier et al., 2007). A Phase 3 trial with Thalidomide, agent with antangiogenic effect via VEGF inhibition, has shown disappointing results in ED-SCLC (Pujol et al., 2007).

Conclusion

SCCUB is a rare cancer and remains a therapeutic challenge for physicians. Cytotoxic chemotherapy will continue to play major role in treatment for limited and extensive-stage SCCUB. Combined modality treatment with platinum based chemotherapy and thoracic radiation therapy performed concurrently, with inclusion of radiation therapy early on has shown survival benefit in limited stage SCLC and thus on SCCUB. Prophylactic cranial irradiation has shown survival benefit in limited stage disease with complete initial response. Surgical resection is offered only in limited-stage SCCUB. Many therapeutic trials are underway involving targeted chemotherapy with novel agents as molecular pathogenesis of the disease becomes clear. Perhaps the successful targeted therapy will be to combine multiple inhibitors targeting different affected mutations at the same time.

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