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Review article

Highlights from the first symposium on upper tract urothelial carcinoma

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Abstract

Objectives: Upper tract urothelial carcinoma (UTUC) is a rare disease in Western countries and garners little focused attention in urologic and oncologic circles. We report highlights from the first symposium on UTUC.

Methods: All participants were asked to provide a summary of their presentation to be included as part of these proceedings. Submitted summaries were synthesized into this document. All contributors reviewed and provided input on the final draft.

Results: Five highlights are included in this report, including landmark research that not only reveals the likely cause of Balkan endemic nephropathy and associated UTUC but also links it directly to UTUC in Taiwan. Because of the ubiquitous use of *Aristolochia* plants in these herbal remedies, a public health problem of considerable magnitude is anticipated in Asian countries. Gene expression signatures reveal some differential expression in bladder carcinoma, such as *CLCA2* and *GABRE*. Few urinary markers have proven utility for the diagnosis and follow-up of UTUC, and no tissue or blood-based markers are currently undergoing clinical application. Novel endoscopic therapies provide some hope of improving tissue sampling, diagnosis, and kidney-sparing therapeutics, but the greatest potential lies in improving clinical (preoperative) risk stratification, which is critically limited in this disease. Biomarkers, currently untested, hold promise in identifying patients most likely to benefit from perioperative chemotherapy and at high risk from cisplatin-induced nephrotoxicity.

Conclusions: Despite its rarity in the West, UTUC is reaching potentially epidemic proportions in the East because of exposure to carcinogenic herbal remedies. Critical trials are needed to improve our understanding and treatment of UTUC. Because of the broad range of comorbid conditions in patients suffering from this disease, it is the consensus of the participants that future clinical trials should be practical in design and applicable to a broad range of patients, diverging from the current dogma of narrow patient selection criteria in clinical trials. Practical designs would maximize accrual for a still uncommon disease, and their findings would be applicable to a larger proportion of patients than current narrowly selected designs.

Keywords: Urothelial carcinoma; Ureteral cancer; Renal pelvis cancer; Epidemiology; Carcinogens; Biomarkers

1. Introduction

Although both upper tract urothelial carcinoma (UTUC) and bladder cancer are derived from the urothelium, they have been referred to as "disparate twin" diseases with practical, anatomical, biological, and molecular differences requiring distinct approaches to clinical management [1]. Microsatellite instability, for example, is seen much more commonly in UTUC than in bladder cancer, and Lynch syndrome, which is associated with UTUC in as many as 15% of cases, does not seem to predispose to bladder cancer [2–5]. Moreover, molecular toxicologic studies (described in the next section) have now linked environmental/dietary

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exposures to the development of UTUC, heralding the discovery that Balkan, Taiwanese, and Chinese herbal nephropathies are probably the same environmental disease.

On November 28, 2012, the first symposium dedicated to UTUC was held in Bethesda, Maryland, in conjunction with—and under the auspices of—the annual winter meeting of the Society of Urologic Oncology. This meeting brought together international stakeholders, including representatives of the National Institutes of Health and the National Cancer Institute, cooperative group representatives, researchers, and clinicians, as well as representatives from patient advocacy organizations and industry. Highlights from that symposium form the thrust of this report.

2. Unraveling the mystery of a global, environmental disease—Arthur P. Grollman, MD

Balkan endemic nephropathy (BEN) is a chronic, progressive tubulointerstitial disease affecting residents of rural farming villages in Croatia, Serbia, Bulgaria, Romania, and Bosnia and Herzegovina [6]. Approximately 50% of all cases of BEN are linked to UTUC. Although many hypotheses have been advanced to explain the etiology of BEN/UTUC, its cause remained a mystery for more than 50 years.

A clue to the etiology of BEN arose unexpectedly when a cluster of otherwise healthy Belgian women developed end-stage renal failure and UTUC following inadvertent ingestion of an established Chinese herbal remedy (*Aristolochia fangchi*) [7,8]. Because of the striking similarities between the pathophysiology of BEN/UTUC and the disease in Belgian women [9], we focused our attention on aristolochic acid (AA), the powerful nephrotoxin/carcinogen found in all *Aristolochia* plants.

After ascertaining that patients with BEN had not used herbal medicines, we resurrected an earlier hypothesis; namely, that exposure to AA could occur if seeds from *Aristolochia clematitis,* which grows abundantly in cultivated fields in the endemic region, comingled with wheat grain used by local residents to prepare home-baked bread, a major dietary staple in this region [10].

Our translational research studies of BEN involved 67 residents of endemic regions who had undergone unilateral radical nephroureterectomy for UTUC [11,12]. Patients living in nonendemic regions served as controls. AA is actively concentrated by the proximal renal tubule; thus, renal cortex DNA was analyzed for aristolactam (AL)-DNA adducts. *TP53* mutations in tumor DNA were identified by chip sequencing [11]. AL-DNA adducts were detected in 70% of patients living in endemic villages and in 94% of patients who exhibited A:T to T:A transversions in *TP53*, a mutation that proved to be a "signature" for urothelial carcinomas associated with AA [13]. Signature A:T to T:A mutations and AL-DNA adducts were absent in all controls. We concluded from these studies that dietary exposure to AA is related *causally* to BEN and its associated UTUC [12]. Accordingly, we agree with the recent recommendation that the term BEN be replaced by aristolochic acid nephropathy (AAN) [14].

We used a similar molecular epidemiologic approach to conduct a study of UTUC in Taiwan [15], where the reported incidence of UTUC is the highest in the world [16]. In Taiwan, as in the Balkans, the *TP53* mutational pattern in patients with AA-induced UTUC was dominated by the otherwise rare A:T to T:A transversions [17]. Unique mutational hotspots, many located at splice sites, were identical to those observed in BEN/UTUC [17]. A:T to T:A mutations were also detected at activating positions in the *FGFR3* and *HRAS* oncogenes [17]. AL-DNA adducts were present in the renal cortex of 83% of patients with signature mutations in *TP53*, *FGFR3,* or *HRAS*. Our data, based on these robust biomarkers of internal exposure and disease, are strongly supported by epidemiologic studies showing that approximately one-third of the entire population of Taiwan has been exposed to Chinese medicinal herbs containing or likely to contain AA [16].

The practice of traditional Chinese herbal medicine in Taiwan mirrors that in mainland China. Moreover, the carcinogenic effect of AA on the upper urinary tract may not manifest itself for 30-40 years after exposure to AA. Therefore, it seems likely that AAN and its attendant UTUC have been prevalent in China, India and, possibly, in other countries where *Aristolochia sp* have been used extensively for the treatment of disease, thereby representing a public health problem of considerable magnitude.

3. Unique gene expression signatures in UTUC—Donna E. Hansel, MD

Several studies have identified individual gene and protein expression differences between urothelial carcinoma arising in the upper tract and that arising in the lower tract, although few have taken a systematic approach to comparing these 2 entities. One recent study specifically evaluated gene expression differences between urothelial carcinomas arising in the renal pelvis and those arising in the bladder [18]. Using Affymetrix GeneChip technology, the investigators evaluated normal urothelium from the bladder and renal pelvis and compared the results to those from urothelial carcinomas arising in the upper and lower urinary tracts. Large-scale gene expression analysis revealed no major differences between the upper and lower tract urothelial carcinomas, although the findings suggested the existence of 2 distinct molecular clusters of carcinomas. Known alterations, such as loss of *CDKN2A*, were identified by cytoband analysis [19].

Numerous genes were differentially expressed between the upper and lower tract carcinomas, including *CLCA2* (11.9-fold lower in bladder urothelial carcinoma) and *GABRE* (9.65-fold lower in bladder urothelial carcinoma).