Invasive urothelial carcinoma after exposure to Chinese herbal medicine containing aristolochic acid may occur without severe renal failure

Joëlle L. Nortier¹, Heinz H. Schmeiser⁴, Marie-Carmen Muniz Martinez¹, Volker M. Arlt⁵, Catherine Vervaet², Christian H. Garbar³, Philippe Daelemans² and Jean-Louis Vanherweghem¹

¹Department of Nephrology, ²Department of Stomatology and ³Department of Pathology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium, ⁴Division of Molecular Toxicology, German Cancer Research Center, Heidelberg, Germany and ⁵Institute of Cancer Research, Haddow Laboratories, Sutton, UK

Keywords: Aristolochia fangchi; aristolochic acid; carcinogenicity; Chinese-herb nephropathy; DNA adducts; herbal remedies

Introduction

Chinese-herb nephropathy (CHN) was initially reported as a progressive renal interstitial fibrosis caused by the regular intake of Chinese herbal medicine belonging to the Aristolochia species containing nephrotoxic and carcinogenic aristolochic acid (AA) [1–3]. Prior exposure to AA was attested by the detection of specific DNA adducts formed by AA metabolites in kidneys and ureters of patients suffering from end-stage renal disease (ESRD) due to CHN [4–6]. Among these patients, a high prevalence of upper urinary tract carcinoma was observed [5,7]. Up to now, urothelial cancer seems to be a late complication of CHN since all the cases have been detected in patients with ESRD. We report here a case of Aristolochia-related urinary tract cancer without significant renal failure, suggesting dissociation between carcinogenicity and nephrotoxicity of AA.

Case

Seven months before her admission in our department, a 69-year-old female without significant previous medical history was treated in another institution for left pyelonephritis associated with hydronephrosis. Serum creatinine was slightly increased to 170 μmol/l, whereas it was always within the normal range before (normal laboratory range 40–150 μmol/l) (Figure 1). Computerized tomography showed a pylonuletral obstructive tumour and lymphadenopathies without any evidence of other extensive process. A left ureteronephrectomy with lymph nodes resection was thus performed. Histologically, a poorly differentiated urothelial carcinoma of the proximal left ureter was diagnosed. The adjacent adipose tissue and three of the removed lymph nodes were invaded. Examination of the renal cortex revealed intact glomeruli and sparse areas of interstitial fibrosis.

Four months after surgery, a left subparotid mass developed. The patient was then referred to our centre for investigation. Serum creatinine was stable at 163 μmol/l. Histological analysis of a percutaneous biopsy specimen from the mass confirmed the neoplastic proliferation of a lymph node of epithelial origin. Analysis of fluorodeoxyglucose regional captation by positron emission tomography scan detected the presence of hypermetabolic lesions (left parotid gland, pulmonary apex, right cervical lymph chain, retroperitoneal region and pelvis), suggestive of metastatic lesions.

Anamnestic enquiry revealed that the patient was an active smoker for > 20 years and that she had not been exposed to well-known nephrotoxic agents, such as analgesics, non-steroidal anti-inflammatory drugs and heavy metals. However, she was prescribed Chinese herbal medicine for slimming purposes from May 1991 to June 1992. Retrospective examination of the prescriptions confirmed the presence of anorectic drugs (diethylpropion and fenfluramine), acetazolamide and the so-called Stephania tetrandra (actually replaced by Aristolochia fangchi [2]) for a cumulative dose estimated to 189 g.

One month after admission, serum creatinine rose to 439 μmol/l and right hydronephrosis was found in relation with extrinsic compression of the proximal ureter by abdominal lymph nodes. After the placement of a JJ ureteral catheter, serum creatinine decreased to 235 μmol/l (Figure 1). On the other hand, despite local radiotherapy and chemotherapy (gemcitabine

Correspondence and offprint requests to: Joëlle L. Nortier, MD, PhD, Department of Nephrology, Erasme Hospital, Université Libre de Bruxelles, 808 Route de Lennik, B-1070 Brussels, Belgium. Email: jnortier@ulb.ac.be

© 2003 European Renal Association–European Dialysis and Transplant Association
(carboplatine), new tumoural masses appeared and the patient died suddenly from septic shock secondary to bronchopneumonia. Autopsic examination confirmed the presence of a generalized carcinoma of urothelial origin.

Significant levels of specific AA–DNA adducts were detected post-mortem in tissue samples from kidney, liver, pancreas and lymph nodes according to the method described elsewhere (Table 1). Highest levels of the DNA adduct [7-(deoxyadenosine-\(N^6\)-yl)-aristolactam I–DNA adduct], which is the major adduct found in the Belgian cohort [5], were detected in the kidney. Typical smoking-related adducts (called the diagonal radioactive zone) were present on the autoradiogram from DNA obtained from lung tissue.

**Table 1.** Specific 7-(deoxyadenosine-\(N^6\)-yl)-aristolactam I–DNA adducts in tissue samples from a patient with invasive urothelial carcinoma

<table>
<thead>
<tr>
<th>Organ</th>
<th>Adducts/10^8 normal nucleotides (means ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>81 ± 22</td>
</tr>
<tr>
<td>Liver</td>
<td>8.7 ± 1.5</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>5 ± 4</td>
</tr>
<tr>
<td>Stomach</td>
<td>19 ± 18 (high radioactive background)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.6 (detection limit); weak DRZ</td>
</tr>
<tr>
<td>Bladder</td>
<td>Not detectable</td>
</tr>
</tbody>
</table>

DRZ, diagonal radioactive zone.

Also, new tumoural masses appeared and the patient died suddenly from septic shock secondary to bronchopneumonia. Autopsic examination confirmed the presence of a generalized carcinoma of urothelial origin.

Significant levels of specific AA–DNA adducts were detected post-mortem in tissue samples from kidney, liver, pancreas and lymph nodes according to the method described elsewhere (Table 1). Highest levels of the DNA adduct [7-(deoxyadenosine-\(N^6\)-yl)-aristolactam I–DNA adduct], which is the major adduct found in the Belgian cohort [5], were detected in the kidney. Typical smoking-related adducts (called the diagonal radioactive zone) were present on the autoradiogram from DNA obtained from lung tissue.

**Discussion**

AAs are nitrophenanthrene derivatives known for their potent carcinogenic action [3]. After metabolic activation, AA forms specific adducts with DNA, which are not only specific markers of AA exposure but could also trigger the process of tumorigenesis, possibly through specific \(p53\) gene mutations [8]. In humans, these adducts were found in renal tissue samples from ESRD patients suffering from CHN [4–6]. Among these patients, a high prevalence of urothelial carcinoma is known [5,7]. Nevertheless, to our knowledge, no case has been described to date of invasive upper urinary tract carcinoma associated with the use of Chinese herbal medicine and without prior evidence of a significant renal impairment. Besides long-term tobacco consumption, there was no evidence of other causes of urothelial carcinoma in this patient, except the exposure to a Chinese herb containing AA. The prevalence of urinary tract cancer is still unknown in patients exposed to AA when their renal function is preserved. As depicted by the US Food and Drug Administration, AA was and might still be present in a large variety of herbs used in traditional medicine [9]. The case reported here thus raises major concerns for public health. Adequate screening for urothelial cancer is obviously impossible in all patients suspected to have ingested AA-containing herbs up to 9 years ago. Nevertheless, faced with urothelial cancer, all physicians should be aware of the interest of a systematic anamnestic investigation about the use of herbal remedies. The search for specific AA–DNA adducts in tissue samples could be a useful test for confirming the causal involvement of AA in such cases.

**References**


*Received for publication: 17.4.02
Accepted in revised form: 13.9.02*