Aristolochic acid as a causative factor in a case of Chinese herbal nephropathy

Sir,

Chinese herbal nephropathy (CHN) is a newly described type of interstitial nephritis with a characteristic histological pattern. It was initially described in a series of Belgian patients who were inadvertently given a contaminated herbal preparation as part of a slimming regimen [1]. The toxic agent was putatively identified as ‘aristolochic acid’ (AA), the active principle from species of *Aristolochia* now known to be a mixture of nitrophenanthrene derivatives such as aristolochic acid I and aristolochic acid II [1]. The likelihood that AA was the causative agent of CHN was strengthened by the finding of AA-DNA adducts in the kidneys and urothelial tracts of patients affected by this condition [2]. In those
cases, the inclusion of AA resulted from the substitution of Aristolochia species for Stephania tetrandra in the slimming pills. Despite these findings, doubt has been cast on the pathogenic role of AA, in part because of the concomitant administration of other prescription medication [3].

We have recently reported two cases of CHN in the United Kingdom that were caused by AA and that led to a permanent ban of AA by the Medicines Control Agency [4]. Similar bans are now in force in Canada, Australia, and other European Union countries. Here we report the case of a 59-year-old man who developed renal failure (urea 26.8 mmol/l (normal range: 2.8–7.6 mmol/l), creatinine 660 μmol/l (normal range: 80–133 μmol/l) and pancytopenia (Hb 7.8 g/l (normal range: 12.5–16.3 g/l), MCV 91 fl (normal range: 76–99 fl), WBC 3.5 × 10⁹/l (NR: 3.1–11.2 × 10⁹/l; normal differential counts), platelets 48 × 10⁹/l (NR: 120–400 × 10⁹/l)) following a 5-year period of ingesting a Chinese herbal preparation to treat hepatitis B. Renal biopsy revealed a histological pattern of cortical interstitial fibrosis with relative glomerular preservation, which is characteristic of this form of nephropathy. Analysis of the herbal preparation by liquid chromatography and mass spectrometry revealed the presence of aristolochic acids I and II, which are nitrophenanthrene derivatives that have been causally associated with the development of Chinese herbal nephropathy (Figure 1). Autoimmune serology was normal or negative, as was protein electrophoresis. Ultrasound examination of the kidneys excluded obstruction. Due to his worsening pancytopenia, he underwent a bone marrow aspirate, which showed a hypocellular marrow with increased macrophage activity with no primary haematological abnormality. A bone marrow trephine showed normal cellularity with all three haemopoietic cell lineages present although there was a slight decrease in megakaryocytes. We concluded that the most likely diagnosis was AA nephropathy and, possibly, associated bone marrow suppression.

The case presented here further implicates AA as the causative agent in this new type of nephropathy. Moreover, given that the appearance of increased macrophage activity in the bone marrow is often due to toxic agents, we suggest that the pancytopenia and bone marrow suppression could have been due to AA. The association of bone marrow suppression and AA has, to our knowledge, never previously been reported, although thrombocytopenia has been causally linked to other herbal preparations [5]. Without further analysis, we cannot exclude the possibility that another toxic constituent of the herbal remedy that the patient was taking was responsible for this phenomenon. It is unlikely that hepatitis was the cause of his bone marrow suppression or renal failure as his liver function tests and coagulation tests were normal. Furthermore, ultrasound scans of his liver, spleen and vena cava were unremarkable and he was hepatitis e antigen negative.

Our previous paper [4] led to a comprehensive ban on the import and use of Aristolochia spp. and commonly confused herbs in the UK. Given the further association of this herb and urothelial carcinoma [2] and AA detection in a range of medications [M. Simmonds, in preparation], we believe that this case raises potentially important public health issues, both in the UK and internationally. We are currently undertaking research to identify the precise distribution of these compounds in other plants.

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