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Acute renal failure associated with prolonged intake of slimming pills containing anthraquinones

與長期進食含有蒽醌類化合物的減肥丸有關的急性腎衰竭

Chinese herbal medicine preparations are widely available and often regarded by the public as natural and safe remedies for a variety of medical conditions. Nephropathy caused by Chinese herbs has previously been reported, usually involving the use of aristolochic acids. We report a 23-year-old woman who developed acute renal failure following prolonged use of a proprietary Chinese herbal slimming pill that contained anthraquinone derivatives, extracted from Rhizoma Rhei (rhubarb). The renal injury was probably aggravated by the concomitant intake of a non-steroidal anti-inflammatory drug, diclofenac. Renal pathology was that of hypocellular interstitial fibrosis. Spontaneous renal recovery occurred upon cessation of the slimming pills, but mild interstitial fibrosis and tubular atrophy was still evident histologically 4 months later. Although a causal relationship between the use of an anthraquinone-containing herbal agent and renal injury remains to be proven, phytotherapy-associated interstitial nephropathy should be considered in patients who present with unexplained renal failure.

中草藥被廣泛應用，公眾普遍認為中草藥對很多病情都可自然和安全地治療。過往曾有報告指中草藥導致腎病，通常涉及使用馬兜鈴酸。本文報告一名23歲女性，在長期使用一種專利減肥中草藥丸後出現急性腎衰竭。該藥丸含有提煉自大黃的蒽醌類化合物的衍生物。後來病人大多因服食非類固醇類消炎藥「雙氯芬酸」，導致腎臟的損傷惡化。腎病理學顯示細胞不足間質纖維化。在停止使用該減肥丸後，病人的腎臟便自行痊癒，但四個月後仍然有輕微間質纖維化和管道萎縮。雖然仍未證實使用含蒽醌的中草藥劑和腎臟受損是否有關，但病人如出現無法解釋的腎衰竭時，醫生應考慮是否因植物藥力導致間質性腎病。

Key words:
Drugs, Chinese herbal;
Kidney failure, acute;
Nephritis, interstitial;
Obesity/drug therapy;
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關鍵詞：
藥物，中草藥；
腎臟衰竭，急性的；
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Introduction

Chinese herbal remedies have been used for thousands of years in Chinese communities. They are now increasingly marketed worldwide as health products for the treatment of an expanding range of conditions, including obesity. Despite the general view that they are safe, natural products, Vanherweghem et al[1] first reported a cluster of cases of extensive interstitial fibrosis with consequent rapidly progressive renal failure in women in Belgium who had taken slimming pills containing powdered Chinese herbs. Aristolochic acids (AA) (馬兜鈴酸), the mutagenic alkaloid extract from the Chinese herb *Aristolochia* (馬兜鈴), are now thought to be the cause for these and over 100 other cases of Chinese herb nephropathy. An increasing number of herbal products are now reported to be renally toxic.[2,3] Proprietary slimming agents have recently become popular among young women, with many of them containing a mixture of Chinese herbal ingredients that were previously restricted for use by trained traditional Chinese medicine (TCM) practitioners. Emodin (大黃素), aloe-emodin (蘆薈大黃素) and related anthraquinone (蒽醌) compounds are the active ingredients of Rhizoma Rhei (大黃), the dry root of medicinal rhubarb (大黃根), one of the plant extracts contained in some slimming drugs now available from healthstores. It has previously been prescribed by practitioners of TCM as a traditional laxative and anti-inflammatory agent. In western medicine, non-steroidal anti-inflammatory drugs (NSAIDs) are notorious for their nephrotoxicity and the possibility of serious nephrotoxicity as a result of

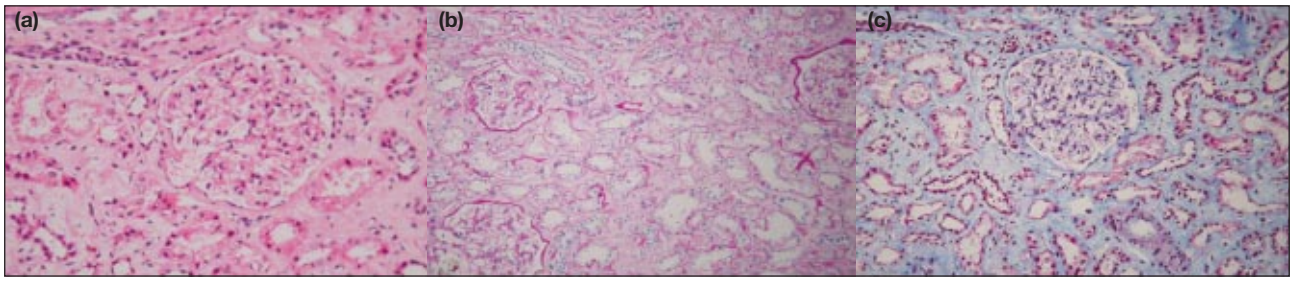

Fig 1. Light microscopic findings of the first renal biopsy showing (a) unremarkable glomeruli with no significant mesangial or endocapillary proliferation; (b) sparse interstitial lymphocytic infiltration with diffuse mild tubular atrophy and inconspicuous proximal tubules. The tubular epithelial cells appear flattened with mild dilatation. Cystic changes are not obvious. Degenerative and regenerative nuclear changes are not evident; and (c) diffuse mild-to-moderate interstitial fibrosis

taking a combination of NSAID and herbal slimming agents has been reported.[4,5]

We report a woman with a history of prolonged intake of a slimming pill containing Rhizoma Rhei who developed reversible acute renal failure that was probably further aggravated by the use of an NSAID.

Case report

A 23-year-old woman was admitted to our hospital in April 2004 for investigation of renal dysfunction. Six weeks prior to her admission, she started taking a proprietary herbal slimming agent bought from a healthstore and took it regularly at the recommended dose of 6 tablets a day. Two days prior to admission she consulted her family doctor for an upper respiratory tract infection and was prescribed symptomatic treatment that included diclofenac 25 mg 4 times daily for 2 days. No antibiotics were prescribed. She presented to us with nausea, vomiting, malaise and poor appetite, but no diarrhoea. On physical examination, she was haemodynamically stable with normal hydration. Blood tests demonstrated impaired renal function with her serum creatinine and urea elevated to 519 μmol/L and 14.6 mmol/L, respectively. Her liver function tests were normal and her haemoglobin was 118 g/L. The urine sediments were bland, but there was mild proteinuria: 0.54 g/day. The serum and urine drug toxicology screen was negative. A renal biopsy revealed mild-to-moderate diffuse interstitial fibrosis with sparse lymphocytic infiltrates (Fig 1); the blood vessels and the glomeruli were normal. Immunofluorescent staining was negative for immunoglobulins and complements. Histologically, it was not suggestive of NSAID-related nephropathy, but rather resembled that of AA-associated interstitial fibrosis.

The proprietary slimming agent was sent for analysis: emodin and aloe-emodin were detected using chromatography.[6] Screening for AA and other prescribed drugs was negative. The overall anthraquinone profile was compatible with the reference herbs listed for medicinal rhubarbs, one of the claimed constituents of the product.

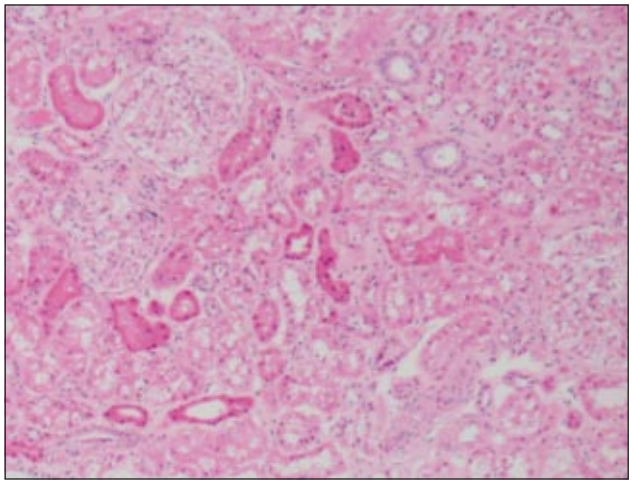

Fig 2. Second renal biopsy 4 months later showing mild and focal interstitial fibrosis and associated tubular atrophy at the corticomedullary junction. The superficial cortex revealed no significant interstitial fibrosis or tubular atrophy. The glomeruli and vessels appeared unremarkable

The absence of AA exposure was confirmed with no evidence of AA-specific DNA adduct, a marker of significant previous exposure to AA-containing herbs, in the renal biopsy tissue.

Following admission our patient's renal function improved spontaneously, with eventual recovery. Six days after admission, her serum creatinine fell to 140 μmol/L and was 59 μmol/L 1 month later; 24-hour urine protein was 0.09 g. A repeat renal biopsy 4 months later showed very focal and mild interstitial fibrosis associated with tubular atrophy that was more prominent in the juxtamedullary than the subcortical region (Fig 2).

Discussion

The use of herbal medicines is gaining popularity worldwide. More than 1400 different crude botanical drugs are commercially available in the European Union. As a result of their increasing popularity, the safety of herbal medicines is emerging as a common global concern.

Li et al[5] previously reported a case of NSAID-induced acute tubular necrosis that was thought to have been aggravated by the volume depletion induced by the cathartic action of another proprietary slimming pill, taken for about 2 weeks.

Although NSAIDs are well recognised as a major cause of renal dysfunction, its occurrence is usually associated with dehydration or hypovolaemia, with consequent haemodynamically-mediated renal impairment. Histologically, NSAID-mediated renal injury is characterised by acute tubular necrosis. Other known renal complications related to NSAIDs include acute tubulointerstitial nephritis, and minimal change and membranous glomerulonephritis.[4]

The renal histology of our patient was diffuse renal interstitial fibrosis with minimal lymphocytic infiltration. Morphologically, the renal pathology was not typical of the NSAID-related nephropathy previously reported. Furthermore, our patient started taking diclofenac only 2 days before symptom onset, and there was no clinical evidence of significant volume depletion throughout this period. Rather, the renal histology was reminiscent of the cluster of AA-nephropathy (AAN) cases reported from Belgium in 1993,[1] and many other subsequent reported cases in which rapidly progressive interstitial renal fibrosis in young women was associated with prescription of a Chinese herbal slimming regimen. The possibility of AA intoxication was excluded in our patient: there was no history of other drug exposure, and AA and its related compounds were not detected in the drug that the patient had taken. Renal tissues were also negative for AA-related DNA adducts. In addition, the pathology of hypocellular interstitial sclerosis, tubular atrophy, and global glomerular sclerosis previously described for AAN decreases from the outer to the inner cortex; in our patient, the outer cortex was spared and the interstitial fibrosis and tubular atrophy were found mainly in the corticomedullary junction. Hence, the histological finding in our patient differed from that of the previously reported phytotherapy-associated nephropathy or AAN. The clinical course of our patient with prompt recovery was likewise not characteristic of the progressive nature of AAN. We postulate that our case represents another kind of non-AA related phytotherapy-associated interstitial nephritis that is largely reversible. It bore some histological resemblance to AAN, but with a predilection for the juxtamedullary cortex. The anthraquinone derivatives, which were the herbal components in the slimming agent our patient had taken for 6 weeks, were probably responsible for the specific renal injury.

Anthraquinone compounds are found in rhubarb root (大黃根), senna leaf (番瀉葉) and pod (豆莢), cascara sagrada (藥鼠李), buckhorn (鹿角) and aloe (蘆薈), all common components of herbal slimming regimens. In our patient, the anthraquinones derived from Rhizoma Rhei (rhubarb), one of the claimed constituents of the slimming product. Rhizoma Rhei consists of the dried root and rootstock of *Rheum palmatum* Linne (掌葉大黃), or *Rheum officinale* Baillon (藥用大黃). The rhubarb root has mainly been used traditionally for its laxative properties and on a short-term basis, usually recommended for a period of no more than 2 weeks. The root contains a complex mixture of 2-5% anthraquinone derivatives (anthranoids) [蒽類], of which the majority are present as glycosides (多忒). The main anthraquinone-aglycones (蒽醌－非糖部份) are chrysophanol (大黃酚), aloe-emodin, emodin, physcion (大黃素甲醚), and rhein (大黃酸).

Colonic bacteria metabolise the anthraquinone glycosides to anthranols (蒽酚) that can be absorbed to a moderate degree and are excreted in the bile, saliva, milk, and urine. Anthraquinones are known to exert a number of biological activities and adverse effects have been reported.[7-10] Chronic abuse of anthraquinone stimulant laxatives can lead to hepatitis and a benign reversible melanotic pigmentation of the colonic mucosa, pseudomelanosis coli.[11-13] The Federal Institute for Drugs and Medical Devices in Germany recommended, since 1996, that anthraquinone-containing laxatives should not be used continuously for periods exceeding 1 to 2 weeks.

This is the first report of Rhizoma Rhei–associated interstitial fibrosis presenting as acute renal failure that was probably potentiated by the concomitant use of an NSAID. The temporal relationship of the patient's symptoms with the intake of the slimming pill, absence of any other identifiable nephrotoxic agent apart from diclofenac, spontaneous improvement and ultimate recovery of renal function upon discontinuation of the offending drug, and a renal biopsy that demonstrated fibrosing interstitial nephritis, all support this diagnosis. The lack of previous reports of such adverse events associated with the use of Rhizoma Rhei may be related to its previously restricted use.

Such Chinese herbal preparations are now widely marketed as health products with increasing use by healthy individuals for prolonged periods of time. Previously they were prescribed only by TCM practitioners for limited periods and their use supervised. There is now an increased chance that these remedies may be taken in conjunction with regular western medications. Potential drug interactions remain largely unknown but are now being tested by consumers themselves.

Physicians need to be alert to the possibility that patients are consuming proprietary herbal health products and be aware of the potential for drug interactions.

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