

Severe pulmonary hypertension possibly due to pyrrolizidine alkaloids in polyphytotherapy

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We report the case of a 66 year old woman with known arterial hypertension, non insulin dependent diabetes, moderate adiposity (BMI 33 kg/m²) and mild renal insufficiency who came to the emergency room in November 2006 because of progressive dyspnoea. She was born in Peru but has been living in Switzerland for twenty years.

On examination, she was tachydyspnoeic with a respiratory rate of 22 breaths per minute, the oxygen saturation was 80% in ambient air, the blood pressure 155/75 mm Hg with a heart rate of 88 bpm. A strong S2 was heard at auscultation. Blood gas analysis showed severe partial respiratory insufficiency, laboratory analysis a mild elevation of liver enzymes, a lactate dehydrogenase of 642 U/l, a D-Dimer value of 1.45 ng/l (normal range <0.5 ng/l) and a brain natriuretic peptide level of 42 ng/ml (normal range <80 ng/ml).

A contrast enhanced chest CT scan excluded pulmonary emboli but showed a mild polyserositis with ground glass opacities in both lungs. An echocardiography revealed moderate pulmonary hypertension (PH) with a systolic pulmonary artery pressure (PAP) of 60 mm Hg, a left ventricular ejection fraction of 65% and a moderate dilatation and dysfunction of the right ventricle. Pulmonary function tests showed a very mild restriction with a total lung capacity (TLC) of 89% and a severe impairment of the diffusion capacity with a DLCO single breath of 40% predicted. No evidence of obstructive lung disease was present. Lung ventilation-perfusion scintigraphy was normal, and a nocturnal respiratory polygraphy documented a normal apnoea-hypopnoea index of 5/h with a basal oxygen saturation of 84% without signs for alveolar hypoventilation. HIV test, thyroid function and immunologic screening (antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti extractable nuclear antigen (ENA) screen and anti-citrullin antibodies) were normal. The patient had not travelled to tropical zones, had no eosinophilia and did not consume appetite suppressants or other drugs known to be associated with PH. After diuretic therapy a high resolution CT scan of the chest was performed showing normal lung parenchyma with complete regression of the previously reported opacities, probably caused by non-cardiogenic pulmonary

oedema. Two pneumologists skilled in interstitial lung diseases and pulmonary hypertension separately judged the CT images as not typical for pulmonary veno-occlusive disease.

The CT scan disclosed a small hepatic nodular lesion, which showed features of an adenoma in the MRI examination without other abnormalities of the hepatic parenchyma or periportal fibrosis, which would be consistent with schistosomiasis, one of the most frequent causes of PH worldwide.

Though extensive investigations were made, no explanation could be found for the PH and the final diagnosis of idiopathic PH was made.

Long-term oxygen therapy was introduced and right heart catheterization performed. The pulmonary hypertension was confirmed with a mean PAP of 40 mm Hg (systolic 59 and diastolic 29 mm Hg), a wedge pressure of 5 mm Hg, a right atrial pressure of 4 mm Hg, a pulmonary vascular resistance index (PVRI) of 1176 Dynes.sec/cm⁵ and a central venous oxygen saturation of 55%. A vasoreactive test by inhalation of nitric oxide (20 ppm) was negative.

Bosentan was started at a dose of 62.5 mg twice a day but was withdrawn because of "liver pain" and generalised discomfort. The patient could hardly understand her disease and probably because of the cultural differences there was no way to convince her to take the medication. She could hardly be persuaded to start with oral anticoagulation and to try low dose sildenafil (12.5 mg) which had to be stopped because of vertigo. A therapy with a calcium antagonist (Nifedipin) could be introduced beginning with a dose of 20 mg bd.

At follow-up, when explicitly asked for the use of alternative and complementary medicines, the patient reported that she used a mixture of several herbs to make a tea, which she described as "excellent for her health". In the months prior to hospitalisation she had drunk between one and one and a half litres a day of this tea.

At the next visit she brought a bag full of herb packages.

All herbs were carefully checked in the internet for possible relationship with PH and one of the compounds, comfrey, was found to contain pyrrolizidine alkaloids, which have been associated with hepatic veno-occlusive disease and possibly with PH in the literature. We told the patient to immediately stop her herbal remedies because of their potential severe side effects. She did not believe us and was still very sceptical even when we gave her printed information about the severe adverse effects of comfrey but finally stopped using them.

She repeatedly declined a new trial with Bosentan or Sildenafil and often failed to come to follow up visits. At follow up in June 2007 she was still hypoxaemic and could walk only 277 meters in the six-minute walk test desaturating to 75%.

In March 2008 she was hospitalised because of severe right heart failure. She was treated with diuretics and bed rest losing 14 kg. Echocardiography showed a widely dilated and hypokinetic right ventricle with a systolic PAP of 60 mm Hg. She finally accepted Sildenafil and the dose was slowly increased to 50 mg three times a day and was well tolerated.

She could be discharged and improved markedly in the following weeks. At a later date she was hospitalised with severe foot ulcers and treated with intravenous Ilomedin. For this reason the six-minute walk test could not be performed and a follow up echocardiography in December 2008 still showed a PAP of 60 mm Hg.

Discussion

There is a steadily growing use of alternative and complementary medicine for many diseases in our societies [1]. Herbal remedies are one of the most popular therapies and represent a \$ 1.8 billion market in the United States. An incidence of 27% of herbal medicine consumption in hospitalised patients on an internal medicine ward was found in one study [2].

Although herbal remedies are marketed as natural products, they can be associated with severe adverse effects. Heavy metals, infective agents, toxic properties of their compounds and interaction with other medications or even adulteration with synthetic drugs are some of the reported risks [3]. Emblematic are the cases of adulteration of herbal slimming remedies with fenfluramine [4], a drug known to have caused PH in the nineties [5] like Aminorex, sadly known for the epidemic of PH in the early seventies [6].

Few of the internet websites marketing herbal weight-loss dietary supplements, one of the most popular ways to sell phytomedicine, list potential drug interactions or adverse reactions [7].

Our patient took a mix of nine different herbal remedies. One of them, comfrey, is made from an herb named *symphytum officinale*, an evergreen plant (fig. 1) with a long tradition of external treatment for inflammatory disorders, which is available as tea, root powder and capsules. It is well known to cause severe toxic effects such as hepatic veno-occlusive disease, hepatic carcinoma and possibly pulmonary hypertension among others [8-10]. There are seven different pyrrolizidines in comfrey: intermedine, acetylintermedine, lycopsamine, acetyllycopsamine, symphytine, echimidine (the most toxic) and symviridine, and all of them are hepatotoxic. Pyrrolizidine alkaloids (PA) contained in comfrey products undergo metabolic transformation in the liver through cytochrome P450 generating highly toxic pyrrole metabolites with alkylating properties that damage endothelium. Some of these metabolites may persist in tissues and may reinduce damage after a variable latency period. The dose-effect relationship remains unclear and differences in interindividual sus-

ceptibility are high. Determining the exact content of PA in teas produced by boiling comfrey leaves is very difficult because of the high variability in their alkaloid content (ranging from 30 to 1150 mg kg⁻¹). Bulk comfrey leaves may have a higher content of alkaloids than roots. Lethal Dose (LD) 50 for symphytine, monocrotaline and echimidine are respectively 130, 175 and 200 mg/kg BW. The WHO stated in 1988 that ingestion of more than 10 µg/kg a day of a heliotrine (LD50 300 mg/kg BW) equivalent may lead to disease in humans. However not all comfrey extracts have the same composition making it very hard to compare their toxicity.

The analytic results in a case of veno-occlusive disease due to comfrey described by Ridker indicated that even low-level, chronic exposure to such alkaloids (it was estimated that the patient had consumed a total of 85 mg of alkaloids – the equivalent of nine days' use of the powder preparation) can cause veno-occlusive disease [11].

Kay, Heath and Chesney induced pulmonary hypertension by feeding rats and non-human primates with *crotalaria spectabilis*, a PA containing plant [12–14]. Since their experiments in the sixties, monocrotaline induced pulmonary hypertension in rats has become the principal animal model for the disease.

PA are present in more than three hundred plants and therefore probably in many herbal remedies. The incidence of their toxic effect in humans is likely to be underestimated [15]. Some authors have even reported small epidemics of hepatic veno-occlusive disease caused by traditional remedies [16]. Heath described the case of a young African who died due to primary PH suspected of having ingested the seeds of *crotalaria laburnoides* (another PA containing plant) and could reproduce right ventricular hypertrophy and medial hypertrophy of the pulmonary trunk in rats fed with seeds of *crotalaria* during 60 days [17]. The true incidence of PH induced by ingestion of comfrey or other PA containing herbal remedies remains unknown.

Although not proven, we believe the PH of our patient to be possibly caused by the prolonged use of large quantities of boiled herbal remedies containing comfrey.

One intriguing feature of this case was the mild polyserositis with ground glass opacities that disappeared after diuretics, which we interpreted as a non-cardiogenic pulmonary oedema because of a very low BNP level and a normal left ventricular function with normal right atrial and wedge pressures. One possible explanation is a capillary lesion produced by the PA as has been reported in some of the



Figure 1
Symphytum officinale.

studies of monocrotaline induced pulmonary hypertension [18], a mechanism similar to that described in the pathophysiology of high altitude pulmonary oedema [19].

Another interesting point was the alteration of liver function without clear signs of decompensated right heart failure (normal right atrial pressure and absence of peripheral oedema) with a hepatic nodule interpreted as adenoma in the MRI investigation. Because of the known hepatic toxicity we cannot exclude an association with the ingestion of comfrey but no signs of hepatic veno-occlusive disease could be seen retrospectively either in the liver CT or in the MRI.

This case underlines the importance of taking an accurate patient history with respect to all possible conventional and unconventional therapies and environmental exposures. Exogenous causes of PH are various and probably underreported, as Egermayer well described in his review on epidemics on vascular toxicity and PH [20]. More investigation of the association between herbal remedies and PH in a systematic fashion is strongly needed.

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