

## CUSHING'S SYNDROME SECONDARY TO ADULTERATED COMPLEMENTARY AND ALTERNATIVE MEDICINE

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### ABSTRACT

This is a case of a 65 year old lady who presented with Cushing's syndrome secondary to ingestion of a complementary and alternative medicine that has been adulterated with exogenous glucocorticoids. In a clinical consultation, it is important to include assessment of complementary and alternative medicine use for a comprehensive care.

**Keywords:** Cushing's syndrome, complementary and alternative medicine, glucocorticoids.

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### INTRODUCTION

Cushing's syndrome is commonly caused by administration of exogenous glucocorticoids.<sup>1</sup> The use of exogenous glucocorticoids has been found as an adulterant in complementary and alternative medicine.<sup>2</sup> Therefore, in clinical consultations, an enquiry about the use of complementary and alternative medicine among certain patients in an important aspect of comprehensive patient assessment. The following case illustrated an unfortunate event which has resulted from the use of complementary and alternative medicine.

### CASE SUMMARY

Puan S, a 65 year old lady, brought by her daughter-in-law for excessive weight gain. She was noted by family members to have increased appetite which was associated with tremendous weight gain of 10kg over 3 months. Puan S had knee pain due to osteoarthritis (OA), worsened by the increased weight. She had no symptoms of hypothyroidism, headache or visual disturbances.

Puan S was under the follow-up of an orthopaedic clinic in a tertiary hospital for many years for her knee OA. She was on intermittent analgesia which did not improve her knees problem. She was offered total knee replacement (TKR) surgery but she declined as she worried that she might not be able to walk after the surgery and the pain might get worse.

On further questioning, she had been taking a herbal medicine called the Mecca powder for her knees problem.

She bought it from a friend and was told that the ingredients were from natural herbs, making it safe to consume. She had consumed the powder for about three months for her knee pain; which improved her symptoms dramatically. During this time, she also noted to have good appetite and weight gain. She had stopped taking the herbs three weeks prior to the consultation as her knees symptoms improved.

She also had hypertension and dyslipidaemia; on regular follow-up with the health clinic. Her medications comprised captopril 50 mg tds and simvastatin 20 mg nocte. She denied having any side effects from her medications and had been compliant with her medications. She was not physically active in view of her knees problem and she liked additional salt in her diet. Puan S is a widow with five children, and currently lived with her son and his family. She was a non-smoker and did not consume alcohol. She was postmenopausal for more than ten years and not on any hormonal replacement therapy. There was no significant family history.

On examination, Puan S's weight was 78 kg (previously was 68 kg according to her) and her height was 156 cm with a body mass index of 32 kg/m<sup>2</sup>. Physical examination revealed moon-like facies, central obesity and a 'buffalo hump' over her posterior aspect of her neck but she was not hirsute. Her blood pressure was 160/80 mmHg with no postural drop. Her pulse rate was 78/min and of regular rhythm. Examination of the eyes revealed no bilateral hemianopia.

The examination of both cardiovascular and respiratory systems was unremarkable. Examination of the abdomen revealed florid tinea infection. However, there was no

abdominal tenderness, hepatosplenomegaly or striae. It was noted she had bilateral pedal oedema. Examination of both knees, revealed marked genu varus, with mild swelling but no effusion. There was crepitus and tenderness along the knee joint lines. The flexion of both knees was limited. She also had weakness of the proximal muscles of the both lower limbs.

The possibility of Cushing's syndrome secondary to the herbal medicine was considered in view of the emergence of sudden weight gain, moon-like facies, central obesity, the buffalo hump, proximal myopathy and florid fungal infection; which coincided with the consumption of the herbal medicine. Puan S was counselled on the possibility of Cushing's syndrome and was advised to avoid stress (both physically and emotionally) as this could trigger adrenal crisis. Fortunately, Puan S had some of the herbal medicine with her which was subsequently sent for toxicological analysis with a tertiary centre laboratory. As for the confirmation on the Cushing's syndrome, a shared care with an endocrinologist of a tertiary hospital was arranged.

During this consultation, her fear of surgery was explored and misconceptions were corrected. She was prescribed with celecoxib 200mg daily and was taught some range of movement exercise for the knees. The option of intra-articular injections with hyaluronate was also discussed but she declined. Her blood pressure control was suboptimal. Puan S was counselled on dietary and lifestyle modification; and hydrochlorothiazide 12.5mg daily was added to achieve better control of her blood pressure. Her random blood sugar was 5.7 mmol/L.

She was seen by the endocrinologist and the further investigations were done. A midnight serum cortisol was 353 nmol/L (normal: less than 100 nmol/L); which confirms hypercortisolism and the adrenocorticotrophic hormone (ACTH) done was 3.5 pg/mL (reference range: 5-20pg/ml); suggest that she had ACTH independent Cushing's syndrome. The thyroid function test, renal profile and liver function test were within normal limits. Chest radiography showed no abnormality. An ultrasound of the abdomen was done, which was a normal study. She was informed of the diagnosis and was commenced by the endocrinologist hydrocortisone 20 mg mane and 10 mg six hours after the morning dose.

The toxicology result reported the presence of both betamethasone and dexamethasone in the Mecca powder. On follow up, Puan S was informed of the toxicology results and was counselled on future use of herbal medicine. A report on the adverse drug reactions secondary to consumption of herbal medicines was sent to the National Pharmaceutical Control Bureau for regulatory control purposes.

Unfortunately, the Mecca powder was packaged in a bottle without any labels. Puan S refused to reveal her source of the herbal medicine, despite counselling; making the report to the National Pharmaceutical Control Bureau incomplete. On further follow up, Puan S was well and her knee pain was bearable with the analgesia and the exercise for her knees. Puan S continued to receive shared care with the endocrinologist and at the primary care level.

## DISCUSSION

Cushing's syndrome is a disorder resulting from chronic exposure to excess glucocorticoids.<sup>1</sup> Most cases of Cushing's syndrome were iatrogenic, resulting from the administration of glucocorticosteroids or adrenocorticotrophin. Other causes of Cushing's syndrome are rare and may result from excess ACTH production usually by a pituitary corticotroph adenoma (Cushing's disease) or by ectopic ACTH secretion (such as small cell carcinoma of the bronchus; carcinoid tumours of the lungs and thymus). Cushing's syndrome can also be ACTH independent when there is excess glucocorticoids secretion by either adrenal adenoma or carcinoma.<sup>1,3</sup>

Exogenous glucocorticoids (such as corticosteroids) therapeutic administration is also ACTH independent. Oral corticosteroids therapy is the most common cause of exogenous Cushing's syndrome but studies has shown that intraarticular, topical, nasal and dermal corticosteroids can cause hypothalamic-pituitary-adrenal axis suppression and cause Cushing's syndrome.<sup>4</sup> After prolonged use of corticosteroids, discontinuation may precipitate secondary hypoadrenalism leading to adrenal insufficiency and exacerbation of underlying disease such as diabetes and hypertension; as well as significant mortality if not promptly treated.<sup>4</sup>

The clinical features of Cushing's syndrome include central obesity, thinned skin, supraclavicular and cervical fat pad accumulation (also known as "buffalo hump"), hirsutism, proximal myopathy, elevated blood pressure, glucose intolerance, purple striae and menstrual irregularities.<sup>3</sup> Neuropsychological disturbances such as depression and emotional irritability were also observed. Diagnosis of Cushing's syndrome is made clinically and the extent of laboratory investigations will depend on the clinical index of suspicion, which usually is to exclude endogenous Cushing's syndrome. The investigations are done to confirm Cushing's syndrome (i.e. to confirm hypercortisolism) and to determine the aetiology of Cushing's syndrome.<sup>6</sup> If Cushing's syndrome is highly suspected but tests are normal; re-evaluation of the patient at a later date is imperative.

The confirmatory tests for Cushing's syndrome include 48 hour low dose dexamethasone test, measurement of urinary free cortisol and circadian rhythm of cortisol production.<sup>3,6</sup> The investigations required to determine the aetiology of Cushing's syndrome include ultrasound or CT scan of the adrenals, ACTH level, chest radiography, glucose level and renal profile to exclude hypokalaemia in ectopic ACTH. The approach to Cushing's syndrome management is to address the underlying aetiology. In addition, adrenal insufficiency may occur due to prolonged hypothalamus-pituitary-adrenal (HPA) axis suppression and adrenal atrophy secondary to loss of endogenous ACTH.

The patient may present with hypotension and hyponatraemia as well as low plasma cortisol and ACTH levels. Therefore, weaning from prolonged corticosteroids use or abuse should be done gradually as recovery of the normal HPA function can be days, months or years. Most would require hormone replacement with hydrocortisone until recovery of the HPA function.<sup>5,7</sup> In Puan S case, the sudden weight gain with the features of Cushing's syndrome should alert the family physician to determine the underlying cause and a shared care with an endocrinologist is required for full assessment and to assist in confirming the diagnosis.

There was a correspondence that reported a case of Cushing's syndrome caused by gout treatment with traditional Chinese medicine.<sup>8</sup> In Malaysia, 44.4% of the population uses of complementary and alternative treatment (CAM).<sup>9</sup> CAM had been practiced to some degree in all cultures. The CAM comprises the Malay traditional medicine (the bomoh), the Chinese traditional medicine (the sinseh), the Indian traditional medicine (the ayurveda-siddha practitioner), homeopathy and alternative medicine such as acupuncture and chiropractor.<sup>10</sup>

The use of complementary and alternative medicine is part of the culture and beliefs for maintenance of health or treating certain ailments.<sup>11</sup> The increased use is also due to the impression that CAM being natural and safe, as well as thought to be more effective and better for physical illness.<sup>11,12</sup>

Patients with chronic diseases frequently use complementary and alternative medicine.<sup>12,13</sup> The use of CAM was common among those with musculoskeletal problems, diabetes and hypertension. Herbal medicine is a widely used form of CAM. Those who utilised CAM are those age more than 50 years, with higher educational level, higher monthly household income and a family history of CAM use.<sup>13</sup>

Among those with chronic diseases, use of CAM concurrently with conventional medicine is common and majority did not inform their doctors on its use.<sup>12,13,14</sup> Interestingly, majority reported that their doctors never asked about CAM use, some believed that it was not important for their doctors to know and a few were afraid that their doctor would disapprove.<sup>13</sup>

In Puan S's case, she had a chronic illness (i.e. her knees OA) which had caused her disability. She was unhappy with the treatment options provided by the medical services. Due to exasperation and advice by friends, she had resorted to complementary and alternative medicine. As family physician, enquiry on use of CAM is an essential component of patient assessment.

In Malaysia, the Drug Control Authority found that almost 18% of 1,000 herbal medicine tested were detected to have suspected adulterants such as lead, mercury and steroids.<sup>15</sup> An adulterant is a synthetic therapeutic substance that are not prescribed or labelled as part of the intended use of a medicine. The adulteration of herbal medicine with synthetic therapeutic substances has been reported in several developed countries including Malaysia.<sup>15,16</sup> Samples of herbal medicine with indications for rheumatoid, analgesic and anti inflammatory problems commonly contained the adulterants.<sup>16</sup> Majority of the adulterated herbal medicine had two or more adulterants. Among the common adulterants in herbal medicine are corticosteroids and non-steroidal anti-inflammatory drugs.

Corticosteroids are naturally occurring and synthetic chemicals.<sup>17</sup> Corticosteroids have been widely used in conventional medicine for the treatment of eczema, skin allergies, asthma, rheumatoid arthritis and many other diseases.<sup>17</sup> They are the preferred adulterant due to its rapid onset of action to relieve symptoms. However, the use of corticosteroids is not without risk. Side effects include musculoskeletal effects such as osteoporosis, avascular necrosis and risk of pathological fracture. It also causes cardiovascular complications such as hypertension, impaired glucose tolerance or diabetes, hyperlipidaemia and hypercoagulability.

Corticosteroids affect behaviour and mood with the risk of depression. It also causes peptic ulcer disease, immunosuppression and ophthalmological problems such as glaucoma and cataract. It was noted that sudden discontinuation of corticosteroids after prolonged use, could lead to adrenal insufficiency and adrenal crisis.<sup>5</sup>

Puan S consumed the dexamethasone and betamethasone laden herbal medicine for 3 months of unknown amount which has led to the development of Cushing's syndrome. Fortunately, she did not have any evidence of adrenal insufficiency as she discontinued the herbal medicine abruptly. She was prescribed the hydrocortisone to aide with the recovery of the HPA function.

## CONCLUSION

Use of complementary and alternative medicine is common in general as well as among patients with chronic diseases. Presence of corticosteroids in herbal medicine not only could cause Cushing's syndrome but is also other potentially dangerous side effects. Family physicians should be aware on the adulteration of complementary and alternative medicine. Hence, enquiry on use of herbal medicine is an essential component of patient assessment especially among patients with chronic diseases. Family physicians have a role to counsel and educate patients as consumers, to exercise vigilance when using complementary and alternative medicine.

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## Research Digest

### *Cranberry is as effective as trimethoprim for the prophylaxis of recurrent UTI*

**McMurdo MET, Argo I, Phillips G, *et al*. Cranberry or trimethoprim for the prevention of recurrent urinary tract infections? A randomized controlled trial in older women. *J Antimicrob Chemother*. 2009;63(2):389-95.**

137 women with recurrent UTI were randomized to receive either 500 mg of cranberry extract or 100 mg of trimethoprim for 6 months. The rate of recurrence of UTI and side effects were not statistically significant in both groups.