Chronic corticosteroid use causing insidious suppression of the hypothalamic-pituitary-adrenal axis with acute decompensation: A case of iatrogenic adrenal insufficiency

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Abstract
Glucocorticoids are used to treat many medical conditions commonly encountered in clinical practice; and is associated with many well-known adverse effects. Iatrogenic suppression of the hypothalamic-pituitary-adrenal axis occurs commonly with all forms of corticosteroids and may be easily missed. We present the case of a 62-year-old patient who presented with non-specific symptoms of: malaise, fatigue, anorexia, anaemia, and weight loss following an elective orthopaedic surgery. After receiving packed red cells, the patient did not have significant symptomatic improvement. A short corticotropin stimulation test confirmed hypoadrenalism, and the patient improved following a therapeutic trial of hydrocortisone. It was later discovered that the patient was receiving regular intra-articular corticosteroid for osteoarthritis from a private family practitioner. This case highlights the importance of searching for potential iatrogenic corticosteroid exposure in high risk patients; and having a low index of suspicion for hypoadrenalism in patients with non-specific symptoms that cannot be otherwise explained. Early recognition of hypoadrenalism can be lifesaving, especially during periods of physiological stress.

Introduction
A recent Systematic Review and Meta-Analysis found that iatrogenic suppression of the hypothalamic-pituitary-adrenal axis occurs frequently with the use of corticosteroids in clinical practice. All routine routes of administration, dosing, and treatment durations were implicated after rigorous criteria were applied to ensure only high-quality studies were included in the analysis. Iatrogenic adrenal suppression was usually mild and insidious but early recognition and management of severe adrenal insufficiency can be lifesaving [1, 2].

Case Report
A 62-year-old female, with a history of type 2 diabetes, hypertension, osteoarthritis, and chronic kidney disease, presented with anorexia, nausea, malaise, and weight loss of 9 Kg over the preceding six weeks. She described being: “unable to recover” following successful right knee replacement surgery six weeks before presentation. There was no pain, swelling or redness of the right knee and her orthopaedic surgeon reassured her. She denied fever, altered bowel habit, melena and haematemesis. She was taking her usual medications: basal insulin, sitagliptin 50mg once daily, simvastatin 40mg once daily, nifedipine 20mg twice daily, bendroflumethiazide 2.5 mg once daily, lisinopril 10mg once daily, aspirin 81mg once daily, omeprazole 20mg once daily, calcium and vitamin D supplement. She denied tobacco and ethanol use. She is a house wife and has been unable to function at home as she did before undergoing the surgery.

Examination revealed conjunctival pallor, blood pressure 126/75 mmHg and pulse 103 beats per minute. Examination of her heart, lungs, and abdomen were unremarkable. Her right knee was unremarkable. Her haemoglobin was 8.6mg/dl (baseline 11.5 mg/dl) but normochromic and normocytic. Her electrolytes were normal, but her creatinine was elevated 1.6 mg/dl (1.3 mg/dl one year previously). A provisional diagnosis of symptomatic anaemia was made, and the patient was admitted and transfused 2 units of packed cells. The
following day there was no significant improvement in her symptoms despite an expected rise in her haemoglobin. On closer examination: the patient was noted to have very thin skin with scattered petechiae, which raised the clinical suspicion of corticosteroid exposure. Her drug history was revisited, and the patient denied any form corticosteroid therapy that she was aware of. A short corticotropin (250 µg) stimulation test was conducted, and a therapeutic trial of hydrocortisone 100 mg administered intravenously every 8 hours was started. Within 24 hours of corticosteroid initiation, the patient reported significant symptomatic improvement and was able to enjoy her breakfast. There was no evidence of bleeding and her haemoglobin remained stable post transfusion. She was discharged on a tapering dose of prednisolone on day three of admission.

One week later, the patient was doing well, her appetite had returned to normal, and her mobility was increased. The corticotropin stimulation test result was consistent with adrenal insufficiency: baseline serum cortisol 1.1 µg/dL and 60 minutes post corticotropin 9.4 µg/dL (normal > 20 µg/dL). After initially denying steroid use, the patient reported having three-monthly intra-articular corticosteroid injections for osteoarthritis of the knees for the past ten years. She was given a steroid treatment card, to alert any future health care providers of her history of steroid exposure, and she was thought "sick day rules". Her prednisolone was tapered off over four weeks, and she was given a supply to keep handy for periods of intercurrent illness. She was scheduled for routine three-monthly follow up.

Discussion
Physicians should have a high index of suspicion for adrenal insufficiency in patients who have non-specific and unexplained symptoms; and in acutely ill patients who are not responding to appropriate treatment or resuscitation.

Patients on corticosteroid treatment of any form are at risk of adrenal insufficiency; clinical clues that may suggest corticosteroid exposure include a history of medical conditions commonly treated with corticosteroids: asthma, arthritis, inflammatory bowel disease, and rheumatological diseases [1-4]. Additionally, patients often acquire potent topical corticosteroids, sometimes without prescription, for a variety of dermatological conditions, and are largely unaware of the systemic complications [5]. In the authors’ experience, and in other developing countries, corticosteroid misuse is a major public health issue [6].

Patients may have subtle clinical features of steroid excess such as central obesity, hyperglycaemia, hypertension, and osteoporotic fractures. However, some of these signs may be overlooked because of phenotypic overlap with the commonly encountered metabolic syndrome [3, 6]. The presence of thin and easily bruised skin, in our experience, is a commonly missed sign of corticosteroid use (see image 1A and 1B) that can be easily detected [8, 9].
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Figure 1 A. Photograph showing the thin skin of the hands of a patient with Crohn’s disease, taking oral corticosteroids for disease relapse.
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Adrenal insufficiency can be diagnosed by a history, physical examination, and biochemical testing such as the corticotropin stimulation test. As demonstrated in our patient’s case, a therapeutic trial of corticosteroids used appropriately can be diagnostic, as the improvement is usually dramatic. When adrenal insufficiency occurs from chronic iatrogenic steroid use it is not known how long the hypothalamic-pituitary-adrenal axis will take to recover fully nor the optimal duration of steroid replacement required. Some patients maybe well during normal conditions but are unable to cope with acute physiological stress or illness [10]. Patient education and steroid cover during periods of physiological stress may avoid precipitation of an adrenal crisis.

Conclusion
Iatrogenic adrenal suppression is common in clinical practice and can be missed if physicians do not have a high index of suspicion. Features of corticosteroid exposure can be subtle and thin easily bruised skin can be a useful sign of corticosteroid excess. Patients maybe well but develop relative adrenal insufficiency during periods of acute stress and intercurrent illness; early recognition and administration corticosteroids can be lifesaving.

References
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