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Case Report

Transient adrenal insufficiency following treatment of rheumatoid arthritis with intramuscular methylprednisolone acetate

Alisa Angus, Emily E. Giles, Olayinka A. Ogundipe*

Department of Medicine of the Elderly, Royal Infirmary of Edinburgh, Edinburgh, Scotland

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***Correspondence:**
Dr. Olayinka A. Ogundipe,
Email: ola_ayodele@hotmail.com

ABSTRACT

An 82-year-old woman presented with dizziness, a fall, and pubic fractures. She had resting severe hypertension, with marked orthostatic hypotension. She was recently diagnosed with cyclic citrullinated peptide (+) rheumatoid arthritis. She had received 120 mg intramuscular methylprednisolone (Depo-Medrone®) eight months prior, and a second dose a day preceding hospitalisation. Two days into the admission, her Glasgow coma scale (GCS) score dropped acutely from 15/15 (E4;V5;M6) to 3/15 (E1;V1;M1). The initial differential diagnoses were: an acute stroke (a total anterior circulation syndrome-TACS or brainstem stroke), opiate toxicity (fracture pains), and possible unwitnessed seizure (in a post-ictal state). Urgent computerised tomography (CT) brain was unremarkable. She had an acute-on-chronic hyponatraemia (nadir 121 mmol/L) while on long-term proton pump inhibitor therapy, and hyperkalaemia (peak 5.8 mmol/L). Initial management included intravenous (IV) naloxone, fluids and diazepam with poor clinical response. Due to persistent low GCS, the admitting team were concerned about a potentially guarded prognosis. However, based on the history of recent high dose steroid injections, plus the evolving clinical picture and abnormal biochemistry, empirical treatment was started (IV hydrocortisone 100 mg QDS and 0.9% saline infusion) for possible adrenal insufficiency. An 'add-on' request for random serum cortisol was made to her admission bloods, and returned low (33 nmol/L). With treatment, her GCS improved rapidly from 3/15 to 15/15. A subsequent planned short synacthen test was abnormal (cortisol level pre-synacthen 100; 30min post-synacthen 340), suggestive of adrenal insufficiency. Following consultation with endocrinology, she was maintained on oral hydrocortisone 10 mg (am)/5 mg(teatime) with sustained clinical improvement.

Keywords: Addisonian crisis, Addison's disease, Adrenal suppression, Adverse drug reaction, Depo-Medrone, Methylprednisolone

INTRODUCTION

An Addisonian crisis (AC) is a life-threatening illness precipitated by a lack of glucocorticoid production and/or release by the adrenal glands.[1,2] The effects of this typically/classically manifest in the form of a haemodynamically unstable patient. Consequently, it is essential for clinicians to recognise and treat the condition promptly. Treatment in the acute phase normally includes intravenous (IV) hydrocortisone and parenteral fluid resuscitation. An AC is the emergency presentation of the progenitor condition, AD or due to adrenal insufficiency (AI).[1-5] AI itself may be primary (adrenal gland dysfunction). Adrenal suppression may also be of iatrogenic nature, e.g., arising after the administration of high dose exogenous steroids.[1,2]

This case report describes a delayed and retrospective diagnosis of an AC in an older woman. She had received a first dose of 120 mg intramuscular (IM) methylprednisolone (Depo-Medrone®) eight months prior, as part of treatment for seropositive (cyclic

citrullinated peptide-CCP) rheumatoid arthritis. She presented acutely to hospital with dizziness and a fall, which occurred within 24 hrs of receiving a second (interval) dose of IM (Depo-Medrone®). During the initial 48hrs of her admission, her symptoms and signs evolved rapidly, and were suggestive of a state of acute AI. However, and unusually, she was observed to have markedly high blood pressure, which the initial admitting clinicians had noted to be out of keeping with the contrasting hypotension that is more commonly/typically observed in patients with an AC.

The report serves as a clinical reminder to still consider the possibility of AI and AC in patients presenting with reduced consciousness i.e., despite the presence of high blood pressure readings or hypertension. The report also highlights the need for clinicians to be mindful of the rough dose equivalents of (commonly used) steroids, and where relevant a reminder to consider the need to taper or wean steroid courses due to the risk of patients developing secondary AI.

CASE REPORT

An 82-year-old woman was admitted to the medical assessment unit following a fall at home. The fall was preceded by dizziness but no loss of consciousness. On admission, she had right pelvic pain and plain radiography noted fractures to the right superior and inferior pubic rami.

Prior to admission, she lived in supported accommodation where she received twice daily carer visits to assist with her basic and extended activities of daily living. She drank minimal alcohol and was a non-smoker. Her weight was 72.8 kg, height 1.56 metres, and body mass index (BMI) 23.61.

Her medical history was notable for previous Grave's disease, ulcerative colitis, essential hypertension, osteoporosis, restless legs syndrome and rheumatoid arthritis (RA). There was no history of malignancy.

Medications on admission were: folic acid 5 mg daily (except on the day of taking her weekly methotrexate), methotrexate 25 mg once weekly, pramipexole 88 micrograms nocte, lansoprazole 15 mg daily, paracetamol 1 g three times daily, ferrous fumarate 210 mg once on alternative days, fybogel effervescent granules - one sachet daily. She had a documented allergy to trimethoprim.

Clinical examination noted an admission GCS of 15/15, temperature 35.1°C, pulse 76 bpm, BP 186/105 mmHg, respiratory rate 16/min, and oxygen saturation 97% breathing air. Random capillary blood sugar was 10.9.

Her admission blood profile noted a mild normocytic anaemia, with haemoglobin 99 g/L (Ref: 115-160) and mean corpuscular volume 90 fL (Ref: 78-98). She had normal white cell and platelet counts, estimated glomerular filtration rate (eGFR), liver function tests, laboratory blood sugar, serum calcium and phosphate. Her serum 25-OH vitamin D level was <24. (Ref: deficiency ≤ 24; insufficiency 25-49; normal ≥ 50). Thyroid function tests (TFTs) were normal, as was serum parathyroid hormone (PTH) 3.6 pmol/L (Ref: 1.6-6.9). Her serum urea and electrolytes noted an acute-on-chronic hyponatraemia (nadir 121 mmol/L) while on a proton pump inhibitor-PPI therapy (lansoprazole), and hyperkalaemia (peak 5.8 mmol/L). Previous immunology (tested one year prior), demonstrated cyclic citrullinated peptide (CCP) 117 U/ml (Ref 0 - 10); and negative screens for anti-nuclear antibody (ANA) and extractable nuclear antigen (ENA) antibodies.

Resting 12 lead electrocardiogram (ECG) showed sinus rhythm, borderline PR interval, Q waves in V1 and V2, and voltage criteria of left ventricular hypertrophy. Initial chest radiograph was unremarkable.

Due to reduced mobility, she started graded physiotherapy. She received short-term oxycodone hydrochloride oral solution 1mg three times daily for acute pain, and subcutaneous dalteparin 5,000 units once daily for prevention of venous thromboembolism. On account of the hyponatraemia, the PPI (lansoprazole) was changed to an H2 receptor blocker, oral famotidine 20 mg daily. The vitamin D deficiency was replaced with oral Invita D3-25,000 units once weekly x three doses, and then maintained on oral Accrete D3 - one tablet twice daily. Oral macrogol 3350 one sachet daily and oral senna 15 mg at night were added for opiate-associated constipation.

Two days into her admission, her GCS dropped unexpectedly, from 15/15 to 3/15 (E1;V1;M1). Trial of uptitrated doses of intravenous (IV) naloxone (for possible opiate toxicity) showed no notable clinical improvement. Another postulate from the admitting team was that she could have had a possible unwitnessed generalised seizure, and be in a prolonged post-ictal state. An urgent computerised tomography (CT) brain was unremarkable. Due to poor resolution of her reduced consciousness, the admitting team prepared her family that this might be a terminal event due to an acute cerebrovascular event (e.g., a total anterior circulation syndrome-TACS or brainstem infarct) which was possibly not yet evident on CT imaging. The patient was moved from the acute medical admissions unit to a side room on a medicine of the elderly (MoE) ward to support a presumed period of transition into end-of-life care.

Shortly after arrival on the ward, her condition was re-evaluated by a consultant physician in MoE. Based on the revisited history (of high dose steroid injections for rheumatoid arthritis), combined with the acute and evolving clinical picture (dizziness, fall, acute drop in GCS), and abnormal blood results (hyponatraemia and hyperkalaemia), and despite the noted high blood pressure readings, the patient was immediately fluid resuscitated and administered IV hydrocortisone 100mg STAT, and then the latter continued four times daily. These measures

resulted in a rapid clinical recovery. By the next morning (~ 15 hrs after x three initial doses of IV steroid injections), she had returned to GCS 15, and was sitting out of bed having her breakfast. A random serum cortisol level was retrospectively added to her admission bloods, and this returned low at 33 nmol/L (Ref: 200-700 for a morning sample; 50-250 for an evening sample). This was interpreted as being suggestive of a possible AI state, and presenting with AC.

The endocrinology team was consulted and a planned short synacthen test (SST) arranged using 250 micrograms of injectable synthetic adrenocorticotropic hormone-ACTH. The SST demonstrated a suboptimal response: serum cortisol levels pre-synacthen 100; 30 minutes post-synacthen 340. Serum adrenal cortex antibodies were subsequently checked and returned negative; making autoimmune adrenal insufficiency (AD) unlikely. Following clinical improvement with treatment (~ 48 hrs of IV hydrocortisone four times daily), her prescription was switched to oral hydrocortisone 50mg four times daily. This was then gradually weaned down to 50mg twice daily. During her period of admission, her peak BP was recorded as 243/106 mmHg, possibly influenced by the fracture pain. Her pre-discharge BP showed some improvement to 169/71 mmHg. At discharge from the medicine of elderly ward, she prescribed a maintenance dose of oral hydrocortisone, 10 mg in the morning and 5 mg in the evening, having been medically well on this regimen. Follow-up was coordinated via an endocrinology clinic where she noted to remain well a few months later.

DISCUSSION

AD, AI, AS, and AC

Thomas Addison is cited as having described what we have subsequently come to consider as primary adrenal (adrenocortical) insufficiency (AI).[1-5] Some now believe the aforementioned to be a likely case of what we now term autoimmune AD. In AI, there is dysfunction or reduced adrenal function due to impaired synthesis and/or release of cortisol (a glucocorticoid). In addition, this state might be associated with inadequate production and/or secretion of aldosterone (a mineralocorticoid), and in some instances could also involve under-production/-release of adrenal androgen (DHEA-dehydroepiandrosterone).[1,2]

AI may be termed 'primary' when the underlying dysfunction affects the adrenal cortex e.g., as in AD.[1.2] Adrenal suppression (AS) may also be of iatrogenic nature e.g., following the administration of high dose exogenous steroids, which is the suspected mechanism in our patient. AI may be termed 'secondary' when the issues stem from pituitary disease e.g., reducing adrenocorticotropic hormone-ACTH synthetic function and/or secretion. The latter in sequence may result in the under-production/-secretion of cortisol and/or DHEA. 'Tertiary' forms of AI could arise in the context of dysfunction of the hypothalamic axis causing reduced corticotropin-releasing hormone (CRH) production and/or release. A lack of CRH could in sequence cause diminished production of ACTH. Some have used the term 'central' to describe both secondary and tertiary forms of AI.[1,2]

An adrenal or AC is an acute and potentially life-threatening illness triggered or precipitated by a deficiency of glucocorticoid hormone production and/or release from the adrenal glands.[1,2] Therefore, patients with AD, AI, or AS may be at risk of presentations with AC.[6] The clinical manifestation and effects of this (AC) would classically/typically be in the form of a haemodynamically challenged or unstable patient. Patients with AC may also present with a range of biochemical abnormalities e.g., hyponatraemia, hyperkalaemia, hypoglycaemia, etc. One limitation to interpreting the index clinical scenario was the observation that she was concurrently taking long-term PPI therapy, which may also result in hyponatraemia.[7] Due to the potential for sudden clinical deterioration and death, it is vital that clinicians recognise and treat the condition (AC) promptly and appropriately. In the acute phase, treatment mainly includes IV hydrocortisone and parenteral fluid resuscitation. In the index case, we postulate that possible AS preceded the AC event, and that this may have been of iatrogenic nature. The administration of high dose exogenous steroids may have been a trigger-event for transient AS. Latter possibly aggravated by subsequent AI and AC in the context of acute stressor events (flare up of her chronic CCP seropositive RA, a fall, and painful pelvic fractures-all occurring simultaneously in physically frail older woman).

Hypertension in AI

Classically, patients presenting in AC are observed to have low (or possibly 'normal range') blood pressure readings. However, our patient was profoundly hypertensive on admission (BP 186/105 mmHg; and later peaking at BP 243/106 mmHg). Such high and atypical blood pressure patterns could potentially mislead clinicians to rationalise that they can 'exclude' an AC from their differential diagnoses. However, this case presentation cautions against this assumption, and emphasises the need to consider exceptions and atypical presentations of AC.

Other than her longstanding history of essential hypertension, no additional driver(s) for the index case's hypertension was confidently identified. However, it is perhaps also noteworthy that orthostatic hypotension is a recognised clinical sign of AI. On examination, she did not have Cushingoid features. There was no evidence to suggest the presence of secondary hypertension due to chronic kidney disease, active hyperthyroid disease or a vasculitis. Of note, her Grave's disease was historic, she was no longer taking oral carbimazole, and her TFTs were normal during the admission period. Due to the presence of orthostatic hypotension and an associated falls risk, the patient had not been routinely taking anti-hypertensive medication prior to admission. Therefore, we considered the likely cause of her persistent hypertension to be

untreated primary hypertension. The aforementioned view was supported by her admission ECG features indicative of left ventricular hypertrophy. In addition, we considered the possibility that factors such as acute fracture pain, and/or the 'white coat effect/phenomenon' may have also played a part in her elevated blood pressure readings.

Methylprednisolone acetate: some basic pharmacodynamic and pharmacokinetic considerations

In the index case, the patient had received IM Depo-Medrone® on two occasions prior to this acute presentation. More commonly known by the generically named content of methylprednisolone acetate, Depo-Medrone® is a glucocorticoid which is administered IM. In this formulation, it is usually prescribed for patients with certain arthropathies or rheumatological disorders, including RA. Our patient had RA, and this was being managed by a rheumatologist on an outpatient basis. She had received 120 mg Depo-Medrone® eight months prior to this acute presentation (the equivalent of ~ 150mg of prednisolone or ~ 600 mg of hydrocortisone). She had received her second 120mg dose of the Depo-Medrone® on the day prior to admission. The clinical suspicion was that this might have resulted in a state of transient AS, and paradoxically predisposing her to AC as the toll of the recent stressor events (flare up of seropositive RA, a fall and acute fracture pain in a frail older patient).

Table 1 illustrates a rough equivalency of some of the commoner glucocorticoids, in terms of their anti-inflammatory effects, and reflected in comparison to a dose of prednisolone 5 mg.[8] The table equivalency does not take account of the named drugs' mineralocorticoid effects, neither does the table take account of the variations in the duration of action of the individual steroids.[8]

Application of ADR causality assessment systems (CAS) to the index case

As part of pharmacovigilance case reporting and clinical assessments, the use of validated CAS may augment transparency of classifications, and could improve the objectivity of reporting suspected cases of ADR. In the index case, applying the Naranjo adverse drug reaction probability scale (Table 2) equates to a score of 4.[9-11] This translates into a 'possible' ADR classification. Applying an alternative validated CAS such as the WHO-UMC method (Table 3) to this index report derives a classification of 'probable' ADR.[12]

Table 1: Adapted to show equivalency of anti-inflammatory doses of corticosteroids.[8]

S. no.	Drugs
1	Prednisolone 5 mg ≅
2	Betamethasone 750 micrograms
3	Deflazacort 6 mg
4	Dexamethasone 750 micrograms
5	Hydrocortisone 20 mg
6	Methylprednisolone 4 mg
7	Prednisone 5 mg
8	Triamcinolone 4 mg

Table 2: Naranjo ADRS algorithm.[9]

S. no.	Questionnaire applied to the index case report
1	Are there previous conclusive reports on this reaction?
	Yes (+1) No √ (0) Do not know or not done (0)
2	Did the adverse event appear after the suspected drug was given?
	Yes √ (+2) No (-1) Do not know or not done (0)
3	Did the adverse reaction improve when drug was discontinued or a specific antagonist was given?
	Yes √ (+1) No (0) Do not know or not done (0)
4	Did the adverse reaction appear when the drug was re-administered?
	Yes (+2) No (-2) Do not know or not done √ (0)
5	Are there alternative causes that could have caused the reaction?
	Yes (-1) No (+2) Do not know or not done √ (0)
6	Did the reaction reappear when a placebo was given?
	Yes (-1) No (+1) Do not know or not done √ (0)
7	Was the drug detected in any body fluid in toxic concentrations?
	Yes (+1) No (0) Do not know or not done √ (0)
8	Was the reaction more severe when the dose was increased/ less severe when dose was decreased?
	Yes (+1) No (0) Do not know or not done √ (0)
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?
	Yes (+1) No √ (0) Do not know or not done (0)
10	Was the adverse event confirmed by any objective evidence?
	Yes √ (+1) No (0) Do not know or not done (0)

Interpretation: > 9=definite ADR; 5-8=probable ADR; 1-4=possible ADR; 0=doubtful ADR.

Table 3: WHO-UMC causality categories.[12]

Causality term	Causality term assessment criteria*
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake
	Cannot be explained by disease or other drugs
	Response to withdrawal plausible (pharmacologically, pathologically)
	Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon)
	Rechallenge satisfactory, if necessary
Probable/ likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake
	Unlikely to be attributed to disease or other drugs
	Response to withdrawal clinically reasonable
	Re-challenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake
	Could also be explained by disease or other drugs
	Information on drug withdrawal may be lacking or unclear
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
	Disease or other drugs provide plausible explanations
Conditional/ unclassified	Event or laboratory test abnormality
	More data for proper assessment needed, or
	Additional data under examination
Unassessable/ unclassifiable	Report suggesting an adverse reaction
	Cannot be judged because information is insufficient or contradictory
	Data cannot be supplemented or verified

(WHO. The Upsalla monitoring centre-UMC); *All points should be reasonably complied with.

CONCLUSION

This report describes the case of an older female patient who developed features of adrenal insufficiency after receiving a high dose of IM methylprednisolone (Depo-Medrone®) as part of treatment for seropositive rheumatoid arthritis.

The report describes a practical clinical learning point or lesson that may be of relevance to clinicians across multiple specialties e.g., general practitioners or family medicine, or hospital-based speciality doctors (e.g., emergency medicine, acute medicine, general internal medicine, rheumatology, geriatric medicine, rehabilitation medicine, etc). The case may also be of interest to other non-medical prescribers/ clinicians practising in extended capacities: such as non-medical prescribers of nursing, pharmacy/physician assistant/associate backgrounds.

Also, to augment the practice of pharmacovigilance, prescribers are encouraged to use ADR reporting systems and CAS that are affiliated with their specific areas of practice.

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