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Case Report

COVID-19 vaccination: a possible trigger for Addisonian crisis in a patient with Addison's disease

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ABSTRACT

Infection with COVID-19 disease is caused by the SARS-CoV-2 virus. Following its identification, the pursuit of the rapid development of effective vaccines became a pandemic-period international public health priority. This report describes the case of an older woman with Addison's disease who developed acute clinical symptoms and signs indicative of an Addisonian crisis following each of two consecutive doses of the Pfizer BioNTech Covid-19 vaccines. Both presentations (with nausea, vomiting, hypotension, tachycardia, and transient hypoglycaemia) occurred within 24 hours of receipt of the vaccines. In each instance, she responded well to treatment with intravenous fluids, and temporarily changing her maintenance oral steroid regimen to higher dose intravenous steroids. She successfully completed a period of rehabilitation and was discharged home. Some pharmacokinetic and pharmacodynamic considerations of the Pfizer BioNTech COVID-19 vaccines are discussed. An overview is presented of Addison's disease and Addisonian crisis. The discussion also applies two causality assessment systems to derive a classification of 'probable' adverse drug reactions for the index case report.

Keywords: Addison's disease, Addisonian crisis, Adverse drug reaction, COVID-19, Pharmacovigilance, Vaccination

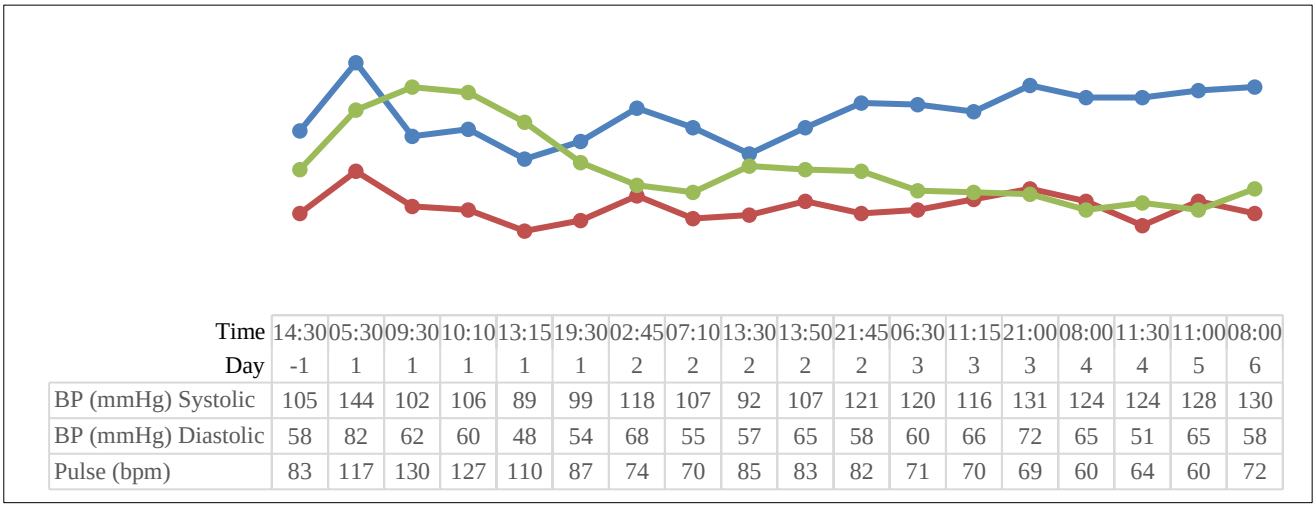
INTRODUCTION

COVID-19 disease is caused by infection with the SARS-CoV-2 virus.[1] In the pandemic period following its identification, the pursuit of the rapid development of effective human vaccines became an international public health priority. Since then, a range of effective vaccines have been successfully developed and introduced for use in mitigating the risk and severity of infection from COVID-19.[1] The world health organization (WHO) cites the safety of a number of the COVID-19 vaccine deployed for use, although there is also acknowledgement of some commoner and often minor side-effects (e.g., arm soreness, mild fever, tiredness, headaches, muscle or joint aches).[1] With some of the COVID-19 vaccines options, there has also been incremental recognition of the occurrence of significantly rarer, but potentially more serious side-effects or adverse reactions (e.g., arterial thrombosis, cerebral venous sinus thrombosis, thrombocytopenia, thromboembolism, venous thrombosis, etc).[2] In this case report, we describe further, but likely very rare clinical events/episodes, in which an adult female patient with well-controlled Addison's disease developed acute features indicative of an Addisonian crisis after she received each of two planned and successive COVID-19 vaccinations.

CASE REPORT

A 67-year-old woman was admitted to hospital following a fall. She sustained right pubic rami and right hemi-sacral fractures. These were managed non-operatively

with analgesia, physiotherapy and a plan for a period of inpatient rehabilitation. Prior to admission, she lived alone and was functionally independent with her activities of daily living. She drank minimal alcohol and was a non-smoker. Her weight was 72.8 kg, height 1.61 metres, and Body Mass Index (BMI) 28.09. Her medical history was notable for autoimmune Addison's disease, autoimmune hypothyroidism (Hashimoto's thyroiditis), bipolar affective disorder, Horner's syndrome, rheumatoid arthritis, osteoporosis, and ulcerative colitis. There was no history of malignancy.



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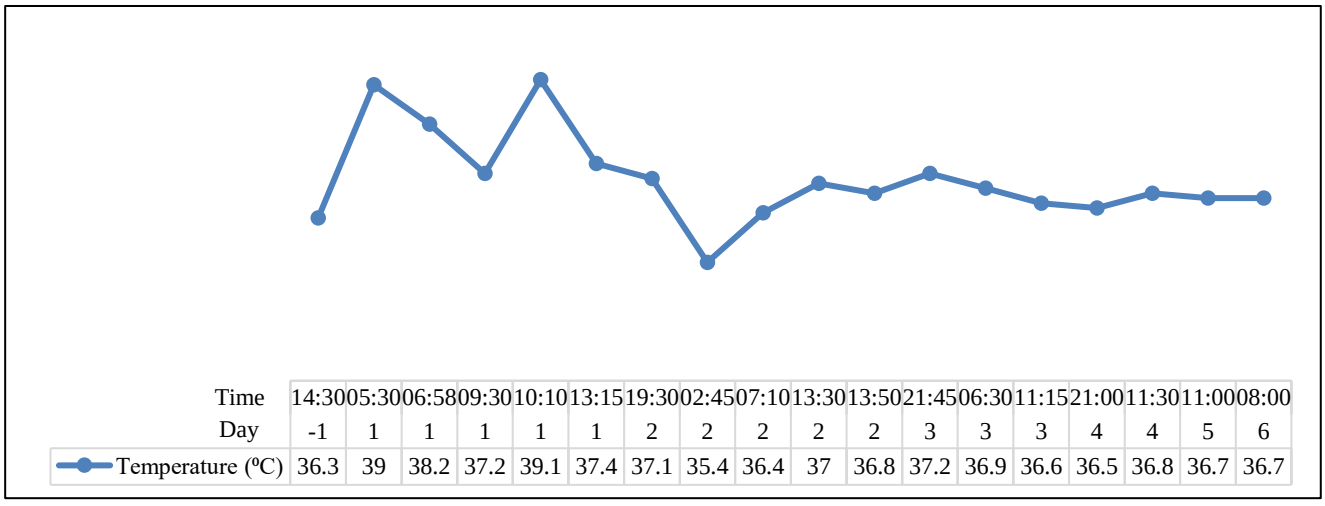
Day	-1	1	1	1	1	1	2	2	2	2	2	3	3	3	4	4	5	6
BP (mmHg) Systolic	105	144	102	106	89	99	118	107	92	107	121	120	116	131	124	124	128	130
BP (mmHg) Diastolic	58	82	62	60	48	54	68	55	57	65	58	60	66	72	65	51	65	58
Pulse (bpm)	83	117	130	127	110	87	74	70	85	83	82	71	70	69	60	64	60	72

Figure 1: Record of clinical observations (blood pressure and pulse) during episode 1.



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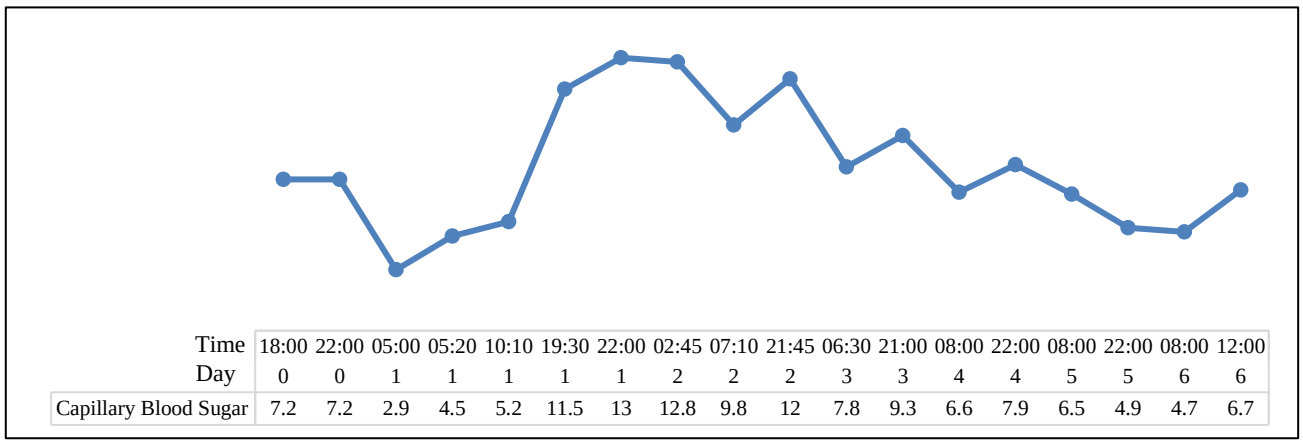
Day	-1	1	1	1	1	1	2	2	2	2	2	3	3	3	4	4	5	6
Temperature (ºC)	36.3	39	38.2	37.2	39.1	37.4	37.1	35.4	36.4	37	36.8	37.2	36.9	36.6	36.5	36.8	36.7	36.7

Figure 2: Record of clinical observations (temperature) during episode 1.

Medications on admission were: adcal-D3 1 caplet twice daily, alendronic acid 70 mg tablet weekly, fludrocortisone tablet 100 micrograms daily, folic acid 5 mg tablet weekly, hydrocortisone tablets 15 mg (morning)/5 mg (afternoon)/ 5 mg (evening), lansoprazole oro-dispersible tablet 30 mg daily, levothyroxine 125 micrograms tablet daily, methotrexate 15 mg subcutaneously (SC) weekly, quetiapine 100 mg tablet daily, sodium valproate enteric coated (EC) tablet 500mg twice daily, sulfasalazine EC tablet 500mg daily, and venlafaxine modified release (MR) tablet 75mg daily. She had no documented allergies. Following her fractures, she was also prescribed analgesics. The latter included oral paracetamol 1 gram four times daily (regular use), oxycodone MR tablet 5mg twice daily (short-term regular use), and oxycodone 5mg immediate release capsule ('as required' use for breakthrough pain). In addition, due to reduced mobility she was prescribed venous thromboembolism prophylaxis with SC dalteparin 5,000 units once daily. Her admission blood profile was unremarkable for full blood count, urea and electrolytes, estimated glomerular filtration rate (eGFR), liver function tests, serum calcium and phosphate. Thyroid function tests indicated optimal supplementation. Her serum 25-OH vitamin D level was mildly insufficient at 44 nmol/l (deficiency ≤24; insufficiency 25-49; normal ≥50).



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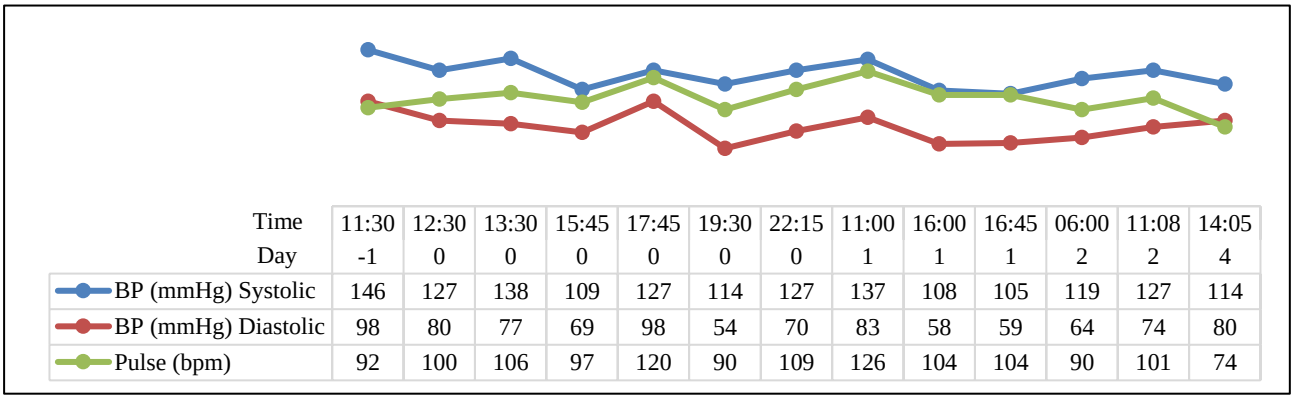
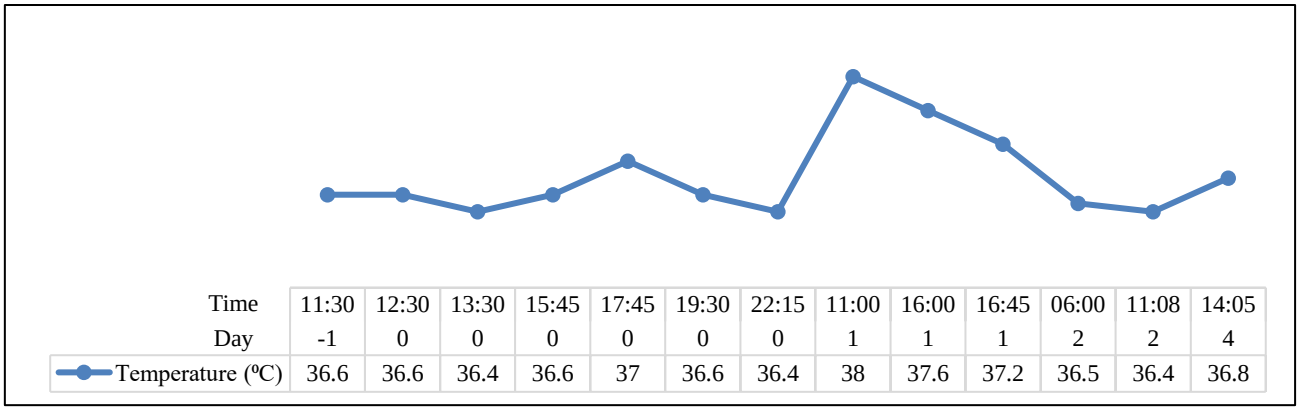
Day	0	0	1	1	1	1	1	2	2	2	3	3	4	4	5	5	6	6
Capillary Blood Sugar	7.2	7.2	2.9	4.5	5.2	11.5	13	12.8	9.8	12	7.8	9.3	6.6	7.9	6.5	4.9	4.7	6.7

Figure 3: Record of capillary blood sugar readings (in mmol/l) during episode 1.



Time	11:30	12:30	13:30	15:45	17:45	19:30	22:15	11:00	16:00	16:45	06:00	11:08	14:05
Day	-1	0	0	0	0	0	0	1	1	1	2	2	4
BP (mmHg) Systolic	146	127	138	109	127	114	127	137	108	105	119	127	114
BP (mmHg) Diastolic	98	80	77	69	98	54	70	83	58	59	64	74	80
Pulse (bpm)	92	100	106	97	120	90	109	126	104	104	90	101	74

Figure 4: Record of clinical observations (blood pressure and pulse) during episode 2.



Time	11:30	12:30	13:30	15:45	17:45	19:30	22:15	11:00	16:00	16:45	06:00	11:08	14:05
Day	-1	0	0	0	0	0	0	1	1	1	2	2	4
Temperature (ºC)	36.6	36.6	36.4	36.6	37	36.6	36.4	38	37.6	37.2	36.5	36.4	36.8

Figure 5: Record of clinical observations (temperature) during episode 2.

Resting 12 lead electrocardiogram (ECG) showed an unremarkable trace in sinus rhythm. Initial chest radiograph was unremarkable. A week into her acute hospital admission, she contracted a presumed nosocomial COVID-19 infection. This was associated with clinical and radiological features of COVID-19 pneumonitis. Her condition deteriorated with an increased oxygen requirement. This required escalation of her clinical care from a general medical ward to an intensive care unit (ICU). Care in the ICU included high flow nasal oxygen (HFNO for hypoxia), a course of oral dexamethasone 6 mg once daily for ten days (for COVID-19 disease), intravenous (IV) amoxicillin (for possible co-existing bacterial pneumonia), paracetamol (anti-pyretic and analgesic), oxycodone (analgesic), and ongoing SC dalteparin (venous thromboembolism prophylaxis). Her usual oral fludrocortisone (a potent mineralocorticoid; weak corticosteroid) was continued during this acute period. Rather than doubling her usual oral hydrocortisone doses (a glucocorticoid) to cover for the period of the acute illness, this was temporarily withheld by the clinical team in ICU on the advice of an

Endocrinologist. This decision was based on the premise that she was adequately covered, in the short term, by the afore-mentioned oral dexamethasone as it also possesses potent glucocorticoid properties.

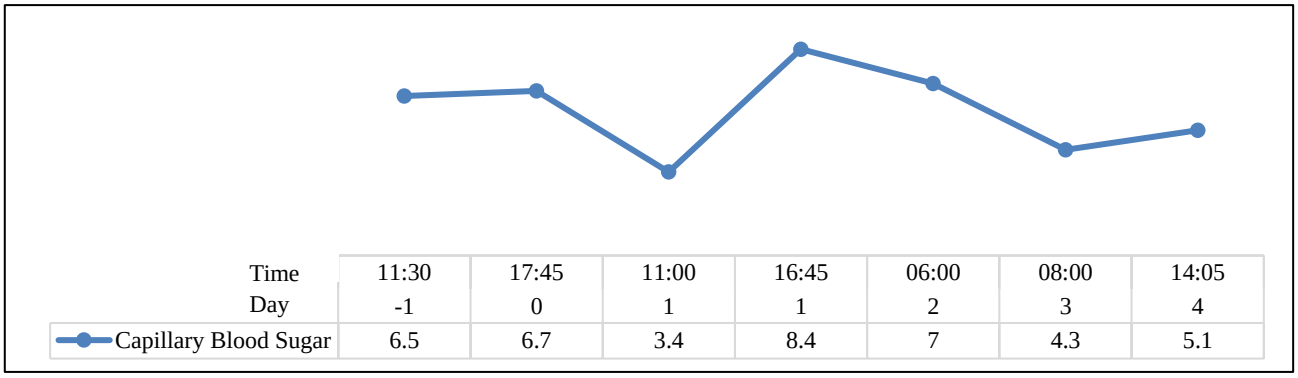


Figure 6: Record of capillary blood sugar readings (in mmol/l) during episode 2.

Over a two-week period, she slowly recovered from the COVID-19 infection. She was stepped down from the ICU to a general medical ward within the acute hospital. After a further two-week period, she was judged to be clinically well enough for transfer to an off-site, non-acute, community-based rehabilitation hospital.

Table 1: Naranjo ADRS algorithm.[21]

Questionnaire applied to the index case report
Are there previous conclusive reports on this reaction? **Yes (+1) No ✓ (0) Do not know or not done (0)**
Did the adverse event appear after the suspected drug was given? **Yes ✓ (+2) No (-1) Do not know or not done (0)**
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? **Yes ✓ (+1) No (0) Do not know or not done (0)**
Did the adverse reaction appear when the drug was re-administered? **Yes ✓ (+2) No (-2) Do not know or not done (0)**
Are there alternative causes that could have caused the reaction? **Yes ✓ (-1) No (+2) Do not know or not done (0)**
Did the reaction reappear when a placebo was given? **Yes (-1) No (+1) Do not know or not done ✓ (0)**
Was the drug detected in any body fluid in toxic concentrations? **Yes (+1) No (0) Do not know or not done ✓ (0)**
Was the reaction more severe when the dose was increased or less severe when the dose was decreased? **Yes (+1) No (0) Do not know or not done ✓ (0)**
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)**
Was the adverse event confirmed by any objective evidence? **Yes ✓ (+1) No (0) Do not know or not done (0)**
> 9 = definite ADR
5 - 8 = probable ADR
1 - 4 = possible ADR
0 = doubtful ADR

During her period of rehabilitation, the opportunity arose for her to receive the Pfizer-BioNTech COVID-19 vaccine. Her first dose of the vaccine corresponded to five (5) weeks after the initial positive COVID-19 nasopharyngeal polymerase chain reaction (PCR) swab. She developed unanticipated adverse drug reactions (ADRs) after each administration of the COVID-19 vaccine. The first and second vaccination doses were thirty-three days apart. Each event presented with a cluster of acute features (nausea, vomiting, hypotension, tachycardia, and transient hypoglycaemia), and with the onset of symptoms starting within twenty-four hours of each dose.

Table 2: WHO-UMC causality categories.[24]

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

Neither episode involved stridor, bronchospasm, urticaria, angioedema, or other acute features to indicate anaphylaxis. The findings are presented as timeline graphic representations depicting her monitored observations (blood pressure; pulse; temperature) and her serial capillary blood sugar readings over the pre- and post-vaccination periods. The first COVID-19 vaccination period is depicted as episode 1 (Figure 1-3), and the 2nd COVID-19 vaccination period is depicted as episode 2 (Figure 4-6). For clarity in the figures, 'day -1' refers to the day prior to the vaccination, 'day 0' references the actual day of vaccination, and 'day 1/day 2/day 3/ etc' refer to the consecutive days after the vaccination.

Both ADR events/episodes responded to treatment with: a temporary switch of her usual oral hydrocortisone regimen to high dose IV hydrocortisone (commencing on day 1 of each episode for a total of 6 days during episode 1, and for a total of 2 days during episode 2). In addition, she received IV fluids and oral glucose/dextrose gel. During both episodes, her oxygen saturations were consistently maintained in the range of ≥92% to 97%, and she did not require supplemental oxygenation. During ADR event/episode 1, she received a longer course of IV steroid cover because she was also noted to have developed a pyrexia which peaked at 39.1°C on day 1 of episode 1 i.e., within twenty-four hours of the vaccination. She was treated with empirical antibiotics (IV co-trimoxazole and IV metronidazole) to cover for possible aspiration related chest infection arising during a period of associated mild hypoactive delirium and vomiting. She improved clinically, and as her blood cultures also later returned negative the antibiotics were stepped down to oral co-trimoxazole and oral metronidazole.

In line with our local hospital's guidance at that time, she was not subject to routine (repeat) nasopharyngeal PCR swabbing for up to ninety days post-Covid infection. This was because she had recently recovered from PCR-confirmed COVID-19 infection, and there was recognition that repeating the swabs in this period could return false positive results.

To safeguard her future clinical care, we created a cautionary 'ADR note' in her computerised hospital clinical records describing the two possible Addisonian crises events that occurred after the first and second COVID-19 vaccinations. In the event of booster COVID-19 vaccinations (if applicable in the future), we recommended a period of close monitoring. Furthermore, we proposed the consideration of additional oral hydrocortisone doses to cover periods around any further COVID-19 vaccinations.

In addition, members of the clinical team a pharmacist episode 1; a doctor episode 2 respectively completed formal online national pharmacovigilance ADR notification reports.

We provided written communication to her primary healthcare provider/ general practitioner (GP) to highlight the ADRs. Thereafter, she made steady and uneventful progress with the period of inpatient rehabilitation, and was discharged home.

DISCUSSION

COVID-19 and COVID-19 vaccines

In late 2019, the first reports of COVID-19 disease were identified following reports of patients presenting with severe respiratory infection in Wuhan City, China.[3] Lower respiratory samples taken from these patients were sequenced and demonstrated a novel coronavirus (SARS-CoV-2). In March 2020, the WHO declared a pandemic.[4] Symptoms of COVID-19 vary significantly, with about 1 in 5 infected patients thought to show no symptoms at all.[5]

The most frequently reported symptoms are new onset cough and fever. Others include headache, loss of smell or taste, lethargy, myalgia, rhinorrhoea, sore throat, diarrhoea, vomiting and confusion.[5] In some patients, disease progression, multiple organ failure and death will follow.[5] Some described risk factors include increasing age, male gender and comorbidities such as diabetes mellitus, obesity, cancer and poorly controlled asthma. Transmission of COVID-19 is primarily by person to person spread through respiratory aerosols, direct human contact, and contact with materials able to carry infection. After initial exposure, the incubation period is normally 5-6 days with maximum transmission occurring in the first week of illness.[5] Also, spread by symptomatic and pre-symptomatic (up to 48 hours prior to symptom onset) patients is considered more significant than asymptomatic transmission.[5] SARS-CoV-2 belongs to the family of Coronaviridae and genus Betacoronavirus.[5] Like other coronaviruses, SARS-CoV-2 is an RNA virus which encodes four major structural proteins. Of these, the S (spike) glycoprotein is the main antigenic target. Of four vaccines approved in the UK which target the S protein, two use a nucleoside-modified messenger RNA (mRNA) platform and two use an adenovirus vector.[5]

The patient in the index report received the Pfizer-BioNTech COVID-19 vaccine (Comirnaty®). This an mRNA vaccine which has been described as being generated entirely in vitro and formulated in lipid nanoparticles, enabling delivery of the non-replicating RNA into host cells.[5,6] The mRNA vaccines use the pathogen's genetic code as the vaccine which then exploits the host cells to translate the code and make the target spike protein. The immune response is stimulated by the protein acting as an intracellular antigen. Both a neutralising antibody and cellular immune response to the S antigen contribute to protection against COVID-19.[5] The manufacturer recommends that Pfizer-BioNTech COVID-19 vaccine be administered as an intramuscular injection into the deltoid muscle.[5] The standard dose of the Pfizer BioNTech COVID-19 vaccine is 30µg contained in 0.3ml of the diluted vaccine (using supplied 0.9% sodium chloride as the diluent). The Pfizer COVID-19 vaccine is generally well tolerated, and the most commonly reported (often mild & transient) adverse reactions include: injection site reactions (e.g., redness/swelling/pain), fatigue, headache, myalgia, arthralgia, chills, pyrexia, and diarrhoea.[2,6] Less commonly these may include lymphadenopathy, and even rarer still are reports of sporadic cases of possible post-vaccine myocarditis, pericarditis, Bell's Palsy, Guillain-Barre Syndrome (GBS), etc.[2,6] In this context, there is need for ongoing monitoring as the post-vaccine implementation phase continues, so as to better identify and delineate any possible associations to rare ADR reports and/or occurrences.[7]

Addison's disease (AD)

The Italian anatomist, Bartolomeo Eustachi is reported to have first described the adrenal glands in 1553.[8,9] We now understand the gland to be divided into a cortex and medulla.[10] We now also know that the adrenal cortex secretes steroids, namely mineralocorticoids from outside the zona glomerulosa, glucocorticoids from the zona fasciculata, and adrenal androgens from the zona reticularis.[10] The adrenal medulla is involved in neuroendocrine functioning, in relation to catecholamines and peptides.[10] It is now understood that the adrenal cortex is controlled by the hypothalamic–pituitary–adrenal axis (HPA) which modulates cortisol production, and the renin-angiotensin-aldosterone system (RAAS) which regulates aldosterone production.[10] It was not until 1855 that Thomas Addison reportedly described what later came to be known as the first case of primary adrenal (adrenocortical) insufficiency.[8-12] In the year 1856, Trousseau referred to adrenal insufficiency (AI) as 'bronze Addison's disease.[8] Over time, the aforementioned descriptions are now recognised to align with autoimmune Addison's disease. In AI, there is reduced adrenal function due to impaired creation/synthesis of cortisol (a glucocorticoid), which in turn may or may not be accompanied by inadequate production of aldosterone (a mineralocorticoid) and adrenal androgen (DHEA-dehydroepiandrosterone).[10]

Therefore, AI can simply be termed primary (Addison's disease) when the problem lies within the adrenal cortex.[10,11,13] This deficiency of cortisol (a glucocorticoid) +/- aldosterone (a mineralocorticoid) induces elevated levels of adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), and renin.[10,13] In a similar manner, AI can be referred to as a 'secondary' when it is due to pituitary disease. Such pituitary disease may result in reduced ACTH synthesis and/or secretion, which in turns results in reduced production of cortisol and DHEA (downstream) and an increased production of CRH (upstream).[10,13]

A 'tertiary' form of AI would arise where there is hypothalamic axis dysfunction, resulting in reduced CRH production or release, and in turn resulting in reduced ACTH production.[10,13] The term 'central' AI has also been used to cover both secondary and tertiary forms of AI.[10,13] Epidemiologically, primary AI is described to occur more commonly in females.[10,13] The causes of

primary AI include: autoimmune adrenalitis- which itself may occur as an isolated variant; as an autoimmune polyendocrine/polyglandular syndrome type 1 variant that is associated with candidiasis and/or hypothyroidism; and as an autoimmune polyendocrine/ polyglandular type 2 variant.[8,14] The latter variant is also called Schmidt's syndrome and includes Addison's disease potentially associated with a (variable) range of other potential (not all inclusive) conditions e.g., hypothyroidism, and/or type 1 diabetes mellitus, gastritis, vitiligo, Coeliac disease, hepatitis, primary ovarian failure, etc.[8,14] Other causes of primary AI include: infectious (e.g., tuberculosis, AIDS, syphilis), bilateral adrenal metastases, bilateral adrenal haemorrhage (e.g., 'Waterhouse-Friderichsen syndrome' associated with meningococcal sepsis), bilateral adrenal infiltration (e.g., amyloidosis, hemochromatosis), bilateral adrenalectomy, drug-induced or iatrogenic (heparin, warfarin, sunitinib, fluconazole, phenytoin, rifampicin, long term glucocorticoid use e.g., for the treatment of rheumatoid arthritis), genetic or neonatal (congenital adrenal hyperplasia, adrenal hypoplasia congenita, infantile Refsum disease, cholesterol synthesis disorders, etc).[8,13,15,16]

Autoimmune Addison's disease (primary AI) is thought to be caused by destruction of the adrenal cortex by T-cell ($CD4^+$ & $CD8^+$) mediated immune responses, with assistance from macrophages and dendritic cells.[10,12,13,15] The mechanism of autoantibody creation is described as being usually aimed towards the 21-hydroxylase enzyme (the autoantigen).[10,12,13,15] In these patients, high levels of certain chemokines have been noted (e.g., CXCL9 and CXCL10).[12,15] These chemokines are interferon-induced and thought to be triggered by inflammatory or stressful events.[12,13,15] A genetic preponderance (MHC class II) is also noted in autoimmune Addison's disease.[10,12,13,15] Certain environmental and immunological factors (e.g., viral infection, type 1 interferons, immune checkpoint inhibitors (like pembrolizumab or nivolumab) are also thought to play a role in the aforementioned processes.[10,12,15]

AI may present with a myriad of features. Some clinical symptoms may include: lack of energy, reduced strength, anorexia, abdominal pain/discomfort, nausea, vomiting, muscle and joint ache.[13] Some potentially noted clinical signs are: skin hyperpigmentation, pyrexia, low blood pressure, orthostatic or postural hypotension, and dehydration. Furthermore, some of the noted biochemical & haematological findings may include: hyponatraemia, hyperkalaemia, hypoglycaemia and anaemia.[13]

Adrenal crises or Addisonian crises

Addisonian crisis (AC) is a potentially fatal emergency in patients presenting with acute AI.[8] The diagnosis may be entertained if relevant patients present with at least two of the following signs or symptoms: low blood pressure, lethargy, pyrexia, acute abdominal symptoms (e.g., abdominal pain, nausea & vomiting), delirium and also with linked abnormalities on laboratory tests (e.g., hyponatraemia, hyperkalaemia and hypoglycaemia).[13,17] The acute phase of AC is treated with intravenous IV glucocorticoids (e.g., hydrocortisone) and IV infusions of 0.9% saline.[8,10] Potential trigger factors for AC include: infection, surgery, arduous/strenuous physical activity, and intense emotional strain.[10] Predisposing risk factors for AC include: previous episode(s) of AC, age > 65 years, diabetes mellitus, diabetes insipidus, etc.[10] The index patient in this report had known (stable) AD. The patient had then developed a cluster of acute features (specifically nausea, vomiting, hypotension, tachycardia, and transient hypoglycaemia) which were indicative of Addisonian crisis related events. The onset of symptoms was within 24 hours of receiving each of the two separate doses of Pfizer-BioNTech Covid-19 vaccines. We hypothesise/postulate that the Covid-19 vaccine likely triggered an additional form of stress response (post-vaccination) that impacted on her stable Addison's disease.[18,19,20] Moreover, in both instances the acute features of the AC improved when the index patient was managed in the acute phase with short-term treatment with IV hydrocortisone and IV fluids.

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

As part of pharmacovigilance case assessments, the use of validated CAS may augment transparency of classifications, and the objectivity of reporting suspected cases of ADR. In the index case, applying the Naranjo adverse drug reaction probability scale (Table 1) equates to an assigned score of 5.[21,22,23] This translates into a 'probable' ADR classification. Applying an alternative validated CAS such as the WHO-UMC method (Table 2) to this index report equally derives a classification of 'probable' ADR.[24]

CONCLUSION

This report describes the case of an older female patient with known Addison's disease who developed acute clinical symptoms and signs suggestive of an Addisonian crisis after each of two separate doses of the Pfizer BioNTech COVID-19 vaccines. The report offers a helpful clinical lesson for a range of clinicians e.g., community-based/primary care, or hospital-based doctors. The report may also prove relevant to other clinicians practising in approved or extended roles e.g., non-medical prescribers with backgrounds in clinical pharmacy, physician assistants or physician associates, nurse practitioners or advanced nurse practitioners, nurse specialists, etc. Furthermore, prescribers should be encouraged to use CAS and/or applicable ADR reporting system(s) linked to their individual countries of practice to enhance pharmaco-vigilance.

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