Acute encephalitis, myoclonus and Sweet syndrome after mRNA-1273 vaccine

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SUMMARY
A patient presented with fever, generalised rash, confusion, orofacial movements and myoclonus after receiving the first dose of mRNA-1273 vaccine from Moderna. MRI was unremarkable while cerebrospinal fluid showed leucocytosis with lymphocyte predominance and hyperproteinorrachia. The skin evidenced red, non-scaly, oedematous papules coalescing into plaques with scattered non-follicular pustules. Skin biopsy was consistent with a neutrophilic dermatosis. The patient fulfilled the criteria for Sweet syndrome. A thorough evaluation ruled out alternative infectious, autoimmune or malignant aetiologies, and all manifestations resolved with glucocorticoids. While we cannot prove causality, there was a temporal correlation between the vaccination and the clinical findings.

BACKGROUND
On 11 March 2020, the WHO declared COVID-19 a worldwide pandemic. As we write this report, COVID-19 cases have reached a total of 176 million with 3.8 million deaths worldwide. Due to the unprecedented nature of this pandemic, vaccines have been developed in record time using novel technologies and are expected to play a key role in preventing further spread of the disease. One of these vaccines, mRNA-1273, manufactured by Moderna, consists of lipid nanoparticle encapsulated mRNA which expresses the prefusion-stabilised spike glycoprotein. This vaccine demonstrated SARS-CoV-2 neutralising activity in non-human primates, with acceptable safety and reactogenicity profiles in healthy adults in multicentre clinical trials. Rare reactions to vaccines may be observed in the postapproval period, due to the larger number of people exposed, as compared with a clinical trial. We report an individual who developed a unique constellation of neurological and dermatological manifestations 1 day following the first dose of the mRNA-1273 vaccine.

CASE PRESENTATION
A 77-year-old man with history of coronary artery disease, hyperlipidaemia and hypothyroidism was hospitalised with confusion, fever and generalised rash after receiving the first dose of the mRNA-1273 vaccine. Fever started 1 day after vaccine administration and was episodic, lasting for minutes to hours and recurring throughout the day. Over the next 48 hours, the patient developed a generalised body rash, starting from the trunk and spreading to the extremities. Thereafter, he began to experience headache, dizziness and double vision, which later progressed gradually to severe encephalopathy in the course of 5 days.

On dermatological examination, he was noted to have deep red, non-scaly, oedematous papules coalescing into plaques on the abdomen, upper chest, proximal upper extremities, bilateral upper flanks and back, with scattered non-follicular pustules (figures 1 and 2). On neurological examination, he had intermittent and irregular orofacial movements and bilateral upper extremity myoclonus. No other cranial nerve, motor or sensory deficits were noted on examination. Deep tendon reflexes were 2+ throughout, without signs of an upper motor neuron lesion. No nuchal rigidity was evident.

INVESTIGATIONS
Table 1 summarises the laboratory work-up. Notably, the patient presented with leucocytosis and neutrophilia, and elevations in creatine kinase, C reactive protein and ferritin. Cerebrospinal...
Clinical features observed in this patient were consistent with an acute encephalitis with myoclonus and neutrophilic dermatosis. We investigated infectious aetiologies that would explain the acute encephalitis, mainly viral agents (especially those that also cause skin rashes such as *Rickettsia* and Lyme disease), and bacterial and fungal causes of meningoencephalitis. Autoimmune encephalitides presented an acute viral encephalitis, mainly viral agents (including herpes simplex virus 1 and 2, West Nile virus, and *Enterovirus*), non-viral agents (especially those that also cause skin rashes such as *Rickettsia* and Lyme disease), and bacterial and fungal causes of meningoencephalitis. Autoimmune encephalitides

**Table 1** Summary of laboratory evaluations

<table>
<thead>
<tr>
<th>Evaluations</th>
<th>Results</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>General toxic and metabolic studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST, U/L</td>
<td>67</td>
<td>5–34</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>93</td>
<td>6–55</td>
</tr>
<tr>
<td>TSH, µIU/mL</td>
<td>0.153</td>
<td>0.350–4.940</td>
</tr>
<tr>
<td>CK, U/L</td>
<td>1200</td>
<td>29–200</td>
</tr>
<tr>
<td>Aldolase, UI</td>
<td>15.8</td>
<td>&lt;8.1</td>
</tr>
<tr>
<td>Serological infectious studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytes, ×109/L</td>
<td>18.5</td>
<td>3.5–10.5</td>
</tr>
<tr>
<td>Neutrophils, ×109/L</td>
<td>15.5</td>
<td>1.78–5.38</td>
</tr>
<tr>
<td>Lactic acid, mmol/L</td>
<td>0.67</td>
<td>0.3–2.2</td>
</tr>
<tr>
<td>Procalcitonin, ng/mL</td>
<td>0.35</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TPM</td>
<td>Non-reactive</td>
<td>Non-reactive</td>
</tr>
<tr>
<td>Cryoglobulins</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Lyme disease IgG/IgM</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Rickettsia IgG/IgM</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Typhus IgG/IgM</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngeal swab infectious studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human metapneumovirus, parainfluenza virus 1–4, rhinovirus, SARS-CoV-2, influenza A, influenza B, RS virus, Bordetella pertussis, Chlamydia pneumoniae, Mycoplasma pneumoniae, coronavirus 229E, coronavirus H1N1, coronavirus NL63, coronavirus OC43</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>Immunology studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>Positive (1/2)</td>
<td>Negative</td>
</tr>
<tr>
<td>ANA</td>
<td>Positive (1/160)</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-dsDNA, RIMP, Ro, La</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti Jo-1, IgG</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>ANCA (Pry, MPO)</td>
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<td></td>
</tr>
<tr>
<td>Anticardiolipin IgG/LgM</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>C3 complement, mg/dL</td>
<td>108</td>
<td>0.2–193</td>
</tr>
<tr>
<td>C4 complement, mg/dL</td>
<td>41</td>
<td>15–57</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>139</td>
<td>0.00–5.00</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>396.70</td>
<td>5–275</td>
</tr>
<tr>
<td>CSF studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White cell count (5% neutrophils, 77% lymphocytes, 18% monocytes), ×10/L</td>
<td>120</td>
<td>≤5</td>
</tr>
<tr>
<td>RBC, HbA, g/L</td>
<td>0</td>
<td>0–5</td>
</tr>
<tr>
<td>Protein, g/dL</td>
<td>65</td>
<td>40–70</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>124</td>
<td>15–45</td>
</tr>
<tr>
<td>IgG index (CSF/blood)</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Immunofluorescent staining</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Immunofluorescent staining</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Culture/gram stain</td>
<td>No organisms seen</td>
<td>No organisms seen</td>
</tr>
<tr>
<td>AFB cultures/ smear</td>
<td>No acid-fast bacilli seen</td>
<td>No acid-fast bacilli seen</td>
</tr>
<tr>
<td>Fungus</td>
<td>No fungi seen</td>
<td>No fungi seen</td>
</tr>
<tr>
<td>India ink</td>
<td>No encapsulated yeast seen</td>
<td>No encapsulated yeast seen</td>
</tr>
<tr>
<td>VDRL</td>
<td>Non-reactive</td>
<td></td>
</tr>
<tr>
<td>Meningitis panel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV, Encephalitis coli K1, N. influenzae, herpes simplex virus type 1, 2 and 6, human herpes viruses 1 and 2, human cytomegalovirus, enterovirus, varicella-zoster virus, Cryptococcus neoformans/gattii, West Nile virus</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>Autoimmune encephalitis panel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANNA 1 (Hu), ANNA 2 (Ro), ANNA 3, PCA1 (Yo), PCA2, PCA-1, TSH, μIU/mL, ANCA, antineutrophil cytoplasmic antibodies; ANA, antinuclear antibodies; dsDNA, double-stranded DNA; GAD, glutamic acid decarboxylase; GPCA, glial cell specific acidic protein; GPR, glutamic acid receptor; HLA, human leucocyte antigens; IFN, interferon; IGF, insulin-like growth factor; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A; IL-1, interleukin-1; IL-6, interleukin-6; IL-10, interleukin-10; MPO, myeloperoxidase; NMDAR, N-methyl-d-aspartate receptor; PCA1, paraneoplastic antibodies; PRR, proinflammatory cytokines; RBC, red blood cells; RNP, ribonucleoprotein; RPR, rapid plasma reagin; RSV, respiratory syncytial virus; RT-PCR, real time PCR; TNF, tumour necrosis factor; VDRL, venereal disease research laboratory test; VGE, voltage-gated potassium channel.</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>
was another main aetiological category; therefore, we obtained both autoimmune and paraneoplastic antibody encephalitis panels from the CSF and serum. Other non-infectious inflammatory processes of the brain, including acute disseminated encephalomyelitis and collagen vascular disorders, were also assessed with serum and CSF testing alongside MRI brain neuroimaging. Finally, other rare causes of encephalitis comprising metabolic, chemical and toxins were excluded by history of exposure together with the respective laboratory work-up. Myoclonus and orofacial movements did not have an EEG correlate that would suggest epileptic seizures despite prolonged EEG monitoring.

The acute fever and the neutrophilic dermatosis suggested Sweet syndrome. Medical conditions most frequently associated with this syndrome include upper respiratory tract and gastrointestinal infections, autoimmune conditions such as inflammatory bowel disease, rheumatoid arthritis, autoimmune thyroiditis, and other connective disorders such as systemic lupus erythematosus and dermatomyositis. The patient had elevated titres of RF and ANA; however, further history, clinical examination and laboratory assays ruled out any of these diagnoses. Sweet syndrome can also be associated with malignancy, but a thorough evaluation for malignancy was negative. Lastly, drug reactions can account for a significant proportion of Sweet syndrome cases. However, there was no recent exposure to new medications except for the mRNA-1273 vaccine.

TREATMENT
The patient initially received empiric broad-spectrum antibiotics and antiviral coverage for suspected sepsis and meningitis, including vancomycin, cefepime (later switched to ceftriaxone), ampicillin, doxycycline and acyclovir (for 9 days) without any improvement. As no infectious aetiology was found, antimicrobial therapy was de-escalated. Given concerns that the clinical picture might be related to an inflammatory reaction to recent vaccination, we started a 4-day course of 1 g methylprednisolone once a day.

OUTCOME AND FOLLOW-UP
After the first day of treatment, the patient had marked improvement in his neurological examination and went from mumbling incomprehensible words to formulating full sentences and regaining orientation to self and place. He was able to follow simple commands consistently. Myoclonus also quickly resolved, as well as the orofacial movements. The patient progressively improved, achieving his baseline before the fourth dose of methylprednisolone. Moreover, the cutaneous findings significantly improved, with near complete resolution of the pustules within 36 hours of administration of steroids. At this time, he met both major and all four minor criteria for the diagnosis of Sweet syndrome. The patient was switched to prednisone 60 mg daily with a plan to taper over the course of 3 weeks. He was discharged 2 days afterwards with no evidence of neurological symptoms and normalisation of initially altered laboratory evaluations.

DISCUSSION
This is the first report of an acute aseptic meningoencephalitis with Sweet syndrome following the mRNA-1273 vaccine. The patient met the Brighton Collaboration Encephalitis/Acute Disseminated Encephalomyelitis Working Group criteria for level 2 of diagnostic certainty for encephalitis after presenting with encephalopathy lasting for more than 24 hours, along with decreased to absent response to environment, decreased to absent eye contact, inconsistent response to external stimuli and decreased arousability, together with fever (>38°C), CSF pleocytosis (>5 white cell count/mm³) and EEG findings consistent with encephalitis (ie, diffuse background slowing), all of them as indicators of inflammation of the central nervous system.

After conducting a thorough infectious, malignant and autoimmune evaluation, no alternate aetiology was identified. Moreover, the patient did not improve with broad-spectrum antimicrobial therapy but showed a remarkable recovery after immunomodulation with steroids, further supporting the rationale that the clinical presentation was attributable to an inflammatory state.

While there are no published cases of isolated myoclonus post vaccination as witnessed in this patient, there are few reports of opsoclonus myoclonus presenting after receiving rubella, human papilloma virus and influenza vaccines, as well as opsoclonus myoclonus and ataxia with the yellow fever vaccine. Similarly, neutrophilic dermatoses, specifically Sweet syndrome, have been associated with several vaccines including pneumococcal, influenza, BCG and smallpox. The reported time frames from onset of cutaneous findings in relation to obtaining the vaccine has been 12 hours to 15
Sweet syndrome has also been described in association with COVID-19; however, our patient tested negative for SARS-CoV-2 infection by RT-PCR, making it unlikely that this was a virus-mediated inflammatory response.

None of the clinical trials testing mRNA-1273 vaccine in humans reported adverse reactions such as those reported here. Commonly described systemic adverse events were dose-dependent and included fatigue, chills, headaches and myalgias, occurring in more than half of the participants, most frequently seen after the second dose of vaccination and lasting for a mean of 2.9 and 3.1 days after the first and second doses, respectively. In one of the phase I trials, one of the participants presented with transient urticaria after the first dose, while in another trial one of the participants developed paronychia 2 days after vaccination and later presented diffuse morbilliform eruption after treatment with trimethoprim-sulfamethoxazole. This reaction was deemed not related to vaccination and responded to systemic glucocorticoid administration. In the phase III trial, 1.5% of patients in the intervention arm reported hypersensitivity reactions, including a diverse array of dermatological manifestations, but none of those was described as fulfilling the diagnostic criteria for Sweet syndrome. Most recently, a series of 12 patients presenting with delayed local skin reactions to the first dose of the mRNA-1273 vaccine were reported; however, none of these patients evidenced similar dermatological features such as those described in this report.

According to the WHO ‘Causality assessment of an adverse event following immunization (AEFI),’ it was determined that both the encephalitis as well as the Sweet syndrome fit in the category for indeterminate B1 (where a temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing the event (may be new vaccine-linked event)). We did not perform SARS-CoV-2 immunology assays in CSF or serum, which would further strengthen the hypothesis of vaccination as the cause of these adverse events.

Phases I–III clinical trials typically lack power to detect extremely rare adverse reactions and therefore postmarketing surveillance is important for the detection of these events. Adverse events are being actively monitored by the FDA as well as the Centers for Disease Control and Prevention, and safety monitoring from the trials are still ongoing and are expected to last for at least 2 years. Appropriate surveillance allows for establishing regular safety updates and risk characterisation while encouraging the use of vaccines as critical tools for disease control. The potential adverse event described in this case report was reported to FDA through the Vaccine Adverse Event Reporting System.

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Contributors All authors have contributed to the work and agree with the presented findings and that the work has not been published before nor is being considered for publication in another journal. GT-A, CRG, EMB and MH conceptually the report and made substantial contributions to the design, drafting and critical revision of the neurological aspects of this work. These authors approved the final version of the manuscript and assume accountability for all aspects of the work. JCM, YH and CW conceptualised the report and made substantial contributions to the design, drafting and critical revision of the dermatological aspects of this work. These authors approved the final version of the manuscript and assume accountability for all aspects of the work. NRS and SKA conceptualised the report and made substantial contributions to the design, drafting and critical revision of the infectious and immunological aspects of this work. These authors approved the final version of the manuscript and assume accountability for all aspects of the work.

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