Severe Varicella Zoster Virus Reactivation After SARS-CoV-2 Vaccination in an Immunocompetent Patient: Case Report

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Learning Objectives

- Differential diagnosis and approach to encephalopathy with focal neurological signs.
- Differential diagnosis and approach to acute respiratory insufficiency.
- Differential diagnosis and approach to acute kidney injury.
- Differential diagnosis and approach to a non-bacterial and non-fungal causes of septic shock.
- Diagnosis and management of Intensive Care Unit complications.
- Ethical issues in treatment withdrawal.

10.1 Introduction

Varicella Zoster Virus (VZV) is part of the alpha-herpesvirus family and can establish latency in cells following an episode of primoinfection known as varicella. Clinical reactivation of this virus usually accompanies a period of physical or emotional stress and is more prevalent in elderly and immunosuppressed patients, most often resulting in a painful vesicular eruption localised to one dermatome known as herpes zoster. Disseminated disease, characterised by extension of cutaneous lesions to more than one dermatome or involvement of ophthalmic, splanchnic, cerebral and motor nerves, have been reported in VZV reactivation, and usually indicates immune system dysregulation (1). Pulmonary reactivation is exceedingly uncommon in the absence of profound immunosuppression. The authors describe a case of disseminated varicella zoster reactivation in an 80-year-old man without a recognisable immunosuppressive cause, complicated by multiple organ failure, requiring intensive care support.

Case Presentation

An 80-year-old man presented to the emergency department of another hospital with a two days history of left eye pain and a painful rash in the left upper third of his face. He was diagnosed with ophthalmic zoster, prescribed brivudine and was discharged, returning two hours later due to sudden onset of agitation, confused speech and left-sided hemiparesis that resulted in a fall and head trauma.

He had past medical history of hypertension, chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung disease—GOLD—stage A) and gout on regular olmesartan/hydrochlorothiazide, nebivolol, amlodipine, alopurinol, furosemide, inhaled fluticasone/salmeterol and glycopyrronium bromide. He had received the third booster dose of SARS-CoV-2 BNT162b2 vaccine 3 days before symptoms onset. He had stopped smoking 6 years before. Nil other history was mentioned.

In the Emergency Department the patient was alert, with a left-sided hemiparesis, dysarthria and neck rigidity. There was a rash involving the dermatome of the ophthalmic branch of the left trigeminal nerve and left eye chemosis. A head computed tomography (CT) with angiographic study revealed a millimetric acute left parafalcine subdural haema-

toma and no other acute traumatic, ischaemic or haemorrhagic lesions. Initial bloodwork showed a C-reactive protein of 4.8 mg/dL and a creatinine of 2 mg/dL. A lumbar puncture revealed elevated cerebrospinal fluid proteins (107 mg/dL, ref. value 15–45 mg/dL) and 6 cells of mononuclear predominance with normal cerebrospinal fluid glucose. A presumptive diagnosis of encephalitis was made, and intravenous (IV) acyclovir was immediately started. He was admitted to the acute medical unit and during the next 24 h the clinical picture deteriorated with the onset of a febrile picture max 39.1 °C, tachypnoea with SpO_2 88–94% on room air. Arterial blood gas showed (ABG) type 1 respiratory failure and the chest x-ray revealed bilateral interstitial infiltrates. The patient was admitted to the infectious diseases ward at our hospital. Further investigations were sought, a chest CT (Fig. 10.1) revealed diffuse bronchial wall thickening, diffuse interstitial peri-hilar infiltrates involving predominantly the upper lobes and apical segments of the lower lobes. The presumptive diagnosis of varicella zoster pneumonia with possible concomitant bacterial infection was made, and in addition to IV acyclovir, he was given 750 U of Human Varicella-Zoster Immunoglobulin and started on amoxicillin/clavulanate and azithromycin. In the following hours, his clinical condition deteriorated further with confused speech and agitation, high lactataemia (39 mg/dL) in the absence of hypotension, oliguria and progression to type 2 respiratory failure (ABG whilst on FiO_2 100%: pH 7.235, pCO_2 52.5 mmHg, pO_2 50 mmHg, HCO_3 19.3 mmol/L), leading to a trial of bi-level non-invasive ventilation. The patient was referred to the

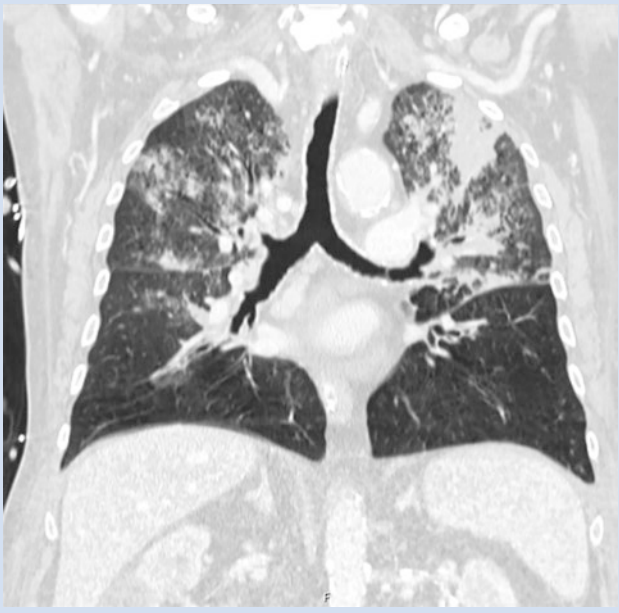

Fig. 10.1 Chest computed tomography scan performed before ICU admission

intensive care medicine team who identified early signs of respiratory exhaustion. He was intubated and mechanically ventilated and transferred to the intensive care unit.

On admission he was sedated targeting Richmond Agitation Sedation Scale (RASS) -5 with isochoric pupils and symmetrical corneal reflexes. He was hypotensive with increased capillary refill time and a peripheral oximetry of 89% under FiO_2 100% on invasive mechanical ventilation. He had a vesicular rash involving the left V1 trigeminal territory, left eye chemosis without keratitis and bilateral lung crackles on auscultation. An ABG revealed a mixed respiratory and metabolic acidaemia. Bloodwork (Table 10.1) confirmed deteriorating kidney function, increasing inflammatory markers, leukocytosis with an absolute lymphopaenia and urinalysis was positive for leukocytes, erythrocytes and proteins. Coagulation and liver parameters were normal. Bedside transthoracic echocardiogram and lung ultrasound excluded obstructive or cardiogenic shock, right ventricular overload and pneumothorax. He was started on noradrenaline and continuous venovenous hsemodiafiltration (CVVHDF) with an effluent dose of 35 mL/kg/h, a fluid removal rate of 100 mL/h without anticoagulation due to subdural haematoma. Oxygenation was compromised with non-protective mechanical ventilation (Table 10.2) so he was proned with an adequate oxygenation response (increase in PaO_2/FiO_2 ratio to 100 under FiO_2 60%). The attending team posed an initial diagnostic hypothesis of septic shock due to bacterial pneumonia, complicated by acute respiratory distress syndrome, meningoencephalitis and acute kidney injury. Previous empiric antibiotic therapy was modified to piperacillin/tazobactam and vancomycin, IV acyclovir was maintained. Several specific diagnostic investigations to confirm both these hypotheses and an immunosuppressive condition were performed in the following days.

Table 10.1 Bloodwork results on ICU admission day 1

	Results	Reference range
Arterial blood gas		
pH	7.18	7.35–7.45
pCO_2	77 mmHg	35–45 mmHg
pO_2	68 mmHg	67–104 mmHg
HCO_3	23 mg/dL	22–30 mmHg
Lactate	19 mg/dL	4.5–14.4 mg/dL
Creatinine	3.32 mg/dL	0.6–1.2 mg/dL
Urea	170 mg/dL	15–43 mg/dL
C-reactive protein	34 mg/dL	< 0.5 mg/dL

Table 10.1 (continued)

	Results	Reference range
Procalcitonin	12 mg/dL	< 0.1 mg/dL
Leukocytes Neutrophyles Lymphocites	15,240x10^9/L 14,290x10^9/L 0,25x10^9/L	3,54–9,06x10^9/L 1,42–6,34x10^9/L 0,71–4,53x10^9/L
Urinalysis		
Leukocytes Erythrocytes Proteins	++ ++ +	– – –

Table 10.2 Ventilation parameters at several timepoints during ICU admission

ICU admission day	**1**	**2**	**4**	**7**	**15**
Ventilatory mode	**Volume-controlled**	**Volume-controlled (prone)**	**Volume-controlled**	**Pressure-support (8 cmH_2O)**	**Volume-controlled**
Tidal volume (mL/kg predicted body weight)	7	6	6	7–8	7
PEEP (cmH_2O)	10	10	10	8	6
Respiratory rate (cycles/min)	28	28	28	20–25	22
Plateau pressure (cmH_2O)	24	22	21	–	25
Driving pressure (cmH_2O)	14	12	11	–	19
Static compliance (mL/cmH_2O)	36	36	38	–	26
FiO_2 (%)	100	40	40	25	40
PaO_2/FiO_2 ratio	74	185	217	303	190

10.2 Investigations

Transthoracic echocardiography (on admission): normal left ventricular size with normal ejection fraction and slight concentric hypertrophy with type 1 diastolic dysfunction with an E/E' of 13 suggestive of normal-high filling pressures; slight right ventricle dilatation with normal longitudinal function and an estimated pulmonary arterial systolic pressure of 40 mmHg.

Flexible Bronchoscopy (on day 3): Diffuse mucosal hyperaemia and oedema involving the trachea, all main and segmental bronchi, with scattered herpetic-like lesions characterised by red papules and vesicles. Clear mucoidal bronchial secretions were aspired and a bronchoalveolar lavage was performed on the right middle bronchus, with a cloudy fluid collected in all syringes.

Head and chest-abdominal-pelvis CT scan with angiographic study (on day 3): reduction in the size of the subdural haematoma, without significant mass effect. Ill-defined densification involving predominantly the central areas in both lungs and in the upper lobes, in some of them with associated small consolidations. There was a small bilateral pleural effusion. No other relevant findings were described.

Electroencephalogram (on day 4, immediately after sedation hold): slow basal electrogenesis activity, ill-differentiated and slightly asymmetrical, without epileptiform or periodic discharges.

Flexible Bronchoscopy (Fig. 10.2) (on day 7): improvement of previous findings, with a subjective reduction in the number and size of the vesicular lesions in the bronchial mucosa.

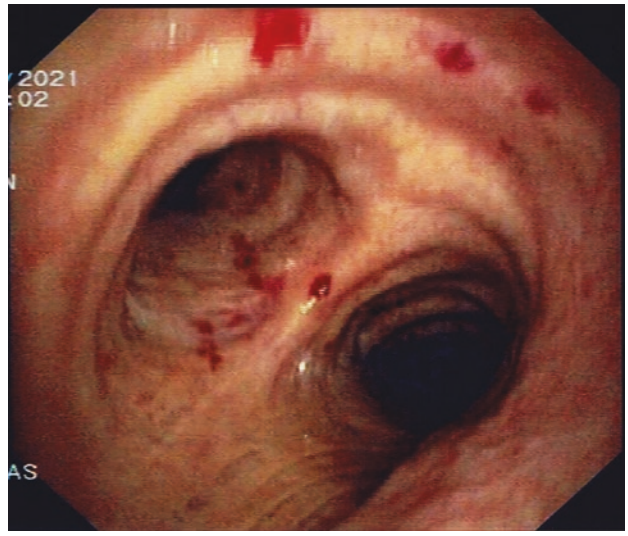

Fig. 10.2 Bronchoscopy performed at day 7 (carina in the image)

Brain magnetic resonance imaging (on day 7): slight hyperintense T2/flair lesions involving the medial temporal, insular and hippocampus bilaterally, compatible with encephalitis. Chronic subdural right frontoparietal and left frontal haematomas with chronicity features and without significant mass effect. Diffuse cortical and subcortical atrophy pattern.

Specific laboratory studies: immunoglobulin levels were normal. Antineutrophil cytoplasmic (proteinase-3 and myeloperoxidase) and anti-glomerular basement membrane antibodies were negative and complement levels were normal. Immunological work-up revealed total lymphopaenia that worsened since admission. No significant alterations were found in major lymphocyte subsets distribution or immunoglobulins production (CD4/CD8 > 1, and normal serum levels of immunoglobulins despite low B cells (1,6%)). No thymoma was observed in Chest CT. Search for plasma autoantibodies against Interferon-γ, Interleukin-17A, Granulocyte macrophage colony-stimulating factor and interleukin-23 were negative in two time points.

Infectious disease screening/ investigation: Polymerase Chain Reaction (PCR) for VZV was positive on blood, cerebrospinal fluid, bronchial secretions, bronchoalveolar lavage and on face vesicles swab. Blood, bronchial secretions, bronchoalveolar lavage, urine and cerebrospinal fluid cultures were negative for aerobic and anaerobic bacteria and fungi. Urinary antigens for pneumococcus and legionella were negative. PCR for other respiratory virus on lower respiratory tract samples and for neurotrophic viruses on cerebrospinal fluid sample were negative. PCR for Human Immunodeficiency Virus 1 and 2 were negative. PCR for *Pneumocystis jirovecci* and *Mycobacterium tuberculosis* on bronchoalveolar lavage were negative.

10.3 Differential Diagnosis

Respiratory failure was an early sign in this patient and appeared 3 days after the rash onset and in the first 24 h of hospital admission. This was associated with fever, bilateral lung infiltrates and elevated inflammatory markers. The most likely attributable causes were viral pneumonia with a possible bacterial superinfection (community or hospital acquired) or other infection associated with an immunosuppressive condition. Pneumonia is a feared complication of acute varicella infection in adult patients, but the fact that only one dermatome was affected by the characteristic vesicular rash indicated a more likely diagnosis of herpes zoster. Therefore, other viral infections and non-infectious causes for acute lung injury were also sought. The patient had risk factors for chronic heart failure, so cardiogenic lung oedema or fluid overload complicating acute kidney injury were investigated. Acute lung injury associated with immunological conditions such as diffuse alveolar haemorrhage or pulmonary-renal syndromes were less probable. Respiratory deterioration preceding ICU admission and motivating urgent endotracheal intubation and ventilation could, therefore, be caused by primary acute respiratory distress syndrome but all other above-mentioned conditions needed exclusion so to confirm this hypothesis.

On ICU admission, the patient was hypotensive with signs of tissue and organ hypoperfusion, so shock approach and haemodynamic evaluation were performed. Previous history suggested septic shock caused by pneumonia, but other concurring conditions could be suspected such as hypovolemia caused by volume depletion, acute heart failure or obstructive shock from pulmonary embolism.

Possible aetiologies for the distributive shock were sepsis caused by bacterial pneumonia. Other infectious non-bacterial organisms were searched. Viral aetiology was considered after cultures for bacterial and fungal organisms were negative and varicella zoster viraemia was confirmed. Organ dysfunctions on ICU admission were precipitated by shock, but they were previously present in the initial clinical picture so other additional causes were considered.

Encephalopathy with focal neurological signs was the initial presentation that motivated hospital admission, and this followed the diagnosis of left V1-trigeminal and ophthalmic zoster, so the most probable cause was varicella encephalitis. The deterioration that preceded ICU admission could be explained by sepsis, uraemia and hypercapnia, but other causes such as subtle status epilepticus and mass effect from subdural haematoma were also considered.

Regarding kidney injury, he had risk factors for chronic kidney disease (age and hypertension), and a previous glomerular filtration rate was not provided so this could not be excluded. Acute kidney injury preceding ICU admission could be attributed to pre-renal causes, namely hypovolaemia secondary to fever and tachypnoea. Renal causes considered were crystal-induced nephropathy complicating IV acyclovir therapy or immunologic phenomena induced by VZV reactivation, namely glomerulonephritis, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis or pulmonary-renal syndromes such as antiglomerular basement membrane disease. Post-renal causes such as renal calculus from previous hyperuricemia history were also possible.

Lastly, varicella-virus reactivation is generally associated with immunosuppressive conditions, but he did not have any as far as it was apparent from previous history. Therefore, acquired immune deficiencies such as human immunodeficiency virus infection, haematological malignancies, or recent SARS-CoV-2 vaccination were the most probable causes. Innate immune defects were less likely, mainly due to his age.

10.4 Treatment

Initial treatment for varicella zoster virus reactivation consisted of IV acyclovir (dose adjusted to CVVHDF and to glomerular filtration rate after CVVHDF interruption on day 6) continued for 21 days due to central nervous system involvement. Empiric antibiotic therapy with piperacillin/tazobactam and vancomycin was interrupted when culture results returned negative.

He was under neuromuscular blockade until day 3, and sedation hold trials were started at day 4. Incomplete consciousness recovery (eye opening to pain stimuli and abnormal flexion response) with purposeless rapid head movements followed sedation hold trials triggered additional investigations (brain CT and electroencephalo-

gram). Epileptic activity and active hydrocephalus caused by possible subdural hematoma expansion were excluded at day 4, so sequelae of encephalitis and possible hyperactive delirium were assumed thereby requiring dexmedetomidine and quetiapine association for patient protection and nonpharmacologic measures such as daily family visits.

He remained on prone ventilation for 17 h (◘ Table 10.2). Ventilation weaning started at day 4. At day 7, he could continuously tolerate pressure support ventilation. Further ventilation weaning and spontaneous breathing trials were not possible due to incomplete neurological recovery and Intensive Care Unit acquired muscle weakness.

Haemodynamic monitoring was performed using conventional haemodynamic parameters, echocardiography and minimally invasive arterial pressure waveform analysis. Initial haemodynamic evaluation was compatible with distributive shock, after exclusion of other aetiologies. Due to increasing dose of noradrenaline that reached 0.75 mcg/kg/min, the patient was started on empiric hydrocortisone 50 mg qid. In the first 24 h, he presented haemodynamic improvement with progressive decrease in the noradrenaline requirements until suspension and achieved complete lactataemia clearance. Hydrocortisone was suspended on day 3. On days 2 and 6, he had episodes of paroxysmal atrial fibrillation without haemodynamic compromise and was successfully submitted to rhythm control with amiodarone. Therapeutic anticoagulation with low-molecular-weight heparin was started after this last episode and after confirming a reduction in the size of his subdural haematoma.

CVVHDF dose was progressively reduced according to metabolic control and fluid removal was adjusted to maintain a neutral/ balanced daily fluid balance. He maintained oliguria until day 5 when spontaneous diuresis of more than 500 mL/day was verified with reasonable uraemia and metabolic control (urea 82 mg/dL), allowing for CVVHDF interruption. Estimated glomerular filtration rate stabilised at 20 ml/min in the following days.

10.5 Evolution, Outcome and Follow-up

Haemodynamic and ventilatory improvements in the first 6 days allowed for spontaneous awakening trial trials, but incomplete consciousness recovery emerged and was characterised by spontaneous eye opening without pursuing the observer, spontaneous non-intentional and non-provoked short amplitude proximal movements of his upper limbs and rhythmic left-right (“no-no”) brisk movements of his head. It was also evident an asymmetric hypotonic quadriparesis with absent osteotendinous reflexes. Repeat head-CT scans excluded any deterioration of previous lesions, and repeat electroencephalograms revealed only slow basal and ill-defined activity without any paroxysmal bursts compatible with epileptic seizures. Initial hypothesis was minimally conscious state due to encephalitis, IV acyclovir toxicity and possible hyperactive delirium. An ICU acquired weakness was also a probable diagnosis. Spontaneous brisk head movements required continuous IV sedation with propofol and dexmedetomidine to avoid self-extubating, thereby prolonging initial ventilation period.

On day 15, the patient worsened with the onset of distributive shock, superimposed acute kidney injury (oliguria and uraemia) and worsening hypoxemia. Ventilator-associated pneumonia diagnosis was confirmed by the identification of a new right inferior lobe consolidation on a CT scan, purulent bronchial secretions and raising inflammatory markers. Cultures were performed, and empiric antibiotic treatment with meropenem and vancomycin was started. A multi-drug resistant *E. coli* with sensitivity to meropenem was isolated on bronchial secretions on day 17, so vancomycin was stopped. He required sedation to target RASS -5 and neuromuscular blockade due to worsening ventilation (Table 10.2), vasopressor support with noradrenaline at a maximal dosage of 1mcg/kg/min, empiric hydrocortisone 50 mg qid and CVVHDF. During the following 48 h, he improved his haemodynamic and ventilatory conditions. At day 17, he stopped vasopressor and attained previous PaO_2/FiO_2 ratio. However, kidney function did not improve to previous level and he remained oliguric and dependent on dialysis for metabolic and fluid balance control.

Ventilatory weaning resumed but on spontaneous awakening trial the previously described neurological syndrome emerged. Another electroencephalogram excluded status epilepticus, uraemia was corrected and no other metabolic disorders were identified. A presumptive diagnosis of nonspecific movement disorder secondary to encephalitis, very similar to Bobble Head Doll syndrome previously described in children with hydrocephalus, was considered. Therapy with clobazam, levetiracetam and valproic acid (doses titrated to 10 mg, 750 mg bid and 500 mg tid, respectively) resulted in brisk head movements control but without consciousness improvement. Percutaneous tracheostomy was then performed at day 21 and at day 30 he had a Full Outline of UnResponsiveness Score (FOURs) of 8 (E3M0B4R1), so active rehabilitation still wasn't possible. He was able to tolerate pressure support-ventilation for only short periods of time, after which increased muscle effort was evident. Diaphragm thickening fraction evaluated at day 38 was 10%, so diaphragm dysfunction probably secondary to prolonged ventilation was confirmed.

Overall condition remained unchanged until day 50. The patient had previously manifested against receiving any measure that could artificially extend his life in the case of an irreversible and severe disabling neurological condition. His case was discussed in a multidisciplinary collegial meeting, and ICU team assumed sequelae of encephalitis preventing him from progressing in rehabilitation and ventilation weaning, associated with persistent kidney failure requiring dialysis. The family was involved to achieve a mutual understanding of patient values and priorities and the role of therapeutic options in achieving patient goals. Life-sustaining treatments were withdrawn, and end-of-life care measures were started. The patient died at day 52.

10.6 Discussion

Sepsis and septic shock are commonly associated with bacterial and fungal infections. Viral sepsis is rare and has been reported in herpes simplex, enterovirus, human parechovirus, influenza, dengue and adenovirus infections in susceptible populations

such as children, pregnant women, immunosuppressed or older individuals (2). Diagnosis of viral sepsis is complex because it requires complete exclusion of bacterial or fungal infection and confirmation of an active viral infection (3). VZV has never been previously reported as a cause of sepsis or septic shock, neither in its acute nor reactivation forms. However, a causal relationship may be established in this case because (1) bacterial, fungal or other viral infections were excluded; (2) VZV was identified by PCR both in affected organs (skin, cerebrospinal fluid and lung) and blood and (3) the patient improved with specific IV acyclovir treatment. This patient presented initially with known complications of VZV reactivation in a dermatome and in the central nervous system, namely ophthalmic zoster and varicella encephalitis. However, he progressed to systemic dissemination with bronchial and lung involvement. All other infectious or immunological conditions were excluded, and bronchoscopy findings associated with a positive PCR for VZV in bronchial secretions and bronchoalveolar lavage support this diagnosis. Pneumonia is the most feared complication of acute VZV infection in adults and has rarely been described in severe immunosuppressed patients with disseminated VZV reactivation (4). In this case, investigation could not demonstrate neither innate nor acquired immunosuppression status. Post-vaccine reactivation of VZV in previously healthy individuals is not unheard of and has most recently been described after SARS-CoV-2 vaccination (5). Although most cases have been mild, a few descriptions of central nervous system involvement have been documented (6). Despite specific treatment that led to an initial improvement, this patient suffered from severe neurological sequelae from encephalitis and several expected complications secondary to prolonged ICU stay and invasive mechanical ventilation, such as ventilator-associated pneumonia complicated by septic shock with irreversible acute kidney injury and ICU-acquired weakness with diaphragm dysfunction. Altogether, these explain the negative outcome of this patient.

This case represents the first account of systemic VZV reactivation with cutaneous, neurologic and pulmonary involvement complicated by distributive shock. It is important to raise awareness of this potential complication so that cases may be rapidly identified and treated like immunosuppressed patients, with intravenous antivirals. Mechanisms involved in VZV reactivation following mRNA vaccines have not yet been elucidated and require urgent investigation.

Take Home Messages

- Varicella zoster virus reactivation may follow SARS-CoV-2 vaccination.
- Disseminated varicella zoster virus reactivation can present as pneumonia and encephalitis in immunocompetent individuals.
- Sepsis and septic shock from viral aetiology is a possibility when all other causes have been excluded.
- Intravenous acyclovir is an effective treatment for disseminated varicella zoster reactivation.

Summary

The authors present the case of a previously immunocompetent 80-year-old patient admitted to the hospital following the onset of an ophthalmic zoster and an acute encephalopathy with focal neurological signs 3 days after SARS-CoV-2 vaccination. Shortly after admission, he developed acute respiratory failure, acute kidney injury and distributive shock and was transferred to Intensive Care Unit (ICU), where he required mechanical ventilation with prone positioning, haemodynamic support and continuous venovenous haemodiafiltration. He was treated with intravenous acyclovir with significant overall clinical improvement in the first 48 h of ICU admission. Haemodynamic failure resolved, dialysis was stopped and oxygenation improved. After extensive investigation, diagnosis of disseminated varicella zoster was confirmed by identification of the virus in blood, cerebrospinal fluid, skin lesions, bronchial secretions and bronchoalveolar lavage. Brain magnetic resonance imaging supported the diagnosis of viral encephalitis. Chest CT scan was compatible with viral pneumonia and bronchoscopy findings suggested mucosal involvement from varicella, both of which were later confirmed by PCR. Bacterial and fungal infections were excluded, as well as has other causes for distributive shock or respiratory insufficiency. Investigation excluded inherited or acquired immunodeficiency. Prolonged ICU stay ensued and was complicated by late ventilator-associated pneumonia, ICU acquired weakness and diaphragm dysfunction. Despite treatment, minimally conscious state persisted and a movement disorder like "bobble head doll syndrome" emerged, presumably as a sequela of encephalitis. Status epilepticus and other structural or metabolic causes were excluded. Further ventilator weaning was not therefore possible, and resuming dialysis was required. Altogether these led to life-sustaining treatments withdrawal after 50 days of ICU stay. Herpes zoster following SARS-CoV-2 vaccination has been previously described, but to the author's knowledge, this is the first report of severe disseminated disease presenting as encephalitis, pneumonia and shock.

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