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Case Report

Adjuvant treatment of severe varicella pneumonia with intravenous varicella zoster virus-specific immunoglobulins

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ABSTRACT

Varicella zoster virus (VZV) pneumonia is associated with significant mortality, especially in the immunocompromised host. VZV-specific immunoglobulins (VZIG) are currently used as post-exposure prophylaxis for at-risk patients, but not as adjunctive therapy. A novel case of VZV pneumonia in an immunocompromised patient, treated successfully with intravenous VZIG in combination with acyclovir, is reported here.

Introduction

Pneumonia is a major complication of varicella zoster virus (VZV) infection in adults (Gershon and Gershon, 2013). Susceptibility is 25-fold greater in adults than in children, and risk factors such as chronic lung disease and immunosuppression have been associated with higher frequency and mortality rates (Puchhammer-stöckl and Aberle, 2015). The main treatment of severe VZV infection consists of high-dose intravenous acyclovir together with supportive intensive care (Gershon et al., 2015; Mirouse et al., 2017). Despite a small number of case reports indicating positive outcomes with the use of standard intravenous immunoglobulins (IVIG) for disseminated varicella in pediatric patients (Prader et al., 2018; Yamada et al., 2015), no data are available on the use of intravenous VZV-specific IgG (VZIG) in the treatment of severe VZV infections.

Case report

We report on a 39-year-old man from Sri Lanka. His past medical history was unremarkable until December 2017, when he suffered from acute myocardial infarction complicated by cariogenic shock and ventricular tachycardia, treated with amiodarone and the implantation of a cardioverter defibrillator. In August 2018, the patient suffered from a new episode of cardiogenic shock and respiratory distress triggered by pneumonia. Cardiac function was severely compromised, with evidence of dilated cardiomyopathy (ejection fraction (EF) of 25%). As respiratory impairment continued despite several courses of antibiotics, amiodarone pulmonary toxicity was diagnosed and the patient was discharged home on steroids (prednisone 25 mg every 24 h).

Two months later, after a transient exposure to a child with chickenpox, he presented to the emergency department for hyperpyrexia, severe dyspnea, and an itchy generalized maculopapular to vesicular rash. Blood tests revealed hypoxemia, respiratory acidosis, elevated liver enzymes, and acute renal failure (Figure 1). Chest radiography showed bilateral lung opacities. The patient was placed on non-invasive ventilation and transferred to the intensive care unit (ICU), where empirical antibiotic and antiviral therapy with piperacillin–tazobactam 4.5 g every 6 h, azithromycin 500 mg every 24 h, oseltamivir 75 mg every 12 h, and acyclovir 10 mg/kg every 8 h was started. Microbiological investigations confirmed the clinical suspicion of varicella

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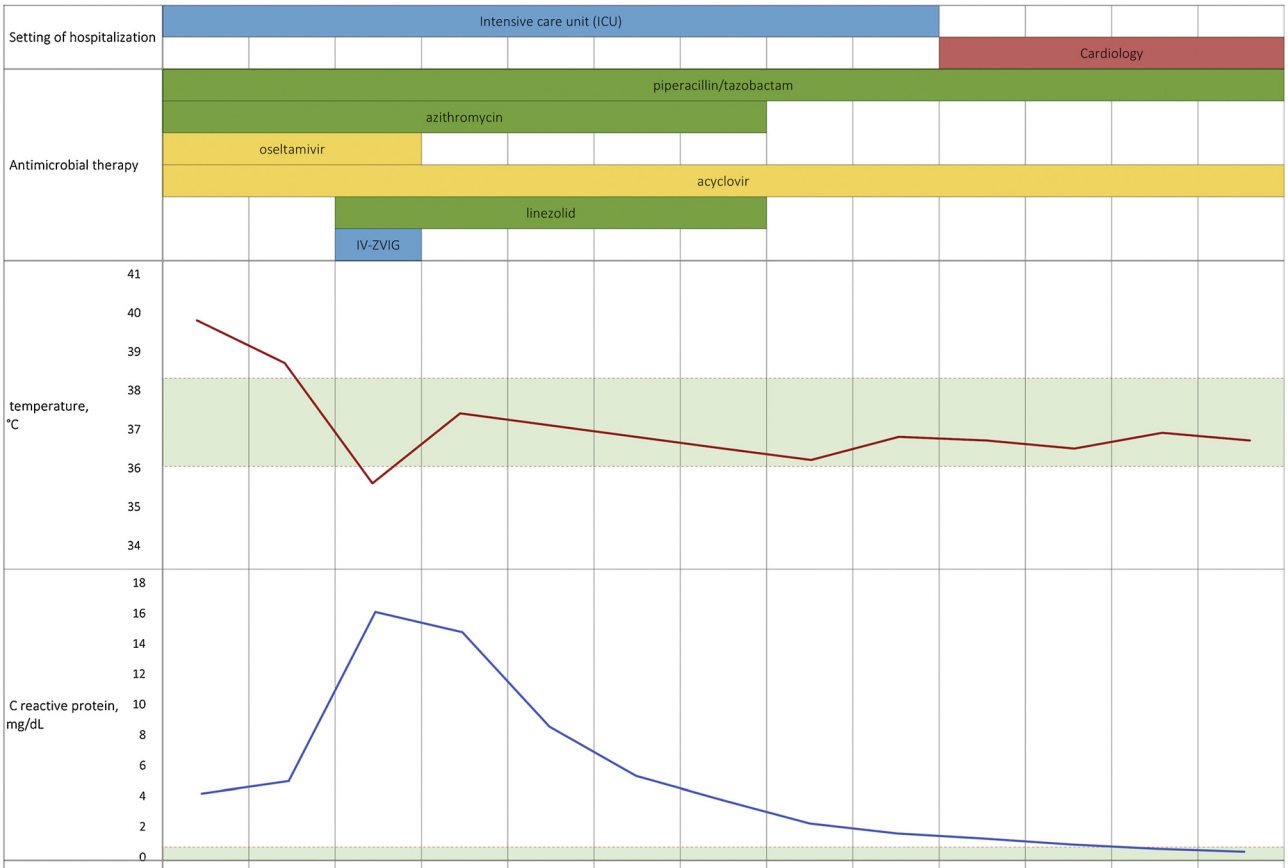

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temperature, °C	39,8	38,7	35,6	37,4	37,1	36,8	36,5	36,2	36,8	36,7	36,5	36,9	36,7
CRP, mg/dL	4,15	4,96	16,06	14,73	8,52	5,29	3,7	2,19	1,54			0,52	0,33
PCT, ng/L						0,89						0,1	
WBC, 10^9/L	8,41	7,52	5,99	7,85	7,83	7,29	7,72	6,96	5,28	7,22	4,64	7,01	8,34
lactate, mmol/L	2,3	1,8	3,7	2,9	3,3	3,1	2,9	2,8	2,8				
LDH, U/L	1292	1272	1137	1316	1101	903	793	635	584				
AST, U/L	707	565	283	346	242	146	95	55	43				
ALT, U/L	514	404	294	315	381	228	192	137	109				
PaO2/FiO2, mmHg	147	172	118	159	195	214	242	281	307				
PLT, 10^9/L	132	92	85	105	107	115	109	109	90	81		79	92
total bilirubin, mg/dL	3,73	2,35	3,13	2,59	2,19	1,93	1,89	1,56	2,2				
MAP, mmHg	64	67	72	dobutamine	dobutamine	dobutamine	dobutamine	dobutamine	dobutamine				
Glasgow coma scale	15	15	15	15	15	15	15	15	15				
creatinine, mg/dL	1,33	1,07	0,91	1,45	1,25	1,06	0,73	0,65	0,73	0,78		0,69	0,67
urinary output, mL/24h	-	<500	>500	>500	>500	>500	>500	>500	>500				
SOFA score	8	11	7	9	9	6	6	6	7				

Legend: IV-VZIG intravenous varicella zoster immunoglobulins; CRP C reactive protein (laboratory range <0,5); WBC white blood cell (laboratory range: 4,8-10,8); LDH lactate dehydrogenase (laboratory range: 135-225); AST aspartate aminotransferase (laboratory range: 10-35); ALT alanine aminotransferase (laboratory range: 9-59); PLT platet (laboratory range: 130-400); MAP mean arterial pressure; SOFA sequential [sepsis-related] organ failure assessment. For each day, the worst clinical/biochemical parameter in the 24h-period was considered.

: normal range

Figure 1. Treatment regimens and clinical and laboratory data from intensive care unit admission to antibiotic and antiviral discontinuation. Improvements in both clinical and biochemical parameters can be noted after intravenous administration of varicella zoster virus-specific immunoglobulins (VZIG).

infection (VZV IgG-negative, IgM-positive; plasma VZV DNA 4 517 860 genome equivalents/ml (real-time PCR, normal value <250 genome equivalents/ml)), while cultures of blood and bronchial aspirate, urinary antigens for *Streptococcus pneumoniae* and *Legionella pneumophila*, and multiplex PCR for respiratory viruses from a nasopharyngeal swab were all negative.

As cardiac function and renal function were severely compromised with an EF of 10–15% and oliguria, dobutamine and continuous infusion of loop diuretics were necessary. Due to the unstable cardiac and respiratory conditions, a bronchoalveolar lavage could not be performed, but chest computed tomography showed bilateral ground glass opacities, hilar lymphadenopathy,

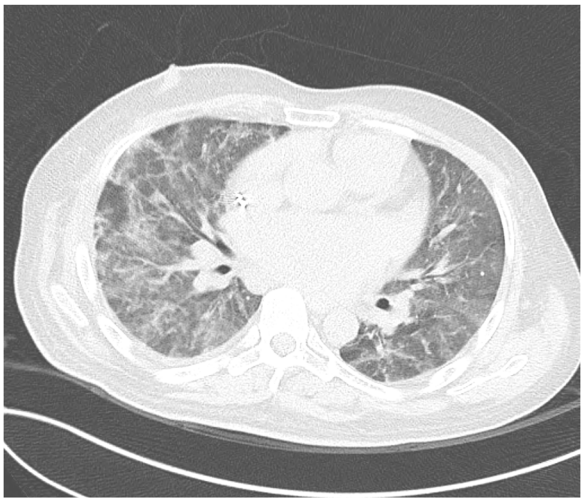

Figure 2. Lung computed tomography scan showing bilateral patchy ground glass opacities, peribronchial thickening, hilar lymphadenopathy, and well-defined subcentimeter nodules. These findings are typical of varicella pneumonia, as discussed by Koo et al. (2018).

and a number of subcentimeter nodules typical of varicella pneumonia (Koo et al., 2018) (Figure 2). Intravenous VZIG 30 IU/kg (2000 IU) in a single dose was therefore added. The patient's hemodynamic, renal, and respiratory functions gradually improved, enabling the weaning of vasoactive and ventilatory support, as well as the de-escalation of antibiotic therapy (Figure 1). Eight days after ICU admission, the patient was transferred to the cardiology department, where respiratory function progressively recovered and cardiac function slowly returned to pre-event values. His fever and alteration of systemic inflammatory markers resolved, leading to the complete discontinuation of antimicrobial therapy. The patient was then transferred to the cardiac rehabilitation center in a stable clinical condition.

Discussion

This article reports a case of severe VZV pneumonia in an immunocompromised patient, treated successfully with intravenous VZIG in conjunction with high-dose acyclovir.

VZV pneumonia is one of the most frequent complications of varicella in healthy adults. The presence of an underlying immune deficiency is associated with higher rates of ICU admission, mechanical ventilation, and mortality (Gershon et al., 2015). Recently, Mirouse et al. reviewed 102 cases of community-acquired VZV pneumonia in adults admitted to 29 ICUs in France. Patients were young (median age of 39 years) and approximately half of them were immunocompromised. Overall hospital mortality was 24%. Interestingly, one patient did receive VZIG in addition to acyclovir, although the doses and timing were not reported (Mirouse et al., 2017).

Passive immunotherapy is currently recommended in several bacterial and viral infections for the protection of seronegative hosts, either as prophylaxis or treatment (Bozzo and Jorquera, 2017). Timing is crucial: immunoglobulins are highly effective in the early post-exposure period and their efficacy then generally decreases with disease progression (Slifka and Amanna, 2018). Yet, when initiated shortly after symptom onset, passive immunotherapy can be highly successful for severe or even life-threatening infections such as hemorrhagic fever, tetanus, and botulism (Bozzo and Jorquera, 2017). Depending on the type of infectious disease, standard (non-specific) or hyperimmune (high-titer IgG-specific) immunoglobulins can be administered. The latter have several advantages over standard immunoglobulins, such as a highly specific activity, a standardized potency, and a more rapid viral clearance (Slifka and Amanna, 2018). In VZV infection, hyperimmune VZIG are preferred, although standard IVIG may be considered if VZIG are not available (Bozzo and Jorquera, 2017).

VZIG are currently recommended as post-exposure prophylaxis in at-risk patients with the aim of reducing the severity of varicella. The US Centers for Disease Control and Prevention (CDC) definition of high-risk groups for VZV infection includes the immunocompromised host (patients treated with steroids, cytostatic agents, radiotherapy, recent stem cell transplantation, or with an immunodeficiency disorder not receiving replacement therapy with immunoglobulins), pregnant women, neonates born to a seronegative mother or whose mother develops varicella shortly before or after delivery, and extremely premature infants irrespective of maternal immunity status (CDC, 2013). Recently, however, a more restricted use of VZIG prophylaxis has been suggested in immunocompromised hosts exposed to VZV, due to its high cost and limited availability (Harrington and Haque, 2018).

The US Food and Drug Administration (FDA)-approved VZIG – VariZIG (Cangene Corporation, Canada) – is administered via intramuscular route at a weight-based dosage within no more than 10 days (ideally within 96 h) after the exposure (FDA (online), accessed 2019). Varitect CP (Biotest Pharma, Germany) is the intravenous formulation of VZIG available in several European countries, although not yet approved by the FDA (Pinot de Moira and Nardone, 2005). Its therapeutic indications for post-exposure prophylaxis are the same as those for VariZIG, but it is also licensed as adjuvant therapy for severe VZV infections in immunocompromised patients or newborns at risk of dissemination. Varitect CP is administered intravenously at 25 IU/kg (1 ml/kg) for prophylaxis and 25–50 IU/ml (1–2 ml/kg) for treatment. As post-exposure prophylaxis it should be administered no later than 96 h after exposure, while as adjunctive therapy, additional administrations can be performed depending on the course of clinical manifestations (Biotest Pharma (online), accessed 2019). Unfortunately, this product is not available in all countries and shortages frequently occur.

Adverse events (AEs) have been reported after standard and varicella-specific IVIG administration, the majority being transient and mild, such as flushing, headache, and flu-like symptoms. Rare serious AEs can occur, mainly related to the infusion rate (hypersensitivity reactions) or in patients with pre-existing risk factors (renal impairment or thromboembolic events) (Biotest Pharma (online), accessed 2019; Guo et al., 2018). In the case described above, no drug-related AEs occurred after a single infusion of high-dose intravenous VZIG (30 IU/kg, 2000 IU).

Over recent years, a few case reports have shown positive results associated with the use of standard IVIG as adjunctive treatment for disseminated varicella infections, mainly in immunocompromised pediatric patients or solid organ transplant recipients. Dosages have varied from 125 mg/kg/day to 1 g/kg/day with different treatment durations (Carby et al., 2007; Kim et al., 2014; Lu et al., 2011; Prader et al., 2018; Sulliger et al., 1984; Tokat et al., 2001; Vales-Albertos et al., 2006; Yamada et al., 2015). No studies are available on the efficacy of intravenous VZIG in the treatment of severe varicella infections in at-risk patients. To the best of our knowledge it appears that the case reported here is novel in describing a positive outcome associated with the use of intravenous VZIG in addition to acyclovir in an adult patient with severe VZV pneumonia. Further studies, ideally randomized trials comparing acyclovir alone to VZIG plus acyclovir, are warranted to support the effectiveness of VZIG in the treatment of severe varicella infections in immunocompromised patients. Until then, we deem that infectious diseases specialists and intensive care physicians should consider adjunctive therapy with intravenous

VZIG in immunocompromised critically ill patients during the early stage of the disease. Since the number of immunocompromised individuals at high risk of VZV infection is on the rise, hospitals and national health agencies should increase their efforts to provide easier access to this drug.

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There are no financial conflicts of interest to disclose.

Ethical approval

Not applicable. A copy of the written consent form signed by the patient for publication of this case report is available for review.

Conflict of interest

None to declare.

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