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CASE REPORT

A case of acute respiratory distress syndrome associated with novel H1N1 treated with intravenous immunoglobulin G

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Influenza A "novel H1N1" with severe acute respiratory distress syndrome (ARDS) is a serious illness that poses a challenge to clinicians managing such cases. This case report reveals a patient with ARDS secondary to influenza A with deteriorating clinical status, who improved tremendously after intravenous immunoglobulin G (IV IgG). Patients with H1N1 associated with ARDS may be given a trial of IV IgG. More case reports and trials are required to ascertain the efficacy of IV IgG and the best dosage and timing of starting IV IgG in relation to antiviral therapy.

Introduction

The 2009 flu pandemic is a global outbreak of a new strain of an influenza A virus subtype H1N1, referred to as the "novel H1N1," first identified in Mexico in April 2009.[1] Since then, the disease spread to all continents, and in June 2009, The World Health Organization (WHO) raised the pandemic alert level to Phase 6.[2] Till December 11, 2009, more than 207 countries had reported laboratory-confirmed cases of pandemic influenza H1N1 2009, including at least 8,768 deaths.[3] In Malaysia, the total number of deaths reported was 77.[4] Clinicians face a great challenge in treating patients with influenza A complicated by ARDS, who require ventilation, as some of these cases do not seem to respond well to conventional therapy. Hence, trials of new modalities of treatment and researches on the pathophysiology of ARDS associated with influenza A are essential in improving treatment outcome. Here, we report the case of a patient who was successfully treated with antiviral therapy, mechanical ventilation, and intravenous immunoglobulin G (IV IgG), even though he was initially given a bad prognosis.

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Case report

A 59-year-old male patient presented to the district hospital in August 2009 with a history of high-grade fever and sore throat for 4 days. Apart from the fever, he complained of tiredness, reduced appetite, and difficulty in breathing, 2 days before presentation. There was no diarrhea, vomiting, cough, runny nose, or body ache. He has no known prior medical illness.

At the district hospital, the patient was treated for pneumonia, but on Day 3 of admission, the patient's condition deteriorated. He was then transferred to this hospital for further management. On arrival, he was tachypneic, dehydrated, and restless; respiratory rate was 40 breaths/min; temperature was 39.5°C; oxygen saturation was 86—88% on room air and 92—93% on high-flow mask; blood pressure was 177/72 mmHg; and pulse rate was 93 beats/min. Examination of the respiratory system revealed generalized crepitations, no rhonchi, and equal breath sound in both lungs. Examinations of the cardiovascular, abdominal, and neurological systems were unremarkable.

Laboratory tests revealed that the arterial blood gas on high-flow mask showed compensated hypoxia with P_aO_2 of 57.9 mmHg and O_2 saturation of 92.5%; the white cell count was 4.38×10^9/L (neutrophil, 77.1%; lymphocyte, 17.1%; monocyte, 5.3%; eosinophil, 0.0%; basophil 0.5%). Chest radiograph showed bibasal consolidation. Other investigation results are shown in Table 1. The patient was immediately sent to the intensive care unit and intubated and ventilated with the diagnosis of influenza-like illness and differential diagnosis of community-acquired pneumonia. He was started on oral oseltamivir 150 mg twice daily, IV ceftriaxone 2 g immediately and 1 g daily, and IV azithromycin 500 mg daily.

Despite adequate treatment with double dose of oseltamivir, antibiotic administration, and no evidence of secondary infection, the patient's condition worsened, as evidenced by the ventilator setting change from synchronized intermittent mandatory ventilation to BiLevel mode on Day 4 of admission, with FiO_2 of 0.5, high/low positive end expiratory pressure of 28/12 mmHg, and pO_2 of only 79 mmHg on Day 6 of admission, and serial chest radiographs showed worsening opacity up to the upper zone (Fig. 1). Blood culture and sensitivity taken on the day of admission grew Gram-positive cocci coagulase—negative staphylococcus (sensitive to ampicilin, erythromycin, fusidic acid, gentamycin, penicillin, oxacillin, and trimethoprin—sulfamethoxazole), endotracheal culture and sensitivity was negative. Real-time polymerase chain reaction result eventually showed novel flu A H1N1 swine lineage, and with the symptoms, he fulfilled the WHO criteria for the diagnosis of a confirmed case of pandemic (H1N1) 2009.[5]

On Day 6 of admission, the decision was made to administer 36 g IV IgG (patient's weight was 90 kg) for a planned duration of 5 days. This was the first patient in this hospital who was treated with IV IgG for ARDS

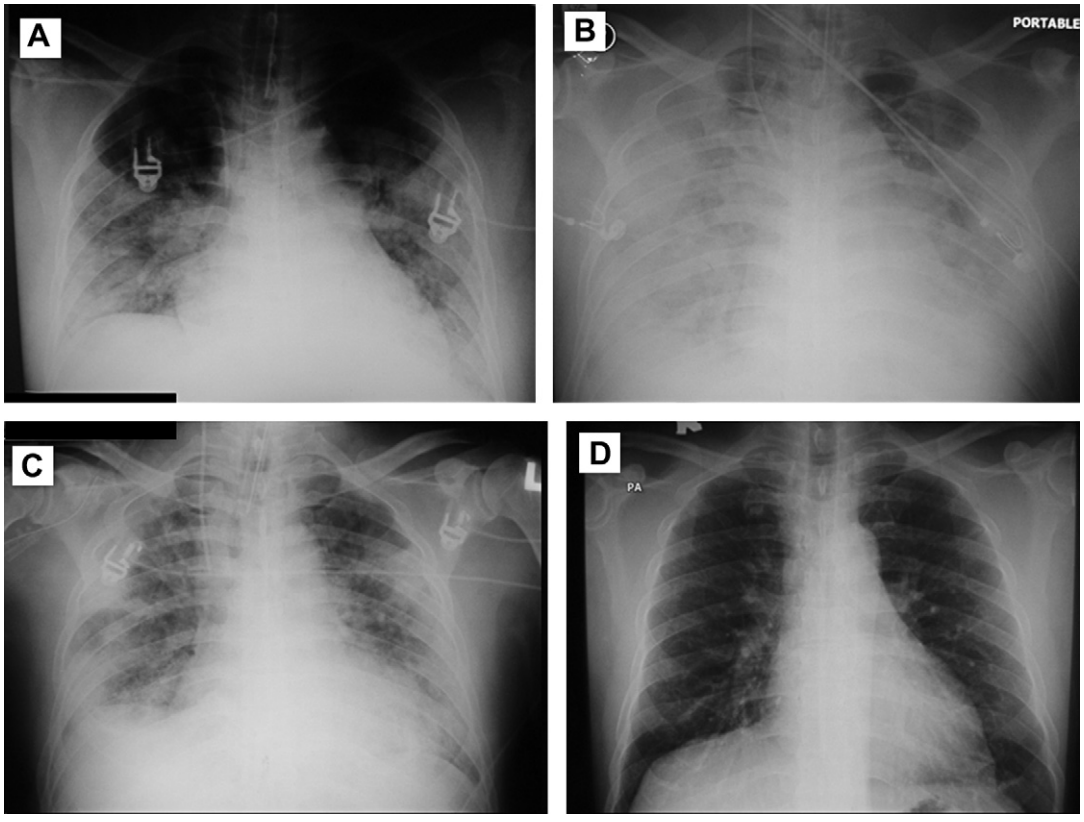

Figure 1. Chest radiographs show (A) bibasal pathy opacity on Day 7 of illness (Day 1 of admission); (B) worsening opacity up to upper zone on Day 13 of illness (Day 6 of oseltamivir 150 mg bd, pre—IV IgG); (C) improvement of chest radiograph on Day 19 of illness (1 day after completion of IV IgG for 5 days); and (D) minimal pulmonary fibrosis 2 months after discharge.

Table 1 Blood investigations and ventilator setting

Investigation	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14
Hemoglobin (g/dL)	14.0	13.3	12.1	12.4	11.7	11.4	11.6	11.5	11.4	11.7	11.0	10.5	103	10.9
White cell count	4.4	6.7	7.6	8.8	11.5	11.5	9.7	10.0	11.6	12.5	16.5	17.2	15.8	15.2
Platelet	139	147	146	170	234	250	316	340	430	508	587	719	800	880
Urea (mmol/L)	3.2	3.7	4.8	4.7	5.6	5.8	5.3	5.1	5.2	5.6	6.3	8.7	9.3	8.5
Creatinine (mmol/L)	81			91			73				80			82
Calcium (mmol/L)	1.81			1.77			1.96				1.98			2.13
AST (u/L)	211	138		110		166	182				162			74
ALT (u/L)	97	81		72		150	200				290			198
ALP (u/L)	45	61		73		131	168				177			126
Bilirubin (umol/L)	9.0	8.5		15.1		22.3	22.8				18.0			25.9

Ventilator setting	Ventilator mode													
	SIMV	SIMV	SIMV	BiLevel	BiLevel	BiLevel	BiLevel	BiLevel	SIMV	SIMV	CPAP	VM60	VM40	NPO_2
FiO_2	1.0	0.8	0.7	0.5	0.5	0.5	0.5	0.4	0.4	0.4	0.4	60%	40%	3 L
PEEP (mmHg)	8	10	10	28/12	28/12	24/10	26/12	26/10	12	10	6	—	—	—
Pressure support (mmHg)	12	12	12	12	12	12	12	12	12	8.6	10	—	—	—
SpO_2 (%)	98	98	97	98	97	94	97	96	96	97	99	99	100	98
pH	7.38	7.38	7.39	7.37	7.36	7.38	7.42	7.37	7.39	7.36	7.41	7.41	7.38	7.38
$PaCO_2$ (mmHg)	33.4	31.5	36.7	38.8	39.2	38.9	34.2	39.2	38.5	41.5	34.7	32.6	36.2	37.8
PaO_2 (mmHg)	138	104	74	79	79	90	85	76	101	82	111	125	120	79.6
Bicarbonate (mmol/L)	21	20	22	22	22	23	23	23	23	23	23	22	22	22

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate transaminase; CPAP = continuous positive airway pressure; FiO_2 = fraction of inspired oxygen; NPO_2 = nasal prong oxygen; PEEP = positive end expiratory pressure; SIMV = synchronized intermittent mandatory ventilation; SpO_2 = oxygen saturation; VM40 = venture mask 40%; VM60 = venture mask 60%.

secondary to H1N1. After 3 days, the patient showed encouraging response with improvement of ventilator setting (Table 1). He was extubated on Day 2 post-completion of IV IgG (Day 19 of illness) and discharged after 20 days of admission. On subsequent follow-up in the outpatient clinic 2 months later, his functional status was back to normal, and his chest radiograph revealed minimal pulmonary fibrosis (Fig. 1).

Discussion

Intravenous immune globulin (IVIG) contains the pooled IgG immunoglobulins (antibodies) extracted from the plasma of more than 1,000 blood donors. The precise mechanism by which IVIG suppresses harmful inflammation has not been definitively established but is believed to involve the inhibitory Fc receptor.[6,7] The donor antibody may bind directly with the abnormal host antibody, stimulating its removal. Alternatively, the massive quantity of antibody may stimulate the host's complement system, leading to enhanced removal of all antibodies, including the harmful ones. IVIG also blocks the antibody receptors on immune cells (macrophages), leading to decreased damage by these cells, or regulation of macrophage phagocytosis. IVIG may also regulate the immune response by reacting with a number of membrane receptors on T cells, B cells, and monocytes that are pertinent to autoreactivity and induction of tolerance to self.[8]

In 2003, Morishima T[9] from Japan reported that a combination of antivirals, high-dose gamma-grobulin, steroid pulse therapy, high-dose Antithrombin III, head cooling, and plasma exchange, could reduce the mortality of pediatric patients with influenza-associated encephalopathy. Satoshi H[10] et al. demonstrated that high-dose IVIG (1,000 mg/kg) decreased the mortality and pulmonary pathology in a rat model of sepsis.

Despite the fact that data regarding IVIG in severe H1N1 infections was limited, one study had reported significant neutralizing activity of human IVIG preparations against the pandemic H1N1 virus.[11] Another observation by researchers was the association of low total immunoglobulin subclass levels, particularly IgG2, in both pregnant and nonpregnant H1N1 2009 patients who developed respiratory failure.[12] In management of this case, IV IgG was administered on the basis of its potential immune-modulator properties and neutralizing antibodies, which may partly contribute to a favorable outcome of this patient.

In conclusion, this patient was successfully treated with a combination of 0.4 g/kg IV IgG and double dose of oseltamivir. Patients with H1N1 associated with ARDS may be given a trial of IV IgG. More case reports and trials are required to

ascertain the efficacy of IV IgG and the best dosage and timing of starting IV IgG in relation to antiviral therapy.

References

1. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom G, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009;**361**:1—10.
2. World Health Organization. Pandemic (H1N1) 2009—update 72. Available from: http://www.who.int/csr/don/2009_10_30/en/index.html. accessed November 20, 2009.
3. World Health Organization. Pandemic (H1N1) 2009—update 77. Available from: http://www.who.int/csr/don/2009_12_04/en/index.html. accessed December 11, 2009.
4. Ministry of Health of Malaysia. H1N1 Epid week 47/2009 (22—28th November 2009). Available from: http://h1n1.moh.gov.my/. accessed December 11, 2009.
5. Human infection with pandemic (H1N1) 2009 virus: updated interim WHO guidance on global surveillance 10/7/2009. Available from: http://who.int/csr/swineflu/guidance/surveillance/who_case_definition_swine_flu_2009_4_29.pdf [accessed 01.12.09].
6. Gern JE. Antiinflammatory activity of IVIG mediated through the inhibitory FC receptor. *Pediatrics*(2):467—8. Available from: http://pediatrics.aappublications.org/cgi/content/full/110/2/S1/467-b, 2002;**110** [accessed 01.12.09].
7. Nimmerjahn F, Ravetch JV. The antiinflammatory activity of IgG: the intravenous IgG paradox. *J Exp Med* 2007;**204**(1):11—5.
8. Bayry J, Thirion M, Misra N, Thorenoor N, Delignat S, Lacroix-Desmazes S, et al. Mechanisms of action of intravenous immunoglobulin in autoimmune and inflammatory diseases. *Neurol Sci* 2003;**24**(Suppl. 4):S217—21.
9. Morishima T. Treatment of influenza-associated encephalopathy. *Nippon Rinsho* 2003;**61**(11):2006—12.
10. Hagiwara S, Iwasaka H, Hasegawa A, Asai N, Noguchi T. High-dose intravenous immunoglobulin G improves systemic inflammation in a rat model of CLP-induced sepsis. *Intensive Care Med* 2008;**34**:1812—9.
11. Yunoki M, Kubota-Koketsu R, Urayama T, Sasaki T, Analiwa D, Konoshima Y, et al. Significant neutralizing activity of human immunoglobulin preparations against pandemic 2009 H1N1. *Br J Haematol* 2010;**148**(6):953—5.
12. Gordon CL, Johnson PD, Permezel M, Holmes NE, Gutteridge G, McDonald CF, et al. Association between severe pandemic 2009 influenza A (H1N1) virus infection and immunoglobulin G(2) subclass deficiency. *Clin Infect Dis* 2010 Mar 1;**50**(5):672—8.