

Prolonged lymphopenia in a patient with lymphoma and severe Pandemic influenza A H1N1 2009 virus infection

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Objective To describe the clinical course of a confirmed influenza A Pandemic (H1N1) 2009 virus infection in a patient with lymphoblastic lymphoma on chemotherapy.

Design Case report.

Setting Instituto Nacional de Cancerología located in Mexico City, a national referral center for cancer patients.

Patient and results A 15-year-old boy, with lymphoblastic lymphoma on chemotherapy. Oseltamivir 75 mg BID was started within 24 hour of first symptoms. The patient developed respiratory failure despite oseltamivir therapy; he presented a prolonged clinical course with severe lymphopenia and deteriorated every time oseltamivir was stopped while lymphopenia persisted. Oseltamivir was reassumed twice; in the second course, rimadine was added. Genetic study of the virus

showed 100% identity for AH1N1SW, and no H274Y mutation for oseltamivir resistance was found. Clinical recovery was apparent until he presented lymphocyte reconstitution after 35 days of disease while still on antiviral therapy.

Conclusion This case exemplifies the need to sustain antiviral therapy while patient continues with severe lymphopenia. Lymphocyte count could be used as a surrogate marker to prolong antiviral therapy in patients with severe lymphopenia and clinically symptomatic Pandemic (H1N1) 2009 infection. This case also highlights the importance of treating patients based on clinical grounds and the variability of rRt-PCR test for H1N1.

Keywords Immunocompromised patient, lymphopenia, pandemic influenza A H1N1 2009.

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Introduction

Pandemic influenza A (H1N1) 2009 can produce mild and self-limited upper respiratory tract infection, but in a small percentage of cases, viral pneumonia and acute respiratory distress syndrome (ARDS) with high mortality even among young immunocompetent patients.¹ Immunosuppressed patients are recognized as a high-risk group for severe seasonal flu with prolonged viral excretion.² Clinical evolution in this group of patients remains unknown; the best oseltamivir dose has not been defined, nor the length of treatment or surrogate markers for treatment extension.

Case report

A 15-year-old boy, with lymphoblastic lymphoma with intra-thoracic and retroperitoneal-space involvement diag-

nosed 7 months prior to current admission, was treated with eight cycles of cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD). He was admitted on April 24, 7 days after his last chemotherapy, within 24 hours of abrupt fever onset (40°C/104°F), chills, diaphoresis, headache, malaise, myalgias, and productive cough. Figure 1 shows neutrophils, lymphocytes, and monocytes counts and chest roentgenogram on admission with confluent lower lung air-space opacities. SpO₂ was 91% at room air. He was started on oseltamivir 75 mg BID, ceftazidime, and amikacin. A nasopharyngeal-swab for A H1N1 was negative. After 8 days on oseltamivir, he continued with fever; chest CT scan showed bilateral alveolar infiltrates (Figure 1); amphotericin B was started. Forty hours after oseltamivir discontinuation, the lung opacities grew and patient developed respiratory failure, requiring invasive mechanical ventilation. A second nasopharyngeal-

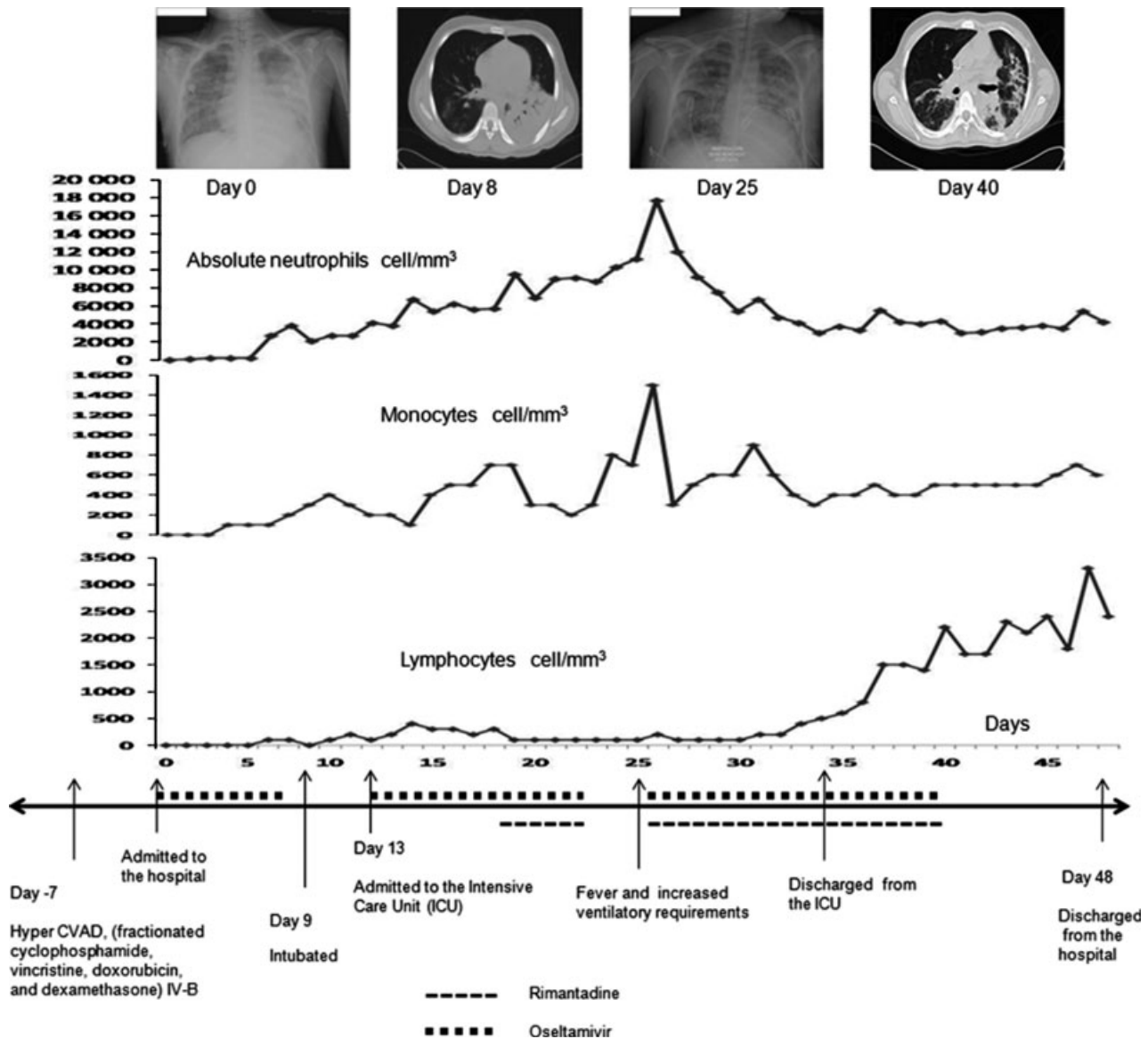


Figure 1. Shows outstanding clinical events, neutrophil, monocyte, and lymphocyte cells counts over time as well as days of oseltamivir and rimantadine therapy. Chest X-ray at hospital admission, computed tomographic (CT) of the chest obtained during the acute phase with clinical deterioration and CT scan of the chest obtained during the late phase of the Acute Respiratory Distress Syndrome.

swab was positive for H1N1; oseltamivir and rimantadine were started, and patient continued on antibiotics and amphotericin B. The patient was transferred to ICU in septic shock and ARDS; Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were 18 and 11 points. A second oseltamivir course was administered for 10 days; 72 hours after discontinuation, the patient developed fever again (39°C/102°F) and breathing difficulty. Oseltamivir and rimantadine were reinitiated and stopped when clinical recovery-associated lymphocyte count reached 500 cells/ml (Figure 1). The patient was discharged after 35 days of

hospital stay and 25 days of mechanical ventilation. Genetic study of the virus on sample taken 20th day of illness showed 100% identity for AH1N1SW, and no H274Y mutation for oseltamivir resistance was found. He underwent successful autologous hematopoietic stem cell transplantation (HSCT) on September 2009 with BEAM plus dexametasone conditioning.

Discussion

Patients with cancer on chemotherapy have increased influenza infection-associated morbidity and mortality.²⁻⁴

Prolonged influenza infection during lymphopenia described among immunocompromised patients with seasonal influenza and even antiviral resistance emergence with prolonged viral shedding during oseltamivir therapy. In this patient group, viral clearance depended on lymphocyte count reconstitution.^{3,4} Profound and prolonged lymphopenia cannot be solely attributed to neoplastic disease or chemotherapy consequence, because severe lymphopenia is common in influenza infection² and was described in patients in the current epidemic.¹ In lethal influenza-strain murine models, profound lymphopenia showed as a viral pathogenicity-inherent consequence.^{5,6} This patient never presented prolonged severe lymphopenia previously while on chemotherapy with Hyper-CVAD, or after autologous HSCT (Figure S1).

The patient presented an unusual evolution; oseltamivir was insufficient in controlling the H1N1 infection despite that clinical diagnosis of influenza established at arrival and oseltamivir started within 24 hours of first symptoms. We consider that oseltamivir offered clinical benefit, as the patient presented with clinical deterioration whenever oseltamivir was suspended even after 10-days therapy. This case exemplifies the need to sustain antiviral therapy while patient continues with severe lymphopenia. Clinical recovery observed at fifth week while patient continued on oseltamivir, associated with recovery of severe lymphopenia (Figure 1). We suggest using lymphocyte count as a surrogate marker to prolong antiviral therapy in patients with severe lymphopenia and clinically symptomatic Pandemic (H1N1) 2009 infection. We employed an oseltamivir and rimantadine combination according to CDC 2008 Guidelines for H1N1 seasonal influenza. The antivirals required re-initiation twice because patient suffered respiratory deterioration. No data from powered randomized trials exist to demonstrate any benefit using combination of antivirals for Pandemic (H1N1)2009⁷ as the virus is resistant to rimantadine, but at least in this patient, no increase in toxicity was observed using this double combination.

This case also highlights the importance of treating patients based on clinical grounds and the variability of rRt-PCR test for H1N1.⁸ Genetic study of the virus showed 100% identity for AH1N1SW, and no H274Y mutation for oseltamivir resistance was found; the patient finally recovered while on oseltamivir therapy.

Consent

As the patient is a minor, the patient's father has given written consent to publish his son's case.

Conflicts of interest

All authors report no conflicts of interest to disclose.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Absolute lymphocyte count from December 18 to June 16, 2009.

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