CASE REPORT

Oseltamivir-resistant h1n1 influenza virus: Case report

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Abstract

Swine flu is mainly caused by influenza virus strain H1N1. This strain of influenza has been found to cause seasonal flu. Animals are common source of influenza virus, in particular, pigs. Transmissions from animals to humans are reported on several occasions worldwide. These cases are usually mild to moderate in nature and are usually not fatal.

Here we describe the case of a healthy woman from Haripur, Pakistan, who presented in the Emergency Department of Quaid-e-Azam International Hospital, Islamabad and later developed a lethal course of H1N1influenza virus that resulted in her death, despite of aggressive management with Osaltemivir and Antibiotics in the Intensive care unit.

Osaltemivir resistance has emerged in many countries including Pakistan. There is a strong need for increasing surveillance and the laboratories that can test for antiviral resistance, particularly in a third world country like Pakistan.

Keywords: H1N1 Virus, Oseltamivir, Influenza A virus, Antiviral Resistance.

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Introduction

Influenza virus is considered as one of the most relentless and inconsistent microorganism worldwide[1]. Influenza keeps on causing customary seasonal epidemics, erratic pandemics, numerous and lethal zoonotic outbreaks around the world.[1] Transmission of Influenza virus occurs through air droplets, and causes a respiratory disease commonly known as "Flu", which can be fatal sometimes in immunocompromised and elderly individuals. Roughly 10%-20% of the world's population is infected with influenza virus each year, resulting in extensive economic burden on our society as well as health system.[2] As indicated by the World Health Organization (WHO), flu infection produces one billion cases of influenza every year, out of which around 4 to 5 million cases are severe in nature and approximately half a million deaths occur around the world.[3] In order to prevent influenza seasonal epidemics, annual influenza vaccine and the antiviral drugs have played an essential role in the last few decades. Currently, there are four drugs which are FDA-approved for the use against influenza virus; oseltamivir, zanamivir, peramivir and baloxavir.[4] However, the world is now facing an immediate threat of antiviral resistance against the influenza virus similar to antibiotic resistance in many other pathogens.[1]

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Case Report

A 32 year-old healthy woman who worked as a school teacher in the city of Haripur Pakistan, presented in the emergency department of Quaid-e-Azam International Hospital, Islamabad on 4th Jan 2019 with 4 days history of fever with rigors and chills, progressive shortness of breath and dry cough. Her past history was unremarkable. There was no history of travelling or contact with animals. On examination, the patient was obese and in acute apparent distress. The patient had tachycardia (Pulse 124bpm) and tachypnoea (RR 50/min). Her temperature was 103^{o}F. On auscultation of lungs, diffuse bilateral crepitations were found. The oxygen saturation was 59% and she was given 5 litres of oxygen via non-rebreathing mask. On admission, complete blood count showed white cell count 8.5 x 10^{9}L (normal range 4-11 x 10^{9}L), Hb 10.2g/dL (normal range 12.5-15 g/dl), AST 122U/L (normal range 5-40U/L) and D-dimers 907ng/ml (normal range 220-500ng/ml). Rest of the laboratory tests were normal. Chest X-ray demonstrated bilateral opacities in the left lower lobe and upper half of right lung (Figure). Results of ABGs were as follows: pH 7.32 (normal range 7.35-7.45), PaO_2 35.1mm Hg (normal range 75-100mmHg), $PaCO_2$ 33.6mm Hg (normal range 35-45mmHg), bicarbonate 17.3 mEq/L (normal range 22-28mEq/L), and O_2 saturations 87% (normal range >92%).

On Day 1, Patient was shifted to intensive care unit. She was kept in isolation. Intravenous antibiotics (Tazocin, Targocid, and Leflox) along with Tamiflu (Oseltamivir) and steroids were started for suspected pneumonia. She was given non invasive ventilation initially but her oxygen saturations were below 80% so she was eventually sedated and intubated. Next day (Day 2), her O_2 saturation was 89% on fiO_2 100%. B.P 101/60 mm Hg. CXR and ABGs improved. Urinary output was 1.1L/24 hours. She was hyperglycaemic. Her Blood Glucose (random) was 382mg/dl (normal range

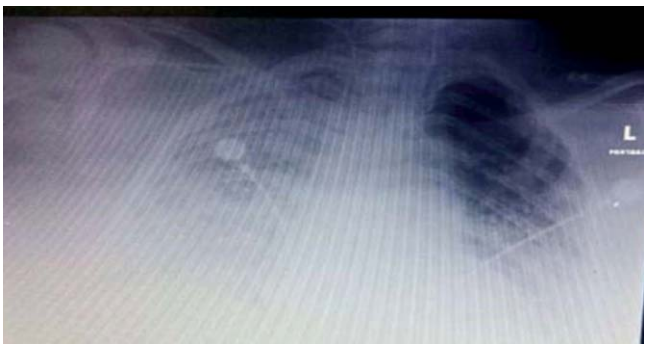

Figure-1: Chest X-ray AP view, showing bilateral infiltrates at the time of admission.

140-200mg/dl) so Insulin (R) was started on sliding scale. Rest of the treatment was continued. On Day 3, her O_2 saturations were 90% on fiO_2 85%. CXR showed Bilateral infiltrates more on left side. Her GFR decreased to 68ml/min from 81ml/min (normal range >90ml/min) but urine output was 1.4L. Her Hb dropped to 10g/dl from 13.3g/dl. Stool for occult blood was done which was positive. Her pulse was below 50bpm so holter monitor was attached. Then on Day 4, CBC showed raised white cell count 14.6 x 10^9/L. Pro-calcitonin was 0.089ng/ml (normal <0.15ng/ml). Holter report showed 2nd degree heart block Mobitz type 1. GFR was 69 ml/min but Creatinine was 1.0 mg/dl (normal range 0.2-1.2mg/dl). Throat Swab was taken and sent to NIH for testing H1N1 influenza. Rest of the treatment was same. On the 5th Day, H1N1 result came back positive. Her white cell count further increased to 18.6 x 10^9/L. She remained on ventilator support with fiO2 65%. ABGs and RFTs were normal. At this point, 5 days of Oseltamivir were completed. Then next day (Day 6), patient was febrile with 101° F temperature. Her Creatinine jumped to 2.47mg/dl, GFR 24 ml/min. Pro-calcitonin also rose to 2.22ng/ml. ABGs showed metabolic acidosis. LFTs showed high bilirubin of 2.9mg/dl (normal range 0.1-1.2mg/dl). Tazocin and Targocid were discontinued and Meronem and tigecycline were added in the treatment plan.

In spite of vigorous management, patient showed minimal improvement in ICU. On the 7th day of her admission, her SpO_2 dropped to 85% on fiO_2 100%. White cell count increased to 26.31 x 10^9/L. Creatinine was 4.3mg/dl, GFR 13ml/min, K+ 6.28 mEq/L (normal range 3.5-5.0mEq/L). Unfortunately, she went into a cardiac arrest. After 45 minutes of unsuccessful resuscitative efforts, she was declared dead. The cause of death was documented to be Influenza Virus H1N1 strain leading to pneumonia.

Discussion

An evaluation of the literature discovered that the Influenza H1N1 strain is fatal for children and immunocompromised individuals. There are only a few instances in immunocompetent hosts that ended in loss of life because of Influenza H1N1 strain. Why our patient became unexpectedly susceptible to H1N1 virus is unclear. One feasible explanation is probably resistance to Oseltamivir. Oseltamivir is the commonly used antiviral medication to treat influenza flu illness.[5] Oseltamivir belongs to the class of drug called "NA inhibitor" because this drug has the ability to bind to NA proteins of influenza virus and inhibit their enzymatic activity.[5] NA proteins plays an important role in spreading of virus from affected cells to healthy cells of the body. If these proteins undergo mutation, oseltamivir loses ability to bind to NA proteins. As a result, virus continues to spread to healthy tissues. This leads to "oseltamivir resistance" (non-susceptibility). A specific mutation known as"H275Y" is the only known mutation currently to cause oseltamivir resistance in 2009 H1N1 flu viruses.[5] The "H275Y' mutation makes oseltamivir unsuccessful in influenza virus by preventing oseltamivir from inhibiting NA proteins activity. This allows virus to spread indefinitely.

Remarkably, the increase in growth of oseltamivir resistance in seasonal influenza viruses has taken place in the absence of significant worldwide use; the reason is uncertain.[6] To lower the risk of antiviral resistance, these drugs must be used correctly and at doses which are according to the published guidelines.

H275Y mutations strains are antigenically similar to vaccine strains. Therefore, immunization remains the major means of preventing the spread of Influenza caused by H1N1 as well as other strains.[6]

In order to overcome this challenge, we need to increase the quantity of surveillance sites in addition to growing the number of laboratories which can check for antiviral resistance. Yearly flu vaccination is an effective way to diminish the risk of influenza virus and its lethal complications.[5] CDC recommends that everybody from 6 months of age and older get vaccinated every year.[5] A range of recent antiviral agents are being developed, and numerous of them display promising outcomes in scientific trials. Furthermore, oseltamivir resistance strain is still vulnerable to zanamivir. However, the zanamivir use is limited because it is available in the form of inhaler and cannot be given to patients who are on ventilator.[6] If the patient is suitable for inhaled zanamivir, it may be rational to change antiviral medications before antiviral resistance testing is made available.[6]

Conclusion

The patient described in the case report was unusually susceptible to H1N1 influenza virus. The reason is still

unclear. Even though she was completely healthy with no co-morbid, her condition deteriorated rapidly and progressed to pneumonia with diffuse alveolar damage. Despite starting oseltamivir (tamiflu) within two days of onset of symptoms, and completing full course, patient did not survive unfortunately.

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