ANNALS of Hepatology

CASE REPORT

January-March, Vol. 9 No.1, 2010: 107-111

Liver involvement in severe human influenza A H1N1

Raúl Carrillo Esper,* Estela Pérez Bustos,**
Sofía Ornelas Arroyo,** Jorge Albores Saavedra,*** Misael Uribe****

* Chief of Intensive Care Unit. ** Internal Medicine Resident. *** Director of the Pathology Department. **** Chief of Internal Medicine Department. Fundación Clínica Médica Sur.

ABSTRACT

Influenza A is a disease caused by a RNA virus, member of the orthomyxoviridae family. The influenza infection is characterized primarily by pulmonary affection that may advance to an acute pulmonary respiratory failure course. Hepatic involvement is not frequent and accounts for < 3% of all cases. We describe two patients with acute Influenza A H1N1 infection who developed hepatic involvement. Needle core liver biopsy of one of the patients revealed only micro and macrovesicular steatosis.

Key words. Human Influenza A H1N1. Hepatic involvement. Cytokine dysregulation.

INTRODUCTION

Influenza A virus is a member of the orthomyxoviridae family consisting of a single stranded RNA virus which has the ability to undergo periodic changes in its antigenic characteristics of the envelope (hemagglutinin and neuraminidase). These antigenic changes are responsible for the distinct outbreaks every year. There are three major subtypes of hemagglutinine H1, H2, H3, and two subtypes of neuraminidase N1 and N2. Major changes in these glycoproteinns are referred to as antigenic shift and minor changes are called antigenic drifts; antigenic shift is associated with epidemics and pandemics.[1]

The Infection can be transmitted through sneezing, coughing and talking, via small particles (aerosols). It is characterized by pulmonary affection with cough, fever, malaise and headache, showing spontaneous remission after 6 to 8 days. Severe infection is characterized by pneumonia sepsis, septic shock and multiorgan failure. Extrapulmonary involvement is rare in uncomplicated infections. Hepatic involvement has been described in children and in cases of fatal infection with avian influenza H5N1 as well as hepatic decompensation in patients with cirrhosis.[2,3] We therefore report two cases of previously healthy patients who suffer severe influenza A H1N1 infection developing liver involvement. In both cases acute and chronic alcoholism was negative as well as viral liver markers (A, B, C). To our knowledge, this is the first report of this complication during the Mexico City epidemic.

CASE 1

A 37 year-old previously healthy female presented with rinorrhea, cough and fever up to 39 ºC of ten days duration. She was admitted to the intensive care unit (ICU) with acute respiratory failure requiring mechanical ventilation. The chest x-ray showed disseminated heterogeneous opacities in both lungs compatible with primary severe acute respiratory distress syndrome (ARDS) caused by atypical pneumonia (Figure 1A). Nasal secretion samples were negative for influenza virus type A. Blood cultures and broncheoalveolar lavage cultures were negative for bacterial or fungal organisms. During her ICU stay she developed septic shock requiring the use of high doses of vasopressor drugs (epinephrine and vasopressin) and hepatic involvement with hypertransaminasemia and hyperbilirrubinemia (Table 1). A liver ultrasound (US) showed no abnormalities (Figure 1B). Initial management included broad spec-

Correspondence and reprint request: Dra. Estela Pérez Bustos.
Fundación Clínica Médica Sur. Puente de Piedra No. 150, Col. Toriello Guerra, Deleg. Tlalpan, C.P. 14050, Tel.: 5424-7200,
E-mail: buzzy_pb@yahoo.com

Manuscript received: August 16, 2009.
Manuscript accepted: September 17, 2009.

trum antibiotics, drotecogin alpha (Human Activated Protein C), antioxidants, hemoderivates, oseltamivir, prone position, alveolar recruitment and high PEEP levels. Despite these strategies the organ failure progressed causing her death on the 16th day of hospitalization, due to severe hypoxemia and refractory septic shock. A postmortem liver biopsy reported micro and macro vesicular steatosis, and the postmortem RT-PCR was positive for influenza A H1N1.

Table 1. Evolution of liver enzymes during the ICU stay in case 1.

Day ICU Stay	Bilirrubins	Conjugated Bilirrubin	Unconjugated Bilirrubin	ALT	AST	ALP	Albumine	Globulin	Prothrombine Time
Laboratory reference	0.4-1.5 mg/dL	0.0- 0.3 mg/dL	0.3- 0.4 mg/dL	17- 63 U/L	15 -41 U/L	32- 91 U/L	3.5- 4.8 g/dL	2.3- 3.8 g/dL	9.0- 12.0 sec
1	1.4	0.6	0.9	64	94	168	5.6	3.4	10.0
2	1.5	1.9	0.6	51	79	1223	1.8	2.3	10.6
3	2.4	1.5	0.8	44	56	96	2.1	2.1	11.3
4	4.8	3.1	1.7	44	70	79	2.4	2.2	11.3
5	5.7	3.7	1.9	51	74	63	2.4	2.6	11.7
6	5.8	3.7	2.2	39	47	58	2.4	2.7	11.8
7	4.4	2.7	1.6	43	81	66	2.7	2.3	10.6
8	4.2	2.5	1.6	71	18	106	3.3	2.3	11.0
9	4.5	1.7	1.6	74	71	170	3.4	2.4	11.4
10	3.0	1.3	1.2	55	73	127	3.2	2.0	13.4
11	2.3	1.5	1.0	98	129	118	3.5	2.1	12.7
12	2.6	1.0	1.1	90	87	135	3.8	2.0	12.7
13	2.2	1.1	1.1	77	62	127	3.5	2.2	12.0
14	2.2	1.14	1.1	64	47	115	3.5	2.2	11.7
15	2.2	2.09	1.1	54	46	109	3.4	2.2	11.4
16	3.2	2.09	1.1	52	63	122	3.1	2.2	11.2
Median	2.6	1.5	1.1	53.7	56.6	100.9	2.9	2.34	10.93
SD	1.37	0.98	0.44	24.74	17.32	33.22	0.88	1.37	4.24

ICU: Intensive Care Unit. **ALT:** Alaninoaminotranferase, **AST:** Aspartatoaminotransferase, **ALP:** Alkaline Phosphatase.

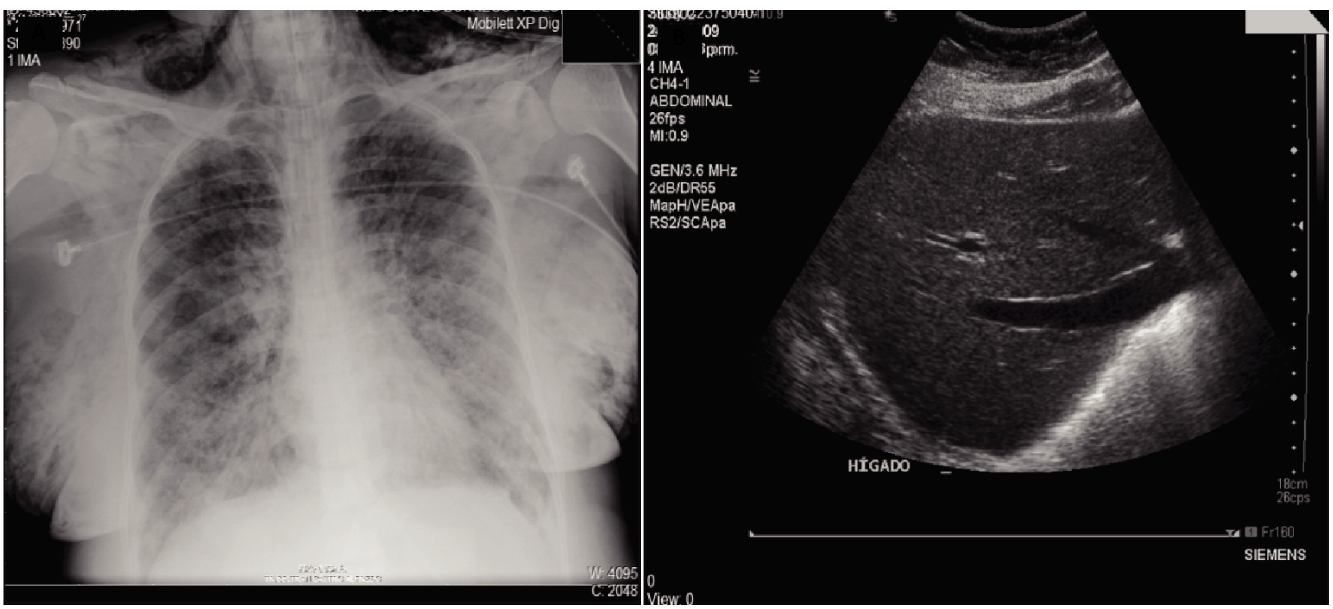

***Figure 1**. A. Chest X-ray showing disseminated heterogeneous opacities, B. Hepatic ultrasound showing a normal parenchyma and intrahepatic bile ducts*

CASE 2

A 57 year old male with arterial hypertension under medical control, presented with fever, malaise and cough of 7 days duration. He was admitted to the ICU with acute respiratory failure and persistent severe hypoxemia, requiring mechanical ventilation. Chest x-ray showed disseminated heterogeneous opacities in both lungs compatible with ARDS (Figure 2A). Nasal secretion samples were positive for Influenza A and RT-PCR confirmed influenza A H1N1. There were no bacterial or fungal organisms in hemoculture and bronchoalveolar lavage. During his ICU stay he developed septic shock and liver involvement characterized by hypertransaminasemia, moderate hyperbilirrubinemia and progressive hyperammonemia (Table 2). Abdominal US showed no abnormalities (Figure 2B). Management included vasopressor drugs (epinephrine and vasopressin) broad spectrum antibiotics, drotecogin

Table 2. Evolution of liver enzymes during the ICU stay in case 2.

Day ICU Stay	Bilirrubins	Conjugated Bilirrubin	Unconjugated Bilirrubin	ALT	AST	FA	Albumine	Globulin	Prothrombine	Amonia
Laboratory reference	0.4-1.5 mg/dL	0.0- 0.3 mg/dL	0.3- 0.4 mg/dL	17- 63 U/L	15 -41 U/L	32- 91 U/L	3.5- 4.8 g/dL	2.3- 3.8 g/dL	9.0- 12.0 sec	19-69 µg/dL
1	1.4	1.09	1.34	48	98	320	3	3	10.7	
2	1.5	1.07	1.11	47	93	318	2.7	3.1	10.7	
3	2.4	1.02	1	51	93	315	3.1	3.5	11.4	
4	4.8	0.9	1.05	55	98	352	3	3.4	11.3	223
5	5.7	0.89	0.86	59	115	464	3.4	3.1	10	193
6	5.8	1.16	1.21	81	158	462	3.1	3.5	11.6	142
7	4.4	0.73	1.05	67	114	353	3.1	3.4	12.3	159
8	4.2	0.99	0.85	103	208	372	2.9	3.7	11.7	149
9	4.5	0.83	0.9	94	149	372	2.8	3.9	11.7	99
10	3.0	0.66	1	80	120	375	2.7	3.8	12	116
11	2.3	0.64	0.83	62	79	358	2.7	4.2	12.7	95
Median	1.87	0.87	0.99	63.54	111.99	363.34	2.93	3.47	10.9	135.69
SD	0.30	0.17	0.15	19.05	37.67	51.29	2.95	0.370	1.41	41.88

ICU: Intensive Care Unit. **ALT:** Alaninoaminotranferase. **AST:** Aspartatoaminotransferase, **ALP:** Alkaline Phosphatase.

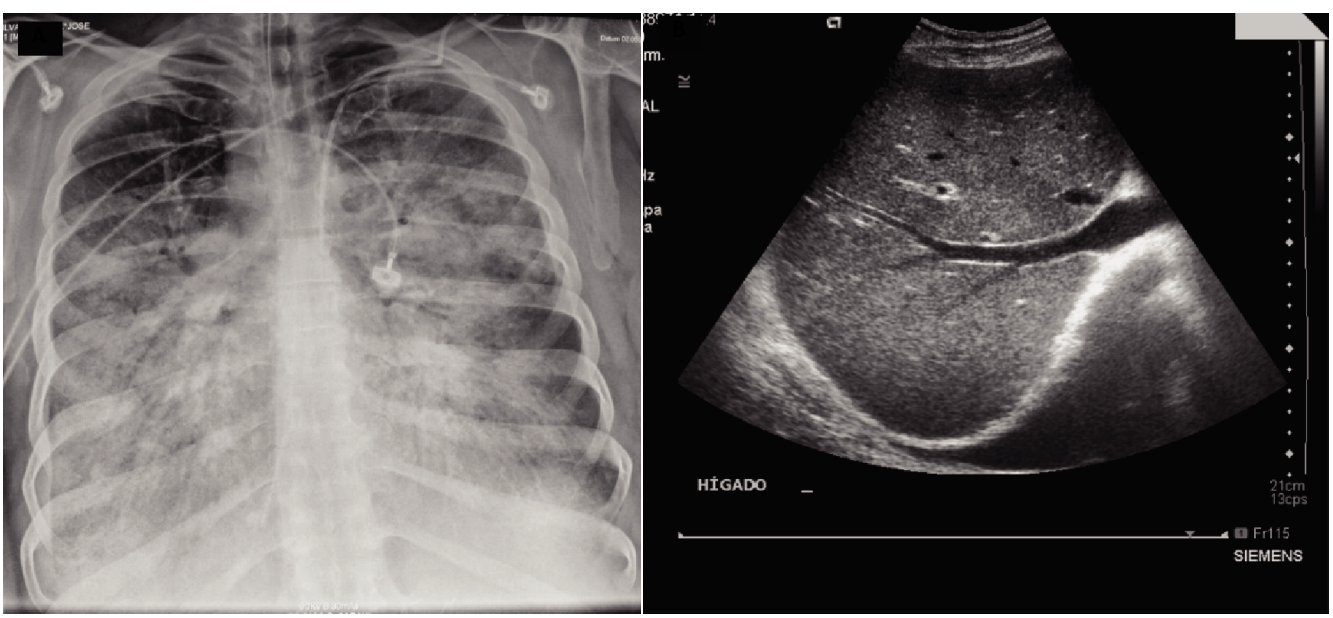

***Figure 2. A.** Chest X-ray showing disseminated heterogeneous opacities, **B.** Hepatic ultrasound showing a normal parenchyma and intrahepatic bile ducts.*

alpha (Human Activated Protein C), antioxidants, haemoderivates, oseltamivir, prone position, alveolar recruitment and high PEEP levels. Hepatic encephalopathy grade 2-3 developed requiring the use of lactulose enemas and L-ornitin aspartate. The patient presented improvement, in his general conditions and no longer required the use of vasopressor drugs. There was normalization of aminotranferases, bilirrubines and ammonia levels and betterment of pulmonary function without hypoxemia. No biopsy was obtained on this patient who is currently in the ICU, alert and with clinical improvement.

COMMENT

Influenza is an acute and generally self limited respiratory illness. Viral replication only takes place in the respiratory epithelium and viral shedding usually lasting between 2 to 5 days since the beginning of the symptoms and then clears out. Common extrapulmonary complications are myositis, renal failure, myocarditis, pericarditis and meningoencefalitis.[2] The uncommon extrapulmonary complications include hepatic dysfunction and failure with elevation of hepatic enzyme levels reported in 2.7% of individuals during an outbreak of influenza A.[4] During de influenza H1N1 outbreak of 1978-1979 in Michigan Monto[5] described liver compromise in 1.5 % of their patients positive for the influenza infection by presenting elevation of aspartatoaminotransferase and alaninoaminotransferase AST up to 60U/L; elevated values were no clinically related to any syndrome. These findings were similar to those found in our patients, who had elevation of aspartatoaminotransferase and alaninoaminotransferase, bilirrubin and in one case blood ammonia elevation and hepatic encephalopathy.

Liver affection during influenza virus infection has been shown in experimental animal models. Mice infected intranasally with influenza A/PR8 virus expressed messenger RNA in the liver, spleen, kidney, heart and muscle; the amount of expression was proportional to the rate of lung involvement. No viral replication is needed to produce hepatic damage as there is evidence of hepatic oxidative stress and decrease in antioxidant defenses even when the virus is isolated only from lung. This might be explained by the production of interleukin-6 (IL-6), IL-8, IL-10, tumor necrosis factor α (TNFα), interferon α, β and γ in the respiratory airway that leads to changes in fatty acid metabolism and decrease activity enzymes like the ornithine carbamyl transferase (OCT),[3] succinic dehydrogenase with impaired β-oxydation of palmitic and octanoic acids at mitochondrial level producing an increase in fatty liver deposits and loss of glycogen in the liver parenchyma.[6,7] In case 1 the liver biopsy showed micro and macrovesicular steatosis findings similar to those reported by Murphy[8] who described that Influenza viruses can directly activate monocytes and polimorphonuclear leukocytes that generate reactive oxygen species (ROS) by an increase in the activity of the xanthine/xanthine oxidase (superoxide-generating enzyme) and decrease in superoxide dismutase, producing oxidative stress as noted in liver samples of mice in early stages of influenza virus infection (before consolidation occurred) with diminished concentrations of antioxidants such as vitamin C and glutathione in early stages of the infection.[8] In a study in mice models they found greater liver expression in the Metallothionein I (MT-I) and MT-II genes;[9] these proteins arrest potent free radicals in order to maintain redox balance. The findings in the studies about liver injury and viral influenza infection performed in animal models supported that the primary insult to produce liver injury is the overproduction of free radicals by the host immune response and the diminished production of mitochondrial antioxidants by the hepatocyte.

The pathogenesis of fatal illness and extrapulmonar involvement associated with influenza A H1N1 is still not well understood. Studies of avian influenza showed an overactive inflammatory response and the severity of the infection is related with virus-induced cytokine dysregulation wich leads to extreme production and secretion of a large number of pro inflammatory cytokines. These changes are not exclusive of influenza H5N1. High expression of cytokine genes have been found in the lungs of mice and nonhumans primates infected with the reconstructed 1918 H1N1 influenza virus. Extrapulmonary dissemination may be the result of viremia and/or the transport infected immune cells to other organs. Viral RNA has been detected in liver tissue specimens, of mice infected with influenza who also showed necrosis, activated Kupffer cells, cholestasis, and fatty changes. The highest viral loads were detected in the fatal case suggesting that high viral loads correlate with cytokine overproduction and extrapulmonary dissemination. Septic shock induced by the infection with influenza virus H1N1 produces tisular hypoperfusion which along with persistent hypoxemia due to pulmonary damage, contributes to cellular damage, that may lead to liver damage and hypertransaminasemia.[10]

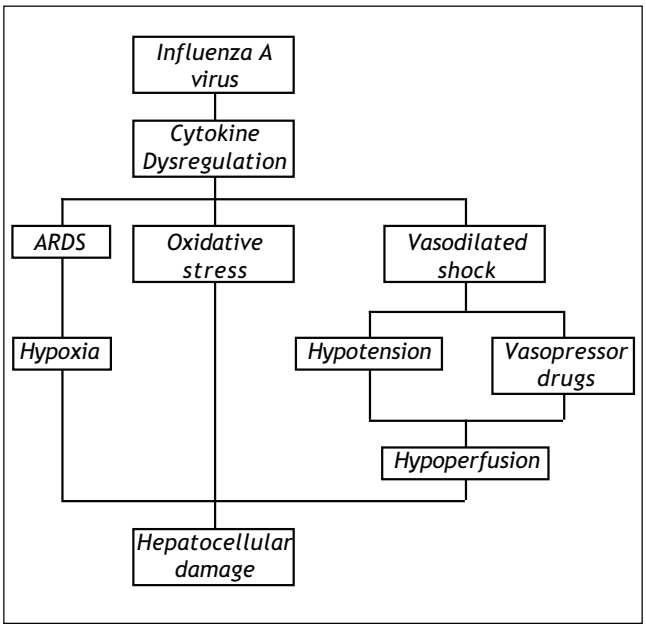

***Figure 3**. Mechanisms of liver damage in influenza H1N1. Severe infection with human influenza A H1N1 generates cytokine dysregulation and cytokine storm which promotes ARDS, oxidative stress and severe sepsis with vasodilatory shock which generate splachnic hypoperfusion and hepatocellular damage.*

In conclusion, this report describes the first two cases of hepatic involvement associated with human influenza A H1N1 during the Mexico City epidemic. The mild hepatic involvement in these patients was probably related to viral infection, amplified the cytokine dysregulation, plus hypoxia and liver hypoperfusion. (Figure 3).

REFERENCES

1. Fauci AS, Kasper DL, Longo DL, Braunwald E, Hauser SL, Jameson L. Influenza. 17th Ed. McGraw-Hil;l 2008.
2. Murphy B, Webster R. Orthomyxoviruses. Philadelphia, USA: JB Lippincott; 1996.
3. Kang ES, Lee HJ, Boulet J, Myers LK, Cook GA, Bean W. Potential for hepatic and renal dysfunction during influenza B infection, convalescence, and after induction of secondary viremia. *J Exp Pathol* 1992; 6: 133-44.
4. Duchini A, Viernes ME, Nyberg LM, Hendry RM, Pockros PJ. Hepatic decompensation in patients with cirrhosis during infection with influenza A. *Arch Intern Med* 2000; 160: 113-15.
5. Monto AS, Ceglarek JP, Hayner NS. Liver function abnormalities in the course of a type A (H1N1) influenza outbreak: relation to Reye's syndrome. *Am J Epidemiol* 1981; 114: 750-9.
6. Duchini A, Hendry RM, Redfield DC, Pockros PJ. Influenza infection in patients before and after liver transplantation. *Liver Transpl* 2000; 6: 531-42.
7. Murphy M. Secuestration of Coenzyme A by the industrial surfactant, Toximul MP8 A possible role in the inhibition of fatyy-acid â-oxidation in surfactant/influenza B virus mause model for acute hepatic encephalopathy. *Biochimica et Biophysica Acta* 1997; 1361: 103-13.
8. Hennet T, Peterhans E, Stocker R. Alterations in antioxidant defenses in lung and liver of mice infected with influenza A virus. *J Gen Virol* 1992; 73: 39-46.
9. Ghoshal K, Majumder S, Zhu Q, Hunzeker J, Datta J, Shah M. Influenza virus infection induces metallothionein gene expression in the mouse liver and lung by overlapping but distinct molecular mechanisms. *Mol Cell Biol* 2001; 21: 8301-17.
10. Korteweg C, Gu J. Pathology, molecular biology, and pathogenesis of avian influenza A (H5N1) infection in humans. *Am J Pathol* 2008; 172: 1155-70.
11. Prevention and control of influenza. Recommendation of the Immunization Practices Advisory Committee. Centers for Disease Control, Department of Health and Human Services. *Ann Intern Med* 1985; 103: 560-5.