Case report

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Fatal Viral and Bacterial Septicemia in a Seventeen-Year-Old Woman with Immunodepressive Influenza A H1N1: An Autopsy Case

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Abstract

The Influenza A H1N1 subtype can present with a wide spectrum of severity, from mild symptoms of influenza to severe respiratory distress. The morbidity and mortality connected to influenza are mostly associated with secondary bacterial infections. The influenza syndrome alone can cause a massive release of cytokines with dysregulation of the immune system, and it can act in synergy with other bacteria which can enhance cytokines secretion. This article deals with a case of severe pneumonia of H1N1 in a 17-year-old woman with bacterial superinfection with Staphylococcus aureus characterized by a high level of interleukine-6 (105900 pg/mL) and the appearance of severe leukopenia with immuno-suppression, such that HIV infection and hematological diseases were included in the initial differential diagnosis. After death, the autopsy confirmed the presence of severe pneumonia, in addition to an hepatic steatosis in absence of other risk factors. This case reports the rapid and lethal course of influenza A / H1N1 in a young and healthy subject without co-morbidities, in an age group in which mortality is about 0.3 deaths per 100,000. The case underlines the importance of quickly diagnosis of viral infections and the differential diagnoses with other immunosuppressive diseases, which can be fatal even in adolescent and healthy subjects. ***Clin Ter 2024; 175 (2):95-100 doi: 10.7417/CT.2024.5039***

Keywords: *Influenza A, H1N1, immune-suppression, Il-6 response*

Introduction

Influenza is an acute inflammatory disease caused by a virus from the Orthomyxoviridae family, usually transmitted through droplets and contact (1). Influenza infections occur worldwide, with an estimated annual global attack rate of 5-10% in adults and 20-30% in children. In temperate zones, epidemics primarily occur during winter (2). According to the CDC, influenza caused between 9 million and 41 million illnesses, with 140,000-710,000 patients treated in clinics/hospitals and 12,000-52,000 deaths per year between 2010 and 2020 (3). Individuals over 65 years old are at a greater risk of developing serious complications from influenza compared to young, healthy adults (3). Statistics from the United States indicate a mortality rate of 22.1 deaths per 100,000 in the age group 65 and over during the 2019-2020 period, while it drops to 0.3 deaths per 100,000 in the age group 5-17 years (4).

Since June 2009, the World Health Organization (WHO) has declared an epidemic of a new type of influenza A/H1N1 (5). Influenza A/H1N1 can present with a wide spectrum of severity, ranging from mild influenza symptoms to severe respiratory distress (6). The morbidity and mortality associated with influenza are primarily connected to secondary bacterial infections, with Staphylococcus aureus emerging as one of the main pathogens involved in superinfections (7-(9). Influenza viruses and Staphylococcus aureus synergistically act in the host's body, which is also linked to cytokine secretions. Furthermore, it has been documented that severe influenza syndromes caused by H1N1 can lead to a massive release of cytokines, resulting in immune system dysregulation regardless of secondary infection (8, 10).

This article discusses a case of severe pneumonia caused by H1N1 in a 17-year-old woman with a secondary bacterial infection by S. aureus, leading to the development of severe leukopenia and immunosuppression. After her death, an autopsy was performed, and further histological investigations were conducted on tissue samples collected during the investigation.

Case report

Medical history

Clinical signs and symptoms

The patient was a 17-year-old female non-smoker who presented with symptoms including sore throat, productive cough, erythema on the arms, and a slight fever in early March 2022. She took a mucolytic agent and paracetamol. A rapid antigen test for SARS-CoV-2 was performed, yielding a negative result. However, her condition worsened over

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the next few days. She experienced retching with saliva emission, followed by the development of a cutaneous rash on her face, neck, hands, and feet. On the fourth day after symptom onset, she developed respiratory distress, exhibiting dyspnea and a blood oxygen level of 88%. The patient was then admitted to the hospital with vital parameters including arterial blood pressure of 90/60 mmHg, a body temperature of 37.8°C, and a heart rate of 150 bpm.

Physical examination revealed signs of respiratory distress at rest, dysphonia, significantly reduced vesicular breath sounds upon lung auscultation, wheal-like marks on her skin, and a hyperemic pharynx. On the second day of hospitalization, the patient was transferred to the intensive care unit and diagnosed with "ARDS due to Influenza." She remained febrile with a temperature of 38.2°C and required orotracheal intubation. Thoracic examination revealed reduced lung sounds throughout all areas with the presence of basal crackles. Despite medical interventions, the patient's clinical condition remained critical, and at 6:00 PM on the third day of hospitalization, she succumbed to multi-organ failure.

The administration of supplemental oxygen with FiO2=28% did not improve the patient's breathing ability, leading to her transfer to the Intensive Care Unit where she was diagnosed with acute respiratory distress syndrome (ARDS) and intubated. Therapeutic interventions included the initiation of Oseltamivir, Piperacillin/Tazobactam, and Ceftobiprole. Film-array testing on a lower respiratory tract sample detected the presence of both Staphylococcus aureus and Influenza A/H1N1. Urine samples tested negative for Legionella pneumophila urinary antigens and Streptococcus pneumoniae. Additionally, the serum galactomannan antigen test and HIV serology were negative.

Laboratory tests

1st day

On the evening of the 1st day (at 9:20 PM), arterial blood gas (ABG) analysis showed a pH of 7.516, pO2 of 49, pCO2 of 32.5, SO2 of 87.6%, with lactate levels at 3.7. Hematochemical tests revealed total bilirubin levels of 2.71, azotemia of 85, leukocytes of 4250, neutrophils of 81%, lymphocytes of 10.2%, blood glucose of 141, AST (GOT) of 56, ALT (GPT) of 42, LDH of 600, PCR of 31.7, PCT of 44.41, and platelets of 177,000. A PCR test for SARS-CoV-2 was negative, while it was positive for influenza A1 and A2. Two hours later, the ABG showed an oxygen saturation (sO2) of 96.4%, pH of 7.519, pCO2 of 32.7, lactate levels of 4.3, and a P/F ratio of 139 with 28% oxygen support.

2nd day

PCR testing revealed the presence of Staphylococcus aureus DNA (>107) and influenza A virus RNA in the bronchoalveolar lavage sample. The HIV test was negative. Urinary antigen tests for Legionella and Streptococcus were negative, as well as the rectal swab. Methicillin-resistant Staphylococcus aureus (MRSA) was isolated from the nasopharyngeal swab. The pharyngeal swab PCR test was negative for atypical bacteria. At 11:44 AM, the ABG showed a pH of 7.24, pCO2 of 67.7, and lactate levels of 2.4. At 3:20 PM, the ABG indicated a worsening of respiratory performance: pH of 7.209, pCO2 of 69.2, pO2 of 71.4, sO2 of 91.8%, and lactate levels of 3.6. The ABG at 10:36 PM showed a pH of 7.162, pCO2 of 65, and lactate levels of 11.2. Hematochemical tests at 5:30 PM showed leukocytes of 710, platelets of 97,000, azotemia of 57, total bilirubin of 1.58, AST (GOT) of 64, ALT (GPT) of 40, and LDH of 517.

3rd day

At 1:13 AM, the hematochemical tests showed HS Troponin of 445.4, myoglobin of 1196, and the ABG revealed a pH of 7.248, pCO2 of 58.3, and lactate levels of 7.1. At 3:49 AM, HS Troponin was 518.9, and myoglobin was 1200. At 6:09 AM, the ABG showed a pH of 7.281, pCO2 of 58.9, pO2 of 111, and lactate levels of 5. At 6:54 AM, the hematochemical tests showed leukocytes of 910, platelets of 56,000, azotemia of 76, creatinine of 1.66, total bilirubin of 2.8, AST (GOT) of 114

The arterial blood gas analysis results are summarized in Table 1.

Further blood tests were performed, and the results are summarized in Table 2.

Tab 1. Main values taken from arterial blood gas analysis performed during hospital stay.

Day in hospital	pH	pO2 (mmHg)	pCO2 (mmHg)	sO2 (%)	Lactate (mmol/L)	FiO2(%)
1^ day	7.519	83.2	32.7	96.4	3.7	60.0
2^ day am	7.442	77.3	44.2	96.0	2.6	80.0
2^ day pm	7.182	77.8	69.6	93.0	3.6	100.0
3^ day	7.275	111.0	47.1	98.0	8.0	60.0

Tab 2. Principal values taken from hematic tests during hospital stay.

Day in hospital	Bilirubine mg/dL	Azotemia Mg/dL	Leukocytes/ mm3	Neutrophi-lis%	Lympho-cytes%	GOT UI/L	GPT UI/L	LDH UI/L	PCR mg/ dL	PCT ng/ml	Piastrine/ mm3
1^ day	2.71	85	4250	81	10.2	56	42	600	31.7	44.41	177000
2^ day am	-	-	1650	72.5	18.8	-	-	-	-	-	145000
2^ day pm	1.58	57	710	57.8	33.8	64	40	517	-	-	97000
3^ day	2.8	76	910	63.7	24.2	114	60	703	56.8	95.87	56000

Imaging Findings

1st day

Upon admission, the chest X-ray revealed acinar consolidations with sporadic inflammatory infiltrate in the mid-basal region of the lungs. Additionally, abdominal ultrasound showed widespread hepatic steatosis.

2nd day

A thoraco-abdominal CT scan showed complete consolidation of the lower left lobe with minimal air bronchograms, along with areas of ground glass opacities. Multiple consolidative opacities surrounded by ground glass opacities were observed. Multiple consolidative opacities were also present throughout the entire lower lobe, predominantly in the medial segment and apicodorsal segment of the right upper lobe. Small areas of ground glass opacities were mainly distributed in the peribronchovascular region of the lower segment of the left upper lobe. Additionally, a thin layer of left pneumothorax was detected in the middle field with a maximum thickness of 9mm. Bilateral basal pleural effusion was also observed. Lymph nodes with short axes were present in the mediastinal hilum and some in the bilateral supraclavicular and axillary regions. There was mild pericardial effusion, while the heart, thoracic aorta, main pulmonary artery, and pulmonary artery were within normal limits. A central venous catheter was positioned in the right subclavian vein, and an endotracheal tube was in place. Mild gastric distension was noted. The upper abdominal sections revealed an enlarged liver and a spleen within normal limits, with a maximum diameter of 7.5 cm. No focal bone lesions were observed within the examined skeletal segments.

The patient tested positive for methicillin-resistant Staphylococcus aureus (MRSA) from a nasal swab, and topical mupirocin therapy was initiated.

External examination and autopsy

At the external examination of the deceased individual, normal skeletal development with proportionate muscle mass and distribution of adipose tissue was observed. The skin exhibited diffuse reddish marbling, particularly prominent on the upper and lower extremities.

During examination of the thoracic organs, strong pleuro-parietal adhesions were found bilaterally in the pleural cavity, accompanied by fibrinous hemorrhagic pleural effusion. No thromboembolic formations were identified in the pulmonary vasculature.

No significant alterations were observed upon opening the head, except for mild congestion of the meninges. No abnormalities were found in the Circle of Willis. The brain appeared congested and slightly edematous, weighing 1050 grams.

The heart was regular in shape, weighing 228 grams, with a transverse diameter of approximately 11 cm, longitudinal diameter of approximately 9 cm, and a short axis of approximately 3 cm. Upon opening, the heart chambers appeared normal, with preserved wall thickness.

The lungs (925 grams on the left; 915 grams on the right) exhibited a normal shape and volume but had increased consistency and a purple color. Pink foamy material was observed leaking from the primary bronchi and terminal bronchioles in the lower airways. Upon sectioning, the lung tissue showed evident hepatization, along with signs of edema and congestion.

Histological

The histological examination of the lungs revealed evidence of acute bilateral interstitial pneumonia with extensive necrotic and hemorrhagic areas, accompanied by edema (Fig. 1 a-c). Both lung specimens exhibited fibrinous acute pleuritis and fibrothorax. Disseminated intravascular coagulation (DIC) was observed in the lungs, kidneys, and dermis, where thrombotic material was present (Fig. 1d). Severe fatty liver disease was observed, characterized by prominent lipid droplets in the perivenular area (Fig. 2). No significant findings were noted in the heart and brain.

Discussion

In the case we are describing, a young patient with Influenza A had a fatal outcome due to pneumonia caused by a bacterial superinfection with *S. aureus* and severe leukopenia. We conducted an autopsy and analyzed histological findings, along with clinical data, to investigate any underlying immunosuppressive conditions that could have contributed to the severity of the influenza infection. However, we did not find any chronic conditions associated with immunosuppression that are typically seen in serious cases of influenza.

It is worth noting that the young age of the deceased is less common for seasonal influenza, as it generally affects older individuals with comorbidities. (11)

In this particular case, both the viral and bacterial infections were acquired within the community, as the pathogens were detected upon the patient's admission to the hospital. The presence of a positive nasal swab for S. aureus from the second day of hospitalization may indicate a bacterial infection originating from within the patient's body. The occurrence of a secondary bacterial infection in influenza-related pneumonia is a widely recognized and common complication, documented in scientific literature. (12)

The laboratory tests have shown in this case a significant quantitative and qualitative alteration in the lymphocyte population, with CD4+ cells at 22% and CD8+ cells at 32%. The severity of this alteration prompted a differential diagnosis for HIV during the diagnostic work-up.

Furthermore, there was a notable increase in the level of IL-6 (105900 pg/ml) on the third day of hospitalization, indicating a massive release of cytokines. This release can be influenced by the septic state but also plays a crucial role in H1N1 infection. It is known that patients with acute respiratory distress syndrome (ARDS) caused by H1N1 exhibit elevated levels of interferons, cytokines, and serum chemokines, resulting in a cytokine storm that is associated with the development of severe multi-organ damage. (15)

Immunosuppression was attributed to the influenza infection and the concurrent bacterial coinfection, as the influenza virus can deplete innate immune responders, limit type I

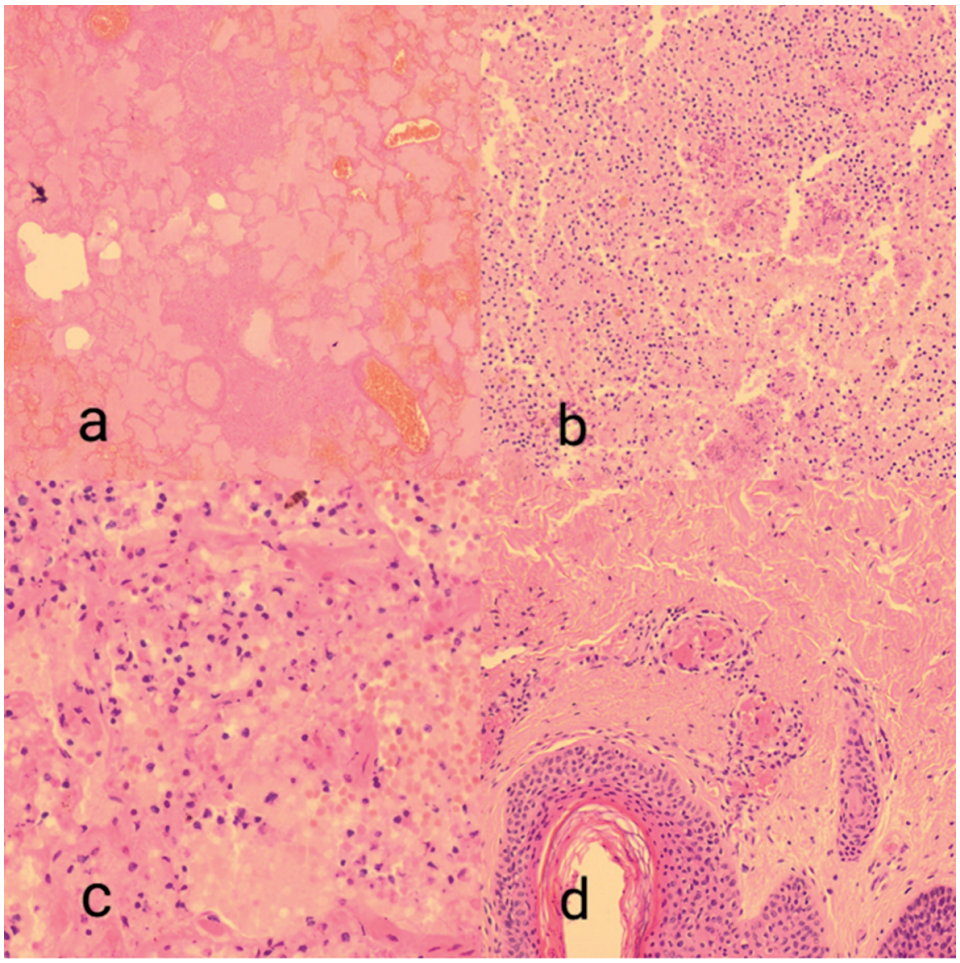

Fig 1. Microscopic examination of the lungs and skin revealed the following pathological findings: a) Lung section showing inflammatory infiltrates occupying the alveolar spaces, surrounded by areas of hemorrhage and necrosis (5x magnification). b) Infiltration of white blood cells primarily composed of neutrophils, along with areas of necrosis (20x magnification). c) Interstitial infiltration of lymphocytes accompanied by hemorrhagic areas (40x magnification). d) Skin section showing thrombosis of the dermal blood vessels (10x magnification).

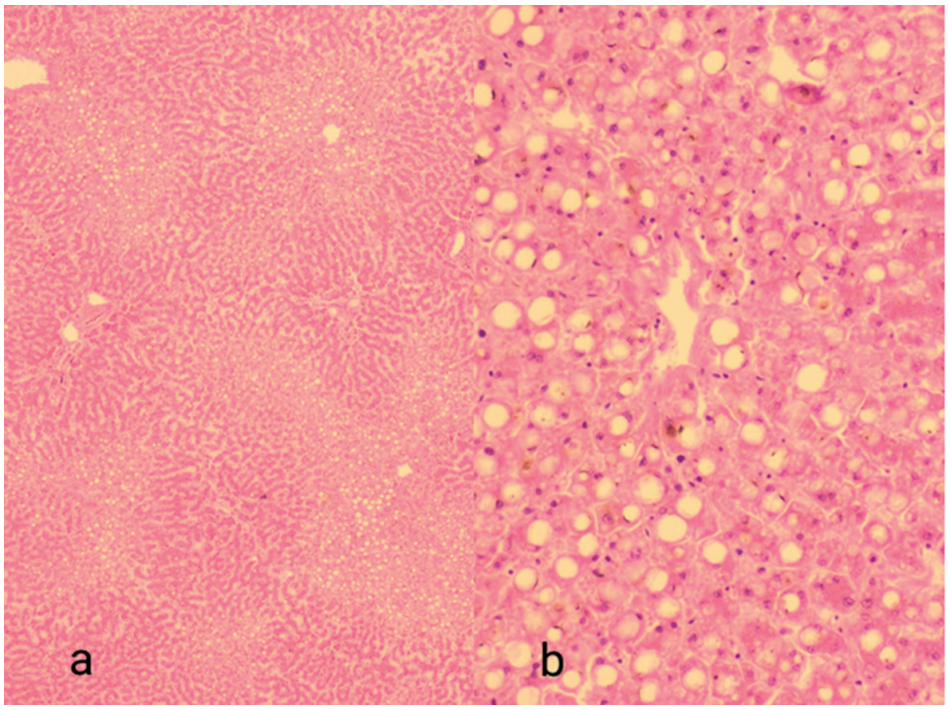

Fig 2. Histological analysis of the liver revealed the following findings: a) Widespread accumulation of fat in the liver parenchyma, known as diffuse hepatic steatosis (5x magnification). b) Close-up view of the liver lobule, highlighting steatosis in the central regions and around the centrilobular vein, accompanied by sporadic infiltration of lymphomononuclear cells. (40x)

interferon, increase oxidative stress and cytokine storm, or even damage lung tissue, thereby increasing susceptibility to secondary infection. Coinfection of influenza virus and certain bacteria can also result in a reduction in the number of germinal center B cells, plasma cells, and T cells in lymph nodes, as well as a decrease in antibody titers; however, this is typically attributed to prior suppression of the innate response.(16)

Therefore, it can be stated that the influenza virus, as described in the literature, can induce an immunosuppressive state by directly targeting activated immune cells, thus leaving patients vulnerable to severe diseases.(17)

From a histopathological perspective, the examination of lung tissue samples has corroborated the clinical information and revealed a pathological pattern indicative of a co-infection associated with extensive damage to the lungs. The presence of significant inflammatory infiltrates represents a crucial clinical feature observed in cases of secondary bacterial pneumonia resulting from viral influenza infection. (8)

It has been suggested that the damage to pulmonary tissue in this case arises from both the characteristics of the influenza virus and the ability of S. aureus to induce inflammation by triggering cellular pathways that activate NF-kB and stimulate the release of inflammatory cytokines (8). Moreover, in vitro studies have demonstrated how the combined infection of S. aureus and H1N1 enhances the inflammatory activity of certain pro-inflammatory bacterial toxins, leading to a significant influx of monocytes, polymorphonuclear neutrophils, and macrophages into the lungs. This process is accompanied by an intensified bacterial cytotoxicity against the recruited cells. (8)

Regarding this point, it has been noted that the poor outcomes related to pneumonia have been correlated to CA-MRSA, because of an increased production of the toxin Phenol-Soluble Modulins (PSM) as well as the leukocidin of Panton-Valentine, which is mostly expressed by methicillin resistant strains compared to methicillin-sensitive strains. (8)

The histological examination revealed severe hepatic steatosis in the absence of any previous history of alcohol consumption or liver disease. This finding was correlated with the progressive elevation of liver enzymes since admission to the hospital. Although it is difficult to exclude the possibility that the increase in circulating liver enzymes was caused by a septic condition in this case, the literature occasionally describes a hepatotoxic effect of the virus as one of the extra-pulmonary complications associated with H1N1 infection. The histological tests demonstrated severe steatosis along with an increase in markers of hepatic damage, indicating either the worsening of pre-existing liver disease or the development of new damage. Proposed mechanisms include dysregulation of cytokine secretion, hypoxia, the generation of free radicals, and reduced hepatic perfusion, although it is not possible to establish a direct correlation between severe steatosis and infection in this case (18), (19).

The remaining histological findings in the kidneys, dermis, and lungs led the authors to hypothesize the occurrence of terminal disseminated intravascular coagulation (DIC) in response to septic shock.

Ultimately, this case highlights the importance of a differential diagnosis between influenza and other pathologies, considering the complex immunological responses induced by the influenza virus, which can present with aggressive clinical manifestations even in young patients without a history of underlying immunosuppressive conditions. In this case, the autopsy and histopathological investigations played a crucial role in establishing a comprehensive understanding of the case and confirming the clinical data.

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Conflicts of interest

All Authors declare no conflict of interest.

Availability of data and material

N/A

Code Availability

N/A

Authors' contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by GC, LT, FF, AP, AU. DF provided the medico-legal reports and clinical charts. Prof AC coordinated the drafting of the article. All authors read and approved the final version of the manuscript.

Ethics approval

N/A

Consent to participate

N/A

Consent for publication

N/A

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