

Bronchiolitis in an infant due to influenza A, necropsy findings: a case report

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Abstract: The influenza virus is an important cause of respiratory disease in infants and presents challenging differential diagnoses to investigate. This is a case report that involves a necroscopic study of a 2-month-old male infant, without previous comorbidities, with a serological diagnosis of influenza A and histopathological presentation of non-obliterating bronchiolitis. Infants are considered a high-risk group for flu complications due to the immaturity of the immune system and the ability to respond to respiratory infections. Furthermore, the severity of infection in infants may be worsened by the difficulty in quickly considering and treating the symptoms of the disease.

Keywords: Bronchiolitis; Infant; Influenza virus; Autopsy; Case report.

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1. Introduction

The influenza virus is an important cause of respiratory illness in children [1, 2]. Although for most of them the flu is a self-limited infection with symptoms resolving within around a week, many pediatric patients experience complications, which can progress to serious illness, including respiratory failure and death [1]. According to the Centers for Disease Control (CDC), the risk of serious complications from the flu is highest among children under 2 years of age, who have much higher rates of hospitalization for complications related to the illness [3].

Additionally, infection rates are consistently higher in children, and each year approximately 870,000 children under age 5 are hospitalized worldwide due to influenza [4]. It is estimated that between 28,000 and 111,500 deaths in children under 5 years of age are attributable to influenza-related causes, the vast majority of which occur in developing countries [5]. We report here a case of autopsy of an infant with positive serology for Influenza A and fatal outcome. The clinical picture involved respiratory failure triggered by bronchiolitis.

2. Case Report

A male patient aged 2 months and 27 days, resident of Botucatu, sought the Children's Emergency Room (PSI) in his city of origin with an episode of fever and respiratory discomfort. Upon admission, he was dyspneic, with subcostal indrawings and slight retraction of the wishbone, in addition to a respiratory rate of 87 rpm. Clinical findings reveal lower respiratory impairment with tachypnea and difficulty breathing in room air.

The patient had been discharged from hospital 3 days ago, after a previous hospitalization lasting 7 days with a suspected diagnosis of viral bronchiolitis and positive serology for influenza A. At the beginning of the first admission, the patient also presented a clinical picture of fever and worsening of the pattern. respiratory, for 1 day, with nasal obstruction and decline in general condition for 3 days, in addition to the sister with flu-like symptoms. Hospitalization was carried out for oxygen therapy and oseltamivir, in addition to support measures and monitoring of vital signs. Therefore, after a week of observation, it was decided to discharge, given good clinical improvement, good general condition, and no use of supplementary oxygen for more than 24 hours. The family was advised to maintain social isolation for 14 days and return early if necessary.

Serology for COVID 19 (quick test) and Respiratory Syncytial Virus (RSV) were negative, but the Influenza test (by immunochromatography) was reactive for Influenza A. The results of the patient's latest laboratory tests are presented in the following table (Tables 1 and 2).

Table 1. The values demonstrate microcytic hypochromic anemia with anisocytosis, platelet anisocytosis and leukocytosis with a predominance of polymorphonuclear cells (neutrophils).

Hemogram	Results	Reference values
Hemoglobin	9.1 g/dL	9.4 - 13.0
Hematocrit	28 %	28.0 - 42.0
Mean corpuscular volume of red blood cells	81.8 fL	87.0 - 103.0
Mean corpuscular hemoglobin	26.5 pg	27.0 - 33.0
Red Cell Distribution Width (RDW)	15.6 %	11.5 - 14.0
Platelets	624.000 /mm ³	210.000 - 650.000
Platelet Distribution Width (PDW)	11.8 %	25.0 - 65.0
Leukocytes	19.5 mil /mm ³	5.0 - 15.0
Neutrophils	7.41 mil /mm ³	1.0 - 5.0
Lymphocytes	8.97 mil /mm ³	4.0 - 10.0
Monocytes	0.98 mil /mm ³	0.4 - 1.2

In the imaging examination that preceded death, it was possible to observe X-ray with an anteroposterior incidence, rotation technique is observed, with the trachea displaced and heart deviated, both to the left, in addition, the clavicles are not equidistant from the center, however it is possible to identify the thymus at the base of the heart (Figures 1A and 1B). Furthermore, in the lung parenchyma on the right, an enlarged thin interstitial network can be seen that reaches the distal third. There are areas of coarse

alveolar consolidation close to the hilum and a slight blurring of the cardiac area on the right, with little visible lung area on the left. In profile, air is observed in the retrosternal region and a certain degree of lung hyperinflation. The diaphragmatic domes are level and slightly straightened. There is an increase in the fine interstitial vascular network with the presence of cisuritis, as well as the presence of two intercisural effusions. There is no evidence of aerobronchogram.

Table 2. C-reactive protein (CRP) shows inflammatory stress and arterial blood gas analysis significant reduction in O₂ partial pressure (tissue hypoxia).

Gasometer	Results	Reference values
pH	7.43	7.35 - 7.45
Partial pressure of CO ₂	38.5 mmHg	35.0 - 45.0
Partial pressure of O ₂	65.4 mmHg	80.0 - 100.0
Bicarbonate	25.3 mmol/L	22.0 - 26.0
Base excess	1.2 mmol/L	-2.00 a +2.00
Lactic acid	0.99 mmol/L	< 2.00
C-reactive protein	8.0 mg/L	0.0 - 1.0

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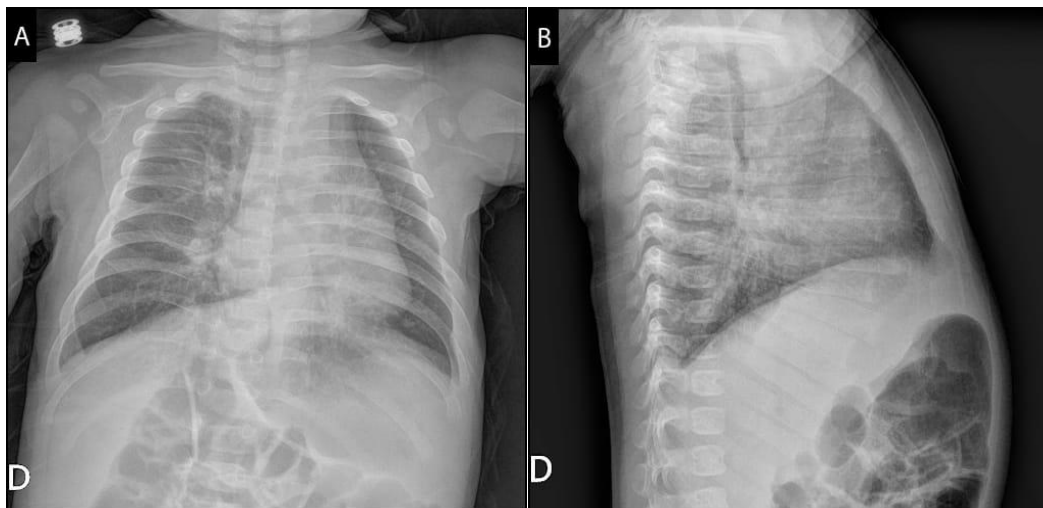
There are areas of coarse alveolar consolidation close to the hilum and a slight blurring of the cardiac area on the right, with little visible lung area on the left. In profile, air is observed in the retrosternal region and a certain degree of lung hyperinflation. The diaphragmatic domes are level and slightly straightened. There is an increase in the fine interstitial vascular network with the presence of cisuritis, as well as the presence of two intercisural effusions. There is no evidence of aerobronchogram.

Considering the clinical, laboratory and radiographic context, treatment with ampicillin 200mg/kg/day, methylprednisolone 1mg/kg/dose and orotracheal intubation and orotracheal intubation began in this last admission, however the patient maintained intermittent bradycardia and a drop in saturation, evolving after 2 days. for cardiorespiratory arrest. After 58 minutes of resuscitation, the patient did not respond to the maneuvers performed and died. Death occurred approximately 11 days after the onset of the first symptoms.

The patient had no comorbidities related to the perinatal period. There is no information on obstetric history, birth conditions and maternal vaccinations during the gestational period. At birth, she presented with early jaundice with hemolytic disease due to ABO incompatibility. Gestational age 40 weeks and 1-day, vaginal delivery, birth weight 3800g and APGAR 8/9/9. Neonatal screenings were adequate. Using 2 drops of Ad-til per

day and vaccination updated for the respective period. Reports history of 'bronchitis' in the paternal family.

Figure 1. A. Hyperinflated chest with straightening of the costal arches and perihilar consolidation on the right. B. Presence of air in the retrosternal space and enlargement of the retrocardiac triangle with diffuse interstitial infiltrate.



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2.1. Macroscopic findings

During the macroscopic examination, some significant changes were found. In the lung, an increase in organ weight and bilateral consolidation was noted, in addition to edema in the lung parenchyma (Figure 2A). The presence of purulent secretion was observed in the airways (trachea and bronchi, main sources), with a large amount in the lower region (Figure 2B). The heart showed weight gain, but no petechiae or structural malformations were found, and the coronaries were pervious (Figure 2C). The spleen also showed weight gain, suggesting reactionary splenitis (Figure 2D). In the kidneys, marked congestion was observed in the medullary to the detriment of the cortical, indicating a condition compatible with acute tubular necrosis (Figure 2E).

2.2. Microscopic findings

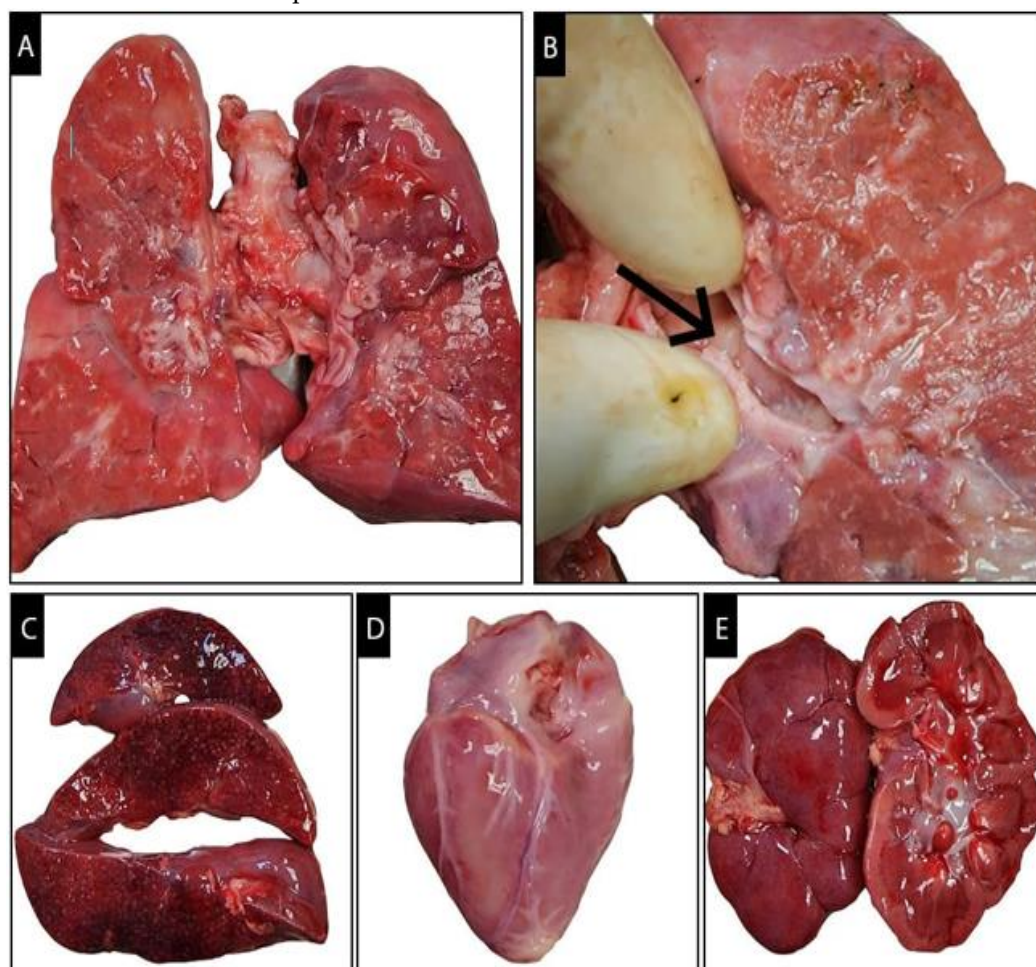
During the microscopic examination, findings were found that revealed the presence of chronic tracheobronchitis, consisting of numerous lymphomononuclear cells and macrophages permeating the lamina propria (Figure 3A). Furthermore, intraepithelial neutrophilic activities and luminal squamous cells were observed (Figure 3B). It is interesting to

note that the same infiltrate surrounds the bronchiolar segments throughout the lung parenchyma, characterizing a condition of non-obliterating bronchiolitis (Figures 3C and 3D).

3. Discussion

The first conclusive evidence that the influenza virus could cause pneumonia occurred during the 1958 to 1959 pandemic [6, 7]. Although characterized by annual seasonal epidemics, sporadic and unpredictable global pandemic outbreaks involving strains of influenza A virus of zoonotic origin also occur [8]. Influenza, in general, is responsible for a simple respiratory condition, with a rapid onset of symptoms such as cough, fever, myalgia, chills and malaise, which persist for around two to eight days. However, in infants under 1 year of age, the Influenza virus can manifest itself only with a high fever or be accompanied by non-specific symptoms such as a drop in general health, difficulty breastfeeding, tiredness and persistent crying [9].

Figure 2. A. Macroscopic lung examination (weight: 250g, reference 81 +/- 14g) edema in the lung parenchyma. B. Presence of purulent secretion in the lower airways (arrow). C. Cardiac macroscopic examination (weight: 40g, reference 28 +/- 4g), absence of petechiae. D. Spleen (weight: 45g, reference 15 +/- 5g) compatible with reactive splenitis. E. Kidneys (weight: 55g, reference 42 +/- 12g) with marked congestion of the medullary to the detriment of the cortical: compatible with acute tubular necrosis.



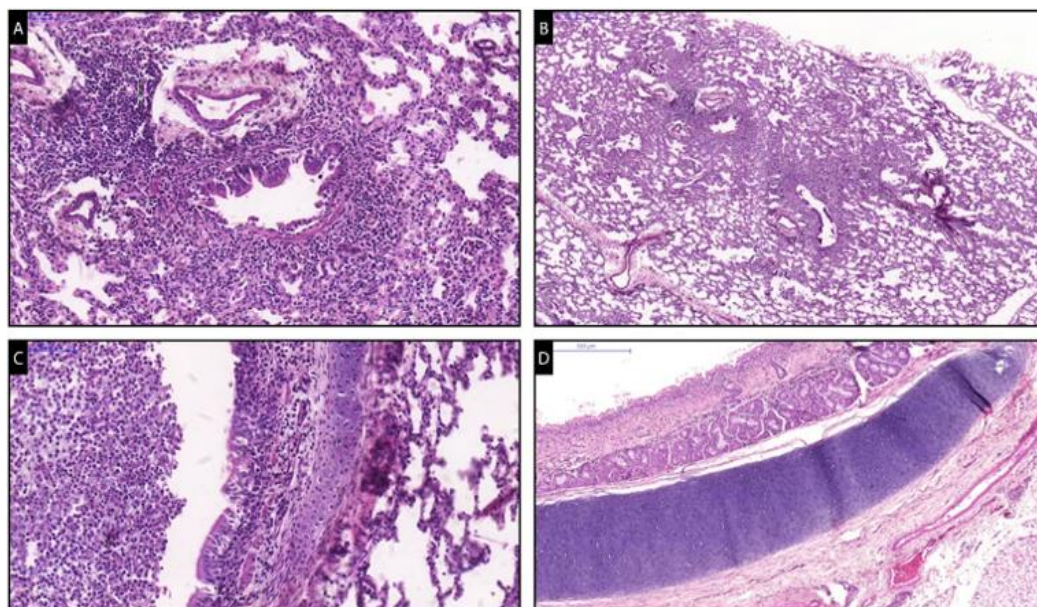
Additionally, infants younger than six months have a higher risk of developing serious complications from influenza, such as pneumonia and bronchiolitis [10]. These patients may present with progressive respiratory failure, including dyspnea, tachypnea,

hypoxia and, later, acute respiratory distress syndrome (ARDS) with possible fatal outcome [10]. Children may be especially susceptible to severe influenza A virus infections due, for example, to specific anatomical characteristics, such as narrow airways prone to obstruction by secretions and a more flexible, cartilaginous chest wall, which makes the lungs more prone to collapse during infection and more difficult to reinflate [11].

Furthermore, the developing adaptive immunity in children makes them dependent on innate immunity to combat threats, which contributes to their vulnerability to infections. However, there is still no complete explanation of why the influenza virus can infect the lower respiratory tract so efficiently in healthy children [11]. Transmission of the Influenza virus in infants can occur in a similar way to what occurs in other age groups, that is, through contact with respiratory droplets from people infected with the virus. Transmission can occur through the air, through coughing, sneezing, and talking, or through contact with contaminated surfaces or objects, followed by contact with the mouth, nose or eyes [12].

In infants, transmission may be favored by close contact with infected people, especially through contact with family members or caregivers who are also sick. Furthermore, infants under six months of age have an immature immune system, which may increase the risk of serious complications if infected with the Influenza virus [12]. Therefore, it is important that preventive measures, such as vaccination of infants and caregivers, and individual protection measures such as frequent hand washing, use of masks and respiratory etiquette, are adopted to prevent transmission of the virus in infants and reduce the risk of complications [13].

Figure 3. A and B. Microscopic findings of chronic tracheobronchitis characterized by numerous lymphomononuclear cells and macrophages permeating the lamina propria (A), with intraepithelial neutrophilic activity and luminal inflammatory and squamous cells (B) (magnification 200X). C (magnification 200X) and 3D (magnification 400 X). We observed this same infiltrate surrounding the bronchiolar segments throughout the lung parenchyma, characterizing non-obliterating bronchiolitis.



Vaccination is still the most effective measure to prevent infections, and in recent years, flu vaccines have become the most widely used vaccines in the world [14]. Furthermore, there are currently several antivirals with proven efficacy for the treatment of influenza virus infections and some can also be used for prophylaxis. In general, most randomized trials of antivirals have been carried out against mild, self-limited illness, and there is relatively less evidence of their effectiveness in treating severe influenza. However, in

practice, antivirals are more useful in treating severe flu and are less commonly used on an outpatient basis [15].

In this regard, non-pharmacological interventions, known as public health measures, also play an important role in mitigating Influenza epidemics and pandemics in the community. They are a set of actions designed to reduce the risk of transmission between individuals, delay and reduce the amplitude of the epidemic peak and spread the number of cases over time to preserve hospital capacity and health systems. Thus, public health measures involve simple and accessible strategies such as individual protection and population actions such as isolation of infected people, social distancing and closing schools, since school-age children are an important source of contamination in the community, this because immunity levels are lower than in adults and there is little or no prior exposure to other types of flu viruses [14].

In the present case report, a 2-month-old child presented symptoms of fever and respiratory distress. Progressively, she exhibited dyspnea, with slight retraction of the wishbone and subcostal insufficiency. These clinical and epidemiological findings are in line with what is found in the clinical manifestations of the disease. Regarding the use of diagnostic tools and complementary exams that help in the diagnostic characterization of respiratory infections, imaging makes an important contribution to patient evaluation. Chest radiography is useful in determining the extent of lung involvement and detecting complications (i.e., cavitation, abscess formation, pneumothorax, and pleural effusion), as well as differential diagnoses [16].

The specific tropism of the virus for the respiratory tract has led to the use of imaging to better characterize the location, distribution, and type of primary lung lesions. In general, viral lung infection can lead to inflammation and fluid accumulation in the lungs, which can be seen on x-rays as whitish or opaque areas in the lung parenchyma. Other characteristics that can also be found are ground glass opacities, consolidation, diffuse infiltrate and enlarged lymph nodes [17]. The radiological examination of our case report, in the first days of the first hospitalization, revealed signs of hyperinflation, with the presence of air in the anterior portion of the chest and straightening of the rib cage. Presenting diffuse infiltrates throughout the parenchyma. The last radiological examination revealed persistence of all the first findings, adding the presence of diffuse perihilar infiltrate, gross alveolar consolidation close to the hilum and increase in the vascular network.

Postmortem diagnosis plays a fundamental role in the epidemiological study of basic causes related to deaths that occur in each region and in a given period of time and aims to map and define health strategies [18]. The macroscopic findings of pulmonary influenza infection in infants are characterized by bronchiolitis, which generally includes inflammation of the lower airways, including the bronchioles, with edema (increase in organ weight) and hyperemia (increased blood flow). Obstruction of the airways due to inflammatory cells and accumulation of mucus, which makes it difficult for air to pass. It is important to highlight that these findings may vary in intensity and extent, depending on the severity of the influenza virus infection and other individual factors [19, 20].

The lung macroscopic findings from the necropsy of our clinical case showed increased lung weight, with a shiny surface appearance and edema in the parenchyma. We observed areas of adhesions between the visceral pleura of adjacent lobes, tracheobronchial tree, with light yellowish, non-viscous content. No areas of hepatization or friability were observed under digital pressure. Severe cases of influenza infection involve dissemination of the virus to the alveolar compartment. The viral infection causes extensive damage to the alveolar walls with endothelial damage to the capillaries and alveolar epithelium that are juxtaposed to the alveolar basement membrane. This condition triggers an inflammatory response, with massive infiltration of leukocytes, extensive apoptosis of bronchial and alveolar epithelial cells and a coagulative response, with the formation of fibrin deposits that adhere to the alveolar walls (hyaline membrane) and prevent respiratory exchange (hematosis) [21].

Cases in infants can also occur with bronchiolitis, which is characterized by narrowing of the bronchiolar lumen, presence of debris, damage to the ciliated respiratory bronchiolar epithelium, mucus, fibrin (due to damage to the bronchiolar epithelium) and squamous cells, including apoptotic cells in the alveolar lumen. There is loss of alveolar integrity (peribronchiolar consolidation), edema and lymphomononuclear infiltrate compressing bronchioles, without a component of bronchospasm, typical of an allergic component. During inspiration, the negative intrapleural pressure is responsible for the passage of air over the obstructed area and the positive pressure during expiration generates great effort in eliminating the remaining air, which makes gas exchange difficult and explains the low O₂ pressure that can be observed in the examination. arterial blood gas analysis [22].

These latest findings of bronchiolitis are in line with what we found in the laminated microscopic sections of our case. Inflammation extending from the tracheal lamina propria to the terminal respiratory bronchioles was observed. The microscopy findings consisted of chronic tracheobronchitis consisting of numerous lymphomononuclear cells and macrophages permeating the lamina propria, with intraepithelial neutrophilic activity and luminal squamous cells associated with a marked lymphomononuclear inflammatory infiltrate permeating bronchiolar segments throughout the parenchyma, characterizing non-obliterating bronchiolitis.

Our macroscopic and microscopic findings are within a particular epidemiological context, as they involve the age range of infants, children under 2 years old, without the presence of previous comorbidities that could justify the severity of the case. Flu-associated hospitalization rates are substantially higher among newborns and young children compared to older children, and those under six months of age are at the highest risk. Research shows that the flu vaccine is not as effective in children under two years of age compared to adults. Therefore, flu prevention and appropriate treatment are important to keep this high-risk group protected from complications [23]. Therefore, disease severity is influenced by influenza virological characteristics and host factors, as well as public health interventions such as influenza vaccination and antiviral treatment [24].

Clinically, it is challenging to differentiate between viral and bacterial pneumonia. Likewise, radiological findings of viral infection are nonspecific. The advent of the polymerase chain reaction (PCR) test has greatly facilitated the identification of respiratory viruses, which has important implications for infection control and treatment measures, mainly because it is a rapid methodology with high sensitivity and specificity [25]. Differentiating between bacterial and viral pneumonia is important to guide clinical management and judicious use of antibiotics. Clinical signs and symptoms between cases of conclusive bacterial pneumonia and presumed viral pneumonia overlap and are nonspecific for differentiation. Empirical use of antibiotics remains the cornerstone of pneumonia treatment in the absence of effective point-of-care diagnostics. Consequently, children with viral pneumonia may continue to receive antibiotics without benefit [26].

At the end of 2019, with the advent of the coronavirus designated as SARS-CoV-2 in the city of Wuhan, China, an outbreak of unusual viral pneumonia occurred. Being highly transmissible, this new disease, also known as coronavirus infection 2019 (COVID-19), spread rapidly throughout the world, causing a pandemic [27]. The primary site of COVID-19 infection is the lungs, and lung findings include nonspecific microscopic criteria such as edema, chronic inflammation, hyaline membranes, acute to organized diffuse alveolar damage (DAD), and superimposed bronchopneumonia [27].

Rapid and accurate diagnosis of lung infections is important for the correct prescription of antivirals, when available, and a better prognosis of the disease, as early treatment, with support and appropriate antivirals, contributes to reducing symptoms and severity of the disease, which consequently reduces the extent of fatal outcomes [28]. Therefore, in relation to the treatment of bronchiolitis, recommendations based on high-quality evidence advise doctors to support only supportive measures, i.e. hydration and oxygenation. Evidence suggests no benefit from the use of glucocorticoids or bronchodilators and further evidence is needed to support the use of hypertonic saline in bronchiolitis.

Furthermore, evidence suggests that the use of high-flow therapy in bronchiolitis is limited to rescue therapy after failure of standard subnasal oxygen only in infants who are hypoxic and does not decrease rates of intensive care unit admission or intubation. Finally, despite systematic reviews and international clinical practice guidelines that promote supportive therapy over interventional therapy, universal deimplementation of interventional care in bronchiolitis has not occurred and remains a major challenge [29].

Necroscopic examinations are essential and can contribute to the diagnosis of viral lung infections. Autopsy is an important tool for diagnostic medicine with three main functions: the first is to contribute to medical knowledge, as it expands our understanding of diseases; the second, is to verify the accuracy of clinical diagnoses and demonstrate the effect of treatments, which provides essential feedback for clinical practice and the third is to provide reliable data for epidemiological studies [30]. Although new imaging techniques and laboratory tests have been introduced, the importance of autopsy in gaining knowledge has not diminished [31]. Post-mortem examination can provide answers to unresolved clinical questions and uncover previously unknown pathological conditions that may have impacted pre-mortem care [31].

4. Final considerations

The patient's initial manifestations demonstrate systemic involvement with probable pulmonary origin. Empirically, he opted for treatment with antibiotic therapy, but he did not progress as expected and within a three-day interval he died. Epidemiologically, this clinical case involved other differential etiological diagnoses, for example, other viral lung infections and typical bacterial infections, among which, one that deserves to be highlighted is the respiratory syncytial virus (RSV), an important causative agent of bronchiolitis in infants.

Table 3. Comparison between morphological findings in the literature of patients who died from the Influenza virus.

Study	Sex and age	Symptoms	Influenza type	Morphological findings	Outcome
[32]	F, 80 years	Lethargy, dyspnea, and chest pain	Influenza A	DAD (autópsia)	Death
[33]	M, 33 years	Respiratory failure	Influenza A (H1N1)	Edema pulmonar grave, DAD (autópsia)	Death
[34]	M, 23 years	Fever, sore throat and cough	Influenza B	Alveolite linfocítica e pneumonia em organização (biópsia)	Remission
[35]	RNP, 50 days	Apnea	Influenza A (H1N1)	-	Remission
[36]	M, NB, 1 day	I Respiratory failure	Influenza A (H1N1) + VSR	-	Remission

Souza et al. (present case)	M, infant and 27 days	2	Fever and dyspnea	Influenza A	Bronquiolite não obliterante (autópsia)	Death
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Legend. M. male. F. female. NB. Newborn. PNB. premature newborn. RSV. respiratory syncytial virus. DAD. diffuse alveolar damage.

RSV infection is clinically indistinguishable from other respiratory viruses. Thus, it can be asymptomatic, present symptoms similar to a cold or progress to acute respiratory distress. Most patients develop signs of an upper respiratory tract infection, such as nasal congestion and runny nose or sore throat, three to five days after infection. However, as the virus progresses to the lower respiratory tract, symptoms such as coughing, wheezing and dyspnea appear [37]. The present case report involves death from influenza A in an infant child just 2 months old, which makes this situation particularly relevant. Infants are considered a high-risk group for flu complications due to the immaturity of the immune system and the ability to respond to respiratory infections. Furthermore, the severity of infection in infants may be worsened by difficulty in quickly recognizing and treating symptoms of the disease.

Another important aspect addressed by the case report is the importance of early diagnosis of influenza in infants. Due to the difficulty in recognizing the symptoms of the disease in such young children, diagnosis is often delayed, which can lead to serious complications and even death. Therefore, it is essential that healthcare professionals are alert to flu symptoms in infants and carry out early diagnosis in order to prevent serious complications and death.

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Supplementary Materials: None.

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