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Sudden unexpected death in infancy: Severe pulmonary anatomopathological findings in spite of inconsistent clinical features

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Abstract

Respiratory tract infections play a considerable pathogenetic role in many cases of sudden infant death (SID). Frequently, clinicians encounter difficulties in diagnosing the disease because of its often unspecific clinical and radiological presentation. We report three cases of sudden unexpected death in infancy (SUDI), involving two males and one female admitted to hospital due to mild respiratory distress. In all three cases, complete post-mortem investigations were successful in uncovering interstitial lung disease as the cause of death. These cases highlight the key role of infection-related interstitial lung diseases in the pathogenesis of some currently unexplained SUDI/SIDS and the diagnostic difficulties due to the variable clinical and histological pattern, thereby explaining the importance of performing complete post-mortem investigations whenever an infant dies suddenly and unexpectedly.

Keywords

Sudden unexpected death, interstitial lung disease, post-mortem investigations

Introduction

Sudden unexpected death in infancy (SUDI) is an umbrella term that describes an unanticipated death occurring within the first year of life. If no cause can be suspected from a thorough review of the clinical history, or a systematic death scene investigation and a complete postmortem examination, such death can be classified as an unexplained SUDI or SIDS (sudden infant death syndrome). In a study from the USA of 3422 SUDIs, 45.6% were reported as SIDS.[1–2] Although the underlying mechanisms remain unclear, SUDI is now considered a multifactorial disorder. The "triple risk hypothesis" is the main pathogenetic hypothesis and claims the presence of three overlapping risk factors (environmental trigger/stress, an intrinsic child vulnerability and a critical period in the development of autonomic regulation of both respiratory and cardiovascular system).[3] Nonetheless, other parameters have been shown to predispose to SUDI such as male sex, sleeping in a prone position, exposure to cigarette smoke, very young age (<6 months), ethnicity, positive family history and prematurity.[4–5]

Frequently, causes of death in SUDI remain undetermined because autopsies are not performed. However, occasional postmortem examinations may detect a previously unknown medical condition, such as an infection or a rare genetic disease.

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Case series

Three cases of SUDI (Table 1) where post-mortem investigations revealed an interstitial lung disease as the underlying cause of death are reported. All the samples tested negative for SARS-Coronavirus.

Case 1

A seven-month-old male infant was found dead in his cot three days after discharge. He had previously been treated at the hospital for bronchiolitis; following a rapidly improved clinical condition he was discharged home. In the history, he had four hospital admissions within three weeks due to persistent cough, wheezing, tachypnoea, fever and dyspnoea. The only parameter that was found to be altered was a slight rise in C-reactive protein (CRP) levels at laboratory tests. The medical history also reported that within the previous month he had been treated by salbutamol administered at home.

The parents mentioned that the baby had been sleeping in their bedroom, but never in their bed and slept in a supine position and was not covered by a quilt.

The autopsy revealed diffuse intra-thoracic petechial haemorrhages involving the visceral pleura and epicardium, a heavy, red-brownish congested lungs and an un-clotted liquid blood within the heart's chambers. Moreover, the histology slides showed thickened alveolar walls, intra-alveolar blood, acute emphysema and an inflammatory infiltrate (Figure 1). These findings were deemed suspect for an interstitial pneumonia.

Case 2

A 12-month-old female presented to the Emergency Department with persistent cough and wheezing, after one month of antibiotics and aerosol-therapy administered at home. Her parents denied co-sleeping and said she had been sleeping in a supine position in a safe sleep environment. Her growth was within the normal range, and her vaccinations were as recommended. At admission, she was an apparently healthy child of 10.6 kg weight, in good general clinical conditions, except for cough, mild wheezing, and a hyperaemic pharynx. Tests for Covid-19 were conducted, with negativity for viral infection.

At physical examination, widespread crackles and whistles were detected in her chest. The oxygen rate

Table 1. Brief summary of presented cases' main features.

	Case 1	Case 2	Case 3
Age	7 months	12 months	3 months
Sex	Male	Female	Male
History Clinical and laboratory findings	4 hospital admissions in 1 month for persistent cough and wheezing, later associated with breathing difficulties. ↑ CRP levels. Found dead three days after discharge.	Persistent cough and wheezing (for a month). At physical examination: hyperaemic pharynx, widespread crackles and whistles. Leukocytosis and ↑ ESR. During the stay in the paediatric ward: cyanosis, hypotonia and bradycardia; SpO_2 ↓ from 98–99% to 80% in air. Died at hospital	Persistent fever and coughing → suspect upper respiratory tract infection. At physical examination: fever (38°C), cough, wheezing, and hyperaemic pharynx. ↑ CRP levels. Found dead the day after discharge.
Autopsy findings	Heavy, red-brownish congested lungs; Intra-thoracic and pleuro-epicardial petechiae; Un-clotted blood inside cardiac chambers	Heavy, congested and oedematous lungs	Heavy, red-brownish, congested lungs
Histopathological findings	Thickened alveolar walls; Intra-alveolar blood; Acute emphysema; Inflammatory infiltrate (mainly lymphocytic)	Thickened alveolar walls; Alveolar collapse; Hyaline membranes; diffuse interstitial neutrophilic infiltrate; Pulmonary oedema; intra-alveolar haemorrhages; microvascular thrombosis	Interstitial lymphocytic infiltrate; thickened alveolar walls; Acute emphysema

at pulse-oximetry (SpO_2) was 98–99% on air. Laboratory investigations produced results within normal range, except for leukocytosis (white blood cells 15,640/mm^3; normal value 4000–10,000) and an increased erythrocyte sedimentation rate (34 mm/h; normal value < 15). During the second day of stay in the paediatric ward, she played, ate, and drank as usual, and then fell asleep with her mother at her bedside. Overnight, she was found cyanotic; physical examination showed hypotonia and bradycardia, in absence of spontaneous breath (the SpO_2 revealed to be 80% in air). Resuscitation was promptly performed, without success.

At autopsy, heavy, congested and oedematous lungs were observed. Histological examination showed thickened alveolar walls, interstitial acute inflammation with diffuse neutrophilic infiltrate, oedema, alveolar collapse, hyaline membranes, along with alveolar haemorrhage and microvascular thrombosis. These pulmonary histopathological alterations were deemed to be suggestive of diffuse alveolar damage (Figure 2).

Case 3

A three-month-old male infant, presenting with persistent fever and coughing, was admitted to the hospital due to suspect upper respiratory tract infection. His parents reported that he had been sleeping in his own bed in a supine position. Physical examination showed a 6.7 kg infant in good general condition, with fever (38°C), wheezing, hyperaemic pharynx and cough. A chest X-ray showed paracardial interstitial thickening in the right lung. Laboratory findings showed a minor rise in C-reactive protein levels (CRP 0.56 mg/dL, normal range <0.5). The admission diagnosis was of right bronchopneumonia. After microbiological tests had come back negative for Covid-19 and other viral infections, he was treated with salbutamol, steroids and

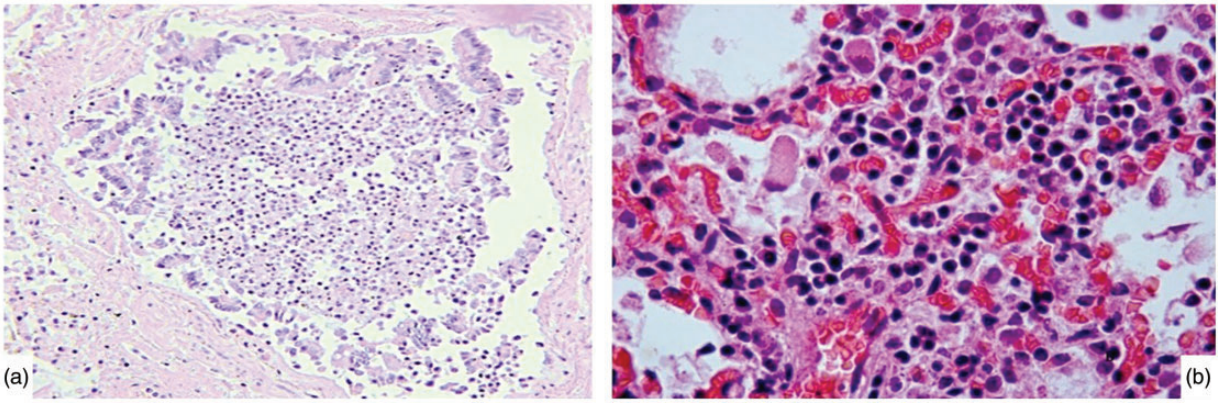

Figure 1. (a) Bronchial walls with epithelial denudation, intraluminal leukocytes (mostly lymphocytes). (b) Interstitial leukocytic infiltrate consisting of lymphocytes, monocytes and plasma cells.

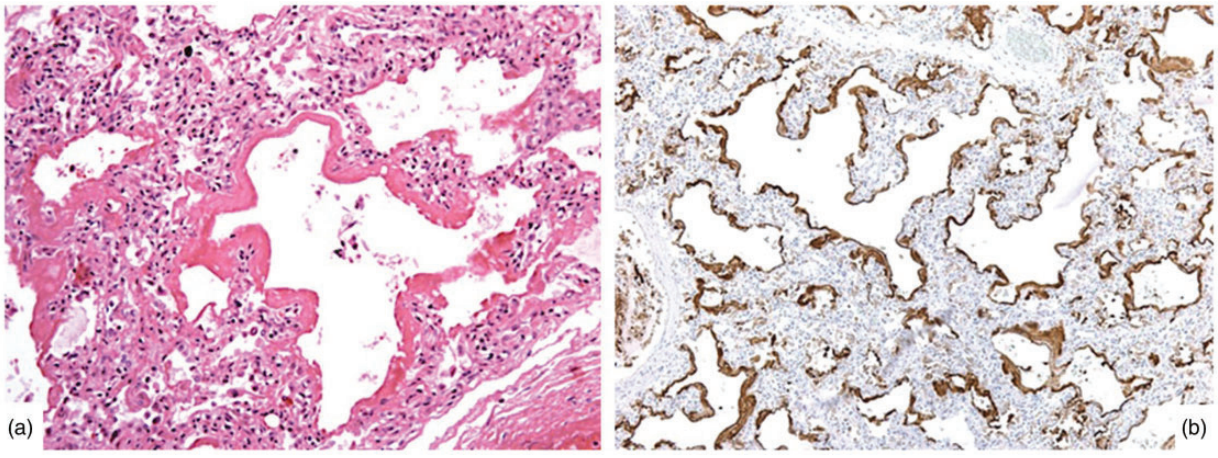

Figure 2. (a) Diffuse alveolar damage in exudative phase: at haematoxylin and eosin staining, hyaline membranes are highlighted. (b) At immunohistochemistry: the monoclonal antibodies anti-surfactant apoprotein (PE-10) positively reacted with hyperplastic type II pneumocytes, lining the alveolar septal surfaces.

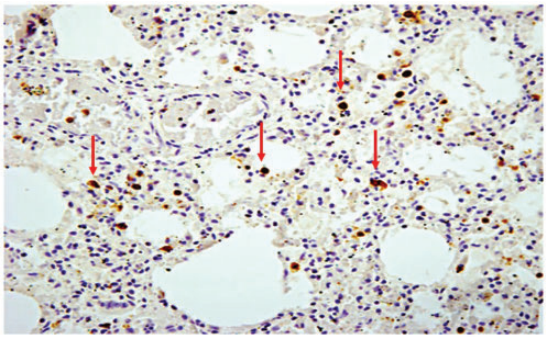

Figure 3. Lymphocytic interstitial pneumonia with positive immunohistochemical reaction to antibody anti-CD20 (red arrows).

amoxicillin. After five days, his clinical condition improved, thus he was discharged. The following day, the child was feverish again, so the mother gave him paracetamol (at about 7.00 a.m.). At 11.00 a.m., the baby was found dead in his cot.

At autopsy, heavy, red-brownish, congested lungs were observed. Histopathological examination revealed lymphocytic interstitial pneumonia (Figure 3), with thickening of the alveolar walls and areas of acute emphysema.

Discussion

Several studies have suggested that many currently unexplained SUDI/SIDS deaths may likewise be infection-related, possibly mediated by an abnormal systemic immune response to otherwise transient or subclinical bacterial or viral infections.[6–7] The so-called "common bacterial toxin hypothesis" postulates that some SIDS may be caused by bacterial toxins, most likely produced by upper respiratory tract organism such as staphylococcus aureus,[8] while other studies suggest the pathogenetic role of viral infections, hypothesising that they might act as "environmental stressors" in the triple risk hypothesis. Alternatively, sudden infant death might also be caused by an overwhelming, disseminated viral infection (unlikely to be detected, if a thorough microbiological examination is not performed).[9]

A wide range of respiratory disorders associated with high morbidity and mortality in children – and, therefore, potential causes of SUDI – is included under the definition "Interstitial Lung Diseases (ILDs)"; this broad term refers to a heterogeneous collection of disorders characterised by abnormal gas exchange due to altered structure of lung interstitial region. The aetiology includes genetic, infectious, and systemic diseases, adverse reaction to drugs and idiopathic forms.[10]

Despite the fact that the above-mentioned definition implies the presence of strictly interstitial abnormalities, some ILDs show minimal changes in the interstitium, with associated increased engagement of distal airways, alveolar spaces, lymphatic vessels or pulmonary capillaries. For this reason, some authors prefer to refer to this group of entities as "diffuse lung diseases".[11]

The cases here demonstrate that ILD diagnosis can be extremely difficult ante mortem, since the symptoms and signs are often variable and nonspecific: tachypnoea; wheezing; shortness of breath; chronic or intermittent coughing; recurring bronchiolitis or pneumonia; hypoxemia; failure to thrive; respiratory failure; abnormal lung function tests; interstitial thickening at chest X-rays or CT scans. In present times, it is crucial to exclude the diagnosis of Covid-19 infection, whose symptoms are similar to those typical of ILD.[12] This variability of clinical manifestations and histological patterns observed in children at different ages may be explained by growing lungs and developing immune system. The rarity of these conditions contributes to hinder the diagnosis, which is almost invariably delayed (sometimes to postmortem).[13]

Conclusions

This report of three cases of SUDI affected by ILD confirms a key role played by infections in some currently unexplained SUDI/SIDS. In these cases, all of which tested negative for Covid-19, the clinical picture was not consistent with the severe autoptic and histological lung findings, and the symptoms and signs would not have otherwise led clinicians to the diagnosis. The present study may enlighten some peculiar physio-pathological mechanisms underlying SUID/SIDS such as immune response in infancy.

Declaration of conflicting interests

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