Evolution of exogenous lipoid pneumonia in children: clinical aspects, radiological aspects and the role of bronchoalveolar lavage*

Evolução da pneumonia lipoide exógena em crianças: aspectos clínicos e radiológicos e o papel da lavagem broncoalveolar

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Abstract

Objective: To present aspects of the evolution of lipoid pneumonia in children, based on clinical, radiological and bronchoalveolar lavage fluid findings, emphasizing the importance of bronchoalveolar lavage for the diagnosis and treatment. **Methods:** We included 28 children, with a mean age of 20 months (range, 1-108 months), diagnosed with chronic pneumonia refractory to antimicrobial therapy, with TB or with a combination of the two. Most of the children had at least one risk factor for aspiration, and all of them had a history of mineral oil ingestion for intestinal constipation (23/28) or complicated ascaridiasis (5/28). Clinical evaluations, tomographic evaluations and analyses of bronchoalveolar lavage fluid were carried out at the beginning of treatment and throughout a follow-up period of 24 months. **Results:** Tachypnea and cough were the most common symptoms. The most common radiological alterations were areas of consolidation (23/28), perihilar infiltrates (13/28) and hyperinflation (11/28). Chest CT scans showed areas of consolidation with air bronchogram (24/28), decreased attenuation in the areas of consolidation (16/28), ground-glass opacities (3/28) and crazy-paving pattern (1/28). In the analysis of the bronchoalveolar lavage fluid, Sudan staining revealed foamy macrophages, confirming the diagnosis of lipoid pneumonia. After treatment with multiple bronchoalveolar lavages (mean = 9.6), 20 children became asymptomatic, 18 of those presenting normal tomographic images. **Conclusions:** A diagnosis of lipoid pneumonia should be considered in patients with chronic refractory pneumonia or TB, especially if there is a history of mineral oil ingestion. Bronchoscopy with multiple bronchoalveolar lavages was an efficient treatment for the clearance of mineral oil from the lung parenchyma and the prevention of fibrosis. This strategy contributed to reducing the morbidity of lipoid pneumonia, which remains a rare diagnosis.

Keywords: Pneumonia, lipid; Bronchoalveolar lavage; Treatment outcome.

Resumo

Objetivo: Descrever os aspectos da evolução da pneumonia lipoide em crianças, com base em aspectos clínicos, radiológicos e de achados no lavado broncoalveolar, enfatizando a importância diagnóstica e terapêutica da lavagem broncoalveolar. **Métodos:** Foram incluídas 28 crianças, com idade média de 20 meses (1-108 meses) e diagnóstico de pneumonia crônica refratária a antimicrobianos e/ou TB. A maioria apresentava um fator de risco para aspiração, e todas apresentavam história de ingestão de óleo mineral para o tratamento de constipação intestinal (23/28) ou de ascaridíase complicada (5/28). A avaliação clínica e tomográfica e análises do lavado broncoalveolar foram realizadas no início do tratamento e em até 24 meses. **Resultados:** Os sintomas mais frequentes foram taquipneia e tosse. As principais alterações radiológicas foram consolidações (23/28), infiltrado peri-hilar (13/28) e hiperinsuflação (11/28). A TC de tórax mostrou consolidações com broncograma aéreo (24/28), diminuição de atenuação nas áreas de consolidação (16/28), opacidade em vidro fosco (3/28) e padrão em mosaico (1/28). O estudo do lavado broncoalveolar apresentava macrófagos espumosos corados por Sudan, confirmando o diagnóstico da pneumonia lipoide. Após tratamento com múltiplas lavagens broncoalveolares (média = 9,6), 20 crianças tornaram-se assintomáticas, havendo normalização tomográfica em 18. **Conclusões:** O diagnóstico de pneumonia lipoide deve ser considerado na pneumonia crônica ou TB refratárias ao tratamento, especialmente se houver história de ingestão de óleo mineral. A broncoscopia com múltiplas lavagens broncoalveolares mostrou-se eficiente para a depuração do óleo aspirado do parênquima pulmonar e a prevenção da fibrose, contribuindo para a redução da morbidade dessa doença, que ainda é pouco diagnosticada.

Descritores: Pneumonia lipoide; Lavagem broncoalveolar; Resultado de tratamento.

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Introduction

Lipoid pneumonia (LP) is not easily diagnosed, since its clinical and radiological findings are similar to those of bacterial pneumonia and TB. Caused by the aspiration of fat substances from endogenous or exogenous sources, LP results in a proliferative, chronic interstitial inflammation of the lung parenchyma. It was first described by Laughlen in 1925,[1] when the author observed the presence of oil in the lungs of 3 autopsied children and of 1 autopsied adult. The most common cause of LP is the aspiration of mineral oil, which is often used in the treatment of intestinal constipation.[2] The high viscosity of mineral oil can inhibit the cough reflex, facilitating the aspiration of oil to the lower airway, even in the absence of risk factors, especially in suckling infants, because of the way in which they are positioned during feedings. Other known risk factors for LP are structural and functional disturbances of the gastrointestinal tract, neurological and muscular diseases that affect respiration and swallowing, comma and anesthesia, as well as accidental and forced oil ingestion.[3-5] The cultural practice, in certain countries (Mexico, Arabia, India and Guatemala), of using oily substances for the body hygiene of suckling infants and for nasal clearance might also be associated with the development of LP.[4,6-8] In Brazil, mineral oil is still often used for the treatment of intestinal constipation and partial bowel obstruction caused by severe ascariasis.[9]

The clinical manifestations of LP range from asymptomatic cases to severe pulmonary involvement, with respiratory failure and death, according to the quantity, quality and duration of the aspiration. The radiological alterations are nonspecific, ranging from perihilar infiltrate to extensive areas of consolidation, with air bronchogram predominantly in the lower and posterior regions of the lungs. The bronchoalveolar lavage (BAL) fluid is opalescent, with a halo of fat, suggestive of alveolitis, and numerous foamy macrophages with intracytoplasmic and extracellular droplets of fat. The objective of the present study was to describe the aspects of the evolution of LP in children, based on clinical, radiological and BAL findings of children monitored for 24 months at the Service of Pediatric Pulmonology of the Antonio Pedro University Hospital, Niterói, Brazil.

Methods

The present study was carried out at the Department of Respiratory Endoscopy of the Antonio Pedro University Hospital, Fluminense Federal University, Niterói, Brazil, between June of 2005 and June of 2008. We investigated children aged 13 or younger, diagnosed with chronic pneumonia refractory to medication and referred for diagnostic bronchoscopy. The inclusion criterion was history of mineral oil ingestion, and the exclusion criterion was the presence of purulent or hemorrhagic BAL fluid. A total of 28 children were included, and the diagnostic data from the BAL indicated LP in all cases. The children were monitored for 24 months. After the diagnosis of LP was confirmed, the parents were given instructions regarding the new treatment, which aimed at curing the disease. After agreeing with what had been proposed, the parents signed a written informed consent. The protocol of the present study included demographic data, as well as clinical, laboratory, tomographic and BAL findings. Most of the chil-

Table 1 - Demographic and clinical characteristics of the children with lipoid pneumonia investigated.

Characteristic	n	%
Age, months		
1-24	22	79
25-72	4	14
> 72	2	7
Indication of mineral oil		
Intestinal constipation	23	82
Ascariasis	5	18
Risk factors		
Age (suckling infant)	22	79
Gastroesophageal reflux	5	18
Swallowing disorder	5	18
None	1	4
Clinical manifestations		
Tachypnea	27	96
Cough	24	86
Fever	23	82
Dyspnea	15	54
Lack of weight gain	9	32
Moaning	8	29
Recurrent respiratory infection	5	18
Rales	14	50
Wheezing	1	4
Normal auscultation	13	46

dren (n = 20) were submitted to treatment with therapeutic BAL; 2 were treated with corticosteroids and BAL; 6 abandoned treatment. The present study was previously approved by the Research Ethics Committee of the Fluminense Federal University School of Medicine (CEP/CMM/HUAP nº 031/06).

Chest CT scan

The HRCT scan of the chest was performed, without sedation, at the time of admission and immediately after the treatment, in a four-channel equipment (Siemens, Erlanger, Germany), using a protocol of low-dose radiation (120 kV and 25-50 mA), and 1.0 mm thick axial slices with high spatial resolution algorithm.

Bronchoscopy and bronchoalveolar lavage

Bronchoscopy was performed using a flexible bronchoscope (FB Olympus 3C-40, Tokyo, Japan), with intravenous sedation (midazolam) and the placement of an oxygen catheter; SpO_2 and heart rate were monitored. After inspection of the tracheobronchial tree, the bronchoscope was introduced into the affected segment or lobe, which had been identified in the HRCT scan. The lavage consisted in introducing three aliquots of sterile saline solution (each 1 mL/kg of body weight) warmed to 37°C, followed by immediate aspiration. The first aliquot was set aside for microbiological study and the remaining aliquots were collected in a single vial for cell analysis. Cellularity was determined using a Neubauer chamber. The cell suspension was centrifuged for 5 min at 200 × *g* (Cytopro; Wescor, Logan, UT, USA) for staining with Sudan, periodic acid-Schiff and May-Grünwald-Giemsa. The therapeutic BAL was performed weekly with five aliquots of 1 mL/kg of body weight of sterile saline solution warmed to 37°C, until the BAL fluid was nearly transparent with cellularity within the normal limits.[10]

Results

A total of 28 children were evaluated for 24 months (15 females and 13 males). Age ranged from 1 to 108 months (mean = 20 months; median = 5.5 months). All of the children had used mineral oil as treatment for intestinal constipation (23/28) or partial bowel obstruction by *Ascaris lumbricoides* (5/28), for a mean period of 32 days (median = 15 days). Nearly all children (27/28) presented respiratory and other symptoms, including tachypnea, cough, fever, dyspnea, lack of weight gain, moaning and recurrent respiratory infection (Table 1). The most common laboratory alterations were neutrophilia (85%), leukocytosis (73%), eosinophilia (11%) and elevated erythrocyte sedimentation rate (58%). The blood workup was normal in 2 children. The mean time between the onset of symptoms and the diagnostic bronchoscopy was 38 days. Regardless of the treatments for bacterial pneumonia or TB, the chest X-rays remained unaltered until the bronchoscopy was performed.

The chest X-rays revealed the following: extensive areas of consolidation, predominantly in the right lung (n = 23); perihilar infiltrate and consolidation (n = 9); bilateral perihilar infiltrate (n = 2); unilateral perihilar infiltrate (n = 2); and hyperinflation (n = 11). The chest CT scans revealed consolidation with air bronchogram (24/28), as well as a few cases of ground-glass opacities (3/28) and crazy-paving pattern (1/28).

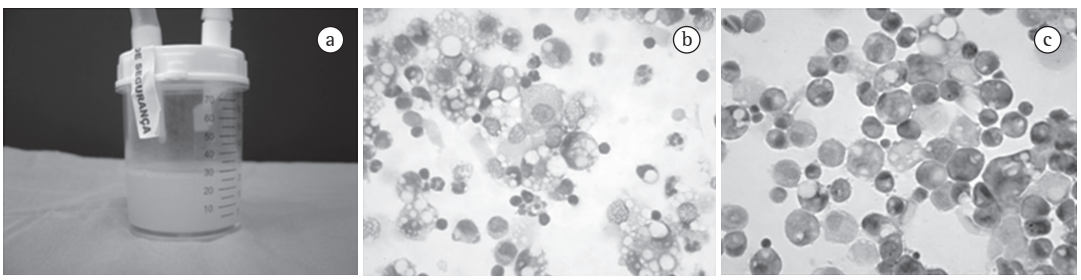

Figure 1 - Macroscopic and microscopic aspect of the bronchoalveolar lavage fluid. In a), opalescent fluid with supernatant halo of fat; in b), numerous foamy macrophages with intracytoplasmic lipid vacuoles stained with Giemsa; in c), foamy macrophages with intracytoplasmic lipid vacuoles stained with Sudan (magnification, ×400).

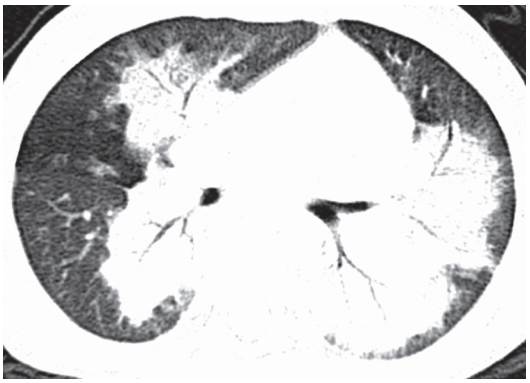

Figure 2 - HRCT scan of the chest, revealing extensive areas of consolidation with air bronchogram in a two-year-old child with lipoid pneumonia. This image was obtained before the treatment with multiple bronchoalveolar lavages.

The lobes most affected were, in decreasing order of frequency, the right upper lobe, the right lower lobe, the left lower lobe, the middle lobe and the left upper lobe. The lingula was affected in 5 cases. In 5 cases, the two lungs had been equally affected. In 16 cases, the density measurements within the consolidation areas ranged between −11 and −118 HU. In spite of the great improvement observed in the CT scan right after treatment, tomographic alterations were still observed in 6 children. These children were reevaluated after 6 months; 2 of them were once again submitted to HRCT after 12 months.

In all of the cases, the BAL fluid was opalescent with a supernatant halo of fat. Cell analysis showed numerous macrophages with intracytoplasmic vacuoles of various sizes, stained orange with Sudan staining (Figure 1). The BAL fluid cellularity ranged from 500 to 7,680 cells/mm^3 (mean = 1,723 cells/mm^3). The microbiological study was negative in all of the cases.

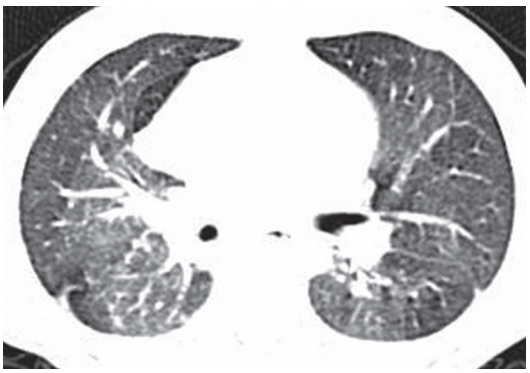

Figure 3 - HRCT scan of the chest of the same child (see Figure 2) after the treatment. This image was obtained 24 months after the treatment with multiple bronchoalveolar lavages and reveals the resolution of the consolidations.

Of the 28 children investigated, 20 were treated with multiple BALs (mean = 9.35; variation: 4-22) and became asymptomatic after the treatment; 18 children had normal CT scan results immediately after the treatment, 1 child presented a cystic image in the right lung and 1 child had a discrete area of segmented atelectasis 12 months after the treatment. Treatment abandonment occurred in 6 cases.

Discussion

The condition known as LP, lipid pneumonia, oil pneumonia, oil aspiration pneumonia, lipoid cell pneumonia, pulmonary steatosis, pulmonary lipidosis or paraffin pneumonia is a chronic inflammation of the lung parenchyma with interstitial involvement due to the accumulation of oily material in the alveoli. This condition can be classified as exogenous LP, endogenous LP or idiopathic LP.[11] Exogenous LP—the most commonly described form of LP—is associated with the aspiration or inhalation of, principally, mineral oil, a substance used as a laxative in cases of intestinal constipation or as adjuvant treatment for partial bowel obstruction by *A. lumbricoides*. Medications in which the oil acts as a vehicle—nasal drops, ointment, enema, contrast medium and industrialized lubricants—are also associated with LP.[9,12,13] Endogenous LP, which is less frequent, occurs due to the distal obstruction of the airways by malignant lesions, suppurative processes, obliterating bronchiolitis and diseases causing lipid deposition.[11] Idiopathic LP is rare, being associated with smoking in healthy individuals.[14] In children, exogenous LP is the most common form of the disease, due to the aspiration of mineral oil, as shown in the present study.

Various pulmonary diseases, such as bacterial pneumonia, TB, cystic fibrosis, bronchiectasis and tumors, can be mimicked by LP.[11,15] None of the cases investigated in the present study were initially diagnosed as LP. All of the children we investigated had been treated with various antimicrobial treatment regimens; 9 of them had also initiated treatment for TB, which

generates costs, increases the risk for the development of resistant bacterial strains and delays diagnosis, as well as increasing morbidity and the risk of complications. In the present study, the diagnosis of LP was established, on average, 38 days after the onset of symptoms. The major risk factors observed were age (79% were suckling infants), gastroesophageal reflux (18%) and swallowing disorder (18%).

Mineral oil is an inert substance that is not metabolized by pulmonary enzymes when aspirated. Instead, it is emulsified and phagocytosed by alveolar macrophages, returning to the alveolar space after cell death. The release of inflammatory cytokines by the activated macrophages probably leads to fever and to the presence of infection markers, which causes the misdiagnosis of LP as bacterial pneumonia.[16] The type and volume of oil aspirated, the time of permanence of such substance in the alveoli and individual defense mechanisms in the pulmonary microenvironment determine the various body responses. Initially, there is the development of a foreign body inflammatory response. Subsequently, with the permanence of the oil, there is the development of chronic interstitial inflammation, which can evolve to pulmonary fibrosis. In some cases, the coalescence of oil drops is slowly surrounded by fibrous tissue and giant cells, taking on a nodular or mass-like aspect, known as paraffinoma, more commonly observed in the adult population.[13,17] The radiological presentation of LP in the initial stage of alveolar involvement is consolidation; followed by the observation of interstitial infiltrate or mixed infiltrate (interstitial and alveolar); in cases of paraffinoma, a tumor lesion is observed.[17,18]

The clinical presentation of LP in adults is oligosymptomatic or asymptomatic; diagnosis is frequently a radiological finding. Children, however, present a widespread, acute aspiration condition, which evolves to respiratory failure and, occasionally, death.[3,9,19,20] In the present study, tachypnea, cough and fever were the most common clinical manifestations. Moaning was related to age (suckling infants) and to the extent of pulmonary involvement. The presence of oil in the lungs predisposes to recurrent infections, including infections caused by atypical germs, causing alveolar macrophages to release inflammatory mediators and leading to fever, leukocytosis, neutrophilia and increased erythrocyte sedimentation rate.[6,18] These alterations were observed in most of the children investigated in the present study, which probably led to the incorrect diagnosis of bacterial pneumonia.

In some cases, there was discordance between the clinical and radiographic findings. Children in whom the pulmonary auscultation findings were normal but chest X-rays showed extensive alterations were incorrectly diagnosed with pulmonary TB. In children, the radiological and tomographic alterations caused by TB vary greatly; such alterations can be similar to those caused by LP, and definitive diagnosis should be established before initiating a specific treatment for TB.[21] However, in cases of LP, there is no epidemiological history for TB, Koch's bacillus cannot be identified in pulmonary granulomas, pulmonary involvement predominates in the lower lobes (preferential zones of aspiration), density measurements in the consolidation areas are negative and BAL fluid cytology reveals foamy alveolar macrophages with lipid vacuoles stained with Sudan.[5,16]

The radiological alterations of LP are nonspecific, generally involving multiple lobes and predominating in the posterior and inferior regions of the lungs.[5] In the present study, there was a predominance of consolidation, perihilar infiltrate (especially in the right lung) and hyperinflation. The principal tomographic alterations in LP are multifocal consolidation; linear and ground-glass interstitial opacities; thickening of intralobular septa; crazy-paving pattern; poorly-defined nodules; pleural effusion; and masses.[17,22] In the present study, the principal findings were consolidations with air bronchogram and few cases of ground-glass opacity. The crazy-paving pattern was seen only in 1 child. Such alterations were bilateral and multifocal, involving from three to five lobes and predominantly in the posterior regions of the right lung. Negative density values (between −30 and −150 HU) within the consolidation area, although nonspecific, can indicate the presence of fat and are frequently associated with LP, as shown in the present study.[23-25]

Currently, analysis of the BAL fluid is considered the diagnostic method of choice for suspected cases of LP.[5] An opalescent macroscopic aspect of the BAL fluid, with a halo of supernatant fat, is a strong indication of LP. However, only the cytochemical examination

using Sudan staining, which stains orange the fat present in the extracellular medium and in the cytoplasmic vacuoles of macrophages, can confirm the diagnosis. All of the children included in the present study were diagnosed as having LP based on the BAL findings.

Although there is still no consensus regarding the treatment for LP, the interruption in the use of mineral oil leads to clinical improvement. The use of corticosteroids is controversial, since they are indicated principally in the most severe cases and in cases in which radiological and functional abnormalities persist in spite of a clinical improvement.[4,26,27] Depuration of the inhaled oil is a slow process, and the permanence of this substance in the lung parenchyma leads to inflammation and fibrosis.[11,17,28] Therefore, the best therapeutic strategy would be to remove the oil as early as possible through bronchoscopy with multiple BALs, especially in the segments most severely affected, therefore reducing the need for corticosteroids and their side effects.[25] In the present study, 2 children were treated with corticosteroids and multiple BALs. The result was clinical and tomographic normalization after 12 months of monitoring (Figures 2 and 3). A recent study involving children with LP caused by aspiration of mineral oil demonstrated the efficacy of the treatment with multiple BALs, with clinical and tomographic resolution.[25]

Cases of chronic pneumonia refractory to antimicrobial therapy, combined with a history of ingestion of mineral oil and the presence of condensation in lower and posterior regions of the lungs, with negative density measurements, should raise the clinical suspicion of LP. However, the diagnosis should be established based on the findings of the BAL, which can also be used as a therapeutic measure. Because health professionals are not aware of the risks of using mineral oil, especially for the very young and the elderly, and because of the indiscriminate use of mineral oil, which is commercialized without directions for use and without the need for a medical prescription, LP continues to be underdiagnosed in Brazil.

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