Non Infectious Cavitary Exogenous Lipoid Pneumonia: A Case-Based Short Review

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Abstract

Lipoid pneumonia (LP) is due to the accumulation of either endogenous or exogenous lipids in the alveoli. The exogenous LP (ELP) results from the chronic aspiration or inhalation of animal, vegetable, or mineral oils or fatty substances that by reaching the pulmonary alveoli cause a foreign body-type inflammatory reaction of lung parenchyma, associated with fibrosis, necrosis, and, possible cavitation. Pulmonary reaction is characterised by symptoms and radiological findings that are common to other pulmonary diseases. The radiologic presentation of ELP includes lung consolidations and ground-glass opacities, with predominant involvement of the lower lobes. Thickening of interlobular septa, adipose or not adipose single mass, and poorly marginated nodules may also occur. Cavitation, when present, is mainly associated with infection by non-tuberculobus mycobacteria or fungi. Thus in patients exposed to lipid aspiration presenting with cavitated mass on CT scan, possible infection should be thoroughly ascertained, and adequate treatment promptly initiated.

Hereby, we report three cases of non-infectious cavitary exogenous lipoid pneumonia. In all three patients, one with acute onset and two with chronic recurrent form, the ELP diagnosis was confirmed by both cytological and histological findings, whereas microbiological examination gave negative results. Moving from these three cases, we review the pathogenesis, clinical and radiological manifestation of ELP.

Keywords: Lipid inhalation; Lung consolidation; Non-tuberculobus mycobacteria

Abbreviations: NTM: Non-Tuberculobus Mycobacteria; ELP: Exogenous Lipoid Pneumonia; CT: Computed Tomography; DLCO: Capillary Diffusion Capacity of Carbon Monoxide; TBLB: Transbronchial Lung Biopsy, BAL: Bronchoalveolar Lavage

Clinical and Pathological Background

Lipoid pneumonia (LP) is a disease state due to the accumulation of either endogenous or exogenous lipids in the alveoli and subsequent parenchymal inflammatory reaction characterised by non-specific symptoms and radiological findings common to other pulmonary diseases [1,2]. The exogenous form of lipid pneumonia (ELP) usually occurs when fatlike material of mineral (including petroleum-derived long-chain, saturated hydrocarbons), vegetable or animal origin, or a miscellanea of substances including radiographic contrast media and oil-based medications are inhaled or aspirated into the respiratory tract. Thus, the aspiration of milk, olive oil, cod or shark liver oil, and paraffin oil used in laxatives, or the inhalation of moisturizing nasal drops, have long been recognised to cause ELP. Once inhaled, mineral oils impair the cough reflex and mucociliary clearance, facilitating their penetration and deposition into the deep lung, where they are hydrolysed by lung lipases, releasing higher amount of free fatty acids. Chronic ELP results from long-term, recurrent inhalation of lipids or fats, whereas the acute form is secondary to accidental aspiration of large amount of these materials over a short period of time [4].

Factors that increase the risk of ELP include extremes of age, anatomical or structural abnormalities of the pharynx and esophagus (e.g. Zenker’s diverticulum), gastroesophageal fistula, hiatal hernia, gastroesophageal reflex, achalasia, psychiatric disorders, episodic loss of consciousness, and neuromuscular disorders that result in swallowing dysfunction or cough reflex impairment [3,5].

In adults, 25% of cases of ELP occur in individuals without any predisposing condition and the accidental inhalation of oily substances is the unique etiologic factor. It is noteworthy that in a relevant proportion of cases the inhalation occurs inadvertently without eliciting airway responses, such as glottic closure or cough. For instance, oily medications introduced into the nose can silently reach the bronchial tree of sleeping subjects without eliciting protective cough reflex, and possibly impairing mucociliary transport, and reducing their clearance from the respiratory tract [3,6].

The acute form of ELP is less common, and is typically due to the aspiration of a large quantity of petroleum-based products. It typically presents with cough, dyspnea, and low-grade fever, and usually resolves with supportive therapy. The accidental aspiration of fat-like materials occurring during “fire-eating” is a common event in which...
the acute ELP may develop. Different substances called pyrofluids are used by the so-called “fire-eaters”, the show performers who “swallow” or “spit” fire. The most common pyrofluid is kerdan, an inflammable petroleum-derivative whose low viscosity facilitates its rapid spread in the bronchial tree. After flame blowing, the fire-eater takes a deep breath thus aspirating the kerdan remaining in his or her mouth. In general, fire-eater pneumonitis has clinical and radiologic profiles that differ from those observed in chronic lipid pneumonia. Symptoms occur within the first 12 hours from aspiration of pyrofluids, and are characterised by the abrupt onset of cough, haemoptysis, chest pain, dyspnoea, and fever. Radiologic signs of pneumonitis develop within 12 h. Chest X-ray shows mottled or patchy, local or diffuse perihilar and basal uni- or bilateral infiltrates, areas of atelectasis and occasionally pleural effusions. Pneumatoceles often form in the areas of the densest infiltrations [7]. If promptly recognised, the disease has, in most of cases, a favourable evolution [8].

Conversely, patients with chronic ELP, particularly the elderly, may be asymptomatic, and a large quantity of oily material must usually be aspirated before symptoms develop. When symptomatic, patients report non-productive cough, fever, and weight loss, shortness of breath and respiratory impairment, which may lead to respiratory failure [1]. Physical examination of the chest may be normal or reveal crackles, wheezes or ronchi. Some cases show a discrepancy in severity between clinical symptoms and radiologic abnormalities. HRCT usually showed unilateral or bilateral lung consolidation, with predominance at the lower lung. Other common abnormalities include an adipose-containing mass, ground-glass opacities with associated interlobular septal thickening (crazy-paving pattern), ground-glass attenuation areas, and low in attenuation consolidative opacities involving one or more lung segments along the broncho-vascular structures [1,3].

Treatment

There is no successful therapy in this disease. The treatment of lipid pneumonia comprises discontinuing exposure to the offending agent, treating any complicating infection, and providing supportive care. Some have striking improvement after corticosteroid therapy but others have experienced little effect. Resection of nodules and masses may be curative [9]. In some advanced cases, transplantation of lungs may be considered [10].

Radiological Aspects

The diagnostic accuracy of the chest radiograph in chronic ELP is rather low. Radiologic appearance includes lung parenchymal opacities and consolidations, or poorly marginated nodules, and less commonly pneumatoceles, pneumothorax, pleural effusions, and pneumomediastinum [1,4]. These findings are not specific, and their extension ranges from focal inflammatory reaction, with little or no radiological abnormalities, to severe disease with lower lobe opacities or diffuse and ill-defined pulmonary consolidation or masses [11].

In the suspicion of lipid pneumonia, high resolution (HRCT) scan is mandatory, usually showing unilateral or bilateral lung consolidations, which predominate in the lower lung”. Other common abnormalities include ground-glass opacities, with associated thickening of interlobular septa with a crazy-paving or geographical pattern, which is suggestive of lipid pneumonia [5]. Occasionally, thin-walled cysts (pneumatoceles) are observed. Sometimes, the pulmonary lesion appears as an adipose or not adipose single mass [1]. If fat-like low attenuation is not evident, the solid lesions may mimic the radiological findings of other lung diseases, including primary lung cancer. Architectural distortion associated with the consolidative opacities has also been reported [1]. Thickening of the interlobular septa or fibrosis in the adjacent lung tissue, due to lipid-filled macrophage migration from the alveolar space into the lung interstitium, can also occur in the later stages.

Gondouin summarized the main TC scan features found in a sample of 44 patients affected by exogenous lipid pneumonia (Table 1) [3].

Cavitation rarely occurs, but few cases have been previously reported, all related to infectious causes [12,13]. When cavitation is present, infection by non-tuberculous mycobacteria (NTM) should be suspected, although in some cases cavitation was related to infection by Aspergillus or Nocardia organism [6,12].

Hereby three cases of non-infectious cavitated exogenous lipid pneumonia are presented, one with acute onset, and the others with a chronic onset. The diagnosis was confirmed by microbiological and cytological findings on bronchoalveolar lavage fluid, and histology at transbronchial lung biopsies.

Case 1

A 69 years-old-male, school teacher, ex-smoker (14 pack/year), reporting recurrent pneumonia episodes, with evidence of a persistent left lung parenchymal consolidation on serial chest x-ray over the last two years, was admitted to our clinic. Chest CT scan at admission showed a cavitated low-attenuation consolidation of the left lower lobe (Figure 1). Physical examination revealed the presence of lower left bronchial breath sounds. Oxygen saturation was 97% at rest while breathing room air. Lung function tests showed lung volumes within the normal range and a mild reduction of the diffusion capacity to carbon monoxide (DLCO). Bronchoscopy was performed, and transbronchial lung biopsies (TBLB) and bronchoalveolar lavage (BAL) fluid at the site of lesion were obtained. The cytological examination of BAL fluid showed mild neutrophilia and vacuolated macrophages, whereas no bacterial isolates or fungal organisms were cultured. The microscopic view of the biopsy showed intra-alveolar clusters of vacuolated macrophages, interstitial fibrosis around lipidoid vacuoles, inflammatory lymphohcytic infiltrates, multinucleated foreign-body cells and fibrosis separating large vacuoles (Figure 2).

Since the histological findings were compatible with the presence of fatty substances, ELP was suspected. Subsequent interview revealed that the patient was a frequent user of both paraffin-based nasal drops and oily laxative products. Therefore besides inhalation, chronic aspiration of gastric content was also suspected. Esophagogastroduodenoscopy showed the presence of hiatal hernia and gastro-esophageal reflux thus confirming possible aspiration of fat-like material into the lungs. Negative results for NTM infection, bacteria or fungi suggested that the cavitation was probably due to central necrosis caused by the chronic accumulation of mineral oils.

We concluded that the patient was suffering from non-infectious chronic cavitory ELP secondary to massive accumulation of fat-like substances and subsequent necrosis.

Case 2

A 75-year-old female, retired teacher and ex-smoker (33 pack/year), underwent a surgical Heller’s myotomy and Dor’s fundoplication in order to treat her severe IV degree esophageal achalasia. Before the surgery, a chest x-ray revealed a consolidation in the upper right lobe (Figure 3a). The chest CT scan (Figure 3b) documented in the postero-basal segment of the right upper lobe a consolidation, measured about...
5x4cm, surrounded by “halo sign” secondary to a moderate perilesional ground glass attenuation. After the esophageal surgery, she was admitted to our unit for further examination. At the admission, the patient was asymptomatic, and physical examination was normal. Lung function testing showed normal volumes, whereas the DL CO was 60% of predicted value. She underwent bronchoscopy with BAL and TBLB at the site of the lesion. The cytological examination of BAL fluid showed numerous alveolar foamy macrophages Oil Red-O stained (Figure 4a). The microbiological tests on BAL fluid were negative for common germs and NTM. The histological examination of TBLB showed an alveolar inflammatory infiltrate rich of giant cells, variable sized fat droplets, inflammatory lymphocytic infiltrates, interstitial fibrosis around lipoid vacuoles, and a large cluster of foamy lipid-filled alveolar macrophages (Figure 4b).

The search for acid-fast bacilli with alcohol-stains, PAS and Ziehl-Nielsen methods both on the biopsy and on BAL fluid were negative. The histological findings, together with the history of achalasia were strongly suggestive for chronic ELP. Based on the normal lung function and on the absence of respiratory symptoms no pharmacological treatment was suggested.

Two years later a control chest CT scan showed enlargement and double cavitation of the solid lesion (Figure 5). Physical examination and laboratory tests were normal. Oxygen saturation was 96% while breathing room air at rest. Lung function tests and DL CO were unchanged compared to those obtained two years before. Bronchoscopy with TBLB and BAL was repeated to assess possible infection. Bacteriological examination was negative for both common germs and mycobacteria. The cytology of BAL fluid was characterized by inflammatory cells, with predominant lymphocytes (total cells 570 10^6/L, macrophages 55%, lymphocytes 35%, neutrophils 9%, eosinophils 1%). The histological findings were characterized by the presence of foreign body granulomas incorporating vacuolated histiocytes and necrosis suggestive for ELP. We concluded that the final diagnosis was chronic cavitated non-infectious ELP caused by chronic aspiration due to esophageal achalasia.

Case 3

A 22-year-old male student, life-long non-smoker was admitted for suspected infectious pneumonia. He worked as fire-eater in a tourist
Discussion

Exogenous lipoid pneumonia is a relatively rare disease state resulting from the acute or chronic inhalation or aspiration of animal, vegetal or mineral oils or fats. This condition may be difficult to diagnose because history of oil inhalation in often missed. Diagnosis is based on a history of acute or chronic exposure to oily substances, compatible radiological findings, and the presence of lipid-laden macrophages on sputum or BAL analysis. If isolated, none of these findings is diagnostic per se of lipid pneumonia [14].

The diagnosis of ELP is often challenging because the disease can mimic several pulmonary disorders such as malignancies, infectious pneumonia or pulmonary tuberculosis. Although computed tomography of the chest has been advocated in the diagnosis, patients with minimal and diffuse infiltration or with extensive fibrosis may not reveal the typical density of lipids. In the appropriate clinical setting the diagnosis may be supported by histological findings, showing a great amount of lipid-laden macrophages that fill and distend the alveolar walls and interstitium, where they might be associated with accumulation of lipid material, inflammatory cellular infiltration, and variable amount of fibrosis [5,15]. In the absence of histology, cytological examination of BAL may be diagnostic per se, showing the presence of foamy lipid-laden macrophages Oil Red O stained, and multinucleated foreign-body cells [5,9,16]. The cavitation is quite an uncommon radiological finding in exogenous lipid pneumonia, but when present it may be associated to NTM infection [3,6,13].

There is growing evidence that exogenous lipid pneumonia is a predisposing factor to non-tuberculous mycobacteria (NTM) infection, and the association between achalasia and NTM has been recognised since 1953 [17,18].

It is therefore interesting to postulate that lipid may act in some way as a trigger for NTM infection. Probably, the chronic accumulation of fatty materials led to the granulomatous reaction with central necrosis allowing mycobacteria to become pathogenic [19]. *M. fortuitum* has been identified as the most common pathogen in this clinical setting.

In 1999 twenty cases of exogenous lipid pneumonia (secondary to esophageal or to other swallowing disorders) with pulmonary infections caused by rapidly growing mycobacteria have been described by Hadjiliadis D, et al. [20]. Fourteen patients (70%) had *M. fortuitum* infection, the remaining had *M. chelonae* infection. In 95% of cases the chest CT abnormalities were the presence of patchy or dense infiltrates, unilateral or bilateral, upper or lower lobe, with an alveolar, reticulo-nodular or mixed pattern. Four patients showed pleural effusions (20%), and three patients cavitary disease (15%). The authors concluded that patients with prolonged or refractory lung infection, in presence of esophageal disorders, should be investigated for atypical mycobacteria infection [12].

**Figure 4:** (a) Cytological Oil Red O stain of BAL fluid showing the lipid nature of the vacuoles (red stained). (b) The histological examination of TBLB shows interstitial fibrosis around lipid vacuoles, and a large cluster of foamy lipid-filled alveolar macrophages.

**Figure 5:** CT scan of the lung, 2 years later: enlargement of the upper right consolidation previously described, with double cavitation of the solid lesion (SA and SB).

**Figure 6:** Thin-walled pneumatoceles on the right lower lobe, with a mild perilobular ground glass attenuation. The surrounding parenchyma was normal.
A reasonably high index of suspicion together to the knowledge of the association between NTM and achalasia or accidental aspiration or swallowing disorders, is pivotal to drive the diagnosis [21,22]. It was reported only one case of lipid pneumonia associated to both NTM infection and Aspergillus fumigatus infection [17].

In the three presented cases, based on the medical past history and on the radiological pictures, the diagnosis of lipid pneumonia was confirmed by the presence of alveolar foamy macrophages Oil Red-O stained on BAL fluid (diagnostic per se), and by the histological findings of fill-in alveoli by a large cluster of foamy lipid-filled macrophages forming foreign body granulomas, interstitial fibrosis around lipid vacuoles, inflammatory lymphocytic infiltrates and some multinucleated foreign-body cells. The microbiological assessment performed on BAL fluid definitely excluded infections, in particular NTM infections. To the best of our knowledge, this is the first description of cavitated forms of ELP not associated to infections.

In conclusion, ELP is a rare disease, and the cavitated form represents a more rare radiological finding. We conclude that in presence of both radiological and clinical suspicion of cavitated ELP, bronchoscopy with BAL and TBLB should be performed in order to confirm (or exclude) the presence of NTM infection.

References