Lipoid pneumonia: an overview

Vijay Hadda & Gopi C Khilnani

To cite this article: Vijay Hadda & Gopi C Khilnani (2010) Lipoid pneumonia: an overview, Expert Review of Respiratory Medicine, 4:6, 799-807, DOI: 10.1586/ers.10.74

To link to this article: http://dx.doi.org/10.1586/ers.10.74

Published online: 09 Jan 2014.
Lipoid pneumonia is an uncommon disease caused by the presence of lipid in the alveoli. It is classified into two major groups, depending on whether the lipid/oil in the respiratory tract is from an exogenous (exogenous lipoid pneumonia) or endogenous/idiopathic (endogenous lipoid pneumonia) source. The usual presentation occurs with insidious onset and nonspecific respiratory symptoms such as dyspnea and/or cough. The main radiological findings include airspace consolidations, ground-glass attenuation, airspace nodules and ‘crazy-paving’ pattern. However, the radiological appearance of the disorder can mimic many other lung diseases, including carcinoma. Owing to the nonspecific clinical presentation and radiological features, the diagnosis is often missed or delayed. Pathologically, lipoid pneumonia is a chronic foreign body reaction to fat, characterized by lipid-laden macrophages. Diagnosis of this disease requires a high index of suspicion and can be confirmed by demonstration of lipid-laden macrophages in respiratory samples such as sputum, bronchoalveolar lavage fluid or fine-needle aspiration cytology/biopsy from lung lesions. Treatment protocols for this illness are poorly defined.

**Keywords**: endogenous lipoid pneumonia • exogenous lipoid pneumonia • lipid-laden macrophages • lipid pneumonia

Lipoid pneumonia is an uncommon form of pneumonia characterized by the presence of intra-alveolar lipid and lipid-laden macrophages on microscopy. It was first reported in 1925 by Laughlen in association with laxative use [1]. Subsequently, there were many reports of this pneumonia caused by inhalation or aspiration of a fatty substance during the first half of the 20th Century [2–5]. Lipoid pneumonia has been reported under different names, such as paraffinoma, cholesterol pneumonia and lipid granulomatosis, denoting its association with inhalation or ingestion of various substances, such as petroleum jelly, mineral oils and nasal drops, and even intravenous injection of olive oil [6–14].

Its precise incidence is not well known, however, one autopsy study from the USA has reported a frequency of 1.0–2.5% [6]. Although awareness about this disease has increased, many physicians are still unfamiliar with this condition, which may be responsible for underdiagnosis. Lack of specific clinical or radiological features may lead to further missed or delayed diagnoses. Therefore, awareness of this type of pneumonia is important. Diagnosis can be established by demonstrating lipid-laden macrophages in various specimens such as sputum, bronchoalveolar lavage (BAL) or lung biopsy. If diagnosed at the right time, the unnecessary use of antibiotics may be avoided. Importantly, the progression may be halted, or at least slowed, by preventing exposure to the offending agent.

Lipoid pneumonia has been classified into exogenous and endogenous lipoid pneumonia, based on the source of the lipid exposure. Exogenous lipoid pneumonia is related to inhalation or aspiration of fatty substances, whereas in endogenous lipoid pneumonia, intra-alveolar lipid accumulation occurs as a result of obstruction, chronic lung infection/disease or a lipid storage disorder. The aim of this article is to acquaint physicians with both these entities and discuss the management options.

**Exogenous lipoid pneumonia**

Historically, the first description of exogenous lipoid pneumonia was given by Laughlen in four patients with a history of chronic laxative and nasal drop use [1]. Exogenous lipoid pneumonia is more commonly reported in the literature.

**Risk factors for exogenous lipoid pneumonia**

Lipoid pneumonia as an unusual cause of respiratory symptoms has been reported in all age groups. Initially, it was reported predominantly in children – often with local anatomic defects, such as cleft palate, or in debilitated adults, but
several reports indicate that it can also occur in healthy individuals [9,16]. The aspiration or inhalation of fatty substances is a central causative factor for exogenous lipoid pneumonia. Aspiration may be due to abnormality in deglutition (anatomical or functional pharyngeal and esophageal abnormality), or neuromuscular diseases affecting pharyngeal motility or the cough reflex. In normal subjects, aspiration may be occupation related (e.g., fire-eater) [17,18] or due to trivial habits such as use of oil-based laxatives, lip balm, lip gloss and petroleum jelly, among others [9,19,20]. Siphoning of various mineral oils (e.g., diesel) from containers is a common practice in India and may be a risk factor for lipid aspiration [21]. Many traditional folk remedies such as the use of oily nasal drops, forceful animal fat feeding, such as ‘ghee’, to establish regular bowel habits or transnasal administration of medicines to treat cough and cold have been described as risk factors for exogenous lipoid pneumonia in infants and small children [22,23]. Other examples of such therapies are use of sesame oil to flush nasal secretions (in India) and to relieve small bowel obstruction due to *Ascaris lumbricoides* (in Brazil) [24,25]. Aspiration has also been reported as an iatrogenic complication following bronchography using the dye propyliodone (now rarely performed) and during nasogastric tube feeding [26,27].

**Clinical features of exogenous lipoid pneumonia**

The usual presentation of exogenous lipoid pneumonia occurs alongside dyspnea and/or cough, in a similar manner to other lung diseases. On the basis of onset of the disease it can have acute or chronic presentation. Acute exogenous lipoid pneumonia is uncommon and may simulate infectious pneumonia with fever, with or without cough [21,28]. It is typically caused by massive exposure to mineral oils/animal fats [29–31]. Chronic exogenous lipid pneumonia is more common and results from the repeated aspiration of mineral oils/fatty substances of animal origin [9]. It usually presents with dyspnea and/or cough. Less commonly described clinical features include chest pain, hemoptysis and intermittent fever, which may be related to the inflammatory reaction to oil or to secondary infection [32]. Some authors have also described weight loss in these patients [9,35]. Physical examination findings are usually normal, although one may find dullness on percussion, crackles, wheezes or rhonchi. In long-standing progressive disease, physical findings related to chronic hypoxia, such as clubbing, can develop [9].

Blood investigation results are usually normal. However, leukocytosis and an increased erythrocyte sedimentation rate may occur, especially when complicated by infection. Pulmonary function test results have shown a restrictive pattern but may also be normal [32,33].

**Radiological features of exogenous lipoid pneumonia**

On radiological imaging, diverse findings have been described that can mimic many other lung diseases including carcinoma, pneumonia, acute respiratory distress syndrome or a localized granuloma [34–36]. Radiologically, manifestations of acute exogenous lipid pneumonia may be seen as early as 30 min after the episode of aspiration or inhalation, and in most patients within 24 h [37]. The typical findings include homogenous dense consolidation, often with air bronchograms and sometimes a fine, ‘spun glass’ appearance may be observed [34]. The most common findings described on CT scan include airspace consolidations, areas of ground-glass attenuation, airspace nodules and ‘crazy-paving’ pattern [38]. Consolidations are usually heterogeneous and their negative density values, as low as -30 to -150 HU, are a diagnostic criteria for lipid pneumonia (Figure 1). However, superimposed inflammation may act as a confounding factor and may increase the attenuation values of the lesion [15,39]. Involvement may be diffuse or focal, and unilateral or bilateral, however, unilateral pneumatic consolidation with lower lobe predominance is more commonly reported [34,35,38,40–42]. Other radiological abnormalities that can be seen in these patients include pneumatoceles, pneumomediastinum, pneumothorax and pleural effusions [37,44,45]. Occasionally, one may also find cavitation [44,45]. Pneumatoceles usually develop within regions of ground-glass opacity or consolidation and usually manifest within 2–30 days of aspiration or inhalation. These are more commonly seen in patients with massive exposure to mineral oils [46]. Pneumothorax and pneumomediastinum are rare and have been reported to occur within 4 days after hydrocarbon aspiration [39]. Importantly, they are associated with a poor prognosis [39].
The radiologic manifestations of acute exogenous lipoid pneumonia usually show a partial to complete resolution over time after stopping exposure to lipids. Resolution of opacities is usually observed within 2 weeks to 8 months, however, they may be progressive or static in some cases, even after stopping the exposure and symptomatic improvement [3,35,39]. There can be scarring of lung parenchyma, which can cause persistence of radiological shadow.

Similar to acute exogenous lipoid pneumonia, the most frequent radiological feature of chronic exogenous lipoid pneumonia is ground-glass opacity or consolidation involving one or more segments, typically with a peribronchovascular distribution and predominant involvement of the lower lobes [39]. Fibrosis and coalescence of oil can result in nodules and masses with irregular margins, closely mimicking lung cancer [34,35]. The most commonly described feature is alveolar consolidations of low attenuation values, ground-glass opacities with thickening of intralobular septa (crazy-paving pattern) or alveolar nodules (Figures 2 & 3) [15,22,42,47]. Magnetic resonance imaging may reveal high signal intensity on T1-weighted imaging consistent with lipid content [19,42,48-50].

Characteristically, chronic exogenous lipoid pneumonia manifests itself as a fat-containing mass [15]. Although the mass is typically irregular or spiculated due to chronic inflammation and fibrosis, the presence of fat in the mass, with a few exceptions, is a diagnostic feature of exogenous lipoid pneumonia. Other conditions that can show similar features are hamartomas and lung metastases from primary extrathoracic sarcomas, such as chondrosarcomas or liposarcomas [39]. Cavitation and calcification of the mass can occasionally occur [9].

Other features of chronic exogenous lipoid pneumonia include single or multiple nodules or masses, with or without fat enclosed. In the absence of fat (an infrequent finding), the nodules or masses can be indistinguishable from other lung masses [51-53]. Recently, 2-deoxy-2-F-fluoro-D-glucose (FDG) and 3-deoxy-3-F-fluorothymidine (FLT) positron emission tomography (PET) have also been used for the diagnosis of chronic exogenous lipoid pneumonia, although it should be noted that it can be misinterpreted as malignancy [54,55]. The radiological manifestations of chronic exogenous lipoid pneumonia can improve slowly over time, however, in many patients there will be progression of opacity even if the exposure to vegetable or mineral oils or animal fats is discontinued [15]. Fibrosis and destruction of normal lung architecture can result in cor pulmonale [56].

Pathophysiology of exogenous lipoid pneumonia

Pathologically, lipoid pneumonia is thought to be caused by a chronic foreign body reaction to fatty substances in the alveoli. The mechanisms by which lipids reach alveoli are aspiration (nonvolatile hydrocarbons) or inhalation (volatile hydrocarbons). Few mineral oils such as gasoline can cause lung injury even after intravenous injection [57]. In the case of exogenous lipoid pneumonia due to inhalation/aspiration, mineral oils/fat enter the tracheobronchial tree without stimulating the cough reflex and impair the mucociliary transport system. The mechanism of lung injury after intravenous injection is complex. It has been suggested that the lung is the first capillary bed encountered during circulation, thereby bearing the majority of the damage [58,59]. Once inside the alveoli, it is difficult to expectorate the lipid. This situation may be complicated by associated neurological and gastrointestinal disorders affecting swallowing, palatal or cough reflex. Once in the alveoli, oil is taken up by macrophages after emulsification. Because alveolar macrophages cannot metabolize the fatty substance, the oil is repeatedly released into the alveoli after death of the macrophages [60]. The oil released illicits a giant-cell granulomatous reaction (hence also called lipid granulomatosis), chronic inflammation, and alveolar and interstitial fibrosis. Evolution of lesions with time has been described [49]. Fresh lesions show alveolar infiltration by lipid-laden macrophages and almost normal alveolar walls and septa. Advanced lesions show larger vacuoles and inflammatory infiltrates in alveolar walls, bronchial walls and septa. The fibrosis and parenchymal destruction around large lipid-containing vacuoles are features of the oldest lesions. Special staining techniques (such as oil red O and Sudan black) can demonstrate more effectively whether the vacuoles are filled with lipid.

Diagnosis of exogenous lipoid pneumonia

Diagnosis of lipoid pneumonia is often difficult, because it is not routinely suspected at the time of presentation. Quite often, cases are treated as an infective community-acquired pneumonia and...
an alternative diagnosis is only considered when the patient does not respond to therapy. This is also because there are no diagnostic radiological features on the chest radiograph. Therefore, a detailed history of exposure to fatty substances should be taken to achieve early diagnosis. In a patient at risk of aspiration/inhalation of mineral oils, an early CT scan is very useful for providing further clues to the diagnosis of lipoid pneumonia. Once suspected, the diagnosis is not difficult. The diagnosis of lipoid pneumonia is confirmed by detecting intra-alveolar lipid and lipid-laden macrophages in respiratory specimens. Various specimens that may be used for confirmation of the diagnosis include sputum, BAL, transthoracic fine-needle aspiration cytology or biopsy from the lesion (Figure 4). A sputum sample is easy to obtain, however, many patients do not produce any sputum and repeated attempts may be required to obtain a representative sample [39]. Furthermore, sputum examination has questionable reliability and lipid-laden macrophages in sputum have been demonstrated in the absence of lipoid pneumonia [61]. Today BAL is widely available and many studies have proven its utility in the diagnosis of lipoid pneumonia [38,39]. Therefore, BAL fluid is the preferred sample for this. BAL may reveal turbid or whitish fluid with fat droplets visible at the surface [62]. Frozen samples should be examined by various stains to discriminate types of oils. Chromatography and infrared spectroscopy may also be used. Transthoracic fine-needle aspiration cytology may be diagnostic but false-negative results can occur [63]. In some cases, transbronchial lung biopsy or even surgical biopsy may be required [64,65].

Although most of the reports have used fat-laden macrophage as a diagnostic marker for lipoid pneumonia, its specificity has been questioned by some authors [66,67]. Therefore, diagnosis of exogenous lipoid pneumonia should be based on the triad of history of mineral oil ingestion, compatible radiological findings, and presence of intra-alveolar lipids and/or lipid-laden macrophages.

**Endogenous lipoid pneumonia**

Endogenous lipoid pneumonia was first described by McDonald et al. in 1949 as ‘obstructive pneumonitis’ in patients with lung neoplasms [68]. The obstructive pneumonitis was characterized by the presence of bronchial obstruction and the accumulation of lipid-filled macrophages. Macroscopically, there is parenchymal consolidation that has a characteristic yellowish

![Figure 3. CT scan of a chest demonstrating areas of ground-glass opacity superimposed on interlobular septal thickening (crazy-paving pattern) on the right side.](image1)

Images provided by Edson Marchiori, Fluminense Federal University (Rio de Janeiro, Brazil).

![Figure 4. Centrifuged bronchoalveolar lavage (hematoxylin and eosin staining) fluid showing multiple lipid-laden macrophages (appearing as vacuoles [arrows]).](image2)

Reproduced from [21].
discoloration due to the accumulation of lipid in the alveoli, hence also called ‘golden pneumonia’ [69]. Histologically, there is an accumulation of lipid-filled macrophages and eosinophilic proteinaceous material derived from degenerating cells, including surfactant from type II pneumocytes, in the alveoli distal to the bronchial obstruction, hence named ‘cholesterol pneumonia’. Endogenous lipid pneumonia has been further classified into three types based on bronchial obstruction: type I lipid pneumonia, localized to the lung parenchyma distal to an airway obstructed by a tumor; type II lipid pneumonia, with features of type I lipid pneumonia and consecutively spreading to the adjacent segment whose airway is not affected; and type III lipid pneumonia, with features of type II lipid pneumonia and spreading to isolated segments [70]. Initially, endogenous pneumonia was thought to be the result of the obstructive pneumonitis caused by infection mainly in the obstructed bronchus [68,71,72]. Later, however, many researchers observed the fact that the condition is indeed due to a noninfectious process such as physical or chemical effects of airway blockage [71,72].

Risk factors for endogenous lipid pneumonia
Historically, endogenous lipid pneumonia has typically been reported in association with bronchial obstruction in patients with non-small-cell lung cancers. However, it can also occur as a manifestation of infection and other diseases that are not associated with bronchial obstruction. Recently, this disease has been reported in a patient with repetitive episodes of fungal pneumonia [78]. Endogenous lipid pneumonia has been described in association with pulmonary alveolar proteinosis where the alveoli are usually filled with protein and lipid material resembling surfactant [69]. Pulmonary alveolar proteinosis typically manifests on CT scan as ground-glass opacities, often with superimposed thickening of the interlobular and intralobular interstitia (crazy-paving pattern) [69]. Niemann-Pick disease, a lipid-storage disorder in which accumulation of intra-alveolar and interstitial fat-laden macrophages and sphingomyelin occurs, is also within the spectrum of endogenous lipid pneumonia [74]. There are many other conditions that may be associated with endogenous lipid pneumonia such as sclerosing cholangitis, bronchiolitis obliterans, necrotizing granulomatosis and connective tissue disease [75–78].

Pathophysiology of endogenous lipid pneumonia
The pathogenesis of endogenous lipid pneumonia is complex and has been thought to be related to several mechanisms, such as retained epithelial secretion, cell breakdown, leakage from vessels, prolonged hypoxia, and local oxygen and carbon dioxide tension [71,72,79]. It has also been suggested that endogenous lipid pneumonia may be a result of transbronchial dissemination of breakdown products of cancer cells, especially those of poorly differentiated adenocarcinoma cells and secretions including mucin [70]. Another mechanism that has been suggested involves the anoxic tissue injury stimulating various enzymes such as phospholipases and mono-oxygenases, which in turn cause modification of low-density lipoprotein cholesterol. This modified low-density lipoprotein cholesterol enhances lipid uptake by alveolar macrophages similar to atherogenesis [80–82]. As for the contribution of infectious changes to endogenous lipid pneumonia, infection is generally localized in airways because the surrounding lung is already consolidated by the noninfectious inflammatory changes, limiting the spread of bacteria [71].

Diagnosis of endogenous lipid pneumonia
Endogenous lipid pneumonia typically manifests radiologically as consolidative opacities with or without a central obstructing lesion (Figure 5) [70]. However, unlike exogenous lipid pneumonia, the accumulation of lipid-rich cellular debris does not manifest radiologically as lipid-containing opacities with low attenuation typical of lipid [39]. The diagnosis of endogenous lipid pneumonia is made on histopathology characteristic of lipid-laden macrophages similar to exogenous lipid pneumonia. Polarized light microscopy after staining with sulfuric acid and acetic acid (Schultz stain) usually reveals cholesterol crystals, a finding indicative of endogenous lipid pneumonia.

Treatment of lipid pneumonia
Treatment of lipid pneumonia is not well studied and published experience is only with case reports [83,84]. In case of exogenous lipid pneumonia, avoiding ongoing exposure and providing
supportive care is the mainstay of treatment. As anti-inflammatory agents, corticosteroids appear promising as a therapeutic option. One trial of corticosteroids in children with mild-to-moderate lipid pneumonia did not show any clinical or radiological benefits [85]. In adults, there are anecdotal reports of systemic corticosteroid use to slow the inflammatory response [21,86]. However, corticosteroids are not indicated in all cases and should only be used if the lung injury is severe and ongoing. There are reports of lipid pneumonia being successfully treated with immunoglobulins [87] and whole-lung lavage [88–91]. Repeated whole-lung lavage is especially useful in children [90,91]. Some authors have described resection of nodules and masses in these cases [22,92]. Surgical resection is usually unwarranted as lipid pneumonia is typically indolent and may regress spontaneously. Resection, however, may be performed in cases where there is a high suspicion of cancer [33]. Similarly, surgery seems a logical therapy in cases of post-obstructive lipid pneumonia.

Prognosis of lipid pneumonia is usually indolent, however, it may also be progressive. Risk factors for progressive disease are concurrent debilitating illness and continued exposure to mineral oil. Patients may show persistent or progressive radiological abnormalities despite symptomatic relief [9]. In addition, this may be complicated by superinfection with microorganisms such as *Mycobacterium chelonae*, *Mycobacterium fortuitum* and other bacteria [93,94]. Colonization by *Cryptococcus* is also reported [32]. Protracted exposure may cause respiratory insufficiency and may lead to cor pulmonale [56]. Hypercalcemia is one of the uncommon complications of granulomatous reaction such as in TB and sarcoidosis [95]. Association of lipid pneumonia with lung cancer is also reported in a few cases [96,97].

**Expert commentary**

Lipoid pneumonia is an uncommon disease characterized pathologically by the presence of lipid-laden macrophages in respiratory specimens. It has been classified further as exogenous or endogenous lipid pneumonia. Inhalation or aspiration of fatty substances is the most important risk factor in case of exogenous lipid pneumonia. Bronchial obstruction and other miscellaneous lung conditions have been reported as risk factors for endogenous lipid pneumonia. Clinical and radiological presentations are diverse, therefore, in suspected cases histopathological/cytological examination is mandatory to diagnose this condition. Treatment, although not well defined, differs significantly from other causes of pneumonia, hence greater awareness of this condition is required. It should be considered as a differential diagnosis in all patients with pneumonia and focus should be on elucidating their risk factors.

**Five-year view**

Owing to its nonspecific symptoms and radiological features, lipid pneumonia often remains undiagnosed or diagnosis is delayed. However, with recent multiple publications on this topic, we expect increased awareness and more frequent diagnosis of this disease. The detailed history of exposure to a variety of substances is often missed in the management of community-acquired pneumonia. Inclusion of this aspect in clinical care of patients with pneumonia will further improve the diagnosis rate. Lipoid pneumonia, although uncommon, should be considered in all cases of respiratory symptoms and lung shadows. This condition further emphasizes the importance of proper collection of respiratory samples and subjecting them to cytological evaluation besides microbiological evaluation. Accurate diagnosis will prevent unnecessary use of expensive antibiotics and lead to better management. With more frequent diagnosis of this disease, we may expect some data on routine examination of these samples for lipid-laden macrophages.

Since the disease is uncommonly diagnosed, there are no systematically conducted trials using corticosteroids. With increased awareness and more frequent diagnosis, we can expect more data regarding the role of various treatment modalities such as corticosteroids and repeated BAL.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.
References
Papers of special note have been highlighted as:
• of interest
** of considerable interest
3 Baron E. Lipid pneumonia due to the use of mineral oil as a laxative. VA Med. Mon. 77(9), 448–450 (1950).
5 No authors listed. WEEKLY retrospective study of 15 patients with both acute and chronic exogenous lipid pneumonia, which has shown that only patients with chronic lipid pneumonia had masses on CT scan. It also showed that acute exogenous lipid pneumonia had better radiological clearance than chronic lipid pneumonia.

** In this retrospective study, the authors have described various high-resolution computed tomography findings in patients with exogenous lipoid pneumonia. The authors have also compared the radiological findings in adults with that of children.


** Excellent review of radiological manifestations of both exogenous as well as endogenous lipid pneumonia.


56 Casey JF. Chronic cor pulmonale associated with lipid pneumonia. JAMA 177, 896–898 (1961).


** Authors in this study included 147 consecutive patients of lung cancer who underwent surgery. This study demonstrated endogenous lipid pneumonia in 29% of surgical specimens.


Lipoid pneumonia: an overview

- Demonstrated the role of bronchoalveolar lavage in diagnosis and treatment of lipoid pneumonia.

- Demonstrated that multiple therapeutic bronchoalveolar lavages are a safe and effective treatment modality of lipoid pneumonia.


- An overview of clinical, radiological and management aspects of exogenous lipoid pneumonia.


