REVIEW

Exogenous lipoid pneumonia. Clinical and radiological manifestations

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Summary
Lipoid pneumonia results from the pulmonary accumulation of endogenous or exogenous lipids. Host tissue reactions to the inhaled substances differ according to their chemical characteristics. Symptoms can vary significantly among individuals, ranging from asymptomatic to severe, life-threatening disease. Acute, sometimes fatal, cases can occur, but the disease is usually indolent. Possible complications include superinfection by nontuberculous mycobacteria, pulmonary fibrosis, respiratory insufficiency, cor pulmonale, and hypercalcemia. The radiological findings are nonspecific, and the disease presents with variable patterns and distribution. For this reason, lipoid pneumonia may mimic many other diseases. The diagnosis of exogenous lipoid pneumonia is based on a history of exposure to oil, characteristic radiological findings, and the presence of lipid-laden macrophages on sputum or BAL analysis. High-resolution computed tomography (HRCT) is the best imaging modality for the diagnosis of lipoid pneumonia. The most characteristic CT finding in LP is the presence of negative attenuation values within areas of consolidation. There are currently no studies in the literature that define the best therapeutic option. However, there is a consensus that the key measure is identifying and

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discontinuing exposure to the offending agent. Treatment in patients without clinical symptoms remains controversial, but in patients with diffuse pulmonary damage, aggressive therapies have been reported. They include whole lung lavage, systemic corticosteroids, and thoracoscopy with surgical debridement.

Contents

Definition and classification

Several pulmonary complications may be caused by the aspiration of different substances into the airways and airspaces. Lipoid pneumonia (LP) is an uncommon condition that results from the pulmonary accumulation of fatlike compounds of animal, vegetable or mineral origin.[1,2] It can be classified into endogenous and exogenous forms.

In endogenous form, also called "cholesterol" or "golden" pneumonia, the fatlike materials are derived from the lung itself.[3,4] It usually develops when lipids that normally reside in the lung tissue — most commonly cholesterol and its esters — are released from destroyed alveolar cell walls distal to an obstructive airway lesion or from lung tissue damaged by a suppurative process, or due to lipid storage diseases.[3,5,6]

The exogenous form can be classified into acute and chronic. Chronic exogenous LP results from long-term, recurrent inhalation exposure to oil, while the acute form is secondary to accidental aspiration of a large quantity of lipid material over a short period of time.[7,8]

Etiopathogenesis and pathophysiology

Exogenous LP is caused by the inhalation of oils present in food, radiographic contrast media, or oil-based medications such as laxatives.[1,9] Traditional oil-based popular medicines are used to treat various diseases in children, and are often associated with respiratory diseases.[10] In adults, most cases result from the use of oil-based laxatives (olive oil, cod liver oil and paraffin oil) for the treatment of constipation, followed by the nasal instillation of oily products for chronic rhinopharyngeal diseases.[3,11]

Chronic constipation is a frequent symptom in the pediatric population. Mineral oil is also used in children for partial small bowel obstruction by *Ascaris lumbricoides*.[12,13] However, it must be remembered that infants and small children often object vigorously to ingest the oil, resulting in gagging that precipitates aspiration.[14]

Different substances called pyrofluids are used by "fire-eaters" (performers that "swallow" or "spit" fire). The most common is the petroleum-derivative kerdan, characterized by its reduced viscosity and rapid diffusion throughout the bronchial tree. After flame blowing, the fire-eater takes a deep breath, and can aspirate the kerdan remaining in the mouth.[8]

It is noteworthy that fire-eater pneumonitis has morphological, radiographic and clinical profiles entirely different from chronic lipoid pneumonia. The history of accidental aspiration during "fire-eating" demonstrations is characteristic. Symptoms occur in the first 12 h after aspiration, and include chest pain, dyspnea, cough, fever, and hemoptysis. The disease has, in most of cases, a favorable evolution. The HRCT usually shows bilateral lung consolidations, often associated with cavitary lesions (pneumatoceles).[8]

Other less commonly reported causes of LP include: aspiration of milk,[15,16] poppy seed oil,[3] and egg yolk[16]; occupational exposure to paraffin (paraffin droplets released by machines) in cardboard crockery factories[17]; oil blasting in industries; use of spray paint[18]; contact with plastic paint[19]; aspiration of oils used in industry as lubricants and cutting fluids, in either fluid or spray form, for turning, milling and grinding operations[3]; cleaning of new cars protected by paraffin, using hot water generated by compressed air jets[20]; cleaning oil-containing vats; siphoning diesel fuel[19,21]; smoking blackfat tobacco, a Kentucky product coated with oil and petroleum jelly to flavor and moisturize the leaf[6]; accidental aspiration of vaseline

used in the placement of nasogastric tubes[22]; longstanding use of petroleum jelly (Vaseline, Vicks™) at bedtime[23]; aspiration of spray lubricant WD-40 (very popular oil spray, for home use)[24]; excessive use of lip balm (Chap Stick, a lipstick that contains petrolatums and lipids) and of flavored lip gloss[6]; and facial application of petrolatum for erythrodermic psoriasis.[25] Some authors also described the development of LP secondary to suicide attempt by mineral oil immersion.[21,26]

Factors that increase the risk of exogenous LP include extremes of age; anatomical or structural abnormalities of the pharynx and esophagus, such as Zenker diverticulum, gastroesophageal fistula, hiatal hernia, gastroesophageal reflux, achalasia; psychiatric disorders; episodes of loss of consciousness; neuromuscular disorders that result in swallowing dysfunction or affect the cough reflex; and, particularly in children, forced oil intake.[1,7,27–29] Because they float on the top of stomach fluids, oils may enter the airway when aspirated by patients with gastroesophageal reflux disease.[3,6–8,27,30]

Critically ill patients receiving nasoenteric feeding may easily develop aspiration pneumonia, as a result of a retrograde regurgitation of feeding solutions.[31]

In some countries the digestive form of Chagas disease, where patients with megacolon have severe and prolonged periods of constipation (over 60 days), should also be remembered.[32,33] The combination of two factors (constipation caused by functional disorder of colon, and tendency to aspiration due to megaesophagus) enhances the risk of lipoid pneumonia in patients with Chagas disease.[34]

In many cases there is no predisposing condition and the excessive use of oily substances is the presumed cause.[1,2,29] In adults, 25% of cases of lipoid pneumonia occur in individuals without any predisposing factors.[3,14]

It is noteworthy that the aspiration of mineral oil usually occurs unnoticed because it does not induce reactive responses in the airways, such as glottic closure or cough. These substances introduced into the nose can easily and silently reach the bronchial tree of sleeping patients without eliciting a normal protective cough reflex[11] and may impair mucociliary transport, subsequently reducing their clearance from the respiratory tract.[3,14]

Clinical findings

The clinical symptoms are nonspecific, and vary according to the patient's age, duration of oil intake, and the amount and quality of oil aspirated.[14,35]

The time of exposure to oil varies widely in the cases described in the literature, reaching up to several years.[3,7,8,30,36,37] In almost all studies, the amount of oil consumed was not quantified.[3,7,8,30,36,37]

In the elderly, these pneumonias are usually chronic, progressive, and asymptomatic. For this reason, it may be discovered only as an incidental autopsy finding. Respiratory failure requiring ventilatory support is an unusual presentation of the disease.[21] In children, massive aspiration may present with acute clinical manifestations and early radiological findings.[36,38]

Symptoms can vary significantly among individuals, ranging from asymptomatic to severe, life-threatening disease.[39] When present, symptoms are usually mild.[26] Lipoid pneumonia usually presents with chronic cough, sometimes productive, and dyspnea.[40] Less common problems include chest pain, hemoptysis, weight loss, and intermittent fever. Physical examination of the chest may be normal or may present dullness to percussion, crackles, wheezes, or rhonchi.[6]

Most cases of lipoid pneumonia shows a discrepancy in severity between the radiological and clinical findings. Patients are often asymptomatic with extensive imaging findings, which are discovered incidentally on routine chest radiographs.[2,6,28]

Extrathoracic symptoms, such as vomiting, stomach pain, dysphagia, vertigo and fainting, are occasionally described in the literature.[8] The presence of hypertrophic osteoarthropathy has been reported in a five-year-old child with a history of forced feeding with animal fat (ghee).[41]

Since its clinical and radiological presentations are nonspecific, lipoid pneumonia may mimic many other diseases,[14] especially bacterial pneumonia, presenting with fever and cough.[19] Occasionally, it can also simulate lung tumours,[42] pulmonary tuberculosis or cystic fibrosis[43].

Diagnosis

The diagnosis of exogenous lipoid pneumonia is based on a history of exposure to oil with radiological findings in keeping with the disease and the presence of lipid-laden macrophages on sputum or bronchoalveolar lavage (BAL) analysis.[3,28] It should be considered, however, that none of these findings alone is diagnostic of lipoid pneumonia.

Clinical history

Exogenous lipoid pneumonias may be difficult to diagnose because a history of oil ingestion is often missed. The exposure is often identified only retrospectively after the diagnosis is made, when a directed history is taken from the patient or their parents.[7,29,35,42]

Bronchoalveolar lavage

Bronchoscopy with BAL has been reported to be successful in establishing the diagnosis of lipoid pneumonia. It allows the assessment of airway anatomy to rule out other causes of chronic nonresolving pneumonia.[1,14] Plugging with oil has been noted bronchoscopically and on post-mortem examination.[43] The macroscopic appearance of BAL may suggest the diagnosis, revealing a whitish or turbid fluid, with fat globules on the fluid surface.[6,14,29] In a series of 10 children with LP, Sias et al.[44] have found that all of them showed a milky BAL fluid on gross examination.

Besides the diagnostic value, BAL has therapeutic implications in some cases.[44] The biochemical analysis of the collected fluid can help to confirm the diagnosis, when using fat stains.[45] The specific type of oil aspirated can be determined by chemical analysis, infrared spectroscopy or chromatography.[6,44,46]

The cytological demonstration of lipid-laden macrophages is consistent with the diagnosis of exogenous LP,[14] although false-negative results may also occur.[14] Both the presence of lipid-laden macrophages per se (Fig. 1), and the finding of high lipid-laden macrophage index (LLMI)[47] are nonspecific
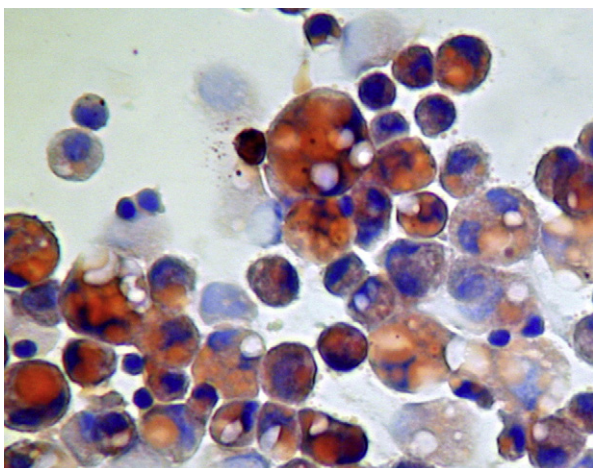
Figure 1 Alveolar macrophages recovered by bronchoalveolar lavage. The cytoplasm is full of large rounded vacuoles that displace the nucleus to the periphery (oil red O stain, ×400).

Figure 2 Chest radiograph shows bilateral extensive consolidations predominantly in central zones of the lungs.

findings, and may be found in a variety of lung diseases where there is no clinical evidence of aspiration.[47—49] However, the presence of extracellular oily droplets is more specific for exogenous LP. Another finding that distinguishes exogenous from endogenous LP is the presence of foamy macrophages with large cytoplasmic vacuoles contrasting to small vacuoles seen in the endogenous form.[6,44] The computation of an LLMI may be helpful in excluding aspiration as a cause of parenchymal lung disease.[50]

Midulla et al.[35] reported marked reduction in normal alveolar macrophages, slight increase in eosinophil numbers and increased number of activated lymphocytes. After oil intake ended, normal and lipid-laden macrophages increased and lymphocyte numbers decreased.

Chest radiograph

The diagnostic accuracy of chest radiograph in aspiration diseases is relatively low.[11] More than half of the patients with exogenous LP are asymptomatic on presentation, and are only identified because of an abnormality seen on a chest radiograph.[2,6] The findings in lipoid pneumonia are nonspecific,[29] and the disease presents with variable patterns and distribution, ranging from asymptomatic focal inflammatory reaction with little or no radiological abnormality to severe life-threatening disease.[11,27,46]

Diffuse and confluent consolidations (Fig. 2), bilateral poorly-defined opacities, irregular mass-like lesions, bilateral and symmetrical reticulonodular pattern, mixed alveolar and interstitial pattern, and unilateral or bilateral nodular lesions may be seen.[51] According to the literature data, the abnormalities on chest radiographs are most commonly observed in the lower and middle lobes.[1,29,42] The upper lobes may also be affected. Alveolar lesions either localized or diffuse, are the earliest changes.

Computed tomography

High-resolution computed tomographyis the best imaging modality for establishing the diagnosis of lipoid pneumonia.[42]

The most frequent findings are airspace consolidations (Fig. 3), ground-glass opacities (Fig. 4), the crazy paving pattern (Fig. 5), interlobular septal thickening, airspace nodules (small poorly-defined centrilobular nodules), and mass-like lesions[1,7,27,28,37,52] (Fig. 6). None of these aspects are a specific radiological feature of LP. In a study comparing adults and children, Marchiori et al.[37] demonstrated that the consolidations were significantly more frequent in children, while the crazy paving pattern was more commonly seen in adults. The prevalence of ground-glass opacities or airspace nodules did not differ between the two groups.

The most characteristic finding in LP is the presence of consolidations with areas of fat attenuation, i.e., negative attenuation values[2,3,7,11,14,37] (Fig. 7). Bottled mineral oil has a computed tomographic attenuation value of −132 Hounsfield units.[6] However, the measured attenuation values are higher than those of pure oil, as the oil is spread within the affected parenchyma and mixed with components of pulmonary fibrosis and/or inflammatory exudates.[52]

Several authors have suggested that negative densities values between −150 and −30 HU inside areas of consolidation
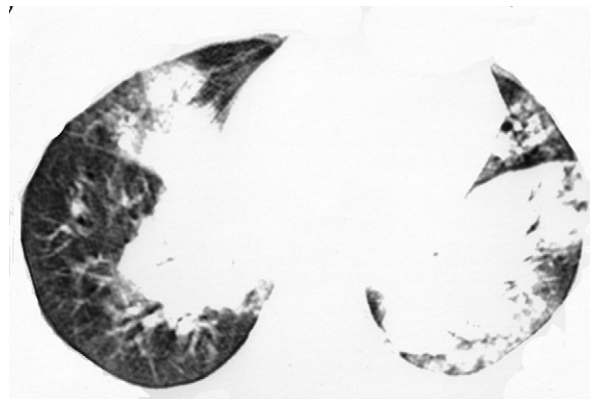

Figure 3 HRCT at the level of the lower lobes demonstrates areas of airspace consolidation with air bronchogram in both lungs.

Figure 4 HRCT demonstrates extensive ground-glass opacities in both lungs, predominantly seen on the right lung.

Figure 6 HRCT demonstrates a mass on the posterior segment of the right upper lobe, with adjacent ground-glass opacities.

are highly suggestive of intrapulmonary fat, and consistent with lipoid pneumonia,[6,14,37,42,52,53] especially when associated with a history of exposure to oil.

However, care must be taken in obtaining these measurements, in order to prevent a false-positive interpretation. These measures should be taken in the most hypodense part of the consolidation areas,[2,28] free of any aerated parenchyma on the periphery of the consolidation or areas of air bronchogram, due to interferences caused by partial-volume averaging of partly aerated lung.[28,54,55] Air and soft tissue, when averaged together, can mimic the characteristic attenuation values of fat.[3,7,10,39]

Unlike the consolidations, the specificity of the finding of fat in PL presenting as pulmonary nodules or masses is much lower, since some tumors such as hamartoma and lipoma may present with this finding. Moreover, the differential diagnosis should also be done with tumors originating from the pleura, mediastinum, or chest wall, which include teratomas, thymolipomas, lipomas and liposarcomas.[56]

The aspiration of different substances can cause symptoms similar to those of LP. These substances can produce pulmonary consolidations resembling lipoid pneumonia, but do not show areas of fat attenuation.
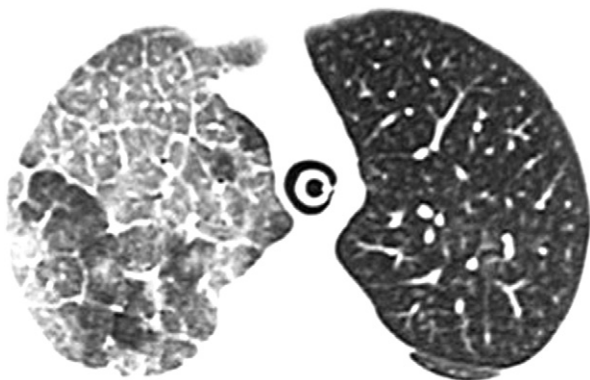
Histopathology

Needle aspiration biopsy has been used for the diagnosis of LP.[53] Cytological examination may be negative despite chemical evidence in the sputum of oil expectoration.[6] On the failure of other methods, open lung biopsy may be indicated, with the disadvantage of being a much more invasive procedure.[9,14]

If the diagnosis remains uncertain, percutaneous fine-needle aspiration biopsy, transbronchial biopsy or open lung biopsy may be necessary.[46] Kameswaran et al.[57] reported that transbronchial biopsy may be helpful in establishing the diagnosis, and suggested that open lung biopsy should be reserved for those few cases where the preceding less invasive methods are unhelpful.

The histological specimens cannot be embebded into paraffin, as the lipids are dissolved by xylol and other substances used in the processing. Therefore the analysis is limited to frozen sections. The diagnosis is made by using

Figure 5 HRCT shows areas of ground-glass attenuation in the right upper lobe, superimposed on interlobular septal thickening (crazy paving pattern). The left lung is normal.
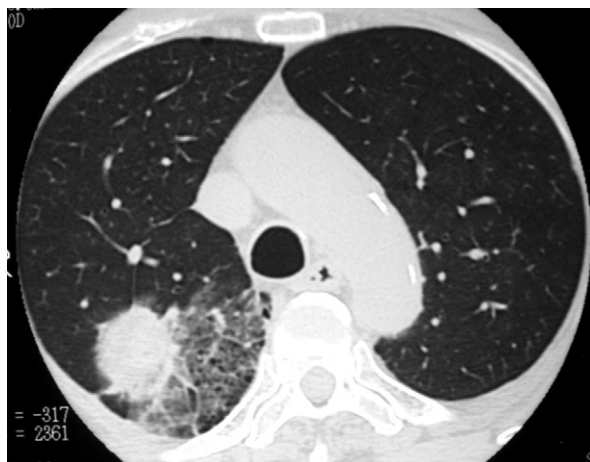

Figure 7 HRCT scan at the level of the lower lobes with mediastinal window shows consolidation with superimposed areas of low attenuation (ranging from −31 to −116 HU) in the right lower lobe (arrows).
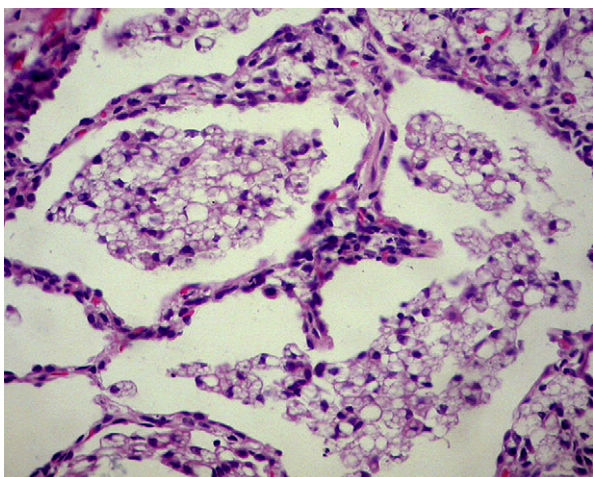
Figure 8 Photomicrography shows the presence of lipid-laden macrophages that fill the alveolar airspaces. Note also macrophages inside the alveolar septa (original magnification, 40×; hematoxilin-eosin stain).

dyes specific for lipids, where vacuoles are stained in orange with Sudan III, brownish-orange with Sudan IV, and deep red with Oil Red O. Sudan black B stains cholesterol esters and triglycerides in dark blue, and some phospholipids in gray.[45]

Histopathologically, chronic exogenous lipoid pneumonia is characterized by the presence of lipid-laden macrophages that fill and distend the alveoli and interstitium, where they may be associated with accumulation of lipid material, inflammatory celular infiltration, and variable amount of fibrosis[1] (Fig. 8). Alveolar hemorrhage and inflammatory exudate may be present.[41]

Complications

Superinfection of an exogenous lipoid pneumonia by nontuberculous mycobacteria is known, but rare.[40,58] Exogenous LP has been described in association with superinfection by nontuberculous mycobacteria and occasionally by Nocardia organisms.[58] Lipids seem to enhance the growth of these organisms, including *Mycobacterium chelonei* and *Mycobacterium fortuitum*, and impede their phagocytosis by the hosts' macrophages.[14,40,58]

Repetitive aspirations may result in variable amount of pulmonary fibrosis,[1] which can be severe when caused by occupational exposure to paraffin[17] Hypoxic respiratory failure can also develop, occasionally leading to *cor pulmonale*. A late-stage emphysematous appearance in adjacent lung may result from volume loss and retraction of the lesion.[6]

Another possible complication is hypercalcemia, probably from inflammatory cells producing calcitriol, a phenomenon observed in other granulomatous diseases such as sarcoidosis, tuberculosis, and systemic fungal diseases.[6]

Treatment

There are currently no studies in the literature that define the best therapeutic option. However, there is a consensus that the key measure is identifying and discontinuing exposure to the offending agent.[3,7] It is important to remember that the prevention in some workplaces is essential. The various forms of exposure should be carefully monitored by occupational physicians, especially when paraffin may be aerosolized.[17] Treatment is primarily supportive and generally conservative, followed by the treatment of complications.[7,26]

Other supportive measures, such as oxygen therapy, respiratory therapy, control of risk factors, and mechanical removal of intrapulmonary fat should be considered.[4,6,14,42] It must be remembered that oil may be only a secondary component of a commercial preparation, and one may be misleaded when considering the substances to which the patient was exposed.[26]

In children, the treatment of lipoid pneumonia is usually supportive. The resolution of signs and symptoms occurs in some months, after discontinuing the use of mineral oil. In patients with diffuse pulmonary damage, aggressive therapies have been reported.[14]

Whole lung lavage, sometimes used in the treatment of patients with symptomatic alveolar proteinosis, may also be therapeutic in treating LP.[6,13,44] However, in some cases, it seems that lipid phagocytosis by macrophages may impede the removal by bronchial lavage.[59]

There are reports of systemic corticosteroids use to slow the inflammatory response.[5,60] However, steroid therapy remains controversial, and should be reserved for severe cases.[5,59]

Treatment in patients without clinical symptoms remains controversial. Bronchiectasis caused by lipoid pneumonia should be treated with aggressive early medical management, but surgical resections designed to remove the most affected portions of lung tissue is recommended for those who do not respond to medical treatment.[35]

Natural history and outcome

The natural history and outcome of LP are variable, and depend on the type, volume, and distribution of oil aspirated.[59] With treatment, the majority of patients with an acute presentation have clinical and radiographic improvement, similar to the usual course of pneumonia.[7] Information about the course of lipoid pneumonia derives largely from case reports, not long-term observational studies. Acute, sometimes fatal, cases can occur, but the disease is usually indolent.[6] Some lesions may heal with fibrosis with subsequent loss of lung volume.[5] If the patient discontinues the exposure to the lipidic substances, both symptoms and radiographic abnormalities may resolve within months, but expectoration of oil may continue for years.[6]

It is important to recognize the various clinical and radiological manifestations of LP, for prompt and accurate diagnosis, resulting in decrease morbidity and mortality rates. The best treatment for this disease is prevention. Mineral oil laxatives are sold without prescription, and no information is provided for consumers or clinicians on possible hazards. It is suggested that changes in the licensing of mineral oil for internal use may contribute significantly to the primary prevention of LP. Health professionals need to be aware of the risks and discourage

the uncontrolled use of mineral oil, especially for the very young and the elderly.

Conflict of interest statement

All authors inform that there are none conflicts of interest.

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