Research Article

Adult exogenous lipoid pneumonia: A rare and underrecognized entity in cytology – A case series

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INTRODUCTION

Exogenous lipid pneumonia (ELP) is an uncommon entity[1] without specific imaging features or clinical presentation. On chest computerized tomography (CT), it may appear as consolidation, ground-glass opacities (GGO), “crazy-paving” pattern (i.e., thickened interlobular septa superimposed on a GGO reminiscent
of irregular paving stones), interstitial thickening,[1‑3] or a mass. Clinically, ELP is described across all ages, but those at the extremes – the elderly and children – are at greatest risk. Predisposing factors include developmental disabilities,[4] anatomical anomalies such as Zenker’s diverticulum and hiatal hernia,[5] loss of consciousness,[6] gastrointestinal reflux, dysphagia, neurologic disease,[6] alcohol abuse,[1] cerebral infarction,[1] tracheal stoma,[1] and illicit drug dependence.[1] ELP may have an acute presentation with fever and cough or it may be asymptomatic, especially in its chronic form. Most commonly, ELP is associated with aspiration of mineral oil, but vegetable and animal oils and other inhalants such as nasal ointments/drops and occupation-related substances are also implicated.[6‑14]

The clinical symptoms and radiographic signs of ELP are nonspecific, with a history of mineral oil (or other inhalant) use rarely elicited or provided at initial presentation. Depending on the clinical presentation and imaging studies, however, the diagnosis may be pursued in one of two ways – with cytology sampling (bronchoalveolar lavage [BAL] or fine-needle aspiration [FNA]) or a biopsy. Despite the fact that cytolically material is obtained in patients, ELP is underrecognized on cytology, and clinicians frequently resort to performing transbronchial or surgical lung biopsies for ultimate diagnosis.[15,16] Furthermore, many of the descriptions of ELP are in the clinical and radiological literature with those in the cytology and surgical pathology literature limited often to case reports making it a low diagnostic consideration. The aim of this study, therefore, was to highlight cytological features of ELP and thereby to increase recognition of this entity by cytopathologists and cytotechnologists.

METHODS

Following approval of the Institutional Review Board, a retrospective computerized search was performed to identify SP and cytopathology cases with the diagnosis (suspicion) of lipoid pneumonia. Additional cases with suspected lipoid pneumonia were also selected. All available CP slides from BALs and FNAs, and follow-up biopsies when available, as well as clinical history and radiologic reports were reviewed.

BAL specimens were received fresh or in CytoLyt. From the BALs, a Pap-stained ThinPrep (TP) slide was prepared, and in some instances, from the residual specimen, a formalin-fixed, paraffin-embedded cell block (CB) was prepared. An Oil Red O stain was performed on cytopsin slides when an unfixed BAL specimen was available and lipoid pneumonia was suspected. FNAs included smears with or without TP and CB.

All slides were evaluated for the presence of vacuoles in macrophages, with “large” defined as at least some vacuoles being equivalent to or larger than the size of the cell nucleus. The background was also evaluated for similar extracellular vacuoles and inflammation. When available, the Oil Red O stain was reviewed for the amount of lipid content (e.g., abundant versus sparse lipid droplets and size of droplets). The clinical history and interpretation of the imaging were recorded.

RESULTS

Clinical findings

Nine cases were identified. Eight had both CP and SP, and one had only CP with a corresponding Oil Red O stain; all biopsies were taken concurrently with BALs or FNAs. The cohort was collected from five men and four women with average age of 68 (range 53–77). All patients had a history of compromised immune system, recurrent respiratory infections, and/or were at high risk for aspiration secondary to conditions such as stroke, prior malignancy or esophageal disorder. No information was available regarding mineral oil use or other oily substances for any of the subjects.

Radiologic findings

CT imaging demonstrated confluent/nodular opacities (6), GGO (3), an infiltrate (1), tree-in-bud pattern (i.e., centriflobular nodules with a linear branching pattern resembling a branching tree with buds) (2), and/or spiculated mass (2) [Table 1]. Two demonstrated an interval increase and one decreased over a few months. Three were suspicious for malignancy, including one with GGO and confluent opacity, for which mucinous adenocarcinoma was in the differential.

Cytomorphologic findings

There were six BALs and three FNAs. The diagnosis of five BALs and three FNAs with histologically confirmed ELP was negative for malignant cells. Three of five BAL cases and two FNA cases had microscopic descriptive diagnoses that included pulmonary alveolar macrophages (PAMs) and multinucleated giant cells. ELP was suspected and indicated in the final diagnosis of two FNAs and one BAL without a corresponding SP.

On intermediate and high magnification, the PAMs in all CP cases were noted to have distinct clear large vacuoles variable in number; PAM with fine cytoplasmic granularity representing uninvolved cells were also noted in the background [Figures 1-3]. An Oil Red O stain was performed in one case on a cytopsin slide that was received unfixed and suspected to represent ELP [Figure 3 inset]. Rare bi- and multinucleated cells containing the same large vacuoles were also present. In the FNA smear samples, the background demonstrated variable-sized empty vacuoles that
| Sex | Age | Clinical history | Radiologic findings | Cytology specimen (BAL, FNA) | Cytological diagnosis | Surgical pathology specimen (TTBX, TBBX) | Histologic diagnosis |
|-----|-----|------------------|---------------------|-----------------------------|----------------------|----------------------------------------|-------------------|
| Female | 53 | Achalasia, status post myomectomy | Multifocal nodular consolidation and foci of ill-defined nodular opacities | BAL | No malignant cells seen | TBBX | Numerous vacuolated macrophages, occasional multinucleated giant cells consistent with exogenous lipid pneumonia |
| Male | 70 | Progressive cranial nerve palsy, dysphagia, dysarthria, multiple episodes of aspiration | Diffuse GGO; tree in bud, ground glass nodules | BAL | No malignant cells seen | TBBX | Intra-alveolar foamy macrophages present consistent with endogenous lipid pneumonia secondary to local obstruction versus exogenous lipid pneumonia |
| Male | 75 | Stroke, Shortness of breath | Irregularly marginated (spiculated) 2 cm bilobed lesion suspicious for neoplasm | FNA | Negative for malignant cells | TTBX | Granulomatous lesion, foreign body-type giant cells surrounding empty vacuoles suggestive of lipid pneumonia |
| Female | 57 | Anorexia, schizophrenia, alcohol abuse, GERD, emphysema | Interval increase in GGO bilaterally; new large confluent opacity in the right middle lobe and increased interlobular septal thickening. Diagnostic consideration is mucinous adenocarcinoma | BAL | Negative for malignant cells | TBBX | Histologic features consistent with exogenous lipid pneumonia |
| Male | 65 | Metastatic prostatic adenocarcinoma, status post chemotherapy. Symptoms of pneumonia | Bibasilar consolidations decreased in size compared to CT from 2 months prior | BAL | No evidence of malignancy | TBBX | Intra-alveolar macrophages with lipid droplets consistent with lipid pneumonia |

Contd...
Table 1: Contd...

| Sex  | Age | Clinical history                                      | Radiologic findings                                                                 | Cytology specimen (BAL, FNA) | Cytological diagnosis                      | Surgical pathology specimen (TTBX,TBBX) | Histologic diagnosis                        |
|------|-----|-------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------|---------------------------------------------|----------------------------------------|--------------------------------------------|
| Female | 77  | Persistent pneumonia and lung infiltrate              | Interval increase in patchy airspace opacities compared to CT 3 months ago         | BAL                          | Negative for malignant cells                | TBBX                                   | Intra-alveolar and interstitial foamy macrophages with associated interstitial chronic inflammation, most likely diagnosis is exogenous lipid pneumonia |
| Female | 77  | None available                                        | Right lower lobe nodule and right middle lobe infiltrate                           | FNA                          | Findings consistent with exogenous lipid pneumonia | TBBX                                   | Exogenous lipid pneumonia                  |
| Male  | 45  | Seminoma. Pulmonary toxicity due to chemotherapy. Asthma | Extensive peribronchovascular and peripheral opacities                             | BAL                          | No malignant cells seen                     | N/A                                    | N/A                                        |
| Male  | 69  | GERD, lacunar infarcts, muscle weakness; wide gait; Parkinson? | 3 cm spiculated mass, consistent with a neoplasm. Nodular, ground glass and tree-in-bud | FNA                          | Negative for malignancy. Foreign body giant cells suggestive of exogenous lipid pneumonia | TTBX                                   | Exogenous lipid pneumonia                  |

BAL: Bronchoalveolar lavage, FNA: Fine needle aspiration, TBBX: Transbronchial biopsy, TTBX: Transthoracic biopsy, N/A: Not applicable, GERD: Gastroesophageal reflux disease, GGO: Ground glass opacity, CT: Computerized tomography, ELP: Exogenous lipid pneumonia

appeared bubble-like on low power. This was best appreciated on the Diff-Quik-stained smears. These acellular empty vacuoles were not identified in BAL specimens, likely due to more extensive fixation and processing for TP. Multinucleated giant cells and scant scattered inflammatory cells including lymphocytes, plasma cells, neutrophils, and rare eosinophils were also noted. Hemosiderin-laden macrophages were described in one case.

**Histological findings**

All of the SP cases were reviewed, and a diagnosis of ELP was confirmed. The SP cases, like the cytology cases, showed numerous intra-alveolar macrophages containing distinct intracytoplasmic vacuoles of varying sizes with rare bi- or multi-nucleated cells [Figures 4 and 5]. Rare scattered inflammatory cells were also present in SP cases in a ratio similar to those in the BAL/FNA samples.

**DISCUSSION**

ELP is a well-recognized entity most frequently diagnosed on surgical biopsies and surgically resected specimens but is often unrecognized or not explicitly diagnosed on cytology alone. Specific benign diagnoses in cytology are most often limited to granulomas[17] and infections. Other entities, such as pulmonary alveolar proteinosis and organizing pneumonia,[17] may not be diagnosed as such without prompting by the clinical history, and the same may hold true for ELP. This is further compounded by its rarity and nonspecific clinical and imaging presentation. To the best of our knowledge, this is the largest series of cytology ELP in the literature [Table 2].

Although the architecture seen in SP specimens may not be evident in CP specimens, BALs and FNAs of ELP have the same characteristic large vacuolated cells. These
are frequently overlooked, and the correct cytologic diagnosis of ELP was only made in 33% of the cases reported here; all of CP cases were noted to be negative for malignant cells, however. The diagnosis is typically confirmed by additional measures – either biopsy or Oil Red O stain – in many instances, as noted in six of nine cases in our series. This is not surprising as the cytology literature on this subject is sparse with most cases of ELP in the adult population appearing as case reports in the clinical or radiological literature. There are larger series of ELP in the pediatric population, but these too are restricted primarily to the pediatric and radiology journals [Table 2]. In both populations, BAL is the most common mode of cytology sampling, and a biopsy or another modality is pursued for confirmation. The purpose of this manuscript is to highlight features of ELP in cytology.

There are two types of lipoid pneumonia, endogenous and exogenous. While endogenous lipoid pneumonia is typically due to an accumulation of lipid-containing macrophages distal to an area of obstruction, infection, or lipid storage disease, ELP results from oral ingestion and aspiration of foreign material, with mineral oil, often used as a form of laxative or for ascaridiasis, being the leading culprit. Other oils and agents implicated include animal fat, vegetable oil, castor oil, shark liver oil (squalene), lip gloss, Vaseline, Vicks, polyurethane, diesel (contains mineral oil), “ghee” (clarified butter), and spray lubricant (WD-40). Certain occupations (e.g., fire-eaters) with exposures to lubricants, paints, pesticides, and other substances may predispose individuals to ELP as well. Moreover, ELP is not restricted to oral ingestion and also described with nasal intake of substances.

The morphology of ELP, at least in the case of mineral oil, is attributed to the inability of enzymes to metabolize...
### Table 2: Lipoid pneumonia: prior literature

| Study                  | Children, adult(s) (n) | Imaging                        | Literature (clinical, radiology, pathology) | Specimen type(s)/confirmation(n) |
|------------------------|------------------------|--------------------------------|-----------------------------------------------|----------------------------------|
| Hugosson et al.[18]    | Children (9)           | Consolidation                  | Radiology                                     | BAL=1; FNA=2; Bx=1; Obx=2         |
| Sias et al.[19]        | Children (28)          | Consolidation; infiltrate, hyperinflation | Clinical                                      | BAL                              |
| Zanetti et al.[20]     | Children (17)          | Consolidation; GGO; crazy-paving | Radiology                                     | BAL (17); Obx (2)                 |
| Bandla et al.[21]      | Child (1)              | Infiltrate                      | Clinical                                      | BAL; OT                          |
| Baron et al.[1]        | Children and adults (15)| Mass; consolidation             | Radiology                                     | BAL (6); Obx (5)                  |
| Osman et al.[13]       | Adults (4)             | Mass; opacity; GGO; hypodense area | Clinical                                      | BAL and EM (2); Obx and EM (1); Bx (1) |
| Lauque et al.[22]      | Adult (7)              | Infiltrate                      | Chest                                         | BAL and EM                       |
| Hadda et al.[23]       | Adult (1)              | Consolidation                   | Clinical                                      | BAL and Bx                       |
| Lococo et al.[24]      | Adult (1)              | Mass                           | Clinical                                      | FNA                             |
| Majori et al.[12]      | Adult (1)              | Infiltrate                      | Clinical                                      | BAL                             |
| Meltzer et al.[25]     | Adult (1)              | Mass; infiltrate; GGO          | Clinical                                      | BAL and Bx                       |
| Mokhlesi et al.[15]    | Adult (1)              | Mass                           | Radiology                                     | Obx                             |
| Nguyen and Oh[3]       | Adult (1)              | GGO; opacity, Crazy-paving     | Clinical                                      | BAL and Bx                       |
| Lizarrábal Suárez et al.[11] | Adult (1)        | Infiltrate                      | Clinical                                      | BAL                             |
| Meltzer et al.[25]     | Adult (1)              | Infiltrate                      | Clinical                                      | BAL and Bx                       |
| Simmons et al.[24]     | Adult (1)              | Infiltrate                      | Clinical                                      | BAL and Obx                      |
| Gattuso et al.[7]      | Adult (1)              | Mass                           | Pathology                                     | FNA                             |
| Worringer et al.[27]   | Adult (1)              | Infiltrate                      | Clinical                                      | BAL and Bx                       |
| Yampara Guarachi et al.[14] | Adult (1)        | Consolidation; GGO; fibrosis   | Clinical                                      | BAL and Bx                       |
| Silverman et al.[28]   | Adult (1)              | Infiltrate                      | Cytology                                      | BAL and Bx                       |
| Gupta et al.[29]       | Adult (1)              | Infiltrate                      | Cytology                                      | FNA                             |
| Bell[4]                | Adult (1)              | Consolidation; GGO             | Clinical                                      | Clinical                         |

BAL: Bronchoalveolar lavage, FNA: Fine-needle aspiration, GGO: Ground glass opacity, Bx: Transbronchial or Tru-cut biopsy, Obx: Open lung biopsy, EM: Electron microscopy, OT: Other-gas chromatography/mass spectrometry. *6 FNAs performed only 2 were diagnostic; open lung biopsy was performed on a non-diagnostic case.

The nonsaponifiable substances that are absorbed by macrophages.[1] Once the macrophages die, they release their contents perpetuating the cycle.[18] When this process is long-standing, it results in fibrosis.[1] Similarly, vegetable oils also produce a minimal inflammatory response.[3] At least in the case of mineral oil, gag reflex,[18] cough, and mucociliary elevator functions are suppressed.[18]

Although patients may have a history of aspiration or inhalation of ELP causing agents, this information is often undiscovered at the time of initial presentation.[22] ELP was not diagnosed on cytology in six of nine cases in our study set. The presenting symptoms and signs were shortness of breath, recurrent pneumonia, persistent imaging abnormalities, history of aspiration, esophageal dysfunction, reflux, and immunocompromised status.

**Figure 5:** Transbronchial biopsy (H and E stain): Exogenous lipoid pneumonia, high magnification.
ELP may be acute due to a massive exposure\cite{23} or more commonly chronic\cite{1} with clinical findings ranging from asymptomatic to nonspecific symptoms of cough, dyspnea, fever,\cite{41} shortness of breath,\cite{23} and hemoptysis.\cite{26} Many ELP patients can present with signs and symptoms mimicking infectious pneumonia and can sometimes mimic a neoplastic process\cite{1,3} as noted in three of the cases in the current cohort.

The imaging was concerning for a neoplasm in three of our cases. When present, recognition of fat attenuation on CT is a clue to the diagnosis,\cite{1} but more often, the findings are nonspecific\cite{35} with a broad differential spanning from neoplastic\cite{15,24} to nonneoplastic processes including pneumonia and granuloma.\cite{23,18} ELP is more likely to manifest in the lower lobes bilaterally with consolidation, GGOs, septal thickening,\cite{6} infiltrates,\cite{11} atelectasis,\cite{11} fibrosis,\cite{11} interstitial lung disease,\cite{13} and crazy paving;\cite{4} pleural effusions are described in acute ELP. Chronic disease is more likely to appear as single or multiple\cite{4} nodules or masses,\cite{11} which may be regular or spiculated\cite{3} and demonstrate progression\cite{1} and increased PET activity\cite{15,16} when accompanied by an inflammatory component making the distinction between ELP and a neoplasm difficult.\cite{1,16}

In our series, the diagnosis of ELP was rendered in three of nine cytology cases, including BAL (n = 1) and FNA (n = 2), and two of these had concurrent biopsies. This is similar to the data in the literature, in which most cases of ELP on BAL were confirmed by another modality [Table 2] with only rare examples of primary diagnosis on cytology.\cite{7} On SP, ELP has a characteristic morphology. The macrophages in ELP have at least some large vacuoles accompanied by a foreign body giant cell reaction, chronic inflammation, and/or fibrosis elicited by the “lipoid” material. This is in contrast to endogenous lipid pneumonia, which contains foamy or finely vacuolated macrophages. Similarly, in the cytology specimens, the vacuoles were large (at least some as large as the cell nucleus) and variable in size. Although the lack of an identifiable source for ELP is a shortcoming of this study, the histology corroborates the findings in eight of nine cases.

Pediatricians often request for evaluation of lipid-laden alveolar macrophages (LLAM) in children, because some medical or structural conditions predispose this population to aspiration leading to ELP.\cite{19,37,36} In the adult patients’ population, however, clinicians may not suspect and/or fail to inform the cytopathologist of relevant clinical history. In our series, in 6 of 8 cases that had corresponding SP and CP, the diagnosis of ELP was not considered on CP specimens. On retrospective review of the slides, numerous multivacuolated macrophages were present on the smears, TP, and/or CB slide(s).

Not all multivacuolated macrophages are LLAMs. PAMs have variable cytoplasm that may be foamy, finely vesiculated, or vacuolated. Multivesiculation may represent an acute inflammatory process, drug toxicity (e.g., amiodarone),\cite{39} infection (e.g., *Rhodococcus equi*),\cite{39} or other reactive conditions.\cite{19} In some of these conditions (i.e., amiodarone and *Rhodococcus equi*), the macrophages have foamy to finely vacuolated cytoplasm, in contrast to the large vacuoles of ELP, and lack multinucleated foreign body giant cells,\cite{39} and in the case of amiodarone, the multivesiculation is present in the pneumocytes as well.\cite{19} Performing special stains, such as Oil Red O or Sudan B, can be useful in confirming the morphological impression of ELP.\cite{28,38,40} An Oil Red O stain can be performed on an unfixed smear or cytospin slide. To do so, the diagnosis has to be clinically suspected, so the specimen is not submitted in alcohol-based fixatives or formalin-fixed and paraffin embedded – both remove the lipids and decrease the sensitivity of these tests. Minimal staining does not correlate with ELP\cite{28} because such lipid-laden macrophages may also be seen other settings including endogenous lipid pneumonia\cite{41} and proteinosis.\cite{42} Oil Red O staining can also be seen in the cytoplasm of neutrophils.\cite{42} Some authors have proposed using a LLAM index,\cite{40} in which the intracellular content of lipid within the macrophages is evaluated; the greater the number of droplets that occupy the cytoplasm and obscure the cytoplasm, the greater the specificity. Some state that finding extracellular lipid in BALs is more specific\cite{35} because intracellular lipid can be seen in cases without ELP. When compared with other pathological states, Oil Red O staining was greatest in the setting of ELP.\cite{42} A gross examination of the BAL provides a clue to the diagnosis, as oil droplets can be identified on the surface of the specimen.\cite{12,14,19,21,22} Other features that might be helpful in identifying ELP are foamy background with variable-sized empty vacuoles and multinucleated giant cells.

Recognizing ELP is important for several reasons. In cases with suspected infection, unnecessary antibiotic treatment can be obviated, unless of course there is suspicion of a superimposed infection. In instances of a mass lesion, invasive procedures (e.g., surgery) can be avoided. Recognizing ELP can prompt additional history to identify the culprit and prevent associated complications such as pulmonary fibrosis,\cite{35} superimposed infection,\cite{35} and cor pulmonale.\cite{15}

**CONCLUSIONS**

Cytology, including BALs and FNAs, is used frequently to assess abnormal features detected on chest imaging. From the data, it can be inferred that ELP, though diagnosed as benign on cytology specimens, may not be specific and overlooked. Awareness of distinct large clear vacuoles
in variable numbers and sizes within macrophages and extracellularly is key in diagnosing ELP on cytology and preventing false-negative diagnosis.[1] A correct diagnosis or suggestion of ELP may avoid further unnecessary procedures and initiate appropriate management.

**COMPETING INTERESTS STATEMENT BY ALL AUTHORS**

The authors declare that they have no competing interests.

**AUTHORSHIP STATEMENT BY ALL AUTHORS**

Each author has participated sufficiently in the work and takes public responsibility for appropriate portions of the content of this article. All authors read and approved the final manuscript. Each author acknowledges that this final version was read and approved.

**ETHICS STATEMENT BY ALL AUTHORS**

This study was conducted with approval from Institutional Review Board (IRB) of the institution associated with this study (Columbia University Medical Center). Authors take responsibility to maintain relevant documentation in this respect.

**LIST OF ABBREVIATIONS** (In alphabetic order)

- BAL - Bronchoalveolar lavage
- Bx - Transbronchial or Tru cut biopsy
- CB - Cell block
- CP - Cytopathology
- CT - Computedized tomography
- ELP - Exogenous lipid pneumonia
- EM - Electron microscopy
- FNA - Fine needle aspiration
- GERD - Gastroesophageal reflux disease
- GGO - Ground glass opacity
- LLAM - Lipid laden alveolar macrophages
- Obx - Open lung biopsy
- OT - Other gas chromatography/mass spectrometry
- PAMs - Pulmonary alveolar macrophages
- SP - Surgical pathology
- TBBX - Transbronchial biopsy
- TP - ThinPrep
- TTBX - Transthoracic biopsy

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