Exogenous lipid pneumonia related to smoking weed oil following cadaveric renal transplantation

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A 30-year-old female presented shortly after cadaveric renal transplantation with respiratory distress typical of a bacterial infection. Following initial improvement, she developed progressive respiratory failure, initially felt to be secondary to cytomegalovirus infection. Two bronchoalveolar lavages were nondiagnostic, and an open lung biopsy was performed, which revealed a pulmonary alveolar proteinosis (PAP) reaction and exogenous lipid pneumonia (ELP). The ELP was considered to be secondary to the use of marijuana, in the form of weed oil, that was smoked daily for over 10 years and stopped just before renal transplantation. This is the first description of both PAP and ELP following renal transplantation, and the first description of ELP related to smoking weed oil. Physicians should be aware of the different forms of marijuana available and of their potential medical complications.

Key Words: *Bronchoalveolar lavage; Bronchoscopy; Exogenous lipid pneumonia; Lipids; Marijuana; Pulmonary alveolar proteinosis; Transplantation*

Stéatose pulmonaire exogène, liée à l'inhalation d'huile de marijuana à la suite d'une greffe d'un rein prélevé sur un cadavre

RÉSUMÉ : Une femme de 30 ans est venue consulter peu de temps après une greffe de rein prélevé sur un cadavre pour de la détresse respiratoire caractéristique d'une infection bactérienne. Après une certaine amélioration, une insuffisance respiratoire, d'abord attribuée à une infection à cytomégalovirus, s'est installée progressivement. On a procédé à deux lavages broncho-alvéolaires, qui se sont avérés négatifs, puis à une biopsie du poumon à ciel ouvert, qui a révélé la présence d'une protéinose alvéolaire pulmonaire (PAP) et d'une stéatose pulmonaire exogène (SPE). On a estimé que la SPE était secondaire à l'usage de la marijuana; en effet, la patiente en avait fumé tous les jours pendant plus de 10 ans, sous forme d'huile, et elle avait cessé d'en consommer juste avant la greffe rénale. Il s'agit de la première description d'un cas de PAP et de SPE à la suite d'une greffe rénale et d'un cas de SPE à la suite de l'inhalation d'huile de marijuana. Les médecins devraient connaître les différentes formes de marijuana vendues sur le marché et les complications médicales qu'elles sont susceptibles d'entraîner.

A case of a pulmonary alveolar proteinosis (PAP) reaction and exogenous lipid pneumonia (ELP), both developing shortly after cadaveric renal transplantation, is described. The ELP was felt to be secondary to the daily smoking of marijuana in the form of weed oil for over 10 years, which was stopped just before renal transplantation. Weed oil is a common preparation of marijuana in southern Ontario because of its low cost to the consumer. This is the first description of both PAP reaction and ELP following renal transplantation, and the first description of ELP related to weed oil use.

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CASE PRESENTATION

A 30-year-old female with end-stage renal disease secondary to chronic vesico-ureteric reflux and a congenital single left kidney presented to the respiratory medicine service on day 12 following cadaveric renal transplant, with a 12 h history of dyspnea, cough, clear sputum, fevers (38.2°C), chills, myalgias, arthralgias, lethargy, nonbloody vomitus, diarrhea and headache. She had already received antimicrobial treatment 12 h before the respiratory medicine service assessment.

Her transplant was complicated by a ureteral leak and transient pulmonary infiltrates presumed to be pulmonary edema on day 1 post-transplant. Notably, a chest radiograph performed before transplantation was normal. Because the patient's risk of cytomegalovirus (CMV) infection was high (positive donor and negative recipient), she was initially given intravenous ganciclovir (Cytovene, Hoffmann-La Roche, Canada) and was scheduled to receive a course of CMV immunoglobulin (Cytogam, Connaught Laboratories Limited, Canada). However, the patient did not comply with this therapy, and oral ganciclovir could not be obtained. As a result, she received inadequate CMV prophylaxis. A culture-negative cystitis was treated with ciprofloxacin (Cipro, Bayer, Canada).

Medications on admission were cyclosporin 375 mg bid (Neoral, Novartis Pharmaceuticals, Canada), prednisone 30 mg once daily, mycophenalate 1 g bid (Cellcept, Hoffmann-La Roche, Canada), acyclovir 800 mg tid, trimethoprim/sulphamethoxazole three times/week, iron, phosphate and erythropoietin (Eprex, Janssen-Pharmaceutica, Canada).

Medical history included two distant pneumonias, several episodes of bronchitis and pertussis as a child with no chronic sequelae. She had a history of noncompliance with medication and anorexia nervosa. There was a remote history of 'nutcracker esophagus' (diagnosis obtained from history alone with no accompanying investigations), which had not been an issue for more than 10 years before the transplant. She also had pelvic inflammatory disease following two prior incomplete pregnancies at ages 15 and 18, and intussusception as an infant requiring partial large and small bowel resection. She had a long history of cigarette smoking (less than one-half a pack/day) and marijuana use since the age of 14 years. She denied any further smoking of either substance since the day of her transplant. The remainder of her history was negative.

Examination revealed a small female (39 kg), comfortable at rest, pulse rate 110 beats/min, respiratory rate 12 breaths/min, blood pressure 135/90 mmHg and temperature 38.2°C. Oxygen saturation was 95% on room air (88% to 90% earlier in the day). There were bronchovesicular breath sounds at both bases, with a few bibasilar crackles. Cardiovascular examination including jugular venous pressure was normal. There was no lymphadenopathy. Her abdomen had two surgical scars, and the transplanted kidney was palpable in the right lower quadrant.

Her chest radiograph at this time (Figure 1) revealed a bi-lateral lower zone inhomogeneous opacification corresponding to both alveolar and interstitial disease. White blood count was 25.8×10^9/L, hemoglobin 66 g/L and platelets 249×10^9/L. Electrolytes and renal function were normal, and creatinine was 82 μmol/L. Whole blood cyclosporin level was 265 ng/mL.

She was started on intravenous ganciclovir 125 mg bid, erythromycin 1 g qid and vancomycin 1 g bid. Her cyclosporin dose was reduced to 150 mg bid. A bronchoscopy with bronchoalveolar lavage (BAL) was completed the following day, and the fluid retrieved appeared clear. Gram stain showed Gram-positive cocci in groups, but final cultures were negative. Studies for *Pneumocystis carinii*, CMV, *Legionella* species, fungi and acid-fast bacilli were negative. A renal allograft biopsy performed the same day showed mild rejection, and the patient was given pulsed intravenous methylprednisolone 250 mg daily for three days.

Over the next 10 days, her antimicrobial regimen included erythromycin, vancomycin, cefuroxime and clarithromycin (Biaxin, Abbott Laboratories, Canada). She continued on low dose ganciclovir throughout. After initial stabilization, she deteriorated clinically, with the development of septal lines and an increase in the transverse cardiac diameter on chest radiograph (Figure 2, left). A high resolution computed tomography scan (Figure 2, right) was also completed at this point, and revealed extensive opacities with air bronchograms most notable in the lower lobes, some ground glass opacities in the upper lobes, along with mild thickening of the interlobular septae and increase in polygons bilaterally. Her weight increased by 10 kg, and she became hypoxemic (partial pressure of oxygen in arterial blood 44 mmHg on room air), requiring supplemental oxygen (fractional concentration of inspired oxygen 28%). On day 23 post-transplant, creatinine was 97 μmol/L and ultrafiltration of 3 L of fluid was done. There was no significant improvement, and an open lung biopsy was performed.

The lung showed areas of PAP reaction (Figure 3, left) with acute inflammation superimposed on a background of longstanding ELP (Figure 3, right). Organizing and organized thrombi were identified in several muscular pulmonary arteries. In the areas of PAP reaction, the alveoli contained eosinophilic granular debris frequently intermingled with neutrophil polymorphs and mucus. The intra-alveolar debris was weakly positive with Periodic Acid-Schiff stain. Sections stained for mycobacteria, fungi, *P carinii* pneumonia and bacteria were negative. It was not possible to identify the nature of the lipid because it was removed from the tissue during the preparation of paraffin sections. Shell vials for CMV from the biopsy were also negative. The patient was discharged shortly thereafter, but her pulmonary condition quickly deteriorated, requiring readmission after eight days. Another bronchoscopy with BAL was performed and the return was cream colored, consistent with PAP. Another BAL was completed three weeks later because of persistent respiratory symptoms, and CMV was isolated. Urine was also positive for CMV. She was treated with intravenous ganciclovir, with rapid improvement in her pulmonary status

Figure 1) *Posteroanterior* **(Left)** *and lateral chest* **(Right)** *radiographs on presentation to the respiratory medicine service*


Figure 2) *Chest radiograph* **(Left)** *and high resolution computed tomography scan* **(Right)** *at the time of open lung biopsy*

within 48 h, and she was sent home on daily intravenous ganciclovir for a total of 10 weeks. The patient remained well five months following discharge, with normal creatinine and mild persistent interstitial disease on chest radiograph.

The patient was questioned in further detail at this juncture about marijuana use, given the unusual combination of findings of her open lung biopsy. She smoked a preparation known as weed oil two to 10 times/day for over 10 years. Hydroponically grown marijuana leaves were combined with isopropyl alcohol, and the result was heated to distill and collect the vapour. The resulting mixture was burned for a short period to eliminate the alcohol, and then mixed with petroleum jelly, vitamin E or another oil-based substance and
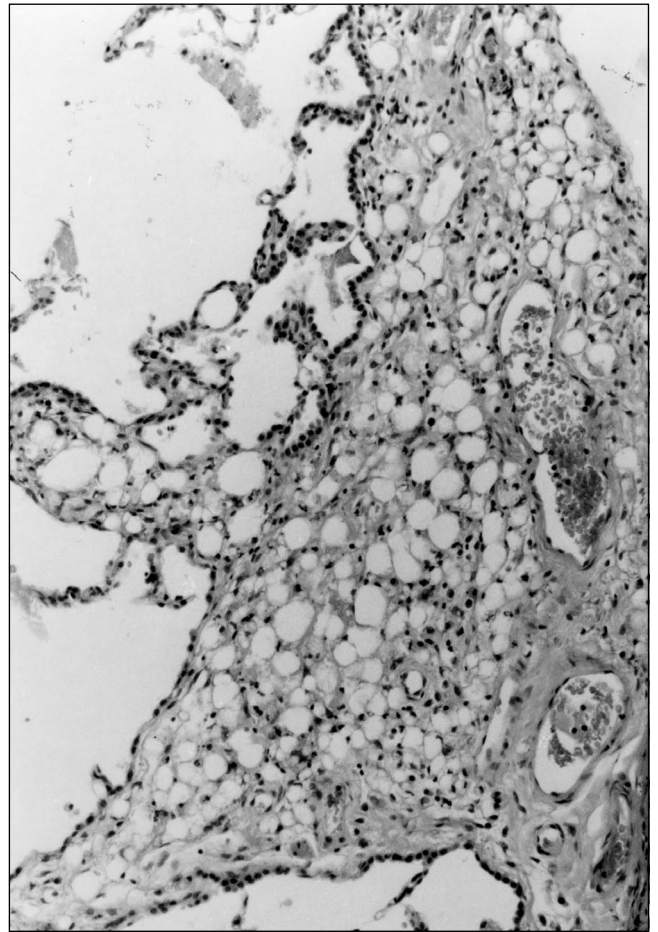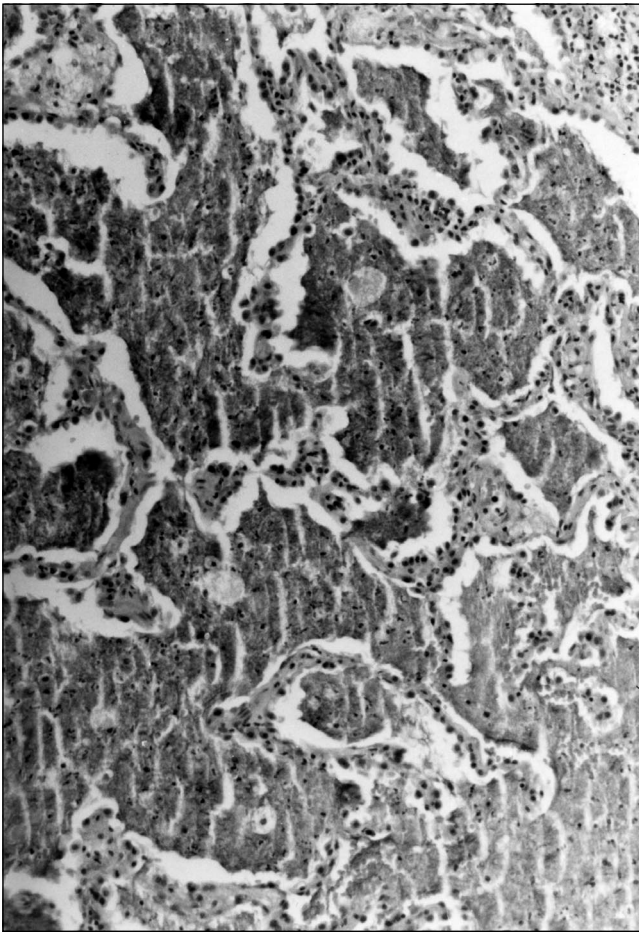
Figure 3) Left *Pulmonary alveolar proteinosis reaction. The alveoli contain eosinophilic granular debris intermingled with scanty neutrophil polymorphs and mucus. Hematoxylin and eosin stain ×200.* **Right** *Exogenous lipid pneumonia. Numerous macrophages distended by globules of lipid have accumulated in an interlobular fibrous septum adjacent to the pleura. Hematoxylin and eosin stain ×200*

placed in a closed container. This mixture was heated and the vapours inhaled. Analysis of the substance revealed that the major component was linoleic acid accompanied by small quantities of oleic acid, stearic acid and palmitic acid. The composition of oil from marijuana seed is very similar, containing 70% linoleic acid and 15% oleic acid (1).

DISCUSSION

ELP can result from aspiration of material of vegetable, mineral or animal origin (2). It elicits a foreign body reaction with a resultant proliferative fibrosis. This type of pneumonia was very common in the first half of the 20th century as a result of mineral oil ingestion used as a laxative. PAP can be either primary or secondary to either a known (ie, infections, medications) or unknown cause. Secondary PAP has a distinctly different staining pattern from the primary form, which make the two entities easy to differentiate on pathological specimens. An association between lipid pneumonia and PAP has been proposed because both involve the accumulation of lipids in the terminal airways and alveolar spaces (3,4).

The literature was reviewed from MEDLINE (1966 to present) and the Science Citation Index (1980 to present)

databases. There are no reports of either PAP or ELP following renal transplantation. Two recent reports describe the development (5) and recurrence (6) of PAP following lung transplantation.

Marijuana smoke causes injury to the airways (7). There are no reports of PAP or ELP developing from marijuana use. There is, however, one citation of a patient who smoked marijuana developing invasive pulmonary aspergillosis following renal transplantation (8).

We do know of an association of lipid pneumonia and PAP reaction with gastroesophageal reflux disease (3,4), but our patient did not have symptoms of gastroesophageal reflux disease despite her remote (greater than 10 years) history of nutcracker esophagus. In addition, a normal chest radiograph just before transplantation argued against this.

CONCLUSIONS

This patient's ELP was related to the smoking of marijuana in the form of weed oil, and the ELP was present before transplantation despite a normal appearance of chest radiograph. She probably had subclinical ELP at the time of transplantation, as is often seen with this disorder. Miller et

al's (9) description of lipid pneumonias in smokers of black-fat tobacco (ie, tobacco moistened with mineral oil or Vaseline) supports our theory. The dysfunction of alveolar macrophages with PAP also predisposed her to infections (10). This is the first description of PAP or ELP following renal transplantation and the first description of ELP related to the smoking of weed oil. Physicians should be aware of the different forms of marijuana available and each of their potential medical complications.

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