Reviewer’s report

Title: Unsuspected Pulmonary Alveolar Proteinosis in a person with AIDS: A case report

Version: 1 Date: 25 March 2010

Reviewer: Andrew Black

Which of the following best describes what type of case report this is?: Unexpected or unusual presentations of a disease

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: No

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: No

Does the case report have diagnostic value?: Yes

Will the case report make a difference to clinical practice?: Yes

Is the anonymity of the patient protected?: Yes

Comments to authors:

The case report offers a concise synopsis of PAP, despite minor grammatical errors it is easy to read and understand. Although secondary PAP has been described in association with both HIV and CMV infection the radiological features on CT are very suggestive for Pneumocystis pneumonia, it would strengthen the case if more emphasis was placed on the exclusion of Pneumocystis in this patient, e.g. mentioning that specific stains for P jirovecii were negative on the biopsy specimen. It would be useful to include duration of time on PCP treatment and when the biopsies were preformed. I am unclear if the patient required mechanical ventilation and if he did were high pressures required?

The most unusual part of this case are the bilateral pneumothoraces and
pneumatocoeles which to my knowledge have not been previously described in secondary PAP and the authors could have placed more emphasis on this. The authors may be interested in the recent article: Haruyuki I, Bruce CT, Ryushi T, et al. Comparative Study of High-Resolution CT Findings Between Autoimmune and Secondary Pulmonary Alveolar Proteinosis. Chest: 136:  .

This article highlights the importance of invasive investigations and histology in the management of HIV infected with pulmonary disease who fail to respond to empiric therapy.

Title: Secondary Pulmonary Alveolar Proteinosis in a person with AIDS: A case report

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Abstract:
Introduction: The differential diagnosis of diffuse lung infiltrates in AIDS patients is extensive and ranges from infectious process to malignancies
or interstitial lung diseases. Pulmonary alveolar proteinosis is a rare pulmonary disorder uncommonly reported in HIV infected patients. Secondary pulmonary alveolar proteinosis develops in association with conditions involving functional impairment or reduced numbers of alveolar macrophages; it has been described in different clinical settings including hematologic malignancies; inhalation of toxic dust, fumes, or gases; infectious or pharmacologic immunosuppression; or lysinuric protein intolerance.

Case presentation:
A 42 year old HIV infected patient was admitted with chronic respiratory symptoms and diffuse pulmonary infiltrates. Chest computed tomogram revealed bilateral spontaneous pneumothoraces for which he required bilateral chest tubes. All septic work up was non contributory. Video assisted thoracoscopy with lung biopsy showed pulmonary alveolar proteinosis concurrent with Cytomegalovirus pneumonitis. He was treated with Ganciclovir with radiologic and clinical improvement.

Conclusion: The differential diagnosis of patients with immunosuppression and lung infiltrates is extensive; due to the rarity of pulmonary alveolar proteinosis, the diagnosis can be easily missed. Tissue diagnosis and careful examination of bronchoalveolar fluid lavage and biopsies is important and a surgical lung biopsy should be considered in cases where the etiology of the infiltrates is unclear or there is progressive clinical deterioration despite treatment.

Introduction
Pulmonary alveolar proteinosis (PAP) was first described in 1958 by Rosen et al. and is a rare pulmonary disorder in which there is an abnormal accumulation of surfactant derived material in the alveoli leading to a disease process that ranges from mild symptoms with complete spontaneous resolution to progression of the disease with ensuing respiratory failure.1,2

Associated infections in PAP have been reported in 5 to 20% of cases; the large differences could be related to reporting bias or difficulties in the
detection of infectious processes. Infectious agents include Nocardia asteroides, Mycobacterium tuberculosis, Mycobacterium aviumintracellulare, Pneumocystis jirovecii (formerly carinii) and Cytomegalovirus (CMV). Most have been reported in immunocompromised non- HIV infected patients. PAP is a rare finding in HIV patients.

Case Report:
We present a case of an HIV-positive patient admitted with chronic respiratory symptoms, diffuse pulmonary infiltrates and bilateral spontaneous pneumothoraces who was found to have PAP concurrent with Cytomegalovirus pneumonitis.

A 42 year-old African-American male was admitted with fever, cough productive of whitish sputum, fatigue and fifteen-pounds weight loss of one month duration. No visual abnormalities. He denied traveling and any medical or surgical history.

He was a 20 pack/year smoker and denied alcohol or substance use; he worked in maintenance. His PPD test was negative a year ago. On examination he was febrile, tachycardic and tachypneic. Lungs were clear on auscultation with the rest of the examination being normal. Arterial blood gases revealed a PaO2 of 79 mmHg and a saturation of O2 of 93% on 2 litres of oxygen/min. Initial laboratory showed elevated lactic dehydrogenase 528 U/L, normal liver and kidney function and haematocrit of 32%. HIV test was positive with a CD4 cell count of 12 cells/mm3. Chest roentgenogram (CXR) showed bilateral interstitial pattern (Figure 1). A chest computed tomogram (CT) revealed bilateral pneumothoraces, multiple pneumatoceles, and bilateral consolidation with ground glass opacities (GGO) (Figure 2). In the following 24 hours after hospital admission, due to progressive dyspnoea, he was transferred to the ICU where he underwent bilateral chest tube insertion. The initial differential diagnosis was community acquired pneumonia or an opportunistic infection, most probably Pneumocystis in a HIV infected patient. Pneumothoraces and elevated LDH were supportive of the diagnosis of Pneumocystis pneumonia. Accordingly, antibiotics and corticosteroids were started (ceftriaxone, azithromycin, TMP-SMX). Sputum studies for
Pneumocystis, AFB, bacteria and influenza as well as all blood and urine cultures were negative. He refused fiberoptic bronchoscopy. Despite treatment, his clinical condition continued to deteriorate, he required a FiO2 of 0.5 to maintain an O2 saturation of 91-92 %. Due to persistent air leak, he required two chest tubes in each lung and subsequently he underwent bilateral sequential video assisted surgical thoracoscopy and lung biopsy. The biopsy (Figures 3 and 4) revealed CMV infection and pulmonary alveolar proteinosis. Ganciclovir was initiated and the other antibiotics discontinued. The patient had clinical and radiologic improvement and he was discharged home 46 days after admission. (Figure 5)

Discussion

Epidemiological data regarding the incidence and prevalence of PAP is gathered from small series and single case reports; PAP has a reported incidence of 0.36-0.49 and a prevalence of 3.70 – 6.2 cases per million population. PAP occurs in all age groups, most commonly between ages 20-50 and with a male: female ratio of 3:1. It is three times more common in smokers than non-smokers; in North America 72 % of PAP patients are smokers. 2,4 5

There are three clinically distinct forms of PAP: congenital (2%), acquired (also referred as primary or idiopathic, 90%) and secondary (5-10%).2 Congenital PAP is a heterogeneous collection of disorders caused by mutation of the genes encoding surfactant protein -B (SFTP-B), Surfactant protein – C (SFTP-C), or ATP-binding cassette transporter A3 (ABCA3 transporter) or by the absence of Granulocyte macrophage-colony stimulating factor (GM-CSF) receptor.3,6

Primary PAP is now being regarded as an autoimmune condition due to excess normal surfactant related to GM-CSF neutralizing antibodies, receptor deficiency or gene deficiency/mutation leading to decreased macrophage stimulation resulting in immature alveolar macrophages incapable of adequate surfactant clearance.4-6

Secondary PAP is uncommon and develops in association with conditions involving functional impairment or reduced numbers of alveolar macrophages, it has been described in different clinical settings including
haematologic malignancies; inhalation of toxic dust, fumes, or gases; infectious or pharmacologic immunosuppression; or lysinuric protein intolerance.

HIV infected patients have two factors that could increase predisposition to secondary PAP: altered immunity and opportunistic lung infections which could lead to breakdown of alveolar pneumocytes, overproduction of substances normally secreted into the alveoli, impairment of alveolar clearance and the transudation of plasma constituents into the alveoli which in turn could contribute to the pathogenesis of PAP.7 Despite the above risk factors, there are few reports of PAP in HIV infected patients and those have been mainly associated with Pneumocystis jirovecii, mycobacterial or rarely CMV infections.7-10 

The clinical presentation of PAP varies from asymptomatic (31% of acquired cases) to a more chronic presentation with dyspnoea (39%), followed by dyspnoea and cough (11%) and cough only (10%). Cough is usually non productive, but occasionally the sputum has been described as “white and gummy” or “chunky”. Fever and weight loss can also occur.6

The physical examination is non-specific; crackles, clubbing, and cyanosis all have been rarely reported.11

The radiographic findings are non-specific with CXR typically demonstrating bilateral central and symmetric lung opacities, with relative sparing of the apices and costophrenic angles and less commonly multifocal asymmetric opacities. Extensive diffuse consolidations suggestive of pulmonary oedema have been reported.

Lymphadenopathy is rarely present. High Resolution Chest CT findings are non-specific and may reveal a network of smoothly thickened reticular (septal) lines superimposed on areas of ground glass opacification (GGO) with a patchy geographic pattern referred to as “crazy-paving”,12,13 Pneumothorax is not a usual finding in PAP or CMV.

Abnormal non-specific laboratory findings in PAP are mild to marked elevated serum LDH and other protein products of pulmonary epithelial cells like carcinoembryonic antigen, cytokeratin 19, mucin KL-6, and levels of the SFTP-A, SFTP-B, and SFTP-D.2 In primary PAP high levels of GM-CSF auto-antibodies
are present, whereas in secondary and congenital PAP levels will be normal.\textsuperscript{2,4}

Pulmonary function testing in PAP usually reveals a restrictive pattern on spirometry, a decreased diffusion capacity for carbon monoxide, an elevated alveolar-arterial PO2 gradient, hypoxaemia and an elevated shunt fraction. The gold standard for the diagnosis of PAP is open lung biopsy, but Fibreoptic bronchoscopy may be diagnostic in up to 75% of cases. Bronchoalveolar lavage and transbronchial biopsy are usually performed to exclude infection. The classic findings on lavage fluid are a “milky” fluid composed of large amounts of granular, acellular, eosinophilic proteinaceous material with morphologically abnormal “foamy” macrophages engorged with diastase-resistant PAS-positive intracellular inclusions. When electron microscopy is available, concentrically laminated phospholipid structures called lamellar bodies can confirm the diagnosis.\textsuperscript{6,11,14}

Lung lavage fluid samples are microbiologically sterile in the majority of cases. It is now recognized that most cases of encountered infection are a secondary event rather than the initiating process.\textsuperscript{2}

The treatment of PAP depends on the physiologic impairment, rate of progression or remission and the underlying pathology. Supportive treatment and occasional lung transplantation are used for the congenital form. Secondary PAP is managed with conservative therapy and treatment of the associated condition. In primary PAP, the standard of care is whole-lung lavage which is performed under general anesthesia. The use of GM-CSF replacement is still experimental. The role of whole lung lavage for secondary PAP with severe respiratory impairment is unclear at the present time.\textsuperscript{2,3,11}

Conclusion:
In conclusion, the differential diagnosis of diffuse lung infiltrates in AIDS patients is extensive and ranges from infectious process to malignancies or interstitial lung diseases. Due to the rarity of PAP, the diagnosis may be easily overlooked in these patients. It is of the utmost importance that clinicians caring for HIV infected patients consider PAP either alone or in combination with CMV or other opportunistic infection in the differential
diagnosis of diffuse lung disease. Tissue diagnosis and careful examination of bronchoscopic lavage fluid and biopsies is important and a surgical lung biopsy should be considered in cases where the aetiology of the infiltrates is unclear or there is progressive clinical deterioration despite treatment.

PS I have emailed the above word document with 'track changes' to jmcreditorial@biomedcentral.com <jmcreditorial@biomedcentral.com>

8

References
9

List of abbreviations
PAP: Pulmonary alveolar proteinosis
CMV: Cytomegalovirus
CXR: Chest roentgenogram
CT: Computed tomogram
GGO: Ground glass opacities

Consent
Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
DT, AED and GDF were responsible for the study conception, data retrieval and draft of the manuscript. MN selected, prepared and commented on the imaging. All authors read and approved the final manuscript.

Acknowledgements
The authors acknowledge the patient on whom the case report is based.

Figure 1- Chest x-ray showing bilateral interstitial-alveolar pattern.
Figure 2- Chest CT showing bilateral pneumothoraces, multiple pneumatoceles, bilateral airspace consolidation and ground glass opacities.

Figure 3- Low power microscopy of the lung biopsy showing proteinaceous material filling up the alveoli.

Figure 4- Lung biopsy showing Cytomegaloviral inclusion body (arrow) in a background of proteinaceous material filling up the alveoli.

Figure 5- Chest x-ray at discharge showing improvement in infiltrates and residual pneumatoceles

Quality of written English: Needs some language corrections before being published

Declaration of competing interests:

I declare that I have no competing interests