Histologically atypical *Pneumocystis carinii* pneumonia

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Abstract

Background—Infection with *Pneumocystis carinii* typically results in a pneumonia which histologically is seen to consist of an eosinophilic foamy alveolar exudate associated with a mild plasma cell interstitial infiltrate. Special stains show that cysts of *P carinii* lie within the alveolar exudate. Atypical histological appearances may occasionally be seen, including a granulomatous pneumonia and diffuse alveolar damage. In these patients the clinical presentation may be atypical and results of investigations negative unless lung biopsies are performed and tissue obtained for histological examination.

Methods—The incidence and mode of presentation of histologically atypical pneumocystis pneumonia was studied in a cohort of HIV-I antibody positive patients.

Results—Over a 30 month period 138 patients had pneumocystis pneumonia, of whom eight (6%) had atypical histological appearances which were diagnosed (after negative bronchoalveolar lavage) by open lung biopsy in five, percutaneous biopsy in one, and at post mortem examination in two. Atypical appearances included granulomatous inflammation in four patients, "pneumocystoma" in two (one also had extrapulmonary pneumocystosis), bronchiolitis obliterans organising pneumonia in one patient, diffuse alveolar damage and subpleural cysts in one (who also had intrapulmonary cytomegalovirus infection), and extrapulmonary pneumocystosis in two patients.

Conclusions—Various atypical histological appearances may be seen in pneumocystis pneumonia. Lung biopsy (either percutaneous or open) should be considered when bronchoalveolar lavage is repeatedly negative and evidence of *P carinii* should be sought, by use of special stains, in all lung biopsy material from HIV-I antibody positive patients.

(Thorax 1993;48:996-1001)

tion in patients infected with the human immunodeficiency virus (HIV).¹ Originally thought to be a protozoon, application of molecular biological techniques now suggest that *P carinii* is a fungus.²

The most frequent pulmonary condition in pneumocystis pneumonia is a radiographically diffuse bilateral pneumonia which histologically consists of an eosinophilic intra-alveolar foamy exudate associated with a mild plasma cell interstitial pneumonitis. By the use of special stains such as Grocott's methenamine silver stain or toluidine blue O, cysts of *P carinii* are seen to lie within the foamy exudate. The exudate consists largely of the non-staining trophozoite forms of *P carinii* which are best seen with electron microscopy. Unusually and atypically, pneumocystis pneumonia may present with infiltrates restricted to the upper lobes, focal consolidation, nodular or cavitating lesions, diffuse alveolar damage, or hilar lymphadenopathy.³⁻⁷

Early in the AIDS epidemic transbronchial biopsies were routinely carried out, in addition to bronchoalveolar lavage, at fiberoptic bronchoscopy for diagnosis of pneumocystis pneumonia and other pulmonary conditions.⁸ Open lung biopsies were also frequently performed in patients with bronchoscopically undiagnosed episodes of pneumonitis. Transbronchial biopsies are no longer routinely performed as they do not add to the diagnostic yield compared with bronchoalveolar lavage, and are associated with morbidity from pneumothorax and haemorrhage.⁹ Open lung biopsies are rarely carried out because of the high yield from bronchoalveolar lavage.

There are few data on the atypical histology of pneumocystis pneumonia based on transbronchial, percutaneous, or open lung biopsy material.^{5,6} Most data on the pathology of pneumocystis pneumonia in HIV-I infected patients are derived from post mortem studies.^{4,10,11} In this study we describe the clinical presentation, chest radiographic appearances, and pathological abnormalities in HIV-I antibody positive patients with histologically atypical pneumocystis pneumonia diagnosed by percutaneous or open lung biopsy or at post mortem examination.

Methods

We retrospectively reviewed the case notes of

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Reprint requests to:
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Received 11 March 1993
Returned to authors
3 June 1993
Revised version received
15 June 1993
Accepted 17 June 1993

Pneumocystis carinii pneumonia remains the commonest pulmonary opportunistic infec-

all HIV-I antibody positive patients with pneumocystis pneumonia treated in the dedicated inpatient unit at the Middlesex Hospital, from July 1989 to December 1991 (all patients were under the care of a respiratory physician). In addition, the histological findings of all post mortem examinations and lung biopsies performed on HIV-I antibody positive patients during this period were reviewed and those patients with pneumocystis pneumonia were identified.

Results

One hundred and thirty eight episodes of pneumocystis pneumonia were identified, of whom eight (6%) had atypical histological appearances diagnosed by either percutaneous or open lung biopsy, or at post mortem examination. Of the other 130 patients with pneumocystis pneumonia, 27 (21%) had atypical chest radiographs. Changes included apical shadowing, focal consolidation, cavities, hilar and/or mediastinal lymphadenopathy. Three patients died with pneu-

monia; at post mortem examination all three had typical pathological changes and, in addition, two had considerable interstitial fibrosis. The clinical presentation, chest radiographic appearance, and results of investigation of the eight patients with atypical histological findings are shown in the table. All were white men of mean (range) age 38.5 (38–56) years. Six were homosexual, one (case 1) was bisexual, and one (case 2) had acquired HIV infection by heterosexual sex with an intravenous drug user. Three were cigarette smokers and none used intravenous drugs. In three patients (cases 1, 2, and 3) the diagnosis of pneumocystis pneumonia from examination of biopsy samples provided an AIDS defining diagnosis. The other five patients had a prior AIDS defining diagnosis on the basis of disseminated *Mycobacterium avium intracellulare* infection (case 4), a previous episode of pneumocystis pneumonia (cases 5 and 6; case 5 also had cutaneous Kaposi's sarcoma), pulmonary non-Hodgkin's lymphoma (case 7), and chronic perianal herpes simplex virus infection (case 8).

Clinical presentation, chest radiographic appearances, and results of investigations in eight patients with atypical histological findings

Case no.	PCP prophylaxis	Chest radiographic appearance	Negative investigations before biopsy/necropsy	Treatment before biopsy/necropsy	Histology (type)	Treatment and outcome
1	None	Bilateral diffuse interstitial shadowing	IS, FOB, BAL	Nebulised pentamidine	Bronchiolitis obliterans organising pneumonia (OLB)	Intravenous co-trimoxazole. Survived
2	None	Bilateral perihilar interstitial shadowing	FOB, BAL FOB, BAL, TBB	Intravenous co-trimoxazole	Granulomatous PCP (OLB)	Intravenous co-trimoxazole. Survived
3	None	Bilateral diffuse interstitial shadowing	IS, FOB, BAL (× 2)	Nebulised pentamidine	Granulomatous PCP (OLB)	Intravenous co-trimoxazole. Survived
4	1°/Nebulised pentamidine	Right pneumothorax Multiple bilateral apical bullae and apical consolidation	Nil	Intravenous pentamidine	Granulomatous PCP (OLB)	Surgical bullectomy and oversewing of bullae, with pleurodesis. Intravenous pentamidine. Survived
5	2°/Nebulised pentamidine	Bilateral interstitial shadowing, some areas had nodular appearances	IS, FOB, BAL (× 2)	Nil	Granulomatous PCP (OLB)	Intravenous co-trimoxazole. Survived
6	2°/Nebulised pentamidine	Bilateral diffuse interstitial shadowing and 3 cm diameter peripheral round lesion at left lung base	IS, FOB, BAL	Nil	Pneumocystoma (Perc B)	Intravenous co-trimoxazole. Survived
7	2°/Nebulised pentamidine	Bilateral diffuse interstitial shadowing and left basal pleurally based mass	Nil	Intravenous pentamidine	Pneumocystoma and widespread typical PCP. Extrapulmonary pneumocystosis (hilar lymph nodes) (Necropsy)	Died
8	1°/Nebulised pentamidine	Bilateral mid zone interstitial shadowing	Nil	Intravenous methylprednisolone Intravenous co-trimoxazole	Diffuse alveolar damage subpleural emphysema. Interstitial inflammation and fibrosis, patchy calcification. Extrapulmonary pneumocystosis (pancreas) Also had CMV infection (Necropsy)	Died

IS—hypertonic saline induced sputum; FOB—fiberoptic bronchoscopy; BAL—bronchoalveolar lavage; TBB—transbronchial biopsy; 1°—primary; 2°—secondary; PCP—*Pneumocystis carinii* pneumonia; CMV—cytomegalovirus infection; OLB—open lung biopsy; Perc B—percutaneous biopsy.

Figure 1 Case 1: pneumocystis plasma cell pneumonia and bronchiolitis obliterans organising pneumonia. Open lung biopsy specimen. (Top) High power view showing an extensive plasma cell infiltrate in the alveolar walls (original magnification $\times 200$ reduced to 54% during origination; haematoxylin and eosin). (Bottom) High power view of another area of the biopsy specimen showing a respiratory bronchiole and alveolar duct filled with proliferating fibroblasts (original magnification $\times 200$ reduced to 54% during origination; haematoxylin and eosin).

In the six patients diagnosed before death by open or percutaneous biopsy, the decision to perform a biopsy was made because of failure to respond to antipneumocystis treatment (cases 1, 2, and 3), or because of atypical radiological appearances (cases 4, 5, and 6). In the two patients diagnosed by post mortem examination the diagnosis of pneumocystis pneumonia had been made clinically before death but both died despite empirical antipneumocystis treatment.

Analysis of lung biopsy material showed that one patient (case 1) had typical pneumocystis plasma cell interstitial pneumonia and, in addition, bronchiolitis obliterans organising pneumonia (fig 1). Four patients (cases 2–5) had granulomatous pneumocystis pneumonia. Cysts of *P carinii* were seen lying within palisades of epithelioid cells forming granulomas; no organisms were seen in the alveolar spaces outside the granuloma (fig 2). Two patients (cases 6 and 7) had a “pneumocystoma” consisting of foamy eosinophilic material surrounded by fibroblasts; Grocott’s methenamine silver staining showed *P carinii* cysts within the foamy material (fig 3). In addition, elsewhere in the lungs case 7 had widespread typical pneumocystis pneumonia. *P carinii* was also found in hilar lymph nodes—that is, the patient had extrapulmonary pneumocystosis. In case 8 diffuse alveolar damage, subpleural emphysema, interstitial inflammation and fibrosis, and patchy calcification were seen in the lungs at post mortem examination (fig 4) and, in addition, evidence of cytomegalovirus infection was seen with both intranuclear and intracytoplasmic inclusions. This patient also had extrapulmonary pneumocystosis; *P carinii* was identified within blood vessels in the pancreas.

Figure 2 Case 2: granulomatous pneumocystis pneumonia. Open lung biopsy specimen. (Left) At high power the eosinophilic material consists of epithelioid cells forming granulomas (original magnification $\times 100$ reduced to 54% during origination; haematoxylin and eosin). (Right) Cysts of *P carinii* are found within the granulomas (original magnification $\times 400$ reduced to 48% during origination; Grocott’s silver stain).

Figure 3 Case 6: pneumocystoma. (Left) Chest radiograph showing diffuse interstitial shadowing and a 3 cm round lesion at the left base. (Right) Computed tomographic guided percutaneous needle biopsy specimen from round lesion. The core of tissue contains foamy eosinophilic material surrounded by fibroblasts (original magnification $\times 200$ reduced to 54% during origination; haematoxylin and eosin). Grocott's silver stain (not shown) showed cysts of *P carinii* within the foamy material.

Figure 4 Case 8: subpleural cyst formation and diffuse alveolar damage in post mortem specimen. (Top) Large subpleural cyst, the walls of which consist of alveoli consolidated with foamy eosinophilic material (original magnification $\times 20$ reduced to 54% during origination; haematoxylin and eosin). (Bottom) High power view showing calcification in the walls of blood vessels (arrows), intra-alveolar haemorrhage (red), and alveoli filled with *Pneumocystis carinii* (pale pink) (original magnification $\times 200$ reduced to 54% during origination; haematoxylin and eosin).

Discussion

In this study atypical histological appearances were seen in 6% of a cohort of HIV-I antibody positive patients with pneumocystis pneumonia. It is possible that the prevalence of atypical histological appearances is even higher than we have seen. Because of the high diagnostic yield for *P carinii* from bronchoalveolar lavage,^{8,9} and because transbronchial biopsy provides little additional diagnostic information and the procedure in HIV-I antibody positive patients is associated with an increased risk of pneumothorax and haemorrhage compared with the general population,⁹ we no longer carry out transbronchial biopsy and open lung biopsy is rarely indicated. However, *P carinii* is still encountered in specimens in transbronchial, open, and percutaneous biopsies performed to evaluate symptoms in HIV-I antibody positive patients with respiratory symptoms and negative results from hypertonic saline induced sputum and bronchoalveolar lavage. Percutaneous or open lung biopsies are also performed in patients when neither AIDS nor pneumocystis pneumonia are suspected, and it is possible that a diagnosis of pneumocystis pneumonia will be overlooked initially if the biopsy shows unusual pathological features.

A retrospective review of atypical histological features in 123 biopsy specimens (117 transbronchial biopsies, six open lung biopsies) from 76 HIV-I antibody positive patients with pneumocystis pneumonia (including 62 homosexual men and two children) from the National Institutes of Health, Bethesda, Maryland, USA (where transbronchial biopsies are routinely performed) revealed interstitial fibrosis in 77 biopsy samples (63%), intraluminal fibrosis in 44 (36%), granulomatous inflammation in six (5%), parenchymal cavities and interstitial microcalcification each in three (2%), and vascular invasion/vasculitis caused by *P carinii* in one.⁵ More than one atypical feature was

identified in some lung biopsy specimens. Overall, six patients (8%) had co-infection with cytomegalovirus.

Although mycobacterial and other fungal infections should be excluded when granulomas are identified in lung biopsy specimens, intrapulmonary *P. carinii* infection may also induce a granulomatous inflammatory response. This was once thought to be rare but is now well recognised in HIV-I infected patients.^{4-6 10-12} It has been postulated that the granulomatous response may be a reaction to inhaled pentamidine rather than to *P. carinii*. Dissolved in water for nebulisation, pentamidine isethionate solution is hypo-osmolar and acidic.¹³ The solution is supersaturated and pentamidine crystals may precipitate out in the lung, inducing a "foreign body" reaction.¹⁴ Four of our patients with granulomatous pneumocystis received nebulised pentamidine, in three as prophylaxis and in one as treatment. Other studies have reported cavitation occurring in granulomas¹⁰ but this was not evident in our patients. As the *P. carinii* cysts are "walled off" by palisades of epithelioid cells and there are no organisms lying within alveoli outside the granulomas, they are not accessible to bronchoalveolar lavage. Also, because of the patchy nature of the inflammatory reaction transbronchial biopsy may be negative, as was seen in our case 2. Pneumocystomas are probably the end result of untreated granulomatous pneumocystis.

Thin walled intrapulmonary cysts are a recognised radiological manifestation of pneumocystis pneumonia. Cyst formation appears to occur with greater frequency in HIV infected patients (in up to 38%) than in non-HIV infected patients, as shown by plain chest radiography and thoracic computed tomographic scanning.¹⁵⁻¹⁸ Cystic changes are found most often in the upper lobes, the majority being multiple and bilateral.¹⁵⁻¹⁸ Occasionally subpleural cysts may rupture and result in spontaneous pneumothorax as occurred in our case 4.¹⁸ The pathogenesis of intrapulmonary cyst formation is unclear; it has been suggested that they are due to exacerbations of pre-existing cystic lung disease, interstitial emphysema, or to remodelling associated with interstitial fibrosis. Alternatively they may arise from necrosis within granulomas¹⁰ or within lung parenchyma,¹⁸ or they may be caused by infarction¹⁹ or by proteolytic digestion of the lung induced by *P. carinii* or HIV infection, or both.^{12 20} Use of nebulised pentamidine for prophylaxis, as in our case 4, may be associated with apical cyst formation; inhalation of the drug by patients sitting upright results in less pentamidine being deposited in the lung apices so *P. carinii* infection is not inhibited.

Diffuse alveolar damage as seen in case 8 has previously been reported in nine open lung biopsy specimens from 17 adult and paediatric patients with pneumocystis pneumonia.⁷ This damage may occur because of increased alveolar capillary "leakiness"

induced by *P. carinii* mediated damage of type 1 pneumocytes²¹ or proteolytic digestion of the lung.¹² Our patient also had cytomegalovirus infection in the lung, which may also be associated with diffuse alveolar damage.²² Occult alveolar haemorrhage, also seen in case 8, is a non-specific finding in HIV positive patients with respiratory illness, occurring in those with pneumocystis pneumonia, pulmonary Kaposi's sarcoma, and bacterial infection.²³ Extrapulmonary pneumocystosis, arising by vascular invasion with *P. carinii*, occurred in two of our patients (cases 7 and 8), both of whom had received nebulised pentamidine. Previous reports of extrapulmonary pneumocystosis have commented on the strong association with use of nebulised pentamidine for prophylaxis. It is postulated that this form of prophylaxis, which does not achieve therapeutic systemic drug levels, does not prevent dissemination of intrapulmonary *P. carinii* infection.²⁴

In conclusion, a range of atypical histological appearances may be seen in patients with HIV infected with pneumocystis pneumonia. Failure to make the diagnosis by biopsy and instigate treatment may result in death; all six patients in our study who were diagnosed before death responded to treatment and survived. In four patients the atypical radiological appearances prompted the decision to carry out open lung biopsy in order to exclude other diseases such as mycobacterial or fungal infection, lymphoma, or interstitial pneumonitis whilst treating the patient for presumptive pneumocystis pneumonia. We recommend that lung biopsy (either percutaneous or open) should be considered when bronchoalveolar lavage is negative. Evidence of *P. carinii* should be sought by use of special stains in all lung biopsy material from HIV infected patients.

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