Pulmonary Radiological Characteristics in Patients with HIV Infection at the Time of Highly Active Antiretroviral Therapy (HAART)

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Abstract

Objective: To report on radiological and epidemiological characteristics of pulmonary disease in patients with HIV infection in times of highly active antiretroviral therapy (HAART).

Methods: Clinical data of 130 HIV infected adults with acute pulmonary symptoms were compared with findings in chest radiography (n = 130) and computed tomography (CT, n = 42). Presence and distribution of consolidation, interstitial changes, pleural effusion, and adenopathy were evaluated. Results were compared to findings from sputum, bronchoalveolar lavage, transbronchial biopsy, or empirical therapy results.

Results: 48% of patients presented pathologic findings. Overall sensitivity for the detection of pulmonary involvement was 0.87 (chest radiography) vs. 0.97 (CT). Disease specific sensitivity was 0.33 compared to 0.70. Bacterial pneumonia (BP, n = 26, 20%) was the most frequent diagnosis, followed by *pneumocystis jiroveci* pneumonia (PJP, n = 17, 13%), mycobacterium avium complex (MAC, 6%), Kaposi's sarcoma and lymphoma (KS and NHL, each 4%), fungal pneumonia (2%), and tuberculosis (TBC, 1%). Focal pulmonary infiltration was predominantly present in BP (50%, n = 13). Reticular (35%; n = 6) and micronodular (35%; n = 6) infiltration were predominantly found in PJP.

Conclusions: Despite HAART, lung involvement is still common. Only contrast-enhanced computed tomography shows an acceptable disease-specific sensitivity. In unclear cases, CT should be performed.

Key words: Highly Active Antiretroviral Therapy, HIV, pulmonary involvement, pneumonia, plain radiography, computed tomography

List of Abbreviations:
HAART - Highly Active Antiretroviral Therapy
PJP - Pneumocystis jiroveci pneumonia
BP – Bacterial Pneumonia
MAC – Mycobacterium Avium Complex
KS – Kaposi's Sarcoma

Introduction

In the developed world, the natural history of HIV infection has changed dramatically in the era of HAART. Different authors described a decreasing incidence of opportunistic infections particularly since introduction of HAART. Regarding PJP, Kaplan et al. reported a decline of 21.5% per year between 1996 and 1998 [1]. For evaluation of epidemiology, patterns of pathology, and therapeutic options, frequently findings from the pre-HAART and the post-HAART eras of HIV treatment are compared. [2] Many studies evaluating these clinical features are available [3, 4, 5, 6, 7]. However, there are only few recent studies that have evaluated patterns of pulmonary HIV-related disease in chest plain radiographs and computed tomography (CT). Some data are available on PJP infection. Characteristic patterns of PJP include cystic lung disease, spontaneous pneumothorax and an upper lobe distribution of parenchymal opacities [8]. However, most information available on morphologic characteristics of different HIV-associated lung diseases is derived from the pre-HAART era.

The spectrum of pulmonary involvement comprises infective diseases (i.e. BP, PJP, MAC, cytomagalovirus pneumonia, and TBC) and non-infective diseases (i.e. KS, NHL, lung cancer) [9].

The objective of the present study was at first to report on the appearance of lung involvement in patients with pulmonary symptoms in context with CD4 counts, in a second step to compare the sensitivities for different pulmonary manifestations in plain radiography and contrast-enhanced multi-slice CT. Finally, the frequency of radiological findings was collected in order to describe typical radiological patterns for different pulmonary manifestations.

Materials, Methods and Statistics

Study Population

Patients with known HIV infection and pulmonary symptoms were selected from a universitary outpatient clinic and hospital in the city centre of Munich (Germany). The study population included 130 HAART-treated, HIV infected patients who were referred to the radiology department due to pulmonary symptoms. Symptoms and findings included cough, fever, dyspnea, thoracic pain, rales, hemoptysis, and enlarged palpable axillary lymph nodes (Fig. 1). Cough was the
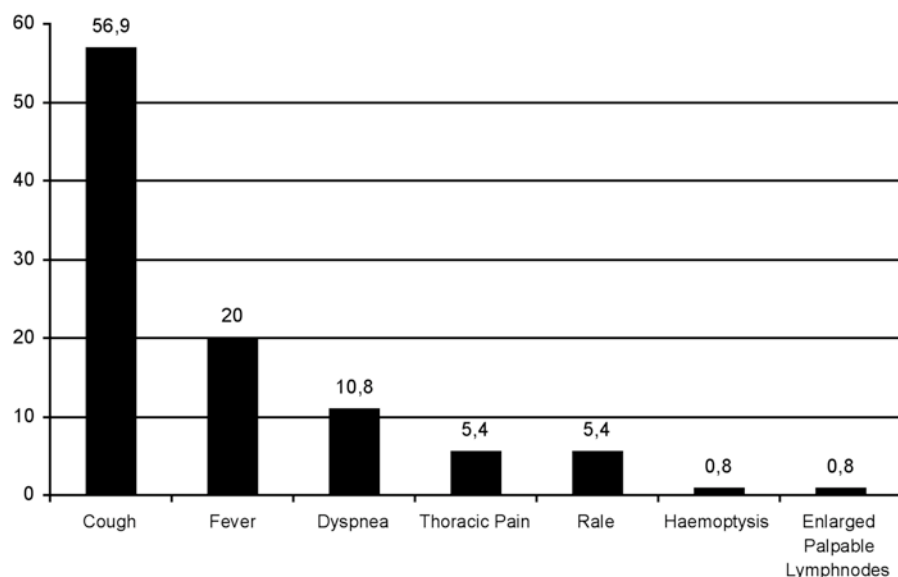
Fig. 1. Frequencies (%) of different pulmonary symptoms in HIV-infected patients leading to referral to radiology.

most frequent symptom (57%).

The mean age of patients was 43.8 years (range 22 – 77 years). The mean CD4 count was 225/µl (>500/µl 21%, 200-500/µl 35%, <200/µl 44%). Clinical stage was A in 16%, B in 28%, and C in 55% of patients. All patients received HAART during the period under observation.

IMAGING

Chest radiography (postero-anterior and lateral view) was performed in all 130 individuals at the day of clinical assessment. 42 patients (32%) had additional CT (Somatom Volume Zoom Plus 4, Siemens Medical Solutions, Erlangen, Germany), 10/2.5/5 mm advance / collimation / reconstruction increment.) within maximum 3 days after plain radiography. In a retrospective analysis, standardized evaluation of all images was conducted. The different morphologic aspects taken into account are summarized in Table 1.

Table 1. Standardized evaluation of radiological findings.

Pleural affection	effusion	Yes / No
Pulmonary affection	interstitial	reticular
		nodular reticulo-nodular peribronchoular
	(interstitial +) alveolar	ground glass focal consolidation
Adenopathy	bihilar monhilar	
Localization	apical segments peri-hilar middle segments basal segments	

Two experienced observers (blinded to all clinical data, except HIV infection) reviewed chest radiographs and CT scans. Each image study was checked for the presence or the absence of the criteria summarized in Table 1. After evaluation of images, the two observers reached a consensus and noted their findings on a standardized check-list (Table 1). Subsequently, definite diagnosis was made under consideration of CD4 counts.

CLINICAL PARAMETERS

Retrospective evaluation of clinical parameters was performed on each individual. Analysis included standard demographic variables, clinical symptoms at the time of presentation, HAART status, and CD4 cell count. Definite diagnosis of pulmonary involvement (gold standard) required typical findings in broncho-alveolar lavage (BAL) or lung biopsy specimens for PJP. Bacterial (community or hospital acquired) pneumonia was diagnosed in those patients with typical clinical, laboratory, and radiographic presentations, as well as response to antibiotics not expected to treat PJP. A diagnosis of NHL and Kaposi sarcoma required tissue biopsy. Diagnosis of TBC or MAC was confirmed through microbiological evaluation of expectoration and/or gastric juice.

STATISTICS

Statistical analysis was performed on SPSS (SPSS standard version 14.0; SPSS; Chicago, IL). Frequencies of different radiological findings were calculated. For chest x-ray and CT sensitivity for pulmonary involvement was computed. In a second step, sensitivity for the definite clinical diagnosis was tested.

RESULTS

The frequencies of different clinical diagnoses are summarized in Figure 2. In 35% of patients with pulmonary symptoms no pathology was found in both, clinical examination and radiography. 17% of patients had mild rhino-bronchitis. 48% of patients presented
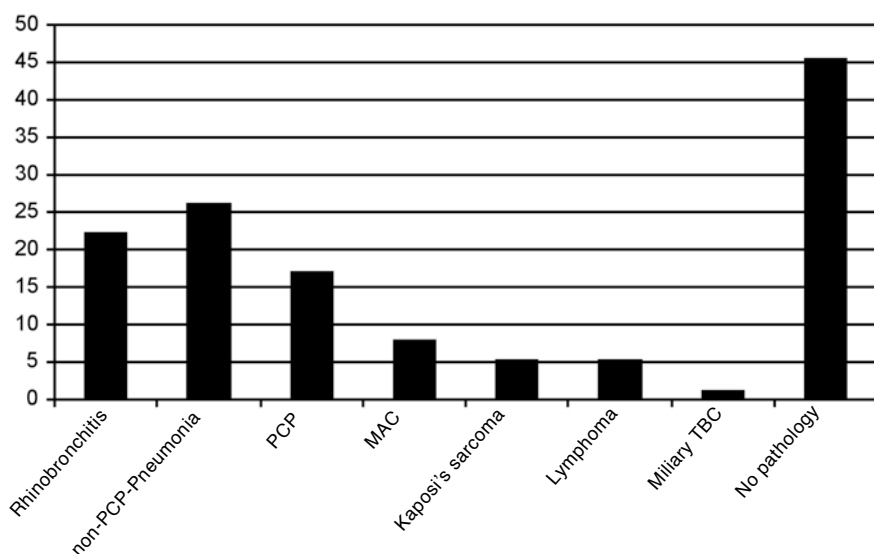
Fig. 2. Frequencies of definite clinical diagnoses (%) of 130 patients with pulmonary symptoms.

pathologic clinical, microbiological, or histopathologic findings.

Bacterial pneumonia (n = 26, 20%) was the most frequent diagnosis within the study population. PJP was the most frequent pathologic finding in BAL and was detected in 13% of patients with pulmonary symptoms (n = 17). Within the entire study population, 9 cases of BAL showed no pathology, but only in 4 of these patients a pulmonary involvement could finally be excluded. False negative results were present in 4 cases with systemic MAC infection (total n = 8). Additionally, in one case of bacterial pneumonia, BAL showed a false negative result.

PULMONARY INVOLVEMENT AND CD4 COUNT

In the high CD4-count group (>500/μL) only BP was observed. 88% of MAC infections (n = 7) as well as 80% of lymphomas (n = 4) were observed in the low CD4-count group (≤200/μl). Within the intermediate CD4-count group (201 to 500/μl) 9 cases of non-PJP pneumonia, 2 cases of PJP, one case of MAC, one TBC, and one lymphoma were diagnosed (Table 2).

Table 2. Frequency of pulmonary manifestations at different CD4 counts.

CD4 count	≤200/μL	201 to 500/μl	> 500/ μl
BP	50%	35%	15%
PJP	88%	12%	
MAC	88%	12%	
KS	60%	40%	
NHL	80%	20%	

RADIOLOGICAL EVALUATION

Overall sensitivity for the detection of pulmonary involvement was 0.87 for chest radiography, and 0.97 for contrast-enhanced CT. Data for the different pulmonary diagnoses are summarized in Table 3. Overall sensitivity for a specific diagnosis was 0.33 for chest radiographs and 0.70 for contrast-enhanced CT (p<0.001). Data for the different pulmonary diagnoses are summarized in Table 4. In patients with radiographic and CT evaluation (n = 42) 13 % of pathologies would have been missed if only chest radiography had been performed.
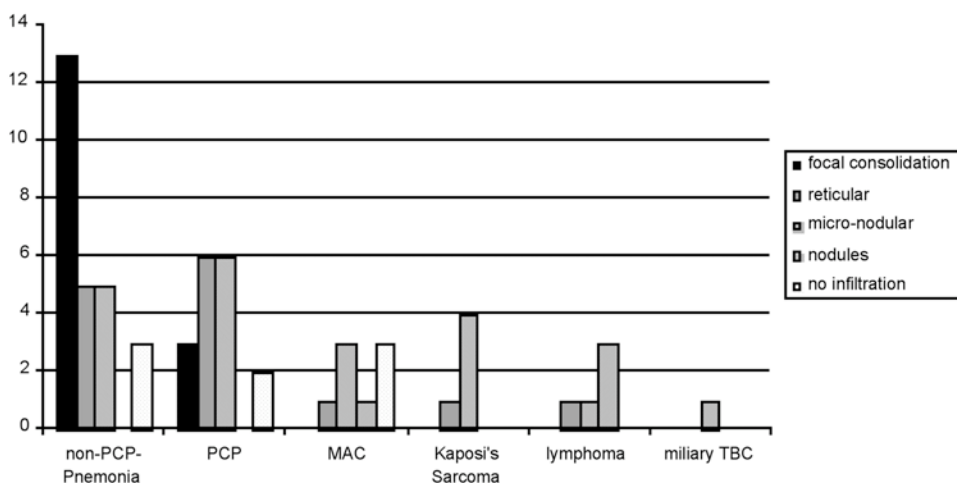

Fig. 3. Frequencies of infiltration patterns in plain radiography (%).

Table 3. True positive results for pulmonary involvement (non disease-specific).

Clinical Diagnosis	n	Radiography (n = 130)		n	CT (n = 42)	
		True positive	False negative		True positive	False negative
BP	23	20 (87%)	3	9	9 (100%)	0
PJP	17	16 (94%)	1	5	5 (100%)	0
MAC	8	7 (88%)	1	6	6 (100%)	0
KS	5	5 (100%)	0	4	3 (75%)	1
NHL	5	5 (100%)	0	4	4(100%)	0

Table 4. Disease specific true positive results of plain radiography and CT scans.

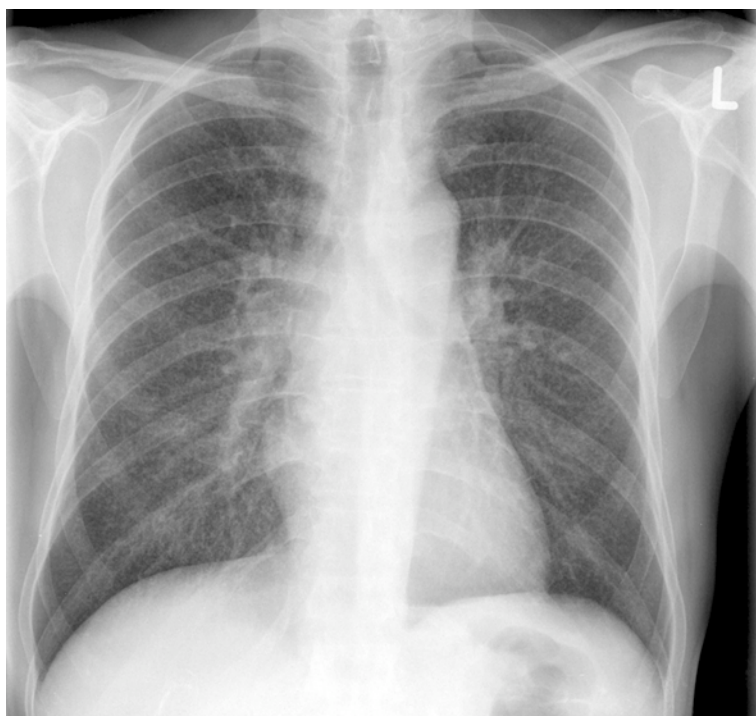| Clinical Diagnosis	n	Radiography (n = 130)		n	CT (n = 42)	
		True positive	False negative for specific diagnosis		True positive	False negative for specific diagnosis
BP	23	15 (65%)	8	9	8 (89%)	1
PJP	17	11 (65%)	6	5	5 (100%)	0
MAC	8	0 (0%)	8	6	2 (33%)	4
KS	5	1 (20%)	4	4	3 (75%)	1
NHL	5	4 (80%)	1	4	3 (75%)	1

Fig. 4. 57 year old male patient with CDC stage C3 and HAART presented with sub-febrile temperature and dyspnea. Plain radiograph shows a homogenous micro-nodular infiltration pattern. PCR test was positive for mycobacterium tuberculosis.

MORPHOLOGIC CHARACTERISTICS AND DISTRIBUTION

Different infiltration patterns for each pulmonary manifestation are shown in Figure 3. Focal consolidation was predominantly present in BP (50%, n = 13). Reticular and micronodular infiltration were predominantly found in plain radiographs of patients with PJP. The only case of TBC infection presented a similar micro-nodular infiltration pattern, however nodules tended to be more prominent compared to PJP (Fig. 4). In few cases of BP (n = 3), PJP (n = 2), and MAC (n = 3), plain radiographs showed no infiltrations.

In PJP, pulmonary infiltrations were predominantly located in the peri-hilar sections (41%, n = 7) and showed a symmetric distribution (59%; n = 10). KS, which also was mainly located in the peri-hilar region, predominantly demonstrated an asymmetric distribution (80%; n = 4, Fig. 5). In contrast, BP was mainly found in the basal segments (n = 16; 62%) with an asymmetric distribution (n = 18; 69%).

Enlarged lymph nodes (> 2cm) were most common in MAC (60%) and NHL (50%). Ground glass attenuation was mainly found in PJP (n = 5). However, there were 12 cases of PJP which did not show a ground
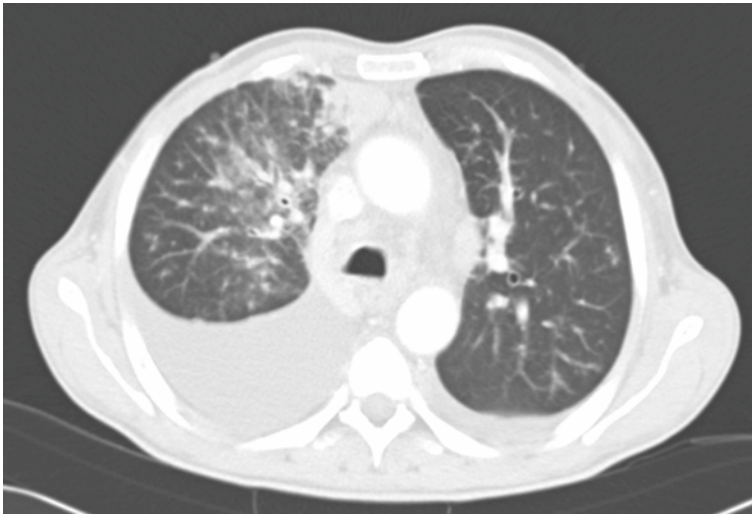
Fig. 5. 39-year-old male patient, CDC stage C3: Kaposi sarcoma of the lung with asymmetric peri-bronchovascular infiltration and associated pleural effusion.
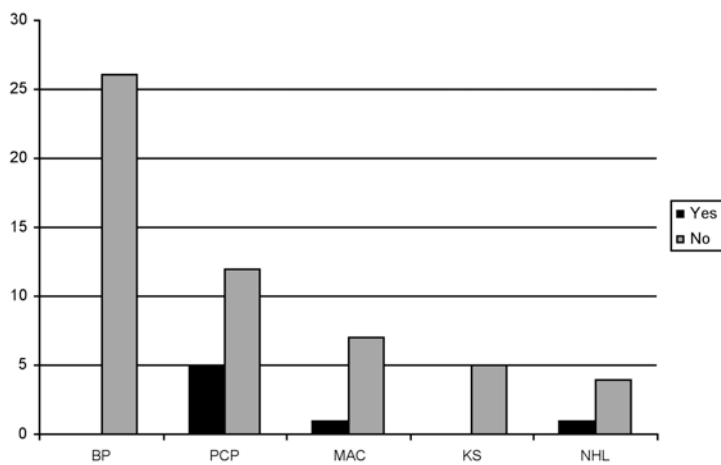

Fig. 6. Frequency of ground glass infiltration in plain radiography (n).
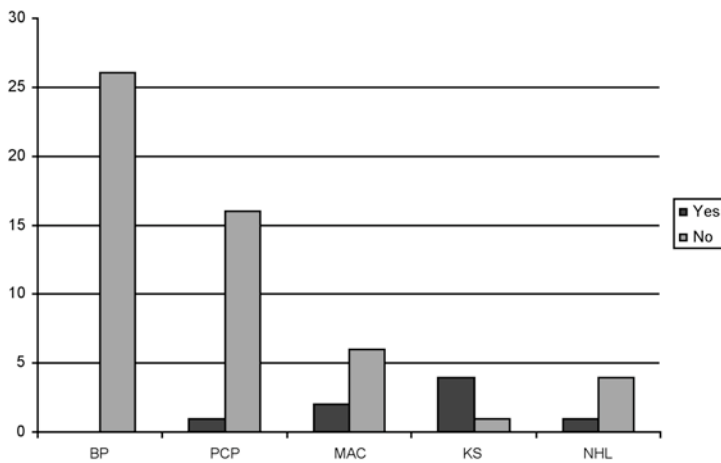

Fig. 7. Frequency of pleural effusion in plain radiography (n).

glass pattern (Fig. 6). Ground glass infiltration was not found in BP. Pleural effusion was predominantly found in KS (n = 4, 80%, Fig. 5), and was not at all found in cases of BP (Fig. 7).

DISCUSSION

Since the introduction of HAART, overall incidences of bacterial pneumonia have significantly decreased [10, 2]. Sullivan et al. (1999) have reported a decline of incidence rates for BP from 22.7 episodes/100 person-years in the first half of 1993 to 9.1 episodes/100 patient years in the second half of 1997 (p < 0.05) [6]. However, in our study population, bacterial pneumonia was still the most frequent pulmonary manifestation, which is consistent with findings from the literature [3]. Relatively to PJP, an increase of BP was reported since introduction of HAART [3, 11]. In the developed world, HAART in combination with anti-PJP prophylaxis has resulted in a significant reduction of PJP. However, the disease still remains the most common AIDS-defining indicator among opportunistic infections [12, 13].

In the present study population, despite HAART, 17 patients with clinical symptoms had bacteriologically confirmed PJP. 88% of patients with PJP had CD4 counts below 200/µl. Individuals might not respond to HAART in same matter at very low CD4 counts.

Only one case of (miliary) tuberculosis (TB) was found. In addition, 8 cases of MAC were confirmed. It has been reported that the incidence of both, TB and MAC, has significantly decreased with HAART. Findings of the present study are therefore consistent with other data from western countries [14]. However, recent progress might be degraded in the future, due to increasing rates of multi-resistant tuberculosis in both, the developing and the developed world.

The distribution of pulmonary infiltrations showed different patterns. Bacterial pneumonia predominantly was associated with a typical asymmetric focal consolidation, whereas PJP was primarily located symmetrically in the peri-hilar sections (micro-nodular or reticular pattern). However, all of the here mentioned infiltration patterns were present in PJP and BP (Figure 3). A reliable radiological diagnosis can not be made without knowledge of CD4 counts. Cases of PJP almost only occur, when CD4 counts are below 200/µl. Ground glass attenuation, which has been reported as a strong indicator for PJP, [15] was absent in 12 cases (71%). In 5 patients with clinically confirmed PJP, CT evaluation was performed. Ground glass attenuation was present in CT images in all of these cases.

KS was associated with a pleural effusion (80%), and was predominantly located asymmetrically in the basal or peri-hilar sections. The combination of clinical information (HIV infection and CD4-count), pleural effusion and the typical peri-bronchovascular infiltration pattern (low-grade vascular tumor) may be a valuable diagnostic tool for the detection of KS.

In times of HAART, pulmonary manifestations still are very common, including PJP, and for certain diseases, typical radiological patterns are observed. There is a good overall sensitivity of plain radiography. However, only contrast-enhanced computed tomography shows an acceptable sensitivity for specific pulmonary diagnoses. In unclear cases with pulmonary symptoms on HIV-infected individuals, contrast-enhanced CT should be performed.

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