Aetiology of pulmonary diseases in immunocompromised patients

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Aetiology of pulmonary diseases in immunocompromised patients. N. Heurlin, C Brattström, B. Lönnqvist, L. Westman, C. Lidman, J. Andersson.
ABSTRACT: Fibreoptic bronchoscopy with bronchoalveolar lavage (BAL), transbronchial lung biopsy (TBB) and brushing was performed, in 134 episodes of pulmonary disease in 118 compromised patients. Sixty eight of the patients were infected with immunodeficiency virus type 1 (HIV-1), 18 were renal and pancreas transplant recipients, 7 were liver and 15 were bone marrow transplant recipients, and 10 patients were undergoing immunosuppressive and/or cytotoxic drug therapy.

Pneumocystis carinii (PC) was the predominant pathogen in HIV-1 infected patients. It was considered to be the aetiological cause of pneumonia in 54/82 (66%) episodes of lung complications noted in these patients.

Cytomegalovirus (CMV) was the most common micro-organism in transplant recipients. CMV pneumonia was diagnosed in 22/42 episodes of pulmonary disease in these patients. CMV was detected by bronchoscopy procedures at a relatively high frequency of 36/82 (44%) episodes in HIV-1 infected patients. However, after analysis of clinical information, cultures from leucocytes and autopsy findings, CMV seemed to be involved in the pathogenicity of pneumonia in only two out of the 36 patients.

Bacterial aetiology, including mycobacterial agents, was unusual, but was the major cause of pulmonary infections in 6/10 episodes in patients undergoing extensive immunosuppressive and/or cytotoxic drug therapy.

Bronchoscopy was helpful in establishing correct aetiology in 98/134 (73%) episodes of pulmonary disease. Growth of *Candida albicans* and bacteria should always be viewed sceptically because of the possibility of contamination from colonization in the upper respiratory tract.
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Disseminated pulmonary lesions seen on chest X-rays in compromised hosts present a diagnostic and therapeutic challenge. Many potential causes must be considered and appropriate treatment initiated without delay. Differential diagnosis of pulmonary diseases includes infections, particularly those caused by opportunistic agents; neoplasmic disorders; pulmonary haemorrhage; drug toxicity; allergic manifestations; and cardiogenic or noncardiogenic pulmonary oedema.

The purposes of the study were to evaluate the diagnostic value of bronchoscopy using bronchoalveolar lavage (BAL), transbronchial lung biopsy (TBB) and brushing in the acute stage of pulmonary disease in compromised hosts, and to determine the presence of various aetiological agents and compare their individual importance in causing pulmonary disease in various groups of immunosuppressed patients.

Material and methods

Patient selection

From December 1983 to November 1987, 134 bronchoscopies were performed in 118 immunosuppressed patients, investigating 134 episodes of pulmonary disease.

The material comprising 94 men and 24 women, aged between 18–76 yrs, was analysed retrospectively. As for primary underlying diseases (table 1) the largest group was 68 human immunodeficiency virus type 1 (HIV-1) infected patients. Twenty one out of sixty eight HIV-1 infected patients were classified as having AIDS according to the criteria established by Centers for Disease Control (CDC), 1985 [1]. The CD_4 (cluster distribution of helper T_4 positive cells) count (n=63) was $\leq 0.2 \times 10^9 \cdot l^{-1}$ in 58/63 HIV-1 infected patients (92%). Risk factors were homo/bisexuality (n=58), intravenous drug

Table 1. – Description of 118 immunocompromised patients who underwent bronchoscopy during a total of 134 episodes of pulmonary disease

Patients	HIV-1 infected patients	Renal transplant patients	Liver transplant patients	Marrow transplant patients	Patients* on immunosupressive and/or cytotoxic drug therapy (>2 yrs)	Total
No. of patients	68	18	7	15	10	118
No. of episodes	82	18	8	16	10	134
Men	64	11	4	12	3	95
Women	4	7	3	3	7	23
Age yrs	23–73	27–69	18–56	21–58	23–76	
Mean age yrs	39	43	35	36	57	

HIV-1: human immunodeficiency virus type 1. *: primary underlying disease: systemic lupus erythematosus (n=3), polyarteritis nodosa (n=3), Sjögren's syndrome (n=1), rheumatoid disease (n=1), respiratory insufficiency due to advanced sarcoidosis (n=1), Wegener's granulomatosis (n=1).

abuse (n=2 women), and blood transfusion (n=5). All HIV-1 infected patients except two, were of Swedish or Finnish Origin. One patient was an immigrant from Yugoslavia and another patient was an Indian student. There were also: 18 renal (n=15) and renal plus pancreas (n=3) transplant recipients; 7 liver and 15 bone marrow transplant recipients; and 10 patients undergoing long-term (≥2 yrs) immunosuppressive treatment with prednisolone (≥35 mg·day^{-1}) and/or azathioprine (≥ 100 mg·day^{-1}) and/or cytotoxic therapy (cyclophosphamide ≥100 mg·day^{-1}).

Indications for bronchoscopy

Inclusion criteria. Patients were included if they had developed one or more of the following respiratory manifestations: cough, dyspnoea, reduced arterial partial pressure of oxygen (Po_2) ≤9 kPa and carbon dioxide (Pco_2) ≤4.2 kPa, and infiltrates on chest X-rays.

Exclusion criteria. TBB and brushing were not performed if bleeding time was greater than 14 min or thrombocytes were less than $30×10^9·l^{-1}$, or if bronchial constriction occurred during the BAL procedure.

Diagnostic procedures

Bronchoscopy

All bronchoscopies were performed under local anaesthetic with a flexible fibreoptic bronchoscope (Olympus BF-10). BAL was performed with the bronchoscope wedged into the most suitable subsegment, usually the middle lobe or lingula or the most abnormal lobe according to chest X-rays. Lukewarm (37°C) saline (150–200 ml) was lavaged in 50 ml aliquots. Each aliquot was aspirated manually. The total amount of fluid recovered was 80–130 ml.

TBB was done under fluoroscopic guidance registered on a TV monitor. Brushing biopsy was done under visual control with an unprotected brush. In two patients with suspected fungal pneumonia a plugged, telescoping brush was used. Patients with arterial hypoxaemia (Po_2 ≤9 kPa) received therapy with supplementary oxygen for at least two hours after the sample collection. Chest X-rays were obtained routinely 24 h after transbronchial biopsy for monitoring late pneumothorax. The specimens were cultured and examined histopathologically as described below.

BAL was performed in all patients except the first eight HIV-1 infected patients, where bronchial washing was performed because BAL was not routinely used at this time. TBB and brushing were only done in 65/134 episodes because of risk of complications (bleeding or pneumothorax). Washing was achieved by instillation of 2–4 ml saline in a suitable bronchial segment, which was then aspirated.

Open lung biopsy was performed in one patient only. Sputum examination for *Pneumocystis carinii* (PC) was introduced within the time of the study [2, 3]. Samples were collected during 35 episodes of clinically suspected *Pneumocystis carinii* pneumonia (PCP) in patients positive for HIV-1 antibodies and the result was compared with that of BAL from the same patient.

Autopsy

Autopsy was performed in 19/22 of the patients immunosuppressed by causes other than HIV-1 infection. In 2/3 patients where autopsy could not be done, post-mortem open lung biopsies were performed and examined according to the same methods as described above for TBB material.

Autopsy was also carried out in the two AIDS patients who died in direct connection with the episode of pulmonary illness.

Specimen handling

Bronchoalveolar lavage (BAL) and bronchial washing fluid were cultured for bacteria, legionella, mycobacteria, fungal species and viruses, such as cytomegalovirus (CMV), adenovirus, herpes simplex 1 and 2 (HSV), Varicella-zoster virus, enterovirus and influenzae virus. Microscopic investigation of smears was also done after staining according to the Gram, Hallberg, Giemsa, Papanicolaou and Ziehl-Neelsen methods and after auramine-staining. Grocott (methenamine silver) staining was used for histochemical detection of *Pneumocystis carinii*. PC was also identified by using mouse monoclonal antibodies (mAb), specific for human pneumocystis antigen and indirect immunofluorescence (IF) technique [2]. Demonstration of CMV- and HSV-antigen was done by IF and monoclonal antibodies in collected and fixed cells [4, 5].

Transbronchial lung biopsy (TBB) material was examined by microscopy after staining with haematoxylin-eosin, and according to the Grocott and Ziehl-Neelsen methods. Cultures for viruses, fungi, mycobacteria and demonstration of CMV antigen in collected cells were made according to the procedure described for BAL fluid.

Material obtained by brushing was air-dried and a smear was then stained according to the Giemsa and Papanicolaou methods. Additional slides were fixed in 95% ethanol and stained by Grocott's method. IF technique was used for CMV antigen detection in collected cells.

Sputum was obtained (for PC detection) within 14 days before and 2 days after bronchoscopy from HIV-1 infected patients in 35/82 episodes. Routine sputum samples were collected (if necessary with the help of a physiotherapist) and treated with an equal amount (mM) of dithiothreitol. An equal volume of 50% (v/v) ethanol was added before the specimen was transported to the laboratory. Induced sputum was obtained after patients had inhaled a mist of saline generated by a nebulizer for about 10 min. PC was identified by the same method as for BAL fluid, using mAb and IF [2].

Diagnosis

Viral infections were diagnosed by either six weeks' culture on human fibroblasts, or by histopathological examination of the transbronchial biopsy material, stained with haematoxylin-eosin, to demonstrate the presence of intranuclear or intracytoplasmic inclusions together with inflammation. Fixed cells, obtained from BAL, TBB or brushing were screened (from September 1986) for intracellular CMV antigen using monoclonal antibodies and IF technique. Virus isolation by culture was routinely performed on cells from heparinized blood, urine and throat washings.

Pneumocystis carinii pneumonia (PCP) was diagnosed by demonstrating the presence of the PC organism either histopathologically by examination of bronchoscopy material (BAL, TBB, brushing) after staining according to Grocott's method; or by investigation with mAb and IF technique on cells collected from BAL fluid and sputum [2, 3]. PCP was also considered in HIV-1 infected patients if the clinical onset was insidious with increasing breathlessness; a progressive dry irritating cough; reduced arterial partial oxygen pressure (Po_2 ≤9 kPa) in combination with reduced carbon dioxide (Pco_2 ≤4.2 kPa); and a prompt response to specific therapy.

Fungal diseases (candida and aspergillus species) were diagnosed by serological tests; or histopathologically by demonstrating characteristic hyphae in tissue; or by identification of the fungus from culture [6]; and for candida also by detection of *Candida mannan* antigen in serum or in biopsy material.

Serological tests

Serological tests were performed for CMV, HSV, adenovirus and influenzae A regularly in transplant patients. IgG and IgM antibodies to CMV were analysed by ELISA [7]. Patients were considered to have an active infection when serology showed the following pattern: appearance of specific anti-CMV IgM (titre ≥1:100) or IgG (seroconversion to titre ≥100) or when a significant increase of IgG titres occurred between paired serum samples.

For diagnosis of PCP, candida or aspergillus species pneumonia, a fourfold rise in specific IgG titre from samples in acute and convalescent stages of disease, or seroconversion, were required.

Tests for HIV-1 antibody were performed in all patients.

Clinical evaluation

Bacterial pneumonia was considered if there was one or more of the following manifestations; an acute onset (over 12–24 h) of respiratory symptoms and absence of granulocytopenia (white blood cells ≤3×$10^9 \cdot l^{-1}$); a localized infiltrate on chest X-rays; a positive bacterial culture from blood; and if there was a prompt response to appropriate antibiotics.

Atypical pulmonary oedema was considered if there was presentation of fever, non-localized pulmonary infiltrates with or without enlargement of the heart on chest X-rays and reduced arterial Po_2 (≤9.0 kPa), and if clearing of infiltrates and normalization of arterial Po_2 occurred after diuretic therapy.

The final diagnosis was established on the following criteria:
1. mode of clinical onset and clinical manifestations;
2. radiological investigation;
3. arterial blood gas analyses while breathing normal air;
4. results from viral, bacterial and fungal cultures from blood;
5. serological analysis, as described in methods section

before and after (if possible) the pulmonary disease;
6. results from cultures of sputum and gastric washings for mycobacteria on Löwenstein-Jensen medium;
7. bronchoscopy findings;
8. response to treatment;
9. autopsy or post-mortem open lung biopsy.

Results

Bronchoscopy was of diagnostic value for the establishment of aetiological cause in 98/134 (73%) episodes of pulmonary diseases. Multiple aetiology was registered in 11 transplant recipients and in 2 HIV-1 infected patients. A clinical diagnosis was registered in all episodes which occurred in the transplant recipients and in the patients undergoing long-term immunosuppressive and/or cytotoxic drug therapy. Sixty eight out of 82 episodes were clinically diagnosed in the HIV-1 infected patients. In the 14 episodes where no clinical diagnosis was registered, the patients recovered quickly.

BAL fluid from an HIV-1 infected patient with a bacterial pneumonia, but without clinical evidence of PCP until three months later.

PC was not identified in bronchoscopy material (only BAL was performed) from three HIV infected patients with a clinical diagnosis of PCP. Two of them had been treated for seven and five days, respectively, before bronchoscopy with trimethoprim-sulphamethoxazole (TMP-SMX). The third patient developed high fever and intra-alveolar infiltrates on chest X-rays during mechanical ventilation (after intoxication in suicide attempt). Because of prompt response to TMP-SMX treatment, PCP was considered. PC was detected in sputum from 13/25 HIV-1 infected patients with PCP confirmed by BAL [2].

All the marrow transplant recipients (n=15) had TMP-SMX as PCP prophylaxis for six months post-transplantation. The only patient in this group who developed PCP, was a patient with a relapsed acute lymphatic leukaemia. He developed PCP nine months after the transplantation and after the prophylaxis with

Table 2. – Comparison of findings from 134 bronchoscopies with final clinical diagnoses (134 episodes of pulmonary disease in 118 immunocompromised patients)

| Diagnosis | Bronchoscopy findings/clinical diagnosis | | | | | |
| | HIV-1 infected patients | Renal transplant recipients | Liver transplant recipients | Marrow transplant recipients | Patients on immunosupressive and/or cytotoxic drug therapy | Total |
	n=82	n=18	n=8	n=16	n=10	n=134
P. carinii pneumonia	51/54	3/3	2/2	1/1	1/1	58/61
CMV pneumonia	36/2	10/10	4/4	7/8	1/1	58/25
Bacterial pneumonia	16/7	7/3	9/2	12/2	3/3	47/17*
Aspergillus pneumonia	0/0	0/0	0/0	2/3	0/0	2/3
Candida pneumonia	10/0	10/1	2/0	9/3	5/0	36/4
M. tuberculosis pneumonia	0/1	0/0	0/0	0/0	2/2	2/3
M. avium pneumonia	2/1	1/1	0/0	0/0	1/1	4/3
Adenovirus pneumonia	0/0	0/0	0/0	1/1	0/0	1/1
Pulmonary oedema	0/1	0/5	0/1	0/1	0/2	0/10
Pulmonary Kaposi's sarcoma	1/1 (PAD)	0/0	0/0	0/0	0/0	1/1
Malignant tumour	0/0	0/1	0/0	0/0	0/0	0/1
Pulmonary a-v shunt	0/0	0/0	0/1	0/0	0/0	0/1
Radiation pneumonitis	–	–	–	0/1	–	0/1
Unknown aetiology	0/14	0/0	0/0	0/0	0/0	0/14
Total	116/81	31/24	17/10	32/20	13/10	209/145

HIV-1: human immunodeficiency virus type 1; *: a bacterial aetiology was confirmed by bronchoscopy in only 12/17 episodes, where bacterial pneumonia was the final diagnosis; PAD: pathological anatomical diagnosis; a-v: arterio-venous.

Pneumocystis carinii *pneumonia*

Aerosol pentamidine prophylaxis was not yet introduced at the time of the study.

Pneumocystis carinii was detected in bronchoscopy material in 51/54 HIV-1 infected patients and in 7/7 patients immunosuppressed by causes other than HIV-1 infection, with a clinical diagnosis of PCP (table 2). PC was also found in small amounts by IF and mAb in

TMP-SMX had been discontinued. One patient who had undergone a renal transplantation six years previously developed a combined PCP and *Candida albicans* pneumonia three weeks after an influenza A_2 infection. Four other transplant recipients fell ill between two to four months after transplantation. PC was also detected in TBB from one patient who had been treated for two years with cyclophosphamide (100 mg daily) and prednisolone (35 mg daily).

Cytomegalovirus pneumonia

CMV pneumonia was the predominant clinical diagnosis in the transplant recipients. Twenty two of the 42 patients had clinical CMV pneumonia, in contrast to only two HIV-1 infected patients (table 2). CMV pneumonia occurred between two weeks and seven months post-transplantation, with a peak at six weeks (day 42). CMV pneumonia was also diagnosed in one patient who had been treated with prednisolone (60 mg daily) and cyclophosphamide (150 mg daily) for two years because of polyarteritis nodosa.

In 22/23 non-HIV-1 infected patients, CMV was found by culture of alveolar cells from BAL and TBB, together with (in five episodes) antigen detection (IF techniques) in cells from BAL, TBB or brushing and (in three episodes) histopathological changes in TBB (inclusions in combination with inflammation). CMV was isolated by culture of blood leucocytes in all patients except one, in whom the test was not performed. In one marrow transplant recipient, for whom CMV was not isolated from bronchoscopy material, CMV pneumonia was thought to be the diagnosis because of isolation of CMV from blood leucocytes, and clinical response to antiviral treatment. The patient had been treated for two weeks before bronchoscopy with suboptimal doses of an antiviral drug (foscarnet). When the doses were adjusted, the patient responded promptly to treatment.

CMV pneumonia associated with pneumonia due to *Candida albicans* and with PCP, occurred in two and four patients, respectively.

CMV was isolated by culture from washing, BAL and TBB in 36 episodes in the HIV-1 infected (table 2) but only two patients had other evidence of CMV pneumonia. One of these patients had disseminated CMV infection combined with PCP, verified by autopsy findings. In contrast to our findings for transplant recipients, we were not able to detect either CMV antigen in alveolar cells from bronchoscopic material

using monoclonal CMV antibodies and IF technique, or histopathological signs of CMV pneumonia in TBB from HIV-1 infected patients.

Atypical pulmonary oedema

Pulmonary oedema in combination with high fever was seen in 10/134 episodes (table 2). Pulmonary oedema due to congestive heart failure was diagnosed in seven of the patients immunosuppressed by causes other than HIV-1 infection and OKT 3 (monoclonal antibodies affecting all T-lymphocytes) induced toxic oedema in two of these patients. Only one episode of pulmonary oedema was noted in the HIV-1 infected group.

Bacterial pneumonia

Clinical diagnoses of bacterial pneumonia were made in 17/134 episodes (table 2). The pneumonia in the transplant recipients appeared between the first week and four years post-transplantation. Forty seven bacterial strains were cultured from BAL, but only 14 strains (12 pneumonia in total) were considered clinically relevant. In two episodes, double bacterial growth was evident. Bronchoscopy failed to demonstrate aetiological cause in five patients. These patients had been treated with antibiotics before bronchoscopy.

Fungal pneumonia

Clinical fungal pneumonia was diagnosed in six marrow transplant recipients *Aspergillus fumigatus* and candida species were the aetiological causes in three patients each (table 2). Candida pneumonia in association with PCP was diagnosed in one renal transplant recipient.

Table 3. – Comparison of findings from bronchoalveolar lavage (BAL), transbronchial lung biopsy (TBB), brushing and washing with final diagnoses (134 bronchoscopies performed in 118 immunosuppressed patients)

Aetiology	BAL n=126	TBB n=65	Brushing n=65	Washing n=8	Nos of episodes n=134
Pneumocytis carinii	44/47	28/42	13/42	0/7	58/61
Cytomegalovirus	55/23	22/16	4/16	2/1	58/25
Bacteria	47/17	NP	NP	0/0	47/17
Aspergillus fumigatus	2/3	1/3	NP	0/0	2/3
Candida species	30/4	10/4	NP	2/0	36/4
M. avium	4/3	2/1	NP	0/0	4/3
M. tuberculosis	2/3	2/2	NP	0/0	2/3
Adenovirus	1/1	NP	NP	0/0	1/1
Kaposis' sarcoma	0/1	1/1	0/1	0/0	1/1
Pulmonary metastases	0/1	0/1	0/1	0/0	0/1
Pulmonary oedema	0/10	0/5	0/5	0/0	0/10
Pulmonary a-v shunt	0/1	NP	NP	NP	0/1
Radiation pneumonitis	0/1	0/1	0/1	NP	0/1
Unknown aetiology	0/14	0/10	0/10	0/0	0/14
Total	184/128	66/86	17/76	4/8	209/145

NP: not performed: a-v: arterio-venous.

Candida albicans was isolated by culture from BAL and/or TBB in 36 patients, out of which only two were clinically considered to have fungal pneumonia (tables 2 and 3). Two other patients with candida pneumonia, where both BAL, TBB and biopsy with a protected brush failed, were diagnosed at autopsy. *Aspergillus fumigatus* was isolated by bronchoscopy in two patients, clinically diagnosed as having aspergillus pneumonia. In a third patient, aspergillus pneumonia was revealed at autopsy.

Mycobacterial pulmonary infections

Infection caused by *Mycobacteria tuberculosis* was diagnosed in three patients, and by *M. avium* complex in another three (table 2).

The diagnosis of mycobacterial infection was established by bronchoscopy in all cases except in an HIV-1 infected patient with tuberculosis, where culture from gastric washing gave the diagnosis. In another HIV-1 infected patient, there was growth of *M. avium* complex from BAL and TBB. The patient had no other evidence of mycobacterial infection (table 2).

Neoplastic pulmonary diseases

Two patients had malignant pulmonary neoplasm. Kaposi's sarcoma was diagnosed in one AIDS patient by histopathological examination of TBB (tables 2 and 3). Open lung biopsy was performed in one patient with pulmonary renal cancer metastases in the lungs, where repeated bronchoscopies had failed to give a diagnosis.

Symptomatology

The clinical onset of a pneumonia due to PC or CMV agents was usually gradual with increasing breathlessness; reduced arterial Po_2 ($\leq$9 kPa) in combination with reduced Pco_2 ($\leq$4.2 kPa); progressive, dry, very irritating cough; intermittent or prolonged fever; and diffuse bilateral infiltrates on chest X-rays. In three HIV-1 infected patients, PCP was present without fever or radiographic abnormalities.

Pulmonary infections due to fungal species, *Mycobacterial tuberculosis* and *M. avium* complex had the same insidious clinical onset, but without the breathlessness and reduction of partial oxygen pressure. The cough was most often productive and chest X-rays revealed cavities and nodular and diffuse infiltrates. The clinical presentation of bacterial pneumonia was the same as in a non-immunosuppressed population.

Evaluation of chest X-rays

Repeated chest X-rays were performed in all patients. The most common pattern was diffuse interstitial bilateral infiltrates, which occurred in 97 episodes. Ten patients, all with uncomplicated bacterial pneumonia had localized abnormalities and two of these also had a pleural effusion. Two patients, one HIV-1 infected patient and one bone marrow recipient, both with diffuse infiltrates were considered to have bacterial pneumonia caused by *Haemophilus influenzae* and *Staphylococcus epidermidis*, respectively. Five other patients with bacterial pneumonia combined with pulmonary oedema (n=2), CMV (n=2), and candida (n=1), had diffuse bilateral infiltrates in association with localized lesions. Two patients, one with a tuberculous infection and one with pulmonary metastasis had nodular infiltrates. All three patients with *M. avium* complex infection and one with tuberculosis had cavities. In another patient with tuberculosis (HIV-1 infected) hilar adenopathy was noted.

X-rays were normal in 14 HIV-1 infected patients and one liver transplant recipient. PCP were found in 5/14 of these HIV-1 infected patients, the other 9 had no diagnosis of lower respiratory tract disease.

Arterio-venous shunt in the pulmonary circulation was diagnosed in the liver transplant patient.

Serology

The renal and liver transplant recipients responded with significant and expected serological changes 12/15 (80%) and 4/6 (66%), while the response in marrow transplant recipients was only 5/16 (31%). Significant serological changes for CMV and PC antibody titres were noted in 12/24 (50%) patients and 3/6 (50%). For aspergillus, candida and adenovirus the serological responses were 3/3, 1/4 and 0/1, respectively.

Serology was not regularly carried out in HIV-1 infected patients and in patients undergoing immunosuppressive and/or cytotoxic drug therapy.

Complications of bronchoscopy

Pneumothorax was seen on chest X-rays taken 24 h after TBB in three HIV-1 infected patients. No therapeutic measures were required.

One patient (with AIDS) became cyanotic and tachypnoeic immediately after a bronchoscopy including BAL, TBB and brushing. His condition improved under observation. No pneumothorax was revealed on chest X-rays. Four days later he suddenly died. Autopsy confirmed the PCP diagnosis but no bleeding or signs of other complications of bronchoscopy were found.

Mortality

The highest mortality rate of pulmonary disease was noted in marrow transplant recipients at 75% (12/16). Renal and liver transplant patients had a mortality rate of 32% (6/18) and 25% (2/8), respectively. Two out of ten patients undergoing immunosuppressive/cytotoxic drug therapy died.

CMV pneumonia was the most common cause of death. It was the cause of death in 12 transplant patients, in seven with CMV pneumonia alone, in two with CMV pneumonia associated with PCP and in two patients associated with candida pneumonia. In another patient with a fulminant pneumonia, both CMV and adenovirus had been isolated in BAL fluid, but autopsy was not permitted.

The mortality rate of the AIDS patients was difficult to ascertain because many of them died within 2–7 months after the episode without having experienced a total recovery. Two AIDS patients, one with PCP who died four days after bronchoscopy and one with PCP combined with disseminated CMV infection who died within less than a month after the bronchoscopy, were considered to have died in direct connection with the pneumonia.

In total 24/118 (20%) patients died of their pulmonary disease.

Discussion

In common with findings from other studies [8–10] we found that the sensitivity of bronchoscopy varied in relation to the underlying pulmonary disease (table 2). The diagnostic yield of PC organisms in all groups and of CMV in transplant recipients was high at 95% (58/61) and 96% (24/25), respectively. In accordance with other authors [11, 12] we established, that in HIV-1 infected patients the correlation between finding CMV in bronchoscopy material and evidence of clinical CMV pneumonia was less significant. BAL was the most sensitive method. Except for one episode each of Kaposi's sarcoma, PCP and CMV pneumonia diagnosed by TBB, TBB and brushing did not add more aetiological information than BAL alone in those episodes (n=57) where all three methods were used on the same occasion (table 3). Similar findings have been reported from other studies [4, 8].

Aetiological organisms were not identified in bronchoscopy material from two HIV-1 infected patients with a clinical diagnosis of PCP, or from one transplant recipient with a diagnosis of CMV pneumonia, and nor from five patients diagnosed as bacterial pneumonia. All patients had received antimicrobial drugs prior to the bronchoscopy (5–14 days), and this may have been the reason for the negative findings. They all responded to a continuation of the drugs they had previously received. PC was not detected in BAL fluid from an HIV-1 infected patient who developed infiltrates during mechanical ventilation. The diagnosis was PCP but pneumonia due to aspiration could also have been considered.

Growth of bacteria and candida without signs of pulmonary infection was found in 35 cultures from BAL samples and in 34 cultures from BAL, washing and TBB material, respectively, (table 3). This was probably caused by oropharyngeal contamination. Several reports [13] have proposed the use of a plugged, telescopic catheter brush to eliminate contamination.

Uncomplicated bacterial pneumonia are rarely documented as the cause of diffuse pulmonary infiltrates in immunosuppressed patients [10, 14].

According to many studies, the diversity of opportunistic infections depends on the underlying disease and its treatment, and it also seems to vary according to the general microflora that the patients are exposed to in different parts of the world [6, 10, 15]. PCP is the predominant pulmonary infection in patients with AIDS in the Western World (60–80%) [11, 15–17, 18–22], and there is a high frequency of CMV pneumonia in transplant patients (40–60%) [9, 11, 23–25]. Primary fungal pneumonia caused by candida and aspergillus species occurs most often in marrow transplant recipients and seldom appears in AIDS patients [6, 10]. Pneumonia due to cryptococcus or histoplasmosis are uncommon in Sweden. These agents were not isolated from any patient in the study.

The prevalence of PCP in HIV-1 infected patients was 54/82 (66%). It would have been higher (76/104; 73%) if the group of patients selected for bronchoscopy had not changed during the study. Twenty two patients did not proceed to bronchoscopy because PC organisms were identified by mAb and IF in sputum [2], in combination with successful treatment. This excluded them from the study.

In common with results from other authors, we found that most cases of mycobacterial lung infections appeared in the group of patients being immunosuppressed by steroid and cytotoxic drug therapy [10, 15]. Only two HIV-1 infected patients were diagnosed as having mycobacterial disease. A further two HIV-1 infected patients excluded from the study because of smear positive sputum, had mycobacterial infections during the study period.

It is well known from transplant patients [10, 12, 16] that once a CMV pneumonia is established with low Po_2 (≤ 9 kPa) and with diffuse bilateral infiltrates on chest X-rays, the clinical effect of treatment is poor. For treatment to be effective, it must be initiated early in the respiratory infection. Reports have indicated that high doses of intravenous gammaglobulin in combination with specific antiviral therapy can dramatically improve survival [24–26]. Fibreoptic bronchoscopy should therefore be performed as soon as the patient presents a dry cough and if possible, before the start or during the very first days of treatment to give reliable results.

Knowing that PCP at present is the most common pulmonary infection among HIV-1 infected patients with severe immunodeficiency ($CD_4 \leq 0.2 \times 10^9 \cdot l^{-1}$), and knowing that the progression of PCP is slower in these patients than in patients immunosuppressed by other causes [20], bronchoscopy need not always be performed. In HIV-1 infected patients with clinical manifestations suggesting PCP, immediate treatment with intravenous TMP-SMX or pentamidine is justified [18–21, 27]. At the same time sputum should be sent for PC antigen detection by IF [2]. If sputum investigation gives a negative result, or the patient fails to respond to treatment, a diagnosis other than PCP or

a pneumonia due to multiple infection organisms must be considered. The patient should then undergo bronchoscopy to establish an aetiological diagnosis before a change of therapy. This is valid under present conditions, but these may change due to the fact that effective pentamidine prophylaxis is becoming an increasingly common form of treatment.

Conclusions

Bronchoscopy with BAL was a safe and informative method. It had a high specificity and sensitivity, when correlated with clinical diagnosis, for detecting PC organisms in all groups and CMV in transplant recipients. In HIV-1 infected patients, the correlation between finding CMV in bronchoscopy material and evidence of clinical CMV pneumonia was less significant.

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Etiologie des maladies pulmonaires chez les patients en état d'immuno-dépression. Etude au moyen de la fibro-bronchoscopie. N. Heurlin, C. Brattström, B. Lönnqvist, L. Westman, C. Lidman, J. Andersson.

RÉSUMÉ: L'on a réalisé une fibro-bronchoscopie avec lavage broncho-alvéolaire (BAL), biopsie pulmonaire transbronchique (TBB) et brossage, au cours de 134 épisodes d'infection pulmonaire chez 118 patients immuno-déprimés. Soixante-huit des patients étaient infectés par le VIH-1, 18 étaient des receveurs de transplantation rénale ou pancréatique, 7 étaient des receveurs de transplantation hépatique, et 15 étaient des receveurs de transplantation moelle. En outre, il y avait 10 patients sous traitement immuno-suppressif et/ou cytotoxique. *Pneumocystis carinii* (PC) s'est avéré le pathogène prédominant chez les patients infectés par le VIH-1. L'on a considéré qu'il était l'agent causal de la pneumonia dans 54 de 82 épisodes (66%) de complications pulmonaires observées chez ces patients. Le Cytomegalovirus (CMV) est le micro-organisme le plus courant chez les receveurs de transplantation. La pneumonie à CMV a été diagnostiquée au cours de 22 des 42 épisodes de maladie pulmonaire observée chez ces patients. CMV a été détecté par des techniques bronchoscopiques à une fréquence relativement élevée, soit dans 36 épisodes sur 82 (44%) chez les patients infectés par le VIH. Toutefois, après analyse des informations cliniques, des cultures leucocytaires et des observations autopsiques, le CMV paraît être un agent pathogène responsable de la pneumonie chez 2 seulement de ces 36 patients. L'étiologie bactérienne, y compris l'étiologie mycobactérienne, s'avère inhabituelle, mais fut néanmoins la cause principale d'infection pulmonaire au cours de 6 des 10 épisodes de patients sous traitement immuno-suppressif et/ou cytotoxique intensif. La bronchoscopie s'est avérée utile pour établir un diagnostic étiologique correct dans 98 des 134 épisodes d'affection pulmonaire (73%). La pousse de *Candida albicans* et de bactéries doit toujours être considérée avec scepticisme, en raison de la possibilité d'une contamination provenant d'une colonisation de l'appareil respiratoire supérieur par ces germes. *Eur Respir J., 1991, 4, 10–18.*