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High Resolution Multislice Computed Tomography in the Early Phase after Stem Cell Transplantation

Dissertation

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Abbreviations

SCT = Stem cell transplantation

BMT = Bone marrow transplantation

PBSCT = Peripheral blood stem cell transplantation

HLA = Human leukocyte antigen

GvHD = Graft versus host disease

GvLR = Graft versus leukemia reaction

IIP = Idiopathic interstitial pneumonias

COP = Cryptogenic organizing pneumonia

HRCT = High resolution computed tomography

FUO = Fever of unknown origin

WBI = Whole body irradiation

SOP = Standard operation procedure

PACS = Picture archiving and communication system

BAL = Bronchoalveolar lavage

CRP = C-reactive protein

AML = Acute myeloid leukaemia

ALL = Acute lymphatic leukaemia

CML = Chronic myeloid leukaemia

VATS = Video-assisted thoracic surgery

Introduction

Stem cell transplantation (SCT) is a potentially curative therapy for patients with haematological malignancies and other haematological disorders. Treatment options include autologous, allogenic and syngenic SCT. Stem cells are extracted from either bone marrow (bone marrow transplantation = BMT) or from peripheral blood (peripheral blood stem cell transplantation = PBSCT). Allogenic SCT is associated with higher risks compared to syngenic and autologous SCT. It is performed either from a human leukocyte antigen (HLA) identical relative or from a HLA compatible foreign donor. The transplantation of immune competent donor cells can lead to graft versus host disease (GvHD) resulting in significant treatment related morbidity and mortality. Conversely it can result in a graft versus leukaemia reaction (GvLR) by the immune competent donor cells, thereby improving the chances of treatment success. Infections related to immunosuppression and GvHD are the main complications of SCT. Pulmonary infections are particularly important after SCT, with an incidence rate of up to 60%, and a mortality rate of 56% [1-2, Breuer 1993 and Gosselin 2002] despite antibiotic prophylaxis. It may be difficult to distinguish between infectious and non-infectious pulmonary complications [1-6, Breuer et al. 1993, Gosselin et al. 2002, Aronchick 2000, Heussel et al. 2004, Maschmeyer et al. 2003 and Ruhnke et al. 2003]. Apart from clinical and microbiological assessment, bronchoscopy with transbronchial biopsy and bronchoalveolar lavage, and in rare instances, thoracoscopy or open lung-biopsy may be necessary [7, Hayes-Jordan et al. 2002]. In individual cases the final diagnosis may be made only at autopsy [8, Chandrasekar et al. 1995]. The risk of pneumonia is especially high during the aplastic and neutropenic early phase after SCT and may be bacterial or fungal [4, 9-11, Heussel et al. 2004, Pannuti et al. 1992, Krüger et al. 1999 and Einsele et al. 2003]. Viral pneumonias such as cytomegalovirus pneumonia are often diagnosed in the non-neutropenic

late phase after SCT. Toxic interstitial pneumonitis due to cytotoxic therapy and radiotherapy may occur. In addition, rare forms of idiopathic interstitial pneumonias (IIP) like a cryptogenic organizing pneumonia (COP) have been reported [12-16, Thirmann et al. 1992, Kleinau et al. 1997, Kanda et al. 1997, Baron et al. 1998 and Kanamori et al. 2001]. Chest-x-ray is not useful for assessment in these patients due to problems of limited resolution and overlay effects [17, 18, Grenier et al. 1991 and Swenson et al. 1997]. High resolution computed tomography (HRCT) of the chest has a higher sensitivity for pulmonary pathology and is able to assess the nature and extent of pulmonary interstitial tissue much better than chest-x-ray. The superiority of high resolution multislice computed tomography (HRCT) for the diagnosis of interstitial pulmonary diseases is undisputed [19-20, Heussel et al. 1996 and et al. Heussel 1997]. However its clinical value in the context of infectious and non infectious pulmonary complications in neutropenic patients after SCT is still not well investigated [21-24, Heussel et al. 1999, Tanaka et al. 2002, Webb et al. 1988 and Webb 1991].

This study evaluated the clinical utility of pulmonary HRCT after SCT. It examined its role in the assessment of fever of unknown origin versus pneumonia when compared to clinical and laboratory findings, and its value in monitoring pulmonary infections in the early phase after SCT. As a secondary objective, a systematic analysis of image patterns in HRCT was performed to allow correlation with specific pulmonary pathogens.

The clinical question of this paper is targeted at how HRCT is able to diagnose pathogen-specific pneumonia, according to subgroups “fungal, bacterial, viral and non specific” when compared to a created composite gold standard in this clinical setting.

Material and Methods

Inclusion criteria for HRCT:

Adult patients (at least 18 years old) who developed fever of unknown origin (FUO) over 38º Celsius after SCT in the neutropenic phase.

The following risk factors were used to identify the potential for pulmonary complications before SCT:

- Age > 50 years
- Allogenic SCT
- Malignant haematological disease
- Progressive tumour stages (stages III, IV)
- Conditioning with whole body irradiation (WBI)
- Pulmonary complications in the clinical history

Patients with a high risk profile (risk score ≥ 3 factors) underwent a baseline HRCT before SCT, while this was not necessary for patients with low risk profile (risk score < 3 factors). The decision to perform a baseline HRCT before SCT in patients with a high risk score was based on the need to definitely exclude pneumonia before SCT and to better delineate early pulmonary pathologies from preexisting pulmonary findings.

High Resolution Computed Tomography

HRCT examinations were performed on a four-row multislice CT scanner (Somatom Volume Zoom, Siemens Medical Solutions) in accordance to standard operation protocols (SOP). The acquisition protocols are shown in Table 1.

MSCT		THORAX COMBI	THORAX SEQUENCE
Collimation		4 * 1 mm	2 * 0,5 mm
SD / Increment		1mm / 10 mm	1 mm
Rotation		1 sec	0,75 sec
Table assistance		7 mm	20 mm
Convolution kernel		B 60 f	B 70 s
Phase of Breath	Bronchiolitis obliterans	Inspiration	Inspiration
		Expiration	Expiration
	Progressive systemic sclerosis	Prone position	Prone Position

Table 1: Acqusition protocols in multislice computed tomography

The HRCTs were performed as helical volumetric scans. A complete contrast-enhanced HRCT of the thorax was performed as initial HRCT after SCT (Thorax Combi, see table 1). The contrast medium was injected using a 18 gauge needle, with total volume of 80 ml and flow rate of 2 ml/s. Out of this data-set the HRCT with the following parameters was reconstructed: slice thickness 1.25 mm, increment 0.6 mm. B 70 s was used as convolution kernel. The field of view added up to 22 cm with a 512 x 512 matrix. The evaluation of the axial image reconstruction was performed on a 512 x 512 matrix (Somatom Plus 4 VZ Wizzard, Siemens Medical Solutions). Multi-planar reconstructions in coronal view were reconstructed at a 3D workstation (Virtuoso V30, Siemens Medical Solutions) using a 256 x 256 matrix. Out of the cohort of 113 patients in the study, 19 (17%) had a contrast enhanced baseline HRCT before SCT due to a high risk score. The initial HRCT after SCT was initiated

based on clinical indications listed earlier and it was performed using the identical contrast-enhanced protocol. Follow up HRCT of the thorax (< 60 days after SCT) were performed without contrast enhancement (thorax sequence, table 1).

Image Interpretation

The following criteria for image interpretation were derived from the current literature on HRCT of the lung and followed criteria established by the Fleischner Society [25-33, Roos et al. 1996, Kauczor et al. 1996, Austin et al. 1996, Webb et al. 1996, Reuter et al. 2002, Escuissato et al. 2005, Tuddenham et al. 1984, Austin et al. 1985 and Friedmann 1983]. Orientation was based on anatomical considerations. The pattern of image from HRCT was described as reticular or nodular, increased or decreased lung opacities. HRCT findings of lung disease were categorized as follow:

- Linear and reticular opacities: peribronchovascular interstitial thickening; centrilobular peribronchovascular interstitial thickening; interlobular septal thickening; parenchymal bands; intralobular interstitial thickening; subpleural interstitial thickening; honeycombing; subpleural line.
- Nodules and nodular opacities: small nodules, less than 1 cm in diameter; large nodules, more than 1 cm in diameter; masses, more than 3 cm in diameter; distribution of nodules: centrilobular, centrilobular rosettes, perilymphatic; ”tree-in-bud”; halo-sign; air crescent.
- Increased lung opacities: focal ground glass opacity; patchy ground-glass opacity; consolidation.
- Decreased lung opacities: cysts and airway abnormalities: emphysema; bullae, more than 1 cm in diameter, bronchiectasis; lung cysts, honeycombing, mosaic perfusion, air trapping.

The pulmonary patterns seldom appeared in isolation and as such were described based on the predominant component [27, Austin et al. 1996].

Data collection and interpretation

Patient case records were reviewed to obtain all relevant clinical and microbiological data. The radiological data were taken from the locally established picture archiving and communication system (PACS; Sienet, Syngo, Siemens Medical Solutions). When clinically indicated, bronchoscopy (P40, T40, T30, Olympus Medical Systems) was performed in accordance to a standardized protocol which consisted of macroscopic inspection, bronchoalveolar lavage (BAL; lavage volume minimum 100 ml) with a cytological and microbiological work up of the bronchoalveolar lavage materials (bacterial, fungal, and viral pathogens), cytology and cell differentiation. Serology was tested for aspergillus, candida, cytomegalovirus, Ebstein-Barr virus, toxoplasmosis, hepatitis B and C, and HIV.

The interpretation of HRCT was performed prospectively by two pulmonary radiologists and the final diagnosis was based on consensus opinion and communicated to the physicians of the transplantation centre using the following format:

- Presence / absence of pulmonary opacity
- Distribution of opacity (left, right lung; upper, middle, lower lobe; central, peripheral; anterior, posterior; focal, patchy, diffuse)
- HRCT image patterns (in accordance to the recommendations of the Nomenclature Committee of the Fleischner Society)
- Presence / absence of pulmonary congestion (defined as a combination of interlobular septal thickening, ground-glass opacity and pleural effusion)
- Presence / absence of pleural effusion (left, right)

- Presence / absence of pericardial effusion
- Presence / absence of pleural thickening
- Presence / absence of atelectasis
- Presence / absence of pneumonia (bacterial, fungal, viral, unspecified)

In accordance to the recommendations of the Nomenclature Committee of the Fleischner Society the authors decided to avoid the terms infiltrate and infiltration as descriptors and used the term opacity instead. This term referred to a poorly defined opacity in the lung that neither destroys nor displaces the gross morphology of the lung and is presumed to represent an infiltrate in the pathophysiologic sense [31-33, Tuddenham et al. 1984, Austin et al. 1985 and Friedmann 1983]

Based on the HRCT findings patients were categorized into one group with pulmonary opacities and another group without opacities. The image patterns in HRCT were compared against a standard for bacterial, fungal or viral pneumonia that was based on combination of findings from bronchoscopy with BAL, microbiology (lavage material, sputum, titer, blood culture, and serology) and C-reactive protein (CRP). The serological examination included the routinely determination of antigen and antibody titers for aspergillus, candida, cytomegalovirus, Ebstein-Barr virus, varicella zoster virus and herpes simplex virus. The clinical as well as the blood chemical data were recorded daily. Microbiological data were evaluated dependent on signs of infections such as fever and elevation of CRP up to four times per week. Within the protocol, for all parameters, the first increase, maximum peak and duration of increase were documented. Lavage material, sputum, blood cultures and serology were categorized as “pathologic” by the investigators, when a significant increase or a new incidental occurrence was observed, recognizing that large amounts of some specific pathogens (e.g. S. epidermidis) in blood cultures might result from skin containment or

infected vascular catheters. Catheters underwent standardized microbiological work up after removal. The final diagnosis of pathogen specific pneumonia was made by the clinicians of the transplantation centre incorporating all clinical findings, including HRCT findings and microbiological data as well as patient symptoms. It separated pneumonia into bacterial, fungal, viral and unspecific origin respectively. This final diagnosis of a pathogen specific pneumonia, which was put in the discharge letter, served as the gold standard. The data interpretation for the definition of the gold standard diagnosis was based on the consensus opinion of the investigators of the transplantation centre, as a transplantation board decision. The sensitivity, specificity and diagnostic accuracy of HRCT was calculated on the basis of the final diagnosis in the discharge letter and matched to the interpretation of HRCT findings made by the radiologists.

Statistic analysis

The sensitivity, specificity and diagnostic accuracy of the HRCT when compared against the gold standard was calculated. Chi-square test was used for categorical variables with a p-value < 0.05 being considered as statistically significant. SPSS software (SPSS, version 14.0) was used.

Results

Patients

The study was approved by the local ethics committee. Over a 5-year period 113 consecutive patients (52 female / 61 male) were recruited prospectively after SCT. The mean age was 46 years (range: 19-77 years). The indications for SCT are shown in figure 1.

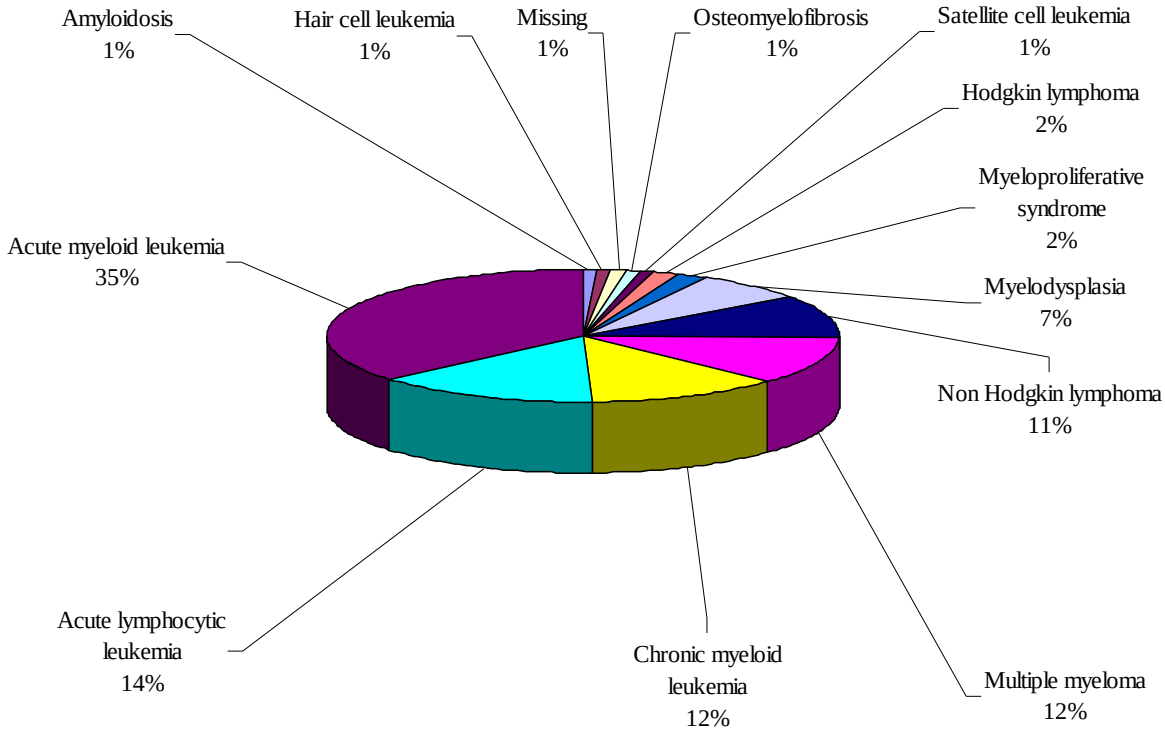

Figure 1: Basic Disease

Overall a total of 232 HRCT scans were reviewed, consisting of 19 baseline, 113 initial and 100 follow-up HRCTs during the study period.

The most common indications (Figure 1) for SCT were acute myeloid leukaemia (AML) (35%), acute lymphocytic leukaemia (ALL) (14%), chronic myeloid leukaemia (CML) (12%) and multiple myeloma (12%).

Based on HRCT results, the 113 patients were divided into 2 groups. In group 1 (n = 40; 35%), pulmonary opacities were absent. In group 2 (n = 73; 65%), pulmonary opacities were present. The mean age at transplantation was similar between both groups (Figure 2).

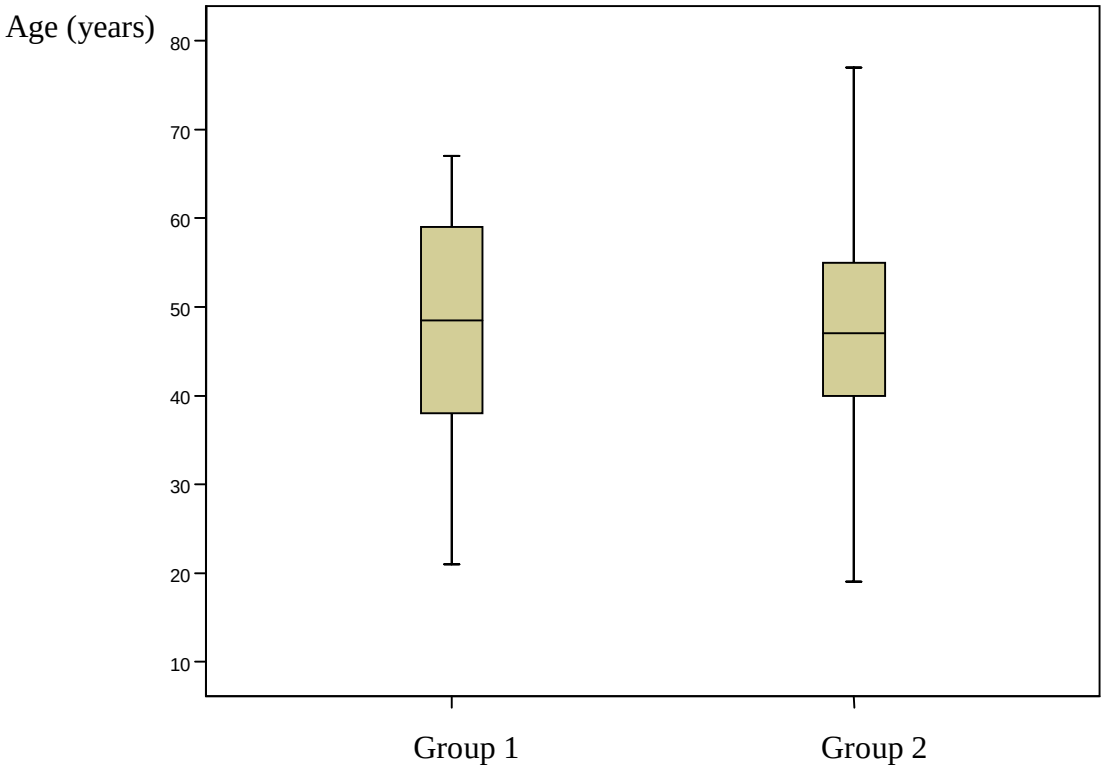

Figure 2: Age distribution clustered by groups

The main method of SCT was allogenic PBSCT (n=74; 66%). Allogenic BMT (n=21; 18%), autologous PBSCT (n=15; 13%), autologous BMT (n=2; 2%) and syngenic BMT (n=1; 1%)

were less frequently chosen. Both groups had similar proportions of patients with risk factors ≥ 3 ($p > 0.05$; table 2).

RISK FACTORS	GROUP 1 (N)	GROUP 2 (N)	TOTAL (N)
0	3	0	3
1	8	23	31
2	25	34	59
3	3	15	18
4	1	0	1
5	0	1	1
TOTAL	40	73	113

Table 2: Number of risk factors to identify the potential for pulmonary complications before stem cell transplantation clustered by groups

In total 24/113 patients (21%) died less than 60 days after SCT; four patients (10%) were in group 1 and 20 patients (27%) were in group 2 ($p < 0.05$). In group 1, three patients died due to respiratory failure. These patients showed pneumonia of unknown origin on autopsy and which was not detected by HRCT despite repeated imaging.

Clinical, biochemical and microbiological findings

Clinical, biochemical and microbiological findings for pneumonia differed in group 1 and 2 (table 3).

INFECTION ASSOCIATED FINDINGS	GROUP 1	GROUP 2
Clinical symptoms (cough, thoracic pain, dyspnoea)	n=19	n=38
Maximum increase of temperature (mean, in °C)	41	39,9
Maximum CRP-Value (mean, in mg/dl)	230	451
Pathologic results of blood culture	n=21	n=46
Pathologic results of bronchoscopy	n=2	n=24
Pathologic results of bronchoalveolar lavage	n=6	n=37

Table 3: Clinical features

Table 4 shows the specific pathogens identified by BAL, blood culture and serology.

BLOOD CULTURE	GROUP 1 (N)	GROUP 2 (N)	TOTAL
Staphylococcus aureus	1	0	1
Staphylococcus epidermidis	13	13	26
Staphylococcus hominis	0	6	6
Staphylococcus xylosus	1	0	1
Staphylococcus haemolyticus	2	4	6
Coagulase-negative streptococcus	2	7	9
Streptococcus salivarius	0	1	1
Enterococcus species	0	1	1
Escherichia coli	0	3	0
Enterococcus faecium	0	1	1
Enterococcus cloacae	0	1	1
Proprionibacterium species	0	1	1
Clebsiella	0	1	1
Corynebacterium species	1	1	2
Lactobacillus species	0	1	1
Bacteroides fragiles	1	0	1
Candida albicans	0	2	2
Candida glabrata	0	1	1
Candida krusei	0	1	1
Candida inconsoicua	0	1	1
TOTAL	21	46	67

Table 4a: Microbiological Findings – Blood Culture

BRONCHOALVEOLAR LAVAGE	GROUP 1 (N)	GROUP 2 (N)	TOTAL
Staphylococcus hominis	0	1	1
Coagulase-negative streptococcus	0	14	14
Vergrünende Streptokokken	1	7	8
Enterococcus species	0	8	8
Clebsiella	0	1	1
Corynebacterium species	0	2	2
Neisseriaceae	0	1	1
Lactobacillus species	0	1	1
Cytomegalia Virus	1	1	2
Pneumocystis carinii	0	1	1
Herpes simplex Virus	0	1	1
Candida albicans	0	4	4
Candida glabrata	0	4	4
Candida krusei	0	1	1
Aspergillus fumigatus	0	3	3
Normal flora	4	6	10
TOTAL	6	56	62

Table 4b: Microbiological Findings – Bronchoalveolar Lavage

SEROLOGY	GROUP 1 (N)	GROUP 2 (N)	TOTAL
Candida	1	7	8
Aspergillus	2	6	8
Toxoplasmosis	16	27	43
Epstein-Barr-Virus	18	33	51
Cytomegalia	21	39	60
HIV	0	0	0
Hepatitis C-Virus (HCV)	2	1	3
Hepatitis B-Virus (HBV)	4	11	15
TOTAL	64	124	188

Table 4c: Microbiological Findings - Serology

In group 2 the detection of specific pathogens was achieved in 22/40 (55 %) patients by bronchoscopy with BAL, in 9/40 (23 %) patients by blood cultures, in 5/40 (13 %) patients by sputum analysis and in 4/40 (10 %) patients by serology. The number of 40 patients, as used in these paragraphs, refers to 40 of 113 patients in whom a specific microbiologic diagnosis could be verified. In these patients, in accordance to the definition of the gold standard based on the consensus opinion of the investigators of the transplantation centre, the final diagnosis of a pathogen specifc pneumonia was made by the clinicians of the transplantation centre incorporating all clinical findings, including HRCT findings and microbiological data as well as patient symptoms. It was a transplantation board decision and for all individuals, all other clinical possibilities such as associated infections like cystits, enteritis, GvHD colitis, polyserositis, sinusitis, catheter infections and skin containment were excluded. As shown in table 4 the large amount of S. epidermidis in the blood cultures was suggestive of skin contaminant or infected vascular catheters but not considered as responsible for pneumonia in any patient by the investigators.

A total of 62 BAL in 43 patients were performed. Some patients received repeated BAL during hospital stay. In all patients with bronchoscopy HRCT was of high clinical value prior to bronchoscopy in identifying specific lung regions for BAL and biopsy, the locations of lymph nodes for endoscopic ultrasound sampling and for the identification of anatomic variants. In group 1, bronchoscopy with BAL was performed in 6/40 patients. The pathologic findings were chronic bronchitis (1), acute bronchitis in (1), pneumocystis jiroveci pneumonia (1) and alpha streptococcus pneumonia (1). In group 2, 37/73 patients underwent bronchoscopy with BAL. The findings were: chronic bronchitis (2), alveolar haemorrhage (5) and acute bronchitis (17). Specific pathogens were isolated in 29/37 patients and included aspergillus (4/29), candida (8/29), coagulase-negative staphylococcus (8/29), staphylococcus hominis (1/29), enterococcus species (5/29), corynebacterium species (1/29), klebsiella species (1/29) and alpha streptococcus (1/29). The results of bronchoscopy for the other patients were unremarkable. Overall bronchoscopy with BAL revealed significantly more pneumonia specific findings in group 2 compared to group 1 ($p < 0.05$) whereas the results of cytological evaluation were similar between both groups.

In group 2, a specific pathogen could be identified in 40 patients (5/40 aspergillus, 13/40 candida, 1/40 pneumocystis jiroveci, 2/40 E. coli, 3/40 enterococcus species, 1/40 klebsiella species, 1/40 pseudomonas aeruginosa, 8/40 staphylococcus, 2/40 streptococcus, 4/40 cytomegalovirus). For the remaining 33 patients with pulmonary infiltrates, microbiological tests were negative and they were classified as non specific pneumonia. If those 33 patients had other diagnoses such as diffuse alveolar damage or GvHD was not the issue of this study.

Radiological findings, diagnostic accuracy

A baseline HRCT was performed in 19/113 patients (17 %) on average 8 days (range: 0-34 d) before SCT. The baseline HRCT revealed pathological findings in 8/19 patients (42 %). The clinical diagnosis was bacterial pneumonia in 1 patient and fungal pneumonia in 2 patients based on biochemical and microbiological tests; patients were treated with antibiotics until recovery before SCT was finally performed. The remaining 5 patients had unremarkable biochemical and microbiological results.

The 113 initial HRCTs were performed on average 14 days after SCT in group one (range: 0-43 d) and 10 days (range: 0-28 d) after SCT in group two. The mean temperature at the time of the initial HRCT was 38.1° Celsius (range 38-41.0 °C) in group one and 38.1°C (range: 38-39.9) in group two. A total of 100 follow-up HRCTs were performed in 61 patients during the study period (8 in group one, 92 in group two). The first follow-up HRCT (61 patients) was performed on average at day +20 (4-61). The second follow-up HRCT (25 patients) was performed on average at day +28 (9-53). The third follow-up HRCT (9 patients) was performed on average at day +35 (14-60). The fourth follow-up HRCT (3 patients) was performed on average at day +37 (28-42). The fifth follow-up HRCT (2 patients) was performed on average at day +53 (50-56) after SCT.

Among the 73 patients with pulmonary infiltrates in group 2, 17 had bacterial pneumonia diagnosed at a mean of 6 days after SCT, 19 had fungal pneumonia diagnosed at a mean of 9 days after SCT and 4 had viral pneumonia diagnosed at mean of 30 days after SCT by HRCT. The remaining 33 patients with non specific opacities were detected on a mean of 10 days after SCT by HRCT. The proven isolated pathogens generating pneumonia in group 2 are displayed in table 5.

GERM	(N)
Aspergillus	5
Candida	13
Pneumocystis carinii	1
Staphylococcus	8
Streptococcus	2
Enterobacteiacea	3
Escherichia coli	2
Pseudomonas aeruginosa	1
Klebsiella	1
Cytomegalia	4
Unspecific	33
TOTAL	73

Table 5: Isolated pathogens generating pneumonia in Group 2

The numbers of patients within each specific pathogen grouping were not sufficient to allow correlations of image patterns with specific pathogens. The presence of opacities in HRCT alone is, to the opinion of the authors, only a “relatively” good stand alone predictor of “pathogen-specific” pneumonia because “pathogen-specific” pneumonia could only be diagnosed by the “extended” microbiological work up in this study in 40/73 (55%) patients in group 2 and in 40/113 (35%) patients with FUO in general. In 33/73 (45%) patients in group 2 no specific pathogen was isolated, therefore the pathophysiological origin of these opacities

could not be resolved and might be, besides undetected pathogens, due to GvHD, diffuse alveolar damage, organizing pneumonias or other pathologic processes. The differentiation from GvHD and other entities might only be possible by strict application of enforced invasive techniques (e.g. guided biopsies, VATS etc.). Nevertheless to sum up, if opacities in HRCT occured in these patients, pneumonia due to pathogens could be verified in a little more than half of these patients (55%), while the rest had to be defined as non specific pneumonia.

The types of additional radiological findings detected by HRCT besides the analysis of image patterns in accordance to the recommendations of the Nomenclature Committee of the Fleischner Society are shown in table 6.

	GROUP 1 (N)	GROUP 2 (N)	TOTAL
Pleural thickening	3	13	16
Pulmonary congestion	4	10	14
Atelektasis	5	15	20
Pleural effusion	3	72	75
Pericardial effusion	2	16	18
TOTAL	20	129	149

Table 6: Additional radiological HRCT findings

The most frequent additional finding in group one was atelectasis in 5/40 (13%) patients. Other findings included: pulmonary congestion in 4/40 (10%) patients, pleural effusion in 3/40 (8%) patients, pleural thickening in 3/40 (8%) patientsand pericardial effusion in 2/40 (5%) patients. The most frequent additional finding in group two was the detection of pleural effusions in 72/73 patients (99%). Other findings included: pericardial effusion in 16/73 (22%) patients, pulmonary congestion in 10/73 (14%) patients, atelectasis in 15/73 (21%)

patients and pleural thickening in 13/73 (18%) patients. More additional findings were described for patients in group 2 (126) in comparison to patients in group 1 (17).

The search for pathogen-specific image patterns by HRCT based on the criteria of the Fleischner Society revealed the picture displayed in table 7.

PNEUMONIA	FUNGAL	BACTERIAL	VIRAL	UN-SPECIFIC
Linear and reticular opacities				
Peribronchovascular interstitial thickening	7	0	0	5
Centrilobular peribronc. interstitial thickening	0	0	0	1
Interlobular septal thickening	2	3	0	0
Parenchymal bands	4	1	1	8
Intralobular interstitial thickening	8	9	2	10
Subpleural interstitial thickening	5	1	0	0
Subpleural line	0	0	0	1
Nodules and nodular Opacities				
Small nodules, Less than 1 cm	6	8	1	10
Large nodules, More than 1 cm	6	5	0	3
Masses, More than 3 cm	1	0	0	0
Less than 5	7	6	1	7
5 to 10	2	5	0	3
More than 10	1	1	0	0
Centrilobular Distribution	3	8	0	9
Centrilobular Rosettes	0	0	0	0
Perilymphytic Distribution	5	4	0	3
Tree-in-bud	4	4	2	5
Halo-Sign	3	1	0	2
Air Crescent	2	3	1	3
Increased lung opacities				
Focal ground-glass	13	7	3	24
Patchy ground-glass	11	6	1	8
Consolidation	10	8	2	10
Decreased lung Opacities				
Emphysema	3	3	0	1
Bullea, bigger than 10 mm	3	3	0	1
Bronchiectasis; Signet-ring sign	2	0	0	0

Table 7: Pathogen specific analysis of pulmonary image patterns in HRCT (in accordance to the recommendations of the Nomenclature Committee of the Fleischner Society)

The heterogeneity of these image patterns for bacterial, fungal, viral and unspecific pneumonia is illustrated in the figures 3-9.

The sensitivity, specificity and diagnostic accuracy of HRCT in the detection of fungal, bacterial and viral pneumonia was 86%, 75% and 80% respectively. Diagnostic accuracy increased to 83% when combined with results from follow-up HRCT. Table 8 summarizes the sensitivity, specificity and diagnostic accuracy of HRCT in the detection of fungal, bacterial and viral pneumonia in comparison to BAL, blood culture and serology.

	SENSITIVITY	SPECIFITY	DIAGNOSTIC ACCURACY
Initial CT	86%	75%	80%
Follow-Up CT	97%	55%	83%
BAL	57%	77%	63%
Blood culture	15%	88%	58%
Serology	61%	87%	54%

Table 8: Sensitivity, specifity and Diagnostic Accuracy of HRCT in detection of germ specific pneumonia

The following HRCT are demonstrating opacities found in patients of this study.

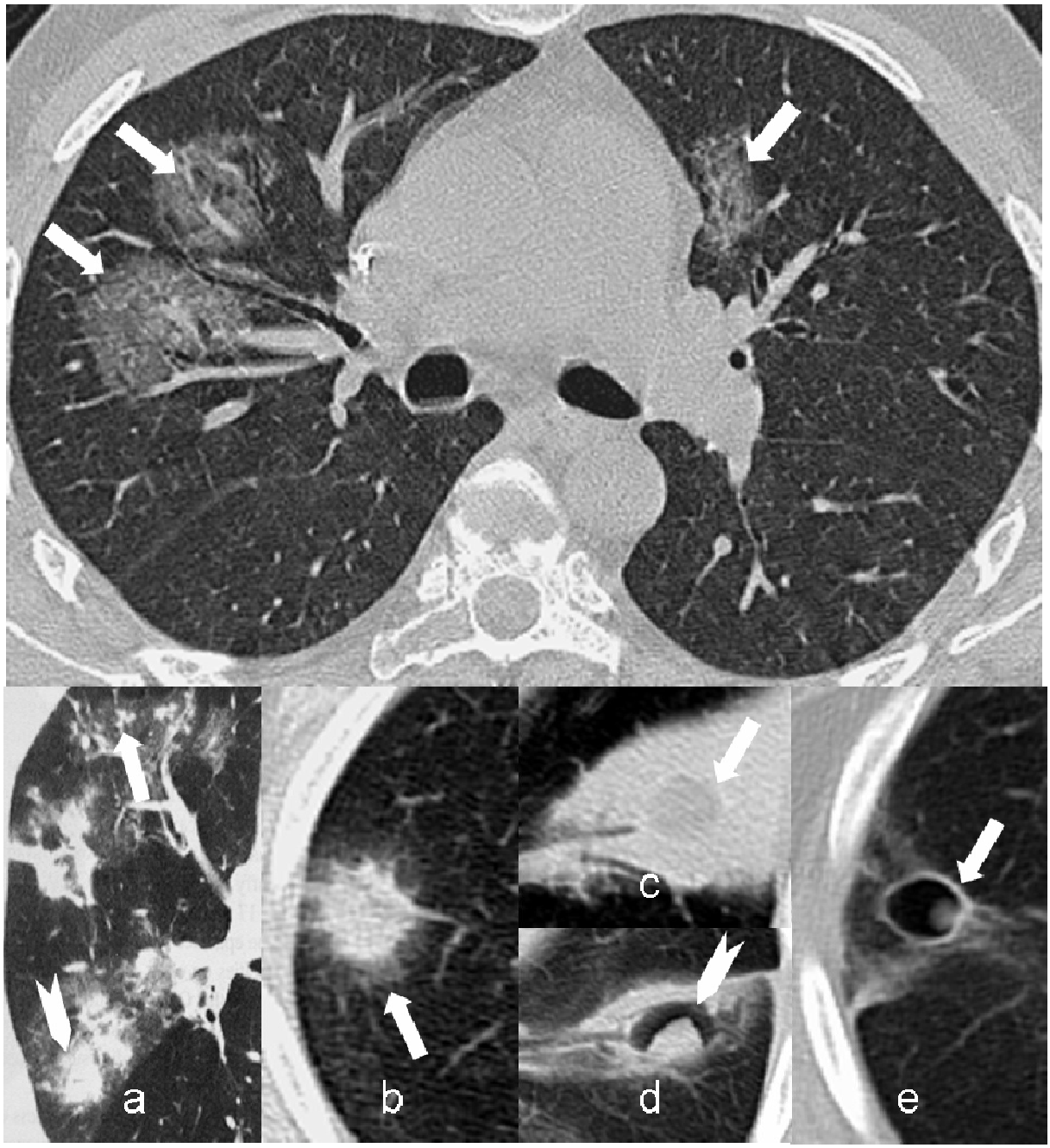

Figure 3: Aspergillus pneumonia

Figure 3 shows a female (56 yeards old) patient with multiple myeloma. Initial HRCT was performed 11 days after SCT and demonstrated large ground-glass attenuation nodules in the right and left side of the lung (*arrows*) which are typical for fungal pneumonia and

compatible with aspergillus pneumonia but which could also represent organizing pneumonia or other infections. Follow-up HRCT (a-e) in this patient revealed additional signs of aspergillus pneumonia such as (a) the development of multiple small (*arrow*) and large (*arrowhead*) nodules surrounded by (b) a halo sign (*arrow*) 16 days after SCT, representing invasive aspergillosis respectively haemorrhage of various causes, (c) an abscess (arrow) within a fungus ball 24 days after SCT, referring to a collection of intertwined hyphae, matted together by mucus, fibrin and cellular debris, (d) an air crescent sign (arrow) 30 days after SCT, standing for air separation of the outer wall of the lesion from the inner sequestrum and (e) an aspergilloma (*arrow*) 40 days after SCT, demonstrating a remaining opacity within a delineated cavity, representing proliferating fungus. The aspergillomas in this patient underwent resection by video-assisted thoracic surgery after 6 months. The BAL had confirmed aspergillus fumigatus on day 16 after SCT.

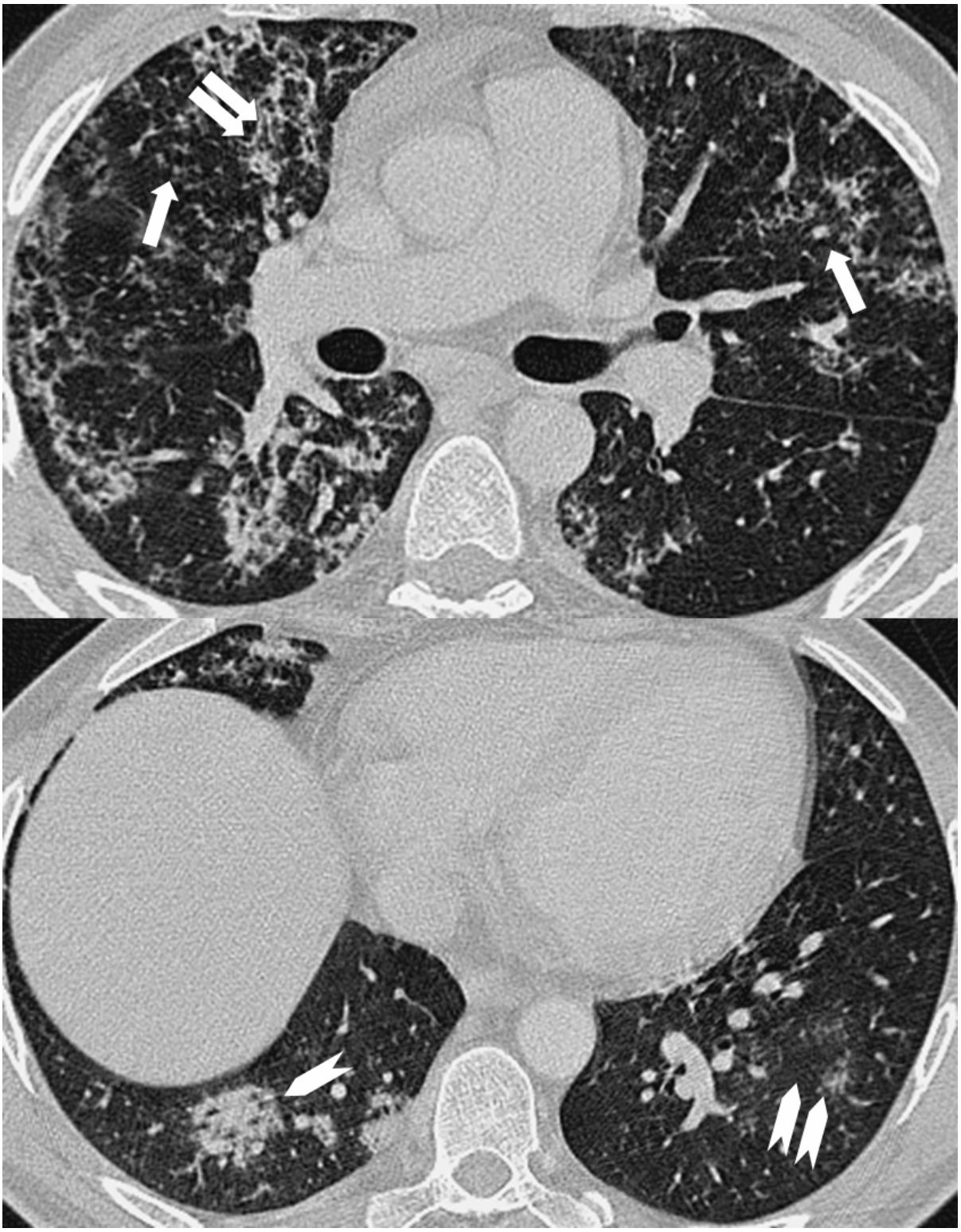

Figure 4: Candida pneumonia

Figure 4 shows a female (43 years old) patient with acute myeloid leukemia. The initial HRCT at 28 days after SCT showed bilateral small and large nodules (*arrows*) and reticular opacities (*double arrows*) which can be seen compatible with fungal pneumonia. A mass with more than 3 cm in diameter with consolidation (*arrowhead*) as well as patchy ground-glass pattern (*double arrowheads*) was also detected. The bronchoalveolar lavage confirmed Candida pneumonia on day 30 after SCT. This patient died 31 days after SCT.

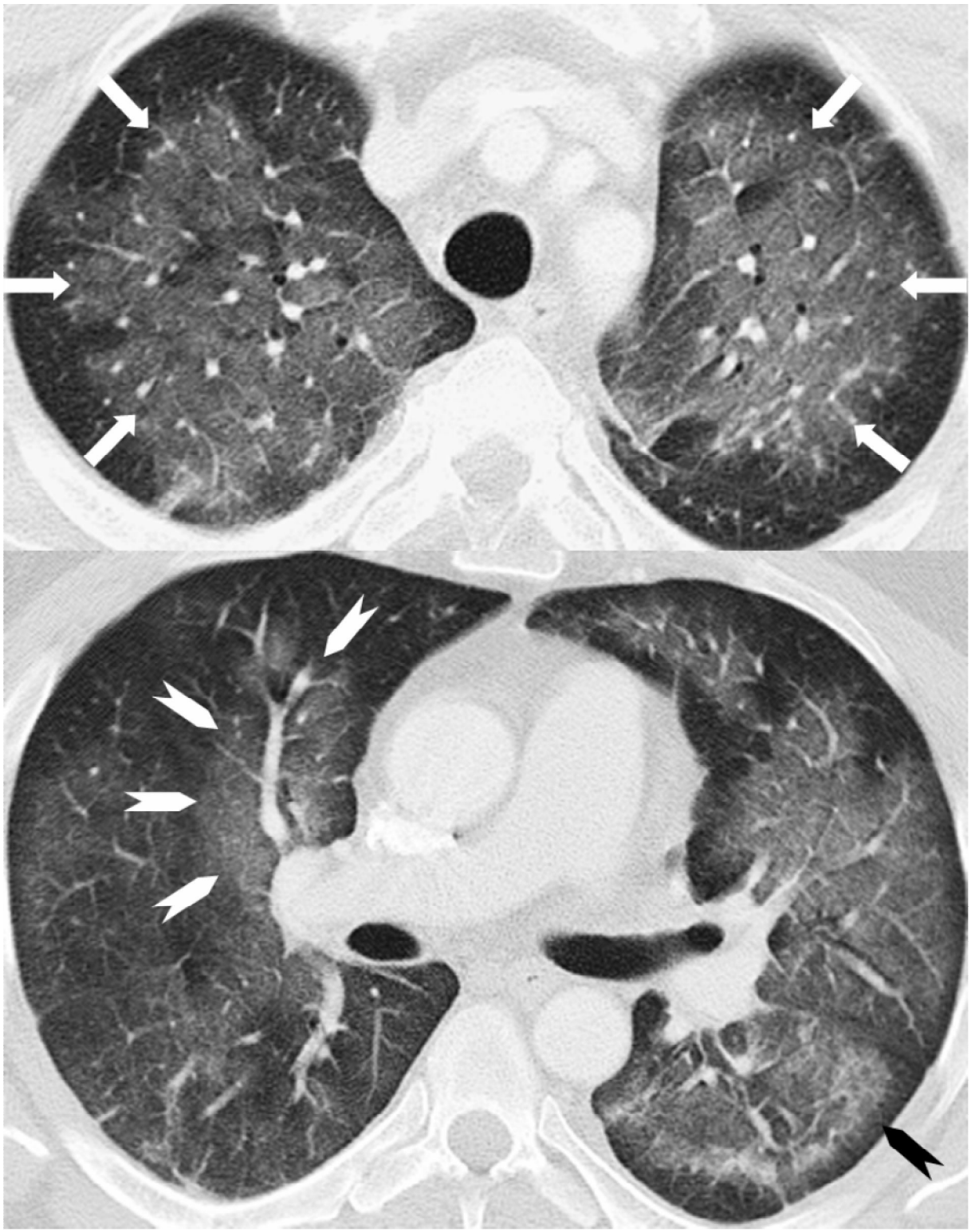

Figure 5: Pneumocystis jiroveci pneumonia

Figure 5 shows a male (43 years old) patient with Non Hodgkin lymphoma. First follow-up HRCT 22 days after SCT showed bilateral patchy ground-glass opacities (*arrows*) with a perihiliar distribution of lung involvement (*arrowheads*) and peripheral sub-pleural sparing (*black arrowhead*), morphologically compatible with an interstitial pneumonia, e.g. Pneumocystis jiroveci pneumonia. Bronchoalveolar lavage confirmed the diagnosis on day 9 after SCT. This patient died three months after SCT.

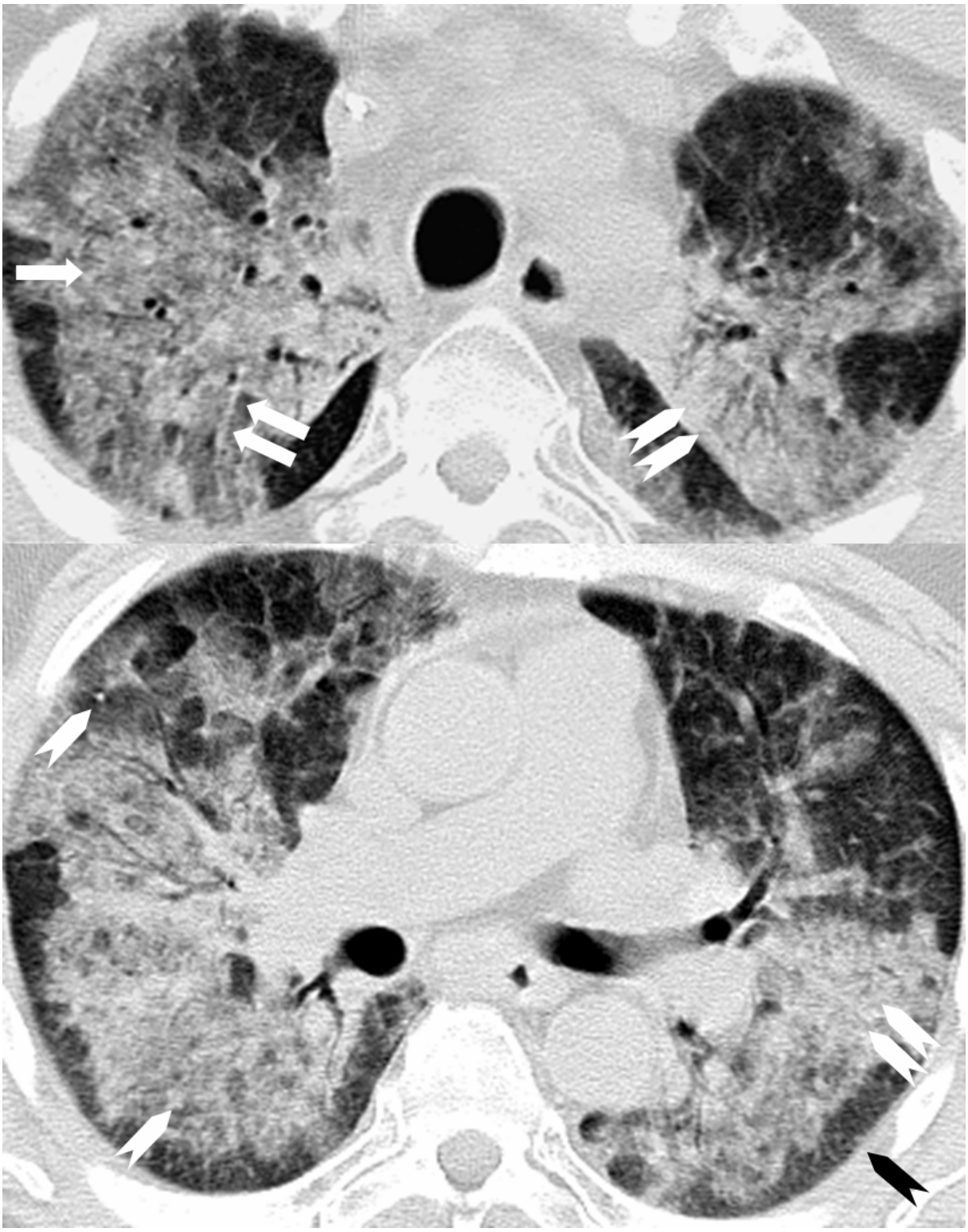

Figure 6: Cytomegalovirus pneumonia

Figure 6 shows a male (40 years old) patient with acute myeloid leukaemia. HRCT 16 days after SCT showed bilateral patchy ground-glass opacities (*arrow*), multiple small centrilobular nodules (*arrowhead*), thickened interlobular septa (*double arrows*), consistent with dilated lymphatics resulting from organization of intraalveolar exudates, large areas of consolidation in the lung apices and lower lobes (*double arrowheads*) and peripheral sub-pleural sparing (*black arrowhead*), morphologically compatible with an interstitial pneumonia, e.g. Cytomegalovirus pneumonia. Blood culture and bronchoalveolar lavage were negative but serology was positive for cytomegalovirus.

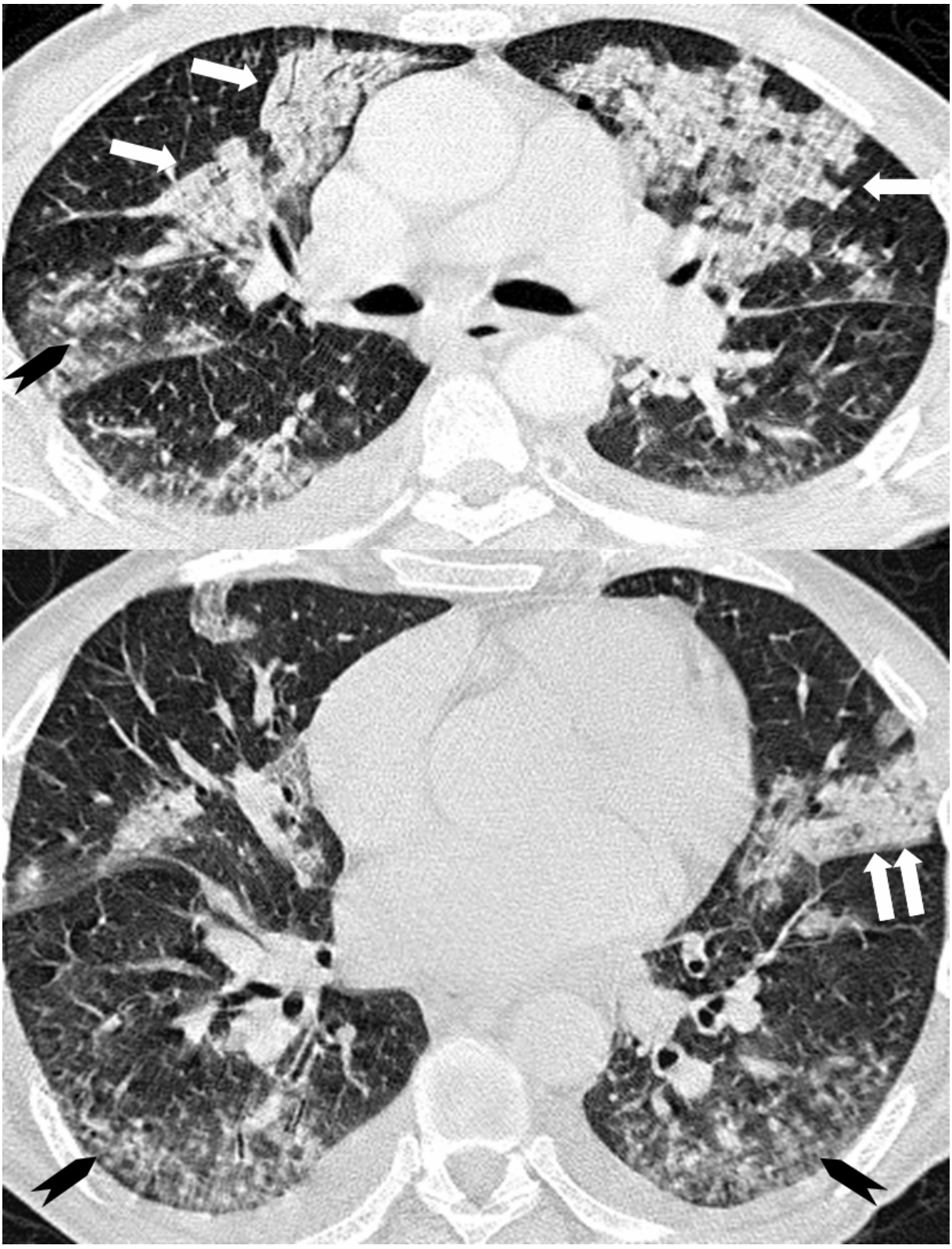

Figure 7: Pseudomonas aeruginosa pneumonia

Figure 7 shows a male (49 years old) patient with Non Hodgkin lymphoma. The initial HRCT 4 days after SCT showed patchy ground-glass opacities (*arrows*) and consolidation (double arrows), thickened bronchial walls (*arrowhead*) and centrilobular nodules in the lower lobes and the posterior right upper lobe (black arrowheads). Pleural effusion showed up as typical side finding of a bacterial pneumonia. Sputum culture was positive.

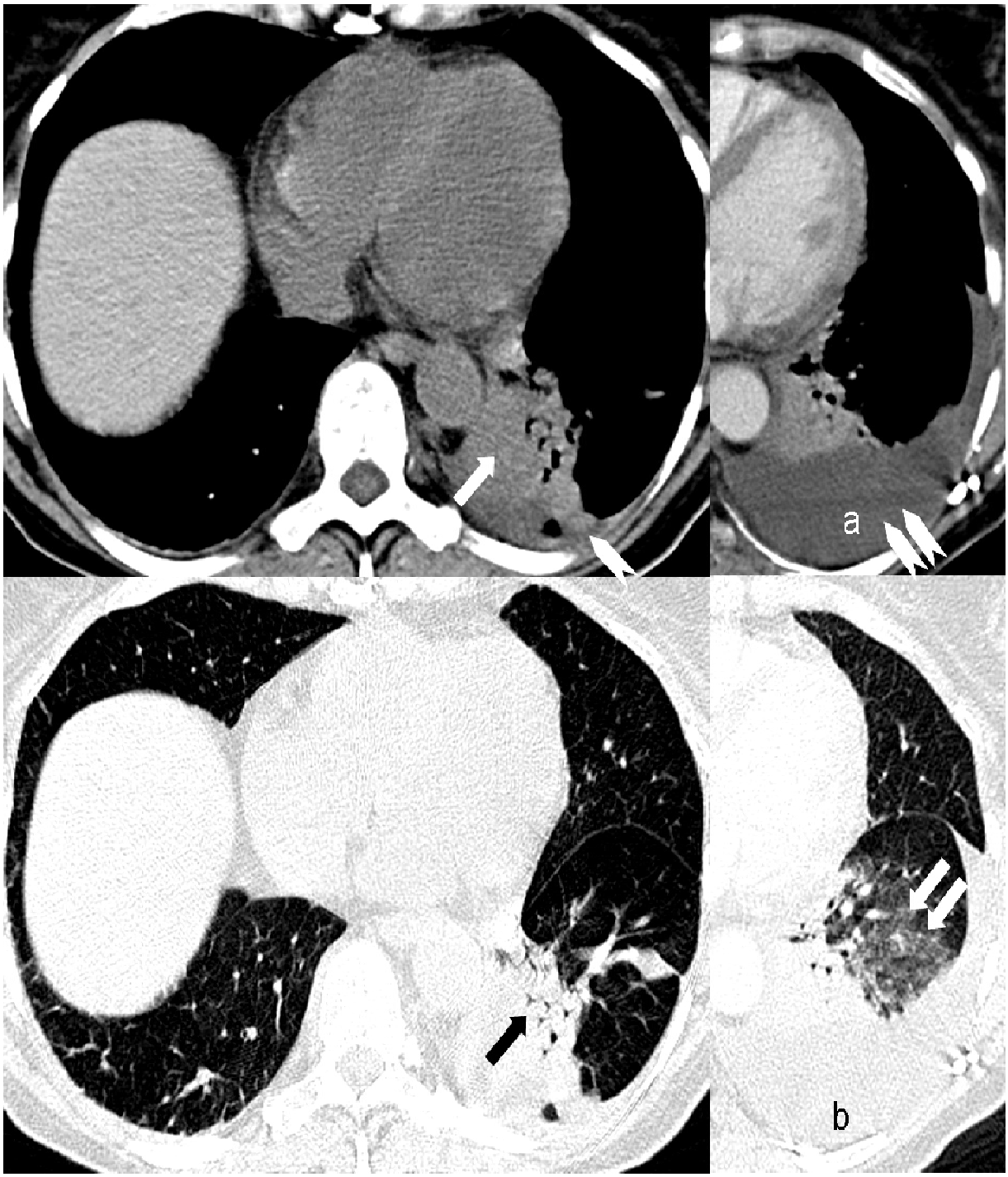

Figure 8: Staphylococcus pneumonia

Figure 8 shows a male (20 years old) patient with acute lymphocytic leukemia. HRCT 9 days after SCT demonstrated a segmental consolidation (*arrow*) with an air bronchogram (*black arrow*) accompanied by a slight pleural effusion (*arrowhead*). The pleural effusion (a; *double arrowheads*) was rapidly progressive such as accompanying opacities in the lower left lung lobe (b; *double arrows*) in the follow-up HRCT two days later. The blood culture was positive for staphylococcus pneumonia. Microbiological work up of the venous catheters showed no indices for a venous catheter infection in this patient.

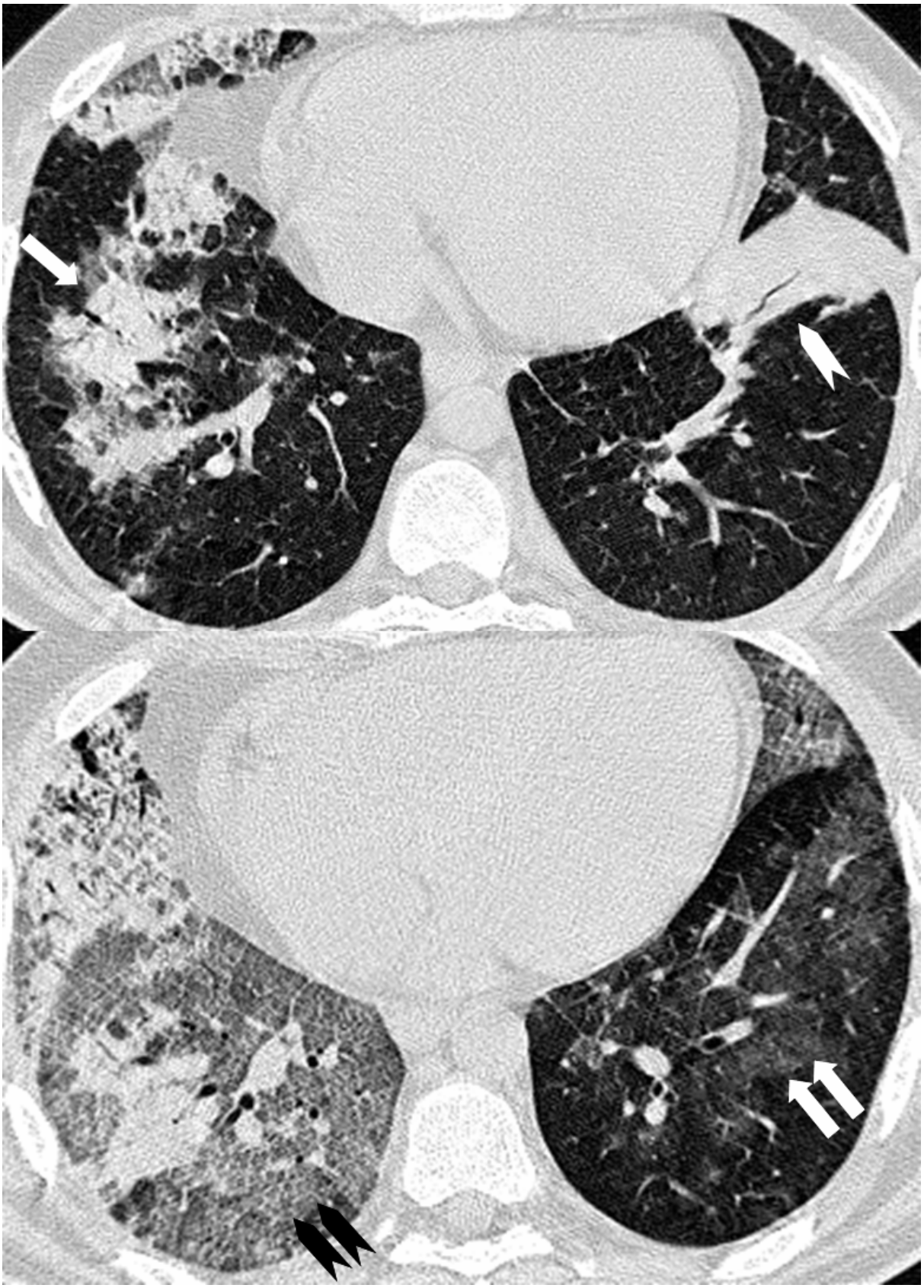

Figure 9: Non specific pneumonia

Figure 9 shows a male (62 years old) patient with acute myeloid leukemia. HRCT 18 days after SCT demonstrated a heterogeneous picture with patchy large nodules (*arrow*), accompanying interstitial thickening, consolidations (*arrowhead*), partly with an air bronchogram and more or less intense ground glass opacities (*arrows, arrowheads*). A pleural effusion was not existent. The HRCT image pattern was suggestive for fungal pneumonia but could be also consistent with organizing pneumonia. Blood culture, bronchoalveolar lavage and serology remained negative and could not isolate a specific pathogen. Therefore this pneumonia was categorized as unspecific pneumonia. The patient died 26 days after SCT due to respiratory failure.

Discussion

The aim of this study was to evaluate the roles of HRCT in monitoring pulmonary complications after SCT during the aplastic phase, and in the identification of pathogen specific pneumonias. This study showed that HRCT had a sensitivity of 86%, specificity of 75% and a diagnostic accuracy of 80% for the diagnosis of pneumonia. The sensitivity and diagnostic accuracy improved to 97% and 83% respectively with the development of more specific image patterns on follow up HRCT.

The prediction of specific pathogen (fungal, bacterial, viral) in follow-up HRCT was correct for 17/40 (43%) patients with pulmonary opacities after SCT. The initial HRCT could confirm a pathogen-specific pneumonia for 10/40 (25%) patients. Bronchoscopy with BAL led to a correct diagnosis of a specific pathogen in 22/40 (55%) patients with pulmonary opacities, and was the examination with the highest positive yield followed by HRCT. It is a limitation of our study that only 37/73 patients in group 2 and 6/40 patients in group 1 underwent bronchoscopy with BAL, but this represents the normal clinical setting, due to the fact that some patients have contraindications for bronchoscopy (e.g. thrombopenia, respiratory insufficiency etc.) in the early phase after SCT. Bronchoscopy with BAL might represent the most accurate reference standard but nevertheless it is still not feasible in all patients at any time after SCT due to these clinical contraindications.

The additional radiological findings revealed by HRCT (table 6) were important in terms of leading to a change and tailoring of therapy such as drainage of pleural effusions and diuresis of pulmonary congestion due to fluid overload, as is commonly seen after SCT and conditioning.

Data concerning the main specific pathogens causing pneumonia in patients after SCT remain sparse [4, 7-8, 21-23, Heussel et al. 2004, Hayes-Jordan et al. 2002, Chandrasekar et al. 1995, Heussel et al. 1999, Tanaka et al. 2002 and Webb et al. 1988]. Fungi such as aspergillus fumigatus also appear to play a key role, although in our study candida species were found more frequently. Altogether 19/73 (26%) had fungi isolated as cause of pneumonia. Candida and aspergillus were isolated in 13/73 (18%) and 5/73 (7%) cases respectively. Pneumocystis jiroveci pneumonia was isolated in 1/73 (1%) cases. The next most common etiology was bacterial pneumonia (23%). In 8/73 (11%) cases staphylococci were isolated and 2/73 (3%) patients developed pneumonia due to streptococci. Enterobacteriacea were present in 3/73 (4%) cases. Escherichia coli occurred in 2/73 (3%) pneumonia. Pseudomonas aeruginosa and Klebsiella each accounted for 1/73 (1%) pneumonia. Cytomegalovirus was detected in 4/73 (5%) patients.

The extensive search for pathogen-specific image patterns by HRCT based on the criteria of the Fleischner Society revealed a very heterogeneous picture (table 7). Contrarily to the literature our results did not satisfactorily correlate specific image patterns to a typical pathogen. The limited pooling of patients for each pathogen category is an inevitable limitation of our study which could only be solved by a multicenter approach. Image patterns of initial HRCT were especially complex to evaluate because the opacities were at an early stage. The development of typical patterns in HRCT like a specific reticular pattern for CMV/PCP-pneumonia could not be confirmed in our study population [4, Heussel et al. 2004]. Follow-up HRCT within 60 days seemed to be more reliable for the emergence of specific image patterns. There was a subtle difference in reticular image pattern for fungal and bacterial pneumonia. Intralobular interstitial thickening was found in 8/19 (42%) fungal

pneumonia and in 9/17 (53%) bacterial pneumonias. Peribronchovascular thickening was seen in 7/19 (37%) cases of fungal pneumonia but not in bacterial pneumonia. Nodular image pattern were comparable between fungal and bacterial pneumonia. Six small and 6 large nodular patterns were found in 19 (32%) fungal pneumonia. In the bacterial group 8 small and 5 large nodular patterns could be detected in 17 cases (47% and 29% respectively) of pneumonia. We found a remarkable difference in nodular distribution between fungal and bacterial pneumonia. The nodules in fungal pneumonia showed a more perilymphytic distribution. The nodules in bacterial pneumonia were more centrilobular distributed. 13 focal and 11 patchy ground-glass opacities were found among 19 cases of fungal pneumonia. Within 17 bacterial pneumonia 7 focal and 6 patchy ground-glass opacities could be detected. A consolidation showed up in 10/19 (53%) fungal pneumonia and in 8/17 (47%) bacterial pneumonia respectively. Viral pneumonia demonstrated nodular and reticular image pattern, with partly ground-glass consolidation.

The limitation of our study is that only 40 patients had verification of specific pathogens, out of 113 patients. Hence not all patients with pulmonary opacities could be categorized to a pathogen-specific pneumonia and hence could not be analyzed according to the pathogen-specific image pattern classification. The term –non specific pneumonia was used. For these cases, the diagnosis of pneumonia was made on basis of computed tomography; appropriate microbiological results may be possible only by autopsy or a biopsy in these cases. It is also possible that toxic epithelium damage with alveolitis of the corresponding lung-area caused those cases [12-16, 19-21, Thirmann et al. 1992, Kleinau et al. 1997, Kanda et al. 1997, Baron et al. 1998, Kanamori et al. 2001, Heussel et al. 1996, Heussel et al. 1997 and Heussel et al. 1999]. A systematic invasive approach (e.g. guided biopsy, VATS etc.) in patients with “non specific” and even pathogen-specific pneumonias might have provided additional specific

diagnoses of pulmonary disease but would need a separate ethical committee approval. Larger multicenter studies may help to address these limitations.

The schemata for diagnostic imaging and prophylactic therapy of stem cell transplanted patients follow the guidelines of various study groups like the “Infectious Diseases Working Party” (AGIHO) of the German Society of Haematology and Oncology (DGHO). The problem of pulmonary infections after stem cell transplantation must be taken very seriously because of the high mortality. Published data remain limited due to the limited number of stem cell transplanted patients worldwide and are often just single case descriptions or small case series with the exception of studies from Heusel et al. and Escuissato et al [4, 19-21, 30, Heussel et al. 2004, Heussel et al. 1996, Heussel et al. 1997, Heussel et al. 1999 and Escuissato et al. 2005]. However, in our experience in these patients bacterial pneumonia is characterized by segmental and lobar nodular patterns with the development of consolidations and pleural effusions in the early phase, fungal pneumonia is characterized by the development of the typical air crescent sign, the halo sign, bronchiectasis and aspergilloma in the follow-up and viral pneumonia is characterized by ground glass opacifications and centrilobular nodules in the early phase, as well as reticular patterns and consolidations in the late phase. Bacterial and fungal pneumonia develop in the early phase after SCT, while viral pneumonias are more common in the late phase after SCT. Overall viral pneumonias are rare compared to fungal and bacterial pneumonias after SCT during aplasia. In nearly half of all cases no pathogen was isolated despite an enforced diagnostic approach including bronchoscopy with a microbiological work up. This may dictate that less imaging, rather than more, is appropriate in this setting. In this respect, our study will add to current available data.

There is a lot of overlap of imaging findings. Nevertheless a standardized interpretation of the HRCT findings can improve the pathogen specific diagnosis of pneumonia by HRCT in the subgroups of bacterial, fungal and viral pneumonia, as shown by relatively satisfactory values for the sensitivity and diagnostic accuracy of HRCT. Therefore HRCT represents an advance in the evaluation of pathogen-specific pneumonia in this clinical setting of patients with fever of unknown origin in the early phase after SCT during aplasia. It will have to be shown in larger series as currently published [34-36, Coppenrath et al. 2004, Dorffner et al. 2005, Wendel et al. 2005] that HRCT with low dose for example, as performed according to the National Lung Screening Trial, could have been just as helpful as this study which exposed the patients to higher radiation doses and exposed these patients to the risk of intravenous contrast administration at least once. Establishing a control group of patients managed without results of HRCT was declined by the responsible clincians of our transplantation centre and by our ethical committee. As a consequence, we extracted data from this study to further investigate the role of radiation dose reduction in an additional experimental study performed at our institution [37, Yamamura et al. 2009]. This study concluded that for the evaluation of pneumonia in immunocompromised patients, MSCT examinations of the chest can be performed with 25 mAS. Thus, radiation exposure was reduced to a quarter compared to the standard protocol. Therefore we changed our protocol at our institution in the meantime, by performing a helical baseline HRCT with the common dosage protocol and low-dose HRCTs in the follow-up when opacities occur in the neutropenic phase after SCT.

To conclude, HRCT appeared useful in the detection of pathogen-specific pneumonia and in monitoring pulmonary complications in the neutropenic phase after SCT.

Abstract

Purpose: To evaluate the role of high resolution multislice computed tomography (HRCT) in the detection and monitoring of pulmonary infections after stem cell transplantation.

Materials and Methods: Over a 5-year period, 113 patients (52f/61m, mean age 46 years, range, 19-77) with fever of unknown origin after stem cell transplantation underwent examination by a multi-detector row HRCT for evaluation of possible pneumonia in a prospective study. A baseline HRCT was performed in 19/113 of these patients before stem cell transplantation due to a high risk profile, and 61/113 patients underwent follow-up HRCT within 60 days after stem cell transplantation. The standard for comparing the diagnosis of pneumonia with the radiological findings in a total of 232 HRCT was based on combination of bronchoscopy, biochemistry and microbiological data.

Results: HRCT detected pulmonary opacities in 73/113 patients after stem cell transplantation (19/73 fungal pneumonia, 17/73 bacterial pneumonia, 4/73 viral pneumonia, 33/73 non specific). The sensitivity, specificity and diagnostic accuracy of HRCT for pneumonia was 86%, 75% and 80% respectively. Diagnostic accuracy increased to 83% when follow-up HRCT was performed.

Conclusion: HRCT was useful for detection and monitoring of pulmonary infections after stem cell transplantation.

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Curriculum vitae

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