Radiological CT Patterns and Distribution of Invasive Pulmonary Aspergillus, Non-Aspergillus, Cryptococcus and Pneumocystis Jirovecii Mold Infections – A Multicenter Study

Radiologische Muster und Verteilung in der CT bei invasiven pulmonalen Aspergillus-, Nicht-Aspergillus-, Kryptokokken- und Pneumocystis-jiroveci-Pilzinfektionen – eine Multicenterstudie

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ZUSAMMENFASSUNG

Ziel Systematische Analyse der CT-Muster bei invasiven pulmonalen Pilzinfektionen in Abhängigkeit vom Immunstatus und dem klinischen Outcome der Patienten.

Material und Methoden In dieser retrospektiven Multicenterstudie wurden 85 konsekutive Patienten mit invasiver pulmonaler Pilzinfektion eingeschlossen (2011–2014). Die CT-Muster der Lunge wurden gemäß dem Glossar der Fleischner-Society klassifiziert. Die Patienten wurden nach Immunstatus (Neutropenie, Steroidtherapie, Organtransplantation und andere Ursachen) und Outcome (positiver Verlauf, progrediente Erkrankung und Tod) unterteilt. Der Chi-Quadrat- und der Fischer-Exact-Test wurden mit der Bonferroni-Korrektur angewandt.

Ergebnisse Die Anzahl der Patienten mit invasiver Aspergillus- und Nicht-Aspergillus-Infektion (IANA), Pneumocystis-jirovecii-Pneumonie (PCP) und Kryptokokken (CRY) betrug jeweils 60, 22 und 3. Die IANA-Patienten wiesen signifikant häufiger Lungenknoten (93 % vs. 59 %; p = 0,001), signifikant weniger Milchglastrübungen (58 % vs. 96 %; p = 0,005) und signifikant weniger pathologische Lymphknoten auf (5 % vs. 41 %; p < 0,001) als Patienten mit PCP. Alle Patienten mit PCP und CRY zeigten einen positiven Verlauf. Bei IANA-Patienten waren Knoten mit Halo-Zeichen häufiger assoziiert mit negativem (Progress, Tod) als mit positivem Verlauf (42,5 % vs. 15,9 %; p < 0,0001). Interessanterweise zeigten Patienten mit positivem Verlauf häufiger Lungeninfarkte als Patienten mit negativem Verlauf (8 % vs. 1 %; p = 0,047). Patienten mit Neutropenie litten signifikant mehr an Lungeninfiltraten (Konsolidierungen, 66 %) als Patienten nach Organtransplantation (27 %; p = 0,045).

Schlussfolgerung IANA-Patienten zeigten eine höhere Prävalenz von Lungenknoten und eine tiefere Prävalenz von Milchglastrübungen im Vergleich zu PCP-Patienten. Bei den IANA-Patienten waren die Noduli mit Halo-Zeichen mit einem schlechteren Verlauf assoziiert. Patienten mit Neutropenie zeigten generell mehr Infiltrate, diese waren allerdings nicht mit negativem Verlauf assoziiert.

Kernaussagen:
- Lungenknoten, Milchglastrübungen und Konsolidierungen sind häufige CT-Zeichen bei allen invasiven pulmonalen Pilzinfektionen.
- Es gibt kein CT-Muster, das einzigartig ist für einen bestimmten Erreger, obwohl Lungenknoten häufiger bei

- IANA und Kryptokokken vorkommen und Milchglastrübungen häufiger bei PCP-Infektionen zu beobachten sind.
  - Der Immunstatus der Patienten beeinflusst die CT-Befunde der Pilz-Pneumonie: Patienten zeigten nach Organtransplantation weniger Konsolidierungen als Patienten mit Neutropenie.
  - Noduli mit Halo-Zeichen sind mit einem schlechteren Outcome assoziiert.

ABSTRACT

Purpose Clinical signs and symptoms related to invasive fungal disease are nonspecific and need to be followed up by appropriate diagnostic procedures. The goal of this study was to analyze CT imaging patterns in invasive fungal infections and their correlation with the immune status and clinical outcome.

Materials and Methods We performed a retrospective multicenter study including 85 consecutive patients with invasive pulmonary fungal infection (2011–2014). Lung patterns on computed tomography (CT) scans were classified according to the Fleischner Society glossary. The patients were grouped according to immune status (neutropenia, steroid therapy, organ transplant recipient, and other cause) and outcome (positive outcome, progressive disease, and death). The Chi square test or Fisher exact test was used. Bonferroni correction was applied.

Results The total number of patients with invasive Aspergillus and non-Aspergillus infection (IANA), Pneumocystis jirovecii pneumonia (PCP), and Cryptococcus (CRY) was 60, 22, and 3, respectively. Patients with IANA demonstrated significantly more nodules (93 % vs. 59 %, p = 0.001), significantly fewer ground glass opacities (58 % vs. 96 %, p = 0.005), and significantly fewer positive lymph nodes (5 % vs. 41 %, p < 0.001) than patients with PCP. All patients with PCP and CRY had a favorable outcome. Patients with IANA and an adverse outcome demonstrated significantly more nodules with halo sign than patients with IANA and a favorable outcome (42.5 % vs. 15.9 %, p < 0.0001). Interestingly, patients with IANA and a favorable outcome had a higher prevalence of pulmonary infarction than patients with an adverse outcome (8 % vs. 1 %, p = 0.047). Patients with neutropenia showed significantly more consolidations (66 %) than organ transplant recipients (27 %, p = 0.045).

Conclusion Patients with IANA showed a higher prevalence of nodules and a lower prevalence of ground glass opacities than patients with PCP. In patients with IANA, nodules with halo sign were associated with an adverse outcome. Patients with neutropenia showed generally more consolidations, but the consolidations were not associated with an adverse outcome.

Key Points:
- Nodules, ground glass opacities, and consolidations are common CT findings in all invasive pulmonary fungal infections.
- There is no pattern that is unique for one specific pathogen, although nodules are more predominant in IANA and Cryptococcus, and ground glass opacities are more predominant in PCP patients.
- Immune status had an impact on CT findings in fungal pneumonia with less consolidation in patients after organ transplantation compared to patients with neutropenia.
- Nodules with a halo sign are associated with a worse outcome.

Introduction
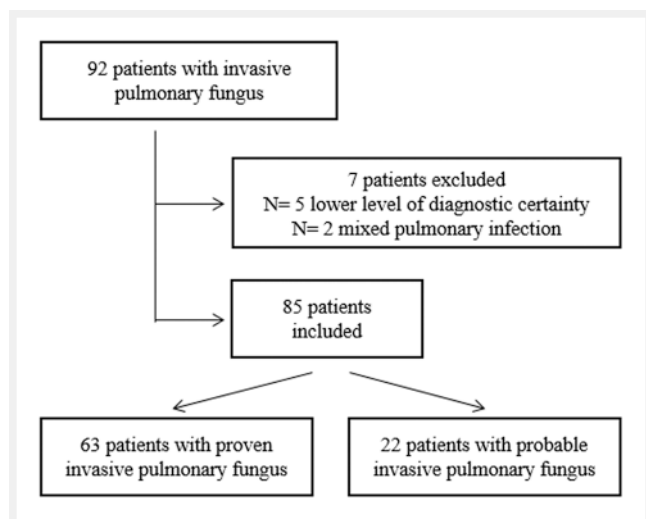
Opportunistic fungal infections of the lung are a common complication in immunocompromised patients and are related to a high morbidity and mortality [1, 2]. Therefore, early and accurate diagnosis of invasive fungal infection (IFI) is important to improve patient survival [3, 4]. When neutropenia lasts more than 7 days, fungal infections may occur (aspergillosis, candidiasis, mucormycosis) [5–7]. The clinical diagnosis of fungal pulmonary infection is based on host factors (i. e., immune status, neutropenic fever), clinical signs (unexplained fever despite broad-spectrum antibiotics), microbiological evidence of infection, and specific patterns on computed tomography (CT) imaging [1, 8–10]. Clinical signs and symptoms related to IFI (i. e. cough, pleural pain, or hemoptysis) are nonspecific and need to be followed up by appropriate diagnostic procedures as part of an integrated care pathway consisting of daily physical examination, microscopy, and mycological culture of all samples, serum, and bronchoalveolar lavage (BAL), Galactomannan (GAL) antigen assay, serum (1–3)-β-D-Glucan (BDG), and high-resolution CT (HRCT) [11–14]. CT plays an important role in the diagnosis and management of patients with pulmonary fungal infections due to its ability to depict disease at an early stage [15].

Chest CT has provided important clues regarding the clinical suspicion and early treatment of invasive mold pneumonia in immunocompromised patients [16]. CT findings in fungal infections such as multiple nodules, ground glass opacities, and (reverse) halo sign are due to parenchymal invasion of the fungus hyphae and/or parenchymal infarctions due to invasion of the pulmonary vessels and are thus seen earlier [15]. Legouge et al. reported that the reverse halo sign was present in 15 (94 %) of 16 patients with pulmonary mucormycosis during the first week of the disease, and the authors proposed that the reverse halo sign could be a sensitive sign for pulmonary mucormycosis, especially early in the disease [17]. However, this could not be confirmed by other authors, making the reverse halo sign relatively nonspecific [18].

▶ **Fig. 1** Patient flowchart.

▶ **Abb. 1** Flussdiagramm der eingeschlossenen Patienten.

The aim of this study was 1) the systematic CT pattern mapping of all invasive fungal infections of the lung in a current consecutive cohort, 2) the depiction of predictive CT findings associated with a positive (regression) or negative outcome (progression or death), 3) to assess the influence of the immune status of patients (neutropenia, high-dose steroid therapy, organ transplant, other) and the infective agent on the CT patterns.

Materials and Methods

Patient population

Chest CT images of 92 consecutive patients with invasive fungal infection were included in this retrospective multicenter study. Informed consent was waived due to the retrospective nature of the study. All adult patients at the three institutions (tertiary referral hospitals) who met the criteria for mold infection – Aspergillosis (IPA, Invasive Pulmonary Aspergillus), non-Aspergillus invasive mold infection (NAIMI, such as Mucormycosis agents), Cryptococcosis (CRY) – according to the 2008 EORTC/MSG criteria as well as patients with Pneumocystis jirovecii Pneumonia (PCP) (proven with immunofluorescence only) were enrolled [10].

The inclusion criteria were a proven or probable fungal infection and a chest CT within one week of the date of diagnosis. We excluded patients with a lower level of diagnostic certainty (possible infection) and those with mixed pulmonary infections (i. e., bacterial or viral co-infections) from our analysis. 85 patients met the criteria (▶ Fig. 1): 39, 33, and 13 patients were recruited at centers 1, 2, and 3, respectively. 63 patients with proven invasive pulmonary fungus and 22 with probable invasive pulmonary fungus were included.

The study population was categorized by type of fungal infection, and four subgroups depending on immune status were built: 1) Neutropenia: neutropenia at the time of CT examination regardless of underlying disease (n = 44). Etiologies for neutropenia were acute myeloid leukemia (AML) (n = 14), chronic lymphocytic leuke-

mia (CLL) (n = 8), non-Hodgkin's lymphoma (NHL) (n = 5), acute lymphocytic leukemia (ALL) (n = 4), chemotherapy, and other rare disease like multiple myeloma, plasmacytoma, and Hodgkin's disease (n = 13). 2) High-dose steroid therapy applied in cases of malignancies, organ transplant, and different rheumatologic or autoimmune diseases (n = 36). 3) Organ transplant recipients (OTR) (n = 11, with n = 7 kidney and n = 4 lung transplant). 4) All other underlying diseases not fitting into one of the previous categories suffering from invasive fungal pneumonia such as HIV infection (n = 3), malignancy (n = 1), COPD (n = 5), tuberculosis infection (n = 1), and autoimmune disease (n = 2). If a patient matched two immune status groups, the pulmonary findings counted in both groups.

Patients with IANA infection were subdivided into the 4 clinical outcome groups: 1) 29 with positive outcomes, 2) 4 with progressive disease, 3) 14 with death due to other causes and 4) 6 with death due to infection; the remaining 7 patients were lost to follow-up.

Imaging acquisition and interpretation

Chest CT studies at the time of initial diagnosis of mold infection were evaluated. Images were acquired with 16, 64, and 128 row CT scanners using a tube voltage of 80–120 kV and automatic tube current modulation (with reference mAs between 80 and 120 mAs or similar noise levels). The slice reconstruction thickness was 1 or 2 mm. IV contrast agent was applied in 36 of the 85 CT scans (e. g., for additional assessment of pulmonary embolism or empyema). The following CT models were used (the number of patients per scanner is indicated): Somatom Definition Flash (n = 28), Somatom Definition AS+ (n = 13), Somatom Definition Edge (n = 13), Somatom Sensation 64 (n = 6) by Siemens (Siemens Healthineers, Erlangen, Germany); GE Light Speed VCT (n = 12), GE Discovery STE (n = 6), GE Bright Speed S (n = 2) by General Electrics (GE, Milwaukee, WI, USA); Toshiba Aquillion (n = 3) by Canon (Canon Medical Systems Corporation, Otawara, Tochigi, Japan) and Philipps Brilliance 64, (n = 2) by Philips (Philips, Best, The Netherlands). Images were anonymized and randomized before radiological reading. All rating was done on a digital Picture Archiving System (PACS) workstation. All cases were read centrally by two independent teams of radiologists, with each team consisting of a resident and a senior consultant thoracic radiologist with five and eight years of experience, respectively. Discordant results between the two rating teams were resolved by consensus read-out amongst the four radiologists. The readers were blinded to the patient demographics and clinical outcomes. Lung patterns were classified as follows: consolidation (±bronchogram, ±enhancement, ±halo sign, wedge-shaped peripheral infarction); ground glass opacity (diffuse, patchy or mosaic); nodules (<5 mm, 5–10 mm, >10 mm, halo sign, lobulated, spiculated, cavitary ±air crescent sign, calcified); interstitial patterns (reticulation, centrilobular, perilymphatic nodules); and bronchial findings (wall thickening, bronchiectasis, tree-in-bud, bullae, and cysts (see table in appendix)) [19]. Each of the five lobes was analyzed separately. The axial distribution was noted as central predominant (inner 1/3 of the lungs), peripheral predominant (outer 2/3 of the lungs), or diffuse and ±subpleural sparing. Angioinvasivity was defined as the presence of infarction and the halo or crescent sign. The probability of invasive mold infection was estimated

by the readers as < 25 %, < 50 %, < 75 %, and over 75 % according to the presence of nodules with the halo sign in the upper lobes and the previously mentioned signs of angioinvasivity. Furthermore, additional findings such as lymphadenopathy (mediastinal or hilar nodes > 1 cm) and pleural effusions were noted.

Clinical findings/diagnostic workup

Proof of invasive pulmonary fungus was established based on the identification of fungal hyphae from BAL, needle aspiration, or in biopsy specimen. Probable IPA was established with a combination of one host factor (< 500 neutrophils for more than 10 days, persistent fever above 38 °C, graft-vs.-host disease or use of steroids for longer than 3 weeks) and one microbiological criterion (i. e., mold detection in culture from BAL, sputum, or sinus aspirate specimens) and one major (or two minor) clinical criteria [9]. The major factors included CT finding of halo sign, air crescent sign, cavity in consolidation, whereas minor factors were the presence of cough, chest pain, hemoptysis, dyspnea, pleural rub, pleural effusion, or consolidation [9]. Neutropenic patients with invasive fungal infections were defined as those patients who received chemotherapy for acute leukemia, lymphoma, or aplastic anemia while having an absolute neutrophil count < 500 cells/mm^3 within 30 days prior to diagnosis of IFI [10].

The outcome after 6 weeks was classified according to Herbrecht et al. [20] and additional categories were implemented (death due to invasive pulmonary fungus or other cause). Complete response was defined by the resolution of all clinical signs and symptoms and more than 90 percent of the lesions due to invasive aspergillosis that were visible on CT. Partial response was defined by clinical improvement and > 50 % improvement in findings on radiology. Stable response was defined by the absence of change from baseline or an improvement of < 50 %. Failure of therapy was defined by worsening disease based on imaging or fatal outcome. For the statistical analysis, the patients were divided into four groups: 1) positive outcome (complete, partial, and stable response); 2) progressive disease 3) death due to causes other than infection; and 4) death due to infection.

Statistical methods

IPA and NAIMI were pooled together into the group of invasive Aspergillus and non-Aspergillus infections (= IANA). The prevalence and distribution of the chest CT patterns of IANA, PCP, and Cryptococcus were analyzed individually. For these three fungal agents, a separate pattern analysis was performed according to the patient's immune status. In addition, patterns were cross-referenced with a positive versus a negative outcome (outcome 1 vs. 2–4). As PCP and Cryptococcus always had a favorable outcome, their outcome was not subdivided. A separate pattern analysis was performed for all included IANA cases versus only the proven IANA cases (probable infections were excluded). The Chi square test or Fisher exact test was used when appropriate. The pattern and distribution were analyzed per patient and per lobe. A Bonferroni correction was made according to the number of patterns examined. For the analysis among the different subgroups of immune status, a correction factor of 3 was applied for the main patterns (consolidations, GGO, and nodules). All tests of significance were two-tailed, and a p-value of < 0.05 was considered to indicate statistical significance. Calculations were performed with MedCalc version 16.4.3 (MedCalc Software, Ostend, Belgium).

Results

Patient characteristics

The mean age of the 85 included patients (54 males) was 60 ± 15 years (range: 20 to 82 years). The total number of patients with IANA, PCP, and Cryptococcus was 60, 22, and 3, respectively (▶ Table 1). Immune status categorization revealed the following numbers per group 1) neutropenia (n = 44), 2) steroid therapy (n = 36), 3) OTR (n = 11, 7 kidney and 4 lung). 4) other diseases (n = 17).

Stratified according to immune status – per patient

Consolidations

Overall, the consolidation pattern was seen in 65.9 % of cases in the neutropenic group, followed by the steroid group with 44.4 %, OTR with 27.3 %, and the group of various diseases with 52.9 % (▶ Fig. 5). OTR vs. neutropenia was significant with a p-value of 0.045. In patients under steroid therapy, patients suffering from PCP demonstrated a significantly lower incidence of consolidations (11.1 %) compared to IANA patients (57.7 %, p-value = 0.045).

GGO

There was no significant difference in GGO incidence among the various groups of immune status (54.5–76.5 %, ▶ Fig. 5). However, patients with PCP demonstrated generally more GGO than patients witch IANA in the neutropenic group: 100 % vs. 55.6 % (p-value = 0.049).

Nodules

There was a high incidence of pulmonary nodules. Each immune status group showed at least one nodule in > 72.7 % of the patients. In the neutropenia group, the invasive fungi patients had significantly more nodules (94.4 %) compared to the PCP group (50.0 %, p = 0.002). In the other groups, the results were similar but did not reach statistical significance. Cavernous nodules were found in 11.4 %, 19.4 %, 18.2 %, and 23.5 % of the patients in the neutropenia, steroid, OTR, and various diseases groups, respectively (p > 0.05). Generally, the frequency of large cavernous nodules was higher at 7.3 %. Intermediate and small cavernous nodules were present in only 3.3 % and 2.3 %, respectively (appendix table). The typical crescent sign in angioinvasive fungal pneumonia was only found in 2 IANA patients (3.3 %), and both had a favorable outcome. The halo sign was observed in 56.7 %, 27.3 %, and 0 % of cases of IANA, PCP, and CRY, respectively.

Lymph nodes, pleural effusion

The incidence of lymphadenopathy was generally low (< 18 %) among the different groups. Also, the incidence of pleural effusion was only < 25 %. Both findings did not differ significantly

▶ **Table 1** Clinical findings of the study populations.

▶ **Tab. 1** Klinische Befunde der Studienpopulation.

		IANA			
	all	IPA	NAIMI	PCP	CRY
age: mean [range]	59.1 [18.3–89.3]	60.8 [18.3–89.3]	49.8 [20.3–61.1]	58.2 [22.2–89.3]	47.2 [42.1–53.7]
n, total	85	53	7	22	3
n, male	54	33	3	16	2
n, female	31	20	4	6	1
risk factors for IFI					
1) neutropenia	**44**	**29**	**7**	**8**	**0**
▪ AML	14	9	3	2	0
▪ ALL	4	3	1	0	0
▪ CLL	8	4	1	3	0
▪ NHL	5	3	1	1	0
▪ other	13	10	1	2	0
▪ (chemotherapy	26	20	5	1	0)
2) steroids	**36**	**24**	**2**	**9**	**1**
3) solid organ transplant	**11**	**7**	**0**	**3**	**1**
4) other	**17**	**9**	**0**	**6**	**2**
diagnostic certainty					
IFI diagnosis proven	67	35	7	22	3
IFI diagnosis probable	18	18	0	0	0
no specific fungal therapy	61	36	2	20	3
specific fungal therapy	24	17	5	2	0
fluconazole	11	11	0	0	0
voriconazole	3	2	1	0	0
posaconazole	8	3	4	1	0
caspofungin	1	1	0	0	0
bactrim forte	1	0	0	1	0

IANA = invasive Aspergillus and non-Aspergillus infection, IPA = invasive pulmonary aspergillosis, NAMI = non-Aspergillus invasive mold infection, PCP = Pneumocystis jirovecii Pneumonia, CRY = Cryptococcus; AML = acute myeloid leukemia, ALL = acute lymphatic leukemia, CLL = chronic lymphatic leukemia, NHL = non-Hodgkin lymphoma, other = other hematologic disease, solid organ transplantation = status post-transplantation of kidney or lung, IFI = invasive fungal infection.

among the groups. Detailed results for all imaging patterns are demonstrated in the appendix table stratified by infective agent and lobar location.

Stratified according to immune status – per lobe

There was no significant difference among the immune status groups regarding lobe predilection (▶ **Table 2**). The signature sign for invasive pulmonary fungal infection was the solid nodule with the halo sign. In general, this nodule was found more often in the upper lobes ($p < 0.001$). The lower incidence for this nodule for organ transplant recipients is not significant.

Stratified according to infective agent

Lung pattern frequency in IANA patients

IANA patients demonstrated significantly more nodules (93.3 %) than GGO (58.3 %) and consolidations (56.7 %) ($p < 0.001$). Solid nodules with the halo sign and ground glass nodules (GGN) were more common than cavitary nodules (▶ **Fig. 2, 3**): 32.7 %, 28.3 %, and 25.3 %, versus 9.0 % ($p < 0.001$). In patients with IANA infection, 4.7 % of the lung lobes showed a wedge-shaped peripheral consolidation (infarction, ▶ **Fig. 4**) compared to 0 % in PCP ($p = 0.1$).

▶ **Table 2** Prevalence of solid nodules with positive halo sign per lobe.

▶ **Tab. 2** Prävalenz von soliden Knoten mit positivem Halo-Zeichen pro Lappen.

immune status	neutropenia	steroids	organ TX	other
right upper lobe	43.2 %	33.3 %	18.2 %	23.5 %
middle lobe	22.7 %	22.2 %	9.1 %	5.9 %
right lower lobe	29.5 %	19.4 %	9.1 %	5.9 %
left upper lobe	36.4 %	36.1 %	9.1 %	17.6 %
left lower lobe	22.7 %	22.2 %	9.1 %	5.9 %

Prevalence is demonstrated as percentage per lobe and per immune status.
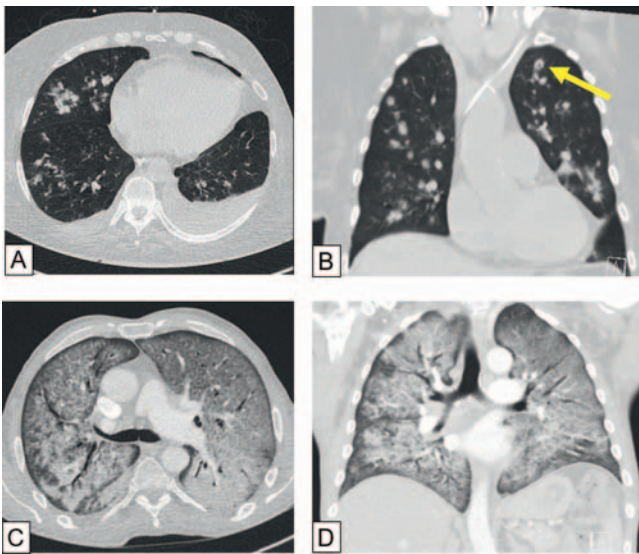
▶ **Fig. 2** Patient examples of invasive Aspergillosis and Pneumocystis jiroveci. A 66-year-old female patient with invasive Aspergillosis is illustrated in the top row **A, B**. Multiple solid, ground glass, and cavernous nodules (arrow) are visible. She died due to the mold infection. In the lower row **C, D**, CT images of a 58-year-old male patient with Pneumocystis jiroveci (PCP) infection are shown. The subpleural sparing of the mainly ground glass changes was only found in PCP cases.

▶ **Abb. 2** Invasive Aspergillose und Pneumocystis-jiroveci-Infektion. Die obere Reihe **A, B** zeigt Bilder einer 66-jährigen Frau mit invasiver Aspergillose. Multiple Knoten, teils solide, teils milchglasartig, oder auch eingeschmolzene Knoten (Pfeil) sind sichtbar. Sie starb an den Folgen der Pilzinfektion. In der unteren Reihe **C, D** werden CT-Bilder eines 58-jährigen männlichen Patienten mit Pneumocystis-jiroveci (PCP) -Infektion gezeigt. Die subpleuralen Aussparungen der milchglasartigen Lungenverdichtungen waren nur bei PCP-Patienten zu sehen.

▶ **Fig. 3** 59-year-old female patient suffering from chronic lymphatic leukemia and Mucor pneumonia. Axial CT slice showing a single nodule with a halo sign in the right upper lobe.

▶ **Abb. 3** 59-jährige Patientin mit chronisch lymphatischer Leukämie und Mucor-Pneumonie. Die axiale CT-Schicht zeigt einen einzelnen soliden Pilzknoten mit peripherem Milchglassaum (Halo-Zeichen) im rechten Oberlappen.
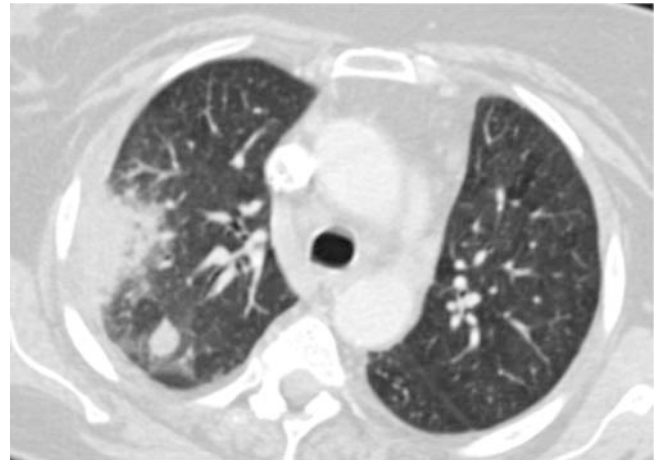
▶ **Fig. 4** Angioinvasive Aspergillus infection of the lung in a patient with acute myeloid leukemia. The right upper lobe demonstrates a hemorrhagic peripheral infarction (wedge shape) and a posterior nodule with a halo sign due to invasion of the pulmonary vessels.

▶ **Abb. 4** Angioinvasive Aspergillus-Pneumonie bei akuter myeloischer Leukämie. Dreieckiger peripherer Lungeninfarkt und dorsaler Knoten mit Halo-Zeichen, verursacht durch die Gefäßinfiltration der Pilze.

Lung pattern frequency in PCP patients

Patients with PCP showed GGO in 95.5 % of cases (▶ **Fig. 2**), nodules in 59.1 %, and consolidations in 45.5 % (p < 0.004). GGO was thus present significantly more often in patients with PCP compared to IANA and CRY (95.5 %, 58.3 %, and 33.3 %, respectively, p < 0.009). Subpleural sparing was found only in patients with PCP (22.7 %, ▶ **Fig. 2**).

Patterns	Consolidation				GGO				Nodules			
Immune status	Neutropenia	Steroids	Organ TX	Other	Neutropenia	Steroids	Organ TX	Other	Neutropenia	Steroids	Organ TX	Other
IA/NAIMI	66.7%	57.7%	42.9%	33.3%	55.6%	57.7%	42.9%	66.7%	94.4%	88.5%	85.7%	88.9%
PCP	62.5%	11.1%	0.0%	83.3%	100.0%	88.9%	100.0%	100.0%	50.0%	55.6%	33.3%	66.7%
Cryptococcosis	N/A	0.0%	0.0%	50.0%	N/A	0.0%	0.0%	50.0%	N/A	100.0%	100.0%	100.0%
Total	65.9%	44.4%	27.3%	52.9%	63.6%	63.9%	54.5%	76.5%	86.4%	80.6%	72.7%	82.4%
p-value	0.045	0.045	0.049	0.002	>0.05							

Prevalence of radiological patterns among the various infective agents and the different immune statuses (per person) are shown as a percentage.
P-values for significantly different prevalence between subgroups are shown color-coded.
N/A: not available; IA: invasive aspergillosis; NAIMI: Non-aspergillus invasive mold infection; PCP: pneumocystis infection; GGO: ground glass opacity; TX: transplantation

▶ **Fig. 5** Prevalence of radiological patterns.

▶ **Abb. 5** Prävalenz der radiologischen Muster.

Lung pattern frequency in CRY patients

All CRY patients demonstrated nodules, while 33 % had consolidations and 33 % had GGO (nodules vs. consolidations/GGO: p = 0.083).

Pattern prevalence according to the clinical outcome (IANA patients only)

Patients who died from the IANA infection showed GGO in 83.3 % of the cases (corresponding to a 31.6 % higher prevalence than patients with a positive outcome; p-value = 0.44), and a diffuse pattern distribution was more frequent (in 33.3 %) compared to patients with positive outcomes (in 0 %, p = 0.005). In a per lobe analysis, we found that IANA patients with negative outcomes (progression or death) demonstrated significantly more nodules with the halo sign. 42.5 % of the lobes were affected compared to 15.9 % of the lobes in patients with a positive outcome (p < 0.0001). Patients with a negative outcome demonstrated especially smaller nodules with the halo sign. Small nodules (< 5 mm), intermediate nodules (5–10 mm), and macronodules (> 10 mm) with the halo sign affected 20.8 %, 19.2 %, and 15.8 % of the lobes in patients with a negative outcome compared to 6.9 %, 5.5 % and 8.3 % of the lobes in patients with a positive outcome (p = 0.007, 0.005 and 0.62). Patients who died from fungal infection demonstrated the highest prevalence of intermediate nodules with the halo sign: 26.7 % (p = 0.002 compared to positive outcomes). Furthermore, patients with positive outcomes showed more pulmonary infarctions (peripheral, wedge-shaped consolidations) than patients with negative outcomes (8.3 % vs. 0.8 %, p = 0.0466).

The frequencies for the presence of each lung pattern per patient are shown in ▶ **Fig. 6** and per lobe in ▶ **Fig. 7**.

Angioinvasivity, probability of fungal infection, and rare patterns

The probability of fungal pneumonia estimated by the reading radiologists based on previously described imaging criteria was observed with equal distribution in 26.4 %, 26.4 %, 25.3 % and 21.9 % of patients in the neutropenia, steroid, OTR, and various diseases groups, respectively, although signs of angioinvasivity were found in 31.0 %. Overall, the radiologists judged the probability of fungal infection in the IANA patients as high (> 50 %) and for the PCP and CRY cases as low (< 50 %, p = 0.023). Subpleural sparing, solitary nodules, or the crescent sign was seen in 5.75 %, 10.34 %, and 0.66 % of the lobes, respectively. Other observed lung patterns that are not typically known for fungal infections were reticulation, bronchiectasis, and centrilobular bullae in 17.93 %, 11.26 % and 6.90 %, respectively, per lobe.

Distribution within the lungs

There was a trend for fungal infections affecting the upper lobes more than the lower lobes (p = 0.0852). The following patterns demonstrated a significantly higher involvement of the upper lobes in IANA patients: mosaic GGO, nodules with halo sign (> 10 mm), and cavitary nodules (> 10 mm) (▶ **Fig. 7**). We observed fungal lung changes significantly more often in the periphery (central vs. peripheral predominant, p = 0.0035).

CT pattern dependency on the fungus test confidence levels (all versus proven IANA infections)

The prevalence of consolidations, GGO, and nodules for all IANA cases (proven and probable) was 56.7 %, 58.3 %, and 93.3 %, respectively, and dropped insignificantly to 55.8 %, 48.1 %, and 86.5 %, respectively, for the proven infections only (all p-values > 0.285). Detailed data regarding prevalence and dependencies on immune status are given in ▶ **Table 3**. Also, the per lobe analysis and the results for the different outcomes did not demonstrate differences in CT pattern prevalence for different test confidence levels.

FUNGUS	Follow-up after 6 weeks		n	Consolidation	GGO	Nodules	LN	PE
IPA/NAIMI	a) Positive response (incl. stable)		29	48.3 %	51.7 %	**89.7 %**	3.4 %	20.7 %
	b) All progressive c, d, e		(24)	62.5 %	58.3 %	**95.8 %**	4.2 %	29.2 %
	c) Progressive		4	75.0 %	25.0 %	**100.0 %**	0.0 %	0.0 %
	d) Death due to other cause		14	64.3 %	57.1 %	**100.0 %**	0.0 %	42.9 %
	e) Death due to IFI		6	50.0 %	83.3 %	**83.3 %**	16.7 %	16.7 %
	f) No follow-up		7	71.4 %	85.7 %	**100.0 %**	14.3 %	42.9 %
	g) All a-f		**60**	56.7 %	58.3 %	**93.3 %**	5.0 %	26.7 %
PCP	All with positive response		**22**	45.5 %	**95.5 %**	59.1 %	40.9 %	13.6 %
CRY	All with positive response		**3**	33.3 %	33.3 %	**100.0 %**	0.0 %	0.0 %
	p-value map							
IPA/NAIMI a)	vs.	IPA/NAIMI b)		1.000	1.000	1.000	1.000	1.000
IPA/NAIMI a)	vs.	IPA/NAIMI e)		1.000	0.741	1.000	0.951	1.000
PCP	vs.	IPA/NAIMI (all, g)		1.000	**0.005**	**0.001**	**< 0.001**	0.996
CRY	vs.	PCP		1.000	**0.008**	0.792	0.792	1.000
CRY	vs.	IPA/NAIMI (all, g)		1.000	1.000	1.000	1.000	1.000

Patients with IPA/NAIMI are grouped based on their outcome after 6 weeks (a-g).
Bonferroni correction applied. Significant differences (p< 0.05) are highlighted in bold font.

GGO = ground glass opacification, LN = lymph nodes; PE = pleural effusion; IPA = invasive pulmonary aspergillosis; NAIMI = non-Aspergillus invasive mold infection; PCP = pneumocystis jirovecii pneumonia; CRY = Cryptococcus; IFI = invasive fungal infection

▶ **Fig. 6** Presence of each pattern in patients with IANA, PCP, and CRY in a per patient analysis.

▶ **Abb. 6** Präsenz der jeweiligen CT-Muster in Patienten mit IANA, PCP und CRY in einer patientenbasierten Analyse.

		IANA						PCP						CRY					
		UL		LL		ML		UL		LL		ML		UL		LL		ML	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Consolidation	Any consolidation	29	38.2 %	34	44.7 %	13	17.1 %	13	36.1 %	16	44.4 %	7	19.4 %	1	33.3 %	2	66.7 %	0	0.0 %
	Only consolidation	13	38.2 %	17	50.0 %	4	11.8 %	8	42.1 %	7	36.8 %	4	21.1 %	0	0.0 %	0	0.0 %	0	0.0 %
	With broncho-pneumogram	9	42.9 %	9	42.9 %	3	14.3 %	3	37.5 %	4	50.0 %	1	12.5 %	0	0.0 %	0	0.0 %	0	0.0 %
	With peripheral GGO	3	21.4 %	7	50.0 %	4	28.6 %	6	60.0 %	4	40.0 %	0	0.0 %	1	33.3 %	2	66.7 %	0	0.0 %
	With enhancement	8	32.0 %	13	52.0 %	4	16.0 %	1	16.7 %	3	50.0 %	2	33.3 %	0	0.0 %	0	0.0 %	0	0.0 %
	Wedge shape (infarction)	5	35.7 %	7	50.0 %	2	14.3 %	0	0.0 %	0	0.0 %	0	0.0 %	0	0.0 %	0	0.0 %	0	0.0 %
GGO = ground glass opacity	Any GGO	37	43.0 %	36	41.9 %	13	15.1 %	35	40.7 %	34	39.5 %	17	19.8 %	2	66.7 %	1	33.3 %	0	0.0 %
	Diffuse	9	50.0 %	7	38.9 %	2	11.1 %	16	41.0 %	15	38.5 %	8	20.5 %	0	0.0 %	0	0.0 %	0	0.0 %
	Patchy	24	41.4 %	26	44.8 %	8	13.8 %	17	38.6 %	19	43.2 %	8	18.2 %	2	66.7 %	1	33.3 %	0	0.0 %
	Mosaic	5	41.7 %	4	33.3 %	3	25.0 %	5	55.6 %	3	33.3 %	1	11.1 %	0	0.0 %	0	0.0 %	0	0.0 %
Nodules	Any nodule (N)	85	49.1 %	65	37.6 %	23	13.3 %	18	52.9 %	11	32.4 %	5	14.7 %	2	50.0 %	1	25.0 %	1	25.0 %
	GGN	38	50.0 %	26	34.2 %	12	15.8 %	11	50.0 %	8	36.4 %	3	13.6 %	0	0.0 %	1	50.0 %	1	50.0 %
	N with halo sign	44	51.8 %	29	34.1 %	12	14.1 %	6	60.0 %	3	30.0 %	1	10.0 %	0	0.0 %	0	0.0 %	0	0.0 %
	Solid N	49	50.0 %	37	37.8 %	12	12.2 %	5	62.5 %	1	12.5 %	2	25.0 %	2	100.0 %	0	0.0 %	0	0.0 %
	Cavitary N	18	66.7 %	6	22.2 %	3	11.1 %	0	0.0 %	0	0.0 %	0	0.0 %	0	0.0 %	0	0.0 %	0	0.0 %

IANA = Invasive Aspergillosis and non-Aspergillus infection; PCP = Pneumocystis jirovecii Pneumonia; CRY = Cryptococcosis; UL = upper lobes; LL = lower lobes; ML = middle lobe; n = number; GGO = ground glass opacity; GGN = ground glass nodule; N = nodule

▶ **Fig. 7** Presence of each pattern in patients with IANA, PCP, and CRY is shown per lobe.

▶ **Abb. 7** Präsenz der verschiedenen Muster in Patienten mit IANA, PCP und CRY in einer lappenbasierten Analyse.

Discussion

The data from this multicenter study show that nodules, GGO, and consolidations are common CT findings in all mold infections. Thus, there was no sign that was unique for one specific pathogen. However, nodules were more predominant in IANA and CRY and GGO was most often correlated with PCP. Solid nodules with the halo sign <10 mm were associated with a worse outcome in our population.

▲ **Table 3** Incidences of radiological patterns dependent on the fungus test confidence level.

▲ **Tab. 3** Inzidenzen der radiologischen Muster in Abhängigkeit von der diagnostischen Sicherheit des Pilztests.

immune status	consolidation					GGO					nodules				
	neutro-penia	steroids	organ TX	other	all	neutro-penia	steroids	organ TX	other	all	neutro-penia	steroids	organ TX	other	all
proven and probable IA/NAIMI[1]	66.7 %	57.7 %	42.9 %	33.3 %	**56.7 %**	55.6 %	57.7 %	42.9 %[3]	66.7 %	**58.3 %**	94.4 %	88.5 %	85.7 %	88.9 %	**91.3 %**
proven IA/NAIMI[2]	69.6 %	52.9 %	25.0 %	37.5 %	**55.8 %**	52.2 %	47.1 %	0 %[4]	62.5 %	**48.1 %**	91.3 %	82.4 %	75.0 %	87.5 %	**86.5 %**
all p-values: all[1] vs. proven[2] > 0.285															

[3] n = 3 of 7

[4] n = 0 of 4

IA: invasive aspergillosis; NAIMI: Non-aspergillus invasive mold infection; GGO: ground glass opacity; TX: transplantation.

Our data are consistent with a study from Xu et al. who compared imaging findings in IPA patients with and without hematological malignancies [21]. While in non-hematological patients, the airway-invasive form, manifesting ground-glass opacity and consolidation or mass formation, was more common, while in patients with hematological malignancy, the angioinvasive form with macronodules (74.5 %) and halo signs (50 %) was more frequent. In the present study, the most common radiologic findings in patients with IANA were nodules (93 %). Nodular lesions were the most common finding on CT in other studies too, and their absence argues against the likelihood of IPA [22]. For example, nodules were seen in 74 % of neutropenic patients in a study by Militio et al. [23]. For most types of nodules (GGN, solid nodules with the halo sign), we observed a higher frequency of small (approximately 20 %) and intermediate size (10 %) nodules than macronodules (2 %). The only exceptions were cavernous nodules with the highest frequency of macronodules (7 %). This might be explained by: a) our definition of size criteria (macronodules were defined as nodules > 10 mm, compared to other studies defining macronodules as > 3–5 mm); and b) our inclusion criteria, because we evaluated early CT scans within the first week of diagnosis, and it is known that nodule size increases during the first 10 days of infection [24].

Whereas it is widely acknowledged that the halo sign is seen frequently in patients with early-stage IPA, not all authors in the literature have reported the same high frequency [18]. In fact, the incidence of the halo sign among neutropenic patients with hematological malignancies has varied widely, ranging from 25 % to 95 % [8, 25–31]. The halo sign was observed in 56.7 %, 27.3 %, and 0 % of cases of IANA, CRY, and PCP, respectively. Although nonspecific, in severely neutropenic patients, the halo sign is highly suggestive of IFI [32, 33]. In addition, the halo sign appears to occur less frequently in patients without neutropenia who have pulmonary aspergillosis than in those with neutropenia, particularly when they are receiving corticosteroid therapy [34], according to our results (▶ **Table 2**).

After the initiation of antifungal therapy, fragments of infarcted lung may separate from the adjacent parenchyma (pulmonary sequestra), resulting in a cavity with an air crescent (air crescent sign) [32]. As this takes some time to develop in the course of aspergillosis [35], we only observed two cases of air crescent sign at this early CT exam time point. As the air crescent sign is a sign of healing [28, 35], it is not surprising that those two patients had a favorable outcome. Other CT findings described in the literature are pleura-based, wedge-shaped areas of consolidation [25, 36]. These findings correspond to hemorrhagic infarcts, and we observed them in the IANA group in up to 5 % of cases.

We observed a significantly higher involvement of the upper lobes in IANA patients for mosaic GGO, nodules with the halo sign, and cavitary nodules. Similar findings were noted by Xu et al. [21]. In our study, the nodular pattern was registered significantly more often in the upper lobes. In contrast, Militio et al. showed an equal distribution between the different lobes of the lungs, with nodular lesions in 81 % of the upper lobes, 81 % of the lower lobes, and 63 % of the middle lobe or lingula [23]. Similar to their study, we observed nodular lesions to be predominantly peripheral and multiple.

Our findings suggest that certain radiologic findings such as infarctions are associated with a favorable outcome and others like GGO with a poor clinical outcome after 6 weeks. In contrast to the literature [37], we cannot confirm the favorable outcome in patients with the halo sign in our cohort. Nodules with the halo sign (< 1 cm) were seen in 20 % of patients who died due to the fungal infection and in 15 % of patients with a negative outcome after 6 weeks as compared to 6 % of patients with a positive outcome. Additionally, larger nodules with the halo sign were more frequent in patients with a negative outcome, but the difference was not significant. Park et al. [22] also suggested that macronodules and multiple infarct-shaped consolidations have prognostic implications in patients with IPA. In a study from Singh et al., lung transplant recipients with IPA had better outcomes if nodular lesions were present [38].

Geltner et al. [39] have shown that the most common infectious agent in transplant recipients is Aspergillus fumigatus (67 %). This is in concordance with our results, which showed 65 % of OTR patients with IANA, 27 % with PCP and 9 % with Cryptococcosis. Hekimoglu et al. [40] evaluated CT patterns in a group of 15 patients post-solid organ transplantation with proven diagnosis of invasive pulmonary aspergillosis. The most frequently observed patterns in their population were nodules and GGO which is in concordance with the results of our study as well as with data from Qin et al. [41]. However, Qin et al. observed nodules in 64 % of cases and masses in 36 %.

Park et al. studied CT patterns in two patient groups and found similar findings in patients with neutropenia (n = 60) and non-neutropenic organ transplant recipients (n = 60) suffering from IPA [22]. In their study, consolidations or masses, halo signs, and an angioinvasive form were observed less often in non-neutropenic transplant recipients than in neutropenic patients (56 %, 26 % and 32 % vs. 78 %, 55 %, 60 % with p = 0.01, p = 0.002 and p = 0.003, respectively). This is consistent with our observations, although our groups were a little different with consolidations, GGO, and nodules being present in 67 %, 56 %, and 94 % of IPA patients with neutropenia and in 43 %, 43 %, and 86 % of OTR patients. It is also known that cavitary formation only happens late in patients with neutropenia when aplasia is resolving. It is an early sign in patients undergoing steroid treatments. This was shown with 11 % of neutropenic patients with cavernous nodule transformation and 19 % of patients undergoing steroid therapy. Although the follow-up of such patients was not included in the scope of the present study, exemplary CT exams of some patients have shown the development of caverns as a sign of immune reconstitution.

Our study has several limitations. First, our population contains a mixed group of different fungal species (IANA n = 60, PCP n = 22, and CRY n = 3). This reflects the daily routine for clinical radiologists when they get a CT order with the suspicion of opportunistic infection but without confirmation or specific diagnosis. The reading radiologist thus needs to know the criteria for invasive infections to enable further diagnostic and therapeutic steps. Due to the strict Bonferroni correction of factor 33 (for all patterns) in the per lobe analysis, the differences had to be huge to be significant between different immune status groups. Some of the important patterns with marginally significant differences may have suffered from the inclusion of rather unimportant patterns. How-

ever, for the sake of completeness, we preferred to include all patterns. Furthermore, due to the retrospective cross-sectional design of our study, potential confounders were not controlled and follow-up of imaging patterns was not within the scope of this study and can be investigated in the future.

Conclusion: Patients with IANA showed a higher prevalence of nodules and a lower prevalence of ground glass opacities than patients with PCP. All patients with PCP and CRY had a favorable outcome. In patients with IANA, nodules with the halo sign were associated with an adverse outcome. Patients with neutropenia generally showed more consolidations, but consolidations were not associated with an adverse outcome.

CLINICAL RELEVANCE

- Chest CT gives important clues for the clinical suspicion and early treatment of invasive mold pneumonia in immunocompromised patients
- This study with a systematic analysis of imaging patterns improves the understanding of CT patterns in invasive pulmonary mold infections.
- Smaller (< 5 mm) and intermediate (5–10 mm) nodules with the halo sign were more often associated with a negative outcome in IANA patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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