CT-patterns of Pneumocystis jirovecii pneumonia differ between HIV-positive and post-transplantation patients

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Aims and objectives

Pneumocystis jirovecii pneumonia (PcP) is a leading cause of opportunistic infections in immune-compromised patients. In HIV-positive patients the clinical presentation and course tends to be sub-acute, indolent, and presents with relatively low mortality. Patients with other types of immune deficiencies have more aggressive disease progression [1-3]. The radiographic features of PcP in patients with HIV have been described previously [4-10], with the dominant radiological pattern being areas of ground-glass attenuation with a background of interlobular septal thickening. The typical radiographic features of PcP in non-HIV are insufficient described [11].

About one-third of PcP cases occur in patients with other immune-compromising conditions such as solid organ transplantation, malignancies, and autoimmune inflammatory diseases [12, 13]. Renal transplant recipients are at high risk of developing PcP, especially in the early post-transplant period, with an incidence ranging from 0.6 to 11.5%, and a mortality rate of up to 50% [14-19]. Current European Best Practice Guidelines therefore recommend at least 4 months of PcP prophylaxis with trimethoprim-sulfamethoxazole, and KDIGO (Kidney Disease: Improving Global Outcomes) guidelines suggest that prophylaxis should be carried out for 3-6 months after transplantation [20, 21]. Both guidelines advocate additional prophylaxis during and following treatment for acute rejection [20]. Several cluster outbreaks of PcP have been reported among renal transplant recipients in recent years [8,13-15]. The major risk factor for PcP in renal transplant recipients appears to be immuno-suppressive therapy [16]. Cytomegalovirus (CMV) infection and rejection treatment have been described as further risk factors, other risk factors remain to be identified [22-25]. CT studies are best suited for the diagnosis, monitoring and screening of the patient population at risk; regardless of HIV infection or solid organ transplant.

The predominant CT finding in PcP are ground glass opacities (GGO) in combination with reticular, septal thickening. GOO distribution in the lung is diffuse, sometimes a mosaic-like pattern distribution can be observed. Another crucial detail in GGO caused by PcP is sub-pleural sparing which is highly specific for PcP. In more chronic course of disease, cystic changes in the lung parenchyma are present underlining destruction of lung parenchyma.

The primary aim is to compare radiological patterns and locations of Pneumocystis jirovecii pneumonia between HIV infected and kidney transplant recipients.

Methods and materials
The local ethics committee approved the present study. HIV and kidney-transplant cohort patients gave their written informed consent, according to the cohorts guidelines. A total of 40 patients were enrolled in this retrospective evaluation. Between 2003 and 2013 all patients with a Pneumocystis pneumonia (PcP) of the HIV and kidney-transplanted patients at our institution, who underwent a chest computed-tomography examination were included. Pneumocystis jirovecii was diagnosed by cytology, histology or positive response to antibacterial treatment, according to the European best Practice guidelines [9]. 24 kidney-transplanted patients and 16 HIV positive patients were retrospectively compared regarding the pattern of lung affection on chest CT. The patient’s demographics and clinical data were retrieved from the hospital information system and the cohort registry. The radiologic examinations were performed on 4 different scanner generations. Images were acquired with 4-, 16-, 64- and 128-row scanners (all by Siemens, Forchheim, Germany) with a slice thickness of 1 to 2 mm. The scanner settings were as follows: Somatom Plus 4 (4x1mm pitch 0.6, slice thickness 2 mm), Somatom Evolution 16, Siemens Medical Solutions (16x0.75mm, pitch 0.8, slice thickness 1.5 mm), Somatom Sensation 64 (24x1.2 mm, pitch 0.8, slice thickness 1.5 mm), Somatom Definition Flash (128x0.6 mm, pitch 0.6, slice thickness 1 mm) and Somatom Definition Edge (128x0.6mm, pitch 0.6, slice thickness 1 mm) all by Siemens (Erlangen, Germany). The scan range was set constant starting at the thoracic inlet and caudally included the whole lung and adrenal glands. Standard kVp and mAs settings for the Siemens Thorax routine protocol (adapted vendor standard) were kept constant on all scanner generations. Automated tube current modulation (Care Dose®, Siemens, Erlangen, Germany) using reference mAs (ref. mAs) to individualize the radiation exposure to patient size was implemented on the later scanners. In addition, care kV was used on the Flash scanner and the Somatom Sensation. Two radiologists with 4 and 15 years of experience in chest imaging did a consensus read out of the cases. The readers were blinded to the clinical data, symptoms and results. Reading was done on a picture achieving and communication system (PACS, Sectra, Linkoping, Sweden). 1 and 5 mm slice reconstructions were examined with a lung and soft tissue window setting with a dedicated lung and soft tissue kernel. The cases were randomized prior to reading. The classification of the lung patterns was done according to the Fleischner society recommendations on the stratification of lung disease [10]: all subgroups of ground glass opacities, consolidations, reticulations and nodules were analyzed. In addition, radiologists recorded the presence of pleural effusions, hilar and mediastinal lymphadenopathy (node > 1cm).

The location of lung pattern was recorded according to the classic lung segment classification [11] with the modification of using 10 segments on the left side. A pathologic pattern located predominantly in the inner or outer half of the thoracic diameter was considered centrally or peripherally located. The symmetry of right and left pulmonary involvement was guessed by the radiologists as percentage of slices that showed congruent findings in the right and left lung. A discontinuous affection of the right or left lung with multiple foci (>2) was considered multifocal. A diffuse disease manifestation of the lung was defined as continuous affection of the lung parenchyma, covering at least 2/3
of a lobe volume (segment 4 and 5 on the left counted as one lobe-Lingula). Sub-pleural sparing was defined as non-pathologic strip adjacent to the peripheral pleura and the diseased parenchyma. The data were collected on an Excel sheet for statistical analysis.

Statistical methods:

Statistical analysis was performed with MedCalc Version 7.6.0.0 statistics software (MedCalc Software, Ostend, Belgium). The absolute frequency of each lung pattern was recorded and compared. In addition to the absolute pattern frequency, a per patient analysis was conducted. Further, the standard error of frequency was assessed. Fisher exact test was implemented to provide the level of significance. P-values less than 0.05 were considered statistically significant. Bonferroni post-hoc-testing was applied to evaluate significant differences between each assessed value. Bonferroni equals p-value times the number of the pattern categories. When exceeding the value of 1, Bonferroni corrected p-value was set to 1.

Results

In the HIV-group, the median time from the initial diagnosis of HIV and the PcP outbreak was 3.5 years (0-20 years range). This group consisted of 11 male (69 %) and 5 female patients (31%) with a median age of 42 years (24-70 years). The PcP cohort containing patients after renal transplantation was composed of 17 male (71%) and 7 female (29%) patients with a median age of 60 years (31-77 years range). The median time frame between onset of PcP and time of renal transplantation was 2 years (0-12 years range).

Patterns (Tab. 1, Fig. 1/2): The kidney-transplant recipients and the HIV-infected group demonstrated 92±6% and 94±6% patchy ground glass opacities (GGO), 83±7% and 81±10% reticulations, 67±10% and 88±8% ground glass nodules (GGN) under 5 mm in diameter, 4±4% and 69±12% GGN measuring over 5 mm in longest diameter, 58±10% and 75±11% mosaic GGO, 21±98% and 31±12% consolidations, 17±8% and 56±12% diffuse GGO, 12±7% and 31±12% solid nodules and 8±6% and 31±12% cysts, respectively. Hilar lymphadenopathy was present in 0±0% and 43.8±12% in post-transplant and HIV-positive patients (p=0.012), respectively.

Lung affection (anatomic distribution, Tab. 1, Fig. 1/2): HIV-associated PcP infections showed significantly more areas with a diffuse pattern distribution: 81±10%, compared to only 25±9% in the kidney transplant recipients group (p=0.019). The areas of multifocal pattern distribution did not differ significantly in both groups (81-88%). Post-transplant and HIV infected patients demonstrated further statistical not significant but indicative differences: in 54±10% and 81±10% an affection of the central lung parenchyma, in 58±10% and 94±6% involvement of the periphery of the lung (outer half of the lung radius) with 33±10% and 50±13% sub-pleural sparing; and on average a 67% and 66% symmetry of right and left lung involvement. The cranial and posterior lung segments
were insignificantly more affected (90-100%) than the anterior and caudal lung segments (middle lobe and lingula, 75-91%) in both groups.

*Images for this section:*
Fig. 1: A) 45 year old HIV positive male patient with Pneumocystis jirovecii pneumonia (PCP) demonstrating typical diffuse ground glass opacities in both lungs, B) 58 year old male patient, 5 years after kidney transplantation suffering from PCP with multifocal patchy ground glass opacities and reticulation.
**Fig. 2:** C) Hilar and mediastinal lymphadenopathie in a 45 years old mal HIV positive patient with PCP (arrows), D) Typical patchy ground glass opacity and consolidation of PCP in a 63 years old recipient of a kidney transplantation.

**Table 1:** CT-patterns and location of Pneumocystis jirovecii pneumonia of post-transplantation and HIV-positive patients
Conclusion

Diffuse distribution of lung affection showed significant results ($p=0.019$) being more prevalent in the HIV positive cohort. Further, significant differences exist regarding ground glass lung nodules with a longest diameter ranging between 5 and 10 mm ($p=0.0004$): those nodules also tend to occur more often in HIV positive individuals. Another crucial finding is, that the presence of enlarged, hilar lymph nodes is significantly more often associated with HIV infection ($p=0.012$). In fact, there were no enlarged lymph nodes in the post- transplant cohort present at all.

The clinical appearance of Pneumocystis pneumonia is well known, showing a more sub-acute behavior in HIV positive patients. On the contrary, PcP in post-transplant patients tends to progress rapidly, especially in the early post-transplant phase. PcP infections occurring in immunodeficient patients without HIV infection have often been grouped into one cohort [11,12,13]. One recent manuscript by Tasaka et al. in 2010 [14] focused on radiological features of Pneumocystis pneumonia between oncologic patients and HIV$^+$ patients. They found symmetric distribution of GGO in both study populations being the most dominant finding on chest CT. This is in accordance with our results. Those GGO represent alveolitis with debris, fibrin and inflammatory response within the terminal respiratory tract. But separating GGO into diffuse and patchy consolidations, we were able to show that diffuse GGO pattern is predominantly found in HIV positive patients. Patchy GGO on the other hand can be found in both patient groups. Hardak et al. [15] compared a mixed collective of immunosuppressed patients versus HIV$^+$ patients in their study. Similar to Tasaka et al., they found diffusely distributed, bilateral GGO representing alveolitis. In general, pneumocystis jiroveci affects more lung volume in HIV-positive than in kidney transplanted patients and displays a larger variety of patterns in our study. Almost all patterns demonstrate a higher prevalence in HIV patients and affect more lung segments centrally and peripherally. Compared to our results, exhibiting diffuse spread of infection predominantly in the HIV positive individuals, these findings may underline the influence of causative immunosuppressive disease on the radiological appearance. Comparing the recent literature with our results, it is suggestive, that there is significant difference between HIV-positive patients with PcP and the population former summarized as immunocompromized. As reported by Tasaka et al. in their study in oncologic and HIV positive patients, a more distinct contemplation of immunodeficient patients with PcP is mandatory for radiological image interpretation.

A further significant finding is the high frequency of ground glass nodules exhibiting a diameter ranging from 5 to 10 mm in the HIV-cohort. Those sub-solid nodules are exceedingly rare in the kidney transplant patients, maybe reflecting a partial granulomatous inflammation with subtotal alveolar consolidation as a response to PcP infection as previously described by Kanne et al [5]. Those ground glass opacifications are reflecting granulomatous inflammation with subtotal alveolar consolidation as a response to PcP infection [6]. Interestingly, this finding is reported to occur in about 5%
of HIV patients. In our population of 16 HIV patients, these GGN were present in 69% of cases.

According to Kanne et al. [6], the overall appearance of nodularity and tree in bud in PcP, as seen with bronchiolitis, may be caused by other infectious agents or superinfection. We were able to detect tree in bud appearance in 17% of renal transplant recipients and 13% of HIV patients, where one could hypothesize, if PcP alone could be responsible for bronchiolitis.

One landmark feature of PcP infection in general is sub-pleural sparing. Fujii et al. found peripheral sparing in 41% of patients presenting with AIDS related PcP [16]. Although the results were not statistically significant, we found a peripheral sparing in 31% of solid organ transplant-cases and in 50% of HIV$^+$ cases. Added together, our data suggests the propagation of a typical finding when referring to sub-pleural sparing of diffuse GGO in context with PcP. Since HIV positive patients demonstrate a larger affection of the lung parenchyma specifically in the periphery of the lungs (94%) and a more homogeneous (diffuse) distribution (81%), the sub-pleural sparing becomes more obvious in these patients.

Typically, PcP is not known for reactive lymphadenopathy [6-10]. In our cohort, PcP in HIV-positive patients demonstrated often hilar lymphadenopathy opposed to post-transplant patients, where lymph node never were enlarged. This hilar lymphadenopathy was probably part of a general systemic lymph node enlargement from the HIV-infection and not a response to the PcP-infection. Nevertheless, it could be the strongest exclusion criterion for post-transplant PcP.

Previous literature states, that PcP infections show a predilection for the upper lobes. This is also true in our study population, regardless whether infected with HIV or after solid organ transplantation, but the upper lobe predominance does not differ significantly between the two study groups.

Interstitial lung alterations are known to occur with more ongoing course of infection. There was a homogenous distribution of interstitial findings in both study populations, except for the arc-like manifestation, that is insignificantly more present in HIV positive individuals. In our experience, the distinction of reticulation, arcades and septal linings as proposed by Fleischner society often remains difficult. Arcades as a unique distinguishing feature between PcP in HIV positive patients and solid organ transplantation may not be of practical use.

Cystic lesions are a feature in AIDS patients representing more chronic, parenchymal damage [17]. Cysts are reported to be found in up to one third of PcP infections [17]. Hardak et al. [15] described a lower incidence of pulmonary cysts in non-HIV infected patients. This data is in accordance with our findings. We found lung cysts in 31% of HIV positive individuals and in about 10% of renal transplantation patients. With this insignificant difference, we propose that cystic changes are not suited for differentiation
between HIV+ patients and organ transplant-cases of PcP. Pneumothorax is a known complication of lung cysts, especially in a sub-pleural location. In the presented cohort, there was no single case of pneumothorax present. This may be due to the fact, that early prophylaxis or earlier detection has reduced complicated course of PcP.

In patients recovering from PcP infections, pulmonary scarring can occur. These scars show a interstitial pattern with volume loss and parenchymal distortions on chest CT. In the investigated study population, signs of pulmonary scarring presented in less than 7% of our cases.

Limitations: One major limitation of the presented data is the relatively small cohort, as compared to previously published data. Another point is the time of the examination in the disease course, which can differ and influence imaging findings. This may be one point missing in evaluations dealing with PcP infections.

Conclusion:

A symmetrical patchy GGO is suggestive of PcP in immunocompromised patients. CT-patterns of PcP differ between HIV-positive and post-transplantation patients. These differences should be considered in the differential diagnosis of pulmonary infiltrates in these patients, and could reflect immunological differences between HIV- and transplant-associated immunodeficiency.

Personal information

References


