High-resolution CT findings of pulmonary infections after orthotopic liver transplantation in 453 patients

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Objectives: The objective of this study was to review the high-resolution CT (HRCT) findings in patients with pulmonary infection after orthotopic liver transplantation (OLT) and to determine distinguishing findings among the various types of infection.

Methods: This study included 453 consecutive liver transplant recipients with pulmonary infection, on whom HRCT of the chest was performed within 24 h of the beginning of symptoms and for whom proven diagnosis had taken place within 1 week of the onset of symptoms. Two radiologists analysed the CT images; final decisions regarding the findings were reached by consensus.

Results: Bacterial and viral pneumonia made up the bulk of infections (63.4% and 29.4%, respectively), followed by fungal infiltrates (24.5%). Large nodules were most common in patients with fungal pneumonia, having been seen in 38 (54%) of the 70 patients with fungal pneumonia, 22 (10%) of 220 with bacterial pneumonia ($p=0.0059$) and 6 (8%) of 78 with viral pneumonia ($p=0.0011$). The halo sign was also more frequent in patients with fungal pneumonia, having been seen in 38 (54%) of the 70 patients with fungal pneumonia, 17 (8%) of 220 with bacterial pneumonia ($p=0.0026$) and 7 (9%) of 78 with viral pneumonia ($p=0.0015$). There was no statistically significant difference in the prevalence of the other HRCT patterns including air-space consolidation, ground-glass attenuation and small nodules among bacterial, viral and fungal infections (all $p>0.05$).

Conclusion: The presence of large nodules with the halo sign is most suggestive of fungal infection after OLT. Other HRCT patterns are not helpful in distinguishing among the various types of infection seen in liver transplant recipients.

Received 8 October 2011
Revised 1 February 2012
Accepted 9 February 2012

DOI: 10.1259/bjr/26230943

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Radiology

Pulmonary infections are a common cause of morbidity and mortality after orthotopic liver transplantation (OLT) [1–3]. These infections occur despite routine prophylaxis for common pathogenic organisms and empiric therapy of febrile episodes during the early post-operation period. Pathogens include bacteria, viruses and fungi. Early and accurate diagnosis of these complications is important because of the high morbidity and mortality associated with infection and the frequent complications associated with the treatment of viral and fungal infections [1, 4].

High-resolution CT (HRCT) is the gold standard imaging technique for early diagnosis or exclusion of pulmonary infections [2, 4]. HRCT may show pulmonary abnormalities in patients with normal findings on radiographs and is superior to radiography in depicting the pattern and extent of abnormalities [5, 6]. Several studies have described the pulmonary infections in liver

transplant patients [1–3]. These studies have been limited to clinical findings or have focused mainly on the description of specific infections. Little information is available about HRCT features that may allow distinction among the various types of infections in liver transplant recipients. The aim of this study was to review the HRCT findings in 453 patients who had pulmonary infections after OLT and to determine distinguishing imaging features among the various types of infections.

Methods and materials

This study was retrospective and included 453 consecutive patients who had proven pulmonary infection after OLT and on whom HRCT of the chest was performed within 24 h of the onset of symptoms. The mean age of the present patient population was 45.3 years [standard deviation (SD), 12.3 years], with 163 females and 290 males. The patients were selected by a review of the medical records and came from a population of 2550 patients who underwent OLT at our institution from January 2000 to January 2011. Of these 2550 patients, 637 had documented pulmonary infections. 184 patients were excluded because the HRCT

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This work was supported by a grant from the National Natural Science Foundation of China (grant number 81101096).

examinations were not performed or were performed more than 24 h after the onset of symptoms. The symptoms included fever, cough and dyspnoea.

Among these 453 patients, 439 received only a single graft, 12 were retransplanted and 2 received 3 grafts (6 owing to vascular ischaemic events, 5 for primary non-function and 3 for acute rejection).

In 453 patients with pulmonary infections, the underlying diseases necessitating OLT included hepatitis B virus liver cirrhosis ($n=257$), acute hepatic failure ($n=82$), primary biliary cirrhosis ($n=57$), hepatocellular carcinoma ($n=26$), post-alcoholic cirrhosis ($n=18$) and primary sclerosing cholangitis ($n=13$). All patients received an immunosuppressive regimen consisting of tacrolimus (FK506), which is an effective immunosuppressive agent for the prevention of organ transplant rejection. Approval was obtained from the local institutional review board of our institution.

The infectious complications after OLT were due to bacteria ($n=287$), viruses ($n=133$) and fungi ($n=111$). 78 patients had more than one organism responsible for the infection, including 37 cases of bacteria and virus, 23 cases of bacteria and fungus, 11 cases of fungus and virus and 7 cases of bacteria, virus and fungus. The bacterial pneumonias were due to *Staphylococcus aureus* in 137 patients, *Pseudomonas aeruginosa* in 98 patients, *Streptococcus viridans* in 43 patients, *Klebsiella pneumoniae* in 6 patients and *Enterococcus faecalis* in 3 patients. Viral pneumonias were caused by cytomegalovirus (CMV; $n=113$), herpes simplex virus type 2 ($n=13$), influenza virus ($n=4$) and parainfluenza virus ($n=3$). Fungal infections were caused by *Candida albicans* in 87 patients, an *Aspergillus* species in 16 patients and both *Candida* and *Aspergillus* species in 8 patients.

The pathogens responsible for the infectious episodes were documented by the following methods: sputum culture ($n=173$), bronchoalveolar lavage (BAL; $n=126$), sputum culture and BAL ($n=94$), biopsy ($n=57$) and autopsy ($n=3$). Diagnosis of bacterial infection was based on a positive culture of sputum or bronchoscopic aspirate combined with positive blood or pleural fluid cultures. The diagnosis of CMV pneumonia was based on detection of the characteristic inclusion bodies in material obtained at BAL, autopsy or lung biopsy. Positive polymerase chain reaction test results of blood, CMV antigenaemia, clinical and imaging evidence of pulmonary disease or improvement after specific treatment were considered diagnostic of CMV pneumonia. Fungal infection was diagnosed from culture or histological evidence of tissue invasion ($n=85$). A positive blood culture in the presence of compatible clinical and radiological findings was considered diagnostic of fungal pneumonia in 26 cases.

CT examinations were obtained with a multidetector row CT machine (LightspeedTM Qx/I; GE Medical Systems, Milwaukee, WI). The images were obtained at end-inspiration using a 2-mm collimation at 10-mm intervals and were reconstructed with a high spatial frequency algorithm and photographed using window settings appropriate to lung parenchyma (width, 1500 HU; level, -500 HU) and mediastinum (width, 400 HU; level, 40 HU).

Two radiologists analysed the HRCT images and reached final decisions regarding the findings by con-

sensus. The following HRCT findings were evaluated: pattern of the pulmonary abnormalities (nodules, tree-in-bud pattern, air-space opacities and ground-glass attenuation), distribution of the lesions (central or peripheral; unilateral or bilateral; symmetrical or asymmetrical; and upper, middle or lower zones), bronchial wall thickening, mediastinal lymph node enlargement and pleural effusions.

Ground-glass attenuation was defined as hazy increased attenuation of the lung without obscuration of the bronchial and vascular margins. Air-space consolidation was defined as homogeneous increase in pulmonary parenchyma attenuation that obscured the margins of vessels and airway walls. A small nodule was defined as a round opacity <10 mm in diameter. A round opacity ≥ 10 mm was considered to be a large nodule. Nodules were also assessed as to whether they were surrounded by ground-glass opacity (halo sign). A tree-in-bud pattern was defined as a centrilobular branching structure that resembled a budding tree. Lymph nodes with a short-axis diameter of >10 mm were considered to indicate lymph node enlargement. The pattern of ground-glass opacities was classified as diffuse, patchy or focal. The distribution of air-space consolidation was classified as segmental or non-segmental and as patchy or focal. Criteria for these findings were those defined in the Fleischner Society's glossary of terms [7].

The clinical and HRCT data were entered into a spreadsheet (Excel 2003; Microsoft Corporation, Albuquerque, NM). Statistical analysis was performed using the Fisher's exact test and multivariate analysis, and a p -value of <0.05 was considered statistically significant.

Results

Infectious pneumonia was observed in 30% of patients after OLT in our study. Bacterial and viral pneumonia made up the bulk of infections (63.4% and 29.4%, respectively), followed by fungal infiltrates (24.5%). 439 patients (97%) had parenchymal abnormalities visible on HRCT, and 14 (3%) had normal findings on HRCT. Of the patients with normal HRCT findings, 11 had viral infections and 3 had bacterial pneumonia. These 14 patients had similar symptoms to the remaining patients—namely, fever, cough and dyspnoea. Like the remaining patients, they underwent HRCT within 24 h of the onset of symptoms.

The parenchymal abnormalities on HRCT in the various pulmonary infections and their time of occurrence are summarised in Table 1. Pleural effusion was seen in 113 patients with bacterial pneumonia, 37 with viral pneumonia, 33 with fungal pneumonia and 41 with mixed pneumonias. None of the patients had mediastinal lymphadenopathy.

Bacterial pneumonia

220 patients had pneumonia caused only by bacteria. 178 of 220 patients (81%) had nodular opacities, including 116 patients (53%) with small nodules, 22 (10%) with large nodules and 20 (9%) with both small and large nodules (Figure 1; Table 1). In 25 patients, the small nodules were associated with a tree-in-bud pattern. 17 patients (8%) had

Table 1. HRCT findings of pulmonary infections after OLT

HRCT findings	Bacterial pneumonia (n=220)	Viral pneumonia (n=78)	Fungal pneumonia (n=70)	Mixed pneumonia (n=78)
Nodules				
Small nodules	116 (53)	40 (51)	24 (34)	35 (45)
Large nodules	22 (10)	6 (8)	38 (54)	17 (22)
Both small and large nodules	20 (9)	5 (6)	10 (14)	9 (11)
Tree-in-bud pattern	25 (11)	11 (14)	10 (14)	12 (15)
Ground-glass attenuation				
Diffuse	26 (12)	11 (14)	6 (9)	10 (13)
Patchy	24 (11)	7 (9)	5 (7)	8 (10)
Focal	26 (12)	7 (9)	8 (11)	10 (13)
Air-space consolidation				
Non-segmental focal	67 (30)	18 (23)	18 (26)	21 (27)
Non-segmental multifocal	42 (19)	12 (15)	12 (17)	14 (18)
Segmental	43 (20)	11 (14)	11 (16)	12 (15)
Halo sign	17 (8)	7 (9)	38 (54)	18 (23)
Pleural effusion	113 (51)	37 (47)	33 (47)	41 (53)

HRCT, high-resolution CT; OLT, orthotopic liver transplantation.
Data are given as number (percentage).

a halo of ground-glass attenuation surrounding the nodules, and 9 had large nodule cavitations.

Air-space consolidation was seen in 152 patients (69%) with bacterial pneumonia (Figure 2). The areas of consolidation were focal non-segmental in 67 patients, multifocal non-segmental in 42 and segmental in 43. The consolidation was bilateral and asymmetrical in 93 patients, and involved mainly the middle lung zones in 76 patients and the lower lung zones in 67.

Figure 1. A 45-year-old female with *Pseudomonas aeruginosa* pneumonia 19 days after orthotopic liver transplantation. High-resolution CT scan obtained at the level of the right lower lobe shows a large nodule with irregular margins, several small nodules and ground-glass attenuation.

76 patients had areas of ground-glass attenuation, 26 of which were diffuse; 24, patchy; and 26. The ground-glass opacities were bilateral symmetrical in 48 patients and asymmetrical in 24. There was no predominant lung zone distribution.

Overall, of the patients with infection caused only by bacteria, 33 (15%) had only nodules and 26 (12%) had only consolidation. Three patients had normal findings on CT. The remaining patients (72%) had various combinations of nodules, consolidation and ground-glass attenuation, including 17 who had a halo sign.

Viral pneumonia

78 patients had pneumonia caused only by viruses. Multiple small nodules were seen in 40 patients (51%; Figure 3), and large nodules were detected in 6 (8%; Table 1). Both small and large nodules were seen in 5 patients (6%). The most common distributions of the lesions were bilateral and symmetrical ($n=34$) and peripheral ($n=44$). No zonal predominance was seen. The small nodules were associated with a tree-in-bud pattern in 11 patients.

Air-space consolidation was present in 41 patients (53%), which mainly involved the peripheral lung regions of the middle and lower zones. Ground-glass opacities were observed in 25 patients (32%), and were diffuse in 11 patients, patchy in 7 and focal in 7 (Figure 4). In 7 patients (9%), the nodules were surrounded by a halo of ground-glass attenuation.

Overall, of the patients with pneumonia caused only by viruses, 14 (18%) had only nodules, 7 (9%) had only consolidation and 7 (9%) had only ground-glass attenuation. The remaining 50 patients (64%) had various combinations of nodules, ground-glass attenuation and consolidation, including 7 (9%) who had a halo sign.

Fungal pneumonia

70 cases of pneumonia were caused only by fungi. Nodules were the most common finding in these patients

Figure 2. A 52-year-old female with *Staphylococcus aureus* pneumonia 32 days after orthotopic liver transplantation. High-resolution CT scan of the right lower lung shows patchy areas of air-space consolidation in the right lower lobe.

(Table 1). Large nodules were seen in 38 (54%) patients. Small nodules in a predominantly centrilobular distribution were noted in 24 (34%) cases, and a tree-in-bud pattern was seen in 10 patients (Figure 5). Both small and large nodules were seen in 10 (14%) patients. One or more nodules were surrounded by a halo sign in 38 patients (54%; Figure 6). Nodules were the only abnorm-

Figure 3. A 37-year-old male with cytomegalovirus pneumonia 49 days after orthotopic liver transplantation. High-resolution CT scan obtained at the level of the main bronchi shows multiple small nodules and small bilateral pleural effusions.

Figure 4. A 48-year-old male with cytomegalovirus pneumonia 62 days after orthotopic liver transplantation. High-resolution CT scan obtained at the level of the aortic arch shows diffuse ground-glass attenuation.

ality in 22 patients. In 16 cases, the nodules were associated with areas of air-space consolidation. No cavitations were seen.

41 patients had areas of air-space consolidation, which were bilateral and asymmetrical. 25 patients had areas of ground-glass attenuation, which were diffuse in 9 patients, patchy in 7 and focal in 11.

Overall, of the patients with pneumonia caused only by fungi, 22 (31%) had only nodules, 3 (5%) had only consolidation and 2 (3%) had only ground-glass attenuation. The remaining 43 (61%) patients had various combinations of nodules, ground-glass attenuation and consolidation, including 38 (54%) who had a halo sign.

Mixed pneumonias

78 patients had more than one organism responsible for the mixed infections, including 37 cases of bacteria and virus, 23 cases of bacteria and fungus, 11 cases of fungus and virus and 7 cases of bacteria, virus and fungus. Small nodules, large nodules/halo sign, ground-glass opacities and areas of consolidation were seen in these patients (Table 1).

Comparison of the HRCT findings of the various infections

Large nodules were most common in patients with fungal pneumonia, having been seen in 48 (69%) of the 70 patients with fungal pneumonia, 22 (10%) of 220 with bacterial pneumonia ($p=0.0059$) and 6 (8%) of 78 with viral pneumonia ($p=0.0011$; Table 2). The halo sign was also more frequent in patients with fungal pneumonia, having been seen in 38 (54%) of the 70 patients with fungal pneumonia, 17 (8%) of 220 with bacterial pneumonia ($p=0.0026$) and 7 (9%) of 78 with viral pneumonia ($p=0.0015$). There was no other statistically significant difference among bacterial, viral, and fungal pneumonias (Table 2).

Figure 5. A 49-year-old male with infection by *Candida albicans* 33 days after orthotopic liver transplantation. High-resolution CT scan obtained at the level of the main bronchi shows several small centrilobular nodules in the middle lobe in a random distribution.

Figure 6. 36-year-old female with invasive aspergillosis 21 days after orthotopic liver transplantation. High-resolution CT scan obtained at the level of the right upper lobe shows a large nodule surrounded by ground-glass attenuation (CT halo sign).

Discussion

Pulmonary infections after OLT have been observed in a range from 15% to 52%, with mortality around 40% [1–3, 8]. This prevalence is much higher than that observed after routine hepatic surgery, as shown in approximately 25% of cases [9]. The 30% prevalence of pneumonia in the OLT population of this series was similar to some previous reports [2, 4, 9]. A wide variability among the reported experiences about rate of infections, prevalence and type of infecting agents in post-OLT follow-up depends mainly on bowel decontamination, patient selection criteria for OLT, immunosuppressive therapy and percentage and type of environmental agents. Gram-negative bacilli, CMV and *Pneumocystis carinii* were the usual pulmonary pathogens in the earlier studies in liver transplant recipients receiving cyclosporine. The most frequent pathogens in our study were gram-positive bacteria and viruses (CMV), followed by *Candida*.

Bacterial pneumonia is the most common pulmonary infection after liver, lung and cardiac transplantations [2, 4, 9]. In OLT, bacterial pneumonia constitutes up to 50% of pulmonary infections and arises during assisted ventilation; pre-transplant prolonged intubation, aspiration pneumonia or post-operative atelectasis and lengthy surgical procedures seem to represent promoting factors [2, 10]. In our study, bacterial infections constituted 63.4% of all pulmonary infections. The most common organisms resulting in bacterial pneumonia in liver transplant patients were gram-negative bacteria from the intestinal flora or oral mucosa and gram-positive organisms, particularly *Staphylococcus* and *Streptococcus* species.

Limited information is available concerning the HRCT findings of bacterial pneumonia in OLT patients. The chest HRCT findings in this group of patients have been described as being similar to those seen in immunocompetent patients, with predominance of focal areas of air-space consolidation [11–14]. Golfieri et al [2] studied the radiological findings of 41 patients with pneumonia after liver transplantation. Of these findings, the most common were segmental or lobar alveolar consolidations, monolateral in 16 cases and bilateral in 6 cases, always associated with pleural effusion. The frequencies of air-space consolidation and ground-glass opacities in the present study were similar to those seen in previous studies: these were seen in 69% and 35% of patients, respectively. However, small centrilobular nodules were seen more frequently in our study, having been observed in 136 (62%) of 220 cases. 42 patients (19%) also presented with large nodules, including 17 (8%) who had a halo sign.

CMV is one of the most common causes of viral infection after liver transplantation [15–17]. The most common HRCT manifestations of viral pneumonia are small centrilobular nodules, air-space consolidation and ground-glass opacities [15, 16]. Similar findings were seen in the present study: ground-glass opacities were seen in 32% of patients, small centrilobular nodules in 57% and areas of air-space consolidation in 52%. These abnormalities are usually bilateral, diffuse and asymmetrical in distribution. Less common findings included large nodules and a tree-in-bud pattern.

Table 2. *p*-values for comparison of the frequency of the various HRCT findings of pulmonary infections after OLT

HRCT findings	Bacterial and fungal infection	Bacterial and viral infection	Viral and fungal infection
Nodules			
Small nodules	0.5567	0.7779	0.7887
Large nodules	0.0059	0.4507	0.0011
Both small and large nodules	0.3238	0.4380	0.3145
Tree-in-bud pattern	0.4389	0.6804	0.6640
Ground-glass attenuation			
Diffuse	0.6171	0.3908	0.1523
Patchy	0.6174	0.3277	0.1523
Focal	0.2422	0.5059	0.6546
Air-space consolidation			
Nonsegmental focal	0.7463	0.2489	0.3897
Nonsegmental patchy	0.2044	0.6345	0.6890
Segmental or lobar	0.7339	0.4601	0.1282
Halo sign	0.0026	0.1036	0.0015
Pleural effusion	0.3178	0.4083	0.3195

Statistically significant *p*-values are shown in bold.

The most common finding of fungal infection in the present study was large nodules, which were seen in 38 (54%) of 70 patients. One or more nodules with a halo sign were found in 38 (54%) patients. Large nodules were more common in patients with fungal pneumonia than in those with bacterial or viral pneumonia. The halo sign was also more frequent in patients with fungal pneumonia than in those with other pneumonias.

Fungal pneumonia is one of the main causes of morbidity and mortality after OLT [18–20]. The most common organism causing fungal pneumonia is *Candida* species, usually *C. albicans*, which is responsible for 90% of such infections [18, 21]. *Aspergillus* species is the second most frequent fungal organism. Pulmonary candidiasis may spread to the lung via a hematogenic or endobronchial route. When it is from endobronchial seeding, candidiasis is usually limited to the lungs, may present with consolidation or nodules and tends to involve mainly the lower lobes. Hematogenic dissemination results in symmetrical nodular lesions throughout the lungs and is often associated with extrapulmonary disease. The characteristic pathological findings consist of haemorrhagic nodules that usually measure 2–4 mm in diameter and frequently have a necrotic centre containing the organisms [18, 22]. The HRCT findings that are suggestive of pulmonary candidiasis include solitary or multiple nodules, ground-glass opacities and areas of air-space consolidation [2, 9]. The lung lesions are characterised by vascular invasion and occlusion of small- to medium-sized pulmonary arteries by fungal hyphae [23, 24]. The areas of haemorrhagic infarction are seen on CT as nodules surrounded by areas of halo signs [25–27]. Several studies have shown the value of HRCT in the diagnosis of invasive pulmonary aspergillosis. Common findings include large nodules, frequently with a halo sign, and focal areas of consolidation [2, 25, 26, 28]. Although the halo sign in OLT patients is most suggestive of invasive aspergillosis, this sign has also been described in patients with bacterial pneumonia, *Candida* infection, cryptococcosis, CMV pneumonia, herpes simplex virus infection and Kaposi's sarcoma [27, 29, 30].

Our study has several limitations. Firstly, although the study included consecutive patients who underwent CT

within 24 h of the onset of symptoms and who had proven diagnoses, we believe that some patients with pulmonary infections were excluded, because many of these patients are treated empirically on the basis of clinical and radiological findings and do not have a definitive diagnosis. However, we feel that it is beneficial to review the HRCT findings in 453 patients who had pulmonary infections after OLT and share our experience with other doctors in order to determine distinguishing imaging features among the various types of infections. Secondly, in some patients, the HRCT scans demonstrated significant artefacts related to respiratory movements, which prejudiced the study of some images. However, these patients usually have severe respiratory symptoms, and even the most recent fast CT acquisitions fail to acquire images without respiratory artefacts.

In conclusion, there is a considerable overlap among the HRCT manifestations of bacterial, viral and fungal pneumonias in liver transplant patients. Large nodules and the halo sign are findings that are statistically more common in patients with fungal pneumonia. Air-space consolidation, ground-glass opacities and small nodules are not helpful in the differential diagnosis of various pulmonary infections after OLT.

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