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Pulmonary complications following orthotopic liver transplant

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Abstract Pulmonary complications after orthotopic liver transplant (OLT) are frequent, involving high morbidity and mortality. We have determined the pulmonary complication incidence in 187 patients submitted to OLT at the General University Hospital "Gregorio Marañón" in the last 4 years, analyzing the type of infection, evolution, diagnostic and therapeutic measures and their influence on OLT mortality. A total of 120 patients had pulmonary complications, the most frequent being pleural effusion (61.94%), pneumonia (43.36%), and pneumothorax (11.5%). Serious pulmonary hypertension was diagnosed by invasive methods in two patients at the time of surgery (unidentified before OLT); both died at early post postoperative times. Pleural effusion was noted in 70 patients, 31.42% of them requiring thoracic tube drainage, complications developing in 22.72%. Thirteen patients were diagnosed of pneumothorax, the most frequent etiologies being percutaneous liver biopsy, thoracic tube drainage for pleural effusion, and postoperative complications in 41.6, 33.3, and 23.3%, respectively. Pneumonia was diagnosed in the 1st month after OLT in 45 patients. Tests to diagnose and identify the etiological agent were made in 71.1% of diagnosed pneumonia patients, identification being obtained in 62.5%. Telescope catheter culture identified the agent in 48%, fiber optic bronchoscopy in 50%, and lung or pleural biopsy in 100%. Respiratory insufficiency was noted in 64 patients (34.22% of transplanted patients). Factors involved in their development were pneumonia (42.18%), graft dysfunction (39.06%, pleural effusion (34.37%), sepsis (28.18%), and poor nutritional status (7.81%). Fifty patients (41.66%) died, pulmonary pathology being the determinant factor in 28.8%. Patient mortality with respiratory insufficiency was greater, especially in those with three factors involved the development of respiratory insufficiency.

Key words Orthotopic liver transplant · Pulmonary complications

Introduction

The causes of death or morbidity after orthotopic liver transplant (OLT) vary depending on the time after transplantation. At the month after OLT, surgical complications, graft dysfunction, and infections are the most frequent. In the early stages of the transplant, pulmonary complications could lengthen the intubation time, thus increasing the number of infectious complications. Pulmonary complications are frequent and rarely severe, although delays in early treatment could lead to the patient's death [1–3].

In the present study, we have analyzed the respiratory complication incidence after OLT (at the 1st month after surgery) for type of infection, evolution, therapeutic, and diagnostic methods. Moreover, their influence on OLT mortality has been evaluated.

Patients and methods

A total of 187 consecutive patients who underwent OLT at the University General Hospital "Gregorio Marañón" during the last 4 years has been studied. A pretransplant protocol was applied to select the correct candidates. This included respiratory functional tests, echocardiography, and a microbiological study to detect infections before OLT. Severe alterations detected at this stage indicated OLT exclusion. Infections indicated a temporary exclusion from the active list until their complete resolution.

The immunosuppression therapy included cyclosporine, azathioprine, and prednisolone. Antibiotic prevention therapy was carried out with ciprofloxacine (200 mg i.v. every 12 h for the first 5 days followed by 500 mg orally every 24 h for the 1st month) and vancomycin (1 g i.v. every 12 h for the first 5 days, but with variations according to blood levels and renal function). Trimethoprim and sulfamethoxazole therapy (160 mg and 800 mg, respectively) to prevent *Pneumocystis carinii* infection was also instituted [4].

Pneumonia and pleural effusion diagnosis was made with clinical and radiological criteria. Blood, urine, and pulmonary secretion culture was carried out in all patients with pneumonia, adding invasive diagnostic tests (telescope catheter culture, fiber optic bronchoscopy, pleural or lung biopsies) in those patients with serious clinical criteria or respiratory insufficiency (RI). RI was defined as a ventilation requirement more than 5 days after OLT or a FiO_2 requirement greater than 50% up to 72 h after surgery.

Results

Pulmonary complications were detected in 120 of 187 patients analyzed (64.17%). Mean age was 46.23 ± 10.89 years (21–65); 80 males and 40 females. Liver diseases indicating OLT were alcoholic or viral cirrhosis in 70.83%, fulminant liver failure in 10%, hepatocellular carcinoma in 5.83%, primary biliary cirrhosis in 2.5%, and metabolic disease in 0.83%. In the 2.6% remaining patients, the OLT indication was retransplant due to serious graft dysfunction. The most frequent pulmonary complications were pleural effusion (61.94%), pneumonia (43.36%), and pneumothorax (11.5%) (Fig. 1).

Pleural effusion was noted in 70 patients in the first 48 h after surgery. In 22 (31.42%), thoracic tube drainage was applied. Five (22.72%) had complications related to the technique; four had mild pneumothorax controlled without additional care; and one had massive hemo-pneumothorax with pulmonary injury leading to the patient's death.

Pneumothorax was detected in 13 patients (6.95% of all OLT patients). Pneumothorax causes were percutaneous liver biopsy in five patients, thoracic tube drainage in five, and postoperative causes in three. Five (38.46%) of 13 patients needed thoracic tube drainage, two of them required thoracotomy; one died after surgical complications.

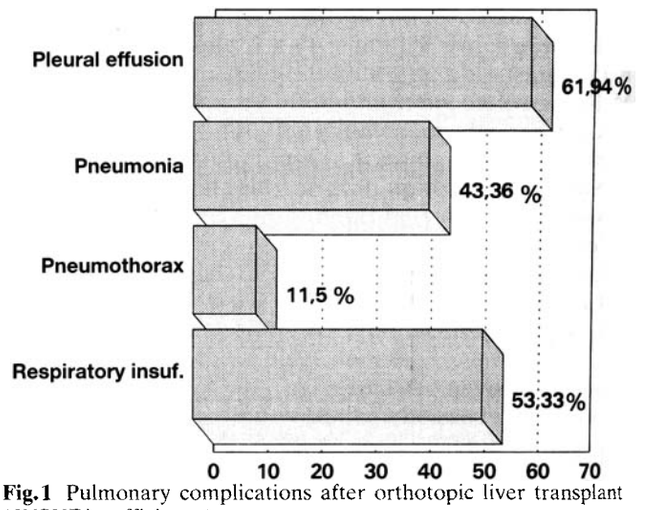

Fig. 1 Pulmonary complications after orthotopic liver transplant (*INSUF* insufficiency)

Table 1 Invasive diagnostic test results in patients with pneumonia

Agent	Patients
Gram-negative Bacillus	1
MRSA	6
Acinetobacter	1
Streptococcus	1
Micrococcus	1
Pseudomonas aeruginosa	1
Enterobacter	1
Serratia marcescens	1
Klebsiella pneumoniae	1
Candida albicans	1
Aspergillus	1

Pulmonary hypertension was detected in two patients at the time of surgery by invasive cardiopulmonary hemodynamic examination. Both patients had normal pre-OLT echocardiography but both died at an early postoperative stage.

Pneumonia was diagnosed in the 1st month after OLT in 45 patients (24.06%). Invasive diagnostic tests were made in 32 patients (71.1%); telescope catheter culture being positive in 12 of 25 (48%), transtracheal puncture in one, and fiberoptic bronchoscopy with bronchoalveolar culture isolating an infectious agent in four of eight (50%). Pleural or lung biopsies were carried out in three patients, an being positive (100%). The infectious agents isolated in the invasive diagnosis test are shown in Table 1.

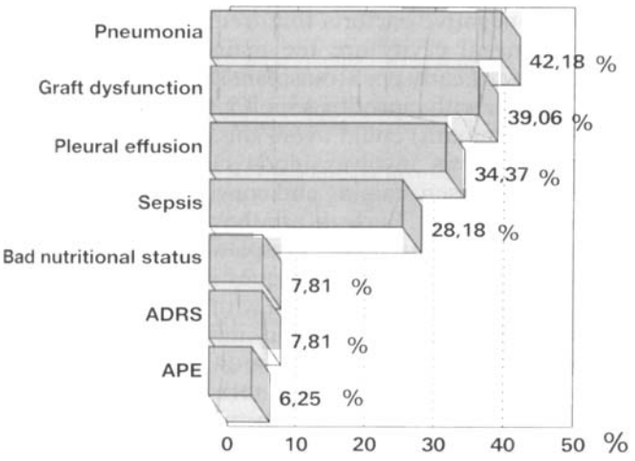

Fig. 2 Respiratory insufficiency etiology (*ADRS* adult respiratory distress syndrome, *APE* acute pulmonary edema)

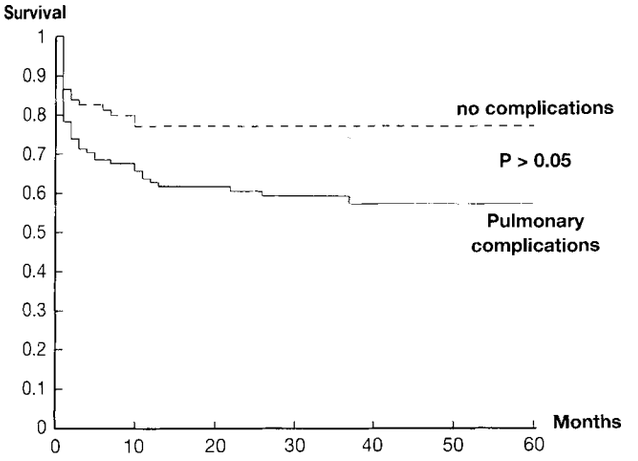

Fig. 3 Survival in patients with pulmonary complications

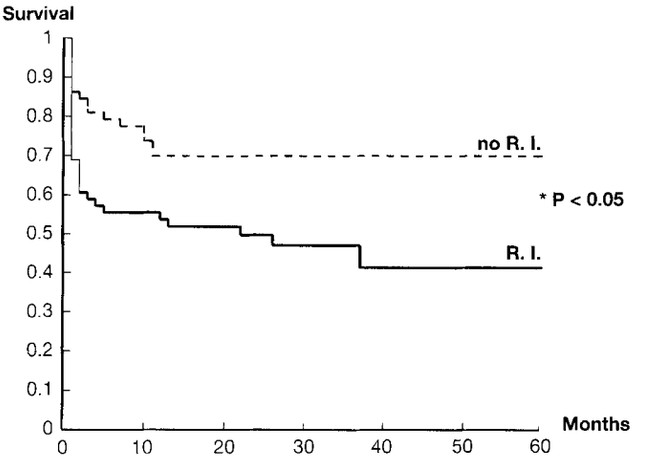

Fig. 4 Patient survival with pulmonary pathology and respiratory

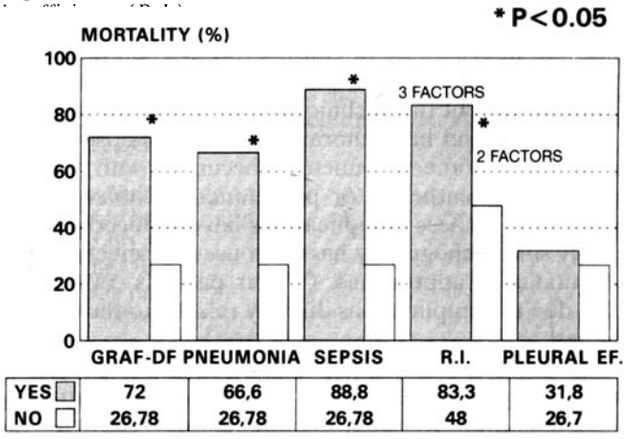

Fig. 5 Etiological R. I. Factors and mortality (*GRAF-DF* graft dysfunction, *EF* effusion)

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According to previously established criteria, RI was diagnosed in 64 patients (53.3%). Factors involved in RI development are shown in Fig. 2. Thirty-six patients had more than one factor involving RI development. Four patients needed tracheostomy due to long-term ventilatory requirements, and all four carried more than one factor leading to RI.

Fifty (41.66%) of 120 patients with pulmonary pathology after OLT died after a 6-month follow-up (Fig. 3). In 12 patients (28.8%), the pulmonary pathology led directly to mortality (eight pneumonia, two pneumothorax, two pulmonary hypertension). Survival was higher in patients without RI (Fig. 4).

Discussion

Ekberg et al. [2] described in patients who underwent major liver surgery, essentially tumor resections, an incidence of 23% of pulmonary complications. This indicated that this kind of surgery, although without OLT, involves a high risk of developing these types of complications. Their incidence after OLT oscillates between 60 and 75% [5, 6], with similar frequencies between infectious and non-infectious complications.

At early post-transplant stages, pulmonary function is of prime importance, since complications here could lead to the patient's death. Early diagnosis and treatment help to ensure that severe complications rarely develop [6]. During the first few days after OLT patients need mechanical ventilation as their, return to full consciousness is delayed due to the slow hepatic metabo-

lism of the anesthetic agents, as well as residual hepatic encephalopathy [7, 8]. There were several factors that lead to pulmonary complications at early post-transplant, such as long surgery time, respiratory mechanical alterations related to abdominal incision, and previous muscular atrophy related to a poor nutritional status before OLT.

Pleural effusion is usually located at the right side, due to mechanical factors, low protein blood levels or high fluid inputs at surgery. Other factors described by Afessa et al. [1] are pre-transplant liver disease, infection, heart failure or renal insufficiency. These are usually transient and do not require specific treatment, although when RI develops due to respiratory mechanical alterations, thoracic drainage may be necessary to prevent infections or other complications. Pleural effusion incidences and thoracic tube drainage requirements are similar to those published by authors such as Costello et al. [9]; they described pleural effusion incidences in 56.52% of their patients, needing thoracic tube drainage in 46.15%. It is important to note that thoracic tube drainage could cause severe complications (22.72% patients died), although well trained physicians carried out this technique.

Pneumo- and hemothorax appearance is usually related to percutaneous punctures occurring with liver biopsy, central catheters or percutaneous cholangiography [10, 11]. These complications have reduced considerably since echography has been used to select correct percutaneous approaches. Of our patients, two (1%) died due to complications directly related to these techniques.

From 0.5% to 1% of cirrhotic patients develop pulmonary hypertension related to portal hypertension, this being more frequent in patients undergoing portocaval surgery [12], which involves serious risk to those patients [12]. Before transplant, a correct patient evaluation was carried out based on clinical and echocardiography tests. Since findings obtained by both methods have not seen efficient in detecting those patients with pulmonary hypertension, we include in our pre-transplant evaluation protocol an invasive cardiopulmonary and hepatic hemodynamic study. This allows a more accurate diagnosis of those patients with serious pulmonary hypertension (artery pulmonary pressure > 40 mmHg), who are subsequently excluded from OLT.

Infections are the most frequent causes of post-transplant complications [13, 14], pulmonary ones being especially severe, leading to the patient's death in 50–60% of cases [15, 16]. The most important mechanisms related to their appearance in early post-transplant stages are the breakdown of mucocutaneous defensive barriers (orotracheal intubation and mechanical ventilation), high hospitalization times for those patients with greater exposure to nosocomial agents, and a decrease in defensive immune mechanisms.

Gram-negative bacteria that frequently colonize the oropharyngeal cavity are the main agents related to pneumonia at early post-transplant stages. Intestinal degermination with ciprofloxacine (500 mg each day during the 1st month) could avoid this colonization. Etiological diagnosis involves blood cultures with Gram and Ziehl-Nielsen staining and conventional and mycobacterial culturing. Bacteria are the main agents related to pneumonia at early post-transplant stages, often diagnosed without invasive techniques and with a positive response to empirical treatment with wide-spectrum antibiotics. However, if pulmonary infiltration progresses and/or worsens, the clinical condition of the patient makes transtracheal puncture, telescope catheter culture, fiberoptic bronchoscopy (bronchoalveolar culture and/or transbronchial biopsy), transthoracic puncture or surgical pulmonary biopsy necessary. These techniques allow the correct micro- and histopathological diagnosis of these opportunist agents. Patients with orotracheal intubation or mechanical ventilation requirements must be considered at high risk of respiratory infection and all diagnostic techniques available must be used as required. In those patients, early diagnosis and treatment leads to improved prognosis. Unfortunately fiberoptic bronchoscopy with bronchoalveolar culture and lung biopsy in the early stages after OLT, involve an additional risk due to hemostatic alterations that usually appear at this stage.

Fungal infection incidence has decreased from 40% to 10% due to improvements in postoperative care [17, 18]. The most frequent fungal agents involved are *Candida* and *Aspergillus*. Pulmonary candidiasis is frequently spread through the blood stream [19]. Aspergillar infection may develop into disseminated aspergillosis [20]. An early diagnosis and treatment improves prognosis although mortality related to aspergillar infection reached 100%. In an attempt to reduce fungal infection in our center we include itraconazol treatment as prevention during the first 3 months after transplant.

Patients with pulmonary complications after OLT have a higher mortality rate, reaching statistical significance in those with RI (Figs. 3, 4). If we analyze factors involved in RI development, in those patients who also developed graft dysfunction, pneumonia or sepsis, mortality was greater, as can be appreciated from Fig. 5. Pleural effusion, although involving greater mortality, did not reach statistical significance. On the other hand, patients with the coexistence of three factors leading to RI had a high mortality rate (83.3% vs 48%, $P < 0.05$). Analyzing these data we can conclude that patients with pulmonary complications after OLT, and especially those with RI, have a high mortality rate. Those patients with three factors causing RI make up a special risk group, early diagnostic and therapeutic management being essential for their survival.

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