Post-transplant obstructive lung disease ("bronchiolitis obliterans"): a clinical comparative study of bone marrow and lung transplant patients

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ABSTRACT: Patients at a single pulmonary centre who developed obstructive lung disease after bone marrow transplantation (BMT) and lung transplantation (LT) were studied, in order to compare the clinical expression of post-transplant obstructive lung disease (PTOLD) (bronchiolitis obliterans) in these two conditions, which have so far been studied separately.

Nine out of 179 patients surviving more than 100 days after BMT (5%) and 9 out of 44 patients surviving more than 100 days after LT (20%) developed post-transplant obstructive lung disease. This was defined by an irreversible airflow obstruction, as characterized by a forced expiratory volume in one second divided by forced vital capacity (FEV_1/FVC) of less than 70%, and a FEV_1 of less than 70% of predicted value.

The mean interval between transplantation and the diagnosis of post-transplant obstructive lung disease was 262 days and 217 days for BMT and LT patients, respectively. In all cases, pulmonary symptoms consisted of dyspnoea and progressively productive cough. Bronchial dilatation on high-resolution computed tomography scans was the main imaging feature present in both groups of patients at the onset of post-transplant obstructive lung disease. The mean FEV_1/FVC ratio was 51 and 54% for BMT and LT patients, respectively. All BMT and LT patients had normal transfer coefficient. Clinical chronic graft-*versus*-host disease was present in all BMT patients before or concurrent with the onset of post-transplant obstructive lung disease, and all LT patients had presented at least one episode of acute lung rejection. Five BMT and six LT patients died of respiratory failure at means of 397 and 228 days, respectively, after the onset of post-transplant obstructive lung disease. Other patients remained stable or improved after increasing immunosuppressive therapy.

These data suggest that clinical, radiological, and functional presentation of obstructive lung disease after lung or bone marrow transplantation is quite similar in both conditions.
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Over the past decade, organ transplantation has been used with increasing success in treating life-threatening disorders, including haematological malignancies and end-stage cardiopulmonary diseases [1, 2]. Long-term survival after transplantation is now achieved in many cases, but severe respiratory late complications may occur, mostly after bone marrow transplantation (BMT) and lung transplantation (LT) (heart-lung, single lung, and double lung transplantation). These complications principally include infectious involvement of the lung, idiopathic interstitial pneumonitis, and obstructive lung disease [3–6].

Post-transplant idiopathic obstructive lung disease occurs exclusively after BMT (allogenic, and rarely autologous) and LT, and is usually associated with the pathological finding of "constrictive" bronchiolitis obliterans [7]. The histological term "bronchiolitis obliterans" has been com-monly used in the literature to name this complication, but histological bronchiolitis obliterans is not always associated with obstructive lung disease, particularly in LT [8, 9]. Recently, the term "bronchiolitis obliterans syndrome" has been proposed to describe lung graft deterioration secondary to progressive airways disease [9]. We presently prefer the term of post-transplant obstructive lung disease (PTOLD), because it takes into account both the functional definition of the syndrome and its context of occurrence. PTOLD has been reported in up to 50% of long-term survivors after LT, and in up to 11% after BMT [2, 10–13]. It represents a major cause of morbidity and death among long-term survivors, thus jeopardizing the success of transplantation.

BMT and LT are performed by distinct medical groups, and their complications are generally studied separately.

We made a comparative study of PTOLD developing both in LT and BMT patients seen at a single pulmonary centre.

Patients and methods

Patient selection

Between 8 December 1979 and 31 December 1992, 400 adult patients (aged >15 yrs) were given BMT (275 allogenic and 125 autologous BMT) for haematological malignancies or aplastic anaemia at the Department of Hematology of Edouard Herriot University Hospital. Between 13 July 1988 and 31 December 1992, 65 adult patients underwent 66 LT (24 heart-lung transplantation, 10 double lung transplantation, and 32 single lung transplantation) for end-stage cardiopulmonary diseases at Louis Pradel University Hospital (one patient was retransplanted).

The present study concerns patients who underwent BMT or LT, and who developed PTOLD as defined by an irreversible airflow obstruction characterized both by (FEV_1/FVC) forced expiratory volume in one second divided by forced vital capacity of less than 70%, and FEV_1 less than 70% of the predicted value. A partial report of seven patients with obstructive lung disease after BMT included in this series has been previously published in the French literature [14].

Bone marrow transplantation management

Patients with haematological malignancies received one of the two preparative regimens, consisting either of busulphan (4 $mg \cdot kg^{-1}$ of body weight (BW) on four successive days) and cyclophosphamide (60 $mg \cdot kg^{-1}$ BW on two successive days, or 50 $mg \cdot kg^{-1}$ BW on four successive days), or cyclophosphamide (60 $mg \cdot kg^{-1}$ BW on two successive days). Most subjects also received total body irradiation (10 Gy in one fraction, or 12–15 Gy in six fractions). Immunosuppressive therapy, consisting of methotrexate (10 $mg \cdot m^{-2}$ body surface area (BSA) on days 1, 3, 6 and 11) and cyclosporin (5 $mg \cdot kg^{-1}$ BW daily) for 6 months, was instituted immediately after BMT to prevent graft-*versus*-host-disease (GVHD). Between 1979 and 1982, the immunosuppression consisted of methotrexate only. For patients with altered renal function, cyclosporin was replaced by methylprednisolone. The clinical signs of GVHD were assessed according to the classical criteria [15]. Patients with acute GVHD received methylprednisolone as an intravenous bolus (1 $g \cdot day^{-1}$ for 3 days) followed by progressively decreasing oral steroid therapy. Chronic GVHD was treated with prednisone and azathioprine.

Lung transplantation management

After LT, the immunosuppressive regimen consisted of cyclosporin (5–10 $mg \cdot kg^{-1}$ BW daily), azathioprine (1–3 $mg \cdot kg^{-1}$ BW daily), and rabbit antithymocyte globulin (125 $mg \cdot day^{-1}$ for the first 15 postoperative days). Methylprednisolone was started after the 15th post-operative day: 0.5 $mg \cdot kg^{-1}$ BW daily until the end of the third month, and 0.2 $mg \cdot kg^{-1}$ BW daily thereafter. Dosages of cyclosporin, measured by radioimmunoassay, were adjusted to maintain a blood level of 150–200 $ng \cdot ml^{-1}$ during the first post-transplantation year, and 100–150 $ng \cdot ml^{-1}$ thereafter.

Fibreoptic bronchoscopy with transbronchial lung biopsies and bronchoalveolar lavage were systematically performed weekly during the first month post-LT, and every 2 months thereafter. This procedure was repeated according to clinical indications, such as dyspnoea, fever, pulmonary infiltrates, hypoxaemia. Acute rejection, defined by characteristic histological features obtained on transbronchial lung biopsies [16], was usually treated with intravenous methyprednisolone (1 g daily for 3 days). Persistence of acute lung rejection on biopsies led to further treatment with rabbit antilymphocyte globulin.

Lung function testing

All lung function tests (LFTs), both before and after transplantation, were performed at the same laboratory for all patients. After BMT, lung function tests were performed only when patients presented with symptoms of respiratory illness. After LT, lung function tests were performed weekly from the time the patient was discharged from the intensive care unit (generally after 1–3 weeks) until discharge from hospital (generally after 8–12 weeks), and then as a routine twice a month during the first year, and once a month thereafter.

Flow-volumes curves were obtained using a P.K. Morgan spiroflow (P.K. Morgan Ltd, Chatham, Kent, UK). To determine the site of airflow obstruction, maximum expiratory flows were measured breathing a helium-oxygen mixture (He 80% and O_2 20%) and ambient air [17]. Total lung capacity (TLC) and residual volume (RV) were obtained by helium dilution technique, using a P.K. Morgan Transfer Test (P.K. Morgan Ltd, Chatham, Kent, UK). The transfer factor of the lung for carbon monoxide (TL_{CO}) was measured by the single-breath technique and expressed as the transfer coefficient (TL_{CO}/V_A - alveolar volume). Predicted values for total lung capacity, FEV_1, TL_{CO}, and maximum expiratory flow in air were taken from QUANJER and co-workers [18, 19].

Imaging

BMT patients underwent chest radiography and high resolution computed tomography (HRCT) only when respiratory symptoms appeared. LT patients underwent surveillance chest radiography systematically twice a month during the first year after transplantation, and monthly thereafter; they also had HRCT every 2 months, or more frequently when respiratory symptoms suggested lung rejection, cytomegalovirus (CMV) infection, or PTOLD.

HRCT scans were examined for bronchial dilatation, as defined by a bronchial diameter at least 1.5 times

greater than that of the adjacent artery, nodular opacities, frosted glass opacities, alveolar consolidation, or abnormal vascularity.

Lung pathology

Lung tissue specimens were obtained by video-assisted surgical biopsy, open lung biopsy, or autopsy. As stated above, transbronchial lung biopsies were systematically taken to monitor acute lung rejection, but the small size of these specimens usually did not permit reliable analysis of the bronchiolar area. Paraffin sections were stained with haematoxylin-eosin-saffran, Gram and periodic-acid-Schiff (PAS). In most cases, tissue was sent to the microbiology laboratory for bacterial, viral and fungal cultures.

Statistical analysis

Fisher's exact test was applied to between-group analyses of categorical data.

Results

Clinical presentation

Of the 275 allogenic BMT patients, 179 survived at least 100 days after transplantation, and nine of these (5%) developed PTOLD over this time. No PTOLD was observed earlier than 105 days post-BMT, and no PTOLD was observed among the 125 autologous BMT recipients. Six patients with PTOLD had received total body irradiation (12–15 Gy) in their preparative regimen, whilst three had not. The clinical characteristics of the nine patients are summarized in table 1. Patients Nos 4 and

9 were mild smokers before BMT (10–20 cigarettes·day^{-1} for 20 yrs), and the other patients were nonsmokers. The average time elapsed between BMT and diagnosis of PTOLD was 262 days (range 105–550 days).

Of the 65 adult patients receiving LT, 21 died perioperatively and 44 survived more than 100 days; nine of the latter (20%) developed PTOLD during the follow-up. No PTOLD was detected earlier than 120 days post-LT. Clinical characteristics of the nine patients are summarized in table 2. Patients Nos. 1–7 had received heart-lung transplantation, patient No. 8 had received single-lung transplantation, and patient No. 9 had received double-lung transplantation. Because of a systematic monitoring of lung function for LT patients, PTOLD was detected at the time or before the onset of respiratory symptoms (dyspnoea, progressively productive cough) at a mean of 217 days post-LT (range 120–303 days) in this group of patients.

Radiographic and high resolution computed tomography features

For BMT patients, chest radiographs were normal in four cases, showed moderate hyperinflation in three cases, and bilateral infiltrates in two cases (Nos. 2 and 5), where PTOLD was diagnosed immediately after bacterial lung infections (attributed to *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*, respectively). HRCT was obtained in only four patients (Nos. 4, 6, 8 and 9) who all showed bronchial dilatation, predominantly in the lower lobes. No vascular attenuation was seen in any case, but patchy frosted glass opacities were observed in cases Nos. 8 and 9.

For LT patients, chest radiographs were normal in four cases, showed moderate hyperinflation in two cases, and bilateral infiltrates in three patients (Nos. 2, 3 and 4)

Table 1. – Clinical data in nine BMT patients with PTOLD

Pt No.	Sex	Age yrs	Primary disease	Onset of PTOLD Day, symptoms	Chest radiograph	Onset of chronic GVHD day	Outcome and cause of death
1	M	18	ALL	323 Dyspnoea, cough	Hyperinflation	200	Died day 817, respiratory failure
2	F	23	ALL	257 Dyspnoea	Bilateral infiltrates	150	Died day 295, respiratory failure
3	M	42	CML	172 Dyspnoea	Normal	120	Died day 402, respiratory failure
4	M	41	CML	105 Dyspnoea	Hyperinflation	110	Died day 367, respiratory failure
5	M	35	ALL	236 Dyspnoea, fever	Bilateral infiltrates	200	Stable (day 1,460)
6	F	23	AML	154 Dyspnoea, cough	Hyperinflation	170	Died day 270, respiratory failure
7	M	39	AML	187 Dyspnoea	Normal	153	Improved (day 334)
8	F	31	AML	275 Dyspnoea, cough	Normal	116	Stable (day 580)
9	M	42	ALL	550 Dyspnoea	Normal	270	Stable (day 832)

Pt: patient; ALL: acute lymphoid leukaemia; CML: chronic myeloid leukaemia; AML: acute myeloid leukaemia; GVHD: graft *versus* host disease; BMT: bone marrow transplant; PTOLD: post-transplant obstructive lung disease; M: male; F: female.

Table 2. – Clinical data in nine LT patients with PTOLD

Patient No.	Sex	Age	Primary disease	Onset of PTOLD day	Chest radiograph	First evidence of bronchectasis	Outcome and cause of death
1	M	22	Thromboembolic pulmonary hypertension	139	Hyperinflation	Day 109	Died day 437, respiratory failure
2	M	17	Cystic fibrosis	120	Bilateral infiltrates	No	Died day 211, ARDS
3	M	15	Cystic fibrosis	247	Bilateral infiltrates	Day 296	Died day 372, MOF
4	M	25	Cystic fibrosis	303	Bilateral infiltrates	Day 565	Died day 1,210, respiratory failure
5	M	35	Histiocytosis X	150	Normal	No	Stable day 1,353
6	F	28	PPH	310	Hyperinflation	Day 310	Died day 697, after retransplant, respiratory failure
7	M	33	PPH	190	Normal	Day 311	Died day 872, respiratory failure
8	F	29	PPH	260	Normal	Day 275	Stable day 877
9	M	59	Emphysema	240	Normal	Day 195	Stable day 649

ARDS: adult respiratory distress syndrome; MOF: multiple organ failure; PPH: primary pulmonary hypertension; LT: lung transplant. For further abbreviations see legend to table 1.

where they were related to infectious involvement of the lung (pulmonary toxoplasmosis, *Pseudomonas aeruginosa* pneumonia, and sequelae of tuberculosis of upper lobes, respectively). HRCT scans showed bilateral infiltrates in these three patients, and bronchial dilatation in 7 of the 9 patients (Nos. 1, 3, 4 and 6–9), predominantly involving the middle and lower lobes. Only 3 of 35 LT patients without PTOLD showed bronchial dilatation, so that the presence of bronchial dilatation in LT patients correlated with clinical and functional evidence of PTOLD ($p<0.0001$). In two cases (Nos. 1 and 9), bronchial dilatation preceded the onset of PTOLD. One patient (No. 1) had decreased vascularity of the lung at the onset of PTOLD.

Lung function tests

For the nine BMT patients, the results of lung function tests before transplantation and at the time of PTOLD are reported in table 3. Patient No. 2 had a previous history of asthma with completely reversible obstruction. Evolution of FEV_1 of the nine patients showed the rapidly progressive decline characterizing PTOLD (fig. 1). Eight patients had a mild decrease of TLC after transplantation. The transfer coefficient remained normal after BMT. Helium-oxygen (He/O_2) maximum expiratory flow studies were carried out on six patients. No improvement of more than 20% was seen in airflow when breathing He/O_2 at 50% of vital capacity as compared to air maximum expiratory flow for patients Nos. 4, 6, 8 and 9; for patients Nos. 5 and 7, the improvement was mild: 40% (680 ml) and 50% (920 ml), respectively.

After LT, all nine patients recovered normal lung function tests, except for a mild reduction of TLC (table 3). No patient had a history of asthma before transplantation.

Changes in FEV_1 are shown in figure 2. According to the staging system of the International Society of Heart and Lung Transplantation [9], five patients had bronchiolitis obliterans syndrome stage 3 (FEV_1 50% or less of baseline value), three patients were stage 2 (FEV_1 51–65% of baseline value), and one patient stage 1 (FEV_1 66–80% of baseline value). Lung function tests showed a global reduction of airflow to low values (table 3). At the time of PTOLD, TLC remained stable as compared with the best lung function tests results obtained after transplantation. The transfer coefficient was normal and stable during follow-up. He/O_2 maximum expiratory flow measurements were carried out on all nine patients, and for eight of them no significant change in airflow at 50% of vital capacity was observed when breathing HeO_2 as compared with breathing air. For patient No. 3, an improvement of 46% (870 ml) was observed.

Table 3. – Lung function tests (LFTs) before and at the time of PTOLD in BMT and LT patients

Variables	BMT patients		LT patients	
	LFT before BMT	LFT at diagnosis PTOLD	Best LFT after LT	LFT at diagnosis PTOLD
TLC % pred	103±11	84±12	76±15	72±14
FEV_1 % pred	102±11	48±15	76±16	42±23
FEV_1/FVC %	79±5	51±8	84±9	54±12
T_{LCO}/V_A % pred	94±22	89±20	98±16	96±21

Values are presented as mean±SD. TLC: total lung capacity; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; T_{LCO}: transfer factor of the lungs for carbon monoxide; V_A: alveolar volume; % pred: percentage of predicted value. For further abbreviations see legend to tables 1 and 2.
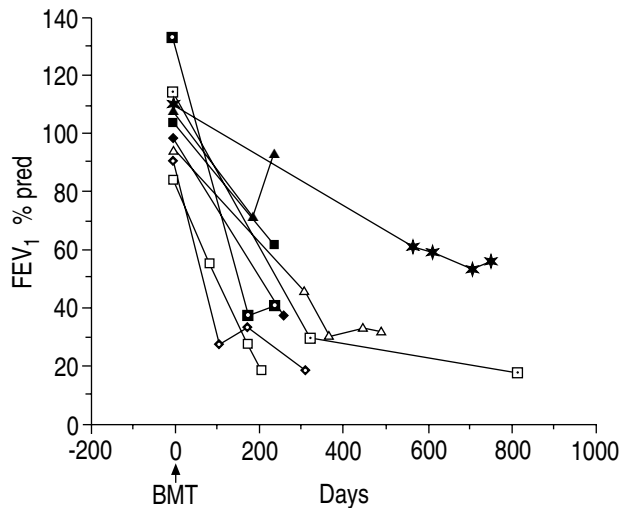
Fig. 1. – Change in FEV_1 (% of predicted value) after BMT. Patients Nos. 1–4 and 6 died of respiratory failure. FEV_1: forced expiratory volume in one second; % pred: percentage of predicted value; BMT: bone marrow transplant. ⊡ : patient No. 1; ◆ : patient No. 2; ◩ : patient No. 3; ◇ : patients No. 4; ■ : patient No. 5; □: patient No. 6; ▲ : patient No. 7; △ : patient No. 8; ✳ : patient No. 9.
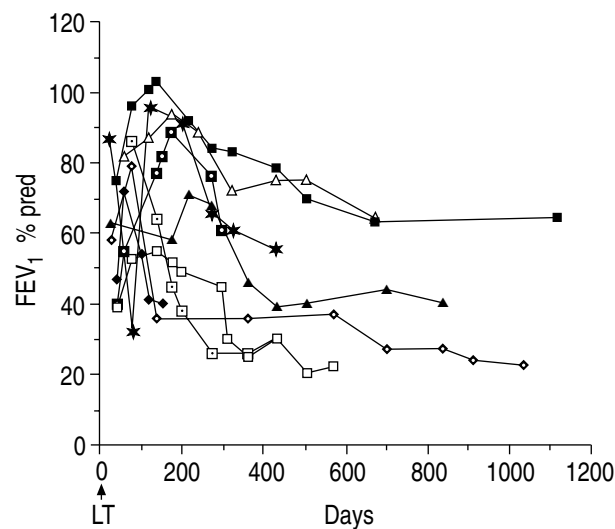

Fig. 2. – Change in FEV_1 (% of predicted value) after LT. Patients Nos. 1, 2, 4, 6 and 7 died of respiratory failure; patient No. 3 died of multiple organ failure. FEV_1: forced expiratory volume in one second; LT: lung transplant. ⊡ : patient No. 1; ◆ : patient No. 2; ◩ : patient No. 3; ◇ : patient No. 4; ■ : patient No. 5; □: patient No. 6; ▲ : patient No. 7; △ : patient No. 8; ✳ : patient No. 9.

Outcome of patients with PTOLD

The nine BMT patients were treated with increased immunosuppressive therapy: prednisolone (1 mg·kg^{-1} BW daily), and azathioprine (2–3 mg·kg^{-1} daily). Patient No. 9 received cyclosporin at a dosage adjusted to maintain a level of 100–150 ng·ml^{-1}. Five patients died of respiratory failure directly related to PTOLD, with a mean interval of 228 days (range 38–494 days) after the onset of PTOLD; three remained stable, and one improved. All nine patients had developed clinical chronic GVHD before or concurrently with the onset of PTOLD. The prevalence of chronic GVHD was 32% in BMT patients

surviving more than 100 days without PTOLD. In two cases (patient Nos. 8 and 9), we observed a major improvement in the cutaneous signs of chronic GVHD (present at the time of diagnosis of PTOLD) during increased immunosuppressive therapy for PTOLD. In patient No. 8, cutaneous GVHD relapsed further when immunosuppression was reduced, with a concomitant decrease of FEV_1/FVC; both respiratory and cutaneous symptoms improved again with reinforced immunosuppression.

All nine LT patients with PTOLD had suffered at least one episode of acute lung rejection (mean number of episodes 3 per patient; range 1–6), which were treated as described above. The treatment of PTOLD for the nine LT patients was not standardized. It included increased immunosuppression with high dose of intravenous methylprednisolone (1 g·day^{-1}, for 3 days), and augmented dosage of azathioprine (3 mg·kg^{-1} daily). Patient No. 1 received rabbit antithymocyte globulin at the onset of PTOLD, without improvement. Six patients died, at a mean interval of 397 days (range 91–907 days) after the onset of PTOLD (four of respiratory failure directly related to PTOLD, one of adult respiratory distress syndrome, and one of septic shock). Patient No. 6 was retransplanted for severe PTOLD 660 days after initial transplantation; she died of respiratory failure 3 weeks after retransplantation.

Lung pathology

Histopathological studies of the lungs were performed in six cases (BMT Nos. 8 and 9, and LT Nos. 2, 3, 6 and 7). Lung tissue was obtained by surgical biopsy with video-assistance in BMT patients Nos. 8 and 9, by open lung biopsy in LT patient No. 2, and by autopsy in LT patients Nos. 3, 6 and 7. The chief common abnormalities were found in and around the bronchioles, and were generally characteristic of constrictive bronchiolitis. In LT patients Nos. 2 and 6, proximal airways were available for pathological examination, and showed inflammatory infiltration associated with bronchectasis. No vascular lesions were observed in any of the LT and BMT pathological lung specimens reviewed in our study. A more detailed pathological study of our patients with PTOLD will be published separately.

Discussion

Our comparative study shows that PTOLD has very similar clinical, imaging, and functional features both in BMT and LT patients. The prevalence of PTOLD after transplantation has been reported by different centres to between 1, 2 and 11% for BMT [4, 11–13], and 20 and 50% for LT [2, 6, 10]. For PARADIS *et al.* [6] the prevalence of PTOLD was based on a survival of more than 60 days after LT, since they did not observe it before this time. We have defined our population at risk of PTOLD as recipients who survived more than 100 days after transplantation, because we observed no PTOLD

earlier than 105 days post-BMT and 120 days post-LT. Furthermore, BMT patients who survive more than 100 days after transplantation are at risk of chronic GVHD, which is a complication strongly associated with PTOLD [11]. We have not considered patients who died in the early post-transplantation period, and had no functional evaluation.

In our study, the prevalence of PTOLD was 5% for BMT and 20% for LT patients. In both conditions, chronic irreversible airflow obstruction usually occurs during the first year after transplantation. Follow-up after transplantation was initially different for the two groups of patients, and this represents a limitation in the interpretation of the clinical and functional data at the time of diagnosis of PTOLD. LFTs were performed as routine in LT because they were used as a tool to detect specific pulmonary events, such as acute rejection, airways complications, or chronic rejection; in BMT, LFTs were performed only when patients had respiratory symptoms. This difference may explain the earlier detection of PTOLD in LT: 217 *versus* 267 days in BMT patients. However, when the respiratory symptoms were present, the clinical expression of PTOLD was identical, with dyspnoea and cough becoming progressively productive, resembling the clinical presentation of patients with chronic obstructive pulmonary disease. As a consequence of the current study, all BMT patients are now followed prospectively, with LFTs performed as a routine.

The moderate-to-severe degree of airflow obstruction in our patients (mean FEV_1/FVC of 51 and 54%, for BMT and LT patients, respectively) was similar to that reported in previous studies [3, 13]. No patient from the BMT group had pre-existing permanent obstructive ventilatory defect (table 3). In the LT group, the best lung function tests obtained after transplantation did not show any obstructive disease (table 3), but a mild decrease of total lung capacity was present, probably secondary to the surgical transplant procedure (sternotomy or thoracotomy). The total lung capacity reduction associated with PTOLD cannot be attributed to an interstitial process, because of the normal transfer coefficient, and the lack of compatible changes on HRCT scans. It could be due to an underestimation of gas-trapping by the helium dilution technique used to measure lung volume, as suggested by CHAN *et al.* [13]. The existence of non-ventilated areas of lung parenchyma distal to the bronchiolar obstruction is another possible mechanism. We did not perform body plethysmography measurement to confirm or not the existence of a true restrictive defect. In the series of CLARK *et al.* [4], the total lung capacity was within normal limits. In 12 patients (4 BMT and 8 LT) He/O_2 maximum expiratory flow did not differ from air maximum expiratory flow. Airflow in small airways is considered to be laminar and density-independent [18]. The absence of improvement (less than 20%) in flow by changing the density of the inspired gas, as with He/O_2 which is less dense than air, suggests that the peripheral airways are the site of obstruction [18]. In contrast to SCHWARER *et al.* [5], who found a marked fall in transfer coefficient associated with late-onset pulmonary syndrome, the transfer coefficient was normal in our patients.

However, their study group included patients with interstitial lung disease.

Imaging findings in post-transplant PTOLD are diverse and nonspecific [20, 21]. Chest radiographs may be normal, or they may show hyperinflation or interstitial infiltrates [22]. Bronchial dilatation has been identified as the most characteristic change on HRCT scans in PTOLD developing after LT [20–22]. Previous studies found a link between bronchial dilatation and bronchiolitis obliterans, and, in a retrospective study of 16 patients, LENTZ *et al.* [22] concluded that evidence of bronchial dilatation by HRCT was more sensitive in predicting the presence of bronchiolitis obliterans than were chest radiographs or transbronchial biopsies. Our results in LT patients confirm the association between the presence of bronchial dilatation in the lower and middle lobes on HRCT scans and PTOLD. Little information is available in the literature about the bronchial size in BMT patients. We found that bronchial dilatation in the lower and middle lobes was also associated with post-BMT PTOLD. The infiltrates seen in five of our patients (3 LT and 2 BMT) were probably secondary to documented previous infection. Parenchymal abnormalities (nodular or alveolar opacities) associated with bronchial dilatation have been described in LT patients with histological evidence of bronchiolitis obliterans [21].

It is now clear that the main pathological feature associated with PTOLD is "constrictive" bronchiolitis, which consists of bronchiolar cellular inflammation followed by fibrosis in the submucosal and peribronchiolar areas, resulting in constriction and stenosis of the airways [7, 23]. In addition to distal airway injury, pathological inflammatory lesions of the large airways have been described in LT and BMT patients [24, 25]. They consist of proximal bronchitis and bronchiectasis [25]. Inflammatory lesions of proximal airways associated with bronchiectasis were present in two LT patients, for whom histological material was available. In BMT patients, bronchiectasis associated with PTOLD has not previously been clearly reported. However, evidence of lymphocytic bronchitis associated with GVHD was reported by BESCHORNER *et al.* [26], and extensive inflammatory lesions of the entire bronchial tree were seen by URBANSKI *et al.* [24]. Both radiological and pathological data, thus, suggest that PTOLD is associated with a diffuse airway inflammatory process involving both the bronchioles and the larger bronchi.

Many potential risk factors for the development of PTOLD have been suspected. Chronic GVHD has been implicated as a risk factor in BMT patients [4, 12, 13], and it was present in all our patients with PTOLD. PTOLD is most often seen in patients with previous clinical signs of chronic GVHD, but may appear in their absence [4]. PTOLD is thought to be the respiratory expression of chronic GVHD directed against the airways (bronchioles and bronchi). PTOLD after LT is generally considered as a manifestation of chronic lung rejection [6, 27]. This is supported by studies suggesting a relationship between the severity, frequency, persistence of acute rejection, and the onset of PTOLD after LT [27, 28]. Infection, chronic aspiration, and

therapeutic agents, such as methotrexate in BMT patients, may also contribute to the pathogenesis of PTOLD [4, 11, 25]

The treatment of PTOLD after transplantation usually consists of an increased immunosuppression, since PTOLD is considered as an immunological process related to either GVHD or chronic lung rejection. In LT patients, azathioprine has been reported to stop the progression of PTOLD [29]. We observed stabilization or improvement of lung function tests after increased immunosuppression in seven patients (4 BMT and 3 LT). Among the other 11 patients, 10 died of respiratory failure. The efficacy of alternative forms of immunosuppression, particularly antithymocyte immunoglobulin, remains unknown, although a recent study suggested that anti-lymphocytic agents could be more effective than corticosteroids [30]. Aerosolized bronchodilators tested in 26 BMT patients with PTOLD improved airflow rates in only three patients [4].

In summary, the comparison of obstructive lung disease complicating BMT and LT clearly shows striking similarities. The clinical presentation is identical, with rapidly progressive dyspnoea and cough becoming productive. Lung function tests show a severe irreversible obstructive defect with normal transfer factor. In both conditions, the obstructive lung disease is associated with a diffuse inflammatory airway disease resulting in ectasia of the large bronchi (the most consistent imaging feature) and constriction of the bronchioles. At the present time, no single risk factor can predict the development of PTOLD. More likely, it is the result of a sequence of events including various infections and other injuries (related to drugs, irradiation, ischaemia), and an inappropriate immunological response, with GVHD in BMT patients and graft rejection in LT patients. Comparative studies of PTOLD in BMT and LT patients may help to improve our understanding of the pathogenesis of this severe complication of transplantation, thus allowing progress in its prevention.

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