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A CHRONIC PULMONARY SYNDROME ASSOCIATED WITH GRAFT-VERSUS-HOST DISEASE AFTER ALLOGENEIC MARROW TRANSPLANTATION[1]

ANTHONY P. SCHWARER,[2,3,4] J. MICHAEL B. HUGHES,[5] BEATRICE TROTMAN-DICKENSON,[6] THOMAS KRAUSZ,[7] AND JOHN M. GOLDMAN[4]

MRC/LRF Leukaemia Unit, Royal Postgraduate Medical School and the Departments of Respiratory Medicine, Radiology, and Histopathology, Hammersmith Hospital, London, W12 ONN, United Kingdom

Of 143 consecutive patients who survived at least 6 months after bone marrow transplantation (allogeneic [n=131]; syngeneic [n=5]; or autologous [n=7]) and whose pulmonary function was evaluated before and on at least 2 occasions after BMT, 29 (20%) developed a chronic pulmonary syndrome without evidence for an infectious etiology. Twenty-eight (97%) presented with cough and 22 (76%) with dyspnea; abnormal chest signs were crackles in 23 (79%) and wheeze in 22 (76%). Chest roentgenogram showed pulmonary infiltrates in 15 (52%) cases but was normal in 14 (48%). All patients had major reductions in lung volumes (forced expiratory volume in 1 sec [FEV_1]; relaxed vital capacity [VC]; and alveolar volume [VA]), and/or diffusing capacity (pulmonary diffusing capacity [TLCO] and single-breath carbon monoxide coefficient [KCO]). The obstructive component varied with only 18 (62%) patients developing overt airways obstruction (FEV_1/VC <75%), and in 6 of this group the fall in lung volumes preceded the onset of airways obstruction. Open lung biopsy (n=4) showed both bronchiolitis obliterans and chronic patchy interstitial pneumonitis. The development of this syndrome was associated with acute ($P<0.001$) and chronic ($P<0.0001$) graft-versus-host disease of other organ systems. Twenty-four (83%) patients had a partial or complete response to immunosuppressive agents. Six (21%) have died, five (17%) of pulmonary complications. We suggest that this syndrome may be a manifestation of chronic GVHD involvement of the lung.

Bone marrow transplantation provides long-term disease-free survival for some patients with a variety of malignant and nonmalignant disorders (*1*). Infectious and therapy-related complications involving the lung are a common cause of morbidity and mortality limiting the success of this treatment (*2, 3*). In recent years, a late-onset pulmonary syndrome associated with chronic graft-versus-host disease has been recognized occurring alone or in combination with other pulmonary complications (*4-6*). Initial reports focused on airflow obstruction, associated histologically with obliterative bronchiolitis (*7, 8*), but others have described interstitial lung disease either alone or in combination with the aforementioned change (*9-12*). The possibility that these changes may be manifestations of chronic pulmonary graft-versus-host disease has been raised (*7, 13*). The one large series to date describing pulmonary syndrome occurring late after allogeneic BMT required overt evidence of airflow obstruction (*14*), but this may unnecessarily limit the description of late-onset pulmonary disease. Here, we report a large series that include patients with airways obstruction and/or interstitial lung disease as possible manifestations of chronic GVHD. We identify risk factors and describe the clinical, functional, radiological, and pathological features of this syndrome and the response to immunosuppressive treatment.

MATERIALS AND METHODS

All patients undergoing allogeneic, syngeneic, or autologous BMT at the Hammersmith Hospital for acute or chronic leukemia, or myelodysplasia (n=275), between August 1979 and December 1990, or severe

[1] This work was supported in part by research grants from the Medical Research Council and the Leukaemia Research Fund (UK).
[2] Address correspondence to: Dr. Anthony P. Schwarer, MRC/LRF Leukaemia Unit, Royal Postgraduate Medical School, London, W12 ONN. United Kingdom.
[3] APS is supported by the Leukaemia Research Fund (UK).
[4] MRC/LRF Leukaemia Unit.
[5] Department of Respiratory Medicine.
[6] Department of Radiology.
[7] Department of Histopathology.

aplastic anemia (SAA)* or Fanconi's anemia (n=18) between August 1988 and December 1990 were considered (prior to 1988 pulmonary function tests were not routinely performed in the latter group). Patients were included in the study population if they survived more than 6 months post-BMT and had pulmonary function tests performed prior to BMT and on at least 2 occasions post-BMT. One hundred and forty-three patients were eligible for inclusion in the study. As a routine, patients had pulmonary function tests performed 1 month prior to, and 3, 6, 9, 12, 18, and 24 months post-BMT, and thereafter every 12 months.

Patients who presented with symptoms and signs of a respiratory illness associated with the development of abnormal pulmonary function tests in the absence of evidence for an infectious cause were included in the study population. There was no history of exposure to irritant gases such as sulphur dioxide, chlorine, or ammonia capable of causing pulmonary damage. Possible infectious etiologies were excluded by appropriate cultures (viral, bacterial, and fungal) and failure to detect cytomegalovirus early antigen by fluorescent foci formation (DEAFF test) usually of sputum, blood, and urine. In addition, bronchoalveolar lavage was undertaken in 14 (48%) patients and open-lung biopsy in four (14%) patients to exclude possible infectious etiologies, with particular emphasis on cytomegalovirus (histology, culture, and detection of early antigen fluorescent foci [DEAFF] test) and *Pneumocystis carinii* (methenamine-silver stain).

Details of the conditioning regimens have been reported previously (*15–17*). Briefly, all patients received either cyclophosphamide alone (n=2), or cyclophosphamide followed by the following: (A) fractionated total-body irradiation totaling either 6 Gy (n=2), 10 Gy (n=33), 12 Gy (n=92), or 13.2 Gy (n=4); or (B) busulphan (n=10). The radiation source was a Philips 8-MeV linear accelerator with a dose rate of 15 cGy/min. GVHD prophylaxis was cyclosporine alone (n=50) or in combination with methotrexate (n=52) or prednisolone (n=8), and/or ex vivo T cell depletion (TCD) of the donor marrow (n=56) with the rat monoclonal antibody, Campath 1M (*18*), or in vivo T cell depletion (in vivo TCD) that consisted of a 5-day intravenous course of the rat monoclonal antibody, Campath 1G (*19*), given to the recipient immediately following the infusion of donor marrow (n=9). All patients received *Pneumocystis carinii* prophylaxis with cotrimoxazole.

The methods for the measurement of lung volumes (forced expiratory volume in 1 sec [FEV_1]; relaxed vital capacity [VC]; alveolar volume [VA]); pulmonary diffusing capacity (TLCO); and single-breath carbon monoxide coefficient (KCO) have been described previously (*20*).

CT scans were performed using 8- or 10-mm collimated scans at 1-cm intervals with selected 2-mm cuts.

Statistical methods. Fisher's exact test, and the chi-square test with Yates' correction, were applied to between-group analyses of categorical data. Mean lung volume measurements were compared using an unpaired *t* test.

RESULTS

One hundred and forty-three patients fulfilled the inclusion criteria of whom 29 (20%) developed a late-onset pulmonary syndrome (LOPS) for which an infectious etiology could not be identified. The median age at BMT of the patients without LOPS (control group) was 33 years (range 9–53 years), and that of the LOPS group was also 33 years (range 8–50 years). Median follow-up post-BMT was 28 months (range 6–133 months) for the control group, and 25 months (range 6–111 months) for the LOPS group. Patient characteristics did not differ significantly between the two groups (Table 1). Recipients of marrow from an unrelated donor had a significantly increased risk ($P<0.0001$) of developing LOPS (Table 2). Analysis of the group of recipients of marrow from a sibling donor showed a trend of increased risk for developing LOPS with higher dose TBI and non-TCD marrow donation. No recipient of a syngeneic (n=5) or autologous (n=7) BMT developed a similar late-onset pulmonary syndrome.

TABLE 1. Patient characteristics

	Controls[a] n (%)	LOPS[a] n (%)	P
Sex			
Male	60 (53)	15 (52)	NS
Female	54 (47)	14 (48)	
Disease			
CML[b]	97 (85)	24 (83)	NS
ALL, AML, MDS[c]	13 (11)	4 (14)	
SAA, Fanconi[d]	4 (4)	1 (3)	
Smoker	38 (33)	12 (41)	NS
Prior lung disease	14 (12)	4 (14)	NS
History of atopy	8 (7)	6 (21)	NS
Busulphan[e]	71 (62)	15 (52)	NS
Methotrexate[f]	41 (36)	11 (38)	NS
CMV+[g]	64 (56)	16 (55)	NS
Total	114 (100)	29 (100)	

[a] LOPS denotes late-onset pulmonary syndrome; controls denote patients without LOPS.
[b] CML denotes chronic myeloid leukemia.
[c] ALL denotes acute lymphoblastic leukemia; AML denotes acute myeloid leukemia; MDS denotes myelodysplastic syndrome.
[d] SAA denotes severe aplastic anemia; Fanconi denotes Fanconi's anemia.
[e] Prior to, and/or as conditioning for, BMT.
[f] Used post-BMT for immunosuppression.
[g] Cytomegalovirus antibody present in the serum of the donor or recipient prior to BMT.

Clinical features of LOPS (Table 3). All patients (n=29) with a diagnosis of LOPS had respiratory symptoms at presentation; 24 (83%) had crackles and/or wheezes on auscultation of the chest. A low-grade fever was seen in only two (7%) patients. The median time post-BMT to diagnosis of LOPS was 5 months (range 1–13 months).

Microbiology. Attempts to exclude an infectious etiology were as described in *Materials and Methods.* By definition, at the time of initial presentation with a respiratory illness, no pulmonary pathogens were isolated in any patient with LOPS. Otherwise, there were 22 documented discrete pulmonary infections, usually supervening on poorly controlled LOPS, in 15 (52%) of the 29 patients in the study population, whereas there were 31 such episodes in 27 (24%) of the 114 patients in the control group.

Radiological features of LOPS (Table 4). All patients with a diagnosis of LOPS (n=29) had a chest roetgenogram at presentation. Pulmonary infiltrates were seen in 15 (52%) cases, but notably, 14 (48%) had normal chest roetgenograms despite the presence of clinical symptoms and signs and markedly abnormal pulmonary function tests. The pulmonary infiltrates varied from a few focal areas to extensive bilateral disease. There was no lung-zone predominance, but a peripheral distri-

* Abbreviations: DEAFF, detection of early antigen fluorescent foci; FEV_1, forced expiratory volume in one second; in vivo TCD, in vivo T cell depletion; KCO, single-breath carbon monoxide coefficient; LOPS, late-onset pulmonary syndrome; non-TCD, not T cell depleted; SAA, severe aplastic anemia; TCD, ex vivo T cell depletion; TLCO, pulmonary diffusing capacity; VA, alveolar volume; VC, relaxed vital capacity.

TABLE 2. Total body irradiation, donor marrow source and T cell depletion, and the incidence of late-onset pulmonary syndrome

	Category[a]	Controls n (%)	LOPS[b] n (%)	Odds ratio[c]
(1)	Sibling donor	91 (80)	16 (55)[d]	
	Non-TCD & no TBI	6 (7)	0 (0)	
	Non-TCD & 6 Gy	1 (1)	1 (6)	
	TCD & 10 Gy	15 (16)	0 (0)	—
	Non-TCD & 10 Gy	16 (18)	2 (13)	0.56
	TCD & 12 Gy	21 (23)	4 (25)	1.09
	Non-TCD & 12 Gy	32 (35)	9 (56)	2.44
(2)	Syngeneic or autologous donor	12 (10)	0 (0)[d]	
	Non-TCD & no TBI	5 (42)	0 (0)	
	Non-TCD & 12 Gy	7 (58)	0 (0)	
(3)	Unrelated donor	11 (10)	13 (45)[d]	
	In vivo TCD & no TBI	1 (9)	0 (0)	
	TCD & 12 Gy	6 (55)	8 (62)	
	Non-TCD & 12 Gy	0 (0)	1 (8)	
	In vivo TCD & 12 Gy	3 (27)	1 (8)	
	In vivo TCD & 13.2 Gy	1 (9)	3 (23)	
	Total	114 (100)	29 (100)	

[a] TBI denotes total body irradiation; Gy denotes dose of TBI; TCD denotes ex vivo T cell depletion of donor marrow; in vivo TCD denotes a 5-day intravenous course of the antilymphocyte rat monoclonal antibody, Campath 1G, immediately following donor marrow infusion; non-TCD denotes unmanipulated donor marrow.

[b] LOPS denotes late-onset pulmonary syndrome.

[c] An increased risk of LOPS was seen with increased TBI dose and non-TCD donor marrow.

[d] (1) vs. (3) and (2) vs. (3): $P<0.0001$; and (1) vs. (2): not significant.

TABLE 3. Clinical details of 29 patients with late-onset pulmonary syndrome

		n (%)
A.	Symptoms:	
	Cough	28 (97)
	Dyspnea	22 (76)
	Sputum	8 (28)
	Wheeze	4 (14)
	Total	29 (100)
B.	Signs:	
	Crackles	23 (79)
	Rhonchi	22 (76)
	Fever	2 (7)
	Total	29 (100)

bution was common. Although 19 patients had CT scans performed, only 9 of these were performed prior to the commencement of treatment, and of these two thirds were abnormal. All 7 CT scans performed in the control group were normal. Figure 1 illustrates the dramatic chest roetgenogram and CT changes that may be present at diagnosis. In this case no pathogenic organism was found on bronchoalveolar lavage or open-lung biopsy. The changes resolved completely within days of commencing immunosuppressive treatment.

Pulmonary function data (Fig. 2). The mean lung volume measurements (FEV_1, VC, and FEV_1/VC) and the KCO prior to BMT for the LOPS and control groups were normal, although both groups exhibited a mild abnormality of the TLCO (88.6% and 89.3%, respectively, of the predicted value). Following BMT, the LOPS group showed a marked fall in lung volumes (FEV_1 and VC) associated with a mild obstructive component, although the FEV_1/VC nadir of individual patients ranged from 33% to 86% with 18 (62%) patients exhibiting an abnormal value (<75%). Of note, in 6 of these 18 patients, a major fall in FEV_1 and VC preceded, by a median of 3 months, the onset of overt airways obstruction. Following BMT, the control group exhibited a higher-than-normal FEV_1/VC (mean >86%) that marginally decreased with time. Both groups exhibited a fall in the TLCO and KCO, but the marked fall in the TLCO with relative preservation of the KCO in the LOPS group suggests either a functional (small airways obstruction) or structural loss of alveoli. Twelve patients in the control group who did not receive TBI as part of their conditioning regimen did not show a prominent fall in the TLCO, while patients who underwent syngeneic (n=5) or autologous (n=2) BMT and did receive TBI did show a drop in TLCO (data not shown) of similar magnitude to that seen in the remainder of the control group.

TABLE 4. Radiological details of 29 patients with late-onset pulmonary syndrome

		n (%)
A.	Chest roentgenogram	
	Normal	14 (48)
	Patchy infiltrate	8 (28)
	Diffuse infiltrate	7 (24)
	Nodular/reticular opacities	4 (14)
	Pleural effusion	3 (10)
	Total	29 (100)
B.	CT scan	
	Normal	11 (58)[a]
	Patchy infiltrate	4 (21)
	Diffuse infiltrate	4 (21)
	Nodular/reticular opacities	3 (10)
	Bronchial wall thickening	3 (10)
	Pleural effusion	2 (7)
	Total	19 (100)

[a] Ten scans were performed after commencement of treatment and after a response had occurred.

Graft-versus-host disease (Table 5). There was a highly significant association between the development of LOPS and the presence of grade II-IV acute GVHD ($P<0.001$), and of chronic GVHD ($P<0.0001$). Twenty-two (76%) patients developed chronic GVHD and LOPS. In 7 (24%) patients the onset of LOPS preceded the onset of chronic GVHD. Onset was simultaneous in 7 (24%) patients, and in 8 (28%) patients the onset of LOPS followed chronic GVHD. Both acute and chronic GVHD were marginally more common in recipients of marrow from an unrelated donor (acute GVHD: 14 of 24 [58%] vs. 38 of 119 [32%], $P=0.03$; chronic GVHD: 14 of 24 [58%] vs. 42 of 119 [35%], $P=0.06$). These data are difficult to interpret due to the varied GVHD prophylaxis used in both groups including the greater use of TCD in recipients of marrow from an unrelated donor.

Histology. Four patients (14%) with LOPS underwent open-lung biopsy. Three showed both bronchiolitis obliterans and chronic interstitial pneumonitis. In each of these cases, histo-

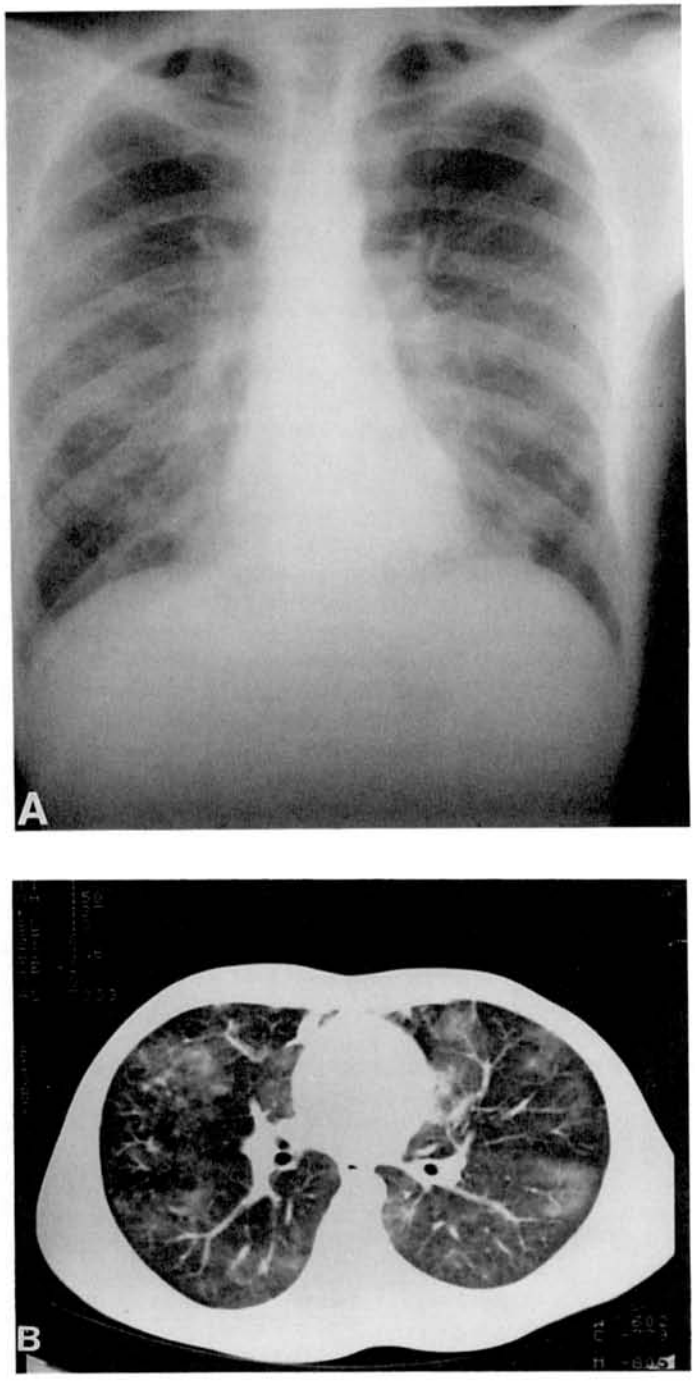

FIGURE 1. (A) Chest roentgenogram, and (B) chest CT scan of a 28-year-old-male patient who presented, 7 months postallogeneic bone marrow transplantation for acute myeloid leukemia, with a respiratory illness associated with a moderate-to-severe fall in lung volumes and moderate fall in the pulmonary diffusing capacity (TLCO). The diffuse interstitial process noted on chest roentgenogram was confirmed on CT scan. Rapid resolution of all abnormalities occurred following treatment with prednisolone.

logical changes in the bronchioles varied from mild lymphocytic bronchiolitis with scattered single-cell damage to segmental mural fibrosis and obliterative bronchiolitis. The interstitial pneumonitis was focal in distribution with moderate mixed chronic inflammatory interstitial infiltrate and regenerative changes of the alveolar lining. The biopsy of the fourth patient showed only mild lymphocytic bronchiolitis although it was probably not representative as there was a marked but patchy infiltrate seen on chest roetgenogram. None of the cases had any evidence for infection.

Treatment of LOPS (Table 6). Twenty-eight (97%) patients with LOPS have received immunosuppressive treatment initially consisting of prednisolone (0.25–2.0 mg/kg/day). Seven (24%) patients also received azathioprine, and of these 3 (10%) received thalidomide. The efficacy of the latter 2 agents was difficult to assess as their use was confined to those patients with severe and steroid-resistant chronic GVHD. Treatment was gradually tapered over 3–12 months in those with sustained complete response.

LOPS grade I (n=7; see Table 6 for definitions): One patient has not yet received treatment. Her pulmonary function tests remain abnormal but stable over a 16-month observation period. The remaining 6 patients obtained sustained complete responses.

LOPS grade II (n=10): Four patients had sustained complete responses, and one patient with an initial complete response had one relapse with subsequent sustained complete response to further immunosuppressive treatment. The remaining 5 patients had partial responses, which were sustained in 3 and followed a prolonged relapsing course in 2 patients, both of whom died.

LOPS grade III (n=12): Only 1 patient achieved a complete response, while 7 had partial responses, all with a relapsing course, and 4 had no significant response to treatment at any time.

Six (21%) patients have died at 1, 4, 6, 11, 36, and 42 months after the onset of LOPS; 5 were respiratory deaths with a terminal pulmonary infection supervening on relapsing or poorly responsive LOPS. The two patients who died 36 and 42 months postonset had progressed to a bronchiectatic-like syndrome. The remaining patient died of fulminant hepatic necrosis secondary to disseminated adenovirus infection. This compares with 20 (18%) deaths among the 114 patients in the control group (relapsed leukemia=13; nonpulmonary sepsis=3; nonpulmonary chronic GVHD=3; CNS hemorrhage=1) making, in our series, LOPS the most frequent nonrelapse cause of death in patients who had survived at least 6 months post-BMT.

DISCUSSION

The present study describes 29 (20%) of 143 patients surviving 6 months or more after BMT who developed a late-onset pulmonary syndrome that is strongly associated with GVHD of other organ systems. Since the first published case report of obstructive airways disease following BMT (*8*), the possibility that chronic GVHD may involve the small airways (*4*, *14*) and/or the interstitium (*10*, *13*) of the lung has become increasingly likely. Although bronchiolitis obliterans has been reported in a variety of situations that suggest an infectious or toxic etiology (*21–24*), other reports suggest that an autoimmune mechanism is of primary importance (*25*, *26*). A chronic pulmonary syndrome seen frequently following heart-lung transplantation, and thought to be a form of allograft rejection, is indistinguishable from that seen after BMT (*27–29*). The strong association

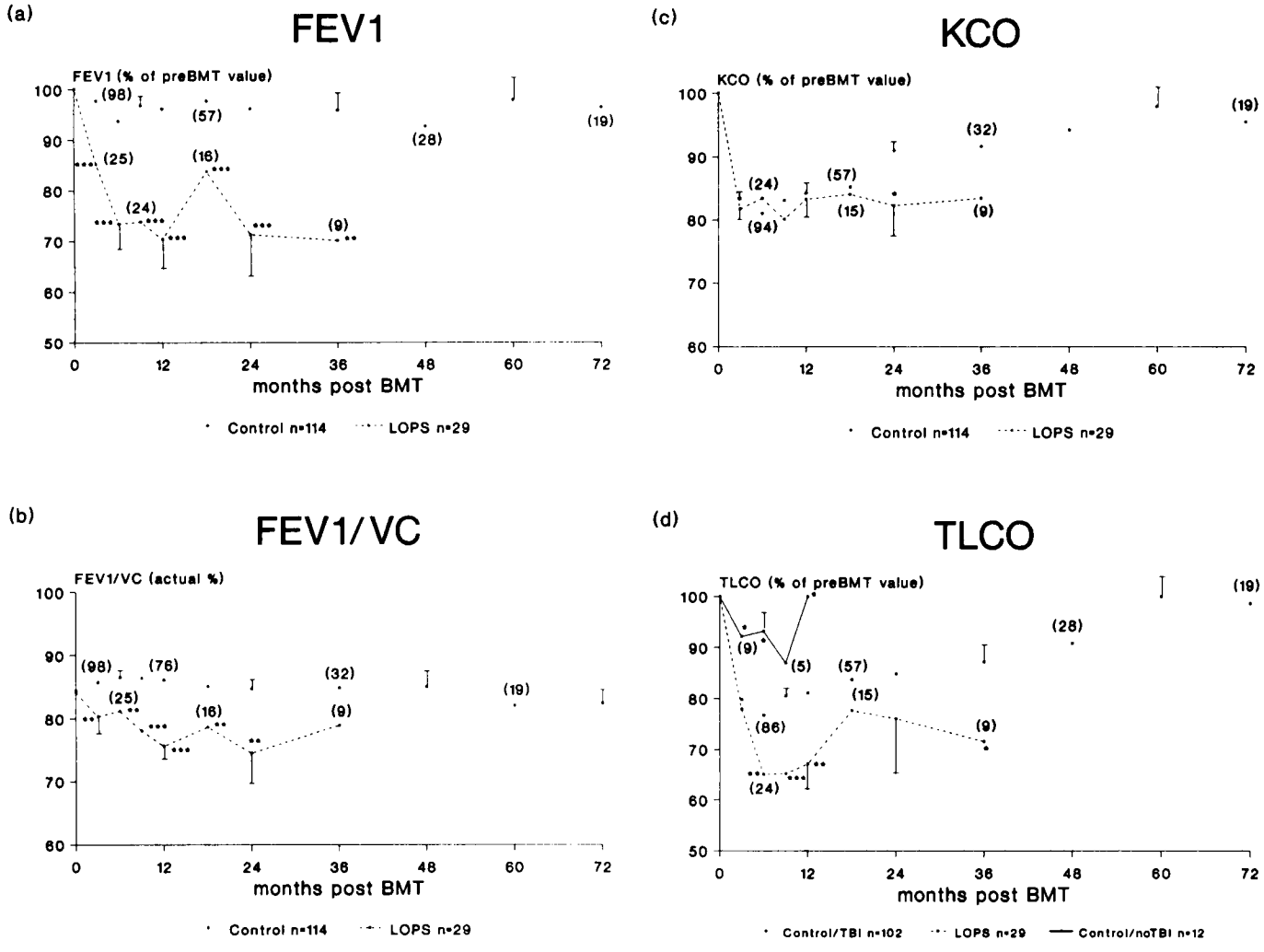

FIGURE 2. Serial pulmonary function tests in patients with late-onset pulmonary syndrome (LOPS) and in the control group without LOPS. The control group in (C) has been subdivided into patients who received total body irradiation (TBI) as part of their conditioning prior to bone marrow transplantation (control/TBI) and those who were conditioned with chemotherapy alone (control/no TBI). The values in the parentheses indicate the number of patients with pulmonary function tests at each particular time point (* P=0.05–0.01; ** P=0.01–0.001; *** P<0.001).

TABLE 5. Late-onset pulmonary syndrome is associated with graft-versus-host disease

	Controls	LOPS[a]	P
	n (%)	n (%)	
Acute GVHD[b]			
Grade I–IV	57 (50)	25 (86)	<0.001
Grade II–IV	33 (29)	19 (66)	<0.001
Chronic GVHD			
All cases	34 (30)	22 (76)	<0.0001
Extensive only	13 (11)	13 (45)	<0.0001
Total	114 (100)	29 (100)	

[a] LOPS denotes late-onset pulmonary syndrome.
[b] GVHD denotes graft-versus-host disease.

TABLE 6. Response of late-onset pulmonary syndrome to immunosuppressive treatment

	Complete[a]	Partial[b]	No response	Total
Grade I[c]	6	0	1[d]	7
Grade II	5	5 (2 Deaths)	0	10
Grade III	1	7 (3 Deaths)	4 (1 Death)	12
Total	12	12	5	29

[a] Complete: improvement of the FEV_1 to >90% of the pre-BMT value.
[b] Partial: improvement of the FEV_1 to a better grade.
[c] Grade I: FEV_1 >65% of the pre-BMT value; grade II: FEV_1 45–65% of the pre-BMT value; grade III: FEV_1 <45% of the pre-BMT value.
[d] To date, this patient has not received any treatment for LOPS.

of LOPS with acute and chronic graft-versus-host disease following allogeneic BMT, its frequent and often dramatic response to immunosuppressive medication in the present and other reports (*4–14*), and the absence of this syndrome in the twelve patients in this report and the 163 patients reported by Holland et al. (*4*) who underwent autologous or syngeneic BMT all suggest that chronic GVHD involving the lung may play an important etiological role. This does not exclude the possibility that infectious and/or toxic agents may also play an important

etiological, permissive, or synergistic role in the development of LOPS. Supporting a combined etiology in at least some instances is the report by Chein et al. (*30*); an allogeneic BMT recipient developed bronchiolitis obliterans following recovery from an episode of cytomegalovirus pneumonia. Novel or previously unsuspected infectious agents may be involved (*31*).

The development of abnormal pulmonary function tests in association with respiratory symptoms was of major importance in the recognition of LOPS in our study. Prior to BMT, mean lung volumes (FEV_1, FEV_1/VC, and VC) in both the LOPS and control groups were normal, although the mean diffusing capacity was mildly decreased at 88.6% and 89.3%, respectively, of predicted values (Fig. 2). This mild abnormality prior to BMT has been noted by others (*32–34*), and although the cause remains unknown, suggested etiologies include pulmonary leukostasis, previous infections, and prior chemotherapy. Following BMT, lung volumes remained within normal limits in the control group, although a small rise in the FEV_1/VC indicated the development of a mild restrictive abnormality. This change was not seen in the group of 12 patients not receiving TBI, suggesting that it was secondary to the pulmonary effects of the irradiation (data not shown). The marked fall in lung volumes in the LOPS group was associated with a moderate obstructive component, but only 18 (62%) patients developed an abnormal FEV_1/VC ratio of <75%, and in 6 of these, a major fall in the FEV_1 and VC with a normal FEV_1/VC ratio preceded the onset of overt airway obstruction by a median of 3 months. Therefore, concentrating only on patients with a prominent obstructive component, as others have done (*5, 6, 14*), would miss the diagnosis (n=11 in our series) or delay the recognition (n=6 in our series) of LOPS.

Both the LOPS and control groups showed a marked fall in the TLCO (Fig. 2) that had its nadir at 9 months, and in the control group gradually returned toward normal over 5 years. This pattern was also seen in the group of seven patients who underwent autologous or syngeneic BMT with TBI as part of the conditioning regimen but was not seen in the group of 12 patients who underwent allogeneic BMT without TBI. This latter group had a significantly smaller fall in TLCO that had returned to normal by 12 months. Radiation is well recognized as capable of damaging lung tissue (*35*), and the data presented here, and by others (*33, 34*), suggest that the abnormality of the diffusing capacity is secondary to injury sustained by the alveolar-endothelial membrane during TBI. The trend of increased incidence of LOPS with higher dose TBI (Table 2) and of the low incidence in those not receiving TBI (nil in our series but occasionally reported to occur following chemotherapy-alone conditioning regimens [*4, 6, 14*]) was noted, suggesting that the damage caused by TBI may play a permissive role in the development of LOPS possibly by augmenting, via tissue damage and altered presentation of self and/or foreign antigens, any immune response that may occur. The greater incidence of LOPS in recipients of marrow from an unrelated donor is explained, at least in part, by the greater risk of developing acute and chronic GVHD, but the more-frequent use of higher-dose TBI may play an important role.

In our series, LOPS was a common late complication occurring in 20% of patients surviving more than 6 months following allogeneic BMT. It resulted in considerable morbidity and mortality, being the most frequent nonrelapse cause of late death. In the absence of a definitive diagnostic test, recognition of this syndrome remains difficult. The earliest abnormality may be a fall in lung volumes (VC and FEV_1), which occurred in 28 (97%) of the 29 patients with LOPS, and preceded the onset of overt airways obstruction in 6 of the 18 patients who developed an abnormal FEV_1/VC ratio of <75%. This point should be emphasized as early recognition of LOPS, following the rigorous exclusion of infectious agents, would allow early treatment with immunosuppressive drugs that may result in the complete reversal of all features of this illness and that may prevent the onset of irreversible lung damage.

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LYMPHOKINE-ACTIVATED KILLER CELLS IN AUTOLOGOUS BONE MARROW TRANSPLANTATION

EVIDENCE AGAINST INHIBITION OF ENGRAFTMENT IN VIVO[1]

BISHAN S. CHARAK,[2] RUSSELL K. BRYNES, MARILYN CHOGYOJI, AND AMITABHA MAZUMDER

Bone Marrow Transplantation Program, Georgetown University, Washington, D.C. 20007; and Department of Pathology, University of Southern California, Los Angeles, California

Lymphokine activated killer cells have potent antitumor effect both in vitro and in vivo. They have been reported to suppress bone marrow (BM) progenitor cell activity (PCA) in vitro, thus raising concern about the feasibility of their use after autologous bone marrow transplantation. The present study was carried out to evaluate the effect of LAK cells on BM engraftment in a syngeneic BMT setting in mice. LAK cells supplemented with or without exogenous interleukin-2 therapy did not impair the hematopoietic reconstitution or survival of mice undergoing BMT. LAK cells also did not reduce the PCA of the engrafted BM. LAK cell therapy did not cause graft-versus-host disease. Finally, LAK cells supplemented with IL-2 therapy improved the graft-versus-leukemia effect. These findings suggest that LAK cells plus IL-2 therapy after BMT does not impede hematopoiesis and should be evaluated as an adjuvant therapy with the aim of eradication of minimal residual disease after autologous BMT.

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[2] Address correspondence to: Bishan S. Charak, M.D., Room S124, Lombardi Cancer Research Center, Georgetown University, 3800 Reservoir Rd., N.W., Washington, D.C. 20007.