

CASE STUDY

Possible recurrence of desquamative interstitial pneumonitis in a single lung transplant recipient

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Possible recurrence of desquamative interstitial pneumonitis in a single lung transplant recipient. G.M. Verleden, F. Sels, D. Van Raemdonck, E.K. Verbeken, T. Lerut, M. Demedts. ©ERS Journals Ltd 1998.

ABSTRACT: Idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis) is a disorder with a very poor prognosis for patients who do not respond to therapy with corticosteroids alone or in combination with immunosuppressive drugs, e.g. cyclophosphamide or azathioprine. For patients with end-stage disease, lung transplantation remains the only possibility for long-term survival.

We describe a patient who received a left single lung transplant for end-stage desquamative interstitial pneumonitis. One year later, the patient again began complaining of exertional dyspnoea and a gradual decline in the transfer factor of the lung for carbon monoxide (TLCO) was apparent. A recurrence of the primary disease in the transplanted lung was suspected on transbronchial biopsies. During treatment with high doses of steroids, a *Pneumocystis carinii* pneumonia developed, which was treated with co-trimoxazole. The patient completely recovered and, after a period of over 2 yrs, remained in an excellent condition, after which time he was lost from follow-up.

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Idiopathic pulmonary fibrosis (IPF) is a clinical disorder which is one of the many interstitial lung diseases of unknown origin. Morphologically the most frequent subgroup is "usual interstitial pneumonia" (UIP) whereas "desquamative interstitial pneumonia" (DIP) is a much rarer condition. Whether these are entirely different entities or merely early (DIP) and late (UIP) stages of a single disorder is a matter of debate. Such a histological classification can be important since it has been reported that DIP has a better prognosis and a better response to therapy compared to UIP [1].

The aetiology of IPF is unknown. A viral cause has as yet not been proven. It is possible that DIP and UIP are just some of the limited ways in which the lungs can react to insults of different causes.

As the cause is not known, therapy is derived towards the pathological process in an effort to stop the self-mutilating inflammatory reaction in the lungs. Corticosteroids alone or in combination with immunosuppressives will bring improvement or stabilization of the disease in only some of the patients [1, 2-4].

The prognosis of IPF is poor and for most patients lung transplantation is the only possibility for long-term survival [5-7]. As of February 7 1997, 3,939 single lung and 2,543 double lung transplantations have been reported to the International Society of Heart and Lung Transplant Registry with an overall 5 yr survival rate of 40%. Approximately, 27% of these lung transplantations have been performed for end-stage interstitial pulmonary fibrosis [8].

As the aetiology of IPF and many other lung diseases such as sarcoidosis and histiocytosis is still unknown, it was initially hypothesized that some diseases might recur in the transplanted lung [9]. This has already been demonstrated for sarcoidosis [10-12], giant cell interstitial pneumonitis [13] and lymphangioleiomyomatosis [14] in lung and also for sarcoidosis in heart [15] and renal transplants [16].

In this article we present a possible recurrence of DIP in a left single lung allograft.

Case report

A male patient began complaining of cough and exertional dyspnoea in 1978, at the age of 37 yrs. Until that time he had smoked around five cigarettes·day⁻¹. One year later an open lung biopsy was performed at the Cedars Sinai Medical Center (Los Angeles) and an idiopathic desquamative interstitial pneumonitis was diagnosed. The patient was initially treated with high doses of prednisolone (60-80 mg·day⁻¹) and the disease remained stable until 1984. From then on there was a progressive downhill course with gross hypoxaemia, which necessitated continuous oxy-gen therapy and a maintenance therapy of high doses of prednisolone. In 1991, the assessment procedure for single lung transplantation was performed and during a training programme the steroid therapy (administration of methyl prednisolone (MP)) was gradually reduced to a dose of 8 mg·day⁻¹.

In January 1992 he entered the waiting list for single lung transplantation at the University Hospital, Leuven, Belgium. Two days later, a left single lung transplantation was performed. The patient's immunosuppressive regimen consisted of MP ($0.4 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$), azathioprine ($1.5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$) and cyclosporin (to maintain a whole blood level of $300\text{--}350 \text{ ng}\cdot\text{mL}^{-1}$). He also received a 7 day course of rabbit antithymocyte globulins ($3 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$). His recovery was uneventful, except for a grade II rejection [9] on the ninth postoperative day, which was diagnosed on transbronchial biopsy (TBB). All viral, bacterial and fungal cultures at the time were negative. Treatment with a 3 day course of *i.v.* MP (day 1: 1,000; day 2: 500; day 3: 500 mg) resulted in a complete recovery. He was discharged on the 30th postoperative day.

During the follow-up period he experienced a traumatic fracture of a lumbar spine, which was treated conservatively. There were no more episodes of rejection or any infectious complications. Routine TBBs (five to eight biopsies during each session) were taken on the third, the sixth and the 12th postoperative month. In one of the biopsies (taken at 6 months), there was some alveolar filling with mononuclear cells and some hyperplasia of the type 2 alveolar epithelial cells. There was, however, no evidence of perivascular lymphocytic infiltration or apparent airway pathology suggestive of obliterative bronchiolitis in any of the biopsies. No cytomegalovirus (CMV) inclusions were seen.

The patient remained in excellent condition until 1 yr after his transplantation. A check-up at that time revealed some ground-glass appearance of the left lower lobe on the computer-assisted tomography (CAT)-scan of the chest; furthermore there was a gradual decline in the transfer factor of the lung for carbon monoxide ($T_L\text{CO}$), which had already been apparent for several months (fig. 1). There was only minimal change in forced expiratory volume in one second (FEV_1). At that time, TBBs, however, could not detect any abnormalities although recurrence of the DIP

was suspected. The dose of steroids (MP) was increased from $8\text{--}32 \text{ mg}\cdot\text{day}^{-1}$, and decreased after 2 weeks to $16 \text{ mg}\cdot\text{day}^{-1}$. Initially there was some improvement of $T_L\text{CO}$, but from then on there was a further decline with reappearance of a dry cough and exertional dyspnoea. Lung auscultation revealed fine crackles at the base of the left transplanted lung. Crackles at the native right lung had been present continuously. Blood gas analysis, which has always been normal after transplantation, now demonstrated marked hypoxaemia (oxygen tension (P_{O_2}) 7.73 kPa (56.8 mmHg) while breathing room air at rest). A chest radiograph demonstrated, besides the known fibrotic changes in the right lung, some increased interstitial lines in the left lower lobe, although this was not different from earlier radiographs (fig. 2). A CAT-scan of the chest again demonstrated ground-glass appearance in the lower lobe, besides the already existing fibrotic changes in the native right lung (fig. 3). TBBs were taken at that time in the left lower lobe and in the lingula, and recurrence of DIP in the transplanted lung was suspected, without any evidence of acute or chronic rejection (fig. 4). Neither bronchoalveolar lavage (BAL) nor TBBs revealed any infectious agent. A differential cell count on the BAL fluid was not performed. The steroid therapy (MP) was augmented to $64 \text{ mg}\cdot\text{day}^{-1}$; azathioprine and cyclosporin doses were not changed. The hypoxaemia improved and the crackles disappeared, but 4 weeks later, the patient again started to complain of an debilitating dry cough with gross hypoxaemia (P_{O_2} 6.4 kPa (47 mmHg) while breathing room air). BAL at that time was diagnostic for *Pneumocystis carinii* pneumonia. No TBB were performed at that time. Co-trimoxazole treatment was instituted with progressive improvement. During a time period of over 2 yrs after the recurrence, the patient was doing very well. There was a normal oxygenation at rest and during exercise, and the $T_L\text{CO}$ again increased to $3.9 \text{ mmol}\cdot\text{min}^{-1}\cdot\text{kPa}^{-1}$ (fig. 1). The steroids (MP) were tapered to a maintenance dose of $12 \text{ mg}\cdot\text{day}^{-1}$.

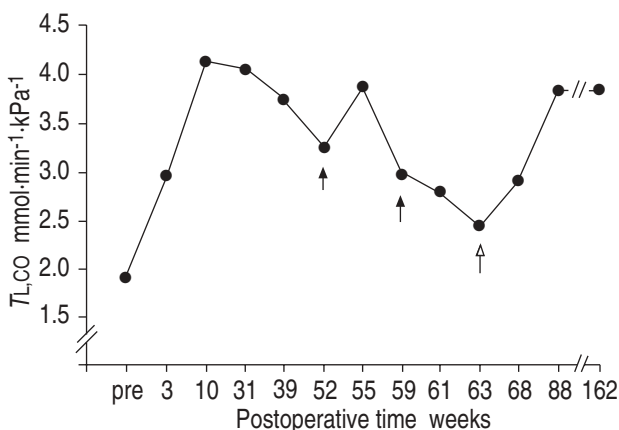


Fig. 1. – The transfer factor of the lung for carbon monoxide ($T_L\text{CO}$) in the postoperative period. There was a gradual decline in the $T_L\text{CO}$ towards the end of 1 yr, although transbronchial biopsies (TBBs) and bronchoalveolar lavage (BAL) (first closed arrow) could not detect any sign of infection or rejection. After an initial improvement, when the dose of steroids had been increased, $T_L\text{CO}$ deteriorated again and repeat TBB and BAL (second closed arrow) suggested a recurrence of desquamative interstitial pneumonia (DIP), without any signs of rejection or infection. Another fall in $T_L\text{CO}$ was apparent during infection with *Pneumocystis carinii* (open arrow). From then on there was a gradual increase in $T_L\text{CO}$, which was sustained up to 3 yrs after transplantation.



Fig. 2. – The chest radiograph, taken at the time of the diagnosis of desquamative interstitial pneumonia (DIP) recurrence, demonstrates some increased interstitial markings in the left lower lobe, besides the fibrotic changes in the right, native lung.

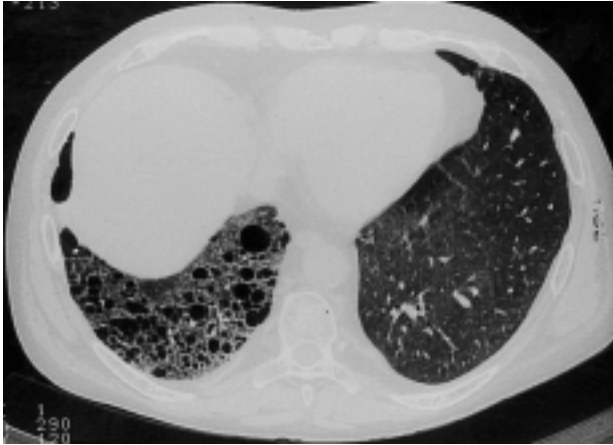


Fig. 3. – Computer-assisted tomography (CAT) scan of the chest, taken at the same time as the chest radiograph demonstrated some ground-glass appearance in the left lower lobe, besides the fibrotic changes in the right lung, which had remained unchanged.

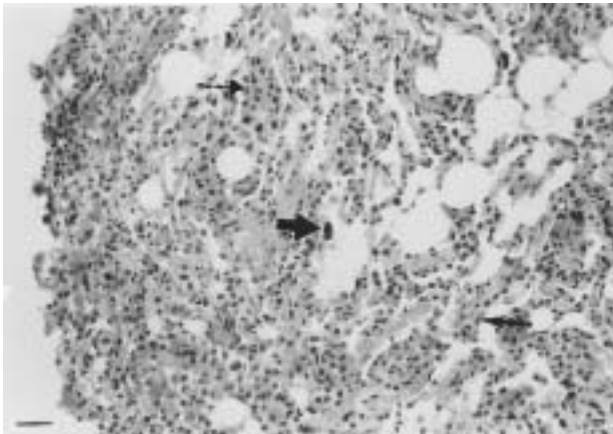


Fig. 4. – Transbronchial biopsy, taken at 59 weeks. Alveolar lumina were filled with dark stained macrophages (••▶). Alveolar walls were lined by a prominent layer of cuboidal type II cells (▶), including an occasional multinucleated cell (▶▶). The alveolar septae were thickened and contained some mononuclear inflammatory cells. There was no perivascular lymphocytic infiltration. Haematoxylin and Eosin stain; internal scale bar = 50 μ m. Unfortunately thereafter, the patient was lost from follow-up.

Discussion

To our knowledge, this is the second report of possible recurrence of DIP in a transplanted lung, however it is the first report in which there is a favourable outcome. The first reported patient [17] also received a single lung transplantation for end-stage DIP. Because of the many complications during the post-transplantation period of this patient, *i.e.*, clinical acute rejection, two viral pulmonary infections (herpes simplex virus and CMV), aspergillary bronchitis and the insertion of a bronchial stent for post-surgical atelectasis, there might be some doubt whether the interstitial infiltrate in the transplanted lung really represented a recurrence of the primary disease.

In another patient with giant cell interstitial pneumonitis (GIP) secondary to cobalt exposure, who received a single lung allograft, BAL, open lung biopsy and finally autopsy provided evidence for a recurrence of GIP with-

out presence of exposure to cobalt or tungsten to the transplanted lung [13].

In our patient, the post-transplantation period was rather uneventful, except for one period of acute rejection on the ninth postoperative day, without any further episodes of rejection or infection.

The recurrent symptoms of our patient could be compatible with acute or even chronic rejection, possibly presenting as bronchiolitis obliterans-organizing pneumonia (BOOP), infection, drug-induced pulmonary disease (*e.g.*, azathioprine) or recurrence of the original disease (DIP). Therefore, there can be some doubt as to the diagnostic yield of transbronchial biopsies, especially for the diagnosis of chronic interstitial pneumonia. Even open lung biopsy is not always diagnostic [18–21]. TBB is, however, very sensitive for the diagnosis of acute rejection, with a diagnostic yield ranging 72–94% [22–24]. Specificity of TBB for rejection, especially the presence of perivascular lymphocytic infiltration, was initially thought to be 100%, but is probably less because perivascular lymphocytic infiltration has recently been found in 33% of diagnostic biopsies and in 40% of follow-up biopsies with infection [25]. On the other hand, TBB have a low yield in the diagnosis of BOOP, chronic rejection or obliterative bronchiolitis [26]. In the latter condition, one can rely much more on the pulmonary function results which will demonstrate a progressively increasing obstructive pattern with a fall in FEV₁ [27]. This was, however, not apparent in our patient. Although the presence of BOOP cannot be excluded for 100%, we do not believe that this condition was present in our patient. First, the TBB did not reveal any evidence of associated airway pathology (not demonstrated in fig. 4) and second there was only minimal decline of FEV₁. There was a very favourable response to high doses of corticosteroids with no occurrence of an obstructive pulmonary function once the dose was again tapered; at least during the 2 yrs of follow-up. This is rather in contradiction to the classical evolution of BOOP in lung transplant patients, which is commonly associated with acute rejection or obliterative bronchiolitis [28], of which we had absolutely no evidence at the time nor during the 2 yrs of follow-up. An open lung biopsy would probably have solved this diagnostic dilemma, however, we felt it inappropriate since there was indeed a very favourable response after treatment.

The sensitivity of TBB for infection is only 36–38%, specificity is probably 100%. The concomitant use of BAL certainly augments the sensitivity, especially for *P. carinii* and CMV pneumonia [29].

An azathioprine-induced pulmonary disease seems rather unlikely in our patient, since the dose of azathioprine was not in any way changed during the recovery of the patient.

Furthermore, later on during the course of the patient's illness, there was no recurrence when the dose of steroids was again tapered, the opposite of which could be expected in the case of drug-induced lung disease.

On the other hand, the pathological findings of DIP including proliferation of type II cells, filling of the alveolar spaces with desquamated macrophages and an occasional giant cell within or lining the alveoli [30] were all present in the TBB (fig. 4). As a consequence, we think that interstitial lung disease and more specifically a recurrence of DIP, is perfectly compatible with all clinical, functional and radiological signs: a gradual fall of the T_LCO , combined with increasing exertional dyspnoea and hy-

proxia, recurrence of fine crackles on auscultation and the presence of an ongoing interstitial lung disease with absence of any signs of rejection or infection on TBB and BAL. We, therefore, believe that in this case, there is enough convincing evidence for a recurrence of the primary disease (DIP) in the transplanted lung, although an open lung biopsy as the final proof is lacking because of the aforementioned reason.

In conclusion, we want to emphasize that in the differential diagnosis of hypoxaemia and clinical deterioration following lung transplantation, recurrence of the primary disease must always be considered, especially in the absence of infection, rejection or signs of obliterative bronchiolitis.

It is noteworthy, that in our patient and in the patients of FROST [13] and BARBERIS [17], the primary disease recurred while they were receiving immunosuppressive therapy (cyclosporin, azathioprine and corticosteroids) in doses not much lower than the doses used by most clinicians to treat pulmonary fibrosis [2–4, 31]. Both the patients of FROST *et al.* [13] and BARBERIS *et al.* [17] ultimately died. Our patient, however, improved rapidly after receiving high doses of corticosteroids, and in a time period of over 2 yrs remained in a very good condition.

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