Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Pleuropericarditis, obliterative bronchiolitis and lymphocytic interstitial pneumonitis after allogeneic haematopoietic stem cell transplantation

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Summary

Chronic graft-versus-host disease (GVHD) is a common complication of allogeneic haematopoietic cell transplantation, with pulmonary involvement occurring in 5–10% of cases. Obliterative bronchiolitis (OB) is recognised as a diagnostic manifestation of chronic GVHD, whereas lymphocytic interstitial pneumonitis (LIP) has been reported but is not considered diagnostic, and pleuritis is not clearly associated. The authors describe a transplant patient who simultaneously manifested three distinct pulmonary processes: OB, patchy LIP and pleuropericarditis. The onset of these entities along with other manifestations of chronic GVHD, their resolution with increased immunosuppression and their recurrence upon tapering support all three entities as manifestations of GVHD in the lungs.

BACKGROUND

Chronic graft-versus-host disease (GVHD) occurs in approximately 50% of allogeneic haematopoietic cell transplant recipients and is the most important factor determining long-term outcome. Obliterative bronchiolitis (OB) is recognised as a diagnostic manifestation of chronic GVHD of the lung.¹ Other late pulmonary complications of transplantation such as lymphocytic interstitial pneumonitis (LIP) and bronchiolitis obliterans with organising pneumonia (BOOP) have been reported in the setting of chronic GVHD, though they are not currently accepted as diagnostic manifestations.^{2–6} Whether there is any association between serositis and chronic GVHD remains unknown. We report here a case of rapidly progressive pleural and pericardial effusions due to biopsy-proven lymphocytic serositis, occurring together with OB and low-grade LIP, in a patient with chronic GVHD.

CASE PRESENTATION

A 34-year-old man with acute myeloid leukaemia and poor risk cytogenetics received a peripheral blood stem cell transplant from his human leucocyte antigen-matched brother following conditioning chemotherapy with busulfan and fludarabine while in first complete remission. He was given GVHD prophylaxis with tacrolimus and mini-dose methotrexate (5 mg/m² on days 1, 3, 6 and 11 after transplantation), achieved full donor engraftment by day 28 and had no evidence of GVHD through day 100. Tacrolimus was further tapered beginning on day 100,

then discontinued 5 months after transplantation. Shortly thereafter, he developed symptoms suggestive of de novo chronic GVHD with eosinophilia, skin itching and pain in his right eye. Ophthalmological examination revealed pseudomembranous keratoconjunctivitis suggestive of grade III ocular GVHD and he received topical therapy. Over the next 2 weeks, his GVHD worsened with progressive eye symptoms, oral ulcers and diffuse skin involvement (poikiloderma, lichen planus, ichthyosis, dystrophic nails and restriction in opening his mouth from presumed sclerosis). Oral methylprednisolone was begun at 1 mg/kg, tacrolimus was restarted and narrow-band ultraviolet B phototherapy was initiated as a steroid-sparing agent. The GVHD responded with resolution of his skin manifestations and improvement in his oral ulcers. He was weaned off steroids and phototherapy 12 months after transplantation, but remained on tacrolimus and topical therapies for occasional oral symptoms.

The patient had a respiratory syncytial virus upper respiratory infection during month 9 and a right lower lobe lung consolidation with a nasal wash positive for parainfluenza type 2 during month 17. Pulmonary consultation was requested in month 23 for non-productive cough and progressive dyspnoea on exertion. History was remarkable for asthma and nasal allergies as a child that he outgrew as a teenager. Chest examination was remarkable for inspiratory crackles at the lung bases. Pulmonary function testing showed mixed restrictive and obstructive defects, with partial bronchodilator reversibility (table 1).

Table 1 Pulmonary function tests

	Time after transplantation (months)						
	0 (%)	15 (%)	19 (%)	23 (%)	28 (%)	35 (%)	36 (%)
FVC	82	66	56	41	63	39	61
FEV1	86 (ND)	58 (14)	50 (8)	36 (17)	58 (10)	34 (16)	53 (5)
FEF 25–75	97	37	32	22	42	21	33
TLC	80	76	68	60	77	59	70
RV	79	92	92	99	101	92	91
DLCO	63	55	50	49	63	42	56

Testing was performed prior to transplantation (month 0) and periodically thereafter to assess physiologic parameters associated with changes in symptoms and the response to treatment. The results shown are the percentages of predicted values; the percentage improvement in FEV1 after administration of a bronchodilator is given in parentheses.

DLCO, diffusing capacity of the lungs for carbon monoxide; FEF 25–75, forced expiratory flow rate between 25% and 75% of vital capacity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ND, not done; RV, residual volume; TLC, total lung capacity.

Figure 1 CT image of the chest and histopathologic findings 23 months after transplantation. (A) A moderate pericardial effusion (arrowhead) and small bilateral pleural effusions (arrows) on a CT image of the chest. Airway and interstitial abnormalities were not identified despite abnormal histopathologic and pulmonary function findings. (B) Dense lymphocytic infiltration (arrow) of interstitial lung tissue underlying the pleural surface (arrowhead). Immunohistologic staining (not shown) reveals a mixed population of CD3-positive T cells and CD20-positive B cells, with polytypic staining for κ and λ light chains and no staining for Epstein–Barr virus by in situ hybridisation. (C) Constrictive bronchiolitis with submucosal (arrowhead) and adventitial (arrow) scarring, loss of normal mucociliary epithelium over the submucosal scar and lymphocytic infiltration of the airway wall. (D) Collection of lymphocytes in the lung interstitium with multifocal lymphoid follicles (arrowhead) and by immunohistochemical staining (not shown) a mixed population of T cells, B cells and plasma cells.

A chest radiograph showed an enlarged cardiac silhouette and small bilateral pleural effusions, and CT imaging showed small bilateral pleural effusions, a moderate pericardial effusion and subsegmental right middle lobe consolidation or atelectasis (figure 1A). Diagnostic right-sided thoracentesis revealed an exudative effusion (protein 5.1 g/100 ml, lactate dehydrogenase 520 IU/l) with sterile inflammation (293 white blood cells/ μ l; 47% neutrophils, 40% mononuclear cells, 10% lymphocytes; stains and cultures for microbes negative). The patient returned 5 days later with increasing dyspnoea and an echocardiogram showed a large pericardial effusion with features of

early tamponade. A left video-assisted thoracoscopy was performed for placement of a pericardial window and a left-sided indwelling pleural catheter. Pericardial biopsy showed fibrosis and chronic inflammation with lymphoid aggregates and plasma cells (not shown), and wedge biopsies of the lung showed OB, localised LIP and lymphocytic pleuritis (figure 1B–D). Serologic studies for autoimmune diseases (ANA, RF, Jo-1 Ab, CCP Ab, PM-Scl Ab, SS-A/Ro Ab, SS-B/La Ab) were all negative.

The patient was restarted on methylprednisone at 1 mg/kg/day and oral inhaled ciclesonide 320 mg twice daily with marked improvement in his symptoms. The pleural

catheter was removed 15 days after placement when drainage decreased below 100 ml/day for 3 days. The methylprednisolone was slowly tapered to 0.1 mg/kg/day by 28 months after transplantation, with no recurrence of pericardial or pleural effusions and improvement in lung restriction and airflow obstruction (table 1). Methylprednisolone was tapered off during month 33, though he remained on tacrolimus and inhaled ciclesonide 160 mg twice daily. In month 35, he experienced recrudescence of exertional dyspnoea, with a chest radiograph showing moderate bilateral pleural effusions and pulmonary function tests indicating worsening of his restrictive and obstructive defects (table 1). Right-sided thoracentesis again showed a sterile exudative pleuritis with numerous small lymphocytes and plasma cells, and he was started on prednisone 40 mg/day that was tapered by 10 mg every week down to 10 mg/day (0.05 mg/kg/day). He again experienced rapid improvement in symptoms, radiographic findings and pulmonary function (table 1).

OUTCOME AND FOLLOW-UP

At this time, the patient remains in remission from his acute myeloid leukaemia and is 3.5 years post-transplant. He continues to have chronic GVHD of his eyes and mouth and OB of his lungs with stable airflow obstruction on his pulmonary functioning testing. He remains on inhaled steroids, tacrolimus and an adrenal replacement dose of prednisone. His performance status is excellent and he has minimal pulmonary symptoms of dyspnoea with severe exertion and intermittent cough.

DISCUSSION

OB is the most common pulmonary manifestation of chronic GVHD, occurring in 5–10% of patients with chronic GVHD and the incidence is even higher with prospective screening.⁷ OB is characterised by new onset airflow obstruction on pulmonary function testing and tissue biopsy is generally not required to establish the diagnosis. It is often precipitated by a viral lung infection, with parainfluenza and respiratory syncytial viruses most commonly associated.⁸ Treatment with high dose inhaled steroids for mild obstruction and systemic steroids for severe obstruction may improve lung function or prevent disease progression.⁹ Our patient developed progressive airflow obstruction after two documented viral respiratory infections, and improved substantially after treatment with inhaled and systemic corticosteroids and tacrolimus despite widespread histopathologic bronchiolitis with luminal granulation tissue.

LIP is a rare late-onset, non-infectious pulmonary complication of chronic GVHD.^{10–12} LIP is better described in the non-transplant setting where it is often associated with adult autoimmune or paediatric immunodeficiency disorders.¹⁰ The diagnosis of LIP is established by the histopathologic demonstration of diffuse interstitial infiltrates that include lymphocytes, plasma cells and histiocytes and it is associated with restrictive physiology on pulmonary function testing. Pleural effusion is rarely reported in LIP.¹² Systemic corticosteroids arrest or improve symptoms in a large proportion of non-transplant patients with LIP,¹⁰ though documentation on the response to steroids for LIP associated with chronic GVHD is limited.¹¹ Our patient showed patchy, low-grade LIP histopathologically

in association with restrictive lung physiology and an improvement in lung restriction after the intensification of his immunosuppressive therapy.

Pleural effusions occur commonly during the first 100 days after haematopoietic cell transplantation due to volume overload and diffuse capillary leak.^{6 13} However, the occurrence of pleuritis due to chronic GVHD remains controversial. One reported case of pleural and pericardial effusions developed in a patient with constrictive pericarditis in association with clinical manifestations of new onset collagen vascular disease and a small pleural effusion that was not further characterised and may have been secondary to cardiac constriction.⁴ In a case series of seven children with unexplained pleural effusions after haematopoietic cell transplantation, only one occurred after 100 days and this effusion was transudative and not further characterised.⁵ More recently, a retrospective review of 205 paediatric autologous and allogeneic stem cell transplants identified nine patients (4%) who had clinically symptomatic pericardial effusions requiring intervention.¹⁴ Seven of these patients received an allogeneic transplant with the majority of these events occurring during the first 100 days of transplant and concurrent with acute GVHD in other organs. A direct relation to GVHD was speculated but was difficult to confirm due to concurrent infection, prior or ongoing cytotoxic therapies or other medical (renal failure) conditions, which may have contributed to these events. Two previous case reports detail pericardial effusions occurring in the setting of chronic GVHD, however, in neither case was a biopsy performed.^{15 16} Thus, to our knowledge, a definite case of pleuritis due to chronic GVHD has not been previously reported.

Our patient developed biopsy-proven pleuropericarditis in association with other pulmonary manifestations of chronic GVHD, namely OB and localised LIP. All three lung disorders progressed simultaneously following two respiratory viral infections superimposed on de novo chronic GVHD, and all three disorders improved simultaneously after the institution of immunosuppressive therapy. When immunosuppressive therapy was reduced due to

Learning points

- ▶ Chronic GVHD of the lung occurs in 5–10% of patients who have chronic GVHD involving other organs.
- ▶ OB is the most common manifestation of chronic GVHD of the lung and currently is the only entity recognised as a diagnostic manifestation of chronic GVHD of the lung.
- ▶ Other late pulmonary complications of allogeneic haematopoietic cell transplantation such as LIP, BOOP and pleuritis have been reported in the setting of chronic GVHD, though they are not currently accepted as diagnostic manifestations.
- ▶ This case report details the simultaneous occurrence of three distinct pulmonary processes: OB, patchy LIP and pleuropericarditis.
- ▶ The onset of these entities along with other manifestations of chronic GVHD, their resolution with increased immunosuppression and their recurrence upon tapering support all three entities as manifestations of GVHD in the lungs.

complications from corticosteroids, there was a worsening of airflow obstruction and lung restriction and the recurrence of bilateral pleural effusions, all of which improved with augmented corticosteroid therapy. The synchronous waxing and waning of these three distinct lung diseases and their responsiveness to immunosuppressive therapy point to a shared aetiology, namely chronic GVHD. Our case report suggests that polyserositis may occur rarely as a consequence of chronic GVHD and that timely initiation of immunosuppressive therapy can bring about a favourable outcome.

Competing interests None.

Patient consent Obtained.

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