# *Case reports*

## Commentary

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The case reports by Morehead[1] and Charoenratanakul and Loasuthi[2] highlight some uncommon but important respiratory conditions associated with haematological malignancies.

Distal airway disease is a well recognised complication of allogeneic bone marrow transplantation. This follows the first reports of rapidly progressive often fatal irreversible airflow obstruction due to obliterative bronchiolitis in patients invariably suffering from chronic graft versus host disease (GVHD).[3] Proximal airway disease in these patients, as described in the cases reported by Morehead,[1] is less formally described in the literature. Isolated reports have alluded to patients progressing to bronchiectatic-like syndromes, providing some limited clinical evidence of concomitant proximal airways involvement in chronic GVHD associated airflow obstruction.[4]

There are numerous potential pathogenetic factors for the development of bronchiectasis in patients with chronic GVHD, many of which overlap with those for obliterative bronchiolitis. The vicious circle hypothesis for the pathogenesis of bronchiectasis suggests that an initial triggering lung insult compromises sinopulmonary mucociliary clearance mechanisms predisposing to microbial colonisation. Much of the subsequent airway damage is due to a host mediated inflammatory response to this persistent intraluminal microbial stimulus.

This initial airway insult in patients who undergo allogeneic bone marrow transplantation may follow cytotoxic therapy and irradiation used in conditioning regimes or recurrent aspiration of gastric contents secondary to oesophageal chronic GVHD. Evidence of direct immune mediated damage to the airway by chronic GVHD has yet to be firmly established. However, host bronchial epithelial cells could serve as targets for donor T lymphocyte and cytokine mediated damage. Bronchial and submucosal gland lymphocytic infiltrates have been found in GVHD but may be the sequelae of multiple lung insults rather than a specific manifestation of lung GVHD. The sinobronchial sicca resulting from this submucosal gland destruction will compromise mucociliary transport.

Airway damage may follow the recurrent sinopulmonary infections common in chronic GVHD. This increased susceptibility to infection is due to severe persistent combined cellular and humoral immune deficiency characteristic of chronic GVHD. Microbial colonisation of these damaged airways with *Pseudomonas aeruginosa* often occurs in these patients, allowing host mediated inflammatory damage to ensue as part of the vicious circle.

Some insights into chronic GVHD associated bronchiectasis may be gleaned from bronchiectasis associated with the obliterative bronchiolitis complicating heart-lung transplantation. Here the obliterative bronchiolitis is considered a manifestation of allograft rejection and bears some immunological similarity to obliterative bronchiolitis associated with chronic GVHD. Retrospective studies of high resolution computed tomographic (HRCT) scans following heart-lung and lung transplantation have clearly shown bronchiectasis as one of the most consistent radiological findings of obliterative bronchiolitis.[5] This predominantly segmental and subsegmental bronchial dilatation correlates with the severity of airflow obstruction. Interest in this finding has therefore centred on its potential use as a marker for the early detection of obliterative bronchiolitis. Preliminary studies suggest the bronchiectasis to be a concomitant rather than antecedent feature of obliterative bronchiolitis related airflow obstruction in these patients.

Evidence of lower lobe bronchial dilatation on the HRCT scan has also been observed in patients with symptomatic chronic GVHD associated airflow obstruction who undergo bone marrow transplantation.[6] However, no prospective imaging study has been done to establish when, in the evolution of chronic GVHD associated airways disease, bronchial dilatation begins. Its relationship to and usefulness as a marker of obliterative bronchiolitis in bone marrow transplantation is therefore unknown.

In view of the many predisposing factors for the development of chronic GVHD related bronchiectasis it may seem surprising that clinically overt disease has not been reported more commonly. Chronic GVHD in combination with the other lung insults mentioned may cause more widespread airways disease than previously appreciated. Early on the proximal disease may exist subclinically, detectable by HRCT scanning as bronchial dilatation. The rate of progression of this proximal disease, however, may lag behind the more aggressive distal disease, with bronchiectasis only occurring as a late manifestation in those who survive long enough. Immunosuppressive agents, in addition to conventional bronchiectasis therapy, are indicated if bronchiectasis

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is considered part of more widespread chronic GVHD related airways disease.

This case report highlights the existence of proximal airways disease as an association of chronic GVHD following allogeneic bone marrow transplantation. The more serious distal disease of obliterative bronchiolitis remains the more major complication in this group.

The case report by Charoenratanakul and Loasuthi[2] highlights some of the difficulties in accurately assessing oxygenation status in patients with extreme leucocytosis secondary to leukaemia. These patients are prone to various pulmonary diseases including a lung hyperleucocytosis syndrome involving leucocyte trapping within the lung vasculature. The arterial blood oxygen tension and the alveolar arterial oxygen difference are used as the first indication of such lung involvement. The result guides important diagnostic and therapeutic decisions such as initiation of cytoreductive therapy or, as in the case reported, the decision to ventilate. It is important to be aware of the specific limitations of using arterial blood oxygen tension and pulse oximetry in these patients.

Temperature dependent oxygen metabolism by the leucocytes in the blood sample limits the accuracy of arterial blood gas analysis in hyperleucocytosis. Fox *et al*[7] showed that, at room temperature, leukaemia samples with a gas of known oxygen concentration had a rapid initial exponential decay in oxygen tension. Controls exhibited minimal linear decay. This rapid decay was abolished by adding potassium cyanide, confirming metabolism as the cause. The rate of decay is greater with higher white cell counts and is affected by the type and the maturity of the proliferating cell. In this study immediate cooling of the sample on crushed ice blunted the oxygen decay but did not abolish it. Reports on the efficacy of immediate cooling of arterial blood gas samples in preventing this oxygen consumption differ. Some studies show that prompt icing prevents the accelerated fall in oxygen while others have found little effect. Variations in the delay between sampling and analysis, and the time the sample is held at 37°C during analysis, may account for some of these discrepancies.

In the presence of raised levels of dyshaemoglobins the haemoglobin oxygen saturation calculated from arterial oxygen tension ($Pao_2$) during blood gas analysis and that derived from pulse oximetry may be incorrect. Significantly raised levels of methaemoglobin and carboxyhaemoglobin are found in patients with leukaemia with extreme leucocytosis.[8] This limits the use of $Pao_2$ as an indicator of functional haemoglobin saturation because a proportion of total haemoglobin will be unavailable for oxygen transport.

In the case reported[2] and in others, pulse oximetry reflected both the oxygen content of the arterial blood and the clinical status better than $Pao_2$. Nevertheless, dyshaemoglobins also limit the accuracy of pulse oximetry. Pulse oximeters use the absorption ratios from two wavelengths of light to estimate oxygen saturation. This ratio is used to find the equivalent oxygen saturation in a table derived from healthy volunteers with normal dyshaemoglobin levels Methaemoglobin has similar absorption coefficients for both light wavelengths. This results in absorption ratios which will correspond to an oxygen saturation of 85% if the databank derived from normal subjects is used. A high percentage of methaemoglobin will bias oximetry towards 85% and a high percentage of carboxyhaemoglobin will cause an overestimate of the oxygen saturation. Blood samples should ideally be analysed in a multiwavelength in vitro oximeter using four wavelengths of light to measure deoxygenated haemoglobin, oxygenated haemoglobin, methaemoglobin, and carboxyhaemoglobin, providing a fractional oxygen saturation that is a truer reflection of functional saturation.[9] Even this may be inaccurate as a turbid hyperleucocytic sample can falsely raise the levels of methaemoglobin measured by this method.

The combination of an arterial blood gas sample cooled rapidly on crushed ice and analysed without delay, a simultaneous pulse oximetry reading, and clinical assessment should provide adequate information on oxygenation status in the absence of significant dyshaemoglobinaemia. Measurement of arterial oxygen tension and pulse oximetry in patients with extreme leucocytosis has limitations. A low $Pao_2$ may be spurious, and even pulse oximetry may be misleading if significant amounts of methaemoglobin and carboxyhaemoglobin are present.


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