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LUNG IMAGES

Thoracic Air-Leak Syndrome Complicating Allogeneic Hematopoietic Stem-Cell Transplantation

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Abstract
We report a case of thoracic air-leak syndrome, an extremely rare complication developed after an episode of organizing pneumonia due to graft-vs-host disease in a 19-year-old male. This unusual non-infectious pulmonary complication occurred 527 days after allogeneic HSCT and led to the patient's death within 1 month due to cardio-respiratory failure. Herein, we highlight chest-imaging aspects which are typical. Early detection by high-resolution chest CT could improve patient management.

Keywords Pneumothorax · Pneumomediastinum · Air-leak · Allogeneic hematopoietic stem-cell transplantation · Graft-versus-host disease

Case Presentation

A non-smoking 19-year-old man was admitted into our pulmonology unit complaining of dyspnoea and cough for 1 month. Ten months prior to admission, he had undergone allogeneic hematopoietic stem-cell transplantation (HSCT) with standard conditioning for acute lymphoblastic leukemia. Thereafter, he had developed chronic graft-versus-host disease (cGVHD), confirmed by a liver biopsy.

At admission, chest auscultation revealed crackles and squeaks in both lungs. A biological workup revealed hepatic cytolysis. Microbiologic blood tests were negative. A high-resolution chest CT (HRCT) showed scattered ground-glass opacities (Fig. 1a). A bronchoalveolar lavage (BAL) revealed mixed neutrophilic (27%) and eosinophilic (21%) alveolitis. Pulmonary function tests showed a restrictive pattern (FVC25% pred, TLC 50% pred) and blood-gas analysis revealed hypoxemia. The patient underwent a lung biopsy, which showed lesions consistent with Organizing Pneumonia (OP). High-dose corticosteroids (10 mg/kg/day) resulted in dramatic improvement and the patient was then weaned off oxygen after a couple of days. After a month, HRCT was normalized. Pulmonary function tests were improved but still showed a severe restrictive pattern with alveolar-capillary gas-exchange abnormalities (FVC 45% pred, TLC 50% pred).

After 5 months, he was readmitted for severe dyspnoea. He was still on systemic steroids (10 mg/day). Blood-gases on room air showed profound hypoxemia (Pa O_2 54 mmHg). HRCT confirmed extensive ground-glass opacities and extra-alveolar perivascular air (Fig. 1b). Persistent hepatic dysfunction prompted a needle liver biopsy, which showed moderate intensity cGVHD. Another steroid burst (120 mg × 3/day) was started once infection had been ruled out.

His respiratory status worsened. HRCT showed extensive lung infiltrates and interstitial emphysema with tension pneumomediastinum (Fig. 1c). At this time, after a multidisciplinary meeting and a review of the scientific literature, a diagnosis of thoracic air-leak syndrome (ALS) was made. Previous HRCTs were reviewed by several radiologists and lung physicians, and an initial lesion of ALS was retrospectively identified from the first HRCT (Fig. 1b: arrows).

Mycophenolate mofetil was added to the corticosteroids without success, and the patient died of cardio-respiratory

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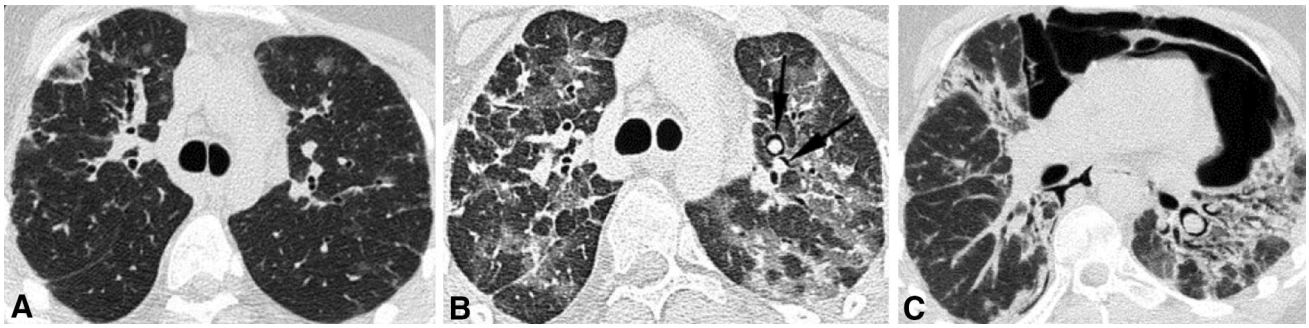

Fig. 1 **a** HSCT on admission showing scattered ground-glass opacities. **b** Five months later, extensive ground-glass opacities and interstitial emphysema with extra-alveolar rims of air around branches of the pulmonary arteries (arrows). **c** Three weeks later, extension or interstitial emphysema with tension pneumomediastinum

failure at 32 days after onset of ALS (527 days after allogeneic HSCT).

Discussion

The present case describes ALS, an extremely rare complication of allogeneic HSCT. ALS was first described by Franquet et al. as a spontaneous air-leak resulting in pulmonary interstitial emphysema, pneumomediastinum, pneumopericardium, pneumothorax, and subcutaneous emphysema [1]. Its primary mechanism remains speculative (viral infection/autoimmunity?). Via a check-valve mechanism, bronchiolar lesions may cause increased intra-alveolar pressure. Disruption of alveolar walls then results in a peri-bronchovascular air-leakage towards the hilum, the mediastinum and pleural cavity (Macklin effect) [1–3]. ALS is a very uncommon syndrome. Its incidence ranges from 1 to 2.3% in allogenic HSCT recipients [3–5] and may reach 20% in cases of cGVHD [3]. The strongest risk factor for ALS in HSCT recipients is GVHD. Other independent risk factors include > 2 HSCTs, male gender, aged <38 years and tacrolimus-based GVHD prophylaxis [5]. Our patient had at least three of these risk factors; i.e., histologically proven cGVHD, male gender and aged <38 years.

ALS-associated mortality ranges from 67 to 100% [2, 3] and it per se negatively impacts on HSCT outcomes. Patients with ALS have significantly lower survival rates (44% at 1 year, 15% at 3 years) than those without ALS (73% at 1 year, 61% at 3 years) [5]. In the most of case, patients with ALS had an underling late-onset non-infectious pulmonary complications (LONIPC) of bronchiolitis obliterans (BO) or interstitial lung disease (ILD). Post allogenic HSCT ILD includes OP, pleuroparenchymal fibroelastosis and the other interstitial lung diseases [6]. Median onset of BO and/or OP after HSCT is 202 days (range 99–1915). Once BO and/or OP are diagnosed, ALS occurs quite quickly (median 23 days; range 6–48) and is rapidly fatal (median 28 days; range 7–195) [4]. In our case, pulmonary complications of GVHD, i.e., OP, occurred 344 days after HSCT, and then ALS appeared 151 days after OP. Our patient died 32 days after ALS was diagnosed on a chest CT: i.e., 527 days after HSCT. No specific treatment for ALS is available; only supportive measures can be used. Indeed, despite proper drainage of pleural and mediastinal air effusion, the majority of patients die from progressive lung GVHD or concurrent pneumonia. ALS acts as a marker for severe GVHD rather than an independent transient "mechanical" pulmonary complication of HSCT [2]. In order to improve the prognosis of ALS, Toubai et al. recommend early detection and treatment of lung GVHD through conducting lung-function tests (and HRCT) in any patient, if symptoms occur [4].

This case report emphasizes several points. (i) HSCT recipients should be closely monitored with physical examinations and non-invasive respiratory tests, including SpO_2 and lung-function tests. (ii) Respiratory signs and symptoms or abnormalities in lung-function tests should prompt HRCT imaging in order to recognize and treat infectious and non-infectious complications as early as possible. (iii) In patients with known or suspected LONIPC, chest pain or sudden worsening of dyspnea should lead to a high index of suspicion for ALS, especially in high-risk patients: GVHD, ≥ 2 HSCTs, males, aged < 38 years and tacrolimus-based GVHD prophylaxis. Physicians and radiologists should be aware that tiny signs of extra-alveolar air, such as seen in our case, should be searched for on HRCTs. Patients with suspected or overt ALS should then be referred to an appropriate care setting with easy access to chest drainage and respiratory monitoring. This case report highlights the scarcity of data and available therapies for this syndrome. Despite its high mortality rate, ALS is largely un-researched. Early detection by high-resolution chest CT could improve patient management.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from parents because the person described in the case report has died.

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