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Lung Transplantation for Pulmonary AL Amyloidosis

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Lung transplantation (LT) is a life-saving intervention in advanced lung disease. Although particular indications depend on the underlying condition, transplantation is generally considered for those in whom further medical therapy is either ineffective or unavailable and for whom there is a high likelihood of mortality without intervention. Systemic disease leading to pulmonary involvement can be a contraindication to transplantation because of concerns for the possibility of recurrence in the transplanted organ and potential complications related to coexisting multiorgan disease.[1] However, there are many reports of successful LT in patients with systemic diseases, such as sarcoidosis, systemic sclerosis, and lymphangioleiomyomatosis,[2] suggesting that transplantation can be a viable option even in systemic diseases.

Evidence for solid organ transplantation in light chain (AL) amyloidosis exists primarily in heart, kidney, and liver transplant literature. Only 1 case report exists describing LT for respiratory failure because of localized AL amyloidosis[3]; no cases have been reported for systemic AL amyloidosis. One particular concern for transplantation in AL amyloidosis is an acquired coagulopathy, typically a result of endothelial disruption and clotting cascade abnormalities, which may pose an operative challenge.[4] We present a successful case of LT for systemic AL amyloidosis causing extensive cystic lung disease and progressive respiratory insufficiency.

CASE DESCRIPTION

A 44-y-old nonsmoker and former marathon runner with no environmental exposures was hospitalized in 2014 for acute dyspnea after 4 y of progressively reduced exercise tolerance. A left-sided pneumothorax and severe bilateral cystic changes in the lungs were found on imaging. She underwent video-assisted thoracoscopic surgery with bleb resection and pleurodesis. Examination of resected tissues revealed extensive pulmonary cystification with diffuse intrapulmonary amyloid deposition. Immunohistochemical staining demonstrated scattered foci of lambda-restricted plasma cells. A fat pad biopsy revealed apple-green birefringence on Congo red staining. Monoclonal gammopathy was absent on serum and urine electrophoresis with immunofixation. Serum-free AL analysis revealed excess lambda AL. Bone marrow biopsy demonstrated atypical plasmacytosis with >10% plasma cells; cytogenetic analysis revealed t(11;14). Lytic lesions were absent on a positron emission tomography–computed tomography (CT) scan. Transthoracic echocardiogram demonstrated elevated bilateral filling pressures, mildly thickened interventricular septum, increased left ventricular wall thickness, and normal ejection fraction. Cardiac MRI showed a lack of delayed ventricular gadolinium enhancement but excess myocardial extracellular volume fraction and nonspecific atrial enhancement suggestive of amyloid deposition. N-terminal pro b-type natriuretic peptide was elevated; high-sensitivity troponin-T was low normal. A cardiac biopsy was not performed. Serum creatinine and 24-h urinary protein measurements were normal. Hepatic abnormalities were not observed. A skin biopsy revealed amyloidosis. Serological testing for the underlying rheumatologic disease was negative, including the antibodies ANA, anti-Smith, anti-SSA and anti-SSB, anti-scl70, anti-U(1)RNP, and anti-Jo-1.

A diagnosis of systemic AL amyloidosis with diffuse pulmonary, skin, and presumed cardiac involvement was established. The patient was treated with 4 cycles of cyclophosphamide, dexamethasone, and bortezomib without response.

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She underwent an autologous stem cell transplant with high-dose melphalan, resulting in complete hematologic remission (hCR). She also participated in a first in-human clinical trial evaluating the novel antifibril monoclonal antibody 11-F4, now CAEL-101, aimed at improving existing organ dysfunction via clearance of amyloid deposits. Treatment with 11-1F4 monoclonal antibodies led to minimal clinical improvement.[5]

The patient's respiratory status declined over the next 5 y despite being in sustained hCR. She developed worsening lung function with severe airflow obstruction, hypercapnia, pulmonary hypertension, and oxygen requirement of 4 L with activity. Cardiopulmonary exercise testing revealed severe exercise impairment and a submaximal effort because of pulmonary limitations. A chest CT scan revealed extensive panlobular emphysema and coalescent cystic lung disease throughout both lungs, chronic right lower lobe and right perihilar consolidations, and left lung apical postoperative changes because of bleb resection (Figure 1). She was eventually listed for LT and underwent right single LT (SLT) with basiliximab induction 6 y after the initial diagnosis. SLT was chosen due to her prior left-sided talc pleurodesis, which would have made the explantation of the left lung challenging with the risk of bleeding, as well as her lack of significant pulmonary hypertension. Lung explant pathology was notable for widespread amyloid deposition around vessels, in the interstitium and pleura, and focally along the alveolar septa; extensive cystic alteration of the lung; large emphysematous-like spaces, particularly subpleurally; and substantial thickening of both the intima and media of the pulmonary arteries consistent with pulmonary hypertension (Figure 2). The intraoperative course was complicated by bleeding requiring massive transfusion protocol and inability to tolerate single-lung ventilation necessitating venovenous extracorporeal membrane oxygenation support, which was continued postoperatively because of grade III primary graft dysfunction. She was decannulated from extracorporeal membrane oxygenation on postoperative day 4 and extubated on day 7. She was maintained on triple immunosuppression with tacrolimus, mycophenolate mofetil, and steroids. She developed venous thromboembolism, was treated with anticoagulants, and had temporary inferior vena cava filter placement. She was discharged home without supplemental oxygen on postoperative day 70.

Twenty-nine months posttransplant, she had no respiratory symptoms and no evidence of recurrent amyloidosis on a chest CT scan or 12-mo transbronchial biopsies. Pulmonary function testing revealed resolution of the preoperative obstructive ventilatory deficit with a forced expiratory volume in one second of 56% predicted and a ratio of forced expiratory volume in one second to forced vital capacity of 89, which is consistent with the expected lung function following SLT. She remained adherent to her immunosuppressive regimen. She was exercising regularly, had gained weight, and resumed normal function. Unfortunately, the patient developed acute lung allograft dysfunction with diffuse pulmonary infiltration and respiratory failure while traveling overseas and ran out of mycophenolate mofetil. She was treated with mechanical ventilatory support, empiric antibiotics, and pulse steroids without response and expired. Although an autopsy

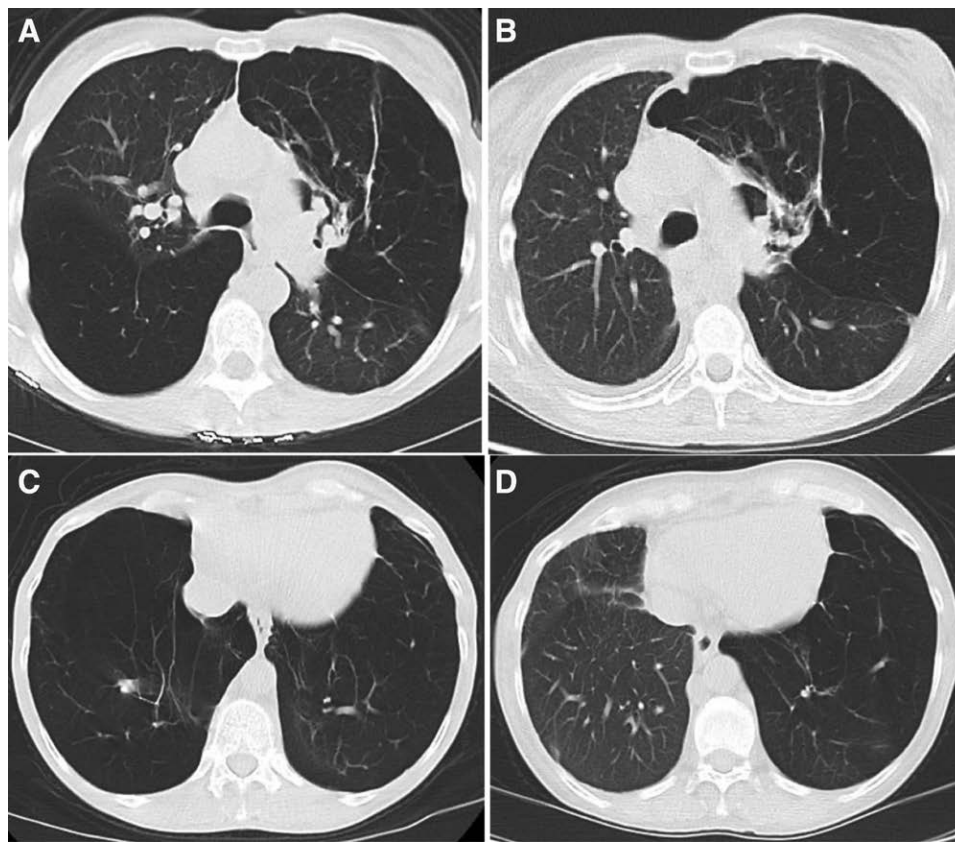

FIGURE 1. A and C, Representative sections from the pretransplant chest CT scan demonstrating extensive panlobular emphysema and coalescent cystic lung disease throughout both lungs with left upper lobe postoperative changes because of bleb resection. B and D, Sections from the posttransplant chest CT scan demonstrating normal right lung allograft parenchyma. CT, computed tomography.

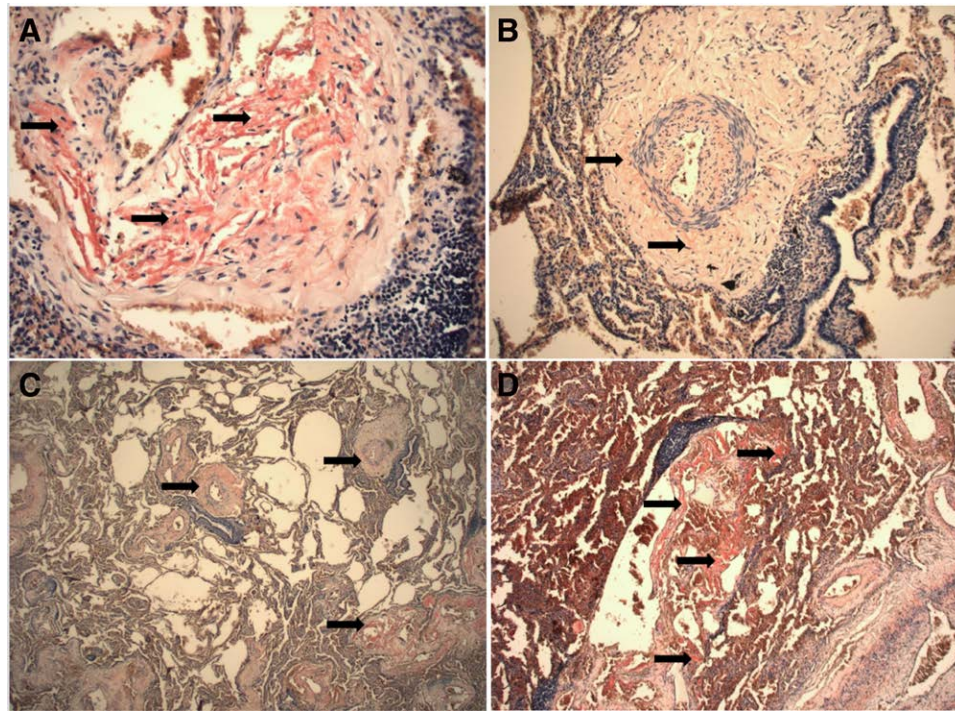

FIGURE 2. Explant pathology. Congo red–stained sections show lung tissue with cystic, emphysematous changes and focal accumulations of pale acidophilic material, which is overserved in and around vessels as well as in the lung interstitium (A–D). Most vessels appear thickened and contain pale acidophilic material (B and C). This material appears to be red on the Congo red stain and on polarization is birefringent. On the crystal violet stain, the material has a metachromatic appearance, and on the trichrome stain, it displays a gray-blue-like color. These findings are consistent with amyloid deposition. The pulmonary arteries show substantial thickening of both the intima and the media, consistent with pulmonary artery hypertension (B and C). There is also dense fibrosis of the adventitia. There are areas with accumulations of lymphocytes and occasionally macrophages (A and B). Arrows show deposits of amyloid.

was not performed, she had no evidence of amyloid recurrence on serologic testing, chest imaging, or transbronchial biopsies before this event, and the acute presentation was not consistent with amyloid recurrence.

DISCUSSION

Pulmonary AL amyloid has 2 primary manifestations: nodular and diffuse forms. Nodular pulmonary amyloid is characterized by limited, slow-growing subpleural foci of fibril deposits and is associated with extranodal marginal zone lymphomas.[6] It has a minimal clinical impact. Diffuse pulmonary AL amyloid is marked by fibrillary deposits in the alveoli and septa. One autopsy series suggests an incidence of 90%[7] in all AL amyloidosis, although it is almost always clinically silent. Occurrence as a dominant manifestation is very rare but devastating.[8]

Treatment of AL amyloidosis involves targeting the underlying plasma cell clone, but end-organ damage may be advanced. During 2000–2020, due to novel antineoplastic therapies, such as the proteasome inhibitor bortezomib and the anti–CD-38 monoclonal antibody daratumumab, the frequency and depth of hematologic response have increased drastically,[9] resulting in improved organ response and increased candidacy for transplantation, irrespective of organ.[10-12] Outcomes for solid organ transplantation in amyloidosis, particularly heart and kidney transplants, remain comparable with those for nonamyloid conditions.[13]

Three major barriers to solid organ transplantation in AL amyloidosis exist: (1) active hematologic disease, which significantly increases the risk of amyloid recurrence in the graft[14]; (2) multiorgan involvement, which severely limits surgical candidacy; and (3) intraoperative bleeding risk. Before novel plasma cell-targeted therapies, such transplantation in AL amyloidosis was performed in <2% of patients.[12] Those patients who did undergo cardiac or renal transplantation after achieving hCR experienced outcomes comparable with those of nonamyloid patients. From a surgical perspective, AL amyloidosis has been associated with significant coagulopathy,[4,15] which, depending on the cause, may persist even after attaining hematologic remission.[16] Described mechanisms include amyloid infiltration of vascular endothelium, acquired factor inhibitors and deficiencies, and dysfibrinogenemia. Additionally, mechanical circulatory support, if needed, necessitates systemic anticoagulation.[17]

Ware et al[3] described the only other reported case of LT in a patient with progressive respiratory failure secondary to biopsy-proven diffuse pulmonary AL amyloid.[3] Notably, unlike in our patient, there was no evidence of extrapulmonary amyloid. The only reported complication was recurrent extrinsic airway compression from hilar adenopathy requiring endobronchial stent placement. A lymph node biopsy was consistent with amyloidosis. There was no evidence of recurrence in the lung parenchyma. Four years posttransplant, the patient had excellent functional status.

We report the first patient with systemic AL amyloidosis, manifesting as diffuse parenchymal pulmonary amyloid and presumed cardiac involvement, to undergo LT for chronic respiratory failure while in hCR. Her underlying pathology was rendered more unique by the findings of diffuse cystic disease

as well as emphysematous changes, which are not typical in pulmonary amyloid.

Two and a half years posttransplant, the patient remained free of supplemental oxygen and had recovered preamyloidosis function with excellent quality of life, including overseas travel. Her unexpected death was unrelated to amyloidosis. The decision to perform LT in patients with AL amyloidosis and pulmonary disease must be individualized and involve a multidisciplinary team including hematologists, cardiologists, and transplant surgeons. In carefully selected patients in hCR, even with evidence of other end-organ involvement, LT may be a viable therapeutic option.

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