Word Count: 1687

Article Title: Autologous Stem Cell Transplant in the Treatment of Pulmonary Light Chain Deposition Disease

Category: Novel Report

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Supplementary:
No personal nor financial support to disclose.

All authors have reviewed the manuscript, agree with its contents, and consent to its submission to CHEST.

The voluntary, fully informed consent of the subject used in this research was obtained as required by 32 CFR 219 and DODI 3216.02_AFI 40-402.

The views expressed are those of the author(s) and do not reflect the official views or policy of the Department of Defense or its Components.

Abstract

Light chain deposition disease is a rare condition resulting in the deposition of light chains in organs and their subsequent dysfunction. It is often the consequence of unchecked light chain production by a plasma cell clone. Rarely does it manifest with solely pulmonary involvement, especially in the young, otherwise healthy patient. This article highlights the presentation and diagnosis of pulmonary light chain deposition disease in an active duty solider, the discovery of a plasma cell clone responsible for his symptomatology, and the therapy targeted at the plasma cell clone inducing pulmonary disease. This therapy included a novel, successful treatment with an autologous stem cell transplant. To date, it is amongst the first such documented successful bone marrow transplants in treatment of isolated pulmonary light chain deposition disease.

Introduction

Light chain deposition disease (LCDD) is a rare condition resulting in the deposition of light chains in organs causing their subsequent dysfunction. It typically presents with an elevation of the monoclonal immunoglobulin κ light chain with multisystem end organ dysfunction involving the kidneys.[1] As a result, kidney function rapidly declines. While it typically results in multiorgan dysfunction, it infrequently presents in a localized fashion, and seldom only involves the lungs.[2] Previous studies have shown a large percentage of patients with LCDD have an underlining lymphoplasmacytic disorder.[3] Radiographic imaging typically reveals nodules or diffuse cystic disease, which may be associated with autoimmune or lymphoplasmacytic etiologies respectively.[4] While multiple organ involvement is commonly seen, rarely has it manifested in a young, otherwise healthy patient with primarily pulmonary involvement.

Case

The patient is a 28 year old active duty US Army solider without previous medical history. He presented to clinic with eight months of progressively worsening dyspnea on exertion associated with a productive cough of thin, white sputum. He was diagnosed with exercise induced bronchospasm and empirically treated with albuterol to little effect.

He was originally from Puerto Rico and joined the army two years prior. He was stationed in the central valley of California for one year and previously was in South Carolina and Virginia. He had exposure to horses on base and dust common to that area, but could not identify any triggers that made his symptoms worse. He had no family history of lung disease and was a lifetime nonsmoker. His physical exam was notable for coarse, dry crackles in the lung bases bilaterally. Pulmonary function testing (PFT) noted a nonspecific spirometry pattern and a diffusing capacity of monoxide (DL_{CO}) of 43% predicted value and forced expiratory volume (FEV1) of 70%. There was no bronchodilator response.

Chest computed tomography (CT) imaging noted a widespread pattern of thin-walled cysts of varying sizes associated with scattered random nodules preferentially affecting mid and lower lung zones (Figure A).

His initial laboratory workup was pertinent for elevated inflammatory markers, elevated protein/albumin dissociation, elevated serum immunoglobulins IgG and IgA, and elevated serum

free light chains (FLC) of both kappa and lambda with a normal ratio and no M-spike. He was without proteinuria and exhibited normal renal and liver function. Nonsmoking status was verified with a negative urine cotinine, cystic fibrosis DNA testing was negative and chitotriosidase was within normal limits in evaluating for Gaucher disease. Further testing was unremarkable for rheumatoid factor, antinuclear antibodies (ANA), anti-Ro and La antibodies, antiscleroderma-70 antibodies, antineutrophilic cytoplasmic antibodies (ANCA), alpha-1 antitrypsin, vascular endothelial growth factor (VEGF-D), and IgG4 levels. CT imaging of the chest, abdomen and pelvis revealed that no other organ systems were anatomically involved. Positron emission tomography (PET) indicated no enlarged nor hypermetabolic thoracic lymph nodes and normal physiologic activity within the chest.

He was referred for surgical lung biopsy, which was completed without complications. The pathology sample showed follicular hyperplasia of bronchial associated lymphoid tissue (BALT) with plasma cell infiltrates (Figure B). There were nodular infiltrates of brightly eosinophilic material that were suspicious for amyloid, but did not have the typical staining pattern of apple-green birefringence with Congo red stains. Pathology on the lung specimen was suspicious for light chain deposition disease, as it had the microscopic appearance of amyloid without the typical staining pattern. However, due to the biopsy not obtaining any cystic nor nodular elements, no light chains were visualized on electron microscopy and the patient declined repeat biopsy. Further evaluation of specimens at the Department of Defense Joint Pathology Center, to include transmission electron microscopy, immunohistochemical staining, fluorescence microscopy, and Congo red staining provided further confidence that light chain deposition disease was likely over amyloidosis. No dominant monoclonal peak was observed on Ig heavy chain polymerase chain reaction (PCR), ruling down lymphomatous processes.

A bone marrow biopsy (BMB) was obtained which showed mild hypocellularity at 50%; with 27% bands and 2% plasma cells. Florescent In-Situ Hybridization (FISH) identified a clonal plasma cell population with a deletion of the MAF gene region (16q deletion) in 8.5% of nuclei, consistent with a myeloma variant.

The patient was subsequently diagnosed with pulmonary light chain deposition disease (PLCDD). With no established guidelines for treatment, therapy was targeted at the light chain producing plasma cell clone believed to be responsible for his pulmonary disease. He completed four cycles of lenalidomide, bortezomib and dexamethasone (RVD). There was no evidence of a plasma cell clone on repeat bone marrow biopsy. Given complete remission, he was consolidated with melphalan 200mg/m^2 and completed an autologous stem cell transplant (ASCT) without complication. He was referred for possible lung transplant, but his pulmonary function and clinical status three months after ASCT had both shown improvement. There were no new cystic lesions on repeat chest CT nine months post ASCT with notable shrinkage in multiple cysts (Figure C). One year after ASCT, the patient's PFTs had stabilized with improvement in DL_{CO} (Table 1), he maintains normalized free light chains and remains clinically stable.

Discussion

LCDD is a rare condition resulting in the deposition of immunoglobulin light chains in tissues. Originally described in 1976, it was believed to primarily affect the kidneys resulting in nodular glomerulosclerosis.[5] Up to 67% of previous cases of LCDD have been associated with a plasma cell dyscrasia, predominantly affecting middle-aged patients.[2] Pulmonary LCDD (PLCDD) manifests as symptomatic shortness of breath in the setting of diffuse pulmonary cysts and nodules. While multi-organ disease is most commonly seen, PLCDD has seldom been documented in the literature with a paucity of case reports.[5-8]

While primarily nodular light chain deposition can be indolent, diffuse cystic disease, which likely affects this patient, has progressed to respiratory failure in previous cases.[2] Another and potentially more accurate notion is to group PLCDD into nodular and diffuse subtypes, with the nodular subtype heralding an autoimmune process whilst the diffuse class is associated with lymphoplasmacytic disorders, the latter afflicting this patient.[7] The differential for radiographic findings of thin-walled pulmonary cysts and nodules with a lower lobe predominance includes Sjögren syndrome, amyloidosis and lymphoid interstitial pneumonia in addition to LCDD. The closest related condition to LCDD is AL (light chain) amyloidosis, which also results in light chain deposition in tissues. Although pulmonary light chain deposits are histologically similar to amyloid, they do not exhibit apple green bifringence when exposed to Congo red stain as seen in this case. LCDD specimens under electron microscopy do not show a fibrillary pattern as seen with amyloid deposits. AL amyloidosis typically presents with elevated lambda chains while LCDD has shown a predilection for elevated kappa. Of note, this patient had elevations of both lambda and kappa with a normal ratio.

This patient's case was indicative of light chain deposition disease early on with the elevation of light chains with the constellation of nodular and cystic changes on pulmonary CT. However, due to an insufficient wedge biopsy not obtaining any cystic nor nodular elements, there were no definitively located light chains on electron microscopy and the patient refused repeat lung biopsy. Nevertheless, a bone marrow biopsy elucidated a plasma cell clone with a 16q deletion indicative of a myeloma variant. In the setting of elevated free light chains with nodules and cysts on pulmonary CT, without any other organ involvement and underlining plasma cell clone, the diagnosis of PLCDD was favored.

With no established guidelines for treatment of PLCDD, management is not definitively determined. Previous patients have remained solely under observation, treated with melphalan and dexamethasone, received methotrexate for an underlining Sjogren Syndrome, or sought treatment with lung transplant, of which one of three patients died post-operatively.[2,7,9] One patient with MALT Lymphoma and Sjogren's Syndrome received steroids and rituximab with stable disease ten years later.[7] Given treatments for PLCDD have ranged from observation to lung transplant, the prognosis is not well established for this entity and the installation of treatment should mirror the rapidity of disease progression and be targeted at the underlining cause if elucidated. Given that it is likely a plasma cell clone producing light chains which induced PLCDD in our patient, therapy was successfully targeted at this plasma cell clone. While a previous patient with PLCDD received an autologous stem cell transplant that had been

preceded by high-dose steroids, dyspnea and radiographic manifestation rapidly progressed.[9] Six previous patients afflicted with LCDD with primarily renal insufficiency have also received ASCT.[10] They were conditioned with dexamethasone alone or in combination with thalidomide, and four achieved criteria for a renal response after ASCT. Our patient underwent a standard initial therapy for multiple myeloma, completing four cycles of RVD, with subsequent autologous stem cell transplant.

Nine months after ASCT the patient showed no progression of cystic nor nodular elements, with some even shrinking. One year after ASCT, the patient maintains normalized serum free light chains with improvement in PFTs, radiographic findings and clinical respiratory status. There are no established guidelines for treating the entity of PLCDD, with previous patients receiving lung transplants, lenalidomide with renal involvement, and an unsuccessful bone marrow transplant.[9,11,12] The utilization of ASCT, following conditioning with RVD, is the first such documented instance of its use in treating PLCDD. This novel approach merits further investigation, and future patients with PLCDD with a clonal population on bone marrow biopsy may also benefit from this treatment modality. This patient has shown hematologic remission along with stabilization of radiographic findings and even improved pulmonary function.

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Pulmonary Function Testing Relative to Autologous Stem Cell Transplant

Pulmonary Function Testing	**6 months pre-transplant**	**At transplant**	**One year post-transplant**
FVC (predicted %)	4.26 (76%)	4.21 (75%)	4.35 (77%)
FEV1 (predicted %)	3.27 (70%)	3.16 (68%)	3.32 (72%)
FEV1/FVC	77%	73.3%	93%
TLC (predicted %)	5.66 (77%)	5.56 (76%)	6.07 (85%)
RV (predicted %)	1.4 (79%)	1.25 (71%)	1.86 (109%)
DL_{CO} (predicted %)	15.6 (43%)	14.5 (40%)	22.5 (66%)
DL_{CO}/VA	3.34 (68%)	3.17 (64%)	3.86 (81%)

Table 1: Pulmonary function testing 6 months pre-transplant, at time of transplant, and one year post autologous stem cell transplant showing stabilization and notable improvement of DL_{CO} in pulmonary function testing.

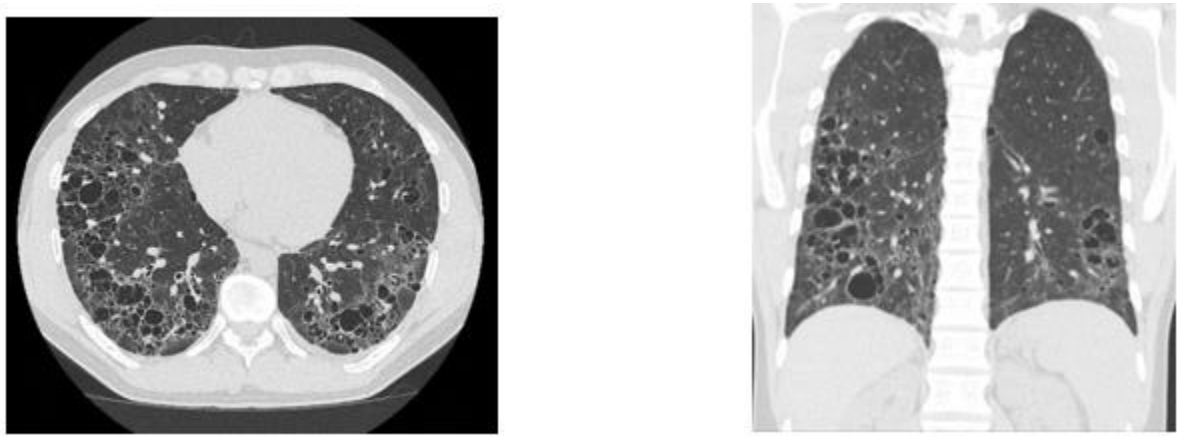

Figure A: Diffuse bilateral cystic lung disease, most prominent within the lung bases, with innumerable thin-walled cysts varying in size from 1 mm up to 2.5 cm; confluent in some areas. Numerous bilateral diffuse solid nodules vary in size from 4 mm up to 2.3 cm, most significant in the right middle lobe.

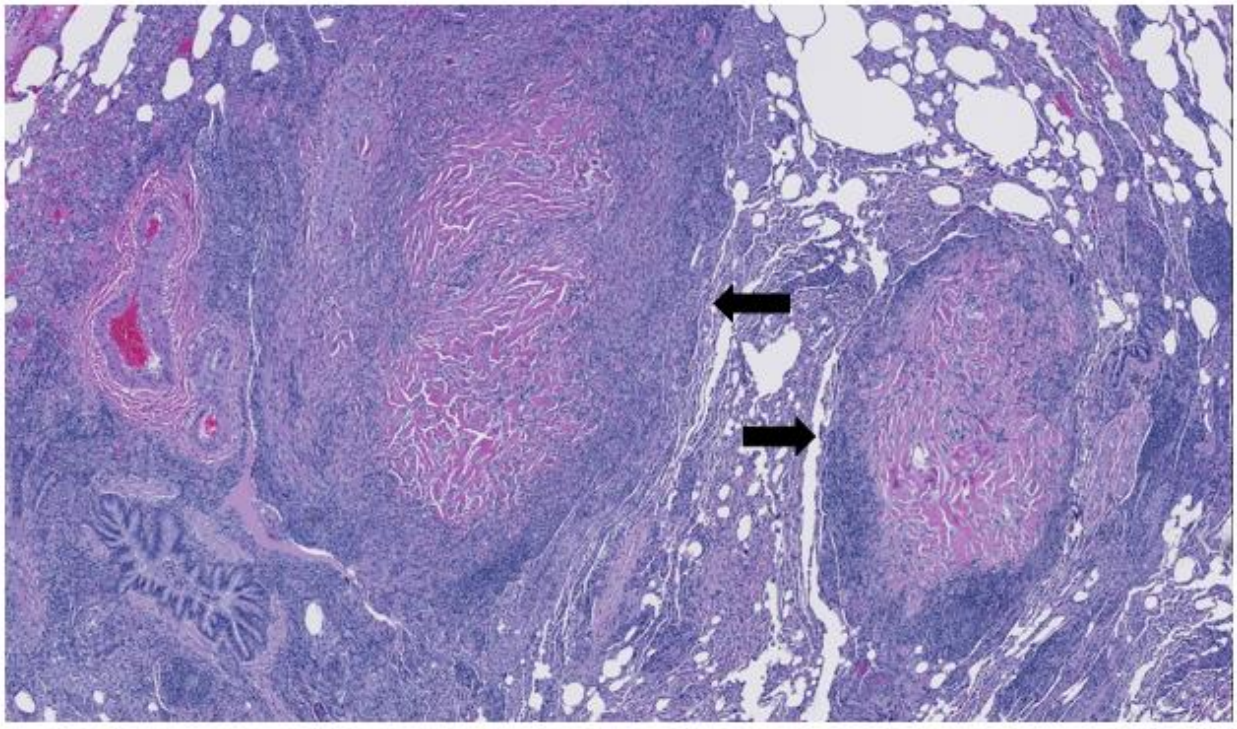

Figure B: Surgical lung biopsy shows airway centered hyperplasia of bronchus associated lymphoid tissue (BALT) outlined by arrows surrounding two nodules of eosinophilic material (H&E stain, 8x magnification).

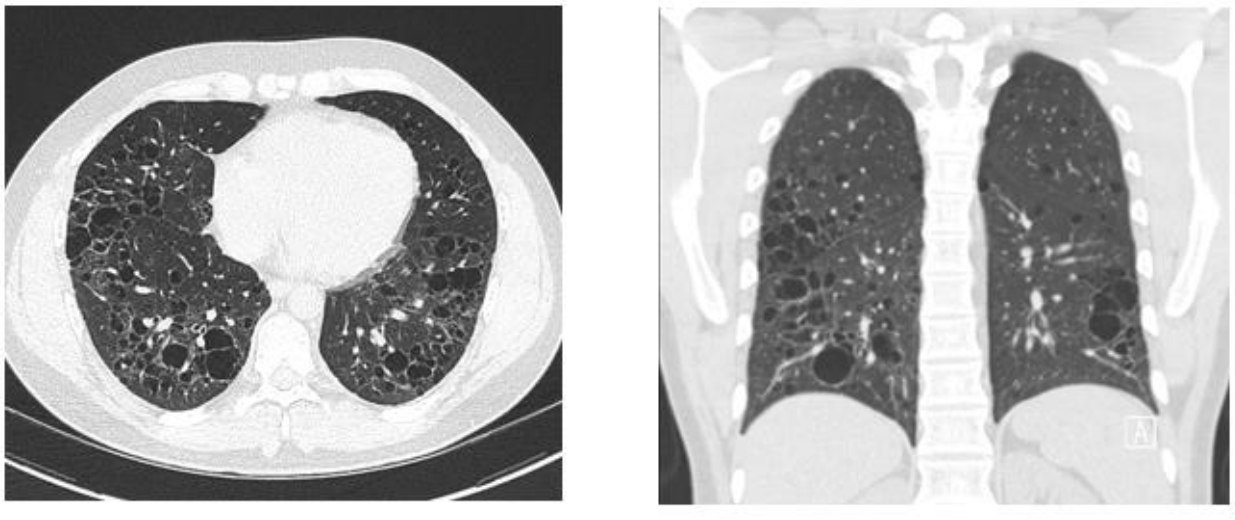

Figure C: CT imaging 9 months post autologous stem cell transplant revealing no new cysts nor nodules. Compared to CT imaging 5 months pre-transplant, a pulmonary nodule in the right apex had decreased from 7mm to 5mm and a 9mm nodule in the right minor fissure had shrunk from 12mm.