PULMONARY STENTING FOR THE TREATMENT OF SARCOID INDUCED PULMONARY VASCULAR STENOSIS

Jose F. Condado, Vasilis Babaliaros, Travis S. Henry, Brian Kaebnick, Dennis Kim, Gerald W. Staton Jr

Divisions of Adult and Pediatric Cardiology, Radiology and Imaging Sciences, and Pulmonary Medicine, Emory University School of Medicine, Atlanta, GA

Abstract. Background: The best treatment of patients with external pulmonary vascular compression due to advanced sarcoidosis is unknown. Objectives: To report a single-center experience of percutaneous treatment for pulmonary vascular stenosis caused by external compression due to advanced sarcoidosis. Methods: We report a case series of 5 patients with biopsy confirmed advanced sarcoidosis, seen at our academic institution with worsening dyspnea despite increase of immunosuppressive therapy. All patients were evaluated by a multidisciplinary team (cardiology, pulmonary and radiology) using a multi-modality approach, including chest-computed tomography angiography, ventilation/perfusion scintigraphy, pulmonary function test, 6-minute walk test and heart catheterization. Results: Three out of five patients underwent pulmonary artery or vein angioplasty and stenting resulting in symptomatic improvement: Patient 1 had persistent symptomatic improvement measured by subjective and objective methods at 30 months; patient 2 required re-intervention due to recurrent pulmonary vein stenosis at 6-months followed by persistent improvement; and patient 3, had a procedure complicated with in-stent thrombosis requiring thrombolysis and anticoagulation with improvement. The remaining two patients were medically treated because underlying thromboembolic disease (patient 4) and diffuse pulmonary vein stenosis not amenable to percutaneous intervention (patient 5). Conclusions: Pulmonary vascular stenosis from external compression can be a rare but unrecognized cause of worsening symptoms in advanced sarcoidosis. Pulmonary vascular angioplasty and stenting can provide clinical benefit in select patients. (Sarcoidosis Vasculitis Diffuse Lung Dis 2016; 33: 281-287)

Key words: sarcoidosis, pulmonary stenting, vascular stenosis

Introduction

Patients with early stages of symptomatic sarcoidosis are often managed with corticosteroids or immunosuppressants. However, once advanced pulmonary fibrosis develops (stage IV), lung transplantation is the only treatment (1). External vascular compression by mediastinal fibrosis, granulomas or hilar lymphadenopathy has been reported in a few cases of advanced pulmonary sarcoidosis (2-7), but the optimal treatment for these rare cases remains unclear.

Pulmonary vascular angioplasty or stenting has been described for the treatment of patients with...
fibrosing mediastinitis without sarcoidosis (8, 9). However, there is little and conflicting evidence regarding the benefit of this procedure in the treatment of sarcoidosis related pulmonary vascular stenosis (7, 10, 11). We describe a single-center experience in the management of patients with stage IV sarcoidosis and concomitant pulmonary vascular compression, as determined by both chest computer tomography angiography (CTA) and diagnostic heart catheterization (HC).

**Material and Methods**

Emory University Hospital (EUH) is a referral medical center for the evaluation and follow-up of patients with pulmonary sarcoidosis and patients with interstitial lung disease. EUH is also a specialized institution for structural heart interventions with a large experience of pulmonary vascular stenting. Of 570 patients with sarcoidosis seen during a 5-year period, five patients (0.9%) with biopsy confirmed pulmonary sarcoidosis were evaluated at our institution with worsening dyspnea despite increasing the immunosuppressive therapy. Thus, a chest Multidetector CTA was ordered for further evaluation.

In these patients, chest Multidetector CTA revealed stage IV sarcoidosis with concomitant pulmonary artery and/or vein stenosis attributed to external compression from a fibrosing mediastinitis-like pattern. The patients underwent further work up including ventilation/perfusion (V/Q) scintigraphy, pulmonary function test (PFT), 6-minute walk test, diagnostic heart catheterization and evaluation by a multidisciplinary team that included a pulmonologist, thoracic radiologist, and adult and pediatric interventional cardiologists. The decision to intervene was agreed upon by the team after careful evaluation of all available tests and detailed discussion with the patient.

**Results**

Patient characteristics are shown in table 1. Our 5 cases of pulmonary sarcoidosis are described below.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (Years)</th>
<th>Race / Gender</th>
<th>Comorbidities beside sarcoidosis</th>
<th>Preprocedure therapy**</th>
<th>Pre-MPA (mmHg)*</th>
<th>Intervention(s)</th>
<th>Post-MPA (mmHg)*</th>
<th>Therapy on follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>African-American /Female</td>
<td>Hypertension, OSA</td>
<td>Prednisone Leflunomide Mycophenolic acid (past) Azathioprine (past)</td>
<td>50 (RPA=45 LPA=40)</td>
<td>Stenting of Left and Right PA, Followed by left PV stenting</td>
<td>45 (RPA=45 LPA=25)</td>
<td>Prednisone (low dose)</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>African-American /Female</td>
<td>Developmental delay, atrial septal defect, diabetes</td>
<td>Treprostilin Bosentan Prednisone</td>
<td>90</td>
<td>Stenting of Right upper lobe PA and Left lower lobe PA</td>
<td>42</td>
<td>Bosentan</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>African-American /Female</td>
<td>Hypertension, asthma, obesity</td>
<td>Prednisone</td>
<td>48</td>
<td>Stenting of left PA and bilateral upper PV. Followed by multiple PV balloon angioplasties</td>
<td>29</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>African-American /Male</td>
<td>Hypertension, history of DVT and PE.</td>
<td>Prednisone Rivaroxaban</td>
<td>N/A</td>
<td>No intervention</td>
<td>N/A</td>
<td>Prednisone Rivaroxaban</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>Caucasian /Female</td>
<td>None Methylprednisolone</td>
<td>Methylprednisolone Methotrexate</td>
<td>18</td>
<td>No intervention</td>
<td>N/A</td>
<td>Methylprednisolone Methotrexate</td>
</tr>
</tbody>
</table>

ACE= Angiotensin Converting Enzyme, PA=pulmonary artery, PV=Pulmonary Vein, MPA=main pulmonary artery, LPA=Left pulmonary artery, RPA=Right pulmonary artery, OSA = Obstructive Sleep Apnea, N/A = Not Available, DVT = Deep Vein Thrombosis, PE = Pulmonary embolism

*All pressures were measured during the index procedure, at baseline (pre) and after stent deployment (post)
**Patient 1**

A 63-year-old female with 10-year history of pulmonary sarcoidosis presented with worsening dyspnea despite treatment with prednisone and leflunomide. Chest CTA revealed a high-grade stenosis at the origin of the left upper and lower pulmonary arteries (PA), complete occlusion of the right upper lobe PA, and high-grade stenosis of the middle and lower right PA. A quantitative V/Q scan also revealed left lung and right apical perfusion defect with air trapping. To exclude other causes of fibrosing mediastinitis, patient had negative fungal stain and cultures, and negative serum histoplasma antibodies. PA stenosis was confirmed with a HC and consequently she underwent a right main and left lower PA stenting, followed by left upper pulmonary vein (PV) stenting 3 months after initial intervention (Figure 1, 2). After both procedures, patient had sustained improvement of dyspnea, V/Q defects (Figure 3), PFT parameters and 6-minute walk distance, even after 30 months (Figure 4). She was weaned off the immunosuppressant and is currently on low-dose prednisone at her three-year follow up.

**Patient 2**

A 42-year-old female newly diagnosed with sarcoidosis presented with worsening dyspnea and pulmonary hypertension on transthoracic echocardiogram. The initial V/Q scan raised a question of chronic thromboembolic disease, but multidisciplinary review of the V/Q and subsequent chest CTA showed extrinsic compression of the pulmonary arteries by hilar lymphadenopathy most likely secondary to patient’s sarcoidosis. Stain and cultures were negative for fungal disease; serum histoplasma antibodies were also negative. HC confirmed pulmonary hypertension (PA pressure 136/43 mmHg with no response to nitric oxide challenge) and signifi-
significant PA stenosis of the right middle and lower lobe PA. Patient underwent right upper lobe and a left lower lobe PA stenting. This intervention was complicated with an acute PA stent thrombosis (despite adequate procedural activated clotting time levels) that was treated with aspiration thrombectomy and local thrombolytic injection. Patient was started on intravenous heparin and oral warfarin, and because of persistent pulmonary hypertension, underwent repeat HC the following day, revealing recurrent PA stent thrombosis, which dissolved with a second local thrombolytic injection. She was discharged on oral anticoagulation with improved clinical symptoms. At 22 months, she has been titrated off steroids, and her pulmonary symptoms remain stable with no-restenosis on follow-up chest CTA

Patient 3

A 60-year-old female with advanced sarcoidosis presented with worsening dyspnea, not relieved by prednisone. On chest CTA, patient had typical sarcoid pulmonary parenchymal involvement (that had been diagnosed by biopsy in the past) and severe bilateral stenosis of superior PA’s and PV’s on chest CTA, with matched perfusion defects of the same region on V/Q scan. She first underwent a confirmatory HC with concomitant PV stenting (two right upper and two left upper PV). Four months later, she had an elective left PA stenting, with simultaneous left bronchoscopy to ensure airway patency and a balloon angioplasty of the right upper, left upper and left lower PV for restenosis with improvement of both symptoms and V/Q defects. She complained of dyspnea at 6 months post-procedure and again underwent angioplasty with a paclitaxel-coated balloon (Lutonix balloon, Boston Scientific, Marlborough, MA) of the left superior, left middle and right superior PV. The clinical improvement after this third procedure persisted on her 1-year follow-up appointment.

Patient 4

A 66-year-old male with history of cutaneous and pulmonary sarcoidosis for more than 30 years was diagnosed in the emergency department with an acute left lower extremity deep vein thrombosis (DVT). Due to concomitant dyspnea he also underwent chest CTA that revealed acute on chronic pulmonary embolism (PE) with concomitant bilateral PA and PV stenosis. He was started on anticoagulation and underwent further work up with a V/Q scan revealing matched bilateral upper lobe defects, worse on the right. However, careful discussion by a multidisciplinary team decided against further vascular intervention due to patient’s stable symptoms (at New

Fig. 2. Coronal CTA images before (A) and after (B) stent placement. Severe stenosis of the left pulmonary artery is visible on the initial study (arrow, A) as a result of compression from confluent mediastinal and hilar lymphadenopathy. A follow-up CTA two years after stent placement shows that the stent remains widely patent (arrow, B) with improved perfusion of the left lung.
York Heart Association class II) and concomitant thromboembolic disease. Patient’s symptoms have been stable after one year of follow up.

**Patient 5**

A 42-year-old female with pulmonary sarcoidosis (diagnosed with biopsy – negative fungal stains and cultures) underwent work up for worsening dyspnea, including a chest CTA that revealed large mediastinal and hilar lymphadenopathy causing external compression of PA’s and PV’s. She was started on methylprednisolone and underwent diagnostic HC, which showed diffuse vascular stenosis limited to small branches of the PA and PV, not amenable to stenting. She clinically improved with titration of her medical therapy, which now includes methotrexate.

Fig. 3. Quantitative perfusion scintigraphy performed before (A) and after (B) artery and venous stenting. At baseline, the left lung only received 24.4% of total lung perfusion (oval, A). After intervention, the flow in the left lung increased to 37.4% (oval, B)
Our case series suggests that pulmonary vascular balloon angioplasty and stenting can be used as a therapy in select patients for advanced sarcoidosis and concomitant external compression of the pulmonary vasculature. This intervention could either be used as a palliative treatment or as a bridge to lung transplantation in patients with sarcoid end-stage lung disease, particularly in high-risk patients (i.e. patients with pulmonary hypertension) (1, 12). The observed improvement of stented patients suggest that the V/Q mismatches from vascular stenosis can be an aggravating cause of dyspnea. However, establishing the diagnosis and determining the indication for intervention can be difficult.

A chest CTA is a reasonable first test to evaluate the vascular anatomy in patients with sarcoidosis and extensive lung fibrosis and/or hilar lymphadenopathy complaining of worsening dyspnea despite an increase of immunosuppressive therapy. However, vascular stenosis can be difficult to differentiate from chronic thromboembolic disease (4, 5, 10), and underscores the value of a multidisciplinary team as evaluation with a V/Q scan and HC may be needed to confirm the diagnosis. Furthermore, the significance of an observed vascular stenosis must be correlated with the location of V/Q mismatches and severity of symptoms measured by PFTs and 6-minute walk test. Ultimately, a HC will determine whether a PA or PV stenosis is hemodynamically significant and amenable for intervention. Steroids and immunosuppressants, should be maximally titrated before any percutaneous intervention since symptoms and stenosis can improve from the decrease in size of hilar lymphadenopathy and granulomas (2) (as seen in patient #5). Ultimately, the decision to intervene must be based on a comprehensive team evaluation (10) and discussion with the patient regarding the potential risk and benefits of these procedures.

In a prior case series of patients that underwent percutaneous treatment to relieve external vessel compression secondary to fibrosing mediastinitis (without sarcoidosis), vascular stenting or angioplasty successfully relieved symptoms in eleven of thirteen patients with only one complication (cardiac tamponade) and with most patients requiring re-intervention at 6–12 months (9) (similarly to patient #3). In our literature review, we also found two case reports with conflicting results regarding the clinical benefit of percutaneous pulmonary vascular intervention in patients with sarcoidosis related vascular stenosis (7, 10), and one case series by Liu et al. of patients with sarcoidosis and pulmonary hypertension, in whom 8 (11.1%) of 72 patients underwent pulmonary artery balloon angioplasty with or without stenting for the treatment of PA stenosis (11). All this 8 patients had improvement of PA pressures and 6-minute walk distance at 3 months, and one patient developed an acute thrombotic complication during intervention (11). In our case series, we found similar results to those described by Liu and colleagues but also show that in this cases concomitant PV stenosis can be present, that PA and PV stenting can provide clinical relief beyond 3 months, and that those patients with stenosis of small pulmonary vessels not amenable to intervention (i.e. patient #4) are better treated with optimal medical therapy. Restenosis can be a problem that prevents clinical improvement. In one of our cases (patient #3), restenosis was successfully addressed with using drug-coated balloons.
Though patients with sarcoidosis might have a two fold increase of pulmonary embolism than the rest of the population (13), evidence from case reports suggests that the majority of these thrombotic events are seen in patients with concomitant pro-thrombotic conditions (e.g. antiphospholipid syndrome) (14, 15). Thus, patients with underlying thromboembolic disease pose an additional challenge to intervention, particularly stent thrombosis, and should be treated with caution (patient #2). Interestingly, both of our patients with thrombotic events (patient 2 and 4) had a negative pro-thrombotic work up, which included screening for systemic lupus erythematosus, antiphospholipid antibodies and factor V Leiden deficiency. This finding could imply that those patients with sarcoidosis related pulmonary vascular stenosis might be at increased risk of regional vascular thrombosis and that anticoagulation (temporary or lifelong) might be needed in some patients in whom an intervention is performed. In our series, patient that did not have indication for anticoagulation were placed on dual antiplatelet therapy (aspirin and clopidogrel) for at least 6 months.

The rarity of external vascular compressions in sarcoidosis (less than 1% of sarcoidosis patients seen at our institution) makes the study of this treatment in a large clinical trial unlikely. The creation of a multi-center registry of patients with sarcoidosis and concomitant vascular compression should be considered to further investigate the role of intervention.

Conclusions

Pulmonary vascular compression is a rare, but under recognized and potentially treatable cause of symptom progression in patients with advanced sarcoidosis. A comprehensive multi-modality evaluation by a multidisciplinary team is critical to determine best treatment strategy. Pulmonary vascular stenting may provide symptomatic relief in properly selected patients.

Disclosures:

Vasilis Babaliaros, MD is a consultant or has research for Edwards Lifesciences, Medtronic, St. Jude Medical, Boston Scientific, Abbott Medical, and DirectFlow Medical. The other authors have nothing to disclose.

References