Anastomotic Pulmonary Hypertension After Lung Transplantation for Primary Pulmonary Hypertension*

Discussion

In this report, we describe a case of recurrence of pulmonary hypertension in a patient who underwent lung transplantation for PPH. The cause, however, was pulmonary artery stenosis due to an anastomotic stricture, rather than a recurrence of PPH, and the condition was successfully corrected surgically.

While a number of other diseases of unknown etiology have recurred after lung transplantation, including sarcoidosis, lymphangiolymphoid hypertrophy, and giant cell arteritis, the recurrence of PPH has not been reported to...
date. Although the pathogenesis of PPH is not completely understood, a genetic basis for this disease has been suggested, in part based on the familial association in approximately 10% of patients and the localization of the responsible gene to chromosome 2 in familial cases. As would be expected in genetic diseases, a recurrence after transplantation would be unlikely unless other factors that can serve as inducers of the disease also play a role.

Vascular complications, including pulmonary artery and vein anastomotic strictures and thromboses, are uncommon following lung transplantation, and although they may be correctable by surgical or radiologic intervention, they are associated with a high morbidity and mortality. Patients present with dyspnea, persistent pulmonary hypertension, hypoxia, ventilator dependence, pleural effusion, or edema. Diagnostic modalities used to define the vascular complications following lung transplants include transthoracic or transesophageal echocardiography, nuclear scanning, and pulmonary angiography. In many instances when lung transplantation is performed on patients with pulmonary hypertension, there is a large size discrepancy between the native and allograft pulmonary arteries. The donor pulmonary artery is anastomosed to the side of the native pulmonary artery, and the distal end is oversewn. Constructing the anastomosis to the upper lobe takeoff may have contributed to the anastomotic stricture in this case. Previous reports of vascular stenoses after lung transplant have been described for the early postoperative period up to 2.3 years after lung transplantation; our patient presented late, with symptoms 6 years following single lung transplant.

In summary, we observed a patient with pulmonary hypertension 6 years after lung transplantation for PPH, which was the result of an anastomotic narrowing of the pulmonary artery rather than recurrence of PPH. This vascular complication of lung transplantation should be considered in the differential diagnosis when patients experience exertional dyspnea after lung transplantation.

Table 1—Right Heart Catheterization

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<tbody>
<tr>
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<td>10</td>
<td>16</td>
<td>8</td>
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<tr>
<td>Systolic</td>
<td>82</td>
<td>101</td>
<td>93</td>
<td>46</td>
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<tr>
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<td>37</td>
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<td>25</td>
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<tr>
<td>Mean</td>
<td>52</td>
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<td>47</td>
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<td>35</td>
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<tr>
<td>PCWP, mm Hg</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>†</td>
<td>10</td>
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<tr>
<td>CO, L/min</td>
<td>3.45</td>
<td>3.6</td>
<td>5.1</td>
<td>4.1</td>
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<tr>
<td>PVR, units</td>
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<td>7.6</td>
<td>†</td>
<td>1.3</td>
</tr>
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</table>

*CVP = central venous pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; PVR = pulmonary vascular resistance; PA = pulmonary artery; PGI₂ = prostaglandin I₂; S/P = status post.
†PCWP not measured perioperatively to minimize immediate complications from anastomosis.
‡Unavailable.

FIGURE 1. Single frame from a pulmonary angiogram shows marked narrowing of the distal right main pulmonary artery (arrow) at the anastomotic site. Only the cephalic part of the vessel is patent.

FIGURE 2. Axial gradient-echo MRI confirms the web-like stenosis in the distal right main pulmonary artery (arrow). A = aorta; S = superior vena cava.
The suggestion of pulmonary hypertension on echocardiography should prompt further evaluation, including meticulous hemodynamic measurements.

References

Development of Nonspecific Interstitial Pneumonitis Associated With Long-term Treatment of Primary Pulmonary Hypertension With Prostacyclin*

Steven Kesten, MD, FCCP; John Dainauskas, MD; Vallerie McLaughlin, MD; and Stuart Rich, MD, FCCP

A young woman with primary pulmonary hypertension presented with interstitial lung disease approximately 5 years after successful treatment with IV prostacyclin. The pathology was consistent with nonspecific interstitial pneumonitis and was unresponsive to steroids and immunosuppressive medications.

We speculate that further cases of this syndrome may be reported as more patients are living beyond 5 years with prostacyclin.

(CHEST 1999; 116:566–569)

Key words: interstitial lung disease; primary pulmonary hypertension; prostacyclin

Abbreviations: ANA = antinuclear antibody; DLco = diffusing capacity of the lung for carbon monoxide; PPH = primary pulmonary hypertension; TLC = total lung capacity

Primary pulmonary hypertension (PPH) is diagnosed predominantly from the absence of secondary causes. Until recently, the treatment for PPH was unsatisfactory and could only assist a minority of afflicted individuals.1,3 The advent of continuous IV prostacyclin is without doubt the most important medical intervention that has been developed for PPH. Significant improvements in survival have been reported.4,5 However, the long-term experience is limited, and it is unknown if any long-term adverse effects of prostacyclin will develop. In addition, it is unknown as to what effect prostacyclin will have on PPH many years after the initiation of therapy. We wish to report a case of a woman with PPH surviving beyond 5 years with IV prostacyclin who developed interstitial lung disease.

Case Report

We evaluated a 20-year-old woman who developed gradually progressive dyspnea on exertion at 13 years of age. At age 15, she was hospitalized and PPH was diagnosed. Her evaluation included the following: chest radiograph (no lung parenchymal abnormalities); transesophageal echocardiography (no intracardiac shunts); ventilation-perfusion scan (mottled perfusion defects and no segmental abnormalities); pulmonary angiography (no evidence of thromboembolic disease); and a right heart catheterization (pulmonary artery pressures, 70/50 mm Hg; pulmonary vascular resistance, 7.9 U). An antinuclear antibody (ANA) was not performed. She was initially treated with a calcium antagonist and had a modest improvement. After approximately 6 months, she was prescribed IV prostacyclin and she responded objectively and subjectively. For the subsequent 5 years, her course was fairly unremarkable, except for five central venous catheter infections.

In 1996, at the age of 20, the patient noted a lack of energy and an increase in dyspnea on exertion. Her dyspnea progressed to the point where she could only walk the equivalent of one city block. She awoke from sleep one morning with dyspnea and anterior pleuritic chest pain. The dyspnea persisted at rest and was most marked when she was in a supine position. She noted a progressive diffuse edema and a dry cough. She denied experiencing hemoptysis, presyncope, syncope, wheezing, fever, chills, and diaphoresis. She also noted a sensation of her heart racing, along with palpitations. The dyspnea and chest discomfort persisted for 3 days and nights. The administration of inhaled albuterol had no effect, and oral furosemide therapy resulted in modest symptomatic improvement. The chest discomfort, however, was markedly diminished in frequency and severity. There were no joint symptoms. Investigations were negative for infection, pulmonary emboli, and pneumothorax. Medications at the time included digoxin, warfarin, furosemide, prostacyclin, amiodpine, and enalapril. The prostacyclin dosage was 102 ng/kg/min. Aside from PPH, her past health was unremarkable.

On examination, the patient was comfortable and in no acute
distress, with a pulse of 72 beats/min and regular. BP of 96/72 mm Hg right sitting; and 12 respirations/min. Aside from facial acne, there were no skin abnormalities. The head and neck examination was unremarkable. There was no cyanosis or clubbing. Chest expansion and breath sounds were normal. There were no crinkles or wheezes. The catheter site was clean. Jugular venous pressure was not elevated. S1 was normal, S2 was increased, and there was no S3 or S4. There were no murmurs. There was trace peripheral edema. The abdomen was soft and without tenderness. There was no organomegaly, and bowel sounds were normal. The findings of the musculoskeletal examination were unremarkable.

Pulmonary function studies (expressed as percent predicted) showed the following: FVC, 62%; FEV1, 59%; total lung capacity (TLC), 81%; residual volume, 138%; diffusing capacity of the lung for carbon monoxide (DLCO), 28% (similar to her DLCO in 1992). Lung volumes were mildly decreased as compared to lung volumes in 1992. A chest radiograph revealed a mild reticular nodular pattern. A ventilation-perfusion scan was essentially normal. A CT scan of the thorax revealed diffuse acinar nodules with no evidence of interstitial fibrosis (Fig 1). In addition, mediastinal adenopathy was present. The largest area within the subcarinal region was 3 cm in diameter. A repeat right heart catheterization showed no significant changes as compared to her previous evaluation (Table 1). Urinalysis, BUN, and serum creatinine results were normal. Other results included the following: ANA, positive with a titer of 1:1,280 (speckled pattern); double-stranded DNA, negative; perinuclear-antineutrophil cytoplasmic antibodies, borderline positive (1:20); proteinase-3 antibody, negative; myeloperoxidase antibody, 8 U/mL; antineutrophil cytoplasmic antibodies, borderline positive (1:20); double-stranded DNA, negative; perinuclear-antineutrophil cytoplasmic antibodies, borderline positive (1:20); proteinase-3 antibody, negative; myeloperoxidase antibody, 8 U/mL; normal is < 7 U/mL); HIV, negative; C3, C4, and CH50 antibodies, normal; cryoglobulins, not detected; ribonucleoproteins, Sjögrens syndrome A, Sjögrens syndrome B, scleroderma and smooth muscle antibody, all negative; and anti-glomerular basement membrane, negative.

An open-lung biopsy was performed (Fig 2, 3). Pulmonary vascular lesions were characterized by mild medial hypertrophy of the muscular pulmonary arteries with focal eccentric intimal fibrosis. The arterioles were muscularized and tended to show mild to moderate medial hypertrophy with focal intimal fibrosis. There was no concentric laminar intimal fibrosis, and there were no plexiform lesions. Pulmonary venules and small veins focally showed mild medial hypertrophy but no luminal obstruction by fibrosis or organized and recanalized thrombus. There were patchy areas of alveolar septal thickening, although the capillaries did not appear to be engorged. The interlobular septa showed mildly dilated lymphatics and mild to focally moderate edema and fibrosis. Special stains suggested that the lesions did not represent capillary hemangiomatosis. After review from several pathologists, the diagnosis was believed to be most in keeping with nonspecific interstitial pneumonia. The patient was prescribed prednisone, 60 mg qd po, tapered to 20 mg qd over approximately 6 months; no significant improvement was observed. Azathioprine, 100 mg po, was added, and prednisone was continued at 15 mg qd. Her symptoms have not worsened, and she continues to complain of dyspnea on mild exertion. The administration of antibiotics and the replacement of the central venous catheter have not led to any discernible clinical changes. She is presently awaiting a lung transplant.

**Discussion**

PPH can affect persons of all ages and both genders; however, it most commonly occurs in younger women.

### Table 1—Hemodynamic Measurements at Diagnosis (December 1992), Prior to Interstitial Disease (November 1996), and After the Development of Interstitial Disease (August 1997)

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<td>70/35</td>
<td>65/40</td>
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<td>PAPmean, mm Hg</td>
<td>40</td>
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<td>44</td>
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<tr>
<td>RAF, mm Hg</td>
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<td>1</td>
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<td>92</td>
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<tr>
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<td>72</td>
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<td>PVR, mm Hg</td>
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<td>68</td>
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<tr>
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<td>108</td>
<td>59</td>
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</tr>
<tr>
<td>TLC, % predicted</td>
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<td>81</td>
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<tr>
<td>DLCO, % predicted</td>
<td>36</td>
<td>28</td>
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*PAP = pulmonary artery pressure; PAPmean = mean pulmonary artery pressure; RAF = right atrial pressure; FCWP = pulmonary capillary wedge pressure; CO = cardiac output; SaO2 = arterial oxygen saturation; Pulmonary artery SO2, % = oxygen saturation in the pulmonary artery; PVR = pulmonary vascular resistance; PV = pulmonary vascular resistance after administration of adenosine.*

![Figure 1. CT scan of thorax (high resolution 1-mm section) illustrating diffuse reticulonodular interstitial changes.](image1.png)

![Figure 2. Open-lung biopsy specimen (original magnification × 100) revealing focal interstitial cellular infiltrates, thick-walled small arteries, and widened interlobular septum with dilated lymphatics.](image2.png)
Symptoms include progressive dyspnea on exertion. When PPH is severe, there is presyncope, syncope, and chest discomfort. Until recently, the prognosis has been extremely poor, with >50% of patients dying within 5 years of PPH diagnosis.\textsuperscript{3,6,7} Initial therapeutic trials with vasodilators led to limited success, although a subset of patients with acute responses to medication interventions appear to have sustained responses to high-dose calcium antagonists.\textsuperscript{1,2} In addition, patients treated with anticoagulants live longer than patients who do not receive anticoagulants.\textsuperscript{3} Nevertheless, the prognosis has remained dismal for many patients with PPH.

Prostacyclin is a vasodilator that appears to have other properties that would be useful in treating PPH. Unfortunately, at the present time, prostacyclin must be administered as a continuous IV infusion. Recent trials indicate that prostacyclin is associated with sustained clinical improvements and prolongation of life.\textsuperscript{4,5,8} Known complications include flushing, diarrhea, jaw discomfort, and catheter infections. Patients typically require a gradual increase in regimen over time. Experience with prostacyclin now extends >5 years.

Our patient appeared to have a characteristic case of PPH. Her initial clinical course and response to medication appeared to be quite typical. She has had a reasonable response to medication, and she has survived with PPH for 7 years. Her duration of continuous infusion of prostacyclin is one of the longest reported in the literature. The development of interstitial lung disease approximately 6 years after the development of PPH has not previously been reported. There are several possible explanations for the findings in this case. Firstly, the patient could have the new onset of a second disease. Pulmonary hemangiomatosis is highly unlikely. Although there has been a case report of interstitial pneumonitis and pulmonary veno-occlusive disease, the radiographic and pathologic features of our case are not consistent with pulmonary veno-occlusive disease.\textsuperscript{9} There are no case reports of interstitial lung disease associated with either furosemide, enalapril, or amlodipine; an adverse effect related to one of these medications is possible but unlikely. There are no identifiable organic or inorganic substances that are new to her environment that would suggest an inhalation-related lung disease. Secondly, the original diagnosis of PPH might be incorrect. Collagen vascular diseases such as systemic lupus erythematosus and scleroderma can lead to pulmonary vascular and interstitial disease. She has no other clinical manifestations of either disease, and aside from a positive finding on ANA testing, her other serology is negative. Thirdly, the interstitial pathology could represent an unreported adverse effect related to chronic prostacyclin use or to the combination of the catheter and prostacyclin. There are now >100 patients who have received prostacyclin for >3 years, and there are no reports to corroborate the last hypothesis; however, the underreporting of associated adverse conditions is common and cannot be ruled out. Finally, the interstitial disease may represent the natural history of PPH. It might be that this manifestation never had the opportunity to develop, given that death would normally occur within 5 years.

Other researchers have documented decreased lung volumes associated with PPH. Scharf and colleagues\textsuperscript{10} described a 24-year-old woman with progressive PPH and a significant restrictive ventilatory defect, decreased lung compliance at TLC, and increased elastic recoil pressures at decreased lung volumes. An autopsy revealed no evidence of interstitial lung disease. The authors\textsuperscript{10} hypothesized that interactions between the airspace compartment and the distended pulmonary vascular bed led to a restrictive ventilatory defect. In a report\textsuperscript{11} from 1983, five of eight patients with PPH were documented to have low lung volumes. There was no association with the severity of pulmonary hypertension. Chest radiographs revealed no evidence of interstitial lung disease; however, there was no mention of a pathologic evaluation of lung parenchyma. One might argue that such cases could represent the early appearance of interstitial lung disease. Our case differs from the aforementioned reports in that there was a change in the chest radiograph appearance from the time of PPH diagnosis, as well as histologic evidence of nonspecific interstitial pneumonitis.

Attempts at immune modulation with systemic steroids and azathioprine have not resulted in clinical or radiologic improvements, suggesting that the process is irreversible. The discontinuation of prostacyclin is not an option, as this would likely lead to an acute increase in pulmonary hypertension and right ventricular failure. Although the etiology of her underlying lung disease is not understood, the only therapeutic option available appears to be lung transplantation. As increasing long-term experience accumulates with PPH, it will be interesting to note whether further cases of interstitial disease with PPH are reported.

**References**

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**Figure 3.** Open-lung biopsy specimen (original magnification \( \times 400 \)) revealing the presence of muscularized arterioles, interstitial fibrosis/chronic pneumonitis with sparse mononuclear inflammatory cell infiltrate, minimal increase in reticulin and collagen fibers in alveolar septa, and no dilated or proliferating capillaries.

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Interferon-α Therapy Associated With the Development of Sarcoidosis*

Anthony Pietropaoli, MD; Joseph Modrak, MD; and Mark Utell, MD, FCCP

Interferons (IFNs) have been implicated in the pathogenesis of sarcoidosis. In particular, IFN-γ has been linked to pulmonary macrophage activation, a characteristic feature of sarcoidosis. IFN-α is now being administered therapeutically in a variety of conditions. To date, IFN-α has not been implicated in the pathogenesis of sarcoidosis. We report the case of a 50-year-old woman who developed sarcoidosis while being treated with IFN-α for chronic myelogenous leukemia. Her disease activity correlated with the dosage of IFN-α. We speculate that the immunomodulatory effects of IFN-α triggered clinical manifestations of sarcoidosis in this patient.

Key words: autoimmune disease; interferon-α; sarcoidosis

Sarcoidosis is a chronic granulomatous disease of unknown etiology. Proposed causes include infectious organisms, environmental agents, and autoantigens, but, to date, a specific etiologic agent has not been identified. Nevertheless, studies have suggested that specific inflammatory mediators, in particular interleukin-2 and interferon (IFN)-γ, are involved in its pathogenesis. While IFN-γ has been repeatedly cited in these reports, less is known about the potential role of IFN-α in the immunopathogenesis of sarcoidosis. We report the case of a 50-year-old woman who developed bilateral interstitial infiltrates and inflammatory skin lesions while receiving treatment with IFN-α for chronic myelogenous leukemia (CML). A skin biopsy revealed noncaseating granulomas consistent with sarcoidosis. Her pulmonary disease and skin lesions improved when the IFN-α was discontinued, recurred when this therapy was resumed, and again improved when the dosage was subsequently reduced. We suggest that the temporal relationship of the treatment with the disease activity implicates IFN-α in the development of this patient’s clinical syndrome of sarcoidosis.

CASE REPORT

In June 1995, CML was diagnosed in a 50-year-old woman after a neutrophilic leukocytosis was noted on a routine CBC; the WBC count was 24.9 × 10^3/L, with 68% neutrophils. A chest radiograph (CXR) at the time of diagnosis was normal. As treatment for her CML, the patient received subcutaneous interferon-α on an escalating dosage schedule, so that after 8 weeks she was receiving 8 million units per day. She received no other medications.

Initially she tolerated this therapy well, but after 4 months a myriad of symptoms developed including alopecia, headaches, sleep disturbance, abdominal cramping with occasional diarrhea, and atypical chest pain associated with occasional coughing productive of clear sputum. A physical examination of the chest was unremarkable. Her WBC count decreased to 4.0 × 10^3/L, and a repeat bone-marrow examination demonstrated the disappearance of the Philadelphia chromosome, indicating a complete remission. The patient’s therapy was continued.

After 7 months of treatment, the patient developed the insidious onset of dyspnea on exertion, which slowly progressed over the next 5 months. A repeat CXR revealed nodular and interstitial changes bilaterally (Fig 1). Concurrently, she noted the development of several painless purplish nodular skin lesions on her forehead, scalp, arms, and legs. Because of these findings, the medication was discontinued after 12 months. Her symptoms improved but did not resolve completely. A physical examination after the discontinuation of the medication was remarkable for scattered dry bibasilar inspiratory crackles on chest auscultation, several firm, nonglobulated skin nodules on the scalp, and several purplish skin nodules on the left arm. A high-resolution CT of the

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chest (Fig 2) confirmed fine nodules in both lungs and demonstrated multiple small mediastinal lymph nodes, the largest of which was a 2-cm subcarinal node. The results of pulmonary function testing were normal: FVC, 3.3 L (103% predicted); FEV₁, 2.92 L (116% predicted); FEV₁/FVC ratio, 85%; and diffusing capacity of the lung for carbon monoxide (DLCO), 18.64 mL/min/mm Hg (82% predicted). The patient did not desaturate with exercise. A purified protein derivative was nonreactive, and the results of histoplasma antibody testing were negative.

Because the skin lesions and pulmonary abnormalities were considered part of the same process, the patient underwent a biopsy of a skin lesion on her forehead, and tests of the specimen showed noncaseating granulomas, with negative results of acid-fast and fluorescence stains for mycobacteria and fungi, respectively. A diagnosis of sarcoidosis was made.

Six weeks after the IFN-α therapy was stopped, all the patient’s symptoms had resolved. Since she was then asymptomatic with a normal DLCO, IFN-α therapy was resumed based on the previously favorable response. However, after 5 weeks of therapy with a dosage of 8 million units per day of IFN-α, the DLCO dropped precipitously. Concomitantly, her dyspnea and cough returned. Approximately 2 weeks later, the dosage of IFN-α was decreased to 4 million units per day. Three months later, the DLCO had rebounded to 72% of the predicted level. The dose-response relationship between IFN-α and DLCO is shown in Figure 3. The improvement in DLCO coincided with the resolution of skin lesions, CXR abnormalities, and other symptoms. She remained asymptomatic 15 months later.

Discussion

This case suggests an association between therapy with IFN-α and sarcoidosis. The patient had pulmonary symptoms, CXR abnormalities, and reductions in DLCO that clearly coincided with IFN-α therapy and improved after the dosage was reduced. This dose-response effect is solid evidence favoring an association between these pulmonary abnormalities and IFN-α therapy. It is unclear whether the IFN-α actually precipitated sarcoidosis de novo or unmasked a previously subclinical case, although this patient had no clinical findings to suggest preexisting sarcoidosis. We based our diagnosis of sarcoidosis on the results of a biopsy of an inflammatory skin lesion that coincided with the development of the pulmonary abnormalities.
There has been one previously reported case suggesting a possible association between sarcoidosis and IFN therapy.4 A 57-year-old woman with renal cell carcinoma metastatic to mediastinal lymph nodes developed bilateral pulmonary infiltrates 8 months after beginning therapy with IFN-β and vinblastine. Transbronchial biopsies demonstrated noncaseating granulomas, and 67Ga scanning revealed new bilateral lung parenchymal uptake. The patient was asymptomatic, and the results of pulmonary function tests, including DLco, were normal. After chemotherapy was discontinued, the parenchymal CXR abnormalities partially resolved. We are also aware of one other case in which sarcoidosis developed in a patient receiving IFN-α, in this case for hepatitis C (S. Sigal, MD; personal communication; May 1995). However, in neither of these cases was a dose-response relationship established between the IFN treatment and disease activity.

IFNs have been increasingly employed in the therapy of various neoplasms (including CML, hairy cell leukemia, Kaposi’s sarcoma, renal cell carcinoma, and malignant melanoma5), viral infections (including hepatitis C and condylomata acuminata6), and multiple sclerosis. As the use of these molecules has increased, numerous adverse reactions have become apparent. The most common, including generalized malaise, fever, arthralgia, and headache, are relatively minor reversible reactions.5 Less commonly, various autoimmune processes have developed. Specifically, IFN-α has been associated with hypo- and hyperthyroidism, diabetes mellitus, idiopathic thrombocytopenic purpura, rheumatoid arthritis, a lupus-like syndrome, and nonspecific polyarthritis.7,8 In some of these cases, the patients appeared to have a subclinical disease that was triggered by the IFN, while in others the drug appeared to precipitate these illnesses de novo. These phenomena are not surprising given the diverse immunomodulatory effects of IFNs,7,6,10 which could upset the balance between self-tolerance and autoimmunity when exogenously administered.

Pulmonary toxicity from IFNs is rare, with clinical evidence of pneumonitis occurring in < 1% of patients.7 However, when patients treated with IFN-α for hepatitis C were examined with 67Ga-citrate scanning, there was a significant increase in radionuclide uptake in the lung after therapy, suggesting a subclinical inflammatory process in asymptomatic individuals.11

Sarcoidosis is a multisystem disease of unknown etiology. Infectious organisms (in particular, mycobacteria), environmental agents acting as haptens to induce an immunologic response, and autoantigens have all been implicated, yet a definition of the specific etiologic agent remains elusive.1 The possibility that there are several different etiologic agents further complicates this search. Pathologically, noncaseating granulomas are typically found, yet there is increasing evidence that the inflammatory process begins as a more diffuse inflammatory reaction. In the lung, alveolitis appears to be the initial pathophysiologic event,12 characterized by a predominance of lymphocyte subsets and macrophages.13 In addition, abnormal macrophage activation is a consistent feature in this disease. Much attention has been focused on the inflammatory mediators responsible for macrophage activation, and IFN-γ (also called “immune IFN”) appears to play a major role.3,7,10,14 IFN-γ is released from lung T-lymphocytes and alveolar macrophages when these cells are obtained from normal subjects and are exogenously stimulated.3,4 Robinson and colleagues have demonstrated that the same cells from patients with sarcoidosis release this cytokine spontaneously.3 These investigators also showed that quiescent macrophages from patients with inactive sarcoidosis are activated by exposure to IFN-γ. Together, these data suggest that dysregulated IFN-γ production plays a role in the enhanced pulmonary macrophage activity that is observed in sarcoidosis.

There is little published evidence implicating any of the other IFNs in the pathogenesis of sarcoidosis. IFN-γ is the only molecule in the class II IFN family; IFN-α and IFN-β are in the class I family. Compared with class I IFNs, the gene for IFN-γ is located on a different chromosome, it binds to a different receptor, its structure is different, and it is the only IFN considered capable of activating macrophages and inducing class II antigens.14 However, recent data suggest that the class I and II IFNs share signal transduction pathways.10 Moreover, there is evidence that exogenously administered IFN-α and IFN-β can activate macrophages in vitro.15 Therefore, the possibility exists that IFN-α could cause macrophage activation when given for therapeutic purposes. We suspect that such a mechanism (acting either in combination with an inherent predisposition or in isolation) was involved in the clinical development of sarcoidosis in the patient reported here.

Serum calcitriol and angiotensin-converting enzyme levels are considered laboratory markers of macrophage activation. Although not done in this case, these levels could be followed as a screening test for drug-induced macrophage activation in future patients receiving IFN-α.

In summary, this case report suggests an association between the use of IFN-α and the development of sarcoidosis. We hypothesize that the immunomodulatory effects of IFNs, in particular macrophage activation, may be implicated in this association.

ACKNOWLEDGMENT: The authors thank Sam Sigal, MD (St. Luke’s Roosevelt Hospital, New York, NY) for providing information about his patient.

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Disseminated Pseudallescheria boydii Infection in a Nonimmunocompromised Host*

Abid Khurshid, MD, FCCP, V. Theodore Barnett, MD, FCCP, Marin Sekosan, MD; Alan S. Ginzburg, MD, FCCP; and Ergun Önal, MD

We present a highly unusual case of pulmonary Pseudallescheria boydii infection in a nonimmunocompromised host with a cavitating mass lesion. The diagnosis was confirmed by open lung biopsy. The patient was treated at another institution with a course of amphotericin B, considered an ineffective therapy for this infection, and presented to us with direct extension and invasion of the left atrial appendage and the pulmonary artery, followed by massive pulmonary embolization and hematogenous dissemination to the liver, spleen, kidney, pancreas, and brain. (CHEST 1999; 116:572–574)

Key words: fungal hematogenous dissemination; fungal pulmonary embolism; nonimmunocompromised host; Pseudallescheria boydii

Pseudallescheria boydii, a common soil and water inhabitant, is the leading cause of Madura foot in the United States. It is also known under the names of Petriellidium boydii and Allescheria boydii, although the anamorph (asexual state) is Scedosporium apiospermum and/or Monosporium apiospermum. Disseminated and invasive infections with this organism are seen primarily in immunocompromised hosts and include pneumonitis, osteomyelitis, endophthalmitis, and prosthetic valve endocarditis. We present an unusual case of disseminated P. boydii infection in an immunocompetent patient with preexisting bullous lung disease who progressed to a widely metastatic disease.

CASE REPORT

A 61-year-old woman presented to the hospital with a 4-week history of weight loss, night sweats, cough, fever, and hemoptysis. She had a history of 50 pack-years of cigarette smoking and severe bullous emphysema, affecting the upper lung lobes most severely. There was no history of chronic steroid administration, and the last use of systemic steroids was 1 year prior to the current episode. The only other significant past medical history was the presence of systemic hypertension.

A chest radiograph revealed a left perihilar mass with central lucency suggesting cavitation. A CT scan confirmed the left hilar mass with encasement of the left pulmonary artery, mediastinal invasion, and mediastinal adenopathy (Fig 1). Initial investigations included bronchoscopy and fine-needle aspiration of the mass. Special stains for fungus and acid-fast bacilli were negative. Cultures for aerobic, anaerobic, mycobacterial, and nocardial organisms yielded no growth. Bronchial washings later grew P. boydii. The results of CBC, serum chemistries, and liver function tests were within normal limits. Serologic tests for HIV were negative. Assays for T-cell subsets and Ig analysis failed to reveal any abnormalities. Pulmonary function tests revealed a severe obstructive ventilatory defect with an FEV1 of 0.8 L (38% of predicted), an FVC of 1.64 L (53% of predicted), and a ratio of 0.50 (53% of predicted), and an FEV1/FVC ratio of 53%. A two-dimensional echocardiogram revealed a mild left ventricular diastolic dysfunction and mild pulmonary hypertension. Results of arterial blood gas analysis revealed a pH of 7.36, PaO2 of 46 mm Hg, and PaCO2 of 69 mm Hg while breathing room air.

The patient underwent a thoracoscopic lung biopsy that revealed a large abscess cavity in the left upper lobe of the lung with parenchymal scarring. Resection of the lesion was not attempted because of limited pulmonary reserve. Tissue examination revealed a locally invasive form of fungal disease. Cultures grew P. boydii. Treatment consisted of IV amphotericin B, cumulative dose of 1 g, with partial resolution of symptoms, and the patient was lost to follow-up.

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The patient presented to our institution several months after the initial episode with progressive symptoms of fever, chills, night sweats, weight loss, generalized weakness, and hemoptysis. Chest radiograph revealed bilateral interstitial and alveolar infiltrates and a large left perihilar mass with cavitation. Treatment with broad-spectrum IV antibiotics and amphotericin B was started. On the second day of admission, the patient developed generalized seizures and a right hemiparesis. A CT scan of the head failed to reveal any focal lesions. An echocardiogram revealed a large multilobulated mass attached to the left atrial appendage and a mass in the left main pulmonary artery. The patient developed progressive hypotension and hypoxemic respiratory failure. Mechanical ventilation was instituted. Her hypotension remained refractory to large doses of vasopressors, and she suffered a cardiac arrest.

Autopsy revealed a necrotic fungal mass in the left lung invading both lobes (Fig 2) and the left pulmonary artery, left atrium (Fig 3), and pulmonary veins. There was a massive fungal embolus in the lower division of the right pulmonary artery with a recent infarct. Extensive fungal abscesses were seen in the right and left ventricles, right lung, liver, spleen, kidney, and pancreas. Brain evaluation revealed multifocal subarachnoid hemorrhages and hemorrhages in cerebellar white matter, parietal cortex, and putamen nucleus. The terminal event was considered to be the massive pulmonary embolization along with disseminated fungal infection. The periodic acid-Schiff stain of the abscesses revealed numerous septate hyphae and terminal, elliptical conidia. Fungal growth was observed on Sabouraud’s dextrose agar. The morphology was consistent with *P. boydii* (Fig 4).

**Discussion**

*P. boydii* has been increasingly recognized as a pathogen in immunocompromised hosts. Disseminated disease and pulmonary, sinus, bone, CNS, and kidney infections have been described in hosts with a variety of underlying conditions, including hematologic malignancies, diabetes, immunosuppressive therapy, and organ transplant. Pulmonary disease is similar to aspergillosis and is acquired by inhalation. Fungus ball in preexisting cavities can be seen in otherwise normal hosts, but invasive disease is usually limited to immunosuppressed patients. Necrotizing pneumonia in a nonimmunocompromised host is a very rare occurrence. The immune status of the patient is thought to be a very important factor in the predisposition.
to infection with this organism. P. boydii infection, similar to Aspergillus fumigatus, usually occurs in the setting of neutropenia or abnormal phagocyte function, eg, due to chronic steroid therapy. Cell-mediated immunity probably does not play a major role in host resistance.

Treatment should include surgical intervention, when possible, in combination with medical therapy. P. boydii is often sensitive to imidazole derivatives, (eg, miconazole and ketoconazole) in addition to the triazoles (itraconazole and fluconazole). There is some evidence that the combination of amphotericin B and an azole in vitro may yield synergistic effects against the organism. The combination therapy may potentially reduce the emergence of resistance and decrease the incidence of drug toxicity by allowing reduced duration of therapy or medication dose. However, there is no direct clinical data showing this to be of therapeutic benefit.

Our patient is highly unusual in that there was no evidence of immunosuppression. She continued to worsen despite amphotericin B therapy because this agent is not effective in the treatment of this fungus. Another unusual feature of this case was the initiation of infection as a locally invasive form of disease, as evidenced by hemoptysis, and the later progression to disseminated disease, all in the absence of any apparent evidence of an immunosuppressed state. This occurred over a period of several months and is definitely more subacute than usually seen with P. boydii in immunosuppressed patients. Also exceptional was the formation of intracardiac and pulmonary arterial fungal masses and subsequent massive embolization to the systemic and pulmonary circulations. To our knowledge, there is no report in the literature of such widespread dissemination of P. boydii infection in a non-immunocompromised host, although reports of invasive pulmonary pseudallescheriasis and brain abscess following near drowning in immunocompetent hosts have been reported.

References


Myocardial Bridging as a Cause of Acute Transient Left Heart Dysfunction*

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The significance of myocardial bridging is still a matter of debate, and although several reports have underlined its pathologic potential, myocardial bridging is often considered to be a benign phenomenon. We present here the case of a 63-year-old woman with a history of acute left heart failure and ECG evidence of ischemia, and whose primary abnormality on extensive workup was myocardial bridging. This case further underlines that myocardial bridging can lead to significant cardiac events.

Key words: acute left heart dysfunction; debridging; ischemia; left ventricular hypertrophy; myocardial bridging

Abbreviations: LAD = left anterior descending coronary artery; LV = left ventricular; LVH = left ventricular hypertrophy; SPECT = single-photon emission CT

Myocardial bridging causing systolic compression of epicardial coronary arteries may be an incidental finding at coronary arteriography, and it is reported in 0.5

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to 33% of cases.\textsuperscript{1–4} In autopsy studies, however, either single or multiple myocardial bridges are more frequently reported (in up to 78% of cases).\textsuperscript{5,6} Bridging rarely causes myocardial ischemia, and this could explain such discrepancies. Even though myocardial bridging is often considered to be a simple variant of the normal anatomy of coronary arteries, some data have demonstrated its pathologic potential; and angina, myocardial infarction, atrioventricular block, or sudden death have been reported to be associated with myocardial bridges.\textsuperscript{7–13} Moreover, myocardial bridges have also been linked to myocardial stunning.\textsuperscript{14} However, to our knowledge, no previous study has mentioned a possible association between myocardial bridging and acute heart failure. This is a report of a case of acute ischemic heart failure related to myocardial bridging of the left anterior descending coronary artery (LAD), which was resolved by surgery.

**Case Report**

A 63-year-old woman was admitted to our Cardiology Department a few days after she received intensive care treatment for acute pulmonary edema, preceded by angina pectoris without myocardial infarction. Her medical history was limited to atrial fibrillation, known since 1991, that was treated with digoxin. In 1995, she began complaining of typical rest angina and showed no evidence of myocardial ischemia by dipyridamole single-photon emission CT (SPECT). On admission, the clinical examination showed only a slight apical mitral murmur. Her heart rate was 84 beats/min, and BP was 110/80 mm Hg. The ECG revealed a biventricular hypertrophy with nonspecific ST-segment changes in the anterior leads and atrial fibrillation (Fig 1). During her hospitalization, various episodes were recorded of angina associated with dyspnea; tachycardia, 130 ± 10 vs 84 ± 3 beats/min at baseline; and decreased BP, systolic BP of 110 ± 4 mm Hg at baseline and diastolic BP of 80 ± 3 mm Hg at baseline. During acute episodes, systolic BP was 80 ± 2 mm Hg and diastolic BP was 64 ± 3 mm Hg, and pulmonary rales, a pronounced mitral regurgitation murmur, and typical ischemic downward ST-segment displacement were recorded (Figs 2, 3).

Several echocardiographic examinations revealed a moderate enlargement of the left atrium; an apical form of left ventricular hypertrophy (LVH); a preserved left ventricular (LV) systolic function (LV ejection fraction, 54%); and moderate mitral valve regurgitation, with no abnormality of the mitral valve apparatus or of LV wall motion. A second dipyridamole SPECT demonstrated ischemia of the LV anterior wall and dipyridamole-induced severe angina, together with subacute pulmonary edema. Baseline right-sided catheterization showed neither pulmonary hypertension nor V wave. In contrast, during angina-induced clinical left heart failure, there was severe postcapillary pulmonary hypertension (pulmonary capillary wedge pressure, 40 mm Hg), and a large V wave (90 mm Hg). Coronary arteriography...
phy only showed myocardial bridging involving the second and third segment of the LAD, the distal part of a diagonal branch, and a left marginal artery (Fig 4). Contrast ventriculography confirmed the apical LVH and showed no wall motion abnormality.

The administration of metoprolol, 100 mg tid, and diltiazem, 60 mg tid, or bepridil, 100 mg tid, were ineffective. The patient’s general state deteriorated, and she suffered from daily episodes of subacute pulmonary edema. A limited non-Q-wave myocardial infarction was suggested by serial cardiac enzymes elevation. Consequently, she underwent debridging, which consisted of a complete dissection of the myocardium overlying the LAD. This procedure produced a dramatic improvement. At 13 months after the operation, she is still asymptomatic without mitral regurgitation murmur. The echocardiogram showed persistence of preserved LV ejection fraction, a moderately enlarged left atrium, and a nonsignificant mitral regurgitant jet; and the monitoring of pulmonary pressure no longer showed a V wave. Unfortunately, no postsurgical cardiac SPECT was available in this case.

**DISCUSSION**

Most reports on myocardial bridging have emphasized its good prognosis. Various arguments support this analysis. First, the high frequency of myocardial bridges in autopsy studies stands in contrast to the rarity of symptomatic cases. Second, symptoms usually start in patients > 30 years old. Nevertheless, this point of view has been challenged in several reports, and serious ischemic events have been linked with myocardial bridges. Induction of ischemia solely by a myocardial bridge has been demonstrated, and different underlying mechanisms such as thrombus formation, vasospasm, endothelial dysfunction, or impaired coronary flow reserve have been proposed to explain this. It has also been suggested that myocardial bridges are involved in the development of atherosclerosis. Moreover, the severity of symptoms induced by myocardial bridges has been related to the localization of the bridge, its length and depth, and the presence of LVH or an increased intraventricular pressure.

In spite of these data, we have so far found no report in the available literature on acute heart failure linked to myocardial bridges without myocardial infarction. The implication of the muscle bridge in our case is based on the following: the presence of myocardial ischemia determined by clinical, ECG, and scintigraphic data; the fact that the coronary artery angiogram showed myocardial bridging as the only abnormality; and the improvement after the debridging procedure. Moreover, this bridge was long and was associated with LVH, which has been reported by Chamber and coworkers to be more severe in such cases. LVH-induced ischemia is a well-known phenomenon related to various mechanisms, including reduced coronary flow reserve, microvascular abnormalities, and smooth muscle cell abnormalities. Nevertheless, in the present case, as demonstrated by the postsurgical improvement, myocardial bridging might be considered to be the main cause, if not the sole cause, of severe ischemia, with LVH acting as an aggravating factor. Chambers et al were able to demonstrate the presence of myocardial stunning. In their case, the patient showed evidence of acute anterior myocardial infarction together with severe LV wall motion abnormalities, and developed pulmonary edema. The diagnosis of myocardial stunning was supported by both the slight increase of serial cardiac enzymes and the complete resolution of wall motion.

**FIGURE 2.** ECG tracings during an acute episode of chest pain together with subacute pulmonary edema. Note the typical downward ST-segment displacement (arrows) related to myocardial ischemia.
abnormalities on subsequent echocardiography 47 days later. It could be argued that very transient episodes of myocardial stunning might have been present, which could explain the left heart dysfunction. However, such a hypothesis seems unlikely, since such a phenomenon could not be observed in our patient. The mechanism of left heart dysfunction reported here might be related to the interaction between myocardial bridging-induced ischemia and LVH. It is well established that LVH is associated with abnormal diastolic function, with slowed relaxation and decreased diastolic distensibility, and that the hypertrophied ventricle is more susceptible than the non-hypertrophied heart to develop a severe impairment of diastolic function in response to brief ischemia. Even though we have no evidence of diastolic dysfunction in this case, it is likely that such a pathophysiologic process could explain our case.

Moreover, the acute mitral regurgitation reported here, which could be aggravated by anterior papillary muscle dysfunction, could also be involved to some extent, although this has been questioned recently by Madu and D’Cruz. Any condition that causes a severe reduction in LV compliance, as is possible in hypertrophic cardiomyopathy-produced ischemia, could account for a significant increase of pulmonary wedge pressure and large V waves. Thus, it is not necessary to propose mitral regurgitation to explain the V wave that was recorded. However, some features favor the involvement of severe mitral regurgitation in our case. These include the abrupt loudness of the apical murmur during the acute episodes; the sudden appearance of the large V wave, suggestive of acute mitral regurgitation; a V wave peaking at more than twice the value of the mean capillary wedge pressure; and its disappearance after surgery. Furthermore, LV afterload was reduced during acute episodes and thus is unlikely to have produced such a V wave.

What could be the underlying process triggering ischemia in this case? The first dipyridamole SPECT, obtained 1 year before the patient’s admission to our institution, did not demonstrate any ischemia, although she had rest angina. No thrombus formation, associated atherosclerosis, or vasospasm was evident on the angiogram. Tachycardia alone cannot be suggested as the cause, because some episodes of tachycardia during hospitalization were associated with neither clinical nor ECG signs of ischemia. The BP drop consistently recorded during the various acute episodes of angina could explain the results of the

Figure 3. ECG tracings during tachycardia, without symptoms. No downward ST-segment displacement is noted, suggesting that ischemia has been recorded. Thus, ECG changes shown in Figure 2 cannot solely be rate-related.

Figure 4. Coronary artery angiogram showing evidence of myocardial bridges. Top, A: systolic compression of epicardial coronary arteries (LAD, diagonal and distal part of the first marginal branch; arrows). Bottom, B: normal aspect of the arteries during diastole (arrows).
second SPECT examination, during which the patient presented with angina, subacute pulmonary edema, and a BP drop. The first dipyridamole SPECT induced no symptoms. The trigger role of the BP drop that we suggest is involved in myocardial bridging-induced ischemia is in agreement with the data reported 15 years ago by Carvalho et al., who showed in a small series of six patients with myocardial bridges that sodium nitroprusside infusion induced an increased systolic coronary artery constriction at the site of the bridge, and that an inverse relationship existed between the degree of systolic coronary artery constriction and aortic pressure. These authors concluded that changes in systemic arterial pressure and coronary perfusion pressure might significantly affect the severity of myocardial bridges by influencing intraluminal coronary pressure. The case report from Bennett and Blomerus, which suggests that coronary vasodilators may induce perfusion defects in patients with myocardial bridging, further supports this view. It is also well known that the administration of nitroglycerin noticeably accentuates the systolic coronary artery narrowing phenomenon. Thus, the BP drop could have induced a clear-cut systolic lumen diameter reduction with a persisting diameter reduction during diastole. Moreover, the fast heart rate could have exacerbated the clinical expression of the bridge, as suggested by data from Schwarz et al. and Hill et al.

The treatment of myocardial bridging is restricted to symptomatic patients and is based primarily on a pharmacologic approach. β-Blockers are in general the first-line therapy. It is likely that β-blockers reduce the degree of systolic coronary artery narrowing and lengthen diastole via their inotropic and chronotropic negative properties, and they may increase coronary artery vascular tone. Moreover, short-term IV β-blocker therapy has been found not only to decrease the reduction in the diameter during both systole and diastole, but also to induce a return of average diastolic peak flow velocity within the bridge to baseline values and a discontinuation of ST-segment changes and symptoms. The other drug family employed consists of calcium channel blockers, the inotropic negative properties of which might explain the reduction of bridge-induced systolic coronary artery constriction. However, these drugs are mainly used in cases of coronary artery spasm associated with myocardial bridging, a feature that has been reported in various studies. In our case, neither of these drugs was effective. The failure of calcium channel blockers to relieve symptoms is possibly related to the absence of superimposed spasm. The reasons for the lack of efficacy of β-blockade to alleviate the bridging expression in this case are less clear. It could be argued that the dose of the drug was inadequate or that the particular β-blocker used, unlike nonspecific ones, had no effect on coronary vascular resistance, although available data suggest that there is little adrenergically mediated epicardial artery tone. These conclusions are difficult to draw at the present time, however, because well-designed studies are still needed to properly assess the efficacy of β-blocker therapy in patients with symptomatic myocardial bridging.

The other therapeutic approaches consist of transluminal coronary artery angioplasty with stent implantation and surgery. The percutaneous approach was initially applied with success by Laifer and Weiner, and a few years later by Stables et al. Klues et al. demonstrated that intracoronary stent implantation could abolish all of the hemodynamic abnormalities induced by the bridges and improve clinical symptoms in otherwise unsuccessfully treated patients. Surgery has been the most frequently used method in symptomatic myocardial bridging. Various techniques have been successfully employed, including coronary artery bypass surgery, either alone or combined with muscle resection, and supra-arterial muscle resection alone, as applied in our case. The operative risk is low and the functional results are excellent, as stated by Iversen et al. and as illustrated by our case. In the small study from these authors, postoperative scintigraphic and angiographic studies demonstrated the restoration of coronary flow and myocardial perfusion without residual myocardial bridges with β-stimulation. Surgical treatment is worth considering in symptomatic patients when an area of ischemia supplied by the affected vessel is detected and previous medical treatment has been ineffective. However, it is likely that in the near future the percutaneous approach will be considered more frequently in this situation, although the risks and advantages of this therapeutic option have not yet been critically evaluated.

CONCLUSION

Myocardial bridging-induced ischemia can be severe enough to generate clinical signs of acute left heart dysfunction, which is reversible after debridging in the absence of evolving myocardial infarction and/or myocardial stunning. Even in the presence of localized LVH, myocardial bridging-induced ischemia might favor further diastolic dysfunction, which can fully explain acute left heart dysfunction. This report, together with those previously published, suggests that myocardial bridging can no longer be considered simply a benign variation of coronary anatomy.

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