Endoscopic Ultrasound/Fine-Needle Aspiration Diagnosis of a Malignant Subcarinal Lymph Node in a Patient With Lung Cancer and a Negative Positron Emission Tomography Scan*

Jana M. Rosenberg, MD; Anthony Perricone, MD, FCCP; and Thomas J. Savides, MD

Transesophageal, endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) and positron emission tomography (PET) scanning are new modalities for staging non-small cell lung cancer (NSCLC), the roles of which are still being defined. A 78-year-old man with a right lower lobe (RLL) mass and mediastinal adenopathy seen on CT scan had a PET scan that revealed only a RLL hypermetabolic area. EUS/FNA cytology of a subcarinal lymph node (LN) revealed the presence of NSCLC. This is a case of a false-negative PET scan for nodal involvement in NSCLC that was diagnosed with EUS/FNA. Patients with NSCLC and suspicious lymphadenopathy may benefit from EUS/FNA of enlarged posterior mediastinal LNs, even with negative findings of PET scanning.

Key words: endosonography; fine-needle aspiration; mediastinal lymphadenopathy; non-small cell lung cancer; positron emission tomography

Abbreviations: EUS = endoscopic ultrasound; FNA = fine-needle aspiration; LN = lymph node; NSCLC = non-small cell lung cancer; PET = positron emission tomography; RLL = right lower lobe

Positron emission tomography (PET) scanning is being used increasingly in the preoperative staging of non-small cell lung cancer (NSCLC) because of a reported sensitivity and specificity of 95%.1–3 Transesophageal, endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) has also been found recently to be very accurate in the cytologic diagnosis as well as the staging of NSCLC.4,5 We present the case of a patient with NSCLC and nodal metastases, which had been diagnosed by EUS/FNA of an enlarged subcarinal lymph node (LN), who had a false-negative PET scan finding for nodal disease.

CASE REPORT

A 78-year-old man, who was a former cigarette smoker, presented to his primary care physician with worsening dyspnea on exertion. A chest CT scan revealed a 5-cm density with irregular margins involving the right lower lobe (RLL), a 1.5-cm right hilar LN, and two 1.0 to 1.5-cm subcarinal LNs (Fig 1). An 18F-fluorodeoxyglucose PET scan revealed a heterogeneously hypermetabolic area in the right lower lung field, which is consistent with the mass seen in the same area on CT scan (Fig 2). However, the PET scan did not show any focal hypermetabolic lesions in the mediastinum.

Because there was a high index of suspicion for malignant lymphadenopathy with the CT scan findings, the patient underwent a transesophageal EUS, which revealed a 19 mm × 7 mm subcarinal LN at 30 cm from the incisors (Fig 3). Transesophageal EUS/FNA using a 22-gauge needle was performed, with cytology revealing NSCLC. Based on these EUS/FNA cytology findings, nonsurgical management was implemented.

DISCUSSION

The false-negative rate for PET scans diagnosing malignant mediastinal LNs in patients with suspected or proven NSCLC and mediastinal lymphadenopathy has been reported to be 7 to 9%.1,2 False-negative findings have been thought to be due to a minimal foci of metastatic cells in the particular LN or an inability of the PET scan to distinguish between the centrally located, primary tumor and the adjacent mediastinal LNs.1–3

In contrast, the reported false-negative rate for EUS/FNA of posterior mediastinal adenopathy is < 5%.4,5 As expected, the false-negative rate with this technique tends to be higher with LNs < 10 mm in diameter, due to the smaller focus of malignant cells.5,6

This report demonstrates a case in which transesophageal EUS/FNA was able to diagnose malignant posterior mediastinal LNs that had not been detected by PET scan. For mediastinal adenopathy, EUS/FNA has an advantage over PET scanning in that actual tissue sampling is performed, thereby providing both radiologic and cytologic diagnoses in one safe and effective procedure. Prospective studies are needed to compare the accuracy of PET scans vs EUS/FNA for the diagnosis of malignant posterior mediastinal LNs in patients with suspected or proven NSCLC. Until such head-to-head studies are
Figure 1. CT scan revealing an enlarged 1.5-cm subcarinal LN. The RLL mass is not seen on this image.

Figure 2. PET scan revealing a hypermetabolic area in the RLL, which is consistent with the 5-cm mass seen on a CT scan. Of note, there are no focal hypermetabolic areas found in the mediastinum.
completed, cytologic confirmation is still indicated for those mediastinal LNs that appear suspicious on CT scans, even after a negative finding on a PET scan.

REFERENCES


Clinical Response of Rheumatoid Arthritis-Associated Pulmonary Fibrosis to Tumor Necrosis Factor-α Inhibition*

Robert Vassallo, MD; Eric Matteson, MD; and Charles F. Thomas, Jr, MD, FCCP

Treatment options for patients with pulmonary fibrosis associated with rheumatoid disease are limited. We report a case of a 71-year-old man with a 3-year history of seropositive rheumatoid arthritis (RA) referred to the pulmonary clinic because of progressive pulmonary symptoms associated with radiographic fibrosis that was progressive in spite of corticosteroid treatment. In an attempt to control his articular symptoms and alter the course of his pulmonary fibrosis, treatment with IV infusion of the tumor necrosis factor (TNF)-α inhibitor infliximab was initiated. Following 1 year of therapy with this agent, the patient reported sustained improvement in dyspnea, cough, and exercise tolerance, in addition to improvement in joint symptoms. Stabilization of pulmonary function was indicated by repeat pulmonary function test findings. This report suggests...
that inhibition of TNF-α may be of significant benefit to patients with fibrosing lung conditions in the setting of RA.  

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**Key words:** infliximab; pulmonary fibrosis; tumor necrosis factor-α

**Abbreviations:** RA = rheumatoid arthritis; TNF = tumor necrosis factor; UIP = usual interstitial pneumonia

Pulmonary fibrosis is a devastating lung disorder that is associated with significant morbidity and mortality. Lung fibrosis occurring in rheumatoid arthritis (RA) has very similar clinical, radiographic, and pathologic characteristics as the idiopathic variety of pulmonary fibrosis that is most commonly attributed to the lesion of usual interstitial pneumonia (UIP). Corticosteroids and other immunosuppressive medications are often advocated for therapy despite a lack of controlled clinical trials demonstrating objective improvement in lung function or mortality. Tumor necrosis factor (TNF)-α is a proinflammatory cytokine that has been implicated as a key mediator in the pathophysiology of lung fibrosis. On the basis of its reported efficacy in the management of RA as a disease-modifying agent, a trial of TNF-α blockade with infliximab was undertaken in a patient with seropositive RA and pulmonary fibrosis. We describe the case of an individual with RA-associated pulmonary fibrosis who responded to treatment with the TNF-α blocking agent infliximab.

**Case Report**

A 71-year-old, retired, male farmer received a diagnosis of seropositive RA after developing pain and swelling in hands and wrists 3 years prior to presentation at our clinic. Following a very brief trial of methotrexate, which was discontinued due to GI intolerance, his rheumatoid disease was managed with low-dose prednisone, hydroxychloroquine, and leflunomide. Approximately a year following the onset of joint symptoms, he noticed the onset of progressive dyspnea on exertion and dry cough that was unresponsive to continued treatment with prednisone. He had no history of pulmonary disease and had no other medical problems. There was no history of exposure to any known occupational irritant or birds. He was a former smoker having quit > 40 years prior to presentation, and denied a history of illicit drug use or alcohol abuse. The patient was receiving the following medications at presentation: prednisone, 5 mg bid; naproxen, 375 mg/d; hydroxychloroquine, 200 mg bid; leflunomide, 20 mg/d; and calcium supplementation.

Physical examination demonstrated mild synovitis in the hands and wrists and rheumatoid nodules over the olecranon bilaterally. Lung examination revealed decreased lung volumes and bilateral fine Velcro-type crepitations bilaterally at the bases.

Laboratory testing demonstrated a mild microcytic anemia, a sedimentation rate of 35/h, a rheumatoid factor of 245 (normal, 0 to 39), and a PO₂ at rest of 75 mm Hg, which declined to 51 mm Hg following mild exercise. Chest radiography showed reduced lung volumes and diffuse fibrosis with honeycombing. High-resolution CT scan of the chest (Fig 1) showed basilar fibrosis with honeycombing, compatible with UIP. Baseline pulmonary function studies demonstrated a restrictive process with reduced lung volumes and moderate reduction in diffusing capacity (Table 1).

Treatment with the TNF-α inhibitor infliximab was initiated in view of the persistent synovitis and the presence of progressive pulmonary symptoms consistent with the development of rheumatoid-associated pulmonary fibrosis in spite of continued use of prednisone for > 1 year. Infliximab was administered at a dose of 3 mg/kg at time 0, week 2, week 6, and every other 8 weeks thereafter. Following the initial two infusions of infliximab, marked improvement in joint pains and synovitis occurred. With continued treatment, a substantial improvement in dyspnea, exercise tolerance, and cough was reported. Following > 1 year of treatment with infliximab, the patient continues to report sustained improvement in exercise tolerance, and repeat pulmonary function test findings demonstrate stabilization of pulmonary function (Table 1). Additionally, although oximetric testing demonstrated substantial desaturation with minimal exercise at the time of presentation (decline of oxygen saturation to 84%) follow-up oximetry at 1 year demonstrates a normal saturation at

![Figure 1. High-resolution CT images of the chest showed fibrotic change with honeycombing in the mid-lung region (top) and the lung bases (bottom), compatible with the lesion of UIP.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21982/ on 04/08/2017)
rest and a saturation decline to only 90% following similar exertion. Although infliximab treatment was well tolerated, oral candidiasis developed, requiring a short course of fluconazole therapy.

**DISCUSSION**

This is the first report documenting subjective improvement in pulmonary symptoms and stabilization of pulmonary function using the TNF-α inhibitor infliximab in pulmonary fibrosis associated with RA. Our patient presented with progressive pulmonary symptoms in spite of long-term prednisone treatment. Although there was no definitive evidence of improvement in lung function following treatment with infliximab, the marked subjective improvement in dyspnea and cough together with stabilization in pulmonary function over a period of 1 year suggests that inhibition of TNF-α may be an effective therapeutic option for the management of lung fibrosis in the setting of RA.

TNF-α is a key cytokine in the early immune response of a variety of inflammatory disorders, and is a critical mediator in the pathogenesis of lung fibrosis.5,7,9 TNF-α can directly promote the secretion of matrix proteins, increases fibroblast proliferation, and promote induction of matrix-degrading gelatinases that can enhance basement membrane disruption and facilitate fibroblast migration to the site of injury.8 Up-regulation of TNF-α gene expression is observed in fibrotic human lungs as well as animal models of lung fibrosis, and inhibition of TNF-α expression using neutralizing antibodies or soluble TNF-α receptors markedly attenuates silica or bleomycin lung toxicity and inhibits fibrogenesis in animal models of lung fibrosis.4,5,7,9 Taken together, this evidence suggests that inhibition of TNF-α may be an important therapeutic strategy in the management of lung fibrosis.

Infliximab is a chimeric (part human and part murine) antibody generated against human TNF-α. Clinical trials in patients with refractory RA demonstrated a significant clinical response with marked improvement in systemic and joint symptoms with this agent.4,10 None of these trials, however, assessed patients with lung fibrosis and RA.

Although lung fibrosis in RA arthritis is usually caused by UIP, studies suggest that it may also result from the predominantly fibrotic lesion of nonspecific interstitial pneumonia (fibrotic nonspecific interstitial pneumonia), although the incidence of this histologic lesion in patients with rheumatoid lung disease is not known.11 Although we do not have biopsy proof of the histologic lesion causing lung fibrosis in our patient, the pattern of high-resolution CT appearance is highly consistent with a chronic fibrotic process. Regardless of the histologic lesion causing lung fibrosis, the treatment of pulmonary fibrosis is difficult and current treatment options are limited. Although there are no prospective studies on the natural course of pulmonary fibrosis associated with RA, the clinical course of patients with pulmonary fibrosis and RA is generally insidious and progressive with a poor prognosis and an estimated median survival of <4 years in one series.12 Although we did not observe objective improvement in lung function in our patient, this report suggests that inhibition of TNF-α may provide significant symptomatic benefit and prevent progression of pulmonary fibrosis in individuals with RA-associated lung fibrosis. Preliminary data from an ongoing open-label study suggests that etanercept may reduce loss of lung function in patients with UIP.13 Prospective clinical trials are required to test the utility of this therapy for patients with pulmonary fibrosis.

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Effects of Continuous IV Prostacyclin in a Patient With Pulmonary Veno-occlusive Disease*

Hiroguki Okumura, MD; Noritoshi Nagaya, MD; Shingo Kyotani, MD; Fumio Sakamaki, MD; Norifumi Nakanishi, MD; Shinya Fukuhara, MD; and Chikao Yutani, MD

Pulmonary veno-occlusive disease (PVOD) is a rare but life-threatening disease. Although prostacyclin (PGI2) attenuates pulmonary hypertension and improves the prognosis in patients with primary pulmonary hypertension, little information is available regarding the effect of PGI2 on patients with PVOD. This report describes a patient with severe PVOD who showed marked improvement in exercise capacity and pulmonary hemodynamics with continuous IV PGI2 treatment. Furthermore, he experienced no clinical events for 12 months and survived for 25 months after the initiation of PGI2 therapy. These results suggest that continuous IV PGI2 therapy may serve as a bridge to transplantation in some cases of PVOD. (CHEST 2002; 122:1096–1098)

Key words: prostacyclin; pulmonary veno-occlusive disease

Abbreviations: PGI2 = prostacyclin; PPH = primary pulmonary hypertension; PVOD = pulmonary veno-occlusive disease

*From the Departments of Internal Medicine (Drs. Okumura, Nagaya, Kyotani, Sakamaki, and Nakanishi) and Pathology (Drs. Fukuhara and Yutani), National Cardiovascular Center, Osaka, Japan.

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Correspondence to: Noritoshi Nagaya, MD, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan; e-mail: nagayann@hsu.nev.go.jp

Pulmonary veno-occlusive disease (PVOD) describes the disease in a subset of patients with pulmonary hypertension histologically characterized by fibrotic occlusion of the smaller pulmonary veins. PVOD is an uncommon form of unexplained pulmonary hypertension that is rarely diagnosed during life and is generally associated with a progressively deteriorating course. In most cases, PVOD is refractory to medical treatment and patients require transplantation, although occasional instances of favorable responses to some agents have been reported.1,2 Continuous IV administration of prostacyclin (PGI2) has been established as a treatment for primary pulmonary hypertension (PPH).3,4 However, the effect of PGI2 on PVOD remains unclear. We report on a patient with PVOD who showed marked improvement in exercise capacity, pulmonary hemodynamics, and probably prognosis after PGI2 therapy was initiated.

CASE REPORT

A 30-year-old man with New York Heart Association functional class IV was hospitalized with chief complaints of syncope and dyspnea, which had begun in November 1998. He had no medical or family history of note. He had smoked one pack of cigarettes per day for 10 years. He was noted to have jugular vein dilatation, a loud pulmonary component of S2, an S3 gallop, right ventricular lift, and hepatomegaly. Arterial blood gas analysis (room air) revealed a pH of 7.45, PPO2 of 66.0 mm Hg, and PCO2 of 26.7 mm Hg. The ECG showed right ventricular hypertrophy. The chest radiograph revealed prominent pulmonary arteries and interstitial shadows in the right lower lung field, indicating pulmonary congestion. The results of a workup for secondary
causes of pulmonary hypertension were normal. Pulmonary function tests showed reduced diffusing capacity of the lung for carbon monoxide (40.0% of predicted). Ventilation-perfusion images revealed normal ventilation and diffuse focal areas of hypoperfusion. Right heart catheterization revealed severe pulmonary arterial hypertension (mean pulmonary arterial pressure, 70 mm Hg; pulmonary vascular resistance, 15.1 Wood U; mean right atrial pressure, 17 mm Hg; pulmonary capillary wedge pressure, 10 mm Hg; cardiac output, 3.97 L/min). Ischemic heart disease, valvular disease, and cardiomyopathy were excluded by echocardiography and cardiac catheterization. Based on these findings and the presence of pulmonary congestion, PVOD, a subtype of PPH, was strongly suspected. Continuous IV PGI2 was immediately begun at 1 ng/kg/min and was progressively titrated by 10 ng/kg/min in a week, because the patient’s general condition deteriorated critically. Thereafter, the PGI2 dosage was gradually increased by 1 ng/kg/min per week. Two episodes of pulmonary edema occurred during follow-up. However, the patient’s symptoms and chest radiographic findings were significantly improved when the dose of PGI2 was titrated to 29 ng/kg/min. Furthermore, his 6-min walk distance increased from 90 to 450 m, and his mean pulmonary artery pressure decreased from 70 to 36 mm Hg. He was discharged from the hospital about 4 months after the start of PGI2 administration.

Although the patient returned to work and was employed in desk work, he was rehospitalized about 12 months after discharge. His general condition worsened despite intensive care. Finally, his respiratory state deteriorated, and marked interstitial shadows appeared in the chest radiograph and CT scan (Fig 1). We tried several agents, such as prednisolone, dobutamine, diuretics, and nitric oxide inhalation, but the patient died of respiratory failure about 2 years after the initiation of continuous IV PGI2.

At autopsy, gross examination of the lungs revealed severe pulmonary edema. Histologic sections from the lungs demonstrated the typical changes of PVOD. Diffuse stenosis of the pulmonary veins and venules by fibrous tissue, thickened media of the veins, and interstitial edema resulted in a thickening of the lobular septa, engorged and tortuous alveolar capillaries, and hemosiderosis in every section. Pulmonary arterioles exhibited severe medial hypertrophy, but plexiform lesions were absent (Fig 2). The final clinical diagnosis of PVOD was made from these autopsy findings.

**Discussion**

Although PGI2 therapy has been established as a treatment for PPH, the use of this treatment for PVOD, a subtype of PPH, is controversial. There are theoretical reasons about why PGI2 may not be efficacious in patients with PVOD and why it may, in fact, worsen the cardiopulmonary status. If the pulmonary arterioles dilate but the resistance of the pulmonary veins remains fixed, an increase in transcapillary hydrostatic pressure may ensue and produce florid pulmonary edema.5,6 Thus, lung transplantation is thought to be the only therapy that improves the prognosis in patients with PVOD.

In this case, however, we successfully administered continuous IV PGI2, and observed its long-term effect on patients with PVOD. Continuous IV PGI2 markedly improved the symptoms, exercise capacity, and hemodynamics in a patient with PVOD, resulting in relatively long-term survival. Holcomb et al7 showed that continuous IV PGI2 had beneficial effects in 3 of 11 patients with PVOD. These findings suggest that some patients with PVOD respond well to therapy with IV PGI2. An experimental study8 has demonstrated that PGI2 dilates not only pulmonary arteries but also pulmonary veins in the porcine model. Furthermore, short-term administration of PGI2 has been reported9 to reverse the increased vasoconstrictor tone in pulmonary venules in a patient with PVOD. Thus,

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21982/ on 04/08/2017)

*Figure 2.* Top left: section of lung shows occlusion of a small pulmonary vein. Alveolar walls are significantly thickened due to interstitial edema (Masson trichrome, original ×400). Top right: alveolar capillaries are so engorged and tortuous as to resemble pulmonary capillary hemangiomatosis. Hemosiderin-laden macrophages are present in the same section (hematoxylin-eosin, original ×200). Bottom left: Elastica van Gieson stain demonstrates arterialized pulmonary veins (original ×400). Bottom right: lobular septa are significantly thickened due to interstitial edema, and pleural lymphatics are dilated (hematoxylin-eosin, original ×100).
it is interesting to speculate that in this case, the administration of PGI2 played a role in the regulation of vascular tone in pulmonary venules rather than in pulmonary arteries. In addition, careful dose adjustments and maintenance of PGI2 may have contributed to the favorable clinical outcome in this patient.

In conclusion, PGI2 therapy may have beneficial effects in some patients with PVOD and thereby may serve as a bridge to transplantation.

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