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Clinical Case Report

# Procainamide-induced pulmonary fibrosis after orthotopic heart transplantation: a case report and literature review

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ABSTRACT

A 33-year-old African-American woman was bridged to heart transplantation with a left ventricular assist device. She had a 14-month history of heart failure secondary to viral cardiomyopathy. The patient's refractory ventricular tachycardia was treated with intravenous procainamide owing to the patient's history of amiodarone-induced thyroiditis. After orthotopic cardiac transplant, she experienced prolonged respiratory failure. Serial computed tomography evaluation of the lung revealed diffuse bilateral ground-glass opacities and septal thickening. Bronchoscopies with tissue biopsies were performed with no conclusive results. Specimen samples displayed septal fibrosis with loose fibromyxoid tissue and some hobnail nodularities with no indication of granulomas, neutrophilic infiltration, malignancy, or fungal, viral, or bacterial growth. Histopathological evaluation of the lung wedge biopsy supported a diagnosis of pulmonary fibrosis and noted interstitial fibrosis with areas of focal alveolar hemorrhage and increased macrophage infiltration. Antinuclear body was found to be negative. After in-depth evaluation of the patient's medication history, procainamide was identified as the cause of the toxicity. As procainamide-induced lung fibrosis is relatively uncommon, we present this case to highlight procainamide's potential harm and the need for careful monitoring in postsurgical patients.


## 1. Introduction

Since its approval by the Food and Drug Administration in 1950, procainamide has been frequently used to control atrial and ventricular arrhythmias [1,2]. Pulmonary accumulation of the drug was noted as early as 1951, and clinical associations with pulmonary toxicity were first described by Ladd in 1962 [2,3]. Procainamide-induced lung injury can take the form of a variety of complications involving any component of the lung and adjacent tissues. It is a dangerous toxicity that requires prompt identification and cessation of procainamide use to prevent morbidity and mortality. Among those affected, posttransplant patients are especially vulnerable to toxicities and may not be able to display early clinical symptoms because of their postsurgical state. Judicious procainamide use is critical in this population, and patients should be closely monitored for potential side effects. We present an interesting case of procainamide-associated pulmonary fibrosis that required prolonged intubation and hospitalization after a cardiac transplant.

## 2. Case report

A 33-year-old African-American woman presented to our clinic for a heart transplantation eligibility evaluation. Her past medical history included obesity, chronic anemia, pulmonary embolism necessitating long-term anticoagulation, and atrial fibrillation. Fourteen months earlier, she was diagnosed with sudden-onset heart failure during an evaluation for shortness of breath. At that time, a transthoracic echocardiogram revealed an ejection fraction of 16%. After extensive assessments to identify the etiology of her heart failure, she was determined to have viral cardiomyopathy secondary to environmental exposure as a child counselor. The patient underwent placement of an implantable cardioverter-defibrillator (ICD) for severe heart failure.

Three months after ICD placement, she suffered cardiac arrest with ventricular tachycardia. Her defibrillator discharged during the subsequent month, which prompted another hospitalization. At that time, she had refractory ventricular tachycardia. Her arrhythmia was not amenable to an increased amiodarone or radiofrequency ablation. Furthermore, her ICD was replaced with a biventricular defibrillator. Her worsening cardiac function necessitated the implantation of a left ventricular assist device (LVAD).

The patient arrived at our clinic 6 months after LVAD implantation to determine her candidacy for a heart transplant. Her heart failure status was New York Heart Association functional class II. She underwent a

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heart transplant eligibility assessment that included endocrine evaluation of thyroid dysfunction as she had experienced amiodarone-induced thyroiditis, electrophysiological evaluation, and right heart catheterizations revealing normal pressures. During her initial assessment (review of symptoms and physical exam) in our clinic, the patient was free of any known pulmonary abnormalities. While awaiting a donor heart, she was treated for refractory ventricular tachycardia with intravenous procainamide continuously for 64 days. She then underwent an uncomplicated orthotopic heart transplant. Posttransplant transesophageal and transthoracic echocardiograms revealed normal heart chamber sizes and function and an ejection fraction of 50–55%. Serial ventricular biopsies were negative for antibody- or cell-mediated organ rejection.

Unfortunately, the patient endured a prolonged and arduous recovery. First, she suffered acute right ventricular failure with renal failure necessitating temporary continuous renal replacement therapy, ultrafiltration, and later hemodialysis. Second, she suffered respiratory failure after a successful postoperative extubation and required reintubation. Initially suspected to be a result of volume overload, the patient's respiratory failure was first treated with careful diuresis until she was normovolemic without improvement. She was weaned off the ventilator after 7 days of intubation, but she required high-flow oxygen supplementation to maintain adequate blood saturation. Serial computed tomography (CT) evaluation of the chest revealed diffuse bilateral lung ground-glass opacities and septal thickening that worsened acutely over 9 days (Fig. 1A and B). Initially suspected to have an infection, she was treated with antibiotics with little improvement.

Several bronchoscopies with tissue biopsies were performed with no conclusive results. The transbronchial biopsy specimens displayed septal fibrosis and reactive epithelial changes with no indication of granulomas, neutrophilic infiltration, malignancy, or fungal, bacterial, or bacterial growth. An immunostain for cytomegalovirus was negative. With continued worsening of pulmonary function, the patient underwent an open lung wedge resection from the right lower lobe. Sections stained with hematoxylin and eosin and by the Movat method revealed an active pulmonary interstitial fibrosis with prominent proliferation of type II pneumocytes with areas of focal alveolar hemorrhage and collections of intraalveolar macrophages (Fig. 2A). A battery of immunohistochemical stains was performed using mouse monoclonal antibodies from Dako (CD68, SMA, and TTF-1) and Leica (CK pan) as the primary antibodies (Fig. 2B–E). The thickened alveolar septa contained foci of elongated smooth-muscle-like cells that stained positively for alpha smooth muscle actin. The proliferating type II pneumocytes stained positively for TTF-1 and pan CK [4]. The alveolar macrophages stained positively for CD68. The macrophages showed variable degrees of foamy cytoplasm. These macrophages stained only focally and weakly positive by Fontana-Masson silver stain in contrast to the inclusions in cases of amiodarone toxicity that stain strongly positive with Fontana-Masson silver stain [5,6] (Fig. 2F).

After careful examination of the patient's medication history, we identified the 64-day course of intravenous procainamide as the most likely culprit for pulmonary toxicity. Antinuclear antibodies were found to be negative, and antihistone antibodies were not evaluated. She gradually improved with methylprednisolone therapy and was successfully extubated. Follow-up CT evaluation of lungs 6 months later showed a significant decrease in the size of ground-glass opacities confined to focal regions (Fig. 1C). She has been followed for 1 year in our clinic. The patient shows improvement in cardiac function as assessed by serial transthoracic echocardiograms with ejection fractions between 55% immediately posttransplant and 60% at 1 year postsurgery. She remains free of graft rejection and able to complete activities of daily living.

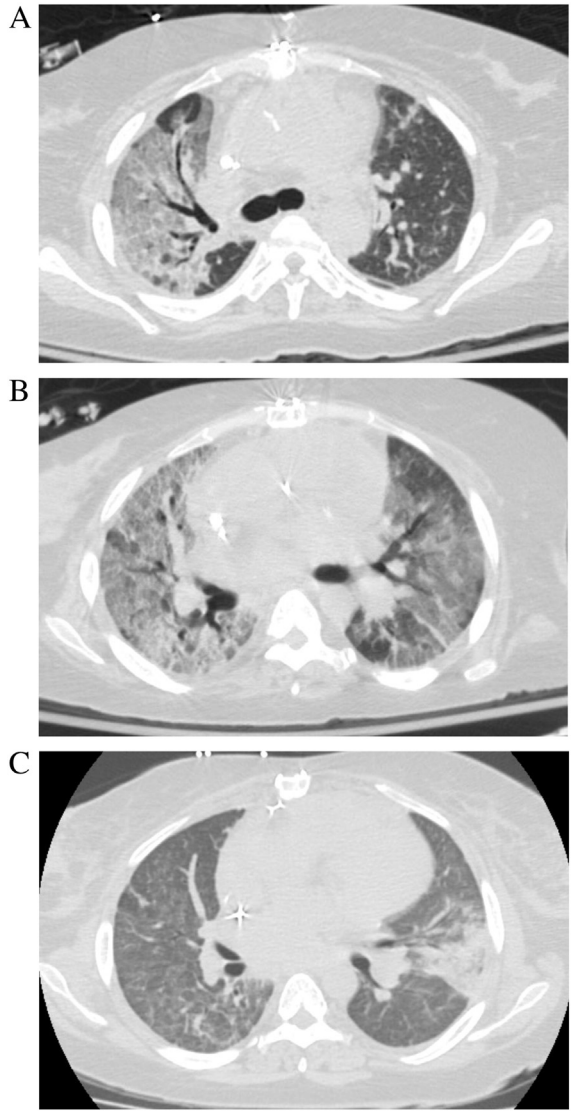


**Fig. 1.** CT scans. Widespread ground-glass opacities with septal thickening, more predominant on the right lung (A). Worsening of diffuse ground-glass opacities and septal thickening with increasing involvement of the left lung (B). Significant improvement in lung parenchyma and septum with noted airspace opacification in the lower lobe of left lung (C).

## 3. Discussion

The transbronchial and wedge resection biopsies confirmed that the patient had developed pulmonary interstitial fibrosis in relationship to chronic procainamide therapy. The interstitial fibrosis was in an active early stage with prominent proliferative smooth muscle and epithelial changes as well as accumulation of alveolar macrophages [4]. The alveolar macrophages showed variable degrees of foamy cytoplasm. These macrophages stained only focally and weakly positive by Fontana-Masson silver stain in contrast to the inclusions in cases of amiodarone toxicity that stain strongly positive with Fontana-Masson silver stain. The patient had not received amiodarone for the last 6 months while she was receiving procainamide [5,6].

Procainamide-induced lung injury has a plethora of presentations ranging from cough and fatigue to hypoxia and respiratory failure [7,8]. Pleural involvement is commonly observed in these injuries and was originally described by Ladd as bilateral pleural effusions presenting with inspiratory chest pain [3]. Other manifestations include pulmonary infiltrates, pleural fibrosis, pleuritis, pulmonary fibrosis, respiratory muscle fatigue, and pulmonary thromboembolism [9–13]. Procainamide-associated lung injury has also been described independently and as part of a group of symptoms classified as drug-induced lupus (DIL) [3,10]. DIL differs significantly from systemic lupus erythematosus (SLE) and occurs in 20–30% of patients on long-term procainamide therapy [14,15]. Traditional cutaneous manifestations of lupus, such as malar