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Case Report

Rapidly Progressive Systemic Sclerosis–associated Interstitial Lung Disease After Intravesical Bacillus Calmette-Guérin Therapy for Early-stage Bladder Cancer

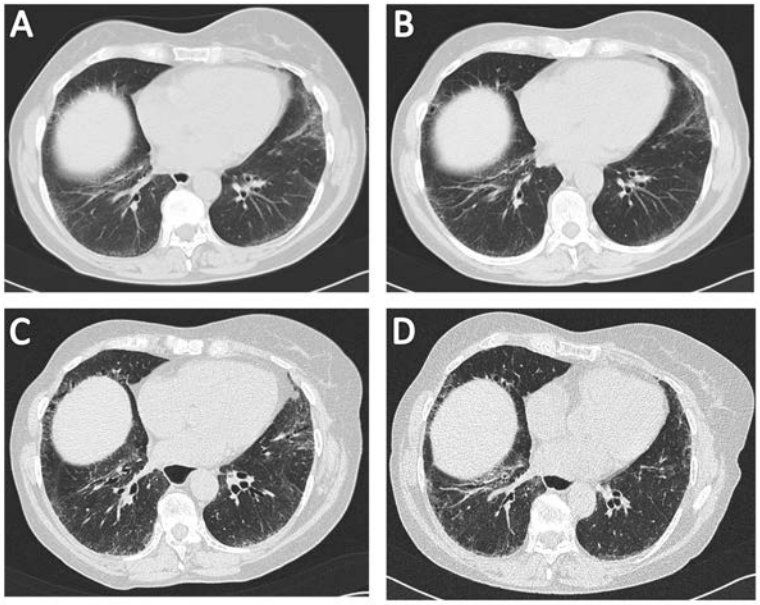
To the Editor:

Despite recent advances in the management of systemic sclerosis–associated interstitial lung disease (SSc-ILD), it remains the most common cause of death and a significant contributor to morbidity.[1,2] SSc-ILD is characterized by a wide spectrum of disease courses, with some patients having limited nonprogressive fibrosis, whereas others develop rapid and extensive fibrosis leading to respiratory failure.[3] Although the pathogenesis of SSc is still poorly understood, extensive fibrosis can result from an inappropriate chronic inflammatory response to a specific trigger. Toxic air pollutants or infections can shape the immune system toward an immunostimulatory status. Here we report the case of a patient with diffuse cutaneous SSc (dcSSc) who developed rapidly extensive ILD after bacillus Calmette-Guérin (BCG) therapy given for noninvasive bladder cancer.

Written informed consent was obtained from the patient and ethics board approval was received (Comité de Protection des Personnes CPP Ile de France III, no. 2008-A00624-51).

A 61-year-old woman with dcSSc with speckled antinuclear antibodies and no antigen-specific antibodies presented with aggravating dyspnea. dcSSc had been diagnosed in 2003 with severe skin disease (peak modified Rodnan skin score [mRSS] at 40/51) and was complicated by ILD with basal ground glass appearance (5–10% of extent) in high-resolution computed tomography (HRCT). In late 2005 she complained of dyspnea on exertion (New York Heart Association [NYHA] class II) and pulmonary function tests (PFTs) showed a forced vital capacity (FVC) of 79%, a forced expiratory volume in 1s (FEV1) to FVC ratio of 84%, and a diffusing lung capacity for carbon monoxide (DLCO) of 75% predicted. Echocardiographic evaluation of the heart and lung vessel pressures was unremarkable. She had been treated with oral cyclophosphamide (CYC) 50 mg daily from October 2005 to July 2008 for both skin disease and ILD. During this period her respiratory symptoms and skin fibrosis improved greatly (mRSS 12/51). HRCT showed stable findings and her FVC improved to reach 99% (Figure 1). Oral CYC was discontinued because of localized noninvasive bladder cancer related to CYC use. She had been treated with intravesical BCG therapy in late 2008. Thereafter, respiratory symptoms, HRCT, and PFTs remained stable without immunosuppressive agents. In late 2011 she received a second course of intravesical BCG to treat a recurrence of noninvasive bladder cancer. In May 2012 she developed progressively aggravating NYHA class III dyspnea and intermittent cough. PFTs showed a marked deterioration of FVC (77% predicted) and DLCO (36% predicted), and thoracic CT angiography revealed an increase in ground glass lesions and no evidence of pulmonary embolism or infection. Echocardiography showed normal systolic pulmonary pressure of 30 mmHg and normal left ventricular ejection fraction. The mRSS was 5/51. She started azathioprine 150 mg daily, which was stopped 4 months later because of liver cytolysis and poor tolerance. Because of her rapidly progressive disease, in October 2012 she was treated with rituximab (RTX) 500 mg 2 weeks apart with 100 mg of methylprednisolone premedication prior to the infusions. Mycophenolate mofetil (MMF) 1 g twice daily was added as a co-therapy. Her respiratory symptoms improved gradually within 6 months. In October 2013 she had class II NYHA dyspnea and PFTs improved dramatically, with FVC 89% and DLCO 84% predicted. Her pulmonary status remained stable thereafter and the patient was eventually lost to follow-up.

To our knowledge, this is the first reported case of SSc-ILD progression after treatment by intravesical BCG. According to a recent study, over 27% of patients with SSc-ILD experienced significant ILD progression at any time



	September 2004	January 2008	May 2012	June 2015
Dyspnoea (NYHA class)	II	II	III	II
FVC %	79	99	77	81
DLCO %	75	75	36	73

Oral CYC
Second course of intravesical BCG
RTX and MMF

Figure 1. HRCT shows a ground glass appearance and basal honeycombing during the course of disease. The table shows the evolution of dyspnea and pulmonary function tests during follow-up period. (A) June 2005. (B) January 2008 (during treatment with oral CYC). (C) May 2012 (after the second course of intravesical BCG). (D) June 2015 (during treatment with RTX and MMF). BCG: bacillus Calmette-Guérin; CYC: cyclophosphamide; DLCO: diffusing lung capacity for carbon monoxide; FVC: forced vital capacity; HRCT: high-resolution computed tomography; MMF: mycophenolate mofetil; NYHA: New York Heart Association; RTX: rituximab.

over a 5-year period. However, only a minority showed a pattern of continuously declining FVC and/or increasing extent of fibrosis with no periods of stability/improvement.[4] In our patient with longstanding stable disease, the development of rapidly progressive disease after a second course of intravesical BCG is unlikely to be coincidental. It is remarkable that despite a severe baseline skin disease, the flare following BCG therapy induced ILD progression without recurrent skin disease. The striking improvement observed after RTX and MMF treatment is unusual in SSc-ILD and possibly related to an altered immune response after BCG therapy. Concerns for pulmonary BCGitis could be raised. However, the clinical presentation, the lack of specific abnormalities on CT scan (i.e., reticulonodular infiltrates) as well as the favorable response to immunosuppressants were very unlikely to be explained by this known side effect of BCG therapy.[5]

Experimental observations showed that after a first challenge with BCG, macrophages exhibit increased inflammatory responses when exposed to a second stimulation.[6,7] Chronic granulomatosis and new-onset autoimmune conditions after intravesical BCG have been previously reported in the literature.[8,9] However, in the setting of fibrosing diseases, the relationship between inappropriate chronic inflammatory responses and progressive fibrosis secondary to an antigenic challenge with microorganisms' components is still debated. Recently, in a mouse model of SSc, Jeljeli, *et al*[10] showed that BCG training exacerbated disease with macrophages, showing a potent capacity to release proinflammatory cytokines (interleukin [IL]-6, tumor necrosis factor, and IL-1β), supporting the concept of "trained immunity" in SSc. This observation highlights the importance of being vigilant with patients with SSc after BCG therapy, particularly in those with more severe disease.

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The authors declare no conflicts of interest.

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