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Case report

Improvement of constrictive bronchiolitis (bronchiolitis obliterans) after rituximab therapy in 2 patients with primary sjögren syndrome

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ABSTRACT

Constrictive bronchiolitis is one of the manifestations of small-airway involvement in primary Sjögren syndrome (SS) and is associated with fixed airflow obstruction despite treatment with bronchodilators, macrolides, corticosteroids, and corticosteroid-sparing agents. Reports have shown a beneficial effect of rituximab on interstitial lung disease associated with SS, but the effect of rituximab on constrictive bronchiolitis is unknown. Herein, we present 2 cases of patients with constrictive bronchiolitis associated with SS who experienced symptomatic improvement and stabilization of pulmonary function testing (PFT) after rituximab therapy. Lung function declined in one of the patients when B cells reconstituted, with improved PFT results on re-administration of rituximab. Our case reports suggest that B cells may be involved in the pathogenesis of SS-associated constrictive bronchiolitis. Therapy targeting B cells may therefore be helpful in treating this debilitating and refractory condition. Further research is warranted.

1. Introduction

Sjögren syndrome (SS) is an autoimmune inflammatory disease characterized by lymphocytic infiltration of exocrine glands, which results in gland dysfunction [1,2]. Lymphocytic infiltration of other organs and immune-complex deposition can result in systemic extraglandular manifestations, which affect over one-third of patients with SS [2,3]. SS can occur as a primary disease (primary SS) or in association with other autoimmune diseases (secondary SS) [4]. Pulmonary involvement occurs in over half of patients who may or may not have associated symptoms [5,6]. Findings in secondary SS are often confounded by the pulmonary disease from the underlying connective tissue process [7].

The most common pulmonary manifestations of SS include interstitial lung disease, small-airway disease, and upper/large airway involvement [8]. The small-airway involvement has primarily been characterized histologically by 2 types of bronchiolitis: follicular and constrictive [9,10]. The latter is associated with worsening airflow obstruction despite treatment with bronchodilators, macrolides, inhaled and systemic glucocorticoids, and other glucocorticoid-sparing agents [5,7]. Several reports indicated improvement in symptoms, radiographic findings, and pulmonary function when rituximab was used for patients with SS-related interstitial lung disease [11–13]. Whether rituximab can be beneficial in SS-related constrictive bronchiolitis is unknown. We describe the cases of 2 patients with SS-associated constrictive bronchiolitis who had symptomatic, functional, and radiographic improvement with rituximab therapy. The relative stabilization of these patients' pulmonary function further supports the potential benefit of this treatment strategy.

2. Case descriptions

2.1. Case 1

A 51-year-old woman, a nonsmoker, came for evaluation of recurrent pneumonias occurring during the preceding 2 years. Associated symptoms included cough, sharp pleuritic chest discomfort, and fever. She had a prior diagnosis of asthma, but her symptoms were not responsive to inhaled bronchodilators, namely budesonide and formoterol. She was also using fluticasone nasal spray and taking montelukast tablets and multivitamin, omega-3, and turmeric capsules. She said she did not drink alcohol or take any other type of drug. She said that she had dry eyes and mouth, oral ulcers, Raynaud phenomenon, unexplained rashes on her face and trunk, and occasional wheezing. On examination, she had normal vital signs, bilateral proximal upper-extremity muscle weakness, and inspiratory squeaks without crackles on auscultation.

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Abbreviations

CT	computed tomography
DLCO	diffusing capacity of the lungs for carbon monoxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
PFT	pulmonary function testing
RV	residual volume
SS	Sjögren syndrome
TLC	total lung capacity

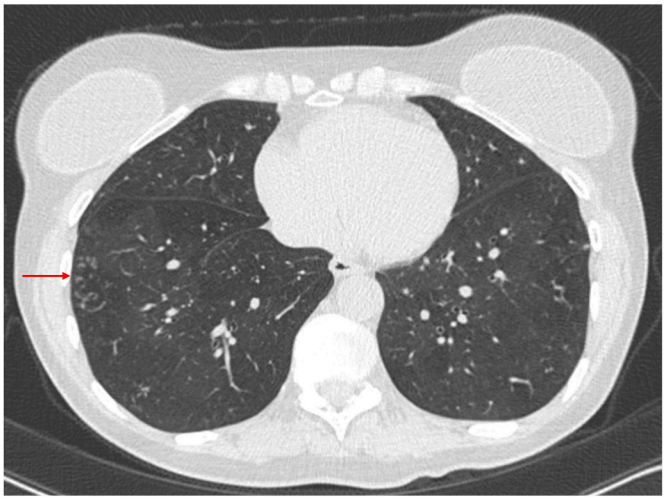

Fig. 1. Computed Tomography Scan of the Chest (Patient 1). The scan shows mosaic attenuation and peripheral tree-in-bud opacities (arrow) in the right-lower lobe.

Diagnostic testing showed the following results. A computed tomography (CT) scan of the chest revealed peripheral tree-in-bud opacities in bilateral upper- and right-middle lobes, which were associated with air trapping on expiratory imaging (Fig. 1). Pulmonary function testing (PFT) identified a mild obstructive ventilatory defect: a forced expiratory volume in 1 second (FEV_1) of 1.92 L (60% of the predicted value) without bronchodilator response; air trapping with residual volume (RV) of 3.68 L (185% of predicted value); hyperinflation with total lung capacity (TLC) of 6.98 L (121% of predicted value); and normal diffusing capacity of the lungs for carbon monoxide (DLCO). A review of outside PFT data showed that FEV_1 had declined steadily over several years before she came to our clinic: 78% of predicted 4 years before, 73% of predicted 3 years before, 66% of predicted 1 year before, and 64% of predicted 6 months before. Exhaled nitric oxide was 28.5 ppb (normal value, <39 ppb). Flexible bronchoscopy, swallowing evaluation, and an esophagram procedure revealed no abnormalities. Autoimmune serologic studies had negative results for SS-A/SS-B, Scl 70, Jo 1, rheumatoid factor, and MPO- and PR3-ANCA. Echocardiography showed normal systolic and diastolic biventricular function and no valvular abnormalities. A lip biopsy showed lymphocytic sialadenitis. Electromyography demonstrated mild proximal myopathy, and a muscle biopsy revealed findings of inflammatory myopathy and denervation atrophy. Serologic tests for myositis were positive for anti-SS-A-52 kD antibodies (114 units [normal <20 units]) and Ku antibodies. The patient also underwent nailfold video capillaroscopy, which showed multiple capillary ectasias, disorganized capillary architecture, and ramified capillaries. She was diagnosed with primary SS with associated constrictive bronchiolitis and inflammatory myositis. After consultation with rheumatology colleagues, she underwent 2 infusions of rituximab (1000 mg) 2 weeks apart.

On follow-up 4 months later, the patient reported having no adverse effects from rituximab therapy. Her dyspnea and cough had improved. Repeat PFT showed a mild obstructive defect without bronchodilator response and stable to slightly improved parameters overall (Fig. 2): forced vital capacity (FVC), 3.13–3.39 L (77%–84% of predicted value); FEV_1, 1.92–2.24 L (60%–70% of predicted value); DLCO, 23.5–25.2 $mL \cdot min^{-1}$ mm Hg^{-1} (96%–103% of predicted value); and TLC from 6.98 L (121% of predicted value) to 6.75 L (117% of predicted value). Hyperinflation remained relatively stable with the RV slightly decreased

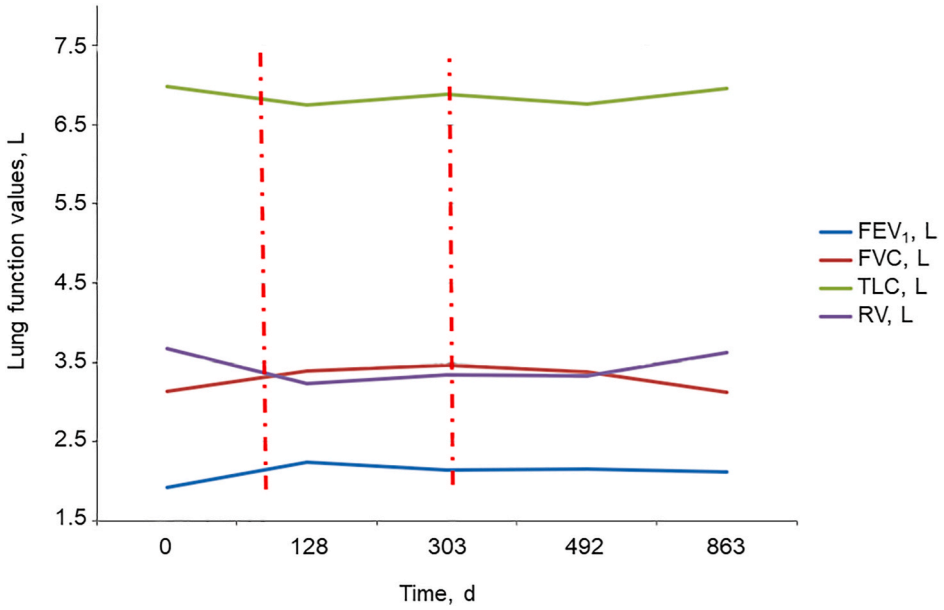

Fig. 2. Changes in Spirometry and Lung Volume (L) After Rituximab Infusion (Patient 1). The red dashed lines mark the times of the infusion. FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Changes in spirometry and lung volumes after rituximab infusion by day from evaluation (case 1)[a].

	Baseline	Rituximab infusions (4/5/2018, 4/19/2018)		Rituximab infusion (12/6/2018)	
Variable	Day 0 (2/7/2018)	Day 128 (6/13/2018)	Day 303 (12/6/2018)	Day 492 (6/13/2019)	Day 863 (6/18/2020)
FEV_1, L	1.92 (60)	2.24 (70)	2.14 (67)	2.16 (69)	2.12 (68)
FVC, L	3.13 (77)	3.39 (84)	3.47 (86)	3.38 (84)	3.12 (79)
TLC, L	6.98 (121)	6.75 (117)	6.88 (119)	6.76 (117)	6.96 (121)
RV, L	3.68 (185)	3.24 (162)	3.34 (166)	3.33 (165)	3.63 (179)
DLCO, $mL \cdot min^{-1}$ $mm\ Hg^{-1}$	23.5 (95.5)	25.1 (103)	23.8 (97)	24.4 (100)	24.8 (102)
CD20, absolute count	NA	NA	11	NA	0

Abbreviations: DLCO, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, not applicable; RV, residual volume; TLC, total lung capacity.
[a] Values provided as No. (% predicted), unless otherwise indicated.

from 3.68 L (185% of predicted value) to 3.24 L (162% of predicted value).

The patient continued regular follow-up with pulmonary medicine for the constrictive bronchiolitis and with rheumatology for the extrapulmonary manifestations of SS. Her respiratory symptoms remained stable for the next 8 months, but at that time she had an episode of pneumonia. Her absolute CD20 count was 11, and she underwent another 1000-mg rituximab infusion. Since then, she has received scheduled rituximab every 6 months and continued regular visits with her practitioners. Her respiratory symptoms, sicca symptoms, and myalgias have been controlled on this regimen for 2.5 years. After rituximab, her pneumonia episodes markedly improved. Her representative PFT continued to show a persistent but stable obstructive ventilatory defect (Table 1, Fig. 3).

2.2. Case 2

A 56-year-old woman, a nonsmoker, came for evaluation of severe dyspnea accompanied by wheezing, blandly productive cough, and chronic chest congestion. Twenty years before, she was diagnosed with mixed connective tissue disease on the basis of polyarticular inflammatory arthritis, sicca symptoms, elevated creatine kinase, and positive anti-RNP, SSA, and SSB antibodies. The diagnosis was revised to primary SS after a surgical lung biopsy showed chronic bronchiolitis consistent with lung involvement of primary SS. The patient's symptoms were progressive despite treatment with chronic oral glucocorticoids, hydroxychloroquine, and a trial of azathioprine.

Laboratory studies included persistently positive results for anti-RNP, SSA, and SSB antibodies and a Schirmer test suggestive of hypolacrimation. The PFT showed progressive, severe, irreversible airway obstruction with an FEV_1 of 0.88 L (33% of predicted value). Three years before this, her FEV_1 was 1.1 L. Chest CT showed mosaic attenuation bilaterally, ground-glass opacities, and scattered small, thin-walled cysts most consistent with lymphocytic interstitial pneumonia and constrictive bronchiolitis (Fig. 4A and B). A bronchoalveolar lavage from the right-middle lobe, which had both ground-glass and cystic abnormalities on the chest CT, showed macrophages predominantly; microbiologic studies had negative results, including polymerase chain reaction testing for *Pneumocystis jirovecii*.

Because of a somewhat refractory previous clinical course, bronchiolitis on lung biopsy, and suspicion of lymphoid interstitial pneumonia on chest CT, the patient began treatment with 2 doses of 1000-mg intravenous infusions of rituximab, with the doses separated by 2 weeks. On follow-up examination 4 months after rituximab therapy, there was substantial symptomatic improvement in wheezing, shortness of breath, and exertional tolerance. Her repeat CT chest scan showed improvement in ground-glass opacities with stable mosaicism, air trapping, and cystic change. On PFT, there was an obstructive defect with stable FEV_1, slightly increased FVC from 1.71 to 1.96 L (51%–58% of predicted value), and improved DLCO (10.5–14.5 $mL \cdot min^{-1}$ $mm\ Hg^{-1}$ or 47%–65% of predicted value) (Figs. 5 and 6). Her chronic symptoms, PFT, and chest imaging remained stable for approximately 2 years after rituximab therapy.

Two years later, the patient developed worsening respiratory symptoms and PFT impairment reminiscent of her condition at the previous evaluation. The chest CT showed worsening patchy centrilobular nodularity, tree-in-bud opacities, nodular consolidation, and bronchial wall thickening consistent with infectious/inflammatory airway disease. The additional findings of mosaic attenuation,

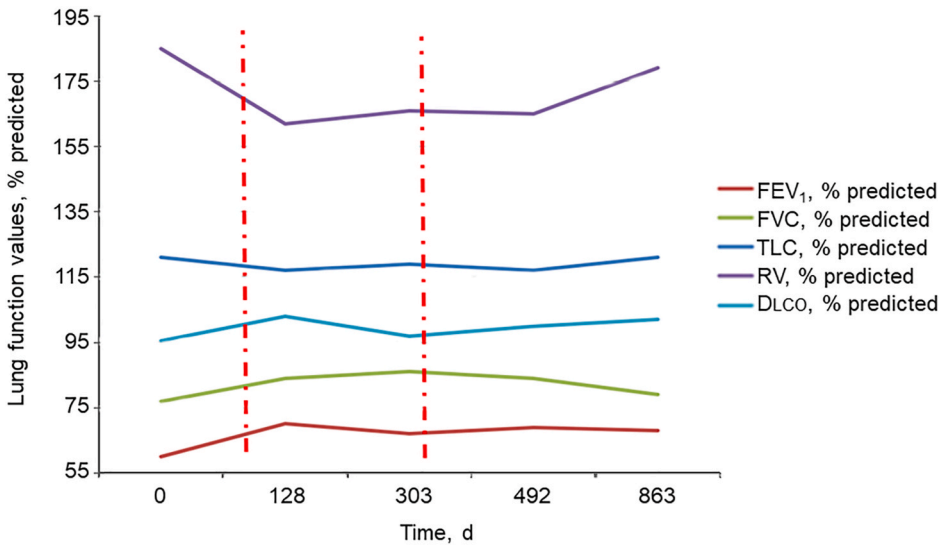

Fig. 3. Changes in Spirometry Values and Lung Volume Measurements (% Predicted) After Rituximab Infusion (Patient 1). The red dashed lines mark the times of the infusion. DLCO indicates diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

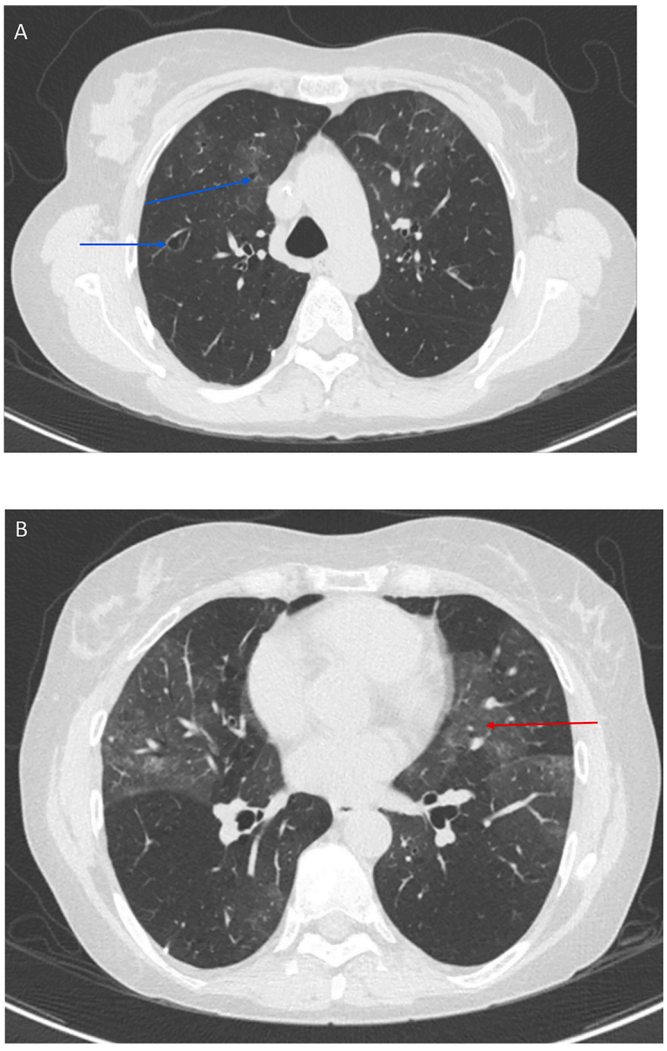

Fig. 4. Computed Tomography Scans of the Chest (Patient 2). The scans show mosaic attenuation with air trapping, scattered cystic air spaces (A, blue arrows), and ground-glass opacities (B, red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

cylindrical and cystic peripheral bronchiectasis, and cystic disease appeared similar. Of her laboratory results, her CD20 absolute count was 123 cells/mcL (normal, 74–441 cells/mcL), which had increased from 33 the year before. Flexible bronchoscopy was performed because of concerns about infection, which revealed copious secretions. Bronchial washing samples were sent for cultures. *Haemophilus influenzae* and *Pseudomonas aeruginosa* were subsequently isolated and treated. During infectious disease follow-up, no further signs of infection were noted, and it was safe to proceed with rituximab retreatment.

Rituximab was given again on the same dosage schedule (2 doses of 1000 mg, 2 weeks apart) approximately 2 years after the first infusion. At 6- and 9-month follow-up assessments, the patient's DLCO value had improved and spirometry results were stable. These changes are summarized in Table 2 and Fig. 6. In exertional capacity, she improved from being able to walk just 50 feet and using up to 2 L/min of supplemental oxygen for dyspnea at rest to walking more than a block and negotiating a flight of stairs with supplemental oxygen needed only at the peak of exertion.

3. Discussion

Constrictive bronchiolitis, a subtype of obstructive small-airway disease, affects a minority of patients with primary SS [5] and is characterized by progressive airflow limitation. No effective treatment is currently available. Rituximab has been used successfully to treat extraglandular primary SS and has shown promise for patients with pulmonary manifestations [12–14]. Herein, we described the cases of 2 patients with constrictive bronchiolitis attributable to primary SS whose symptoms and radiographic findings improved as pulmonary function measurements stabilized after rituximab infusions.

Pulmonary involvement in primary SS can have various presentations. For our patients, cough was 1 of the main presenting symptoms and was accompanied by wheezing, which caused both patients to be mistakenly diagnosed with asthma. Prior studies have also described dyspnea with cough and bronchial responsiveness to be predominant subjective features of patients with primary SS and pulmonary involvement [5,7].

Airway involvement was further confirmed by repeated radiographic evidence of cylindrical bronchiectasis, bronchiolar wall thickening, and mosaicism. Prior studies similarly identified mosaic attenuation, air trapping, and bronchiectasis as the most common presenting radiographic features of primary SS. Additionally, ground-glass and cystic lesions have been infrequently described [5,11,12]. These characteristics were present in our second patient, likely representing manifestations of nonspecific interstitial pneumonia and/or lymphocytic interstitial pneumonitis. In case 2, we performed bronchoalveolar lavage to exclude opportunistic infection but elected not to perform a lung biopsy to sample a cystic area of lung injury for the following reasons: 1) she had a prior surgical lung biopsy that showed a pattern of lung injury compatible with primary SS; 2) rituximab was being considered on the basis of her small-airway disease and extrathoracic disease, regardless of whether the cystic areas represented lymphocytic interstitial pneumonitis; 3) lung biopsy is associated with morbidity and mortality, particularly in patients with rheumatologic disease [15]; and 4) patient preference.

For both patients, PFT results reflected the small-airway disease along with predominantly obstructive ventilatory defects. DLCO was moderately decreased in both patients, likely reflecting some degree of parenchymal lung disease. While consistent with constrictive bronchiolitis, these characteristics are not frequently reported as pulmonary manifestations of SS. Most patients have preserved ventilatory function or a restrictive defect [7,11].

Lymphocytic infiltration appears to have a major role in the pathogenesis of primary SS. The infiltration and proliferation of B cells has been identified in glandular and systemic disease [16]. Persistent activation of B cells likely leads to ongoing autoantibody production, further contributing to disease [12]. Primary SS is commonly linked to the development of various types of hematologic cancer [17]. Several B-cell targeted therapies have shown potential for controlling SS [18]. Rituximab, an anti-CD20 monoclonal antibody, has been evaluated in prospective trials and observational studies and has shown effectiveness in controlling glandular disease and promise in managing systemic involvement [12,19].

Evidence of improved pulmonary manifestations after rituximab therapy has been limited to observational studies and case series [11–13,20,21]. No studies conclusively showed beneficial effects on primary SS-associated constrictive bronchiolitis. One series of 16 patients showed a predominantly restrictive pattern with reduced diffusing capacity and improvement in lung volumes after rituximab [11]. Another series described 2 patients with pleural and parenchymal involvement who had symptomatic and radiographic improvement after treatment with rituximab [12]. A study from the Autoimmune and Rituximab Registry [21] described 9 patients with pulmonary manifestations, 1 of whom had bronchial involvement and other features of interstitial lung disease. All but 1 patient (without airway disease) reportedly responded to the first rituximab infusion.

Consistent with other reports, symptoms improved and there was radiographic improvement for both of our patients after their initial

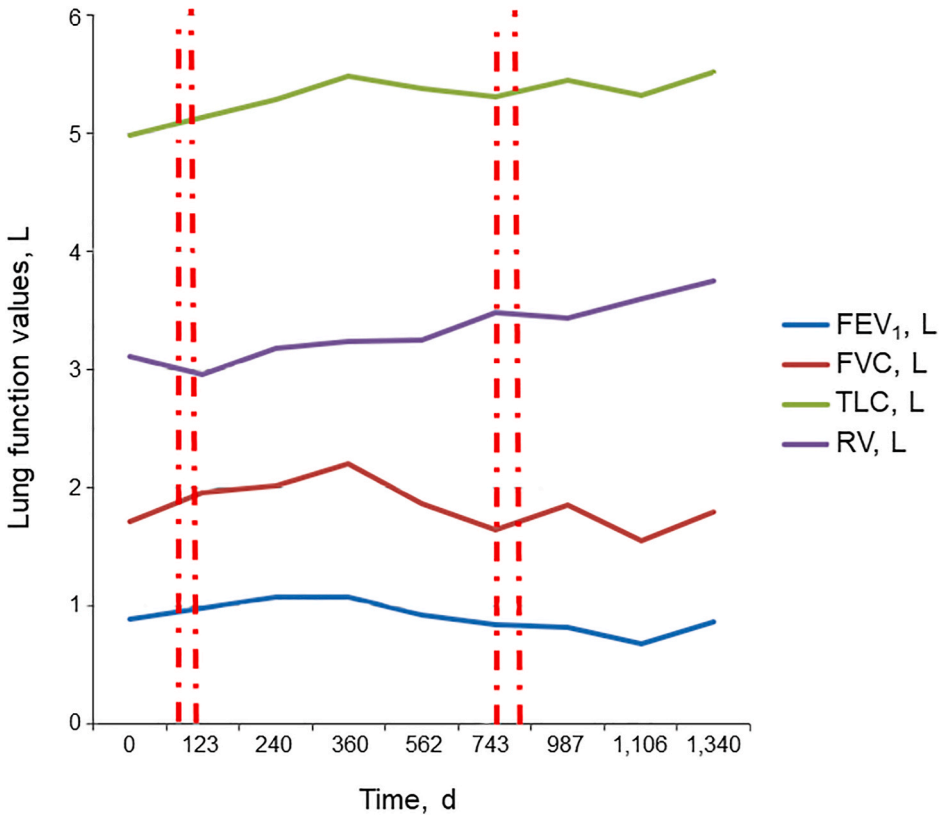

Fig. 5. Changes in Spirometry and Lung Volumes (L) After Rituximab Infusions (Patient 2). The red dashed lines mark the timing of the infusions. FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

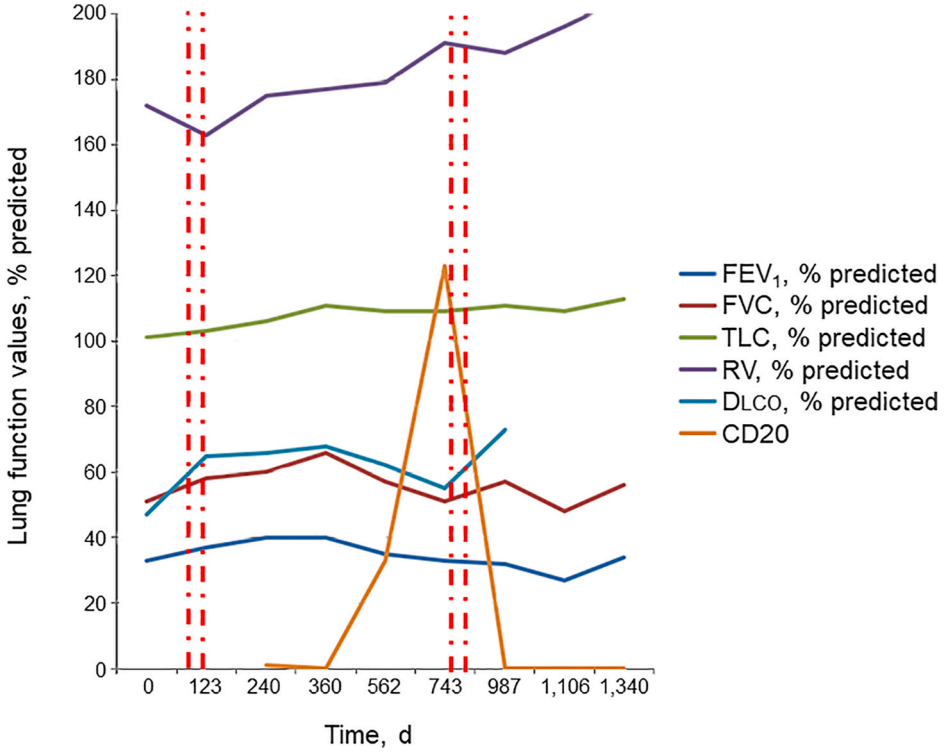

Fig. 6. Changes in Spirometry Values and Lung Volume Measurements (% Predicted) After Rituximab Infusions (Patient 2). The red dashed lines mark the timing of the infusions. D_{LCO} indicates diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Changes in spirometry and lung volumes after rituximab infusions by day from evaluation (case 2)[a].

	Baseline	Rituximab infusions (7/27/2017, 8/10/2017)					Rituximab infusions (7/15/2019, 7/29/2019)		
Variable	Day 0 (5/23/2017)	Day 123 (9/23/2017)	Day 240 (1/18/2018)	Day 360 (5/18/2018)	Day 562 (11/26/2018)	Day 743 (6/5/2019)	Day 987 (2/4/2020)	Day 1106 (6/2/2020)	Day 1340 (1/22/2021)
FEV_1, L	0.88 (33)	0.98 (37)	1.07 (40)	1.07 (40)	0.92 (35)	0.84 (33)	0.82 (32)	0.68 (27)	0.86 (34)
FVC, L	1.71 (51)	1.96 (58)	2.01 (60)	2.20 (66)	1.86 (57)	1.64 (51)	1.85 (57)	1.55 (48)	1.79 (56)
TLC, L	4.98 (101)	5.13 (103)	5.28 (106)	5.48 (111)	5.38 (109)	5.31 (109)	5.44 (111)	5.32 (109)	5.51 (113)
RV, L	3.11 (172)	2.96 (163)	3.18 (175)	3.24 (177)	3.25 (179)	3.48 (191)	3.43 (188)	3.60 (196)	3.75 (205)
D_{LCO}, $mL \cdot min^{-1}$ $mm\ Hg^{-1}$	10.5 (47)	14.5 (65)	14.6 (66)	15.0 (68)	13.6 (62)	12.1 (55)	16.0 (73)	NA	13.7 (68)
CD20, absolute count	NA	NA	1	0	33	123	0	0	0

Abbreviations: D_{LCO}, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, not applicable; RV, residual volume; TLC, total lung capacity.
[a] Values provided as No. (% predicted), unless otherwise indicated.

rituximab infusions. The FEV_1, FVC, TLC, and D_{LCO} values were stable, and, on some occasions, showed a trend toward improvement. A similar pattern occurred after the second rituximab treatments. Of note, in case 2 the second series of infusions was postponed for nearly 2 years because B-cell counts remained low (Table 2). During this time, initially stable spirometry measurements started to decline outside of the degree that would be expected due to aging alone (FVC, 1.96–1.64 L and FEV_1, 0.98–0.84 L).

Neither of our patients reported adverse events related to rituximab infusion, which is consistent with prior reports that rituximab is generally well tolerated. Of 11 patients in 1 series, 3 had mild flu-like reactions, with variable degrees of arthralgia and limited cutaneous eruptions [12]. In another series, half of the patients reported mild headache or fatigue that resolved during the infusion. In that study, 25% of patients experienced arthralgia days to months later, and 1 patient had associated synovitis and purpura [11]. Despite observational data, a randomized controlled trial comparing rituximab to placebo did not show a difference in rate of infections [14].

Given the current understanding of the role of B cells in the pathogenesis of SS [2], our observations suggest that B cells may also be involved in the development of constrictive bronchiolitis, a disabling complication of the disease. Therapy targeting B cells may be a useful mechanism-based therapy for constrictive bronchiolitis in primary SS, which is usually refractory to conventional systemic immunosuppressive therapy. Further investigation of this treatment modality is warranted.

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Declaration of competing interest

None of the authors have any conflicts of interest to disclose.

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