



A case of anti-aminoacyl tRNA synthetase (ARS) antibody-positive polymyositis (PM)/dermatomyositis (DM)-associated interstitial pneumonia (IP) successfully controlled with bosentan therapy



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ABSTRACT

A 72-year-old woman was admitted to our hospital and was diagnosed with interstitial pneumonia (IP) associated with amyopathic dermatomyositis (ADM). The patient experienced three acute IP exacerbations in the 7 years that followed, which were each treated and resolved with steroid pulse therapy. The patient was closely examined for respiratory failure with right heart catheterization (RHC), which demonstrated that she had a mean pulmonary artery pressure (mPAP) of 34 mmHg. The patient was thus diagnosed as having pulmonary hypertension (PH) associated with anti-synthetase syndrome (ASS) and was started on bosentan therapy, which led to improvements in mPAP as well as in subjective symptoms over time. Indeed, she had had no acute exacerbations with serum markers of IP remaining low over 6 years following initiation of bosentan therapy, suggesting that bosentan may have a role in controlling IP. In addition, she was confirmed to be anti-ARS antibody-positive after 5 years of bosentan therapy, when anti-aminoacyl tRNA synthetase (anti-ARS) antibody testing became available.

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1. Introduction

Anti-aminoacyl tRNA synthetase (anti-ARS) antibodies are known to be specific to polymyositis (PM)/dermatomyositis (DM). Interstitial pneumonia (IP) is frequently observed in patients with anti-ARS antibody syndrome, often accompanied by pulmonary hypertension (PH). Given that PH is associated with decreased exercise tolerance, impaired quality of life (QOL), and increased mortality [1–4], it is clinically important to evaluate these patients for the presence of PH.

Again, it remains unclear who, of all patients with IP, may benefit from bosentan as a treatment option for IP [5]. Herein we report our experience with a case of ARS antibody-positive PM/DM-associated IP in which bosentan proved likely effective in controlling IP.

List of abbreviations: ADM, amyopathic dermatomyositis; ASS, anti-synthetase syndrome; CVD, collagen-vascular disease; IP, interstitial pneumonia; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PM, polymyositis; TR, tricuspid regurgitation.

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2. Case presentation

A 72-year-old woman became aware of dyspnea on exertion since around February 2003 and was admitted to our hospital for worsening of dyspnea two months later. Chest CT examination revealed a honeycomb accompanied by bronchial dilation along the chest lining and a pulmonary consolidation around the bronchial vessels. A lung biopsy was then performed using video-assisted thoracoscopic surgery (VATS), which led to the patient being diagnosed as having cellular non-specific IP (NSIP). Again, the patient was associated with mechanic's hands and Gottron's sign and a skin biopsy suggested DM but with no evidence of increased serum creatinine kinase (CK) or muscle weakness, which led to the diagnosis of amyopathic DM (ADM)/collagen-vascular disease (CVD)-IP associated with ADM in this patient.

The patient experienced three acute exacerbations over a 7-year period, each of which was successfully treated and resolved with massive-dose steroid therapy followed by therapeutic steroid therapy; the patient was also started on long-term oxygen therapy (LTOT) for chronic respiratory failure. She was then admitted to our hospital for acute exacerbation of IP and worsening dyspnea that required examination and treatment in November 2011.

The patient was found to be lucid at admission and her vital signs were as follows: blood pressure (BP), 100/60 mmHg; heart rate, 105/min (regular); body temperature, 37.5 °C; respiration rate, 30/min; and arterial oxygen saturation (SAT), 94% (while using a reservoir mask).

Her laboratory data were as follows: white blood cell count, 13140/ μ L; hemoglobin, 9.7 g/dL; platelet count, 140,000/ μ L; lactate dehydrogenase, 436 mg/dL; C-reactive protein, 11.12 mg/dL; sialylated carbohydrate antigen KL-6 (KL-6), 1505 U/mL; surfactant protein D (SP-D), 594.0 ng/mL; brain natriuretic peptide (BNP), 175 pg/mL; anti-Jo-1-antibody, negative; anti-aminoacyl tRNA synthetase, positive; hydrogen index (pH), 7.416; partial oxygen pressure (PaO₂), 36.8 mmHg; partial pressure of arterial carbon dioxide (PaCO₂), 36.8 mmHg.

The partial oxygen pressure was shown to be clearly decreased at admission compared to that pre-admission. Chest x-ray examination revealed new bilateral diffuse infiltrates (with the relatively lateral to intermediate areas shown to be significant). Blood samples demonstrated increases in serum markers, LDH, KL-6, and SP-D following the inflammatory response, which led to the patient being diagnosed as having an acute exacerbation of IP (Fig. 1). Thus, the patient was put on bi-level positive airway pressure (biPAP) therapy from day 1 of her hospital stay and treated with

methylprednisolone (mPSL) 1000 mg/day for 3 days. On day 3, the patient showed signs of improvement in respiratory failure and was put off biPAP. On day 4, she was started on massive-dose prednisolone (PL) therapy and continued to show signs of gradual improvement in respiratory failure with the radiographic findings shown to follow a similar clinical course to that in previous IP exacerbations.

Echocardiography performed on day 45 of her hospital stay revealed findings suggestive of severe PH. On day 51 of her stay, the patient was closely examined for PH with right heart catheterization, which revealed increases in pulmonary artery pressure with the pulmonary systolic/diastolic artery pressure (PAP) (mean) being 50/21 (34) mmHg, the pulmonary systolic/diastolic artery wedge pressure (PAWP) (mean) being 10/0 [5] mmHg, and the pulmonary vascular resistance (PVR) being 7.9 Wood (Table 1).

Then, the patient underwent a series of examinations including a ventilation-perfusion scan to rule out pulmonary thromboembolism (PTE), which suggested that she had PH associated with CVD and CVD-IP. Given that PH did not improve with diuretic or oxygen therapy, the patient was started on bosentan therapy at 125 mg and discharged while on supplemental long-term oxygen therapy (LTOT) (during rest on room air; during exertion, 2L). The patient was continued on bosentan therapy on an outpatient basis with the

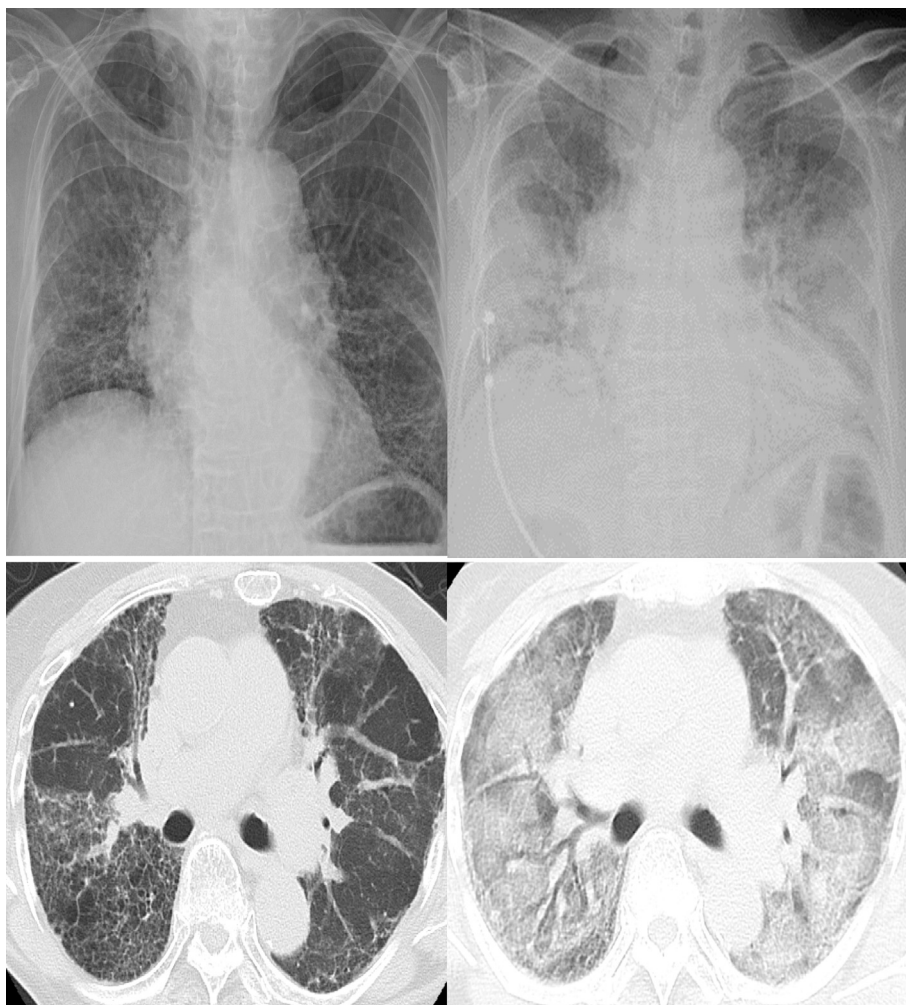


Fig. 1. Chest x-ray and computed tomography (CT) (a) prior to admission: Honeycombing, along with traction bronchiectasis in the subpleural and basal areas of both lungs, was detected; (b) at admission: Compared to pre-admission, chest x-ray revealed new bilateral diffuse infiltrates (with the relatively lateral to intermediate areas shown to be significant), suggesting marked progression of idiopathic pulmonary fibrosis (IPF).

Table 1
Clinical course.

RHC	PAP (mmHg)	PAWP (mmHg)	CO (L/min)	CI (L/min)	PVR (Wood)
Baseline	50/21 (34)	10/0 [5]	3.8	2.8	7.9
Month 6	37/13 (24)	7/1 [4]	4.5	3.3	4.3
Month 12	35/15 (25)	5/0 [2]	4.7	3.1	4.9
Month 18	40/20 (28)	11/1 [6]	4.6	3.3	4.8
Month 24	28/20 (24)	3/3 [3]	4.9	3.6	4.3
ADL	mMRC	SGRQ (total)	6WMD (m)		
Baseline	4	77.6	120		
Month 6	3	56	175		
Month 12	3	56	200		
Month 18	4	51.1	200		
Month 24	4	51.1	200		
Pulmonary function test	VC (L)	FVC (%)	FEV1 (V)	FEV1.0 (%)	
Baseline	1.15	52.1	0.95	84.82	
Month 6	1.13	53.1	1.00	90.10	
Month 12	1.25	59.4	1.04	84.60	
Month 18	1.17	57.0	1.03	87.30	
Month 24	1.32	61.8	1	78.10	

Abbreviations: RHC, right heart catheterization; ADL, activities of daily living; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedged pressure; PVR, pulmonary vascular resistance; mMRC, modified medical research council; SGRQ, Saint George's respiratory questionnaire; 6WMD, 6-min walk distance; VC, vital capacity; FVC, forced vital capacity; FEV1 (V), forced expiratory volume in 1 s; FEV1.0%, forced expiratory volume % in 1 s.

dose increased to 250 mg/day.

Bosentan therapy led to improvements in subjective symptoms; 1 year after its initiation, it also led to improvements in WHO functional class, maximum treadmill exercise tolerance, 6-min walk test, QOL testing, and PAP as assessed by right heart catheterization (Table 1).

The patient's condition showed no signs of worsening in pulmonary function tests or arterial blood gas measurements; again, with the PSL dose titrated down to and maintained at 5 mg, the patient had no such acute exacerbations as she had had earlier, with the KL-6 value remaining lower than previously observed.

3. Discussion

Given the negative results reported earlier with bosentan in patients with IPF-PAH [10], our patient was thought likely to represent a case of PH associated with CVD and thus to have shown improvements with bosentan, which, quite unexpectedly, also led to IP improving and becoming stable as never seen before, with no acute exacerbation seen.

There are several potential reasons for improvement and stabilization of IP in our patient with bosentan therapy. First, the earlier acute exacerbations of IP repeatedly seen in this patient may have been due to pulmonary edema associated with the worsening of IP. Second, IP may represent an underlying disease for PH. Third, CVD may have led to the worsening of PH thus triggering acute exacerbations of IP earlier. Finally, bosentan may have the potential to arrest the progression of IP.

Given that PH was present in our patient after recovery from acute exacerbations of IP and that imaging studies and hematology demonstrated that IP was likely involved independently of PH in our case, however, the earlier acute exacerbations of IP were thought less likely to be due to pulmonary edema associated with the worsening of PH but more likely to be due to the CVD in place.

Indeed, our patient was characterized as being anti-ARS antibody-positive, suggesting that the effect of bosentan therapy on IP in this patient may be consistent with that reported for anti-ARS antibody-positive CVD-IP. The eight different anti-ARS antibodies identified to date are reported to be associated with common clinical symptoms, such as IP, fever, arthritis, Raynaud's phenomenon, mechanic's hand, and are thus collectively called anti-ARS

antibody syndrome [6]. Again, while reported to be associated with PH, anti-synthetase syndrome (ASS) remains less well described. To date, there is only one report in which ASS patients were retrospectively examined for incidence of PH and prognosis [7].

Of note, of the 21 patients suspected of having PH on echocardiography (possible PH, 10; likely PH, 11) in this last study, all the 16 patients diagnosed with PH with right heart catheterization were found to have interstitial lung disease (ILD) with severe PH found in 13 of these patients (mean PAP, 46.9 mmHg). The presence of severe PH is reported to be associated with poor prognosis, with the 3-year survival rate among those with severe PH being 58%, suggesting that it is not rare for PH and CVD-IP to coexist among anti-ARS antibody-positive patients.

In our case, however, no acute exacerbations of IP were observed following initiation of bosentan therapy, with the serum KL-6 concentration remaining lower than that at baseline.

Thus, our study results appear to offer a few important clinical implications. First, improvements in PH with bosentan therapy may have led to the progression of IP being arrested in our patient. Second, bosentan per se may have the potential to arrest the progression of IP. Third, anti-ARS antibody syndrome may have subsided over time.

CVD-PH is classified as group 1, and respiratory disease-associated PH as group 3 in the Nice classification of pulmonary artery hypertension (PAH). Of note, the prognosis of group 1 PH has been drastically improved after 3 classes of PAH-specific therapeutics have become available, i.e., prostacyclins, endothelin receptor antagonists, and phosphodiesterase type 5 (PDE-5) inhibitors [8]. However, bosentan as a dual endothelin receptor antagonist remains to be evaluated for its efficacy against IP and its indications remain to be established [5].

The BUILD-3 study, a phase III randomized trial of bosentan in patients with idiopathic pulmonary fibrosis (IPF), failed to show the efficacy of bosentan in suppressing progression of IPF/mortality from IPD, while IPF did not worsen among those receiving bosentan compared to those receiving placebo [9]. While whether or not patients with IP may benefit from bosentan therapy still remains to be clarified, our study findings suggest that bosentan may be efficacious against CVD-IP.

While it is difficult to conclude from this case alone that

bosentan may have the potential to control IP, currently, it remains unclear who, of all patients with IP, may benefit from bosentan as a treatment option for IP [5]. However, given that clinical and x-ray/CT findings as well as clinical course in our patient suggested that bosentan may be effective in controlling CDV-IP which is unlikely to be due to PH, the present case was thought worth reporting as providing evidence of efficacy for bosentan in IP.

Further study is required in a larger population of PH and IP patients to explore the comprehensive pharmacological profile of bosentan, including its efficacy against CVD-related PH and IP.

Disclosure statement

The authors have no conflict of interest to declare. Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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