

[ CASE REPORT ]

## Cryptogenic Fibrosing Pleuritis with Rapidly Progressive Restrictive Ventilatory Dysfunction

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### Abstract:

Cryptogenic bilateral fibrosing pleuritis is a rare condition, and its pathogenesis and clinical course are poorly understood, with no established therapy available. A 61-year-old man presented with bilateral pleural thickening and lymphocytic exudative effusions. The patient was diagnosed with fibrosing pleuritis with no evidence of a known etiology on a surgical pleural biopsy. Within 16 months from the onset of respiratory symptoms, restrictive ventilatory impairment progressed rapidly, resulting in hypercapnic respiratory failure requiring home oxygen and non-invasive positive pressure ventilation therapies.

**Key words:** cryptogenic fibrosing pleuritis, hypercapnic respiratory failure

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### Introduction

Fibrosing pleuritis develops as a result of various infectious and non-infectious causes (1). Cases of cryptogenic fibrosing pleuritis were first reported in 1988 (2). Unlike fibrothorax, which is often experienced in daily clinical practice, cryptogenic fibrosing pleuritis is characterized by bilateral pleural effusions progressing to diffuse pleural thickening in the absence of any infectious, embolic, or occupational cause (3-6). The details of the clinical course are poorly understood, and no effective treatment has yet been established, although the administration of glucocorticoids and/or pleural decortication has been attempted.

We herein report a case of cryptogenic fibrosing pleuritis with rapidly progressive restrictive ventilatory dysfunction. The patient developed hypercapnic respiratory failure within 16 months after the first appearance of respiratory symptoms, with no response to systemic glucocorticoid treatment. Unlike previously reported cases developing respiratory failure, our patient has survived for more than one year with adjustment of non-invasive positive pressure ventilation

(NPPV) and oxygen therapy at home.

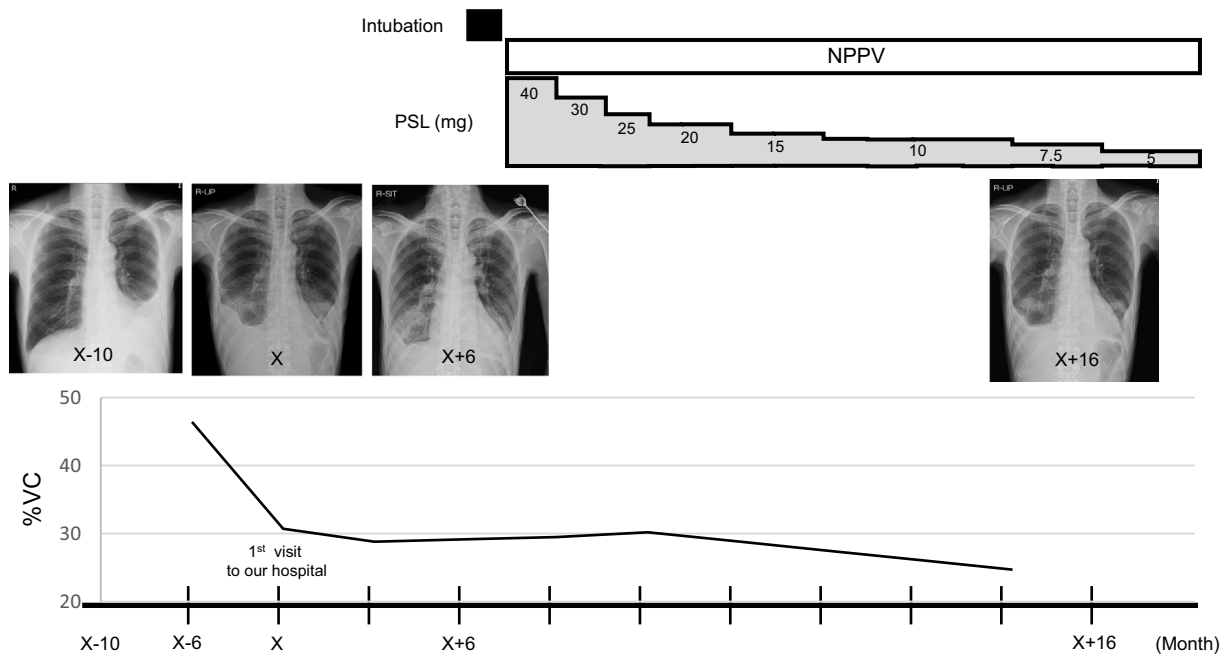
### Case Report

Ten months before the first visit to our hospital, a 61-year-old office worker became aware of cough and sputum. He was an ex-smoker (3.75 pack-years, no smoking since he was 25 years old) without a history of exposure to any other chemicals or dust, including asbestos, and he had an unremarkable medical history aside from Meniere's disease, for which he was taking isosorbide. Blood tests at a local clinic showed no abnormal findings (both normal liver and kidney functions) except elevated C-reactive protein (CRP; 4.02 mg/dL). There were no findings suggestive of collagen vascular disease on a physical examination or blood tests (negative for antinuclear antibody and anti-cyclic citrullinated peptide antibody). A chest radiograph showed bilateral pleural effusion, predominantly on the left side (Fig. 1), and computed tomography (CT) showed bilateral pleural effusion and pleural thickening without any intrapulmonary lesions. He was therefore referred to local hospitals for further examinations. Thoracentesis showed pale-red pleural effusion with exu-

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**Figure 1.** Clinical course. Treatments (upper), chest radiographs (middle), and vital capacity (lower) are shown. NPPV: non-invasive positive pressure ventilation, PSL: prednisolone, VC: vital capacity

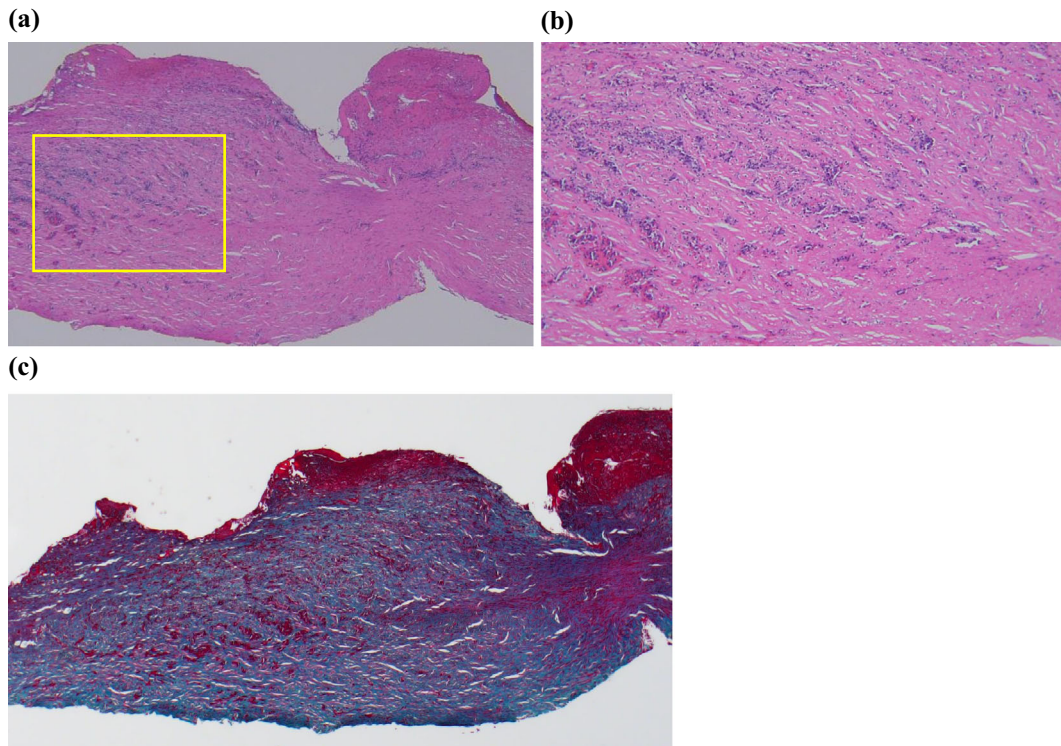
dativ characteristics [total protein (TP) 4.2 g/dL, lactate dehydrogenase (LDH) 407 U/L, glucose 95 mg/dL, adenosine deaminase (ADA) 15.7 U/L] and lymphocytic predominance (neutrophils 47.8%, lymphocytes 47.8%, monocytes 14.8%, eosinophils 15.9%); a cytological examination and cultures for bacteria, including acid-fast bacilli, were negative. A surgical pleural biopsy was performed. The pleural surface was covered by fibrin. The thickening pleural tissue was mostly fibrous and scattered with fibroblasts, small blood vessels, and nodular inflammatory cell infiltration (Fig. 2), and these histopathological findings were consistent with previous cases (2). There were no findings suggestive of malignant mesothelioma, asbestosis, amyloidosis, collagen vascular diseases, or immunoglobulin G4 (IgG4)-related disease on immunostaining (calretinin, WT-1, CD138, IgG4) and iron staining in addition to Hematoxylin and Eosin staining and Masson's trichrome staining. He was thus diagnosed with cryptogenic fibrosing pleuritis.

Since his vital capacity (VC) had decreased significantly from 1.67 L (46.4% of the predicted value) to 1.14 L (31.8%) in 5 months (Fig. 1), he was referred to our hospital. CT showed bilateral pleural effusion, pleural thickening, and round atelectasis in the lower lobes of both lungs (Fig. 3a). Positive emission tomography (PET)-CT was conducted to exclude thoracic malignancy or detect any active lesions targeted for a pleural re-biopsy. However, only a very mild accumulation of  $^{18}\text{F}$ -fluorodeoxyglucose was detected in the thickened areas of the bilateral pleura (Fig. 3b).

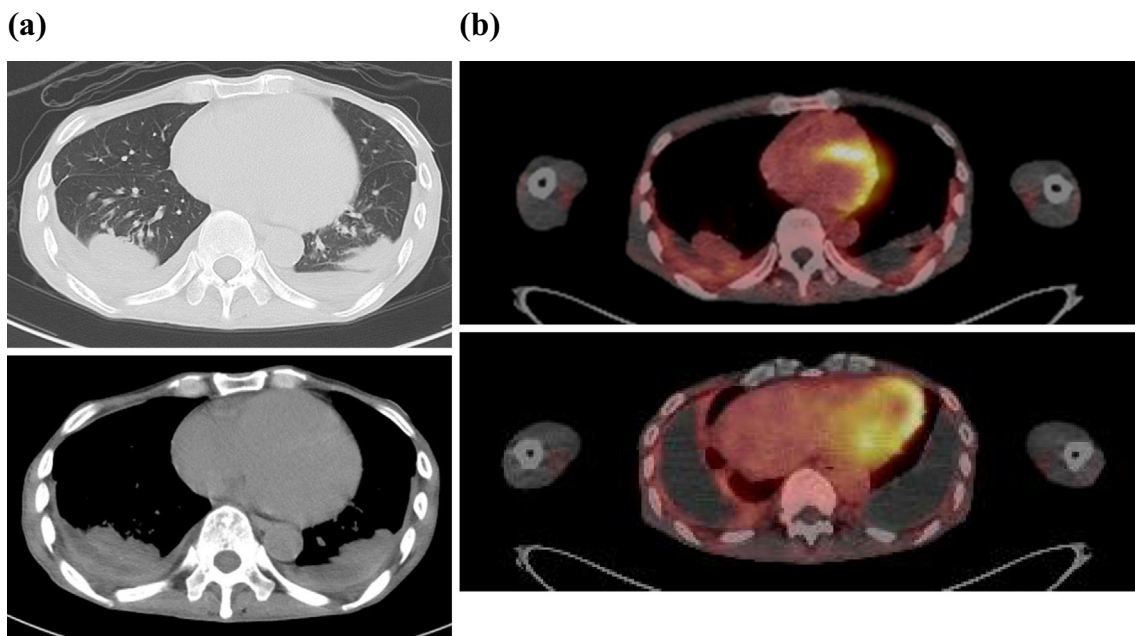
Seven months later, the patient visited the emergency room due to worsening dyspnea and anorexia. Vital signs showed a blood pressure of 118/90, a pulse of 100 beats/min, a respiratory rate of 24 breaths/min, and  $\text{SpO}_2$  of 85%

on room air. A physical examination was unremarkable except for bilateral respiratory sound attenuation. An arterial blood gas analysis showed hypoxemia, hypercapnia, and respiratory acidosis (pH 7.225,  $\text{PaO}_2$  75.7 Torr,  $\text{PaCO}_2$  97.4 Torr, and  $\text{HCO}_3^-$  38.9 mEq/L under 2 L/min oxygen administration). His blood tests showed elevated serum levels of aspartate aminotransferase (882 U/L), alanine aminotransferase (844 U/L), brain natriuretic peptide (342.1 pg/mL), CRP (2.61 mg/dL), and increased erythrocyte sedimentation rate (ESR; 39 mm/h). There were no findings suggestive of collagen vascular diseases at this point in the blood, either. An electrocardiogram showed sinus tachycardia without any ischemic changes. Chest imaging showed no findings suggestive of airway infection.

First, he was treated with NPPV therapy, but his respiratory acidosis had not improved by 30 minutes later (pH 7.222,  $\text{PaO}_2$  70.3 Torr,  $\text{PaCO}_2$  102.0 Torr, and  $\text{HCO}_3^-$  40.4 mEq/L under spontaneous/timed mode:  $\text{FiO}_2$  0.3, expiratory positive airway pressure 4 cm, inspiratory positive airway pressure 17 cm), although his consciousness remained clear. Therefore, he was intubated and treated with mandatory invasive ventilation. Five days later, he was extubated due to improvement of his respiratory acidosis, followed by NPPV therapy. Prednisolone (PSL; 40 mg/day as 1.0 mg/kg/day) was initiated along with nutrition therapy and respiratory rehabilitation. He was discharged on home oxygen therapy and NPPV therapy at night. There was no exacerbation of respiratory failure with a gradual reduction of VC (0.95 L, 26.7%) for 1 year after discharge.



**Figure 2.** Pleural biopsy pathological findings. Hematoxylin and Eosin (H&E) staining (low-power field 2X): Pleural surface was covered by fibrin (a), H&E staining (high-power field 10X): Fibroblasts and small blood vessels are scattered within the fibrous tissue, but no definitive image of carcinoma cells or mesothelioma is evident, and some nodular inflammatory cell infiltration is seen (b), Masson's trichrome staining (low-power field 2X): Pleural thickening by blue-stained fibrous tissue was seen (c).



**Figure 3.** CT images at the first visit to our hospital. Chest CT at the first visit to our hospital shows bilateral pleural effusion, pleural thickening, and round atelectasis in the lower lobes of both lungs (a). PET-CT after the first visit to our hospital shows a very mild accumulation of <sup>18</sup>F-fluorodeoxyglucose in the thickened areas of the bilateral pleura (b).

**Table. Previously Reported Cases of Cryptogenic Fibrosing Pleuritis.**

case	Age (years)	Gender	Pleural lesion	Pleural decortication	Lung lobectomy	Glucocorticoid	Dead/Alive	Ref
1	29-62	Man	Bilateral	+	-	-	Alive	(2)
2		Man	Bilateral	+	-	-	Alive	
3		Man	Bilateral	+	-	+static	Alive	
4		Man	Bilateral	-	+	+static	Alive	
5	39	Man	Bilateral	-	-	-	Alive	(4)
6	26	Man	Bilateral	-	-	+failed	Dead	(3)
7	56	Man	Unilateral	-	-	+failed	Dead	(6)
8	46	Man	Bilateral	-	-	+static	Alive	(5)
9	61	Man	Bilateral	-	-	+failed (not static)	Alive	Our case

## Discussion

Fibrosing pleuritis can be caused by bacterial and tuberculosis infections or non-infectious factors, including asbestos exposure, connective tissue diseases, IgG4-related disease, amyloidosis, post-coronary artery bypass surgery, uremia, hemothorax, and drugs (1). In the present case, there was no evidence of any of the diseases listed above, although a persistent increase in the serum CRP levels and lymphocytic inflammation in the pleural cavity were observed. Fibrosing pleuritis of unknown cause was first reported in 1988 as cryptogenic fibrosing pleuritis in four cases (2). To our knowledge, cryptogenic fibrosing pleuritis is a very rare disease, and only eight cases have been reported (3-6) (Table). Interestingly, all nine afflicted patients, including ours, were men.

Little is known about the natural course of cryptogenic fibrosing pleuritis. The first four cases described by Buchanan had restrictive ventilatory dysfunction, but their disease progression courses have not been described in detail (2). The clinical courses of the other four cases presented with rapidly progressive respiratory dysfunction, similar to ours. In one case, left-sided pleural decortication was performed first, and six months later, restrictive ventilatory dysfunction with right pleural thickening developed rapidly but was not noted afterward (4). In another case, an extremely low VC (0.58 L, 12% of predicted value) was detected within 3 years after the first appearance of respiratory symptoms, followed by hypercapnic respiratory failure requiring mandatory invasive ventilation after 5 months, leading to death (3). In another case, the FVC had decreased by 1,560 mL over the previous 3 years, and 1 month later, a further 2,500 mL reduction in the FVC was observed, followed by death (6). In the most recent case, restrictive ventilatory dysfunction developed within four months after the first complaint of respiratory symptoms, followed by glucocorticoid treatment without further progression (5). In the present case, the VC decreased by over 500 mL during the first 5 months after the diagnosis, and hypercapnic respiratory failure requiring home NPPV therapy developed within 16 months after the first appearance of respiratory symptoms.

No treatments have yet been established for cryptogenic fibrosing pleuritis. Six patients, including ours, were treated with glucocorticoids, the dosages and durations of which were generally not described in detail, whereas some cases were treated with a starting dose of PSL 0.25-1 mg/kg/day. Systemic glucocorticoid treatment was initiated after surgery (2) or before the occurrence of respiratory failure in three cases (5), and their condition remained static even after discontinuation. However, the efficacy of glucocorticoid treatment at the onset of respiratory failure is disappointing, and among the three total cases (3, 6), including ours, the two previously reported cases died within two weeks of starting glucocorticoid treatment. In the present case, there was no improvement in the VC or hypercapnia after starting glucocorticoid administration. Pleural decortication of the ipsilateral lung was successfully performed in all three cases (2, 4). However, it was difficult to perform major surgery in the present case due to the rapid deterioration of the pulmonary function.

Progressive cryptogenic fibrosing pleuritis is extremely rare, and it is currently difficult to establish standard therapies for this disease. However, glucocorticoid therapy and pleural decortication should be considered as a treatment option in the early stages of the disease.

**The authors state that they have no Conflict of Interest (COI).**

## References

- Huggins JT, Sahn SA. Causes and management of pleural fibrosis. *Respirology* **9**: 441-447, 2004.
- Buchanan DR, Johnston ID, Kerr IH, Hetzel MR, Corrin B, Turner-Warwick M. Cryptogenic bilateral fibrosing pleuritis. *Br J Dis Chest* **82**: 186-193, 1988.
- Verweel E, Noble J, Zoelen CG, et al. Failure to wean caused by cryptogenic fibrosing pleuritis and bilateral lung trapping: case report. *Rev Bras Ter Intensiva* **19**: 504-508, 2007.
- Lee-Chiong TL Jr, Hilbert J. Extensive idiopathic benign bilateral asynchronous pleural fibrosis. *Chest* **109**: 564-565, 1996.
- Manco A, Alfieri V, Gnetti L, et al. Cryptogenic fibrosing pleuritis. *Eur J Case Rep Intern Med* **8**: 002498, 2021.
- Castaniere I, Tonelli R, Fantini R, et al. The encaged lung: rapidly progressive idiopathic pleurisy. *Oxford Med Case Rep* **2018**: omy041, 2018.

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