

Idiopathic fibrous mediastinitis with refractory pleural effusion: a case report and literature review

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Abstract

Fibrous mediastinitis is a rare progressive disease characterized by invasive proliferation of fibrous tissue in the mediastinum. This tissue proliferation leads to compression of the mediastinal structures in the thoracic cavity, including the pulmonary vessels, esophagus, and trachea, causing corresponding symptoms and complications such as pulmonary hypertension. In clinical practice, the diagnosis of fibrous mediastinitis is often delayed or missed because of the rarity and variable clinical manifestations of this condition. This article presents a case of idiopathic fibrous mediastinitis that manifested as pleural effusion of unknown etiology along with a review of the relevant literature.

Keywords

Fibrous mediastinitis, pulmonary hypertension, pulmonary vein stenosis, pleural effusion, computed tomography, biopsy, case report

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Introduction

Fibrous mediastinitis (FM) is a rare disease characterized by invasive proliferation of fibrous tissue in the mediastinum. The disease course is long and involves benign tissue changes, but the accumulation of fibrous tissue can lead to compression of mediastinal structures such as the bronchi,

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blood vessels, and esophagus.¹⁻⁴ Patients with longstanding pulmonary vein stenosis may have atypical dyspnea and fatigue, and the late stage of the disease is characterized by asymmetric pulmonary edema, repeated development of pleural effusion, chest pain, and hemoptysis. The pathogenesis of FM is not clear but is thought to involve immune-mediated hypersensitivity,³ mainly related to histoplasmosis, mycobacteria and certain fungal microorganisms, and sarcoidosis.^{1,5} In many cases, the etiology is unknown; such cases are classified as idiopathic. We herein report a case of idiopathic FM with pleural effusion. The study protocol was approved by the authors' institutional review committee, and the patient provided written informed consent. The reporting of this study conforms to the CARE guidelines.⁶

Case report

A healthy 60-year-old man had been employed in cotton fluffing for >10 years. He had a >10-year history of coughing and expectoration and a 2-year history of chest tightness. Chest computed tomography (CT) 10 years earlier showed bilateral hilar and mediastinal lymph node enlargement with calcification (Figure 1). No chest tightness, other symptoms, or activity limitation were noted at that time, and a follow-up examination was not performed. Chest tightness with limitations of daily physical activity had begun 2 years ago, when repeat CT revealed slight stenosis of the right bronchus, a small amount of pericardial effusion, left pleural hypertrophy, and multiple calcified lymph nodes in the hilum and mediastinum. No obvious abnormalities were found on bronchoscopy, and pulmonary function tests suggested mild obstructive ventilatory dysfunction. The patient was clinically diagnosed with chronic obstructive pulmonary disease (COPD). Although he quit smoking and started

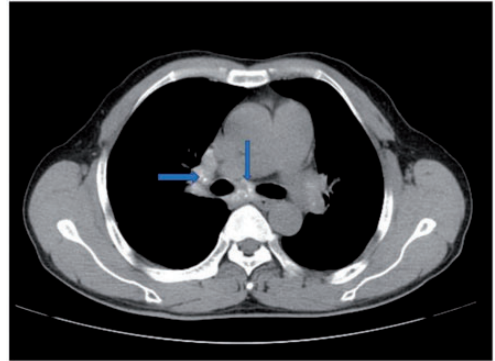


Figure 1. Chest computed tomography in 2010. Mild bilateral hilar and mediastinal lymphadenopathy with calcification were evident (blue arrows). The mediastinal tissues were not compressed.

inhalation of budesonide formoterol powder and other therapeutic measures, the chest tightness worsened. Two years later, a large amount of right pleural effusion was observed, and he was admitted to our hospital.

His vital signs were as follows: heart rate, 84 beats/minute; temperature, 36.7°C; respiratory rate, 20 breaths/minute; and blood pressure, 110/83 mmHg. His lips were not cyanotic. The supraclavicular lymph nodes were not enlarged. Lung examination revealed that on pulmonary palpation, the sound tremor of the right lower lung was weakened, percussion was marked, and breath sounds were reduced; the left lung was clear; and no dry or wet rales were present. There were no arrhythmias or pathological murmur. The abdomen was soft, with no tenderness or rebound pain.

No abnormalities were found in the laboratory workup, which included measurement of C-reactive protein, liver and kidney function tests, measurement of the erythrocyte sedimentation rate, measurement of tumor markers, a blood coagulation test, a cryptococcal capsule test, a 1,3- β -D-glucan test, a galactomannan test, measurement of anti-neutrophil

cytoplasmic antibody, and a complete anti-nuclear antibody spectrum set. The analysis results for the immunoglobulin series, light chain, rheumatoid factor, and immunoglobulin G4 were also normal. The complement C4 concentration was 0.15 g/L (reference range, 0.16–0.47 g/L), the anti-streptococcal hemolysin O concentration was 141.0 kU/L (reference range, 0–125.0 kU/L), and the N-terminal B-type natriuretic peptide progenitor concentration was 852 ng/L (reference range, 0–125 ng/L). A purified protein derivative test was positive. A T-cell spot test for tuberculosis infection was nonreactive. Examination of the pleural effusion revealed a yellow, turbid fluid with no coagulation; a negative mucin qualitative test; a nucleated cell count of $2484 \times 10^6/L$; lymphocyte percentage of 71%; monocyte percentage of 24%; red blood cell count of $6600 \times 10^6/L$; glucose concentration of 6.5 mmol/L; protein concentration of <20 g/L; adenosine deaminase concentration of 0.5 U/L (reference range, 0–25 U/L); lactate dehydrogenase concentration of 90 U/L (reference range, 120–250 U/L); carcinoembryonic antigen concentration of 0.4 $\mu\text{g/L}$ (reference range, 0–5.0 $\mu\text{g/L}$); total protein fluid/plasma ratio of <0.5; and lactate dehydrogenase fluid/plasma ratio of 0.375. A smear of the pleural effusion showed no tumor cells. Repeat thoracic CT after drainage revealed a right middle lobe bronchial occlusion with right middle lobe atelectasis, multiple enlarged calcified lymph nodes in the hilum and mediastinum, and cardiac enlargement with a small amount of pericardial effusion (Figure 2). Three-dimensional reconstruction of the thoracic vessels on enhanced CT showed a mediastinal soft tissue mass surrounding the pulmonary vessels and completely occluding the right superior pulmonary vein (Figure 3). Echocardiography revealed an enlarged right atrium and right ventricle and severe pulmonary hypertension (pulmonary

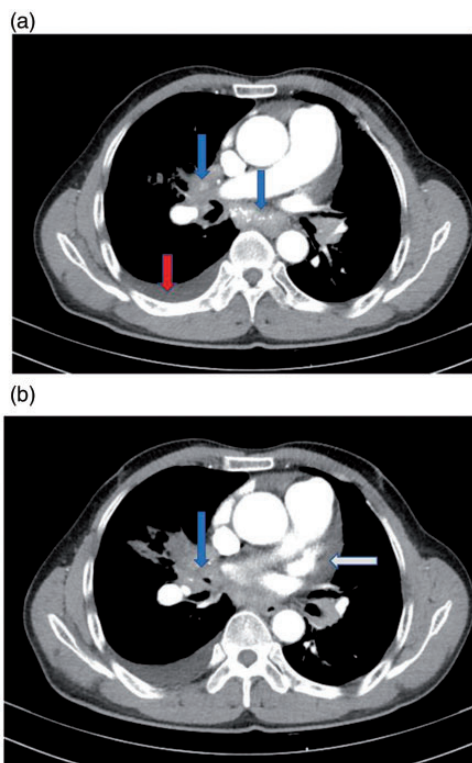


Figure 2. Chest enhanced computed tomography in 2019. (a) Right pleural effusion (red arrow) with multiple enlarged and calcified lymph nodes in the hilum and mediastinum (blue arrows). (b) Right middle lobe bronchial stenosis (blue arrow) and an enlarged heart with a small amount of pericardial effusion (white arrow).

arterial systolic pressure of approximately 84 mmHg). Pulmonary function tests showed mild restrictive ventilatory dysfunction (forced expiratory volume in 1 second was 72.2% of the expected value), with moderate small airway disease and mild diffusion dysfunction. Tracheoscopy showed occlusion of the right middle lobe, a twisted bronchus in the right upper lobe, and multiple carbon deposits in the tracheal mucosa (Figure 4). Examination of the lavage fluid revealed a negative cryptococcal capsule antigen test, negative acid-fast bacilli staining, and no *Mycobacterium tuberculosis*

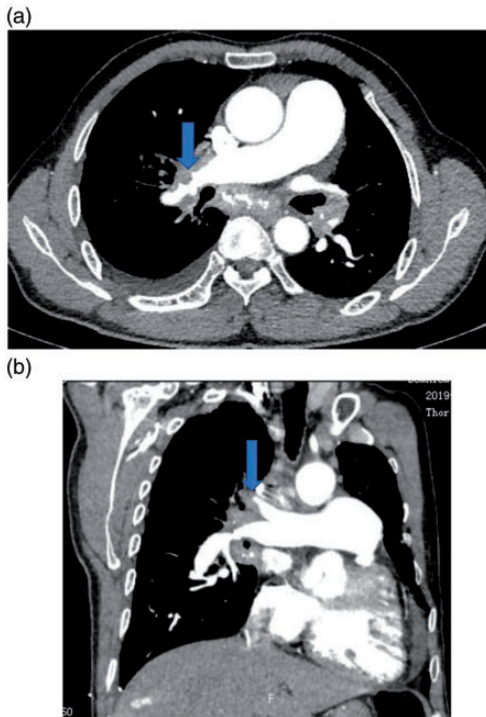


Figure 3. Enhanced three-dimensional reconstruction computed tomography. (a, b) The upper right pulmonary vein was not seen (blue arrows).

complex in the tuberculosis and rifampicin resistance gene (Xpert assay). Bronchoalveolar lavage fluid smear pathology showed no tumor cells. Whole-body positron emission tomography showed right middle lobe bronchial occlusion, right middle lobe obstructive atelectasis, and inflammation; multiple calcified hilar lymph nodes bilaterally with increased glucose metabolism, which were considered reactive proliferative lymph nodes; scattered infective and fibrous foci in both lungs; a left coronary artery calcified plaque; and pericardial effusion. There was slight thickening of the left lower pleura and a small amount of effusion in the right pleural cavity, which was partially encapsulated. Pleural effusion tests revealed leakage of the pleural effusion; however, its etiology was unknown because tests for

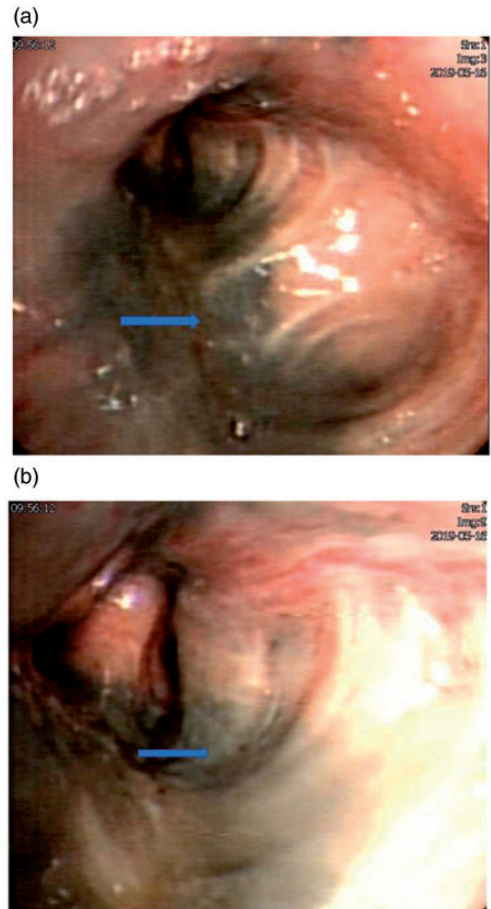


Figure 4. Bronchoscopy findings. (a) Right upper lobe bronchial distortion and (b) right middle lobe occlusion were present, and multiple carbon deposits (blue arrows) were present in the tracheal mucosa.

infection, tuberculosis, fungi, tumors, and autoimmune disease were negative. After a thoracoscopic examination, the subcarinal lymph nodes showed obvious collagenization of the submitted tissues, but no metastatic tumor tissues. Gissam staining, acid-fast staining, and silver amine staining were all negative (Figure 5).

Because all etiological tests were negative and the patient had no relevant family history, history of drug use, or history of radiotherapy, idiopathic FM was

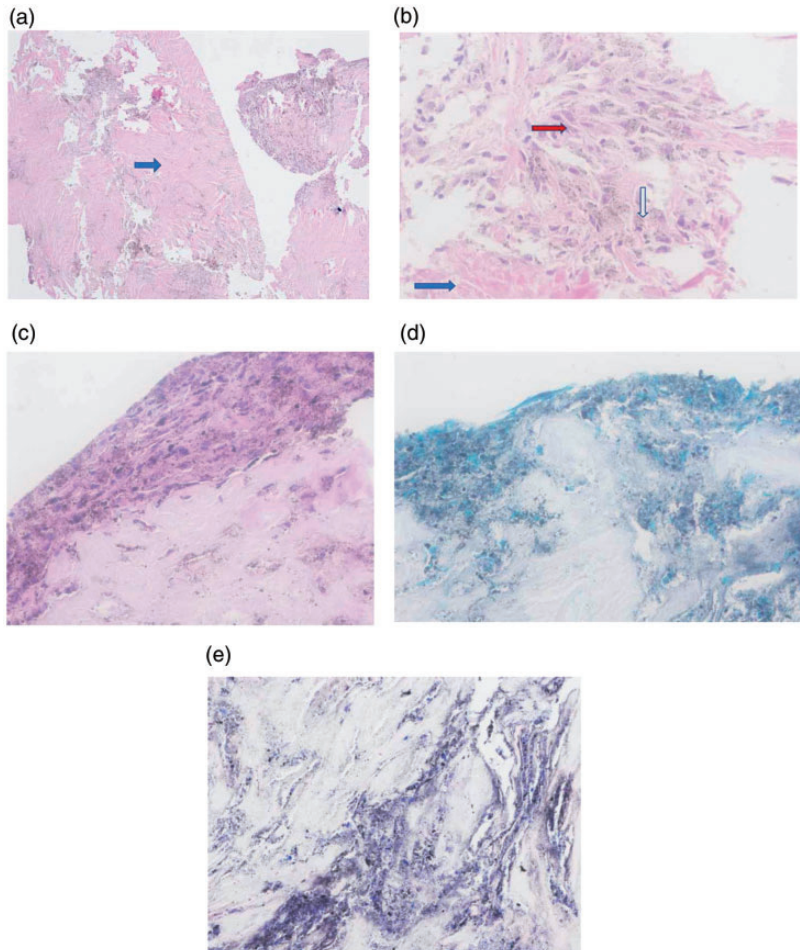


Figure 5. Hematoxylin-and-eosin-stained mediastinal biopsy (magnification, 4×10). (a) A large amount of collagen tissue (blue arrow in (a) and (b)) and (b) fibroblast infiltration (red arrow) were observed. The white arrow in (b) indicates carbon deposition. The mediastinal biopsy was negative on (c) periodic acid-Schiff staining, (d) acid-fast staining, and (e) Gissam staining.

considered. Since 2019, the patient had undergone repeated anti-infection, antitussive, and expectorant treatments; atomization and antiasthmatic treatments; and repeated drainage of pleural effusion. In June 2019, the patient underwent thoracoscopic pleurodesis combined with mediastinal lymph node biopsy under general anesthesia, but his intractable pleural effusion persisted. The patient thereafter refused surgical treatment to relieve the

pulmonary arteriovenous stenosis; he began to take anti-pulmonary hypertension drugs in October 2019 and visited the hospital every 1 to 2 months to drain the pleural effusion. In January 2020, pleurodesis/pleural sclerosis was performed, but this was ineffective and the pleural effusion persisted. One month later, the patient's dyspnea became aggravated and he was rehospitalized. Continuous high-flow oxygen therapy, pleural effusion drainage,

and anti-inflammatory and antiasthmatic drugs did not relieve the chest tightness. Because an effective treatment method for idiopathic FM has not been established, we began hormone therapy with the patient's consent. The initial dose of methylprednisolone was 24 mg/day. After 1 week of treatment, the patient's symptoms were significantly relieved, and he was discharged from the hospital. His methylprednisolone dose was thereafter decreased by one tablet every other week, and his dose at the time of this writing was two tablets every morning. The patient's symptoms improved and the pleural effusion volume decreased. We plan to maintain him on a low dose of methylprednisolone.

Discussion

FM, also known as sclerosing mediastinitis, is a rare disease characterized by the proliferation of dense fibrous tissue in the mediastinum.¹⁻³ This causes narrowing or complete occlusion of vascular and nonvascular mediastinal structures, resulting in specific symptoms, pulmonary hypertension, and other complications. The pathogenesis of FM is not clear. Some studies have shown a relationship among human leukocyte antigen-A2, CD20-positive B lymphocytes, and the pathogenesis of this disease.^{1,3,8} FM may be an immune-mediated hypersensitivity to fungi or other antigens.^{3,7} There are many known causes of FM. Granulomatous FM is associated with infections such as histoplasmosis, tuberculosis, blastomycosis, and cryptococcosis or with noninfectious diseases such as sarcoidosis. Non-granulomatous FM results from idiopathic reactions to different autoimmune diseases, radiotherapy, Behçet's disease, silicosis, familial multifocal fibrosclerosis, Hodgkin's disease, or drugs.^{5,9-11} However, the etiology is often unknown, and such cases are classified as idiopathic FM. All etiological tests in our

patient were negative. Although the patient had a history of working with cotton, no previous reports have described an association between cotton exposure and FM.

FM can occur at any age, but it typically occurs in individuals aged 20 to 40 years.^{2,12} In 1999, Flieder et al.¹³ reported 30 cases of idiopathic FM in patients ranging in age from 10 to 64 years, with no significant difference in sex. The clinical manifestations of FM are nonspecific. Patients may be asymptomatic for months to years before developing severe mediastinal obstruction, although pulmonary dysfunction is more common. Misdiagnosis of early FM as asthma or COPD can readily occur. The symptoms of FM vary according to the specific mediastinal structures that are compressed. For example, bronchial compression can cause coughing, dyspnea, hemoptysis, obstructive pneumonia, or even shunt formation due to atelectasis; esophageal compression may cause dysphagia and swallowing pain; thoracic duct compression can lead to chylothorax; recurrent laryngeal nerve and diaphragmatic nerve compression injury can produce hoarseness or shortness of breath; pulmonary vascular compression can lead to pulmonary hypertension, hemoptysis, intractable pleural effusion, and pulmonary edema; and compression of the superior vena cava can cause facial swelling, superficial vein dilatation, headache, hoarseness, and shortness of breath.^{12,14} The incidence of compression of the pulmonary vessels, bronchial vessels, superior vena cava, and esophagus is 47%, 26%, 19%, and 2%, respectively.^{1,15} The symptoms may be progressive and are usually characterized by progressive shortness of breath and coughing. Pleural effusion is a relatively rare complication of FM, and its pathogenesis may be attributed to the increased hydrostatic pressure caused by pulmonary vein stenosis and cardiac insufficiency secondary to pulmonary hypertension, which can manifest

as either unilateral or bilateral pleural effusion.^{16,17} Because of the different etiologies and mediastinal compression sites of FM, the nature of the pleural effusion can be exudative or leaky. During the first few decades, the patient may have only a mild cough and expectoration. No obvious compression of the pulmonary bronchi or mediastinum was seen on chest CT in the present case; thus, the patient was initially misdiagnosed with COPD. As the lesion progressed, right pulmonary bronchial stenosis gradually appeared until complete occlusion occurred, resulting in atelectasis, pulmonary hypertension, pleural effusion, dyspnea, and other symptoms. The patient presented with intractable right pleural effusion, which was exudative for the first time and leaky after repeated re-examination.

There is no single standard method of diagnosing FM, but biopsy is the gold standard.³ Because biopsies are invasive, FM can also be diagnosed according to the clinical manifestations and imaging findings; however, other mediastinal diseases must be excluded, especially bronchogenic carcinoma and lymphoproliferative diseases.^{11,14,17,18} Thoracic contrast-enhanced CT is the first choice for diagnosing suspected FM.¹⁹ On CT, FM usually presents as focal or diffuse attenuating infiltrative soft tissue lesions with or without calcification; these lesions most often involve the middle mediastinum and wrap around important mediastinal structures, exhibiting less involvement of the anterior and posterior mediastinum.^{11,14,17,18} Statistically, 75% to 95% of the lesions are focal, while 5% to 25% are bilateral.^{1,4,7} The severity of stenosis of the involved vessels can be non-invasively evaluated by echocardiography, CT angiography, or magnetic resonance imaging. Although magnetic resonance imaging is inferior to CT in terms of evaluating calcification, it can accurately identify invasive mediastinal soft tissue lesions in FM and invasion of adjacent structures.

In the present case, pulmonary CT revealed that the FM had progressed gradually, and there was initially no obvious mediastinal compression. As the FM progressed, mediastinal structures such as the pulmonary bronchi and pulmonary vein became compressed, followed by severe pulmonary artery compression and intractable right pleural effusion.

Histologically, FM is characterized by mediastinal fat deficiency, cellular collagen, fibrous tissue hyperplasia, and eosinophil or other inflammatory cell infiltration.^{18,19} If a granulomatous reaction is observed, histochemical staining and appropriate serological laboratory tests are needed to evaluate venereal and IgG4-related diseases and tumors. Rossi et al.¹⁸ classified cases of fibrotic non-granulomatous lesions in patients with normal serum and tissue IgG4 concentrations as idiopathic FM and staged the pathology of these lesions to guide treatment and follow-up. In our patient, a mediastinal lymph node biopsy showed fibrous hyperplasia and collagen infiltration with negative Gissam staining, acid-fast staining, and silver amine staining. His serum IgG4 concentration was normal, and there was no evidence of other organ involvement. Because all etiological examinations were negative, the diagnosis was idiopathic FM.

There is no definitive treatment for FM. Several medical and surgical treatment strategies have been reported. Medical interventions include steroids, methotrexate, and rituximab; autoimmune FM can be treated with corticosteroids or immunosuppressants.^{7,15,20} Antifungal and antituberculosis therapy for FM with evidence of an active granuloma is not efficacious and is not currently recommended.¹ In one report, the symptoms of idiopathic FM improved significantly after treatment with high-dose steroids and rituximab.⁷ Patients with severe vascular occlusion with hemodynamic impairment are treated with stenting and

surgical intervention (bypass occlusion). Endovascular therapy is feasible and shows good safety and technical success.²¹ Seferian et al.²² retrospectively analyzed 27 patients who had FM with pulmonary hypertension and reported that the 1-, 3-, and 5-year survival rates of patients treated with steroids alone were 88%, 73%, and 56%, respectively; however, these results have not been confirmed. Lung transplantation is recommended for patients with severe pulmonary hypertension and FM.²² Yang et al.¹⁶ reported a case of FM-induced left pleural effusion that was treated by percutaneous vascular intervention combined with anticoagulation. The pleural effusion did not recur for 2 years thereafter. Intravascular stent implantation can be used to treat refractory pleural effusion caused by FM, although further research is necessary to evaluate this technique. As shown by the present case, hormones can be considered for idiopathic FM, whereas pleural fixation and pleurodesis/pleural sclerosis are not recommended for treatment of FM-induced pleural effusion. The reason for failure may be that the pulmonary vein stenosis cannot be relieved and that the hydrostatic pressure of the parietal pleural fluid does not decrease. At the time of this writing, continued hormone therapy was effective for our patient. Hormone therapy has been mentioned in several previous reports,^{7,22} but the underlying mechanism of its efficacy is rarely mentioned. We speculate that hormone therapy may reduce the concentration of inflammatory factors in the mediastinal tissue and inhibit collagen fibrosis. The prognosis of patients with FM is poor, and their survival depends on the underlying etiology, severity of complications, and treatment.

Conclusion

In this patient, the duration from symptom onset to diagnosis exceeded 10 years. Therefore, in clinical practice, if the

normal mediastinal structure disappears and is filled with calcified tissue similar to enlarged lymph nodes, FM should be considered and early examinations should be performed to assess the pathological characteristics and etiology. Additionally, FM should always be considered when a patient develops intractable pleural effusion of unknown cause accompanied by pulmonary embolism, a high pulse pressure, and pulmonary vein compression. Because FM is rare, it is difficult to diagnose. Further studies are needed to clarify the disease spectrum, natural history, and outcome of FM and to explore effective treatments.

Ethics statement

This study was approved by the Ethics Committee of the Dingli Clinical Institute of Wenzhou Medical University (Wenzhou Central Hospital) (approval number L 2021-01-050). The authors have no ethical conflicts to disclose. The patient provided written informed consent.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Authors' contributions

X-J.D. and S-X.D. designed the study. X-J.D. collected the data. Y.J. and J-Y.Z. analyzed the data. S-X.D. wrote the paper. All authors read and approved the final manuscript.

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