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Case Report

A patient with pleuroparenchymal fibroelastosis carrying a novel *fibrillin-2* gene variant

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ABSTRACT

Pleuroparenchymal fibroelastosis is a recently recognized clinical entity characterized by interstitial pneumonia with proliferating elastin in the upper lung regions. Pleuroparenchymal fibroelastosis is categorized as idiopathic or reported depending on the coexistent initiating factors; however, congenital contractural arachnodactyly, which is caused by abnormal production of elastin based on a mutation in the *fibrillin-2* gene, is rarely reported with lung lesion resembling pleuroparenchymal fibroelastosis. We present a case of pleuroparenchymal fibroelastosis in a patient with a novel mutation in the *fibrillin-2* gene, which encodes the prenatal fibrillin-2 protein as a scaffold for elastin.

1. Introduction

Amitani et al. reported pleural and subpleural fibrosis in the upper lung regions complicated by lung cysts, that were later termed pleuroparenchymal fibroelastosis (PPFE) [1]. Here, we report that PPFE with multiple cysts developed into chronic necrotizing pulmonary aspergillosis (CNPA) in a patient suffering from severe micrognathia as a manifestation of congenital contractural arachnodactyly (CCA) carrying a novel *fibrillin-2 (FBN2)* gene variant known to be the responsible gene [2]. We examined lung specimens from this autopsied case to explore the relationship between lung fibroelastosis and mutations in the *FBN2* gene using an immunohistochemical (IHC) method and evaluated the features of the elastic and reticular fibers using specific staining.

Abbreviations: pleuroparenchymal fibroelastosis, PPFE; congenital contractural arachnodactyly, CCA; fibrillin-2, FBN2; chronic necrotizing pulmonary aspergillosis, CNPA; fibrillin-1, FBN1; Marfan syndrome, MFS; transforming growth factor-β, TGF-β; hematoxylin-eosin, HE; immunohistochemical, IHC; latent transforming growth factor TGF-β binding proteins −4, LTBP-4.

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2. Case presentation

A 45-year-old man who had severe micrognathia resulting in difficulty with mouth opening but no problems at birth and in childhood development was referred to us with a complaint of cough and fever. The patient had a history of smoking, with a Brinkman index of 250, alcohol consumption, carpal tunnel syndrome and Achilles tendon rupture. The patient's mother had died of rectal cancer at age 45, and a maternal aunt had died of collagen disease at age 50.

The patient's height was 160 cm, weight was 43 kg, and body mass index was 16.8. Except for a slender and thin body habitus and micrognathia, there were no other specific physical findings. However, chest imaging revealed pleural or subpleural fibrosis with multiple and subpleural cysts, mild elevation of the hilum, and consolidation in the apical regions of both lungs, which were more marked on the right than on the left (Fig. 1A, D, 1G). With no evidence of *Aspergillus* infection in the work-up result of antigen and precipitating antibody and improvement on the images after the prescription of an antibiotic agent (moxifloxacin 400 mg once a day orally), a diagnosis of bacterial pneumonia superimposed on upper lung fibrosis with subpleural cysts was made. Two years later, after a second referral with a complaint of dyspnea, both upper lung lobes were reduced in volume on his chest images (Fig. 1B, E, 1H). Lung function test was difficult to perform because the mouthpiece could not kept in place due to micrognathia, and accurate data could not be obtained. Three years after the second referral, the patient was admitted to our hospital because of progressive respiratory insufficiency and recurrent pneumothorax. His breathing was tachypneic and shallow, oxygen saturation was 89% while the patient was breathing ambient air, pitting edema in both lower extremities, and decreased breath sounds on both sides of the lung were observed. Hypercapnic respiratory failure, cor pulmonale and CNPA were diagnosed based on the laboratory data, which revealed elevated partial pressure of arterial carbon dioxide, serum galactomannan antigen, and *Aspergillus* precipitating antibody positivity, and right heart failure on transthoracic echocardiography. A computed tomography scan of the chest obtained during the final admission showed a platythorax with a marked reduction in the size of the upper lobes of both lungs and cavitary lesions (Fig. 1C, F, 1I). Treatment was with antifungal agents (micafungin sodium 75 mg once daily intravenously) and diuretics (furosemide 20 mg once daily in-

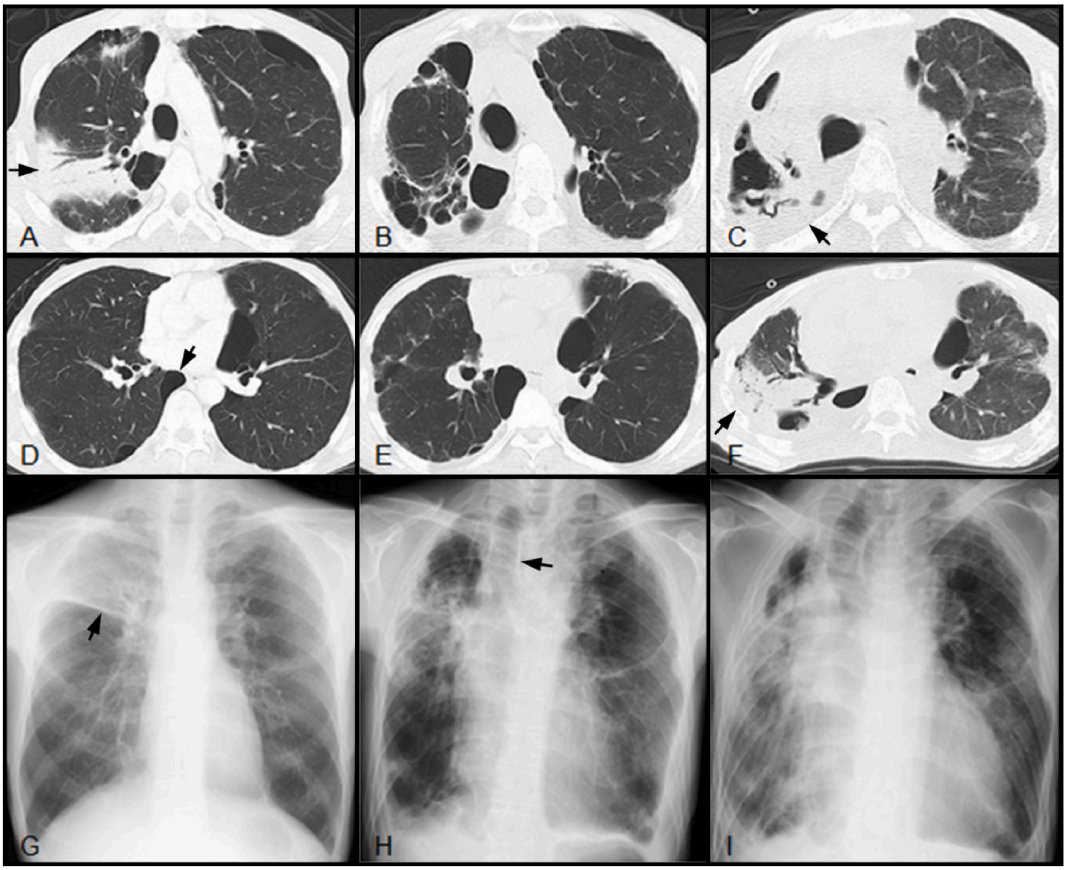

Fig. 1. Computed tomography scans and chest radiographs obtained during the course of the patient's illness. (A, D, G) Computed tomography scans obtained at the time of the first visit to our hospital showed consolidation in the right upper lobe (A, black arrow) and multiple subpleural bullae (D, black arrow) with mild pleural fibrosis and subpleural atelectasis. A chest radiograph showed elevation of the right hilum (G, black arrow) caused by the reduced volume of the right upper lobe. (B, E, H) Images obtained 2 years after the first visit. Computed tomography scans showed extensive reductions in the volume of the upper lobes on both sides (B, E), and a chest radiograph showed traction on the trachea (H, black arrow). (C, F, I) Images taken 5 years after the first visit. Computed tomography scans revealed a cavity in the apex of the right lung (C, black arrow) with consolidation extending to the right lower lobe (F, black arrow). A chest radiograph showed a marked reduction in lung volume with mild cardiomegaly (I).

travenously) and the initiation of noninvasive positive pressure ventilation failed, and the patient died on the fifth day of hospitalization. Multiple lung cysts and a history of severe micrognathia suggested a hereditary connective tissue disease, such as Marfan syndrome (MFS). Therefore, genetic tests for hereditary connective tissue diseases were performed at Shinshu University Hospital. A novel variant of *FBN2* (NM_001999.3:c.3160C > A:p.Arg1054Ser) was identified by next-generation sequencing and confirmed by Sanger sequencing. The variant was not found in the patient's healthy younger brother, suggesting that it was pathogenic. An autopsy was performed after informed consent was obtained from the next of kin. At autopsy, the right upper lobe was consolidated, including cavitary lesions, and the lobe was impossible to separate from the thorax because of severe adhesion. Histopathologically, subpleural atelectatic indurations composed of marked fibroelastosis with collapse and traction bronchioloectasis were seen in the left upper lobe (Fig. 2A). Near the large cavity of the right upper lobe, there were tiny cavitary lesions surrounded by fibrosis (Fig. 2B). Hyphae-like structures (arrow) and brown colored spores (arrowhead) were found in the necrotic tissue in the cavities (Fig. 2B inset) and *Aspergillus niger* was suspected. PPFE coexisting with CNPA was the most likely pathological diagnosis in this case. By IHC staining for FBN2 antigen with an FBN2 antibody according to a previous report [3], compared to the control lung obtained from non-cancerous and autopsied lung tissues from a patient with the pancreatic cancer, the FBN2 antigen was intensely identified in this case of autopsied lung parenchyma (Fig. 3A and B). Additionally, elastic fibers were seen on microscopy with resorcin-fuchsin staining as thickened, wavy, frayed, and granular compared to the control lung (Fig. 4A and B). The reticular fibers were sparse and did not have a typical mesh-like structure as observed by silver staining in the whole lung parenchyma compared to the control lung (Fig. 4C and D). Significantly increased elastic fibers and decreased reticular fibers compared to the control were confirmed by the image analysis method (data not shown).

3. Discussion

3.1. Clinical discussion

CCA (also known as Beals syndrome or distal arthrogryposis type 9, OMIM #121050) is a rare autosomal dominant disorder of connective tissue caused by mutation in *FBN2,* which encodes the FBN2 protein and is located at 5q23-31 [2]. Fibrillin is necessary for the assembly of elastin and its scaffold and contributes to tissue elasticity and resilience. CCA shares a clinical phenotype with MFS caused by mutation of the *fibrillin-1 (FBN1)* gene [2]. The variant in our case was localized to a mutation hotspot in *FBN2* that is not registered in any of the population databases or supported by any of the predictive in silico programs; therefore, it was classified as a variant of uncertain significance in accordance with the guidelines published by the American College of Medical Genetics and Genomics and the [4]. The skeletal features in CCA such as joint contracture are present in infant and improve in the postnatal period,

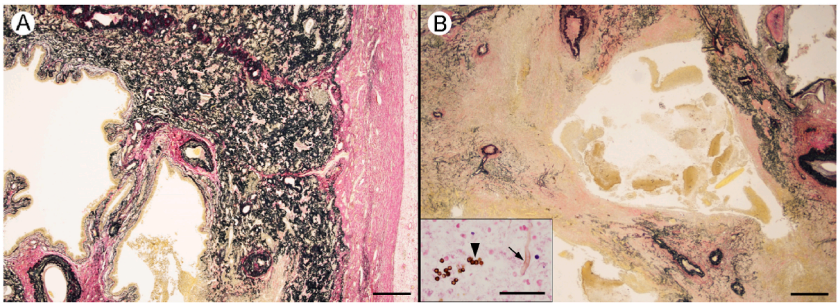

Fig. 2. Micrograph of lung specimens stained with hematoxylin-eosin, Elastica van Gieson (A–B) Micrographs of lung specimens stained with hematoxylin-eosin (HE) and Elastica van Gieson methods. (A) Marked fibroelastosis with collapse, traction bronchiectasis, and pleural fibrosis in the lingula (Elastica van Gieson staining, ×20, scale bar 0.5mm). (B) Tiny cavities surrounded by fibrosis (Elastica van Gieson staining, ×10, scale bar 1mm) and Hyphae-like structures (arrow) and brown colored spores (arrowhead) were found in the necrotic tissue in the cavities (Fig. 2B inset) (HE staining, ×400, scale bar 50 μm). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

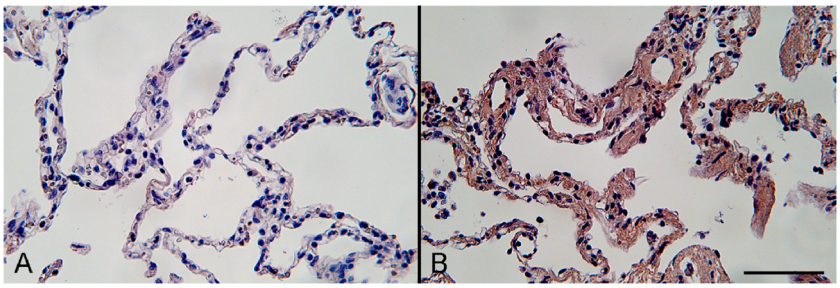

Fig. 3. Micrograph of lung specimens stained with anti-FBN2 antibody
(A-B) Anti-FBN2 antibody staining using IHC revealed more intense expression of FBN2 antigen in the lung parenchyma from our case (B) than in control lung tissue (A) (anti-FBN2 antibody, IHC, ×60). Scale bar, 100 μm.

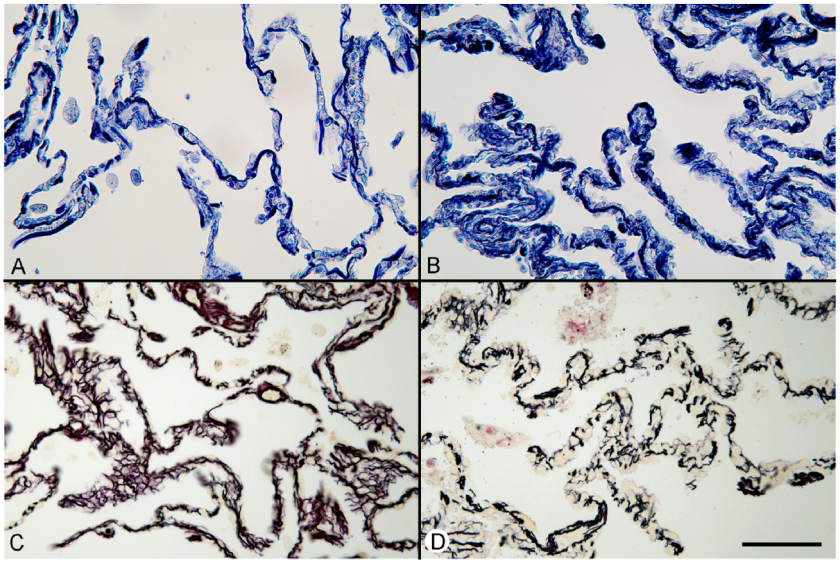

Fig. 4. Morphological analysis of the features of elastic and reticular fibers. Morphological analysis of the elastic and reticular fibers using specific staining (A, B, C, D).The increases elastic fibers in lung tissue from our patient were thickened, wavy, frayed and hazy (B) in comparison with those in the control lung tissue (A) (resorcin-fuchsin staining, ×60). Reticular fibers were sparse and had a disorganized structure (D) compared with those in the control lung tissue (C) (silver staining, ×60). Scale bar, 100 μm.

unlike the persistent skeletal features in MFS [2]. The diagnosis of CCA is established with suggestive findings and heterozygous *FBN2* pathogenic variants identified by molecular testing [2]. However, *fibrillin* genes variants shows various clinical phenotype without marfanoid features or classical features without FBN2 gene mutation [5]. Especially, the occurrence of FBN2 related disorder make it more difficult for it to be diagnosed because some of the features either improve or are overlooked in infant, thus, the need to prove the *FBN2* mutation is crucial. Even though our case had fewer characteristic features than the classical CCA, except for micrognathia, the proof of the pathogenic *FBN2* gene variant play a predominant part in the diagnosis of nonclassical CCA or adult onset *FBN2* related disorder. Tracheomalacia or *Nontuberculous mycobacterium* infection, has been reported in CCA but PPFE or *Aspergillus* infection had not been reported [2,6]. PPFE is reported in relation to genetic disorders such as short telomere length but not fibrillin related disease [7].

3.2. Imaging discussion

Bullae and blebs, aspergillosis, and pneumothorax are reported as the radiological and pathological manifestations of MFS [8–11] and also known to be complicated by PPFE [7]. To explain the mechanism of lung cyst in *FBN1* gene mutation, the mutated fibrillin protein is believed to alter the molecular organization thus making it susceptible to proteolytic degradation over increasing elastin synthesis [11].

3.3. Pathological discussion

PPFE is defined by intra-alveolar fibrosis with collapse and septal elastosis with pleural fibrosis in the upper lung region, which was observed in the left upper lung region in our presented case [7]. In developmental lung, FBN2 occurs earlier and is a stronger inducer of elastin synthesis than FBN1, furthermore, it is buried within the postnatal microfibrils and may be unrecognized in the postnatal period [12]. Fibrillin also regulates transforming growth factor -β(TGF-β)by sequestration of the extracellular matrix, through binding to other protein such as the latent TGF-β binding proteins 4 (LTBP-4) [5]. Elevated LTBP-4 has previously been reported in PPFE patients [13]. Moreover, the expression of FBN2 antigen demonstrated by IHC indicated the re-appearance of FBN2 protein in adult tissues, which is reported to be involved with wound repair and fibrosis [3]. Increased proliferation of elastic fibers in skin tissues in MFS related disorder has already been reported [14]. It is hypothesized that the mechanism by which elastin synthesis is increased in *FBN2* gene mutation is by altering microfibril organization; also aberrant FBN2 protein that induces deposition of elastin is continuously expressed while exposed to the surface, and accelerate the elastin crosslinking against the degradation in adult lung in a similar manner to that of a developing lung. In contrast to increase in elastin, the reticular fibers (composed of collagen III, the second most abundant collagen subtype in normal lungs after collagen I) decreased and showed a disorganized appearance. Increased and aberrant synthesis in elastic fibers and decreased or disorganized synthesis in reticular fibers, might play a part in the fatality of the fibroelastosis in the case described in this report.

4. Brief review of literature

Amitani et al. reported a slender body habitus with a low body mass index among those with idiopathic pulmonary upper lobe fibrosis [1], subsequently, Frankel et al. termed it PPFE in 2004 [15].

Both PPFE and fibrillin related disease have specific body habitus characteristics and a pathogenesis of aberrant elastin production, but the association has rarely been reported.

This case is also worth reporting to highlight the relationship between the body habitus and PPFE.

5. Conclusion

PPFE occurred in the lungs of a patient carrying a novel *FBN2* gene variant who exhibited aberrant proliferation of elastic fibers and decreased synthesis in reticular fibers with the expression of prenatal FBN2 antigen.

Ethics approval and consent to participate

All procedures performed in this case report were approved by the Ethics Committee of Kokura Medical Center (No. 248) and in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the patient's next of kin for inclusion in this case report, as the patient was deceased.

Consent for publication

Written informed consent was obtained from the patient's next of kin for publication of this case report and accompanying images, as the patient was deceased.

Availability of data and material

All data generated or analyzed during this case report are included in this published article.

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Author contributions

HK is the corresponding author and contributed to the collection and analysis of clinical data and writing the manuscript, IT contributed to the histological and imaging analysis and to the preparation of figures, KT and YT contributed to the genetic analysis and diagnosis, KY contributed to the pathological diagnosis and preparation of figures, IS participated in the histological analysis as a cytotechnologist, IY participated in the discussion as a dentist, and SS participated in the discussion of the pathological diagnosis. All authors have critically read the manuscript and given final approval for its submission.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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