Pulmonary Histologic Changes in Marfan Syndrome

A Case Series and Literature Review

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Abstract

Marfan syndrome is one of the most common connective tissue diseases and may manifest with a range of symptoms and pathologic changes. We present a retrospective series of 5 cases of patients with Marfan syndrome and pulmonary pathology. Patients were young to middle-aged adults with absent or minimal smoking histories and absent to severe clinical pulmonary symptoms. Tissue specimens were obtained from the surgical pathology and autopsy services. Histologic examination revealed a consistent pattern of distal acinar emphysema in all patients. Comparisons are made with other cystic-type diseases of the lung that may histologically mimic this pattern. This is the largest contemporary series of histologic pulmonary involvement of Marfan syndrome and the first to describe this pattern of pulmonary changes in this patient population.

Marfan syndrome is an autosomal dominant connective tissue disorder with an incidence of about 1 in 5,000. Approximately 25% of cases arise from de novo mutations. Mutations are present in the \textit{FBN1} gene on chromosome 15, which encodes for the connective protein fibrillin-1. Fibrillin-1 is the main component of microfibrils, which, in turn, are constituents of elastic fibers. Microfibrils confer mechanical stability, contribute to growth factor regulation, and are thought to have a role in tissue development and homeostasis. Fibrillin-1 mutations are thought to lead to haploinsufficiency and/or dominant negative activity of the mutant fibrillin-1 protein. Tissues with abundant type I collagen are most prominently affected, including the skeletal, ocular, and cardiovascular systems. Although pulmonary symptoms are not generally considered a main feature of Marfan syndrome, many patients have a degree of underlying pulmonary pathology. Spontaneous pneumothorax is a commonly reported clinical manifestation.

The pulmonary histologic changes in Marfan syndrome have been described in a number of small series and case reports. These include widespread or patchy cystic changes, emphysema, and spontaneous pneumothorax; focal pneumonia or bronchiectasis, bullae, congenital pulmonary malformations (particularly middle lobe hypoplasia), and apical fibrosis have also been described. However, no literature exists that has reported a critical microscopic examination of these tissues for histologic similarities. As medical and surgical treatments continue to improve, patients with Marfan syndrome are living longer and experiencing age-related disease. In addition, the inheritance of Marfan syndrome does not preclude the presence or development...
of a second pulmonary disease process. It will be important in the future to be able to separate true Marfan-related pulmonary changes from those attributable to other pathologic processes. We present a relatively large contemporary series of 5 cases of Marfan syndrome in the lung and show the spectrum of pathology with comparison with other cystic diseases of the lung.

**Materials and Methods**

After obtaining institutional review board approval, the archives of the Department of Anatomic Pathology, Cleveland Clinic Foundation, Cleveland, OH, were searched from 1980 to the present for cases that included “Marfan” in the final diagnosis (top line or comment). In total, 27 specimens were identified, 6 of which included pulmonary tissue; 5 cases with adequate (ie, multiple) pulmonary slides were obtained. All surgical and pathology reports were completely reviewed, including gross and microscopic descriptions by the originating pathologists. Demographic data are summarized in **Table 1**. All H&E-stained slides of lung tissue were examined (range, 3-19 slides total per case). A pentachrome stain was performed to further evaluate the connective tissue. The authors rereviewed all slides.

**Case 1**

**Clinical Data**

The case involved a 33-year-old woman with marfanoid habitus and a history of aortic dissection, which included coronary arteries. She was admitted with chest pain radiating to her jaw, and an angiogram showed a narrowed diagonal saphenous vein graft. She was taken to surgery for repair, but could not be weaned from the bypass pump.

**Gross Findings**

The combined weight of the lungs was 1,320 g. The right and left lungs had a normal lobar configuration, with smooth and glistening visceral pleura. The parenchyma was grossly unremarkable, and no subpleural emphysematous bullae were noted.

**Case 2**

**Clinical Data**

A 29-year-old woman with marfanoid habitus had aortic arch dissection and underwent corrective surgery. The day after surgery, she had a laceration of the right subclavian artery with subsequent right hemothorax during a central venous line change. She was taken to surgery and afterward could not be weaned from cardiopulmonary bypass.

**Gross Findings**

The left lung weighed 480 g. The right lung was of similar size. Right and left lungs had normal lobar configuration. Both lungs had multiple adhesions and petechiae on the pleural surfaces. Bilateral congestion was present, and subpleural emphysematous bullae were not seen.

**Case 3**

**Clinical Data**

The case involved a 20-year-old man with a history of Marfan syndrome (diagnosed at 7 years) and cardiac surgery.

**Table 1**

**Demographic Data for Five Patients With Marfan Syndrome**

<table>
<thead>
<tr>
<th>Case No./Sex/Age (y)</th>
<th>Smoking History</th>
<th>Cause of Death</th>
<th>Pulmonary Symptoms</th>
<th>Source of Lung Specimen</th>
<th>Right or Left Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/33</td>
<td>Unknown</td>
<td>Unable to wean from cardiopulmonary bypass after cardiothoracic surgery</td>
<td>Minimal shortness of breath and chest pain</td>
<td>Autopsy</td>
<td>Unknown</td>
</tr>
<tr>
<td>2/F/29</td>
<td>Unknown</td>
<td>Unable to wean from cardiopulmonary bypass after aortic arch dissection and hemothorax</td>
<td>None</td>
<td>Autopsy</td>
<td>Both</td>
</tr>
<tr>
<td>3/M/20</td>
<td>None</td>
<td>Massive hemorrhage and pulmonary failure after surgery</td>
<td>Cardiopulmonary arrest and right pleural bleeding</td>
<td>Autopsy</td>
<td>Unknown</td>
</tr>
<tr>
<td>4/M/50</td>
<td>16 pack-years</td>
<td>NA</td>
<td>Severe COPD with recurrent pneumothorax</td>
<td>Explant</td>
<td>Both</td>
</tr>
<tr>
<td>5/M/18</td>
<td>Minimal</td>
<td>NA</td>
<td>Chest pain, shortness of breath</td>
<td>Wedge resection</td>
<td>Left</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; NA, not available.
(mitral valve repair and reimplantation of the aortic valve in a dilated aortic root) complicated by pulmonary edema and bleeding between the graft and right coronary button. The patient was admitted 1 month after surgery with chest pain and a mediastinal abscess and was taken to surgery for abscess drainage and redo sternotomy. One week later, the patient went into cardiac arrest with massive bleeding from his endotracheal tube. In surgery, bleeding was seen in the right pleura and a bleeding ulcer was identified in the left atrium. The patient could not be resuscitated despite aggressive volume support.

**Gross Findings**

The combined weight of the lungs was 1,250 g. The left lung had 4 separate lobes. The right lung had fibrosis, an organizing pleural exudate, and surgical changes (laceration, suture line). The right lower lobe had an area of early consolidation and a small infarct near the hilum. The left upper lobe had a 1-cm hollow cavity.

**Case 4**

**Clinical Data**

A 50-year-old man was diagnosed with Marfan syndrome in October 2008 during a workup for lung transplantation. The patient has a 16 pack-year smoking history, severe chronic obstructive pulmonary disease, and pulmonary hypertension. He has had spontaneous left (>20 years ago) and right (May 2008) pneumothoraces complicated by a persistent right-sided bronchopulmonary fistula. He also has a chronic superior mesenteric artery dissection. The patient underwent bilateral lung transplantation on June 14, 2010.

**Gross Findings**

The combined weight of the lungs was 919 g (right, 455 g; left, 464 g). The right and left lungs had a normal lobar configuration. Both lungs had severe emphysematous changes with marked bullae formation, predominantly in the upper lobe. There were bilateral dense fibrous pleural adhesions with multiple pleural lacerations. The majority of each lower lobe was uninvolved. The left lower lobe had some features of congestion and chronic atelectasis. No mass-type lesions were identified in either lung. Examination of the right and left pulmonary vessels revealed the absence of fatty streaks in the proximal vessels and no peripheral thickening in the distal vessels.

**Case 5**

**Clinical Data**

An 18-year-old man had a history of Marfan syndrome, aortic root dissection with repair in 2007, and left spontaneous pneumothorax in July 2010. He has a smoking history of unspecified intensity and duration. The patient was admitted in December 2010 with sudden chest pain and shortness of breath after sneezing. He was found to have a left pneumothorax and underwent left upper lobe wedge resection and (mechanical and chemical) pleurodesis.

**Gross Findings**

The left upper lobe wedge resection specimen weighed 27.7 g. The pleural surface was tan-brown, smooth, and glistening. The parenchyma was red-brown and grossly unremarkable.

**Results**

Pulmonary specimens from our case series all showed distal acinar emphysema. These changes occurred just beneath the pleural surface with sparing of the surrounding acini. Areas of scarring may be present in the distal septa, although with significant separation from other areas of more typical emphysematous changes. Some cases showed discrete foci of emphysematous change, while others displayed more extensive alveolar destruction. In case 4, centrilobular emphysema was also present within the lung parenchyma. Excluding the distal acinar type, other subtypes of emphysema were not present in any other case. However, every case displayed additional nonspecific histologic changes: pneumonia (acute or organizing, 2 cases), congestion (2 cases), fibrous pleural adhesions (2 cases), hemorrhage (1 case), and pleuritis (1 case).
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**Image I** Distal acinar emphysema. **A**, Case 2 (H&E, x40). **B**, Case 5 (H&E, x40). **C**, Case 4 (H&E, x40). **D**, Case 3 (H&E, x40). **E**, Case 1 (H&E, x40).
Discussion

Although patients with Marfan syndrome may have pulmonary pathology, the specific histologic changes have not been adequately characterized in any microscopic detail. The literature has so far been poorly developed and without specific findings. Our study is the largest contemporary case series of pulmonary Marfan syndrome from a single institution and the first to report a specific histologic pattern in Marfan syndrome.

Previous studies have reported spontaneous pneumothorax (unilateral and bilateral), congenital lobar abnormalities, bullae, bronchiectasis, cystic disease and changes, honeycombing, apical fibrosis, and emphysema. These studies have largely relied on imaging and gross examination, with spontaneous pneumothorax being the pathologic change most often described. The few studies that explore histologic classification tend to report nonspecific microscopic descriptions. Emphysematous changes are of particular interest. They have been previously described in terms of geographic location (eg, upper vs lower lobe, bilateral vs unilateral). Emphysematous subtypes are currently histologically defined, but there are no descriptions in terms of histologic location that would help classify the Marfan-type emphysema with current subtypes.

The main strength of our study lies in our number of cases and microscopic review. The last reported histologic case series this large was in 1975. A majority of the relevant literature reviews only single cases. In addition, only a minority of previous reports include microscopic descriptions. It is interesting that a 1964 article by Bolande and Tucker includes a picture of subpleural emphysema with the caption of “microcyst” without further classification. The pathology appears essentially identical to that seen in our case series, lending further strength to our findings. Weaknesses of the study include the fact that it is retrospective and that not all cases are equally well-sampled. In addition, our samples came from a variety of sources, including the autopsy service. However, because Marfan syndrome is a rare condition that usually does not generate pulmonary pathologic specimens, these shortcomings are somewhat expected and (arguably) unavoidable.

Distal acinar emphysema (also known as paraseptal emphysema) involves the distal-most alveoli, with changes directly beneath the pleural surface. The surrounding acini are often spared, creating a characteristic morphologic pattern of emphysema juxtaposed to normal lung parenchyma. This process tends to follow the interlobular septa that are present in the outer third of the lung.

In addition to distal acinar emphysema, each case had at least 1 other identifiable histopathologic change. These alterations are likely secondary to other factors because no consistent pattern of alteration was found. Notably, the patient in case 4 also had superimposed centrilobular emphysema, which was easily found owing to the ample tissue available for examination from the bilateral explant pneumonectomies in this case. Although 3 of our cases originated from autopsy specimens, we were limited to the representative samples that were obtained at the time of dissection, in most cases more than 20 years earlier. For this reason, it is difficult to determine if the abnormalities in case 4 (the only smoker) are more severe than those seen in the other cases.

These changes at the periphery of the lobule seem distinct from other diseases of the lung that, at first glance, may appear to have similar histologic features. In a young patient population (younger than 20 years), the main differential diagnosis includes emphysema (centrilobular, panacinar, interstitial, and paracartilaginous), lymphangioleiomyomatosis, and Birt-Hogg-Dubé syndrome. Centrilobular emphysema is included because 1 of our cases involves a 50-year-old man. Many of the differential diagnoses can be differentiated from Marfan syndrome based on clinical history and imaging studies. However, some of the pathologic changes also have distinguishing features.

Centrilobular emphysema affects the proximal acini with sparing of the distal. It is typically worse in the upper lung lobes, notably the apices. Panacinar emphysema shows uniformly enlarged acini, from the bronchioles to the terminal alveoli. It usually concentrates in the lower lung zones, especially the bases. Interstitial emphysema is characterized by air tracking along the subpleura and down the interlobular septa, with compression of the lobules. Paracartilaginous emphysema is defined by emphysematous changes adjacent to focal areas of scarring. Lymphangioleiomyomatosis can have subpleural emphysematous changes, but also has distinguishing smooth muscle–like spindled cells and clusters of hemosiderin-laden macrophages that are characteristic of the diagnosis. Last, Birt-Hogg-Dubé syndrome typically affects the middle and lower lobes, with pneumocyte-lined cysts occurring in pleural and subpleural regions. These alterations are distinct from the pattern of distal acinar emphysema. However, nonspecific bullae arising as secondary changes may also be seen in these cases. Careful examination is required so as to not miss the unique cystic changes located in other regions.

It is important to remember that distal acinar emphysema is not a distinguishing feature of Marfan syndrome and may be seen in other disease processes, notably in tall, thin males with spontaneous pneumothoraces. Distal acinar emphysema has been described in these cases and is an important reminder to interpret pathologic findings in the context of clinical history and imaging studies. However, the consistency of this pattern in our case series suggests that an association with Marfan syndrome may also be present. Although this pattern has been reported in another cohort, it has not been described in the Marfan syndrome population.
Histologic differential diagnosis. Subtypes of emphysema. **A**, Centrilobular (H&E, ×40). **B**, Panacinar (H&E, ×40). **C**, Interstitial (H&E, ×40). **D**, Paracicatricial (H&E, ×40). **E**, Also included in the differential diagnosis, lymphangioleiomyomatosis (H&E, ×40).
This is the largest contemporary series of pulmonary involvement of Marfan syndrome from a single institution. The findings of distal acinar emphysema have been suggested in a previous report, but this series represents a new pattern of pulmonary injury for patients with Marfan syndrome.

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References