

# X-linked myotubular myopathy and pulmonary blebs: Not just a muscle disorder

## 1 | INTRODUCTION

X-linked myotubular myopathy (XLMTM) is a rare, congenital muscle disorder caused by mutations in the *MTM1* gene at Xq28.<sup>1,2</sup> Transcription of a normal gene produces myotubularin, a phosphatase enzyme. Myotubularin removes phosphate groups from two molecules called phosphatidylinositol 3-phosphate and phosphatidylinositol 3,5-bisphosphate within muscle cell membranes and is likely involved in transporting molecules within myocytes. In XLMTM, resultant lack or dysfunction of the myotubularin protein leads to severe, progressive skeletal myopathy.<sup>3,4</sup> Affected boys experience respiratory failure and dysphagia and aspiration risk in early infancy, often requiring mechanical ventilation and feeding tubes.<sup>5,6</sup> Neuromuscular weakness contributes to cumulative morbidities throughout childhood as well as high mortality rates from respiratory events. Technological supports have contributed to expanded survival into adulthood.<sup>7</sup>

Recent preclinical studies of novel therapeutic approaches, including gene replacement using an adeno-associated viral vector, have brought XLMTM to the forefront of translational science.<sup>8-13</sup> Coupled with extended survival, due to shared decisionmaking and technological supports, providers are now recognizing additional myotubularin-related complications. Hepatic peliosis with hemorrhage has long been recognized as a fatal complication attendant to XLMTM. Herein, we describe two unrelated patients with XLMTM and different gene mutations and associated pulmonary blebs.

Common features for both young men included presentation as newborns and subsequent progressive myopathic findings of low muscle mass, myopathic facies (patient 1 with limited extraocular movements and both with limit eyelid excursion), areflexia, intact sensation, and gross motor movement limited to the fingers. Muscle biopsies in 2001 and 1997, respectively, were consistent with MTM with subsequent genetic confirmation. Neither patient has other conditions that would lend to the development of pulmonary blebs.

Informed consent was obtained from the individuals described in this series.

## 2 | CASE REPORTS

### 2.1 | Patient 1

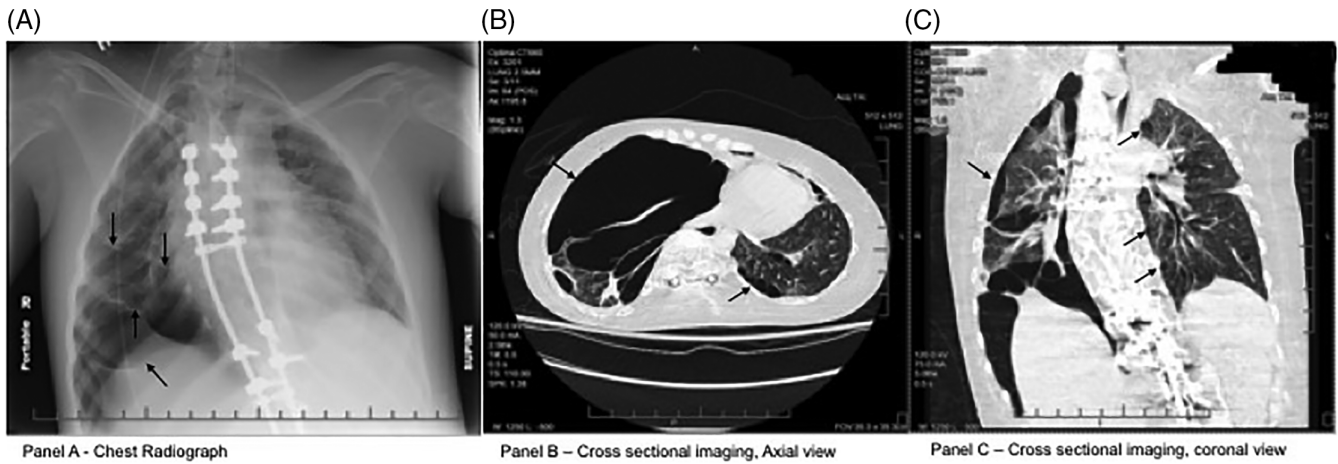
A 15-year-old boy with XLMTM (*chrX:149783061G>A, c.232-1G>A*), chronic respiratory failure with tracheostomy and ventilator dependence,

gastrostomy tube dependence, neurogenic scoliosis with posterior spinal fusion, shunted hydrocephalus, history of cholelithiasis, and other associated complex care needs presented to emergency care with a 2-day need for oxygen supplementation, progressive tachycardia, and new-onset diaphoresis. There was no history of fever, intercurrent respiratory illness, or other systemic processes. Vital signs were notable for 84% room air saturations on ventilator support, mild tachycardia, and normal blood pressure. Examination revealed diminished aeration on the right lung field, with coarse breath sounds on the left. A palpable liver was appreciated below the right costal margin, but no jaundice or scleral icterus. Laboratory studies were notable for a white blood cell of 12.4 K/ $\mu$ L, hemoglobin 15.6 g/dL, aspartate aminotransferase 1320 U/L, and alanine aminotransferase 3443 U/L. Evaluation included a routine chest radiograph (Figure 1A) and subsequent cross-sectional imaging (Figure 1B,C), that identified extensive bullous disease of the lungs with mass hyperinflation of the right hemithorax.

The patient was admitted to the intensive care unit (ICU) after volume repletion. Routine respiratory support provision was modified with lower ventilator pressures and elimination of insufflation-exsufflation cough assistance in an attempt to minimize further bleb expansion. A right-sided percutaneous drain was placed with near-complete resolution of an apparent ruptured bleb. Clinical status improved. The pleural drain was removed. The patient was discharged home with a plan for gradual titration of respiratory supports. Four weeks after discharge, the patient returned with hypoxia and overtly asymmetric chest rise with apparent left-sided hyperinflation. Fluoroscopic-guided pleural drainage on the left was pursued. Unilateral pleurodesis without blebectomy was performed. Clinically significant lung parenchymal changes have not evolved over the subsequent 2.5 years.

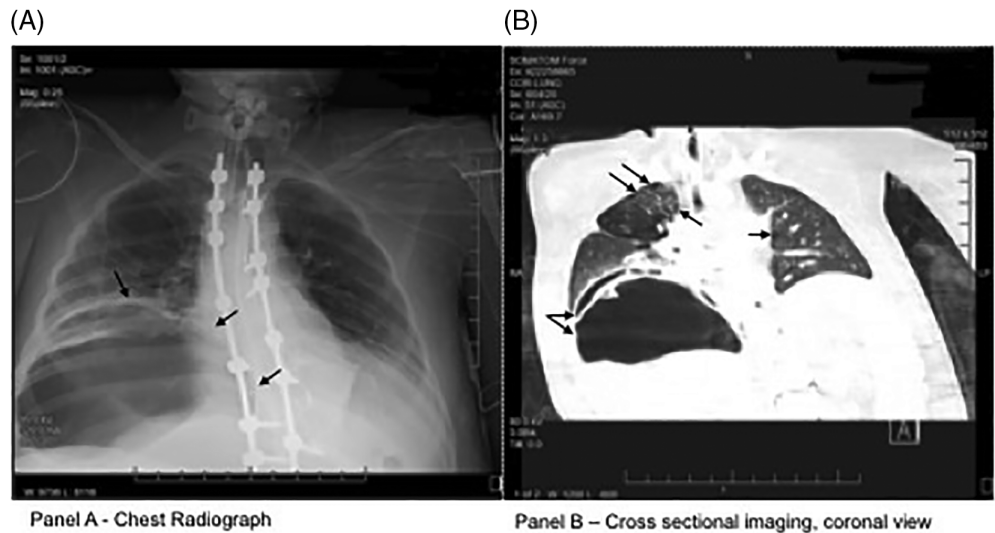
### 2.2 | Patient 2

A 21-year-old man with XLMTM (*chrX:149807436\_149807436delT, c.465\_465delT, p.Asn155Lysfs\*31*), chronic respiratory failure with tracheostomy and ventilator dependence, gastrostomy tube dependence, neurogenic scoliosis, idiopathic thrombocytopenia, macrocytosis, and other associated needs presented to the ICU after posterior spinal instrumentation and T3-pelvic fusion facilitated by intraoperative halofemoral traction; of note, the procedure did not require intrathoracic approach for anterior spinal ligament release and incidental abdominal cavity intrusion did not occur. On postoperative day 5, chest and abdominal



**FIGURE 1** Chest imaging of patient 1. A, Chest radiograph revealing multiloculated lucencies over the right middle and lower thorax (delineated by arrows), corresponding atelectasis, indwelling tracheostomy tube, and ventriculoperitoneal shunt tubing. B,C, Cross-sectional imaging reveals multiple bilateral subpleural, peripheral, thin-walled pulmonary blebs, right more than left, with largest at right base (delineated by arrows) and associated atelectatic compression, and no pneumothorax or effusion

**FIGURE 2** Chest imaging of patient 2. A, Chest radiograph revealing low lung volumes, massive right, lower intrathoracic vs subpulmonic lucency (delineated by arrows), corresponding atelectasis, and indwelling tracheostomy tube. B, Cross-sectional imaging revealing multiple thin-walled blebs (delineated by arrows) in the right upper lobe and a massive, right-lower-lobe, septate pulmonary bleb without pneumothorax



radiographs were obtained due to mild distention on exam and persistent ileus. These revealed a large subdiaphragmatic air collection and subsequent cross-sectional imaging revealed a complex, septate lesion with air-fluid levels of the right lower lobe depressing the diaphragm (Figure 2A,B). Utilizing fluoroscopy, it was determined that the process was pulmonary in origin, not infradiaphragmatic. A percutaneous drain was placed under fluoroscopic guidance. Pleural drainage was successfully removed with resolution of air-leak on postoperatively day 20, after 12 days of evacuation. The patient and his family elected not to pursue more invasive surgical interventions, pleurodesis, or blebectomy.

### 3 | DISCUSSION

Other organ system involvement in XLMTM has been appreciated, but pulmonary blebs and pneumothoraces have not been reported. Although young men with XLMTM are vulnerable to aspiration

pneumonias/pneumonitis as well as impaired secretion clearance and resultant pneumonias or bronchiectasis, the pattern and extent of peripheral and centrilobular pulmonary blebs reported in these cases are not typically associated with these mechanisms in other conditions. The use of long-term mechanical ventilation is also not associated with this pathology. This process is most likely gradual in its evolution. Recognition of this association is of significant clinical consequence and has implications for screening, management of respiratory supports, and anticipatory guidance. It is possible that the development of structural changes and, consequently, clinically significant manifestations of myotubularin deficiency outside of the muscular system reflect variations in gene mutations. In this era of gene-targeted and gene-replacement trials and therapies, understanding of myotubularin gene modification and protein function in other tissues is crucial when studying outcomes and determining risks and benefits.<sup>12,13</sup> Further exploration of myotubularin function in pneumocytes may also provide insight into the pathophysiology of peliosis hepatis and the associated endothelium.

**CONFLICT OF INTEREST**

The authors have no conflicts of interest to disclose related to this report.

**ETHICAL PUBLICATION STATEMENT**

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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# Utility of neuromuscular ultrasound for electromyographic needle localization within diseased muscle

## 1 | INTRODUCTION

The availability of low-cost, high-frequency linear-array transducers has led to the increased use of ultrasound in the diagnosis of neuromuscular disorders.<sup>1</sup> Ultrasound is particularly sensitive for detecting atrophy, fibrosis, and fatty infiltration within muscle.<sup>1,2</sup> It can be used to establish a pattern of muscle involvement and to grade severity between muscles.<sup>3</sup> Low-level muscle contraction is also discernible by ultrasound, even when there is no obvious movement on visual inspection of the limb.<sup>4</sup> In the electromyography (EMG) laboratory, the ability of ultrasound to identify the pattern of muscle involvement in real time provides a useful guidance tool for selecting muscles with the highest yield for EMG recording. In this report, we further

demonstrate the utility of ultrasound guidance for localizing small areas of viable muscle tissue for EMG recording within a large muscle that has undergone extensive atrophy, fibrosis, and fatty infiltration.

## 2 | CASE REPORT

A 46-year-old man was referred to the EMG laboratory with progressive weakness over 20 years. He first noticed an inability to jump while playing basketball in his early 20s. He went on to develop increased weakness in his limbs and trunk and now requires a wheeled walker to ambulate. He has been observed to have apparent episodes of sleep apnea and evidence of dysphagia. On examination, he had prominent